Recipient Information

1. Recipient Name
BETH ISRAEL DEACONESS MEDICAL CENTER, INC
330 BROOKLINE AVE
BOSTON, MA 02215

2. Congressional District of Recipient
07

3. Payment System Identifier (ID)
1042103881A1

4. Employer Identification Number (EIN)
042103881

5. Data Universal Numbering System (DUNS)
071723621

6. Recipient's Unique Entity Identifier
C1CPANL3EWK4

7. Project Director or Principal Investigator
Yu Jing Jan Heng, PHD (Contact)
Assistant Professor
yheng@bidmc.harvard.edu
617-667-4132

8. Authorized Official
Darlene M Janis

Federal Agency Information

9. Awarding Agency Contact Information
Jennifer S Meininger

NATIONAL CANCER INSTITUTE
jennifer.meininger@nih.gov
(240) 276-6330

10. Program Official Contact Information
TAPAN K BERA
Program Director
NATIONAL CANCER INSTITUTE
berat@mail.nih.gov
240-276-6220

Federal Award Information

11. Award Number
1R56CA284564-01

12. Unique Federal Award Identification Number (FAIN)
R56CA284564

13. Statutory Authority
42 USC 241 42 CFR 52

14. Federal Award Project Title
Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes

15. Assistance Listing Number
93.393

16. Assistance Listing Program Title
Cancer Cause and Prevention Research

17. Award Action Type
New Competing

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information

19. Budget Period Start Date 09/18/2023 – **End Date** 08/31/2024	
20. Total Amount of Federal Funds Obligated by this Action	$299,940
20 a. Direct Cost Amount	$173,476
20 b. Indirect Cost Amount	$126,464
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$299,940
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$299,940
26. Project Period Start Date 09/18/2023 – **End Date** 08/31/2024	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$299,940

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Jennifer S Meininger

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

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Uncovered by a White Coat Waste investigation

RESEARCH
Department of Health and Human Services
National Institutes of Health

NATIONAL CANCER INSTITUTE

SECTION I – AWARD DATA – 1R56CA284564-01

Principal Investigator(s):
Yu Jing Jan Heng (contact), PHD
GERBURG M WULF, MD

Award e-mailed to: resadmin@bidmc.harvard.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $299,940 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to BETH ISRAEL DEACONESS MEDICAL CENTER in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R56CA284564. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Jennifer S Meininger
Grants Management Officer
NATIONAL CANCER INSTITUTE

Additional information follows

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Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Federal Direct Costs	$173,476
Federal F&A Costs	$126,464
Approved Budget	$299,940
Total Amount of Federal Funds Authorized (Federal Share)	$299,940
TOTAL FEDERAL AWARD AMOUNT	$299,940
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$299,940

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$299,940	$299,940

Fiscal Information:

Payment System Identifier:	1042103881A1
Document Number:	RCA284564A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2023

IC	CAN	2023
CA	8479565	$299,940

NIH Administrative Data:
PCC: EHTB / **OC**: 41021 / **Released**: Meininger, Jennifer 09/11/2023
Award Processed: 09/18/2023 12:15:55 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R56CA284564-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 1R56CA284564-01

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

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Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R56CA284564. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

This award represents the final year of the competitive segment for this grant. See the NIH Grants Policy Statement Section 8.6 Closeout for complete closeout requirements at: http://grants.nih.gov/grants/policy/policy.htm#gps.

A final expenditure Federal Financial Report (FFR) (SF 425) must be submitted through the eRA Commons (Commons) within 120 days of the period of performance end date; see the NIH Grants Policy Statement Section 8.6.1 Financial Reports, http://grants.nih.gov/grants/policy/policy.htm#gps, for additional information on this submission requirement. The final FFR must indicate the exact balance of unobligated funds and may not reflect any unliquidated obligations. There must be no discrepancies between the final FFR expenditure data and the Payment Management System's (PMS) quarterly cash transaction data. A final quarterly federal cash transaction report is not required for awards in PMS B subaccounts (i.e., awards to foreign entities and to Federal agencies). NIH will close the awards using the last recorded cash drawdown level in PMS for awards that do not require a final FFR on expenditures or quarterly federal cash transaction reporting. It is important to note that for financial closeout, if a grantee fails to submit a required final expenditure FFR, NIH will close the grant using the last recorded cash drawdown level. If the grantee submits a final expenditure FFR but does not reconcile any discrepancies between expenditures reported on the final expenditure FFR and the last cash report to PMS, NIH will close the award at the lower amount. This could be considered a debt or result in disallowed costs.

A Final Invention Statement and Certification form (HHS 568), (not applicable to training, construction, conference or cancer education grants) must be submitted within 120 days of the expiration date. The HHS 568 form may be downloaded at: http://grants.nih.gov/grants/forms.htm. This paragraph does not apply to Training grants, Fellowships, and certain other programs—i.e., activity codes C06, D42, D43, D71,

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DP7, G07, G08, G11, K12, K16, K30, P09, P40, P41, P51, R13, R25, R28, R30, R90, RL5, RL9, S10, S14, S15, U13, U14, U41, U42, U45, UC6, UC7, UR2, X01, X02.

Unless an application for competitive renewal is submitted, a Final Research Performance Progress Report (Final RPPR) must also be submitted within 120 days of the period of performance end date. If a competitive renewal application is submitted prior to that date, then an Interim RPPR must be submitted by that date as well. Instructions for preparing an Interim or Final RPPR are at: https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf. Any other specific requirements set forth in the terms and conditions of the award must also be addressed in the Interim or Final RPPR. *Note that data reported within Section I of the Interim and Final RPPR forms will be made public and should be written for a lay person audience*.

NIH strongly encourages electronic submission of the final invention statement through the Closeout feature in the Commons, but will accept an email or hard copy submission as indicated below.

Email: The final invention statement may be e-mailed as PDF attachments to: NIHCloseoutCenter@mail.nih.gov.

Hard copy: Paper submissions of the final invention statement may be faxed to the NIH Division of Central Grants Processing, Grants Closeout Center, at 301-480-2304, or mailed to:

National Institutes of Health
Office of Extramural Research
Division of Central Grants Processing
Grants Closeout Center
6705 Rockledge Drive
Suite 5016, MSC 7986
Bethesda, MD 20892-7986 (for regular or U.S. Postal Service Express mail)
Bethesda, MD 20817 (for other courier/express deliveries only)

NOTE: If this is the final year of a competitive segment due to the transfer of the grant to another institution, then a Final RPPR is not required. However, a final expenditure FFR is required and should be submitted electronically as noted above. If not already submitted, the Final Invention Statement is required and should be sent directly to the assigned Grants Management Specialist.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of

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sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html. For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.

- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – CA SPECIFIC AWARD CONDITIONS – 1R56CA284564-01

Clinical Trial Indicator: No

This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

INFORMATION: This award is issued as an NIH High Priority, Short-Term Project Award (R56). Information regarding this award mechanism is provided at: http://grants.nih.gov/grants/funding/r56.htm

INFORMATION: As described in NOT-CA-21-096, Principal Investigators (PIs), including Project Leaders on multi-project grants, will be required to commit a minimum level of effort to be eligible for NCI funding through R01, R37, U01, P01, and R21 grant mechanisms. This award has been issued based on the PI/MPI and Project Leaders (if applicable) devoting the NCI required minimum effort. Any reduction below the minimum level of effort requires NCI prior approval.

INFORMATION: To help expedite NCI's response to prior approval requests, please submit requests for change of PD/PI, carryover or no cost extensions electronically through the eRA Commons at Prior Approval Module. All other post award requests should be submitted to NCIGrantsPostAward@nih.gov. All electronically submitted requests will be tracked and forwarded to the appropriate Grants Management personnel.

INFORMATION: This award is contingent upon the following: No individual who receives salary support from this project may receive compensation for more than 12 calendar months (i.e., 100%) total effort from all of their sources of support.

INFORMATION: Although the budget period start date for this award is 09/18/2023, this award includes funds for twelve months of support. Allowable pre-award costs may be charged to this award, in accordance with the conditions in the NIH Grants Policy Statement, and with institutional requirements for prior approval.

INFORMATION: This award, including the budget and the budget period, has been discussed between Jennifer Meininger of the National Cancer Institute and Dr. Heng on 09/11/2023.

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SPREADSHEET SUMMARY
AWARD NUMBER: 1R56CA284564-01

INSTITUTION: BETH ISRAEL DEACONESS MEDICAL CENTER

Facilities and Administrative Costs	Year 1
F&A Cost Rate 1	72.9%
F&A Cost Base 1	$173,476
F&A Costs 1	$126,464

WHITE COAT WASTE PROJECT

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Uncovered by a White Coat Waste investigation

PI: **Heng, Yu Jing Jan**	Title: Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes	
Received: 08/01/2023	Opportunity: PAR-21-322	Council: 01/2024
Competition ID: FORMS-H	FOA Title: Basic Research in Cancer Health Disparities (R01 Clinical Trial Not Allowed)	
1R01CA284564-01A1	Dual:	Accession Number: 4863897
IPF: 758101	Organization: BETH ISRAEL DEACONESS MEDICAL CENTER	
Former Number: 1R01CA284564-01	Department: Pathology	
IRG/SRG: ZRG1 BTC-S (02)M	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 435,441 Year 2: FUTURE COSTS [redacted] Year 3: Year 4: Year 5:	Animals: Y Humans: N Clinical Trial: N Current HS Code: 10 HESC: N HFT: N Special Topics: Data Management Sharing	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Li Jia	Brigham and Women's Hospital	Co-Investigator
Gabrielle Baker	Beth Israel Deaconess Medical Center	Co-Investigator
Yu Jing Jan Heng Ph.D.	Beth Israel Deaconess Medical Center, Inc.	PD/PI
Gerburg Wulf	Beth Israel Deaconess Medical Center	MPI
Frank Slack Ph.D.	Beth Israel Deaconess Medical Center	Co-Investigator

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

OMB Number: 4040-0001
Expiration Date: 11/30/2025

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
CA284564

b. Agency Routing Number

2. DATE SUBMITTED	Application Identifier	c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **UEI*:** C1CPANL3EWK4

Legal Name*: Beth Israel Deaconess Medical Center, Inc.
Department: Research and Academic Affairs
Division: Sponsored Programs Contracting
Street1*: 330 Brookline Avenue, OV-540
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5491

Person to be contacted on matters involving this application
Prefix: First Name*: Darlene Middle Name: M Last Name*: Janis Suffix:
Position/Title: Research Administrator
Street1*: 330 Brookline Avenue, OV-540
Street2:
City*: Boston
County: MA
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5491
Phone Number*: 617-667-1332 Fax Number: Email: djanis@bidmc.harvard.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1042103881A1

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*	10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
National Institutes of Health	TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes

12. PROPOSED PROJECT		13. CONGRESSIONAL DISTRICTS OF APPLICANT
Start Date*	Ending Date*	MA-007
04/01/2024	03/31/2029	

Uncovered by a White Coat Waste investigation

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Yu Jing Jan Middle Name: Last Name*: Heng Suffix: Ph.D.
Position/Title: Assistant Professor
Organization Name*: Beth Israel Deaconess Medical Center, Inc.
Department: Pathology
Division:
Street1*: 330 Brookline Avenue
Street2: Dana 527B
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5491
Phone Number*: 617-667-4132 Fax Number: Email*: yheng@bidmc.harvard.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$3,830,811.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$3,830,811.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Beth Middle Name: Last Name*: Doiron Suffix:
Position/Title*: Research Administrative Director
Organization Name*: Beth Israel Deaconess Medical Center, Inc.
Department: Research and Academic Affairs
Division: Sponsored Programs Contracting
Street1*: 330 Brookline Avenue, OV-540
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 02215-5491
Phone Number*: 617-667-1305 Fax Number: Email*: resadmin@bidmc.harvard.edu

Signature of Authorized Representative*
Sabrina Heisey

Date Signed*
08/01/2023

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1249-00 2023 Cover Letter.pdf

Uncovered by a White Coat Waste investigation

424 R&R and PHS-398 Specific
Table Of Contents

Uncovered by a White Coat Waste investigation

OMB Number: 4040-0010
Expiration Date: 11/30/2025

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Beth Israel Deaconess Medical Center, Inc.
UEI: C1CPANL3EWK4
Street1*: 330 Brookline Avenue
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02215-5491
Project/Performance Site Congressional District*: MA-007

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Brigham and Women's Hospital
UEI: QN6MS4VN7BD1
Street1*: 75 Francis Street
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02115-6110
Project/Performance Site Congressional District*: MA-007

Additional Location(s) File Name:

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ❍ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ❍ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ● No

IACUC Approval Date: 06-16-2023

Animal Welfare Assurance Number D16-00093

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1250-01 2023 Summary.pdf
8. Project Narrative*	1251-02 2023 Narrative.pdf
9. Bibliography & References Cited	1252-21_References_V2_HENG.pdf
10.Facilities & Other Resources	1253-Heng Facilities.pdf
11.Equipment	1254-Heng Equipment.pdf

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

This proposal will address the unmet breast cancer (BC) risk and treatment concerns of transmasculine people (assigned female at birth). We will also elucidate the molecular mechanisms of testosterone in mammary gland development, carcinogenesis, and response to BC treatment. Most transmasculine individuals pursue testosterone therapy (TT) to treat their gender dysphoria. The breast is a sex hormone-sensitive organ. Transmasculine individuals who receive TT are now a subject of concern. Very little is known about how high levels of testosterone affect the breast, and the risk of developing BC. Prospective human studies will take decades to collect cancer risk data. Mouse aging is accelerated by a factor of 70 compared to humans, and the hormone regulation of breast development is similar in mice and humans. As such, we will use two mouse models in Aim 1 to clarify the extent to which TT affects the development of estrogen receptor positive (ER+) and negative (ER-) BC. In Aim 1, we will compare BC incidences and tumor specific survival in female mice and oophorectomized female mice receiving TT with their respective controls that do not receive TT. On the other end of the spectrum, when transmasculine patients are diagnosed with BC, there is no clinical guideline on whether they can continue TT while being treated for BC. There is a knowledge gap about whether testosterone affects the efficacy of BC treatment. The discontinuation of TT during cancer treatment is undesirable as it affects the transmasculine patients' emotional wellbeing and compounds their cancer-induced emotional distress. Aim 2 will address the clinical treatment dilemma of whether continuing testosterone affects BC treatment outcome. Aim 2 will use the same mouse models to investigate whether continuing testosterone affects response to alpelisib (FDA approved therapy for ER+ tumors harboring a *PIK3CA* mutation), olaparib (FDA approved therapy for ER- tumors harboring a *BRCA1* mutation), or paclitaxel (a non-nucleoside-based chemotherapy). Testosterone mostly binds to the androgen receptor, and this hormone-receptor complex regulates mRNA of downstream target genes and microRNAs (miRNAs). We will study mRNA and miRNAs in conjunction with AR signaling to gain a comprehensive understanding of how testosterone affects mammary gland development, carcinogenesis, and response to BC treatment. Transgender people are the fastest growing group in the LGBTQ community. We need to start understanding their cancer risk. As the transgender population ages, we need to understand the effect of TT on cancer treatment. Our proposal will lead to fundamentally new insights to understand BC risk and develop treatment guidelines to improve BC outcome in the medically underserved transmasculine population. The increased understanding of the role of sex hormones and miRNA landscape in BC risk and treatment are not only important in improving transmasculine health and reducing their healthcare disparities; these knowledge will have direct implications for understanding BC risk and open up new avenues of treatment for cisgender men and women as well.

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Project Narrative

There is a lack of knowledge about the effect of gender-affirming hormone therapy on cancer risk and cancer treatment. We will utilize mouse models to understand the extent to which testosterone therapy affects breast cancer development (Aim 1) and breast cancer treatment outcome (Aim 2). Our proposal will gain new insights about breast cancer risk as well as develop new approaches to improve cancer outcome in both the underserved transmasculine community and the cisgender population.

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Facilities

BIDMC environment: Beth Israel Deaconess Medical Center (BIDMC), a teaching hospital of Harvard Medical School (HMS), is located in the Longwood Medical Area and within 10 minutes of walking distance to other HMS-affiliated institutions such as the Dana Farber Cancer Institute (DFCI), righam and Women's Hospital (BWH), the Countway Library, and Harvard T.H. Chan School of Public Health (HSPH).

Beth Israel Deaconess Medical Center in Longwood Medical Area, Harvard Medical School

BIDMC has an integrated multidisciplinary approach that joins scientists and clinicians in pioneering research areas such as vascular, transplantation, signal transduction in cancer, and molecular imaging. Faculty level cancer researchers at BIDMC are embedded in the BIDMC Cancer Center headed by Dr. Frank Slack. The BIDMC Cancer Center is part of the larger Dana Farber/Harvard Cancer Center (DF/HCC), an NCI-designated cancer center. The research teams at BIDMC lead more than 850 active sponsored projects and 500 clinical trials, and regularly publish results in leading scientific journals. Additionally, BIDMC has strong links with the Broad Institute of MIT and Harvard.

BIDMC is also home to the first-of-its kind *HMS Institute for RNA Medicine*, which is building the foundation for entirely new lines of inquiry, creating vital new research methodologies, and exploring applications for developing personalized diagnostics and therapies for some of the most challenging diseases of our time, most notably cancer. Dr. Slack is also the inaugural Director of the Institute for RNA Medicine. This institute aims to strengthen RNA research and medicines by harnessing the brainpower of the RNA community at Harvard. Members currently include Drs. Jeannie Lee, Judy Lieberman, George Daley, Richard Gregory, Anna Krischevsky, Carl Novina, Anders Naar and Dan Tenen, all world leaders in non-coding RNA discovery and validation and in RNA-based therapeutics in pre-clinical settings effrey Saffitz Chair of DMC's Department of Pathology, who is deeply invested in next-generation pathology; and Drs. Avigan, Moser, Costa and their teams are pioneering multidisciplinary care for cancer and innovative cancer clinical trials.

BIDMC space and core facilities: BIDMC research is conducted in 400,000 net assignable square feet of space. BIDMC is the anchor tenant of the Center for Life Science (3 Blackfan Circle), a state-of-the-art biomedical research facility which is connected to BIDMC East via a bridge and houses the majority of BIDMC's scientific investigators and research staff on six floors (350,000 square feet). BIDMC provides a host of leading-edge core facilities: flow cytometry, confocal imaging, bioinformatics, genomics, proteomics, small animal *in vivo* imaging, and histology services.

Center for Life Science at 3 Blackfan Circle, Boston, MA

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- Genomics, Proteomics, and Bioinformatics Center

The Genomics, Proteomics and Bioinformatics Center provides investigators with the instrumentation, expertise and services required to study gene expression and is equipped with state-of-the-art technologies for RNAseq, WES, genotyping, real-time PCR, proteomics and bioinformatics. Protein biomarkers in biological samples can be comparatively measured using the iTRAQ isobaric tagging system followed by MALDI-TOF/TOF mass spectrometry. SOMAscan, a high multiplex, high sensitivity aptamer-based biomarker discovery platform that simultaneously quantifies 1310 human proteins, is also available.

- Mass spectrometry core

The mass spectrometry, metabolomics, lipidomics and proteomics core was established in 2004. The core has cutting edge equipment operated at optimal sensitivity and work and publish with world class researchers. The core's expertise is in identifying and quantifying protein modifications and dynamic protein-protein interactions in addition to polar metabolomics profiling including metabolic flux analyses and non-polar lipidomics profiling. Several different types of mass spectrometers are available including high resolution Orbitraps for protein identification, hybrid linear ion trap-high resolution Orbitrap for protein quantification, post-translational modification (PTM) mapping and lipidomics profiling, and hybrid triple quadrupole QTRAP mass spectrometers for targeted quantification of metabolites, lipids and peptides.

- REDCap data core

REDCap is a free, secure, web-based application designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. Data collection is customized for each study or clinical trial by the research team with guidance from Harvard Catalyst.

- Biomedical Research Informatics Core (BRIC)

BRIC provides services to BIDMC research an informatics unit with a focus on delivering services to BIDMC researchers related to: Creating and managing HIPAA compliant databases; assisting with the selection and use of data analysis tools; and developing novel analysis techniques. BRIC also helps coordinate projects between several other informatics groups including: Academic and Research Computing, Clinical Data Repository, General Clinical Research Center (GCRC) and Genomics Center.

- Precision RNA Medicine Core

The HIRM Precision RNA Medicine Core is a state-of-the-art preclinical facility designed to accelerate discovery of RNA diagnostics and therapeutics. Dr. Frank Slack is the co-director. The facility offers both wet and dry lab services in its four interconnected units: Detection, Delivery, Spatial Transcriptomics, and Bioinformatics.

  - *The Detection Unit* enables miRNA quantification by highly sensitive and selective qRT-PCR technology from MiRXES. The methods used allow for unbiased screens of 384 microRNAs. Dr. Jan Heng is the director of this unit.
  - *The Delivery Unit,* for both in vitro and in vivo purposes, packages ncRNA in nanoparticles using the NanoAssemblr Spark, Benchtop, and Blaze from Precision NanoSystems and uses dynamic light scattering techniques for characterization of the nanoparticles.
  - *The Spatial Transcriptomics Unit* offers cutting-edge spatial transcriptomic technologies, addressing distinct levels of resolution, including:

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- Super resolution microscopy (below the diffraction of light limit nm resolution), with the ability to perform spatial studies, 3D reconstructions and real-time video capture of *in vitro* samples, organoids, and tissue using the Bruker Vutara VXL
- High resolution Multiplexed Error-Robust Fluorescence in situ Hybridization (MERFISH) technology using the Vizgen MERSCOPE
- Hypothesis-free spatial tissue sequencing at nearly single cell resolution using the 10x Genomics Visium
- Region of interest (ROI)-based whole transcriptome spatial assays using the NanoString GeoMx
- Ultrahigh multiplex imaging up between 6 to 50 proteins using the Akoya Biosciences Opal® or Codex®, and whole slide scanner Akoya Vectra and accompanying image analysis software, Akoya inForm®.
- Nikon T2i Eclipse an inverted microscope with a 25mm field of view and large-format CMOS camera, with the ability to capture brightfield (monochrome, color), and fluorescence. The scope is connected to a dedicated analysis server equipped with the Nikon Elements Software, with additional high-end packages enabling automated programmed captures, and large image stitching.
- Leica Bond Rx, an automated unit for immunohistochemistry and in situ hybridization.
- Leica cryostat and microtome
- Agilent Fragment Analyzer for quality assessment of NGS libraries as well as for the evaluation of RNA/DNA sample quality and properties.

o *Tissue Microarray Unit* is available for the construction and evaluation of tissue microarrays for cancer research using the 3DHISTECH TMA Master II and GrandMaster. Core services include construction of standard and custom tissue microarrays, preparation of slides, image acquisition and analysis as well as consultation, and high throughput isolation of DNA and RNA from formalin-fixed paraffin- embedded tissue cores.

o *The Bioinformatics Unit* uses best practice *in silico* technology for the analysis and prioritization of all species of RNAs in basic, applied, and translational research. The Bioinformatics Unit helps clients in grant development for applications, including coding and non-coding RNAs, provides consultation for coding and non-coding RNA biology and research, and develops datasets for use by researchers.

- Animal Care Facilities

BIDMC maintains its own fully accredited animal facilities on site in the Center for Life Science building and adjacent Slosberg Building. The animal research facility on the 8th Floor of the Center for Life Science building is equipped as a mouse hospital, suitable for co-clinical trials. The animal care and use program, which has been fully accredited by AAALAC since 1972, is maintained in accordance with all applicable state and federal regulations, and maintains a PHS Assurance through OPRR. Dr. Linda Angelbeck is the IACUC Administrator. Dr. Barbara Garibaldi is the Director and Attending Veterinarian (AV) of the Animal Research Facility at BIDMC and is a board certified laboratory animal veterinarian. BIDMC maintains a transgenic animal facility that provides full service transgenic and knock-out services. Full-service veterinary care is provided at all facilities. A high resolution digital ultrasound machine Vevo® 2100 from VisualSonics is available for use. Dr. Wulf is a member of the IACUC protocol committee.

- Specialized Histopathology Services

The Specialized Histopathology Core provides professional and technical research pathology services to members working in diverse organisms, including man, non-human primates, rodents, and zebrafish. The core performs routine histology and special histochemical stains and also assists in experimental design and the development, application, and interpretation of biomarker

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tests and their results. Specific services include immunohistochemistry, *in situ* hybridization, and laser capture microdissection.

- Small Animal Imaging Core

The Longwood Small Animal Imaging Facility (LSAIF) provides investigators with a streamlined system for the transport, testing and imaging of small animals used in research studies. High-quality technologies, including computed tomography (CT), positron emission technology (PET), single-photon emission computed tomography (SPECT), bioluminescence imaging, fluorescence light imaging and magnetic resonance imaging MR are available to scientists. The Core's services extend to experimental design, advanced data analysis, image fusion resources and a satellite animal facility for longitudinal studies. Customized contrast agents are also made possible for projects on the leading edge in nuclear, fluorescence and MRI. In 2011, the Longwood SAIF is expanding with the addition of the Animal Blood Testing Facility –providing researchers access to quick and inexpensive testing of virtually any species for a wide variety of blood tests available in the clinic.

- Tumor Imaging Metrics

The Tumor Imaging Metrics Core provides standardized, consistent, longitudinal radiological measurements to evaluate therapeutic response for clinical trials. Services include accurate, consistent, and timely analysis of imaging studies. Measurements available include linear, volumetric measures for CT or MR scans, and Standardized Uptake Value (SUV) for PET scans. Results of analyses are offered on a password-protected secure web-based report. This core also provides an independent service with verifiable measurement of treatment response for patients enrolled in trials, and serves as a centralized, computerized resource to facilitate efficient internal or external auditing.

Other Available BIDMC Institutional Resources:

- ICCB Longwood Screening facility for high content imaging and screening

The screening facility at HMS provides robotics for pin transfer of siRNA from library stock plates to assay plates, screening microscopes that image wells from 96- and 384-well assay plates, automated plate washers, liquid handling robots for filling assay plates, tissue culture hoods and incubators, multichannel pipettes, plate sealer and bar code labeller, screening microscopes for high content screening (an ImageXpress Micro, a cellWoRx , and an Evotec Opera) and Molecular Devices MetaXpress Software for High Content Screening. In addition we are routinely using the high content IncuCyte live cell imager (Essen Bioscience) located in the screening facility.

  - High content microscopes suitable for organoid imaging: ImageXpress Micro Confocal: Widefield imaging options for high-throughput screening, High-quantum efficiency sCMOS detection camera with a large field of view
  - Molecular Devices ImageXpress Micro Confocal: An inverted fluorescent microscope with a transmitted light option for label-free imaging, Features a 60 uM pinhole single spinning disc for confocal imaging, Integrated with a PAA GX robot arm and 45-plate hotel suite.
  - Molecular Devices ImageXpress Micro Confocal Laser: An inverted fluorescent microscope with a transmitted LED light (red 630nm), Features 2 spinning discs for confocal imaging: 60 uM pinhole with a 50 uM slit/42 uM pinhole, Equipped with a Lumencor Celesta light engine, a solid-state laser light source with up to 1 watt of output power.

- HMS computing resources

HMS Orchestra Shared Research Cluster is a service provided by the Research Information Technology Group at HMS. The Orchestra platform provides UNIX-based high performance

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computing, web hosting and database hosting services. Orchestra provides an open and powerful environment for researchers to conduct computational research. Orchestra terminal specifications include a total of: 476 compute nodes, 5128 processor cores, 37.67 TB aggregate memory, and 118.91 TB aggregate local disk capacity.

- BROAD Institute

The Broad Institute of Harvard and MIT was launched in 2004 to improve human health by using genomics. Since then it has become a world leader in developing novel high throughput methods, in assay development and in revealing underlying causes for human disease by combining biology, chemistry, mathematics, computation and engineering. As an affiliate member of the Broad Institute, Drs. Heng and Muranen has access to the collaborative facilities available to all Broad researchers, such as data sciences platform, drug screening platform and genetic perturbation platform.

- The Harvard Clinical and Translational Science Center (Harvard Catalyst)

Harvard Catalyst offers rich resources for collaboration, opportunities for education and training in translational research, grant writing workshops, and new funding opportunities. The scientific community of clinicians, scientists, epidemiologists and statisticians at Longwood Medical Area makes it a supportive environment that is highly accessible. As such, the Longwood Medical Area represents one of the most important and stimulating campuses for biomedical research in the world. With more than 50 clinical departments and 11,000 faculties, HMS conducts vast amounts of basic and clinical research.

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Facilities and resources at HENG laboratory, Department of Pathology, BIDMC

Laboratory Space Dr. an Heng's laboratory is located in the Dana Research uilding at DMC ast Campus. Her laboratory occupies ~600 square feet in BIDMC East (330 Brookline Avenue, Dana 5th floor): a wet-laboratory room for tissue-based molecular and pathological analyses with sufficient space for up to 4 students/fellows, and a separate dry-laboratory room to accommodate computational work for up to 4 students/fellows.

Office Space Dr. Heng's personal office will serve as the primary meeting site for informal meetings. The office includes a phone, 2 desktop computers, a laptop and two large monitors for reviewing data with collaborators.

Molecular Biology and Pathology Equipment: The wet-laboratory is equipped for DNA and RNA extractions: a Nanodrop 2000 spectrophotometer for quantifying DNA/RNA quantity, a PCR machine (GeneAmp PCR System 9700), two Eppendorf centrifuges and a Qiagen tissue lyser. The laboratory possesses the HybEZ Hybridization System for RNA in situ hybridization. For pathology/histology work, the laboratory has two Nikon Ellipse microscopes, a microtome, a whole slide scanner (Pannoramic Scan - Fluorescence and Brightfield, with Carl Zeiss 40x/0.95 objective) and Tissue Microarray (TMA) Master Fully Automated System for tissue microarray construction and coring for molecular biology assays. The wet-laboratory has a dedicated area for tissue molecular work, H&E staining, IHC staining procedures and DNA in situ hybridization.

Research Resources: The Department of Pathology at BIDMC has many resources for tissue processing, constructing tissue microarrays, histology, image analysis, molecular biology equipment and RNA/DNA extraction. As a full member of the DF/HCC Breast as well as Cancer Epidemiology programs, Dr. Heng has access to a rich set of resources for investigators, including core facilities sponsored by the DF/HCC (e.g., biomedical research informatics core, genomics/proteomics core, histology core, and tissue microarray and imaging core). Dr. Heng is also affiliated with the Broad Institute of MIT and Harvard. She has access to their core facilities. Dr. Heng is a member of the BIDMC Spatial Transcriptomic Unit and has direct access to the equipment and software, including the Nanostring GeoMX, Akoya Opal and inForm®, and Akoya Vectra whole slide scanner for immunofluorescence.

Computing Resources: The dry-laboratory is well-equipped with computing resources and various software including: statistical (Python and R), word processing (Microsoft Office Suite), creating manuscript-quality figures (Adobe Illustrator), image analyses (Definiens Tissue Studio 4.0 and QuPath 0.3.0), and a web-based image viewer/annotation software (ImagePath). Every fellow or student will have an independent desktop or laptop and full access to all software in the laboratory. Dr. Heng has password protected computers with printing capability and access to various essential statistics and computing software, the online resources of the various Harvard institutions and the Countway Library. All computers have access to Zoom via Harvard Medical School and GoToMeeting through BIDMC.

Logistical Support: Dr. Heng has administration support for grant assistance and management via the BIDMC Research and Academic Affairs department.

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Additional facilities and resources available at the WULF laboratory, Department of Medicine, BIDMC

Laboratory Space: Dr. Wulf has laboratory space (approx 700 sqft) within the Dana Research Building at BIDMC East. The facilities support full biochemical, molecular and cell biological experiments, and are fully available for this project. Her laboratory is on the same floor as Dr. Heng's.

Office Space Dr. Wulf's personal office includes a phone, des top computer, and a laptop. Dr. Wulf's office is adjacent to Dr. Heng's.

Animal facility: A new animal facility is on the 8th floor of the Center for Life Science building. Dr. Wulf is allowed room for 200 cages of mice. Dr. Wulf holds IACUC-approved protocols that allow for the proposed treatments.

Laboratory Equipment: Dr. Wulf's laboratory is well-equipped with standard wet-laboratory equipment to carry out the proposed research.

Research Resources: As a full member of the DF/HCC Breast Program, Dr. Wulf also has access to a rich set of resources for clinical investigators, including core facilities sponsored by the DF/HCC (e.g., biomedical research informatics core, genomics/proteomics core, histology core, and tissue microarray and imaging core).

Computing Resources: Apple Macintosh and PC computers, laser printers (black and white and color) are available to all lab personnel. Dr. Wulf has password protected computers with printing capability and access to various essential statistics and computing software, the online resources of the various Harvard institutions and the Countway Library. All computers have access to Zoom via Harvard Medical School and GoToMeeting through BIDMC.

Logistical Support: Dr. Wulf has administration support for grant assistance and management via the BIDMC Research and Academic Affairs department.

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Additional facilities and resources available for Dr. Frank Slack, Department of Pathology, BIDMC

Laboratory Space: The Slack laboratory occupies approximately 1,800 square feet of space in the Cancer Research Institute (CRI) on the 4th floor of the Center for Life Sciences (CLS) on the Longwood Medical Campus. This building was constructed in 2008 and houses several of the research units of BIDMC, one of the three major teaching hospitals of Harvard Medical School. Directly accessible for the proposed research is access to the shared departmental facilities for tissue culture, animal handling and surgery, darkroom work, radioisotope handling, and glass washing and sterilization. Laboratory space comprises 12 laboratory benches and desks, plus additional benches for microscopes and small equipment.

Office Space: Dr. Slac 's office is immediately adjacent to the lab space on the th floor of the CLS. He has access to a well- outfitted office suite with photocopiers, fax machine, scanners etc. An Executive assistant sits directly outside this office.

Laboratory Equipment: Dr. Slac 's laboratory is well-equipped with standard wet-laboratory equipment to carry out the proposed research.

Research Resources: As a full member of the DF/HCC, Dr. Slack also has access to a rich set of resources for clinical investigators, including core facilities sponsored by the DF/HCC.

Computing Resources: n Dr. Slac 's office is an Apple ntel iMac computer. There are workstations available in the laboratory (including 2 PCs, 8 Apple Mac). All of the laboratory computers are hardwired to the internet and capable of accessing the BIDMC server. In addition, each lab member has a personal laptop. A Dell Dimension 2.2 Ghz computer is connected to each Zeiss Axioplan microscope for image capture.

Logistical Support: Dr. Slack has administration support for grant assistance and management via the BIDMC Research and Academic Affairs department.

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Additional facilities and resources available for Dr. Li Jia, Department of Surgery, Division of Urological Surgery, BWH

BWH is an integrated hospital network consisting of both tertiary care hospitals and outpatient facilities. With over 900 hospital beds, 60 operating rooms, 150 ambulatory practices, it delivers care on a regional, national and international level. Measures of patient served include inpatient admissions of 47,000 and 1.8 million ambulatory encounters annually. The Division of Urology at righam and Women's Hospital/Dana arber Cancer nstitute constitutes clinical services at three institutions. The righam and Women's Hospital is a bed teaching hospital of Harvard Medical School. The primary satellite Hospital is the righam and Women's aul ner Hospital which is a bed teaching hospital located 2 miles from the main campus. In addition, the Division of Urology coordinates care of its cancer patients with the Dana Farber Cancer Institute as a primary provider of care within the Dana arber/ righam and Women's Cancer Center. Over , outpatient visits were made to the Division of Urology with approximately 1000 trans rectal ultrasound biopsies of the prostate performed each year and over 500 radical prostatectomies performed each year. The urology clinic has numerous active clinical trials and research programs with coordinators. BWH has dedicated space that is adjacent to the clinical offices for facilitating patient enrollment.

Laboratory Space: 600 square feet of modern research laboratory space in the Thorn Research uilding at righam and Women's Hospital is assigned to Dr Jia. An additional 1,250 square feet of common research space is immediately adjacent to his laboratory. This is located within the Brigham and Women's Hospital comple , within minutes wal of Divison of Urology academic offices, Harvard School of Public Health, Channing Laboratory and the Dana Farber Cancer Institute. The laboratory has bench space for 4 research personnel as well as a separate shared tissue culture room, cold room, dark room and equipment room. The laboratory is fully equipped and used for cell culture, biochemical, molecular, histological, and immunohistochemical procedures. This lab is licensed and equipped for the use of all chemicals, including appropriate arrangements for lab personnel safety and temporary waste storage.

Office Space: Dr. Jia has office space within the Division of Urology located within the BWH main campus.

Laboratory Equipment: Dr. ia's laboratory is well-equipped with standard wet-laboratory equipment to carry out the proposed research.

Computing Resources: PC computers with internet access are available at multiple locations throughout the work environment. Peripheral hardware, such as laser printers, image scanners, Ethernet and CD/DVD recorders are present. Software support for database analysis, word processing, presentation software and statistical programs are available. Patient data is stored as part of the electronic medical record under a secure server.

Logistical Support: Administrative support includes an administrative assistant as well as access to a full range of office equipment including printers, copier, fax, and telephones.

Other resources that Dr Jia has access to:

BWH Cores: BWH provides its scientific investigators with the tools they need to move research forward. A variety of resources – both services and educational opportunities – are available to members of the BWH research community. Additionally, investigators have access to numerous research core facilities, which include: Center for Clinical Investigation (CCI) Biostatistical Consulting Services, CCI Clinical Trails Center, CCI human Genetics Consult Service, CCI laboratory and

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Specimen Processing, Tissue and Blood Respository, BWH Antibody Core Facility, Confocal Microscopy Core, DNA Sequencing Core, Flow Cytometry Core, BWH Research Imaging Core, Harvard Catalyst Imaging Consulting Program, Tumor Imaging Metrics Core, Cell Culture and Microscopy Core, Single Cell Genomics Core, Trangenic Core, PHS Research Computing Cloud and Database Services, Resaerch Computing High Performance Computing.

Animal facility: If necessary, Dr Jia has access to the Lurie Family Imaging Center of Dana-Farber Cancer Institute, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC). Their laboratories will abide by the provision of the PHS “Guide for the Care and Use of Laboratory Animals” and the “U.S. Government Principles for the Utilization and Care of Vertebrate Animals”. The animals are subjected to regular veterinary care on a routine basis. The IACUC serves as the approval body for all protocols involving animal research, and assists faculty, students and staff in upholding their commitment to providing the finest care and most humane utilization of laboratory animals. In addition to basic husbandry services, the ARF staff provides technical and veterinary services, mouse breeding management and mouse irradiation.

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Equipment

Heng Lab, Department of Pathology, BIDMC

Molecular Biology Equipment:
GE Refrigerator
Thermo Fisher Scientific -20 freezer
Humm Stirling Ultracold -80 freezer
Thermo Fisher Scientific Isotemp Oven
Thermo Fisher Scientific Isotemp Water Bath X2
Thermo Fisher Scientific Forma DirectHeat Incubator
Eppendorf 5430R Centrifuge
Eppendorf 5415R Centrifuge
GeneAmp PCR System 9700
Thermo Fisher Scientific Nanodrop 2000 Spectrophotometer
Advanced Cell Diagnostics HybEZ Hybridization System

Histology and Digital Pathology Equipment:
Panoramic Scan - Fluorescence and Brightfield, with Carl Zeiss 40x/0.95 objective
TMA Master System (Caliper Life Sciences)
Definiens Tissue Studio (4.0)
Thermo Fisher Scientific Finnesse Me Microtome
Qiagen TissueLyser LT

Microscope:
Nikon Ellipse E200
Nikon Ellipse E400

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Wulf Lab, Department of Medicine, BIDMC

Laboratory Equipment:
Scintilation counters (institution shared resource)
Ultracentrifuges (institution shared resource)
Low and medium speed refrigerated centrifuges SW-27, 41, 50.1 rotors
Laminar flow hoods
Lyophilizer
Liquid nitrogen tanks
UV-vis spectrophotometer
Fractionation collectors
Gel equipment
Eppendorf centrifuges
Refractometer
Miccoinjection apparatus
Roller bottle tissue culture devices
CO_2 incubators
Analytical balances
Thermal cyclers

Microscopes:
Confocal microscope (Zeiss and BioRad)
Dissecting Microscope
Fluorescence microscope
Various Light Microscopes

Cytometers:
FACScan Flow Cytometer (Beckton Dickinson; institution shared resource)
MoFlo Cytometer (5 colors, Cytomation; institution shared resource)

Additional research rooms:
Tissue Culture room
Photographic dark room (institution shared resource)

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Slack Lab, Department of Pathology, BIDMC

Dr. Slack's laboratory is well-equipped with standard wet-laboratory equipment to carry out the proposed research. Dr. Slack additionally have the following equipment:

Cell culture room: Three incubators (CO_2 Water jacketed incubators, Forma Scientific) for cell cultures, and four cell culture hoods of Class II A2 Biosafety cabinet, (Thermo Forma).

Imaging: Light microscope (Primovert, ZEISS), a cellometer (Nexcelom), another microscope EVOS-FL (Life Technologies) with a standard red, green, and blue fluorescent filter sets and an incorporated digital imaging system.

Real-Time PCR Instrument: Real-Time PCR machine (Roche LightCycler 480 II PCR system)

Nanodrop: DeNovix® DS-11

Luminometer: luminometer Glo Max explorer (Promega) for luciferase reporter studies.

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Jia Lab, Department of Surgery, Division of Urological Surgery, BWH

The lab is equipped with standard molecular biology equipment including RNA/DNA and protein electrophoresis apparatus, transfer apparatus for Northern, Southern and Western blotting, multiple thermal cyclers for standard and real-time PCR, gel documentation imaging system, regular and refrigerated centrifuges, -20C and -80C freezers, biosafety cabinet, and CO2 incubator.

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OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Yu Jing Jan Middle Name Last Name*: Heng Suffix: Ph.D.

Position/Title*:	Assistant Professor
Organization Name*:	Beth Israel Deaconess Medical Center, Inc.
Department:	Pathology
Division:	
Street1*:	330 Brookline Avenue
Street2:	Dana 527B
City*:	Boston
County:	
State*:	MA: Massachusetts
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	02215-5491

Phone Number*: 617-667-4132 Fax Number:

E-Mail*: yheng@bidmc.harvard.edu

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2010

Attach Biographical Sketch*: File Name: 1235-03_Biosketch_HENG.pdf

Attach Current & Pending Support: File Name:

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PROFILE - Senior/Key Person

Prefix: First Name*: Gerburg Middle Name M Last Name*: Wulf Suffix:

Position/Title*: Associate Professor
Organization Name*: Beth Israel Deaconess Medical Center
Department: Medicine
Division: Hematology/Oncology
Street1*: 330 Brookline Avenue
Street2:
City*: Boston
County: MA
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02215-5491

Phone Number*: 617-667-4765 Fax Number:

E-Mail*: gwulf@bidmc.harvard.edu

Credential, e.g., agency login: [eRA COMMONS USERNAME redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD/PhD Degree Year: 1987, 1989

Attach Biographical Sketch*: File Name: 1236-Biosketch_GWulf.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Frank Middle Name J Last Name*: Slack Suffix: Ph.D.

Position/Title*: Professor
Organization Name*: Beth Israel Deaconess Medical Center
Department: Medicine
Division: Genetics
Street1*: 330 Brookline Avenue
Street2:
City*: Boston
County:
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02215-5491

Phone Number*: 617-735-2601 Fax Number:

E-Mail*: fslack@bidmc.harvard.edu

Credential, e.g., agency login: [eRA COMMONS USERNAME redacted]

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 1993

Attach Biographical Sketch*: File Name: 1237-Biosketch_FSlack.pdf

Attach Current & Pending Support: File Name:

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PROFILE - Senior/Key Person

Prefix: First Name*: Gabrielle Middle Name M Last Name*: Baker Suffix:

Position/Title*: Assistant Professor
Organization Name*: Beth Israel Deaconess Medical Center
Department: Pathology
Division:
Street1*: 330 Brookline Ave
Street2:
City*: Boston
County: Sulfolk
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02215-5491

Phone Number*: 617-667-5744 Fax Number:

E-Mail*: gbaker1@bidmc.harvard.edu

Credential, e.g., agency login: [redacted]

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 2008

Attach Biographical Sketch*: File Name: 1238-Biosketch_GBaker.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Li Middle Name Last Name*: Jia Suffix:

Position/Title*: Assistant Professor
Organization Name*: Brigham and Women's Hospital
Department: Surgery
Division:
Street1*: 20 Shattuck Street - Thorn 1529
Street2:
City*: Boston
County: Sulfolk
State*: MA: Massachusetts
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 02115-6110

Phone Number*: 617-525-7397 Fax Number:

E-Mail*: ljia@bwh.harvard.edu

Credential, e.g., agency login [redacted]

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 1995

Attach Biographical Sketch*: File Name: 1239-Biosketch_LJia.pdf

Attach Current & Pending Support: File Name:

WHITE COAT WASTE PROJECT

BIOGRAPHICAL SKETCH

NAME: Yu Jing Jan Heng

eRA COMMONS USER NAME: [redacted] eRA COMMONS USERNAME

POSITION TITLE: Assistant Professor of Pathology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Tasmania, TAS, Australia	B.Biomed.Sc	07/2005	Medical Laboratory Science
University of Tasmania, TAS, Australia	B.Biomed.Sc (Honors)	02/2006	Neuropharmacology
University of Melbourne/Melbourne Business School, VIC, Australia	Graduate Certificate	12/2009	Research Commercialization
University of Melbourne/Mercy Hospital for Women, VIC, Australia	Ph.D.	10/2010	Clinical Proteomics in Obstetrics and Gynecology
University of Toronto/Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, ON, Canada	Post-Doctoral Fellow	08/2014	Clinical Omics in Obstetrics and Gynecology
Harvard Medical School/Beth Israel Deaconess Medical Center, Boston, MA, USA	Research Fellow	07/2015	Computational Biology in Breast Cancer
Harvard Catalyst, Boston, MA, USA	Certificate	07/2023	Applied Biostatistics: Core Curriculum and Advanced Topics

A. Personal Statement

My role in this proposal is that of contact PI. I am an Assistant Professor of Pathology at Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School. My research focus is on translational breast cancer research to understand risk, prognosis, and response to treatment. I have a multi-disciplinary training in wet- and dry-laboratory techniques, and animal work.

I am part of the The Cancer Genome Network (TCGA) breast cancer working group whereby I published 1) the largest integrative morphology-genomic analyses in breast cancer, and 2) the first study linking epidemiological exposures to genomic signatures in breast cancer. I led molecular pathology epidemiology projects to understand breast cancer risk and survival within the Nurses' Health Studies.

Together with Dr. Gerburg Wulf (PI), we have been leading efforts in both mouse and human studies to understand gender-affirming hormone therapies and cancer. I established a transmasculine research cohort at BIDMC (*n*=578) and led the largest histopathology study investigating how testosterone therapy affects breast morphology in transmasculine individuals. That study was awarded "Best Clinical Paper 2021" by the BIDMC Cancer Center and featured in a few Podcasts. Dr Wulf and I were also awarded a R21 to conduct preclinical studies to investigate estrogen therapy and transfeminine breast cancer treatment outcomes. As such, I have the necessary experience and expertise to co-lead this project.

Ongoing and recently completed projects that I would like to highlight include:

12/1/2021-11/30/2023 NIH/NCI 1R21CA267088-01 (PI: Heng and Wulf)
Gender-affirming estrogen therapy and breast cancer treatment outcome

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This project is to understand to how gender-affirming estrogen therapy affects breast cancer treatment outcomes.
Role: Contact PI

1/14/2020-1/15/2021 NIH/NCI 2P50 CA168504-06A1 (PI: Winer)
Breast histopathology in transgender men and gender non-conforming individuals
This project examined how testosterone therapy affects breast histology.
Role: PI— Breast SPORE Career Development Award

12/6/2019-11/30/2023 NIH/NCI R01CA240341 (PI: Yaghjyan)
The role of breast stem cells in breast cancer etiology and risk prediction
This project will examine the role of stem cell markers in breast carcinogenesis to shed light on molecular pathways behind the observed associations of breast cancer risk factors with breast cancer risk.
Role: Subcontract PI

04/01/17-03/31/2022 NIH/NCI R01CA207369 (PI: Hankinson)
Endogenous hormones and postmenopausal breast cancer: Etiologic insights and improving risk prediction
This project aims to identify and validate hormonal markers—27-hydroxycholesterol, estrogen, and plasma c-peptide—to predict risk of invasive breast cancer in postmenopausal women from the Nurses' Health Study.
Role: Subcontract PI

Citations:

a) Baker GM, Guzman-Arocho YD, Bret-Mounet VC, Torous VF, Schnitt SJ, Tobias AM, Bartlett RA, Fein-Zachary VJ, Collins LC, Wulf GM and **Heng YJ**. Testosterone therapy and breast histopathological features in transgender individuals. (2021) *Mod Pathol*, 34, 85-94. PMCID: PMC7854981
b) **Heng YJ**, Lester SC, Tse GMK, Factor RE, Allison KH, Collins LC, Chen Y-Y, Jensen KC, Johnson NB, Jeong JC, Punjabi R, Shin SJ, Singh K, Krings G, Eberhard DA, Tan PH, Korski K, Waldman FM, Gutman DA, Sanders M, Reis-Filho JS, Flanagan SR, Gendoo DMA, Chen GM, Haibe-Kains B, Ciriello G, Hoadley KA, Perou CM, Beck AH. The molecular basis of breast cancer pathological phenotypes. (2017). *J Pathol*, 241, 375-391. PMCID: PMC5499709
c) Eismann J, **Heng YJ**, Waldschmidt JM, Vlachos IS, Gray K, Matulonis U, Konstantinopoulos PA, Murphy CJ, Nabavi S, Wulf GM. Transcriptome analysis reveals overlap in fusion genes in a phase I clinical cohort of TNBC and HGSOC patients treated with buparlisib and olaparib. (2020). *J Cancer Res Clin Oncol*. 146, 503–514. PMCID: PMC7083129
a) Vellal AD, Sirinukunwattana K, Kensler KH , Baker GM, Stancu AL, Pyle ME, Collins LC, Schnitt SJ, Connolly JL, Veta M, Eliassen AH, Tamimi RM and **Heng YJ**. Deep learning image analysis of benign breast disease to identify subsequent risk of breast cancer. (2021). *JNCI Cancer Spectr*, 5, pkaa119. PMCID: PMC7898083

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-Current	Director, Detection Unit, Precision Medicine Core, BIDMC
2022	Grant Reviewer, Breast Cancer Research Program, Department of Defense Congressionally Directed Medical Research Programs
2021, 2022	Grant Reviewer, NIH Study Section ZRG1 SBIB-Q 57 Academic Industrial Partnership
2021	Pre-Proposal Reviewer for Keck Foundation, The University of Texas at San Antonio
2020	Formula Grants Reviewer, Pennsylvania Department of Health
2020	Grant Reviewer, Biomedical Research Program, Florida Department of Health

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2019-Current	Staff Scientist II, Department of Pathology, BIDMC
2017-Current	Assistant Professor of Pathology, HMS
2018-Current	Director, Image Digitizing and IHC Quantitation Core, Dept of Pathology, BIDMC
2016-Current	Associated Scientist, Broad Institute, Cambridge, MA
2015-2019	Staff Scientist I, Department of Pathology, BIDMC
2015-2017	Instructor of Pathology, HMS
2014-2015	Research Fellow, Department of Pathology, BIDMC, HMS, Boston, MA
2010-2014	Post-Doctoral Fellow, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital; Departments of Obstetrics & Gynecology and Physiology, University of Toronto
2006-2010	Medical Laboratory Technician, Dorevitch Pathology, Heidelberg, VIC, Australia
2006	Research Assistant, School of Human Life Sciences, University of Tasmania

Honors

2021	Best Clinical Paper 2021, BIDMC Cancer Center, Boston, MA
2017	Harvard Catalyst "Good Questions Meet Big Data" Ideation Challenge Award, MA
2016	Rising Investigator Award, International Molecular Pathology Epidemiology Meeting, MA
2016	Women in Cancer Research Scholar Award, American Association for Cancer Research, LA
2013	Travel Award, US Human Proteome Organization, MD, USA
2012, 2015	Pfizer President's Presenter Award, Society of Reproductive Investigation, CA
2011	Michael Smith Foundation for Health Research Award, Perinatal Research Society, Roanoke, WV
2011-2014	Canada Institutes of Health Research (CIHR) Fellowship
2009	GlaxoSmithKline Prize for Scientific Research Winner, Austin LifeSciences Research Week, Austin Hospital, VIC, Australia
2008	Graduate Certificate in Commercialization for Research Students Scholarship, University of Melbourne/Melbourne Business School
2007	Melbourne Research Scholarship, University of Melbourne (declined in acceptance of the NHMRC scholarship)
2007-2009	Dora Lush Biomedical Postgraduate Training Scholarship, National Health and Medical Research Council of Australia (NHMRC)
2007-2009	Special Postgraduate Scholarship Top-Up, Department of Obstetrics & Gynecology, University of Melbourne
2006	University Medalist, University of Tasmania
2006	Dean's Citation, Faculty of Health Science, University of Tasmania
2006	Ph.D. Scholarship in Clinical Proteomics, Department of Obstetrics & Gynecology, University of Melbourne
2005	Tasmania Honors Scholarship, University of Tasmania
2004	Golden Key Organization Undergraduate Scholarship Award, University of Tasmania
2003, 2004	Dean's Roll of Excellence, Faculty of Health Science, University of Tasmania
2002-2005	Tasmania International Scholarship, University of Tasmania

C. Contributions to Science

1. **Effect of transgender testosterone therapy in the breast.** I established the transmasculine research cohort at BIDMC to understand how testosterone therapy modulates the breast. We published the largest histopathological review of transmasculine breast tissues, and were the first to characterize Toker cell hyperplasia in this population. We are also studying the effects of testosterone on breast tissue composition and mammographic density, which will have implications for understanding transmasculine breast cancer risk
Role: Project supervision, study design, data collection, analysis, and manuscript writing.

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a) Baker GM, Bret-Mounet VC, Xu J, Fein-Zachary VJ, Tobias AM, Bartlett RA, Clohessy JG, Vlachos IS, Massicott ES, Wulf GM, Schnitt SJ and **Heng YJ**. Toker cell hyperplasia in the nipple-areolar complex of transmasculine individuals. (2023) Mod Pathol, 36, 100121. PMCID: PMC10293043
b) **Heng YJ**, Zhang KJ, Valero MG, Baker GM, Fein-Zachary VJ, Irwig MS and Wulf GM. Invasive ductal carcinoma of the breast in a transgender man: a case report. (2023). *Case Rep Oncol*, In Press.
c) Baker GM, Guzman-Arocho YD, Bret-Mounet VC, Torous VF, Schnitt SJ, Tobias AM, Bartlett RA, Fein-Zachary VJ, Collins LC, Wulf GM and **Heng YJ**. Testosterone therapy and breast histopathological features in transgender individuals. (2021) *Mod Pathol*, 34, 85-94. PMCID: PMC7854981
d) Baker GM, Pyle ME, Tobias AM, Bartlett, RA, Phillips J, Fein-Zachary VJ, Wulf GM and **Heng YJ**. Establishing a cohort of transgender men and gender non-conforming individuals to understand the molecular impact of testosterone on breast physiology. (2019) *Transgender Health.* 4, 326-330. PMCID: PMC6863056

2. **Breast cancer investigations in the Nurses' Health Studies.** The Nurses' Health Studies is an ongoing prospective study of ~250,000 US registered nurses who provide biological samples and information about breast cancer risk and outcome. I was the leader who coordinated pathological annotations, tissue coring, and gene expression profiling (n>1000). I personally conducted data pre-processing and created a R package of this dataset. I also studied how lifestyle factors such as high body mass index influences breast cancer etiology and outcome. *Role:* Data collection, analyses, and manuscript writing.
   a) **Heng YJ,** Wang J, Ahearn TU, Brown SB, Zhang X, Ambrosone CB, de Andrade VP, Brufsky AM, Couch FJ, King TA, Modugno F, Vachon CM, DuPre NC, Garcia-Closas M, Troester MA, Hunter DJ, Eliassen AH, Tamimi RM, Hankinson SE and Beck AH. Molecular mechanisms linking high body mass index to breast cancer etiology in post-menopausal breast tumor and tumor-adjacent tissues. (2019). *Breast Cancer Res Treat*, 173, 667-677.
   b) Kensler KH, Sankar VN, Wang J, Zhang X, Rubadue CA, Baker GM, Parker JS, Hoadley KA, Stancu AL, Pyle ME, Collins LC, Hunter DJ, Eliassen AH, Hankinson SE, Tamimi RM and **Heng YJ**. PAM50 molecular intrinsic subtypes in the Nurses' Health Study cohorts. (2019). *Cancer Epidemiol Biomarkers Prev*, 28, 798-806. PMCID: PMC6449178
   c) Kensler KH, Poole EM, **Heng YJ**, Collins LC, Glass B, Beck AH, Hazra A, Rosner BA, Eliassen AH, Hankinson SE, Winer EP, Brown M and Tamimi RM. Androgen receptor expression and breast cancer survival: results from the Nurses' Health Study. (2019). *J Natl Cancer Inst*, 111, 700-708. PMCID: PMC6624168

3. **The Cancer Genome Network (TCGA): breast cancer histopathological annotations and epidemiological data.** I established a histopathological database for 850 TCGA invasive breast cancer cases and conducted the largest integrative morphology-genomic analyses in breast cancer. This work will facilitate future refinement of breast cancer classification, predict response to therapy, and increase our biological understanding of breast cancer morphology. My histopathological data were leveraged for international computer science challenges. I was also involved in the collection of breast cancer risk factor data for a subset of TCGA cases and conducted the first study linking epidemiological exposures to genomic signatures. *Role:* Data collection, analysis, and manuscript writing.
   a) **Heng YJ**, Lester SC, Tse GMK, Factor RE, Allison KH, Collins LC, Chen Y-Y, Jensen KC, Johnson NB, Jeong JC, Punjabi R, Shin SJ, Singh K, Krings G, Eberhard DA, Tan PH, Korski K, Waldman FM, Gutman DA, Sanders M, Reis-Filho JS, Flanagan SR, Gendoo DMA, Chen GM, Haibe-Kains B, Ciriello G, Hoadley KA, Perou CM, Beck AH. The molecular basis of breast cancer pathological phenotypes. (2017). *J Pathol*, 241, 375-391. PMCID: PMC5499709
   b) **Heng YJ,** Hankinson SE, Wang J, Alexandrov LB, Ambrosone CB, de Andrade VP, Brufsky AM, Couch FJ, King TA, Modugno F, Vachon CM, Eliassen AH, Tamimi RM and Kraft P. The association of modifiable breast cancer risk factors and somatic genomic alterations in breast tumors: The Cancer Genome Atlas Network. (2019).*Cancer Epidemiol Biomarkers Prev*, 29, 599-605. PMCID: PMC7060119

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c) Veta M, **Heng YJ**, Stathonikos N, Ehteshami Bejnordi B, Beca F, Wollmann T, Rohr K, Shah MA, Wang D, Rousson M, Hedlund M, Tellez D, Ciompi F, Zerhouni E, Viana M, Kovalev V, Liauchuk V, Ahmady Phoulady H, Qaiser T, Graham S, Rajpoot N, Sjoblom E, Molin J, Paeng K, Hwang S, Park S, Jia Z, Chang EI, Xu Y, Beck AH, van Diest P and Pluim JPW. Predicting breast tumor proliferation from whole-slide images: the TUPAC16 challenge. (2019). *Med Image Anal*, 54, 111-121.

4. **Computational Pathology.** My team has developed three methods. One method computes breast tissue composition. The second method captures breast lobular involution measures. The third method predicts clear cell renal cell carcinoma prognostic grade. *Role:* Project supervision, study design, data collection, analyses, and manuscript writing.
   a) Vellal AD, Sirinukunwattana K, Kensler KH , Baker GM, Stancu AL, Pyle ME, Collins LC, Schnitt SJ, Connolly JL, Veta M, Eliassen AH, Tamimi RM and **Heng YJ**. Deep learning image analysis of benign breast disease to identify subsequent risk of breast cancer. (2021). *JNCI Cancer Spectr*, 5, pkaa119. PMCID: PMC7898083
   b) Wetstein SC, Onken AM, Luffman C, Baker GM, Pyle ME, Kensler KH, Liu Y, Bakker B, Vlutters R, van Leeuwen MB, Collins LC, Schnitt SJ, Pluim JPW, Tamimi RM, **Heng YJ** and Veta M. Deep learning assessment of breast terminal duct lobular unit involution: towards automated prediction of breast cancer risk. (2020). *PLoS One*, 5:e0231653. PMCID: PMC7159218
   c) Kensler KH, Liu EZ, Wetstein SC, Onken AM, Luffman CI, Baker GM, Collins LC, Schnitt SJ, Bret-Mounet VC, Veta M, Pluim JPW, Liu Y, Colditz GA, Eliassen AH, Hankinson SE, Tamimi RM and **YJ Heng**. Automated quantitative measures of terminal duct lobular unit involution and breast cancer risk. (2020) *Cancer Epidemiol Biomarkers Prev.* 29:2358–68. PMCID: PMC7642012
   d) Tian K, Rubadue CA, Lin DI, Veta M, Pyle ME, Irshad H and **Heng YJ**. Automated clear cell renal carcinoma grade classification with prognostic significance. (2019). *PLoS One*, 14, e0222641. PMCID: PMC6776313

5. **Understanding vanilloid treatment in overactive bladder in rats.** I showed that capsaicin-like vanilloids treatments ablate TRPV1 receptors and deplete SP in both the rat bladder and spinal cord. My finding partly explains why capsaicin-like vanilloids treatments can decrease spinal reflex activity, irritation, and mechanical stimulation in the bladder, thus reducing urination frequency. *Role:* Animal and laboratory work, data analyses, and manuscript writing.
   a) **Heng YJ**, Saunders CI, Kunde DA and Geraghty DP. TRPV1, NK1 receptor and substance P immunoreactivity and gene expression in the rat lumbosacral spinal cord and urinary bladder after systemic, low dose vanilloid administration. (2011) *Regul Pept*, 167(2-3), 250-258.

Complete List of Published Work in MyBibliography:
https://pubmed.ncbi.nlm.nih.gov/?term=Heng+YJ&sort=pubdate

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OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

NAME: Gerburg M. Wulf

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Associate Professor, Harvard Medical School; Attending Physician Beth Israel Deaconess Medical Center

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Westfaelische Wilhelmsuniversitaet, Muenster, Germany, Medical School	MD	12/1987	Medicine, Clinical Chemistry
Max Planck Institute for Biochemistry, Munich, Germany		01/1989	Cell Biology
Westfaelische Wilhelmsuniversitaet, Muenster, Germany, Medical School	PhD	03/1989	Medical Sciences
Ruprecht-Karls University, Heidelberg, Germany			
Beth Israel Hospital, Harvard Medical School, Boston MA	Resident	09/1991	Medicine
St. Elisabeth Med. Ctr. Tufts Medical School, Boston MA	Postdoctoral Fellow	06/1994	Hematology
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA	Resident	06/1996	Medicine
Beth Israel Deaconess Medical Center, Boston, Harvard Medical School	Clinical Fellow	06/1999	Cllinical Hem/Onc
	Postdoctoral Fellow	06/1999	Cancer Cell Biology

A. Personal Statement

I am a PI on this application. I am a physician-scientist in Medical Oncology. I have >15 years of preclinical breast cancer mouse model experience. My research focuses on preclinical mouse models of breast cancer in preparation for early-phase in-human trials. An example is the preclinical exploration of the combination of a PI3K- and a PARP-inhibitor to treat *BRCA1*-related breast cancer, which was translated into early phase clinical investigation (NCT01623349). A similar approach was taken prior to that with the combination of a mTOR and HER2-inhibitor (NCT00458237). I am an active laboratory investigator within the Dana Farber/Harvard Cancer Center (DF/HCC). I am an active clinical and laboratory investigator within the NCI Experimental Therapeutics Clinical Trials Network (ETCTN) program, and the translational team leader for a suite of trials with the PI3K-inhibitor Copanlisib.

I have a faculty and clinical appointment at the Cambridge Health Alliance (CHA) where the majority of patients have a minority background. I am currently working on a clinical research program to enhance the participation of minority patients in clinical trials at Dana Farber/Harvard Cancer Center. I foresee an increase in LGBTQIA+ patients receiving oncology treatment in the future and breast cancer research in this unique population are urgently needed. At BIDMC, I manage the breast cancer care for transgender individuals. I have the necessary clinical and scientific expertise to co-lead this R01 application.

Ongoing and recently completed projects that I would like to highlight include:

R01CA205153 (PI Wulf since 10-2020, Gray NS) 01/01/2017 – 12/31/2021
NIH
Development of selective Pin1 inhibitors to target a common oncogenic mechanism
Goal oof this project is to develop novel Pin1 inhibitors and to determine their mechanisms of action

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R01CA226776-01 (PI Wulf) 03/01/2018 – 02/28/2023
NIH
Novel Uses for PI3K-inhibitors for the Treatment of Advanced PIK3CA-mutant Breast Cancer
Goal of this project is to develop novel treatment combinations that include PI3K-inhibitors

2P50CA168504-06 (PI Winer; Project 4 PI: Wulf) 07/05/2019 – 05/31/2024
Dana-Farber/Harvard Cancer Center (DF/HCC) SPORE in Breast Cancer
The program will fund P50 SPORE grants to support state-of-the-art investigator-initiated translational research that will contribute to improved prevention, early detection, diagnosis, and treatment of an organ-specific cancer or a related group of cancers.

[redacted] (PI Wulf) 10/01/2022 - 09/30/2023
PRIVATE SUPPORT
Novel Treatment Combinations to Treat Triple-Negative Breast Cancer
The goals of this project include correlative studies to determine parameters of resistance and responsiveness and to examine the efficacy of an optimized PI3K-inhibitor containing regimen in breast cancer.

1R21CA267088-01 (PIs Wulf and Heng) 12/01/2021-11/30/2023
NIH/NCI
Gender-affirming estrogen therapy and breast cancer treatment outcome
This proposal will determine the extent to which transgender estrogen therapy affects breast cancer treatment outcomes.

Citations:

1. Juvekar A, Hu H, Yadegarynia S, Lyssiotis CA, Ullas S, Lien EC, Bellinger G, Son J, Hok RC, Seth P, Daly MB, Kim B, Scully R, Asara JM, Cantley LC, **Wulf GM**. Phosphoinositide 3-kinase inhibitors induce DNA damage through nucleoside depletion. **Proc Natl Acad Sci U S A**. 2016 Jul 8. pii: 201522223. doi: 10.1073/pnas.1522223113 PMC4968752
2. Hu H, Juvekar A, Lyssiotis CA, Lien EC, Albeck JG, Oh D, Varma G, Hung YP, Ullas S, Lauring J, Seth P, Lundquist MR, Tolan DR, Grant AK, Needleman DJ, Asara JM, Cantley LC, **Wulf GM**. Phosphoinositide 3-Kinase Regulates Glycolysis through Mobilization of Aldolase from the Actin Cytoskeleton. **Cell**. 2016 Jan 28;164(3):433-46. doi: 10.1016/j.cell.2015.12.042. PMC4898774
3. Juvekar A, Burga LN, Hu H, Lunsford EP, Ibrahim YH, Balmañà J, Rajendran A, Papa A, Spencer K, Lyssiotis CA, Nardella C, Pandolfi PP, Baselga J, Scully R, Asara JM, Cantley LC, **Wulf GM.** Combining a PI3K Inhibitor with a PARP Inhibitor Provides an Effective Therapy for BRCA1-Related Breast Cancer. **Cancer Discov**. 2012 Nov;2(11):1048-63. doi: 10.1158/2159-8290.CD-11-0336. PMCID: PMC3733368
4. Eismann J, Heng YJ, Fleischmann-Rose K, Tobias AM, Phillips J, **Wulf GM***, Kansal KJ. Interdisciplinary Management of Transgender Individuals at Risk for Breast Cancer: Case Reports and Review of the Literature. **Clin Breast Cancer.** 2019 Feb;19(1):e12-e19. *Corresponding author

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-Current	NIH Study Section Standing Member of Basic Mechanisms in Cancer Health Disparities (BMCD)
2022	NIH Study Section ZRG1 OBT-Y (55) For Basic Research in Cancer Health Disparities, Special Emphasis panel
2022	NCI Clinical and Translational Cancer Research (PAR20-292 for R21s and PAR20-052 for R03s), Special Emphasis Panel
2021	NIH Study Section ZRG1 F09C-Z (20) Fellowship: Cancer Immunology and Immunotherapy, Special Emphasis panel
2021-Current	Executive Committee, Cancer Research Institute, BIDMC
2020	NIH Study Section ZRG1 OBT-B 55 Cancer Health Disparities, Special Emphasis Panel
2021-Current	Executive Committee, Cancer Research Institute, BIDMC
2020-Current	Scientific Director, Phase I Program, BIDMC
2020-Current	Scientific Review Committee (SRC), DF/HCC
2017-Current	Early Therapeutics Clinical Trials Network (ETCTN), member

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2014-Current Associate Professor in Medicine, Harvard Medical School, Boston MA
2014-2015 DOD, Breast Cancer Research Program, grant review
2014 UK Prostate Cancer Programme, grant review
2013 Swiss National Science Foundation, grant review
2013 NIH Study Section ZCA1 SRLB-1 O1 S, NCI Omnibus Biology
2012 AVON consortium, infectious agents and breast cancer
2012 American Institute for Cancer Research (AICR), grant reviewer
2009 NIH Study Section ZRG1 OTC-K 58 Challenge Grants, NIH, ad hoc
2008 Institutional Animal Care Committee (IACUC), Beth Israel Deaconess Medical Center
2006-2014 Assistant Professor in Medicine, Harvard Medical School, Boston MA
2003-Current Attending Physician, Beth Israel Deaconess Medical Center, Boston, Division for Hematology/Oncology
2002-2003 Committee for Excellence in Research in Womens' Health, Harvard Medical School
2002 ABIM, re-certification in Medical Oncology
2001-2010 Attending Physician, Youville and Cambridge Hospitals, Cambridge
1999-2006 Instructor in Medicine, Harvard Medical School, Boston MA
1999 ABIM, subspecialty board certifications in Hematology and Medical Oncology
1998-2010 Attending Physician, Mt. Auburn Hospital, Cambridge and Hallmark Health System
1998 American Board of Internal Medicine (ABIM), board certification
1996 Licensing Board of Registration in Medicine, Massachusetts, MA 180560

Honors and Awards

2016 Chief Academic Officer (CAO) Award, Beth Israel Deaconess Medical Center
2013 AVON Progress for Patients Award
2010-2012 Stand-up-to-Cancer SU2C PI3K-inhibitors to treat women's cancers, dream team, member
2010 AVON Progress for Patients Award
2004 DFHCC Breast Cancer SPORE Career Development Award
2002 Physician Scientist Award, National Institutes of Health (NIH)
1999 Aid for Cancer Research Foundation, Newton MA
1999 U.S. Department of Defense Fellowship (Breast Cancer Research Program)
1991-1993 Mildred Scheel Foundation (Germany) for Cancer Research Fellowship (2 years salary support)
1989 Prize of the Westfaelische Wilhelms University (Germany) for Excellent Doctoral Thesis

C. Contributions to Science

I. Rational Combinations to treat Breast Cancer. Targeted treatment options for endocrine-resistant BC are currently limited but urgently needed because chemotherapeutic regimen don't achieve sustained remissions. Dr. Wulf spearheaded an early combination study in collaboration with PK Morrow at MD Anderson, NCT00458237, combination of Trastuzumab and Everolimus to treat metastatic Her2-positive breast cancer. Her laboratory work laid the foundation for this study. The currently ongoing study NCT01623349 Phase I Study of the Oral PI3kinase Inhibitor BKM120 or BYL719 and the Oral PARP Inhibitor Olaparib in Patients With Recurrent Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer is a second example for a study where Dr. Wulf's laboratory findings prepared the rationale for this combination.

Clinical Trials:

1. Konstantinopoulos PA, Barry WT, Birrer M, Westin SN, Cadoo KA, Shapiro GI, Mayer EL, O'Cearbhaill RE, Coleman RL, Kochupurakkal B, Whalen C, Curtis J, Farooq S, Luo W, Eismann J, Buss MK, Aghajanian C, Mills GB, Palakurthi S, Kirschmeier P, Liu J, Cantley LC, Kaufmann SH, Swisher EM, D'Andrea AD, Winer E, **Wulf GM***, Matulonis UA*. Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. **Lancet Oncol.** 2019 Apr;20(4):570-580. doi: 10.1016/S1470-2045(18)30905-7. PMC7025391 *Co-senior authors
2. Matulonis UA***, Wulf GM***, Barry WT, Birrer M, Westin SN, Farooq S, Bell-McGuinn KM, Obermayer E, Whalen C, Spagnoletti T, Luo W, Liu H, Hok RC, Aghajanian C, Solit DB, Mills GB, Taylor BS, Won H, Berger MF, Palakurthi S, Liu J, Cantley LC, Winer E. Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. **Ann Oncol.** 2017 Mar 1;28(3):512-518. doi: 10.1093/annonc/mdw672 PMC5834157 *Co-first authors.
3. Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, Wahner-Hendrickson AE, Forero A, Anders C, **Wulf GM**, Dillon P, Lynce F, Zarwan C, Erban JK, Zhou Y, Buerstatte N, Graham JR, Arora S, Dezube BJ, Telli ML. Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic

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Triple-Negative Breast Cancer. **JAMA Oncol**. 2019 Jun 13;5(8):1132-1140. doi: 10.1001/jamaoncol.2019.1029 PMC6567845

4. Morrow PK*, **Wulf GM***, Moore J, Krop I, Winer E, Kindelberger D, Coviello J, Hortobagyi G, Esteva FJ. Phase I/II Study of Trastuzumab in Combination with Everolimus (RAD001) in Patients with HER2-Overexpressing Metastatic Breast Cancer That Progressed on Trastuzumab-Based Therapy. **Journal of Clinical Oncology**, 2011 Aug 10;29(23):3126-32; PMCID: PMC3157979 *equally contributing authors.

II. Signal Transduction in Breast Cancer. Dr. Wulf's group has for over a decade worked on aberrant phosphorylation patterns of cellular signaling molecules that govern the growth of cancer cells. Most recently, her group has discovered that PI3K-signaling regulates cellular metabolism, and specifically glycolysis, in mid-glycolysis through the reversible association of aldolase A from the cytoskeleton. The activation of glycolysis thorugh redistribution of aldolase from the cytoskeleton into the cytoplasm is a novel mechanism of signaling that offers new opportunities for intervention in cancer.

1. Juvekar A, Hu H, Yadegarynia S, Lyssiotis CA, Ullas S, Lien EC, Bellinger G, Son J, Hok RC, Seth P, Daly MB, Kim B, Scully R, Asara JM, Cantley LC, **Wulf GM**. Phosphoinositide 3-kinase inhibitors induce DNA damage through nucleoside depletion. **Proc Natl Acad Sci U S A**. 2016 Jul 26;113(30):E4338-47. doi: 10.1073/pnas.1522223113 PMC4968752
2. Juvekar A, Burga LN, Hu H, Lunsford EP, Ibrahim YH, Balmañà J, Rajendran A, Papa A, Spencer K, Lyssiotis CA, Nardella C, Pandolfi PP, Baselga J, Scully R, Asara JM, Cantley LC, **Wulf GM.** Combining a PI3K Inhibitor with a PARP Inhibitor Provides an Effective Therapy for BRCA1-Related Breast Cancer. **Cancer Discov**. 2012 Nov;2(11):1048-63. doi: 10.1158/2159-8290.CD-11-0336. PMCID: PMC3733368
3. Hu H, Juvekar A, Lyssiotis CA, Lien EC, Albeck JG, Oh D, Varma G, Hung YP, Ullas S, Lauring J, Seth P, Lundquist MR, Tolan DR, Grant AK, Needleman DJ, Asara JM, Cantley LC, **Wulf GM.** Phosphoinositide 3-Kinase Regulates Glycolysis through Mobilization of Aldolase from the Actin cytoskeleton, **Cell**, Jan 28;164(3):433-46. PMC4898774
4. Pantelidou C, Sonzogni O, De Oliveria Taveira M, Mehta AK, Kothari A, Wang D, Visal T, Li MK, Pinto J, Castrillon JA, Cheney EM, Bouwman P, Jonkers J, Rottenberg S, Guerriero JL, **Wulf GM***, Shapiro GI*. PARP Inhibitor Efficacy Depends on CD8+ T-cell Recruitment via Intratumoral STING Pathway Activation in BRCA-Deficient Models of Triple-Negative Breast Cancer. **Cancer Discov**. 2019 Jun;9(6):722-737. doi: 10.1158/2159-8290.CD-18-1218. PMC6548644 *Co-senior authors

III. Regulation of Cancer Growth by phospho-specific prolylisomerization. Dr. Wulf introduced the concept of aberrant phospho-specific prolyl isomerization, a novel layer of cell signaling control, as a major driver of cancer cell growth. This has spurred the development of inhibitors that target the prolyl isomerase Pin1 and its targets, which are currently in pre-clinical development.

1. **Wulf G**, Garg P, Yih-Cherng Liou, Iglehart D. and Lu KP. Modeling breast cancer in vivo and ex vivo reveals an essential role of the prolyl isomerase Pin1 for tumorigenesis. **EMBO J**, Aug 18;23(16):3397-407. PMCID: PMC514501
2. **Wulf G**, Ryo A, Wulf GG, Lee SW, Niu T, Petkova V and Lu KP. Pin1 is overexpressed in breast cancer and cooperates with Ras signaling in increasing c-Jun transcriptional activity towards cyclin D1. **EMBO J.** 2001 20: 3459-3472; PMCID: PMC125530
3. Lam PB, Burga LN, Wu BP, Hofstatter EW, Lu KP, **Wulf GM**. Prolyl isomerase Pin1 is highly expressed in Her2-positive breast cancer and regulates erbB2 protein stability. **Mol Cancer**. 2008 Dec 15;7:91. doi: 10.1186/1476-4598-7-91. PMCID: PMC2632646

IV. Biomarkers for Triple-Negative Breast Cancer. A consistent problem that we face in our clinical trials is the absence of a reliable, and easily obtainable, biomarkers for response. I am tackling that issue on two fronts: Together with my colleague Aaron Grant, I am spearheading an effort to examine the predictive power of changes in tumor bioenergetics for responses to tumor treatments. A second effort is the prospective, systematic evaluation of circulating tumor cell DNA in the plasma of patients; the effort is being conducted in collaboration with the BROAD institute in Cambridge MA. My goal is to use the markers that are being developed in this context to accelerate and refine the next set of clinical trials for patients with metastatic cancer.

1. de Oliveira Taveira M, Nabavi S, Wang Y, Tonellato P, Esteva FJ, Cantley LC, **Wulf GM**. Genomic characteristics of trastuzumab-resistant Her2-positive metastatic breast cancer. **J Cancer Res Clin Oncol**. 2017 Feb 28. doi: 10.1007/s00432-017-2358-x. PMID: 28247034; PMCID: PMC5486569
2. Gómez-Miragaya J, Díaz-Navarro A, Tonda R, Beltran S, Palomero L, Palafox M, Dobrolecki LE, Huang C, Vasaikar S, Zhang B, **Wulf GM**, Collado-Solé A, Trinidad EM, Muñoz P, Paré L, Prat A, Bruna A, Caldas C, Arribas J, Soler-Monsó MT, Petit A, Balmaña J, Cruz C, Serra V, Pujana MA, Lewis MT, Puente XS, González-Suárez E.

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Chromosome 12p amplification in triple-negative/BRCA1-mutated breast cancer associates with emergence of docetaxel resistance and carboplatin sensitivity. **Cancer Res**. 2019 2019 Aug 15;79(16):4258-4270. doi: 10.1158/0008-5472.CAN-18-3835.

3. Liu H, Murphy CJ, Karreth FA, Emdal KB, White FM, Elemento O, Toker A, **Wulf GM**, Cantley LC. Identifying and Targeting Sporadic Oncogenic Genetic Aberrations in Mouse Models of Triple-Negative Breast Cancer. **Cancer Discov**. 2018 Mar;8(3):354-369. PMID: 29203461 PMCID: PMC5907916
4. Hu H, Luo ML, Desmedt C, Nabavi N, Yadegarynia S, Hong A, Konstantinopoulos PA, Gabrielson E, Hines-Boykin R, Pihan G, Yuan X, Sotirious C, Dittmer DP, Fingeroth JD, **Wulf GM**. Epstein-Barr Virus Infection of Mammary Epithelial Cells Promotes Malignant Transformation. Epstein-Barr Virus Infection of Mammary Epithelial Cells Promotes Malignant Transformation. **EBioMedicine** doi: 10.1016/j.ebiom.2016.05.025. PMCID: PMC4972522

V. Research and Cancer Care for Minority Populations. Dr. Wulf maintains a faculty and clinical appointment at the Cambridge Health Alliance (CHA) where the majority of patients have a minority background. She is currently working on a clinical research program to enhance the participation of minority patients in clinical trials at DFHCC. She is also working with Dr. Jan Heng, a translational breast cancer scientist, to identify cancer risk factors for transgender people who receive longterm hormone treatment.

1. Eismann J, Heng YJ, Fleischmann-Rose K, Tobias AM, Phillips J, **Wulf GM***, Kansal KJ. Interdisciplinary Management of Transgender Individuals at Risk for Breast Cancer: Case Reports and Review of the Literature. **Clin Breast Cancer.** 2019 Feb;19(1):e12-e19. doi: 10.1016/j.clbc.2018.11.007. PMCID: PMC7083129 * Corresponding author
2. Baker GM, Guzman-Arocho YD, Bret-Mounet VC, Torous VF, Schnitt SJ, Tobias AM, Bartlett RA, Fein-Zachary VJ, Collins LC, **Wulf GM**, Heng YJ. Testosterone therapy and breast histopathological features in transgender individuals. **Mod Pathol**. 2021 Jan;34(1):85-94. doi: 10.1038/s41379-020-00675-9. PMID: 32939016.
3. Baker GM, Bret-Mounet VC, Xu J, Fein-Zachary VJ, Tobias AM, Bartlett RA, Clohessy JG, Vlachos IS, Massicott ES, **Wulf GM**, Schnitt SJ and Heng YJ. Toker cell hyperplasia in the nipple-areolar complex of transmasculine individuals. (2023) **Mod Pathol**, 36, 100121.
4. Heng YJ, Zhang KJ, Valero MG, Baker GM, Fein-Zachary VJ, Irwig MS and **Wulf GM**. Invasive ductal carcinoma of the breast in a transgender man: a case report. (2023). **Case Rep Oncol**. In Press.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/gerburg.wulf.1/bibliography/50134819/public/?sort=date&direction=ascending

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Slack, Frank John

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Shields Warren Mallinckrodt Professor of Medical Research, Departments of Pathology and Medicine, Beth Israel Deaconess Medical Center/Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Cape Town	B. Sc (Hons)	12/1987	Microbiology/Biochem
Tufts University School of Medicine	Ph.D.	09/1993	Molecular Genetics
Stanford University School of Medicine	Postdoc	10/93-8/94	Molecular Biology
Harvard Medical School/MGH	Postdoc	9/94-12/99	Genetics

A. Personal Statement: My lab has pioneered various aspects of the non-coding RNA (ncRNA) and microRNA (miRNA) field and continues to make important contributions to this aspect of post-transcriptional control of gene regulation in stem cell development, cancer and aging. We have been at the forefront of the emergence of miRNAs as diagnostics and therapies. We intend to continue at the vanguard of this emerging field, focusing on translating discoveries in ncRNAs into a better understanding of disease and better medicines. We hope to discover how ncRNAs are expressed, what they regulate, how they function, how extensive their reach is, what roles they play in cancer and aging, and harnessing this new mechanism to combat diseases of old age, such as cancer and Alzheimer's Disease. We performed the first comprehensive resequencing of the non-coding genome in cancer. For this project we will apply our expertise in whole genome and non-coding RNAs to cancer medicine.

Ongoing and completed projects I would like to highlight include:

Ongoing Research Support

NIH 1R01AG082093 – 01 (PI Slack) 05/2023-03/2028
Non-coding RNAs in resilience to Alzheimer's Disease
The goal is to define key roles that miRNAs and long noncoding RNAs play in prevention of cognitive loss in subjects who have Alzheimer's related pathologies but no or negligible loss of cognition.

NIH R35 CA232105 (PI Slack) 08/2019-07/2026
Precision microRNA medicine in cancer
The goal is to translate microRNA discoveries into the clinic.

NIH **R01 CA 241194-01** (Slack (PI); Bahal co-PI) 04/01/2020-03/31/2025
Targeting microRNAs with novel PNA chemistry and direct pHLIP conjugation.
The aim is to identify and test specific improvements/modification for targeting antimiRs to the tumor microenvironment in DLBCL.

NIH R01 CA 235740-1A1 (Doyle PI, Slack co-PI) 07/01/2019-06/30/2024
Microengineered Technologies for Quantitative, Multiplexed and Spatially Resolved Measurement of miRNA in Tissue Sections.
The goal is to develop a sensitive method to detect and quantify microRNAs in situ.

[redacted] **(**PI Slack) 03/01/2015 – 6/30/2025
MicroRNA-based Tools for Understanding and Combating Drug Resistance in Cancer

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The major goals of this project are to determine miRNA profiles as part of the multi-dimensional landscaping of different tumor cell types and treatment regimens and utilize miRNA oligo technology to target tumor vulnerabilities and epigenetic regulators.

Completed Research Support

NIH R01 AG058816-01 (PI Slack) 04/01/2018-03/31/2023
Juvenile microRNAs promoting healthier adult aging
To identify novel microRNAs that could promote lifespan and healthy aging.

PRIVATE SUPPORT (PI: Slack) 03/01/21-02/28/2022
Spatial Technologies Unit in the Precision Medicine Initiative
The aim is to creation of the first Spatial Technology Unit (STU) in Massachusetts, providing comprehensive derisked access to a suite of cutting-edge spatial transcriptomic and proteomic modalities.

NIH 1 R01 CA212649-01 (PI Avigan; Co-I Slack) 12/9/2016-11/30/2021
Personalized vaccine for patients with AML
The goal is to study the interactions between microRNAs and tumor vaccines.

PRIVATE SUPPORT (co-PIs Slack/Avigan) 11/1/2018-10/30/2021
Biomarkers for a Phase I/II trial with anti-miR-155 in Diffuse Large B-cell Lymphoma
To identify novel microRNA and mRNA biomarkers for the anti-miR-155 clinical trial.

U54 CA 156732-07 (Developmental project co-PIs Slack/Celli) NIH (Dana Farber) 09/15/2019-09/14/2021
Development of light-activated anti-microRNA therapies for pancreatic ductal adenocarcinoma.
The goal of this project is to perform mechanistic studies that will identify promising candidate microRNA targets for PDT combination therapies.

- (PI Avigan; Co-I Slack) PRIVATE SUPPORT 3/1/2018-2/28/2020
Combined Chimeric Antigen Receptor Therapy (CAR-T) and Active Immunization for Multiple Myeloma
The goal of the Slack portion is to identify microRNAs affecting response to the therapy.

NIH 5 R01 AG033921-11 Slack (PI) 02/1/2014-01/31/2020
MicroRNA mediators of stress, dietary restriction and aging
To identify novel microRNAs linking stress response to aging.

NIH P50 CA196530-03S1 (PI Slack) 8/1/2017-7/31/2019
MicroRNA-based interventions to prevent progression from lung preneoplasia to adenocarcinoma
The goals were to identify miRNAs that control NSCLC progression from hyperplasia to adenoma to adenocarcinoma.

Citations:

1. Kasinski, A. and **F. J. Slack**. (2011) MicroRNAs en route to the clinic: progress in validating and targeting microRNAs for cancer therapy. *Nature Reviews Cancer*. 2011 Nov 24;11(12):849-64. doi: 10.1038/nrc3166. PMCID: PMC4314215
2. Rajesha Rupaimoole and **Frank J Slack** (2016) MicroRNA therapeutics: towards a new era for therapeutic management of cancer and other diseases. *Nature Reviews Drug Discovery*, 2017 Mar;16(3):203-222. doi: 10.1038/nrd.2016.246. Epub 2017 Feb 17. Review. PMID: 28209991
3. Anastasiadou, E., L. Jacob and **F.J Slack.** (2018) Noncoding RNA networks in cancer. *Nat Rev Cancer*. Jan;18(1):5-18. doi: 10.1038/nrc.2017.99. Epub 2017 Nov 24. Review. PMID:29170536
4. **Slack FJ** and Chinnaiyan AM. (2019) The Role of Non-coding RNAs in Oncology *Cell*. 2019 Nov 14;179(5):1033-1055. doi: 10.1016/j.cell.2019.10.017.

B. Positions, Scientific Appointments, and Honors
Positions and Employment
Present positions:

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2020 - : Associate Deputy Director for Basic Science, Dana Farber/Harvard Cancer Center.
2020 - : Director, Cancer Research Institute, Beth Israel Deaconess Medical Center.
2017 - : Co-Director, Precision RNA Medicine Core at BIDMC.
2016 - : Director, Harvard Medical School Initiative for RNA Medicine.
2014 - : Full member, Dana-Farber/Harvard Cancer Center (DF/HCC).
2014 - : Full Member, Harvard Stem Cell Institute.
2014 - : Director, Institute for RNA Medicine, Beth Israel Deaconess Medical Center.
2014 - : Shields Warren Mallinckrodt Professor of Medical Research, BIDMC/Harvard Medical School.

Faculty positions:
2009-2014: Professor, Department of Molecular, Cellular and Developmental Biology, Yale University, 2007-2009: Associate Professor (with tenure), 2000-2005: Assistant Professor, Department of Molecular, Cellular and Developmental Biology, Yale University.
2010 - 14: Director, Yale Center for RNA Science and Medicine.
2009 - 14: Program Leader, Cancer Genetics and Genomics, Yale Cancer Center.
2007 - 14: Member of the Yale Stem Cell Center.
Postdoctoral: 1994-1999: Postdoctoral research in the laboratory of Dr. Gary Ruvkun. Department of Genetics, Harvard Medical School, and Department of Molecular Biology, Massachusetts General Hospital. Temporal pattern formation by heterochronic genes in *C. elegans*.
Postdoctoral: 1993-1994: Postdoctoral research in the laboratory of Dr. Dale Kaiser, Department of Biochemistry, Stanford University School of Medicine. Signal transduction by C-factor during development of *Myxococcus xanthus*.
Graduate: 1988-1993: Ph.D. Thesis in the laboratory of Dr. Linc Sonenshein, Department of Molecular Biology and Microbiology, Tufts University School of Medicine. "Function and regulation of *dciA,* the *Bacillus subtilis* dipeptide transport operon".
Undergraduate: 1984-1987: B. Sc. (Honors) Thesis in the laboratory of Dr. Frank Robb, Department of Microbiology, University of Cape Town. "Mutagenic analysis of the *Vibrio alginolyticus glnA* gene promoter, and sequencing of these mutations".

Honors and Awards.

2022	Distinguished Alumnus Award, Tufts University School of Medicine
2019	NCI Outstanding Investigator Award
2018	Distinguished Alumnus Lecture, University of Cape Town
2016	MicroRNA Innovator Award, Appasani Research Conferences and Educational Institute
2014	Heath Memorial Award, MD Anderson Cancer Center
2013	ProMeritus Award, Westville Boys High School
2010- 2014	Charter member of the BMCT Study Section
2010	Yale Cancer Center Research Prize
2009	Yale Cancer Center Research Prize
2009	Kavli Fellow of the National Academy of Science
2006	Ellison Foundation Senior Scholar Award
2003	Junior Faculty Fellowship (Yale University)
2001	American Cancer Society Young Investigator Award - Total costs $800,000/4 yrs - Gratefully declined
2001	National Science Foundation - Total costs $375,000/3 yrs - Gratefully declined
1997-1999	NIH NRSA Individual Postdoctoral Fellowship
1995-1996	Fund for Medical Discovery Postdoctoral Fellowship (MGH/Harvard)
1993-1994	Dean's Postdoctoral Fellowship (Stanford University)
1992	Alla Korjagin Fellowship (Tufts University)
1990	Marine Biological Laboratory Scholarship
1988	FRD Masters Fellowship (gratefully declined)
1987	B.Sc. (Hons) With Distinction (1st-in-Class Medal)
1987	CSIR Honours Fellowship
1986	B.Sc. With Distinction, Microbiology (1st-in-Class); Industrial Microbiology (1st-in-Class)

C. Contribution to Science

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1. I have been at the forefront of ncRNA discovery. I was a co-discoverer of the second known microRNA, *let-7*, and the co-discoverers of the first known human microRNA. We showed for the first time that microRNAs indeed base pair *in vivo* with their predicted complimentary sequences in target genes. We provided the first *in vivo* evidence that a single miRNA can regulate multiple targets. This work was pivotal in expanding the phenomenon of gene regulation by microRNAs into humans. We recently showed important contributions for lncRNAs in cancer and development.

1. Reinhart, B.*, **F. J. Slack***, M. Basson, A. Pasquinelli, J. Bettinger, A. Rougvie, R. Horvitz, and G. Ruvkun. (2000) The 21 nucleotide *let-7* RNA regulates *C. elegans* developmental timing. *Nature* **403**:901-905. *Contributed equally PMID: 10706289
2. Pasquinelli AE, Reinhart BJ, **Slack F**, Martindale MQ, Kuroda MI, Maller B, Hayward DC, Ball EE, Degnan B, Müller P, Spring J, Srinivasan A, Fishman M, Finnerty J, Corbo J, Levine M, Leahy P, Davidson E, Ruvkun G. (2000) Conservation across animal phylogeny of the sequence and temporal regulation of the 21 nucleotide *let-7* heterochronic regulatory RNA. *Nature* **408**:86-89. PMID: 11081512
3. Singh N, Ramnarine VR, Song JH, Pandey R, Padi SKR, Nouri M, Olive V, Kobelev M, Okumura K, McCarthy D, Hanna MM, Mukherjee P, Sun B, Lee BR, Parker JB, Chakravarti D, Warfel NA, Zhou M, Bearss JJ, Gibb EA, Alshalalfa M, Karnes RJ, Small EJ, Aggarwal R, Feng F, Wang Y, Buttyan R, Zoubeidi A, Rubin M, Gleave M, **Slack FJ**, Davicioni E, Beltran H, Collins C, Kraft AS. The long noncoding RNA H19 regulates tumor plasticity in neuroendocrine prostate cancer. *Nat Commun.* 2021 Dec 21;12(1):7349. doi: 10.1038/s41467-021-26901-9. PMID: 34934057
4. Haswell JR, Mattioli K, Gerhardinger C, Maass PG, Foster DJ, Peinado P, Wang X, Medina PP, Rinn JL, **Slack FJ.** Genome-wide CRISPR interference screen identifies long non-coding RNA loci required for differentiation and pluripotency. *PLoS One.* 2021 Nov 3;16(11):e0252848. doi: 10.1371/journal.pone.0252848. eCollection 2021. PMID: 34731163

2. I discovered that human *let-7* is a critical determinant of lung cancer and that it regulates the important oncogene, *RAS*. This provided the first mechanism for a microRNAs role in cancer, and helped propel microRNAs in to the spotlight as potential causes and cures for cancer. My group was the first to show *in vivo* efficacy of delivered microRNAs as anti-cancer agents. I also showed that microRNAs can sensitize cancer cells to therapeutics including immune checkpoint inhibitors. This work was pivotal in launching the field of microRNA therapeutics.

1. Johnson, S., H. Grosshans, J. Shingar, M. Byrom, R. Jarvis, A. Cheng, E. Labourier, K. L. Reinert, D. Brown, and **F. J. Slack.** (2005) *RAS* is regulated by the *let-7* microRNA family. *Cell*. 120:635-647. PMID: 15766527
2. Wen Cai Zhang, Julie M. Wells, Kin-Hoe Chow, He Huang, Min Yuan, Tanvi Saxena, Mary Ann Melnick, Katerina Politi, John M. Asara, Daniel B. Costa, Carol J. Bult & **Frank J. Slack** (2019) miR-147b-mediated TCA cycle dysfunction and pseudohypoxia initiate drug tolerance to EGFR inhibitors in lung adenocarcinoma. *Nature Metabolism* **1**, pages 460–474
3. Lee SM, Kaye KM, **Slack FJ.** Cellular microRNA-127-3p suppresses oncogenic herpesvirus-induced transformation and tumorigenesis via down-regulation of SKP2. *Proc Natl Acad Sci U S A.* 2021 Nov 9;118(45):e2105428118. doi: 10.1073/pnas.2105428118.PMID: 34725152
4. Miliotis C, **Slack FJ.**miR-105-5p regulates PD-L1 expression and tumor immunogenicity in gastric cancer. *Cancer Lett.* 2021 Oct 10;518:115-126. doi: 10.1016/j.canlet.2021.05.037. Epub 2021 Jun 23.PMID: 34098061

3. I was the first to discover cancer risk- and outcome-associated alleles in miRNA binding sites in 3'UTRs of cancer genes. My group performed the first resequencing of the 3'UTRome and miRNAome from cancer patients. This work revealed the importance of sequence variation in the non-coding portions of the genome.

1. Lena J. Chin, L.J., S. Nallur, Y. Zhu, S. Leng, E. A. Burki, R. E. Crowell, E. Straka, E. Ratner, S. A. Belinsky, K. K. Kidd, R. Homer, **F. J. Slack*** and J. B. Weidhaas*. (2008) A SNP in a *let-7* microRNA complementary site in the *KRAS* 3′UTR Increases Lung Cancer Risk. *Can. Res*. 68:8535-40. *joint corresponding author PMCID: PMC2672193
2. S.E. Godshalk, T. Paranjape, S. Nallur, W. Speed, A. M. Molinaro, A. Bacchiocchi, K. Hoyt, K. Tworkoski, D. F. Stern, M. Sznol, S. Ariyan, R. Lazova, R. Halaban, K. K. Kidd, J. Weidhaas, **F. J. Slack**. (2010) A Variant in a MicroRNA Complementary Site in the 3'UTR of the *KIT* Oncogene Increases Risk of Acral Melanoma. *Oncogene* 30(13):1542-50. PMCID: PMC3069149

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3. Xiaowei Chen, Trupti Paranjape, Katie Keane, Sunitha Naller, Kenneth Kidd, Hongyu Zhao, Joanne B. Weidhaas and **Frank J. Slack** (2014). Targeted resequencing of the microRNAome and 3'UTRome reveals functional germline DNA variants with altered prevalence in epithelial ovarian cancer. *Oncogene,* 2014 Jun 9. doi: 10.1038/onc.2014.117. [Epub ahead of print]. PMCID: PMC4326598
4. Minlee Kim, Nicole Kogan, and **Frank J. Slack**. (2016) Cis-acting elements in its 3' UTR mediate post-transcriptional regulation of *KRAS*. *Oncotarget,* 2016 Feb 22. doi: 10.18632/oncotarget.7599. [Epub ahead of print].

4. I discovered that cancers become addicted to microRNA oncogenes, setting the stage for targeting microRNAs as cancer therapeutics. My group developed novel nanodelivery methods for targeting oncogenic miRNAs in the tumor microenvironment. This work set the stage for targeting microRNAs as cancer therapeutics in human clinical trials.

1. Medina, PP, M. Nolde, and **F. J. Slack**. (2010) OncomiR addiction in an *in vivo* model of miR-21 induced lymphoma. *Nature*. 467, 86-90 PMID: 20693987
2. Christopher J. Cheng, Raman Bahal, Imran A. Babar, Zachary Pincus, Francisco Barrera, Connie Liu, Alexander Svoronos, Demetrios T. Braddock, Peter M. Glazer, Donald M. Engelman, W. Mark Saltzman, **Frank J. Slack** (2014) MicroRNA silencing for cancer therapy targeted to the tumor microenvironment. *Nature*. 2014 Nov 17. doi: 10.1038/nature13905. [Epub ahead of print]. PMCID: PMC4367962
3. Maud-Emmanuelle Gilles, Liangliang Hao, Ling Huang, Rajesha Rupaimoole, Pedro P. Lopez-Casas, Emilia Pulver, Jong Cheol Jeong, Senthil K Muthuswamy, Manuel Hidalgo, Sangeeta N Bhatia, **Frank J Slack** (2018) Personalized RNA-medicine for pancreatic cancer, *Clinical Cancer Research*, 2018 Jan 12. pii: clincanres.2733.2017. doi: 10.1158/1078-0432.CCR-17-2733. [Epub ahead of print] PMID: 29330203
4. Anastasiadou E, Seto AG, Beatty X, Hermreck M, Gilles ME, Stroopinsky D, Pinter-Brown LC, Pestano L, Marchese C, Avigan D, Trivedi P, Escolar DM, Jackson AL, **Slack FJ.** Cobomarsen, an Oligonucleotide Inhibitor of miR-155, Slows DLBCL Tumor Cell Growth *In Vitro* and *In Vivo*. *Clin Cancer Res*. 2021 Feb 15;27(4):1139-1149. doi: 10.1158/1078-0432.CCR-20-3139. Epub 2020 Nov 18. PMID: 33208342

5. I identified the first instance of a microRNA regulating lifespan and aging and have subsequently discovered many additional gerontomiRs. My group also discovered the first role for microRNAs in regulating Alzheimer's Precursor Protein genes; microRNAs controlling longevity-induced by dietary restriction; and microRNAs as biomarkers of aging. This work revealed the role and potential utility of miRNAs in aging.

1. Boehm, M., and **F. J. Slack.** (2005). A developmental timing microRNA and its target regulate life span in *C. elegans*. *Science.* 310:1954-1957. PMID: 16373574
2. Smith-Vikos, T., A. deLancastre, S. Inukai, Mariel Shlomchik, Brandon Holtrup, and **F. J Slack.** (2014) MicroRNA Mediators of Dietary-Restriction Induced Longevity Functioning through PHA-4/FOXA and SKN-1/Nrf Transcription Factors. *Current Biology.* 2014 Oct 6;24(19):2238-46. doi: 10.1016/j.cub.2014.08.013. Epub 2014 Sep 18. PMCID: PMC4208828
3. Smith-Vikos, T, Z. Liu, C. Parsons, M. Gorospe, L. Ferrucci, T. Gill, and **F.J. Slack** (2016). A Serum MiRNA Profile of Human Longevity: Findings from the Baltimore Longitudinal Study of Aging (Blsa), *Aging (Albany NY),* 8 (2016), 2971-87. PMCID: PMC5191881
4. Mavrikaki M, Lee J, Solomon I, **Slack FJ.** Severe COVID-19 is associated with molecular signatures of aging in the human brain. *Nature Aging* (in press).

Partial List of Published Work in MyBibliography (out of 222) (h-index 91): http://www.ncbi.nlm.nih.gov/sites/myncbi/frank.slack.1/bibliography/40524929/public/?sort=date&direction=descending

Uncovered by a White Coat Waste investigation

BIOGRAPHICAL SKETCH

NAME: Gabrielle M. Baker

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor of Pathology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Eastman School of Music, Rochester, NY	BM	05/2000	Flute
University of Illinois, College of Medicine, Chicago, IL	MD	06/2008	Medicine
Massachusetts General Hospital, Boston, MA	Resident	06/2012	Anatomic and Clinical Pathology
Beth Israel Deaconess Medical Center, Boston, MA	Fellow	06/2013	Breast Pathology

A. Personal Statement

My role in this proposal is that of a co-Investigator. I am a breast pathologist at Beth Israel Deaconess Medical Center (BIDMC) and Instructor of Pathology at Harvard Medical School in Boston, MA. I trained in both anatomic and clinical pathology at Massachusetts General Hospital and received my subspecialty fellowship training in breast pathology at BIDMC. I served as a breast pathologist at the University of Chicago (2013 to 2016) before returning to BIDMC and HMS in 2016.

I have an ongoing research interest in the pursuit of novel biomarkers that have the potential to meaningfully impact patient care, as well as to further our understanding of the etiology and development of breast cancer and benign breast disease. During my training and practice as a breast pathologist, I have acquired the expertise and necessary qualifications to evaluate the full spectrum of histopathological features in breast pathology.

I have been collaborating with Drs. Jan Heng and Gerburg Wulf (PIs) on breast cancer research projects for the past 8 years. I am the lead pathologist and first author of our breast histopathological publications in transmasculine individuals. I am excited to continue to support and work with Drs. Heng and Wulf on this application by contributing my breast histopathological expertise.

Recently completed projects that I would like to highlight include:

09/01/2014-08/31/2019 5R01CA050385-030 (PI: Willett)
Risk Factors for Breast Cancer Among Younger Nurses
The goal of this grant is to examine plasma metabolites in relation to breast cancer risk and explore the role of potentially modifiable risk factors in activation of the PI3K pathway. The aims will be conducted within the Nurses' Health Study cohort of 116,430 women followed since 1989.
Role: Pathologist

07/01/15-06/30/2020 2P01CA87969-020 (PI: Tamimi)
Dietary and Hormonal Determinants of Cancer in Women
This competing renewal continues the scientific pursuit of modifiable determinants of breast, colorectal, and ovarian cancers.

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Role: Pathologist

Citations:

a) **Baker GM**, Bret-Mounet VC, Xu J, Fein-Zachary VJ, Tobias AM, Bartlett RA, Clohessy JG, Vlachos IS, Massicott ES, Wulf GM, Schnitt SJ and Heng YJ. Toker cell hyperplasia in the nipple-areolar complex of transmasculine individuals. (2023) *Mod Pathol*, 36, 100121.
b) **Baker GM**, Guzman-Arocho YD, Bret-Mounet VC, Torous VF, Schnitt SJ, Tobias AM, Bartlett RA, Fein-Zachary VJ, Collins LC, Wulf GM and Heng YJ. Testosterone therapy and breast histopathological features in transgender individuals. (2021) *Mod Pathol*, 34, 85-94.
c) **Baker GM**, Pyle ME, Tobias, AM, Bartlett, RA, Phillips J, Fein-Zachary VJ, Wulf GM and Heng YJ. Establishing a cohort of transgender men and gender non-conforming individuals to understand the molecular impact of testosterone on breast physiology. (2019) *Transgender Health*, 4, 326-330.
d) Kensler KH, Regan MM, Heng YJ, **Baker GM**, Pyle ME, Schnitt SJ, Hazra A, Kammler R, Thürlimann B, Colleoni M, Viale G, Brown M and Tamimi RM. Prognostic and predictive value of androgen receptor expression in postmenopausal women with estrogen receptor-positive breast cancer: results from the Breast International Group Trial 1–98. (2019). *Breast Cancer Res*, 21, 30.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-Current	Assistant Professor of Pathology, Harvard Medical School
2016-2021	Instructor of Pathology, Harvard Medical School.
2016-Current	Breast Pathologist, Beth Israel Deaconess Medical Center, Boston, MA.
2015-2016	House of Delegates, Alternate (Illinois), College of American Pathologists
2015-2016	Vice-President, Chicago Pathology Society
2013-current	International Society of Breast Pathology
2014-2016	Board of Directors, Chicago Pathology Society
2013-2016	Assistant Professor, Department of Pathology, The University of Chicago, Chicago, IL.
2012-2013	Fellow, Breast Pathology, Beth Israel Deaconess Medical Center, Boston, MA.
2011-2012	Chief Resident, Anatomic Pathology, Massachusetts General Hospital, Boston, MA.
2010-2012	Resident Forum Delegate, College of American Pathologists
2008-2012	Resident, Anatomic and Clinical Pathology, Massachusetts General Hospital, Boston, MA.

Honors

2021	Best Clinical Paper 2021, BIDMC Cancer Center, Boston, MA
2012	Stowell-Orbison Award Competition, Poster Presentation at the United States and Canadian Academy of Pathology 102nd Annual Meeting, Baltimore, MD
2011-2012	Chief Resident, Anatomic Pathology, Massachusetts General Hospital
2008	Alpha Omega Alpha Medical Honor Society
2000	Graduation with Distinction, Flute Performance, Eastman School of Music
1996-2000	George Eastman Merit Scholarship, Eastman School of Music

C. Contributions to Science

1. Transgender individuals in the United States are increasingly pursuing gender-affirming hormone therapy and/or surgery. We have established a cohort of transmasculine individuals who have undergone gender-affirming chest-contouring surgery at our institution. We have catalogued histological alterations

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including degree of lobular atrophy in this cohort and are well-positioned to continue to evaluate the influence that exogenous testosterone exposure may have on the breast tissue.

a. **Baker GM**, Bret-Mounet VC, Xu J, Fein-Zachary VJ, Tobias AM, Bartlett RA, Clohessy JG, Vlachos IS, Massicott ES, Wulf GM, Schnitt SJ and Heng YJ. Toker cell hyperplasia in the nipple-areolar complex of transmasculine individuals. (2023) *Mod Pathol*, 36, 100121.
a. Heng YJ, Zhang KJ, Valero MG, **Baker GM**, Fein-Zachary VJ, Irwig MS and Wulf GM. Invasive ductal carcinoma of the breast in a transgender man: a case report. (2023). *Case Rep Oncol*. In Press.
b. **Baker GM**, Guzman-Arocho YD, Bret-Mounet VC, Torous VF, Schnitt SJ, Tobias AM, Bartlett RA, Fein-Zachary VJ, Collins LC, Wulf GM and Heng YJ. Testosterone therapy and breast histopathological features in transgender individuals. (2021) *Mod Pathol*, 34, 85-94. PMCID: PMC7854981
c. **Baker GM**, Pyle ME, Tobias, AM, Bartlett, RA, Phillips J, Fein-Zachary VJ, Wulf GM and Heng YJ. Establishing a cohort of transgender men and gender non-conforming individuals to understand the molecular impact of testosterone on breast physiology. (2019) *Transgender Health,* 4, 326-330. PMCID: PMC6863056

2. Breast cancers that express the estrogen receptor, progesterone receptor, or overexpress HER2 provide actionable therapeutic targets. However, 15-20% of breast cancers are triple negative, lacking a therapeutic target, and are associated with a worse prognosis. Activation of the glucocorticoid receptor (GR) has diverse effects depending on cell type. In ER negative breast cancer, activation has been demonstrated to inhibit apoptosis of tumor cells, whereas its antagonism is associated with increased tumor cell death. Therefore, GR represents a potential prognostic and therapeutic target. During the time that I was a member of the faculty at the University of Chicago, my research endeavors primarily focused on identifying the patterns of glucocorticoid receptor expression in invasive breast cancers and in gynecologic malignancies. I have helped develop an assay for GR expression that will be used in clinical trials internationally. I have also examined the SV40Tag and Sprague-Dawley mammary gland specimens with Drs. Conzen, Brady, and McClintock and their students and staff for evidence of ductal developmental defects and malignancy.
   a. **Baker GM**, Murphy T, Block T, Nguyen D, Lynch FJ. Development and validation of an immunohistochemistry assay to assess glucocorticoid receptor expression for clinical trials of mifepristone in breast cancer. *Cancer Manag Res*. 2015;7:361-8. PMCID: PMC4675647
   b. Stringer-Reasor EM, **Baker GM,** Skor MN, Kocherginsky M, Lengyel E, Fleming GF, Conzen SD. Glucocorticoid receptor activation inhibits chemotherapy-induced cell death in high-grade serous ovarian carcinoma. *Gynecol Oncol*. 2015; 138(3):656-62. PMCID: PMC4556542

3. I am one of the lead breast pathologists in the Nurses' Health Study (NHS) and NHSII. As part of the NHS/NHSII, I have been involved in manual reading of tissue microarrays as well as annotations of whole-slide scanned images for subsequent molecular work and computational pathology endeavors.
   a. Kensler KH, Beca F, **Baker GM**, Heng YJ, Beck AH, Schnitt SJ, Hazra A, Rosner BA, Eliassen AH, Hankinson SE, Brown M and Tamimi RM. Androgen receptor expression in normal breast tissue and subsequent breast cancer risk. (2018). npj Breast Cancer, 4, 33. PMCID:PMC6155011
   b. Wetstein SC, Onken AM, Luffman C, **Baker GM**, Pyle ME, Kensler KH, Liu Y, Bakker B, Vlutters R, van Leeuwen MB, Collins LC, Schnitt SJ, Pluim JPW, Tamimi RM, Heng YJ and Veta M. Deep learning assessment of breast terminal duct lobular unit involution: towards automated prediction of breast cancer risk. (2020). PLoS One, 5:e0231653. PMCID: PMC7159218
   c. Kensler KH, Sankar VN, Wang J, Zhang X, Rubadue CA, **Baker GM**, Parker JS, Hoadley KA, Stancu AL, Pyle ME, Collins LC, Hunter DJ, Eliassen AH, Hankinson SE, Tamimi RM and Heng YJ. PAM50 molecular intrinsic subtypes in the Nurses' Health Study cohorts. (2019). *Cancer Epidemiol Biomarkers Prev*, 28, 798-806. PMCID: PMC6449178
   d. Kensler KH, Liu EZ, Wetstein SC, Onken AM, Luffman CI, **Baker GM**, Collins LC, Schnitt SJ, Bret-

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Mounet VC, Veta M, Pluim JPW, Liu Y, Colditz GA, Eliassen AH, Hankinson SE, Tamimi RM and YJ Heng. Automated quantitative measures of terminal duct lobular unit involution and breast cancer risk. (2020) *Cancer Epidemiol Biomarkers Prev.* 29:2358–68. PMCID: PMC7642012

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/12W6dqp5fEvQ9/bibliography/public/

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Li Jia

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor of Surgery, Director of Urologic Research, righam and Women's Hospital/Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Nanjing Medical University, Nanjing, China	B.M.	07/1987	Medicine
Nanjing Medical University, Nanjing, China	Ph.D.	07/1995	Nephrology
University of Southern California, Los Angeles, CA	Postdoctoral	07/2006	Urology

A. Personal Statement

My expertise lies in linking basic molecular biology with translational medicine. During the past 16 years, the major focus of my research has been on determining the molecular mechanisms of prostate cancer development and progression. Much effort has been devoted to understanding epigenetic mechanisms of androgen receptor-mediated transcription in prostate cancer. Using high-throughput next-generation sequencing, my lab has investigated dynamic chromatin modifications mediated by androgen receptor binding at a genome-wide level. These genomic analyses have led to the discovery of functional non-coding genetic variants that influence cancer-specific gene transcription. Specifically, we have determined that prostate cancer risk loci within the chromosomal region 8q24 acting as tissue-specific enhancers for the proto-oncogene c-MYC. Since I joined Brigham and Women's Hospital/Harvard Medical School in , my lab continues to focus on androgen receptor signaling and its related pathways (including WNT signaling and DNA repair pathway) that drive prostate cancer growth, metastasis, and drug resistance. The goal of my research is to understand how these genes and pathways function under androgen-deprived conditions and identify therapeutic vulnerabilities in castration-resistant prostate cancer when androgen receptor-directed therapies fail. In summary, I have the expertise, leadership, training, expertise, and motivation necessary to successfully carry out the proposed research project.

Ongoing and recently completed projects that I would like to highlight include:

NIH/NCI 1R21CA252578-01A1 **Jia** (PI) 04/01/2021-03/31/2023
Title: RNASEH2B Loss to Predict Response to PARP Inhibitor in Prostate Cancer
The goal of this project is to determine whether and to what extent RNASEH2B deletion in prostate cancer can be used as a biomarker to predict PARP inhibitor response.
Role: PI

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NIH/NCI 1R01CA262524-01 **Jia** (PI) 07/01/2021-06/30/2026
Title: Androgen receptor pathway inhibition through targeting PARP-2 in castration-resistant prostate cancer
The goal of this project is to determine the molecular mechanisms by which selective targeting of PARP-2 inhibits castration-resistant prostate cancer (CRPC) growth through disruption of FOXA1 function and define PARP-2 as a therapeutic target for CRPC.
Role: PI

NIH/NCI 1R21CA267496-01A1 **Jia** (PI) 07/01/2022-06/30/2024
Title: CHEK2 loss promotes prostate cancer resistance to PARP Inhibitors
The goal of this project is to determine whether loss of CHEK2 in prostate cancer can be used as a biomarker to predict PARP inhibitor resistance and understand the underlying mechanisms.
Role: PI

DoD W81XWH-22-1-0477 **Jia** (PI) 07/01/2022-06/30/2025
Title: Concurrent genomic deletions impact the response to PARP inhibition in Prostate Cancer
The goal of this project is to determine whether and to what extent chromosome 13q14.2-14.3 deletion in prostate cancer can be used as a biomarker to predict PARP and ATR inhibitor response.
Role: PI

Citation:

1. Decker KF, Zheng D, He Y, Bowman T, Edwards JR, **Jia L**. Persistent androgen receptor-mediated transcription in castration-resistant prostate cancer under androgen-deprived conditions. ***Nucleic Acids Res.*** 2012 Nov;40 (21):10765-79. PubMed Central PMCID: PMC3510497
2. Gui B, Gui F, Takai T, Feng C, Bai X, Fazli L, Dong X, Liu S, Zhang X, Zhang W, Kibel AS, **Jia L**. Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. ***Proc Natl Acad Sci U S A.*** 2019 Jul;116(29):14573-14582. PubMed Central PMCID: PMC6642419
3. Miao C, Tsujino T, Takai T, Gui F, Tsutsumi T, Sztupinszki Z, Szallasi Z, Mouw KW, Zou L, Kibel AS, **Jia L**. RB1 loss overrides PARP inhibitor sensitivity driven by RNASEH2B loss in prostate cancer. ***Sci Adv.*** 2022 Feb 18; 8(7):eabl9794. PubMed Central PMCID: PMC8856618
4. Tsujino T, Takai T, Hinohara K, Gui F, Tsutsumi T, Bai X, Miao C, Feng C, Gui B, Sztupinszki Z, Simoneau A, Xie N, Fazli L, Dong X, Azuma H, Choudhury AD, Mouw KW, Szallasi Z, Zou L, Kibel AS, **Jia L**. CRISPR screens reveal genetic determinants of PARP inhibitor sensitivity and resistance in prostate cancer. ***Nat Commun.*** 2023 Jan 17;14(1):252.doi:10.1038/s41467-023-35880-y. PubMed Central PMCID: PMC9845315

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2016-	Assistant Professor of Surgery, Harvard Medical School, Boston, MA
2014 -	Lead Investigator, Director of Urologic Research, Division of Urological Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA
2009 - 2014	Assistant Professor, Center for Pharmacogenomics, Department of Medicine, Washington University, St. Louis, MO
2006 - 2009	Research Assistant Professor, Department of Urology, University of Southern California /Norris Cancer Center, Los Angeles, CA
2002 - 2006	Postdoctoral Fellow, Department of Urology, University of Southern California/Norris Cancer Center, Los Angeles, CA
1997 - 2001	Research Associate, Hematology/Oncology Division, University of Southern California/Norris Cancer Center, Los Angeles, CA
1990 - 1995	Ph.D. candidate and Lecturer, Nanjing Medical University, Nanjing, China
1996	Visiting Research Scholar, Department of Hematology/Oncology, Children's Hospital of Los Angeles, Los Angeles, CA
1987 - 1990	Resident, Department of Pediatrics, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

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Other Professional Experience and Membership

2021- Member, American Urological Association
2019- Member, Society for Basic Urologic Research
2016- Reviewer, American Cancer Society, Tumor Biochemistry & Endocrinology
2015- Reviewer, Hong Gong Research Grants Council
2014- Reviewer, The European Research Foundation Flanders
2011- Reviewer, DoD Prostate Cancer Research Program
2005- Member, American Association for Cancer Research
2004-2006 NIH Postdoctoral Fellowship

C. Contributions to Science

1. The Androgen receptor signaling pathway
My early research work focused on molecular mechanisms of androgen receptor (AR)-mediated gene expression in prostate cancer. I precisely characterized dynamic AR binding events and chromatin modifications at the prostate specific antigen (PSA) locus and at a genome-wide level using high-throughput genomic approaches. The goal of my research is to understand how AR and AR target genes drive prostate cancer growth and progression.

    a. **Jia L**, Choong S-Y, Ricciardelli C, Kim J, Tilley WD, Coetzee GA. Androgen receptor signaling: mechanism of IL-6 inhibition. ***Cancer Res.*** 2004 Apr;64:2619-2626
    b. **Jia L**, Coetzee GA. Androgen Receptor-Dependent PSA Expression in Androgen-independent prostate cancer cells does not involve androgen receptor occupancy of the PSA Locus. ***Cancer Res.*** 2005 Sep;65(17): 8003-8008
    c. **Jia L,** Shen HC, Wantroba M, Khalid O, Liang G, Wang Q, Gentzschein E, Pinski JK, Stancyk FZ, Jones PA, Coetzee GA. Locus-wide chromatin remodeling and enhanced androgen receptor-mediated transcription in recurrent prostate tumor cells. ***Mol Cell Bio.*** 2006 Oct;26(19): 7331-7341. PubMed Central PMCID: PMC1592894.
    d. **Jia L**. Berman B, Jariwala U, Cogan JP, Walters A, Yan X, Chen T, Hengen PN, Buchanan G, Frenkel B, Coetzee GA. Genomic androgen receptor-occupied regions with different functions, defined by histone acetylation, collaborators and transcriptional capacity. ***PLoS One.*** 2008;3(11):e3645. PubMed Central PMCID: PMC2577007

2. Functional prostate cancer genomics
In addition to the contributions described above, with a collaborative team, I investigated functions of non-coding genetic variants identified from genome-wide association studies (GWAS). I was one of the leaders in the multi-institute research group and initiated the project. Common variants on chromosome 8q24 regions are associated with multiple cancer types including prostate, breast and colon carcinoma. However, there are few candidate genes in this region. We identified transcriptional enhancers that are occupied by functional AR and FOXA1. Not only do the risk variants at 8q24 facilitate both stronger transcription factor binding and stronger androgen responsiveness, the 8q24 variants are also linked to c-MYC regulation. Our studies both solved the mystery of the 8q24 cancer risk region and established an approach to elucidate the regulatory functions of non-coding genetic variants.

    a. **Jia L**, Landan G, Pomerantz M, Jaschek R, Herman P, Reich D, Yan C, Kantoff P, Oh W, Manak J, Berman BP, Henderson BE, Frenkel B, Haiman CA, Freedman M, Tanay A, Coetzee GA. Functional enhancers at the gene-poor 8q24 cancer-linked locus. ***PLoS Genet.*** 2009 Aug;5(8):e1000597. PubMed Central PMCID: PMC2717370
    b. Pomerantz M, Ahmadiyeh N, **Jia L**, Herman P, Verzi M, Beckwith C, Chan J, Haiman CA, Yan C, Henderson B, Frenkel B, Barretina J, Bass A, Tabernero J, Baselga J, Shivdasani R, Coetzee G, Freeedman M. The 8q24 cancer risk variant rs6983267 demonstrates long- range interaction with MYC in colorectal cancer. ***Nat Genet.*** 2009 Aug;41(8):882-884. PubMed Central PMCID: PMC2763485
    c. Ahmadiyeh N, Pomerantz MM, Grisanzio C, Herman P, **Jia L,** Almendro V, He HH, Brown M, Liu XS, Davis M, Caswell JL, Beckwith CA, Hills A, Macconaill L, Coetzee GA, Regan MM, Freedman ML. 8q24 prostate, breast, and colon cancer risk loci show tissue-specific long-range interaction

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with MYC. ***Proc Natl Acad Sci U S A*** 2010 May;25;107(21):9742-6. PubMed Central PMCID: PMC2906844

d. Ting MC, Liao CP, Yan C, **Jia L,** Groshen S, Frenkel B, Roy-Burman P, Coetzee GA, Maxson R. An enhancer from the 8q24 prostate cancer risk region is sufficient to direct reporter gene expression to a subset of prostate stem-like epithelial cells in transgenic mice. ***Dis Model Mech.*** 2012 May;5(3),366-374. PubMed Central PMCID: PMC3339830

3. Targeted therapies in castration-resistant prostate cancer

During the past several years, my laboratory has been studying AR-mediated transcriptional regulation in castration-resistant prostate cancer. We uncovered a subset of AR target genes (including WNT7B, CXCR7, SLPI, miR-221/222, and miR-345-5p) that are necessary for the growth of prostate cancer cells after androgen withdrawal. More recently, my laboratory has focused on understanding the roles of DNA damage response (DDR) genes in castration-resistant prostate cancer progression and finding novel therapeutic vulnerabilities.

a. Rafiei S GB, Wu J, Liu XS, Kibel AS, **Jia L**. Targeting the MIF/CXCR7/AKT signaling pathway in castration-resistant prostate cancer. ***Mol Cancer Res*** 2019;17(1):263-276
b. Gui B, Gui F, Takai T, Feng C, Bai X, Fazli L, Dong X, Liu S, Zhang X, Zhang W, Kibel AS, **Jia L**. Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. ***Proc Natl Acad Sci U S A*** 2019 Jul;116(29):14573-14582. PMCID: PMC6642419
c. Miao C, Tsujino T, Takai T, Gui F, Tsutsumi T, Sztupinszki Z, Szallasi Z, Mouw KW, Zou L, Kibel AS, **Jia L**. RB1 loss overrides PARP inhibitor sensitivity driven by RNASEH2B loss in prostate cancer. ***Sci Adv.*** 2022 Feb 18; 8(7):eabl9794. PubMed Central PMCID: PMC8856618
d. Tsujino T, Takai T, Hinohara K, Gui F, Tsutsumi T, Bai X, Miao C, Feng C, Gui B, Sztupinszki Z, Simoneau A, Xie N, Fazli L, Dong X, Azuma H, Choudhury AD, Mouw KW, Szallasi Z, Zou L, Kibel AS, **Jia L**. CRISPR screens reveal genetic determinants of PARP inhibitor sensitivity and resistance in prostate cancer. ***Nat Commun.*** 2023 Jan 17;14(1):252.doi:10.1038/s41467-023-35880-y. PubMed Central PMCID: PMC9845315

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1z3K4o-pCIqQk/bibliography/public/

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OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Yu Jing Jan		Heng	Ph.D.	PD/PI	[redacted]				45,500.00	12,422.00	57,922.00
2 .	Gabrielle	M	Baker		Co-Investigator					10,605.00	2,895.00	13,500.00
3 .	Gerburg		Wulf		Co-PI					42,420.00	11,581.00	54,001.00
4 .	Frank		Slack		Co-Investigator					10,605.00	2,895.00	13,500.00

INST. BASE SALARY, CAL. MONTHS

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **138,923.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			68,000.00	18,564.00	86,564.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	12.00			50,000.00	13,650.00	63,650.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**150,214.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**289,137.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	2,000.00
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	62,480.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	54,566.00
6. Equipment or Facility Rental/User Fees	49,340.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
Total Other Direct Costs	**166,386.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**459,523.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	72.90	429,957.00	313,439.00
		Total Indirect Costs	**313,439.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Dept. HHS Rebecca Kaplan, Tel: 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**772,962.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	772,962.00

L. Budget Justification*	File Name: 1234-Budget_Justification_R01_Resub_Heng.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Yu Jing Jan		Heng	Ph.D.	PD/PI	[redacted]				45,500.00	12,422.00	57,922.00
2 .		Gabrielle	M	Baker		Co-Investigator					10,605.00	2,895.00	13,500.00
3 .		Frank		Slack		Co-Investigator					10,605.00	2,895.00	13,500.00
4 .		Gerburg		Wulf		Co-PI					42,420.00	11,581.00	54,001.00

[redacted] INST. BASE SALARY, CAL. MONTHS

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **138,923.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			68,000.00	18,564.00	86,564.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	12.00			50,000.00	13,650.00	63,650.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**150,214.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**289,137.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	2,000.00
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	62,480.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	54,566.00
6. Equipment or Facility Rental/User Fees	49,340.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
Total Other Direct Costs	**166,386.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**459,523.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	72.90	404,957.00	295,214.00
		Total Indirect Costs	**295,214.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Dept. HHS Rebecca Kaplan, Tel: 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**754,737.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	754,737.00

L. Budget Justification*	File Name: 1234-Budget_Justification_R01_Resub_Heng.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Yu Jing Jan		Heng	Ph.D.	PD/PI	[redacted]				45,500.00	12,422.00	57,922.00
2 .		Gabrielle	M	Baker		Co-Investigator					10,605.00	2,895.00	13,500.00
3 .		Frank		Slack		Co-Investigator					10,605.00	2,895.00	13,500.00
4 .		Gerburg		Wulf		CO-PI					42,420.00	11,581.00	54,001.00

[redacted] INST. BASE SALARY, CAL. MONTHS

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **138,923.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			68,000.00	18,564.00	86,564.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	12.00			50,000.00	13,650.00	63,650.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**150,214.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**289,137.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	2,000.00
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	62,480.00
2. Publication Costs	7,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	54,566.00
6. Equipment or Facility Rental/User Fees	49,340.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
Total Other Direct Costs	**173,886.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**467,023.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	72.90	412,457.00	300,681.00
		Total Indirect Costs	**300,681.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Dept. HHS Rebecca Kaplan, Tel: 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**767,704.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	767,704.00

L. Budget Justification*	File Name: 1234-Budget_Justification_R01_Resub_Heng.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Yu Jing Jan		Heng	Ph.D.	PD/PI	[redacted]				45,500.00	12,422.00	57,922.00
2 .	Gabrielle	M	Baker		Co-Investigator					10,605.00	2,895.00	13,500.00
3 .	Frank		Slack		Co-Investigator					10,605.00	2,895.00	13,500.00
4 .	Gerburg		Wulf		CO-PI					42,420.00	11,581.00	54,001.00

INST. BASE SALARY, CAL. MONTHS

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **138,923.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			68,000.00	18,564.00	86,564.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	12.00			50,000.00	13,650.00	63,650.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**150,214.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**289,137.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	2,000.00
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	62,480.00
2. Publication Costs	7,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	54,566.00
6. Equipment or Facility Rental/User Fees	49,340.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
Total Other Direct Costs	**173,886.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**467,023.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	72.90	412,457.00	300,681.00
		Total Indirect Costs	**300,681.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Dept. HHS Rebecca Kaplan, Tel: 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**767,704.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	767,704.00

L. Budget Justification*	File Name: 1234-Budget_Justification_R01_Resub_Heng.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Yu Jing Jan		Heng	Ph.D.	PD/PI	[redacted]				45,500.00	12,422.00	57,922.00
2 .		Gabrielle	M	Baker		Co-Investigator					10,605.00	2,895.00	13,500.00
3 .		Frank		Slack		Co-Investigator					10,605.00	2,895.00	13,500.00
4 .		Gerburg		Wulf		CO-PI					42,420.00	11,581.00	54,001.00

INST. BASE SALARY, CAL. MONTHS

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **138,923.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	12.00			68,000.00	18,564.00	86,564.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	12.00			50,000.00	13,650.00	63,650.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**150,214.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**289,137.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	2,000.00
2. Foreign Travel Costs	2,000.00
Total Travel Cost	**4,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: C1CPANL3EWK4

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: Beth Israel Deaconess Medical Center, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	62,480.00
2. Publication Costs	7,500.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	54,566.00
6. Equipment or Facility Rental/User Fees	49,340.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
Total Other Direct Costs	**173,886.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**467,023.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	72.90	412,457.00	300,681.00
		Total Indirect Costs	**300,681.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Dept. HHS Rebecca Kaplan, Tel: 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**767,704.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	767,704.00

L. Budget Justification*	File Name: 1234-Budget_Justification_R01_Resub_Heng.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Uncovered by a White Coat Waste investigation

Budget Justification for BIDMC

Senior/Key Personnel

Dr. Jan Heng, Contact Principal Investigator (- calendar months or % effort; Years 1 to 5): Dr. Heng is an Assistant Professor of Pathology at Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School (HMS). She has led multidisciplinary breast cancer projects in cisgender and transgender populations. She is the PI of the transmasculine research cohort at BIDMC. She has over 10 years of experience with clinical translational research, omics, image analyses and computational data analysis. Dr. Heng will oversee all work, including experimental design, laboratory assays, histopathology, data analyses, and co-supervise the Research Assistant and Post-Doctoral Fellow.

Dr. Gerburg Wulf, Principal Investigator (- calendar months or % effort; Years 1 to 5): Dr. Wulf is an Associate Professor of Medicine at BIDMC, HMS. She is a physician-scientist with >1000 breast oncology outpatient visits annually, and has managed the care of transgender patients with breast cancer. She leads a basic research laboratory with established mouse models of breast cancer to investigate tumor signaling and metabolism. She will lead the animal work, contribute to study design, data analyses, and co-supervise the Research Assistant and Post-Doctoral Fellow.

Dr. Gabrielle Baker, Co-Investigator (- calendar months or % effort; Years 1 to 5): Dr. Baker is an Instructor of Pathology at BIDMC, HMS. She is a breast pathologist. She will review the murine mammary glands and tumors, and support the interpretation of the immunohistochemistry staining for this proposal. Dr. Baker will also contribute to data interpretation and manuscript writing.

Dr. Frank Slack, Co-Investigator (- calendar months or % effort; Years 1 to 5): Dr. Slack is a Professor at BIDMC, HMS. He is also the Director of the BIDMC Cancer Research Institute and the Director of the HMS Initiative for RNA Medicine. He is a basic scientist renowned for his discoveries in non-coding RNA. He will contribute his microRNA expertise to this project. He will also contribute to data interpretation and manuscript writing.

Other Personnel

TBD, Research Assistant (12 calendar months or 100% effort; Years 1 to 5): The Research Assistant will assist with mouse work, histology and molecular assays, and data collection.

TBD, Post-Doctoral Fellow (12 calendar months or 100% effort; Years 1 to 5): The Post-Doctoral Fellow will lead the animal work, data collection, molecular assays, and data analysis.

Fringe

Fringe benefits and the indirect cost rates are determined by the federally negotiated hospital rate agreement.

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Travel

Participation at domestic scientific meetings (Years 1 to 5): An annual budget of $4,000 is requested for 1) two team members to either attend a US domestic meeting such as the American Association for Cancer Research Annual Meeting, the San Antonio Breast Cancer Symposium, the Society of Breast Imaging, or transgender health/health disparities meetings; or 2) one team member to attend one international scientific meeting in oncology/breast cancer/transgender health/health disparities.

Other Direct Costs

Molecular work materials and supplies (Years 1 to 5): An annual budget of $45,580 is requested for the following:

- $5,000 for histology related work (creating tissue blocks, sectioning, H&E staining, and performing immunohistochemistry or multiplex immunofluorescence assays)
- $2,500 for antibodies for histology and molecular assays
- $28,080 for ChIPSeq, total RNAseq, and miRNA screening
    - ChIPSeq, total RNAseq, and miRNA screening are estimated at $600/sample.
    - For Aim 1, 24 samples for AR ChIPSeq x $600, 12 samples for ER ChIPSeq x $600, 24 samples for total RNASeq x $600, and 24 samples for miRNA screening x $600 = $50,400 / 5 years = $10,080 per year
    - For Aim 2, 30 samples for AR ChIPSeq x $600, 24 samples for ER ChipSeq x $600, 30 samples for total RNASeq x $600, and 30 samples for miRNA screening x $600 = $ 68,400/ 5 years = $13,680 per year
    - An additional samples is requested for trial runs. 6 samples for AR ChIPSeq x $600, 6 samples for ER ChIPSeq x $600, 12 samples for total RNASeq x $600, and 12 samples for miRNA screening x $600 = $21,600 / 5 years = $4,320 per year
- $10,000 for laboratory supplies, consumables and chemical reagents

Animal work materials and supplies (Years 1 to 5): An annual budget of $16,900 is requested for the following:

- $10,000 for supplies related to animal work—drugs, meloxicam, testosterone cypionate, laboratory consumables, and syringes.
- $6,900 for animal purchase
    - For Aims 1 and 2, $25/mouse x 1380 mice (including 5 extras x 8 investigations in case of death during or after shipping) = $34,500 / 5 years = $6,900 per year

Facility Rental/User Fees (Years 1 to 5): An annual budget of $49,340 is requested for the following:

- $24,840 for animal facility
    - For Aims 1 and 2, 1380 mice / 5 per cage = 276 cages x $1.50 per diem rate x 300 days = $124,200 / 5 years = approx. $24,840 per year
- $24,500 for testosterone administration by the Preclinical Murine Pharmacogenetics Facility
    - Testosterone is a steroid and is classed as a Schedule III controlled substance. Dr. John Clohessy, Director of the Preclinical Murine Pharmacogenetics Facility, will administer weekly testosterone. He is licensed to administer controlled substances. For Aims 1 and 2, 700 mice in testosterone arms / 5 per cage = 140

Uncovered by a White Coat Waste investigation

cages x $35 fee per cage x approximately 25 weeks of treatment = $122,500 / 5 years = $24,500 per year for testosterone administration.

Publication Costs (Years 3 to 5): An annual budget of $7,500 is requested for publication costs in high-impact journals such as Nature, Cell, and Science.

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		694,615.00
Section B, Other Personnel		751,070.00
Total Number Other Personnel	10	
Total Salary, Wages and Fringe Benefits (A+B)		1,445,685.00
Section C, Equipment		
Section D, Travel		20,000.00
1. Domestic	10,000.00	
2. Foreign	10,000.00	
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		854,430.00
1. Materials and Supplies	312,400.00	
2. Publication Costs	22,500.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	272,830.00	
6. Equipment or Facility Rental/User Fees	246,700.00	
7. Alterations and Renovations		
8. Other 1	0.00	
9. Other 2		
10. Other 3		
11. Other 4		
12. Other 5		
13. Other 6		
14. Other 7		
15. Other 8		
16. Other 9		
17. Other 10		
Section G, Direct Costs (A thru F)		2,320,115.00
Section H, Indirect Costs		1,510,696.00

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

Section I, Total Direct and Indirect Costs (G + H)	3,830,811.00
Section J, Fee	
Section K, Total Costs and Fee (I + J)	3,830,811.00

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Li		Jia	MD	Consortium Pi	[redacted]				11,850.00	3,674.00	15,524.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **15,524.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	2.40			11,000.00	3,960.00	14,960.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**14,960.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**30,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2024 **End Date*:** 03-31-2025 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**30,484.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	79.00	30,484.00	24,082.00
		Total Indirect Costs	**24,082.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Michael Stanco, (212) 264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**54,566.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	54,566.00

L. Budget Justification* File Name: 1255-Budget Justification_Jia_R01 Resub.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Uncovered by a White Coat Waste investigation

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Li		Jia	MD	Consortium Pi	INST. BASE SALARY, CAL. MONTHS				11,850.00	3,674.00	15,524.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **15,524.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	2.40			11,000.00	3,960.00	14,960.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**14,960.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**30,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2025 **End Date*:** 03-31-2026 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	30,484.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	79.00	30,484.00	24,082.00
		Total Indirect Costs	**24,082.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Michael Stanco, (212) 264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	54,566.00

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	54,566.00

L. Budget Justification* File Name: 1255-Budget Justification_Jia_R01 Resub.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Li		Jia	MD	Consortium Pi	INST. BASE SALARY, CAL. MONTHS				11,850.00	3,674.00	15,524.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **15,524.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	2.40			11,000.00	3,960.00	14,960.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**14,960.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**30,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2026 **End Date*:** 03-31-2027 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	30,484.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	79.00	30,484.00	24,082.00
		Total Indirect Costs	**24,082.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Michael Stanco, (212) 264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	54,566.00

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	54,566.00

L. Budget Justification* File Name: 1255-Budget Justification_Jia_R01 Resub.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Uncovered by a White Coat Waste investigation

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Li		Jia	MD	Consortium Pi	[redacted]				11,850.00	3,674.00	15,524.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **15,524.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	2.40			11,000.00	3,960.00	14,960.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**14,960.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**30,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2027 **End Date*:** 03-31-2028 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	30,484.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	79.00	30,484.00	24,082.00
		Total Indirect Costs	**24,082.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Michael Stanco, (212) 264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	54,566.00

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	54,566.00

L. Budget Justification* File Name: 1255-Budget Justification_Jia_R01 Resub.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT13949180 Uncovered by a White Coat Waste investigation

Opportunity Number: PAR-21-322 . Received Date: 2023-08-01T15:21:42.000-04:00

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

A. Senior/Key Person

Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Li		Jia	MD	Consortium Pi	[redacted]				11,850.00	3,674.00	15,524.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **15,524.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	2.40			11,000.00	3,960.00	14,960.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	**Total Number Other Personnel**					**Total Other Personnel**	**14,960.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**30,484.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

UEI*: QN6MS4VN7BD1

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: The Brigham and Women's Hospital, Inc.

Start Date*: 04-01-2028 **End Date*:** 03-31-2029 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**30,484.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	79.00	30,484.00	24,082.00
		Total Indirect Costs	**24,082.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Michael Stanco, (212) 264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**54,566.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	54,566.00

L. Budget Justification* File Name: 1255-Budget Justification_Jia_R01 Resub.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Uncovered by a White Coat Waste investigation

BUDGET JUSTIFICATION

Jia, Ph.D., Consortium PI ([redacted] % effort [redacted] - calendar months): Dr. Jia is an Assistant Professor at Harvard Medical School and the Director of Urology Research in the Department of Surgery at Brigham and Women's Hospital. The major focus of his research has been on prostate cancer genomics and targeted therapies. His experience and expertise in prostate cancer biology have prepared him to conduct the proposed research. Dr. Jia will direct the proposed research on sex hormone signaling in breast cancer pre-clinical models. He will be involved in coordinating study design, interpretation, and integration of results from the project's personnel and other significant contributors. Dr. Jia will contribute [redacted] % effort to this project in all calendar years.

TBD, Postdoc (20% effort; 2.4 calendar months): Will oversee the project including managing all the compliance and regulatory aspects of the award (IRB,lab safety, etc.).Will also assist with purchasing data, organizing any publications that arise from the work, and any reporting requirements. S/he will also be responsible for the day-to-day coordination, data collection, and responsible for part of all the analytics.

Fringe Benefit Rate: As of 10/01/2022, until amended

	Fringe Rates		
Employee Category	**FY22**	**FY23**	**FY24 and after**
Professional Staff – MDs	31%	31%	32%
Professional Staff – PhDs	35%	35%	35%
Non-professional Staff (Weekly Staff)	36%	36%	36%
Fellows	32%	34%	35%
Interns & Residents	28%	28%	28%
Temporary Student Employees	12%	12%	12%

Facilities & Administrative Costs

Facilities & Administrative (F&A) Costs are negotiated with the Department of Health and Human Services (most recent agreement dated September 28, 2020.

Rate Type	FY20	FY21 and after
Onsite Research (MTDC Base)	79% Fixed	79% Provisional

Uncovered by a White Coat Waste investigation

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)
Section A, Senior/Key Person	77,620.00
Section B, Other Personnel	74,800.00
Total Number Other Personnel	5
Total Salary, Wages and Fringe Benefits (A+B)	152,420.00
Section C, Equipment	
Section D, Travel	
1. Domestic	
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	
9. Other 2	
10. Other 3	
11. Other 4	
12. Other 5	
13. Other 6	
14. Other 7	
15. Other 8	
16. Other 9	
17. Other 10	
Section G, Direct Costs (A thru F)	152,420.00
Section H, Indirect Costs	120,410.00

Uncovered by a White Coat Waste investigation

Section I, Total Direct and Indirect Costs (G + H)	272,830.00
Section J, Fee	
Section K, Total Costs and Fee (I + J)	272,830.00

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	435,441	435,441	442,941	442,941	442,941	**2,199,705**

WHITE COAT WASTE PROJECT

Uncovered by a White Coat Waste investigation

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 01/31/2026

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ● Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

● Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

WHITE COAT WASTE PROJECT

 Uncovered by a White Coat Waste investigation

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ❍ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ❍ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

WHITE COAT WASTE PROJECT

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PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 01/31/2026

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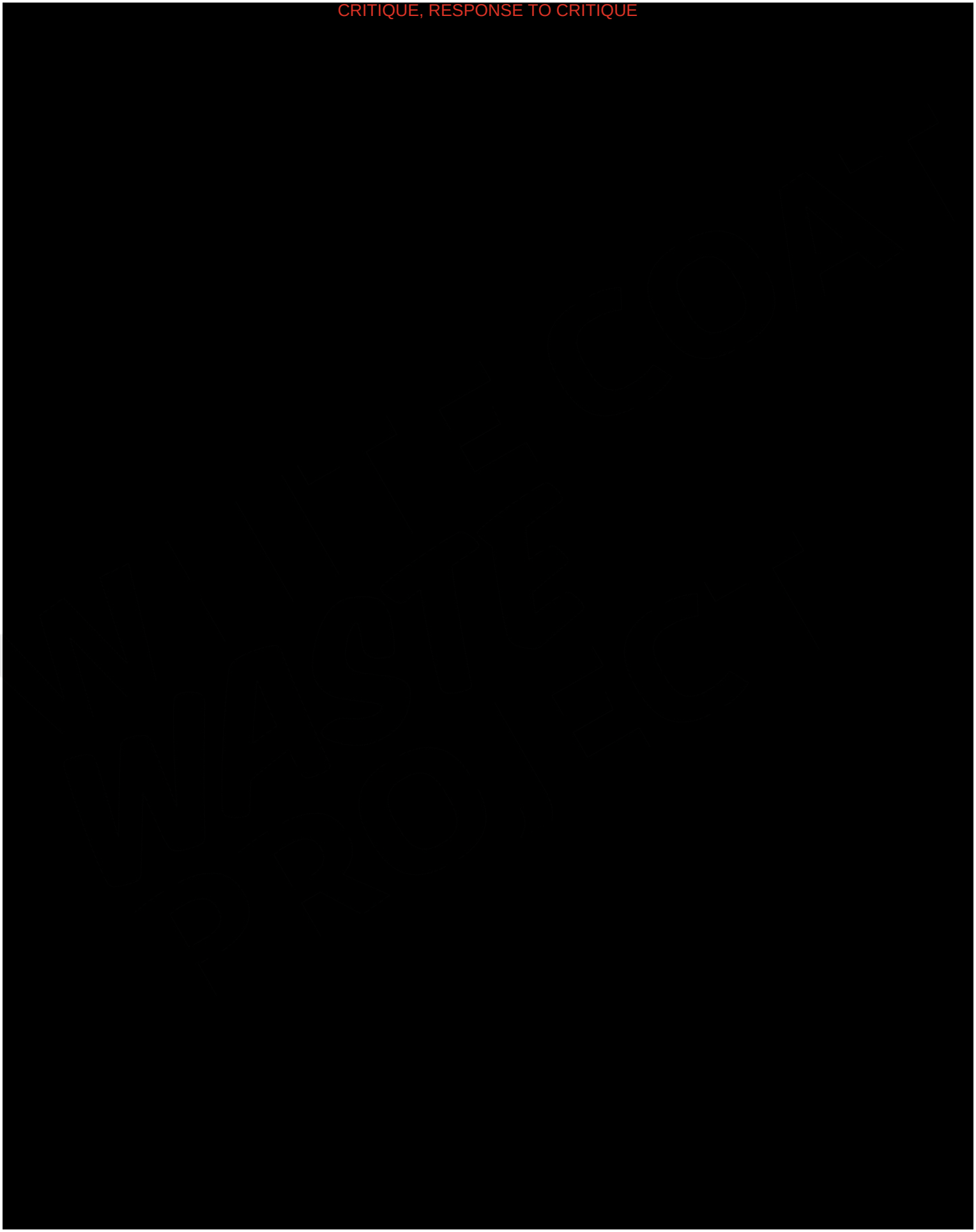
CRITIQUE, RESPONSE TO CRITIQUE



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Specific Aims. We will address breast cancer (BC) risk and treatment concerns of transmasculine people (assigned female at birth). Most transmasculine individuals (65%) pursue testosterone therapy (TT) to treat their gender dysphoria. TT increases the circulating testosterone levels of transmasculine individuals by ≥10-fold comparable to cisgender men. The balance between the stimulating effects of estrogens and the inhibitory effects of testosterone regulates normal breast proliferation. By altering that balance, individuals who receive long-term TT are now a subject of concern regarding their BC risk. *There is a lack of knowledge about the extent to which TT affects BC risk.* There are only 2 retrospective transmasculine BC risk studies to date and both suggested that TT does not increase BC risk. However, at least 8 studies demonstrate a positive association between circulating testosterone levels and female BC risk. Prospective studies to understand transgender cancer risks will take decades. The hormone regulation of breast development is similar in mice and humans. Aim 1 will use 2 mouse models to investigate the effect of TT on the risk of developing estrogen receptor positive (ER+) and negative (ER-) BC. When transmasculine patients are diagnosed with BC, *it is unknown whether testosterone affects the efficacy of the BC treatment.* The discontinuation of TT during BC treatment is undesirable as it affects the patients' emotional wellbeing and adds to their cancer-induced emotional distress. Aim 2 will investigate whether continuing testosterone affects BC treatment outcomes. Testosterone exerts most of its effects via the androgen receptor (AR) present on tumor cells and cells in the tumor microenvironment. AR regulates both mRNA and microRNAs (miRNAs) expression in BC. Therefore, our proposal will also study mRNA and miRNAs in conjunction with AR signaling to increase our understanding of how testosterone affects mammary gland development, carcinogenesis, and response to BC treatment.

Transgender people are the fastest-growing group in the LGBTQ community. They experience barriers to receiving health care, a problem that is compounded when they consider preventive measures for gender-specific cancers such as mammograms, or treatment for BC. The medical community needs to be ready to manage the cancer care of transmasculine individuals. *Research is critically needed to understand how TT affects BC risk, to manage TT during BC treatment to reduce BC mortality, and to reduce healthcare disparities in the underserved transgender community.* Transgender health research is a priority for the NIH (NOT-MD-19-001). Our proposal is responsive to Basic Research in Cancer Health Disparities (PAR-21-322). If we fail to understand the effect of TT on BC risk and BC treatment, we may unknowingly increase the BC risk of some individuals, and/or mismanage their cancer care leading to higher mortality. Our overall objective in this proposal is to utilize mouse models to understand how gender-affirming TT affects BC risk and BC treatment outcomes. Our long-term goal is to reduce cancer disparities for the transgender community.

Aim 1. Determine the effect of TT on ER+ and ER- BC development using MMTV-Cre Pik3ca$^{f/wt}$ mice and K14-Cre Brca1$^{f/f}$p53$^{f/f}$ mice, respectively. We hypothesize that TT does not increase BC incidence compared to female controls, BC incidence in TT-treated mice is higher than in male controls, and that the effects of TT are mediated by alterations in transcriptional programs. We also hypothesize breast tumor development is delayed in TT-treated female mice, and that delay is similar for both mouse models when compared to their female controls.

Aim 1.1: Determine tumor incidence and tumor-free survival by following 5 arms of mice for 10 to 18 months.

Aim 1.2: Investigate the effect of TT on AR-mediated transcriptional programs (mRNA and miRNA expression) in regulating mammary gland development and carcinogenesis.

Aim 2. Determine the effect of TT on treatment outcomes for ER+ and ER- BC. We hypothesize that the continuation of TT does not affect BC treatment outcomes when treated with 1) alpelisib, 2) alpelisib plus letrozole, 3) alpelisib plus fulvestrant for *PIK3CA*-related tumors, 4) olaparib for *BRCA1*-related tumors, and 5) paclitaxel for both tumors.

Aim 2.1: Implant *Pik3ca^{mut}* or *Brca1^{mut}* murine tumors into recipient mice and compare BC treatment-related survival between mice that continued or discontinued testosterone.

Aim 2.2: Investigate the effect of TT on AR mediated transcriptional programs (mRNA and miRNA expression) in drug-treated tumors.

Aim 1 will provide clarity on how TT modulates BC risk, especially for those with a genetic predisposition to develop BC so that the benefits of TT outweigh cancer risk. Aim 1 will also elucidate whether the biology of transmasculine BC (exposed to TT) is different from BC in cisgender women. Aim 2 will enable oncologists to have informed discussions with their patients about their TT use after BC diagnosis and during BC treatment. Understanding how sex hormones modulate miRNAs and their downstream signaling will open new avenues for the prevention and/or treatment BC in both transgender and cisgender people. Transmasculine individuals are currently excluded from BC clinical trials because of their TT use. This proposal will clarify to what extent TT affects BC biology and risk, paving the way for transgender patients to participate in research and clinical trials, an essential aspect of addressing discrimination, and reducing health care disparities.

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A. GENERAL BACKROUND

Studies regarding gender-affirming testosterone therapy (TT) and cancer risk are urgently needed. The US transgender population, estimated at 1.4 million adults and 150,000 youths in 2016, is expected to rapidly expand in the next 20 years [1,2]. Transmasculine individuals is an umbrella term for transmen (female-to-male) and gender non-binary people. About 65% of transmasculine individuals pursue gender-affirming care such as receiving TT, undergoing chest-contouring surgery and/or bilateral salpingo-oophorectomy [3]. An individual will receive TT for at least 50 years, where they can start TT as early as 16 years old and will likely pursue lifelong TT to maintain virilization. TT increases transmasculine individuals' baseline circulating testosterone levels by ≥10-fold to achieve levels comparable to cisgender men [2]. TT is considered safe with regard to cardiovascular disease in the short- and mid-term, but cancer risks associated with long-term testosterone use is unknown [4]. History has demonstrated that assumptions about hormone therapies can be wrong. Menopausal hormone replacement therapy of combined estrogen and progesterone, widely popular and considered safe, was later identified as the primary culprit for increasing the breast cancer (BC) risk in postmenopausal women [5,6]. We need more research to understand TT and cancer risks.

We demonstrated that TT alters breast morphology. Very little is known about the extent to which TT affects the breast. Our team has been leading the charge to understand how TT affects normal breast tissues. Dr. Heng [Contact PI] established a cohort of 578 transmasculine subjects who had chest-contouring surgeries at BIDMC between 2013 and 2022 to study the effect of TT in healthy breast tissues. Our team collected the subjects' clinical data, digital mammograms, and archival post-surgical breast specimens [7,8]. We showed that alterations in breast histology were evident after >12 months of TT exposure. Moderate to marked lobular atrophy were more frequently observed in individuals who use TT compared to non-users (p<0.001; Fig 1A) [8]. We reported that transmasculine individuals were more likely to have Toker cell hyperplasia in their nipple-areolar complexes compared to cisgender women (p=0.06), and we were the first to show that Toker cells express the androgen receptor (AR; Fig 1B) [9]. Toker cells are hypothesized to be a precursor of Paget disease, a rare form of BC of the nipple [10,11]; the clinical significance of Toker cell hyperplasia in the transmasculine population remains to be determined. Lastly, we used our computational pathology algorithm [12,13] to estimate that breast lobules of transmasculine individuals shrank by 3.9% for every 6 months of TT use (adj p<0.001) [14]. We successfully showed that TT has an effect on normal breast morphology. However, the effect of TT on BC risk remains unknown.

A.

	TT users *n* (%)	TT non-users *n* (%)	*p*-value
Minimal	69 (18.8)	26 (32.9)	<0.001
Mild	97 (26.4)	27 (34.2)	
Moderate	139 (37.9)	23 (29.1)	
Marked	62 (16.9)	3 (3.8)	

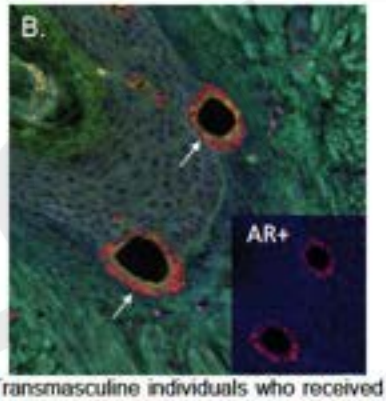

Fig 1. (**A**) Transmasculine individuals who received TT were more likely to have moderate to marked lobular atrophy compared to those who did not take TT. (**B**) Toker cell hyperplasia (white arrows) in the nipple-areolar complex of a transmasculine individual express AR (10× magnification).

A1. Background, rationale, and significance of Aim 1.

We need to understand the effect of TT and BC risk to support clinical practice. The intricate balance between the stimulating effects of estrogens and the inhibitory effects of testosterone regulates normal breast tissue proliferation. Altering that balance may affect the BC risk for those who opt for TT [15]. Drs. Wulf [MPI; oncologist-scientist] and Heng published 2 transmasculine BC case reports of a 29 year old who received TT for 4 years [15] and a 52 year old who received TT for 2 years [16]. Both had strong family histories of cancers but tested negative for hereditary BC. The impact of TT on those patients' BC risk was unclear. Dr. Wulf is attending to more transgender cancer cases in the clinic. The increase in transgender cancer patients spurred us to conduct research studies to address the unmet medical needs of the rapidly growing transgender community. Besides oncologists, endocrinologists are also often faced with the clinical dilemma of prescribing gender-affirming hormone therapy to their transgender patients knowing the fact that the patients have a genetic predisposition to developing BC or have BC (personal communication with Dr. Koen Dreijerink, Center of Expertise on Gender Dysphoria, Amsterdam University Medical Centers, The Netherlands).

As this is a new field of research, any knowledge about TT and BC risk is cobbled together from the limited number of transmasculine studies and studies in cisgender women. There are only 2 transmasculine BC risk epidemiological studies [17,18], and those studies only consisted a total of 11 transmasculine BC cases. The authors

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of those studies concluded that transmasculine individuals do not have increased BC risk (~4%) compared to cisgender females (12%) but their risk remains higher than cisgender men (<0.12%) [17,18]. In contrast, a transcriptomic profiling study showed that transmasculine breast biopsies taken 2 years after TT were enriched for genes that overlapped with BC signatures when compared to paired biopsy samples taken before starting TT [19]; the authors concluded that TT could potentially lead to BC development. Studies in pre- and postmenopausal women also support a link between higher testosterone levels and increased BC risk [20–25]. One explanation for that phenomenon is that testosterone can be aromatized to estradiol, contributing to mammary gland proliferation and BC development [26]. Since transmasculine individuals who take TT have circulating testosterone levels >10-fold higher than cisgender women, it is conceivable that TT may affect BC risk, minimally in a subset of individuals.

Critics assume that transmasculine individuals have almost no BC risk because they remove their breast tissue during chest-contouring surgeries. We want to emphasize that chest-contouring surgery, as opposed to oncologic mastectomies, focuses on esthetics and does not remove the entire gland. In this aspect, chest-contouring surgery resembles reduction mammoplasty more than an oncologic mastectomy. BC can, and has, occurred in residual breast tissue after chest-contouring surgery [17,27,28], indicating that individuals who had chest contouring retain their inherent BC risk in their residual breast tissue and TT could modulate that risk. This lends to the argument that we need to understand the effect of TT on BC risk, especially for those who do not undergo chest-contouring surgery and for those with a genetic predisposition. *BRCA1/2*^{mut} carriers have a > 70% lifetime BC risk, and BC frequently occurs at <40 years old [29]. As sex hormones are strong drivers of BC carcinogenesis [30–32], and ovaries are the main source of estradiol in premenopausal women, female *BRCA*^{mut} carriers who develop predominantly ER- BC may elect to undergo prophylactic mastectomy and/or bilateral oophorectomy to prevent breast and ovarian cancer [33]. In our transmasculine research cohort, ≈20% had oophorectomies [7,8]. The BC risk for those who had oophorectomy and receive TT is also unclear. The aromatization of exogenous testosterone to estradiol in nongonadal tissues may play an important role in affecting the BC risk of those who had oophorectomy and receive TT. Our Aim 1 will address the BC risk in those individuals as well. Lastly, while some transmasculine individuals may choose to undergo pubertal blockage [34], most will go through some degree of puberty with estrogen exposure and breast development, and remain at risk for BC [35].

Knowledge about the relationship between TT and BC risk will empower clinicians to manage BC in this fast growing transmasculine population as they age. If we fail to investigate the impact of TT in the breast, we may unknowingly put a subset of individuals at higher risk of BC. Poor understanding of TT combined with lack reluctance of transmasculine people undergo female-specific screening such as mammograms ultimately increases the risk for worse disease outcomes in the transmasculine population.

Aim 1 rationale. BC is broadly classified into estrogen receptor positive (ER+) or negative (ER-) subtypes. The proportion of ER+/ER- BC is similar for both the transmasculine and cisgender population (65%/35%) [15,17]. Aim 1 will use 2 mouse models to investigate the effect of TT on the risk of developing ER+ and ER- BC. Prospective human studies will take decades and will not be useful for those receiving TT today. Our transmasculine research cohort was not designed to assess transmasculine BC risk as the subjects had chest-contouring surgeries and the follow-up is short (10 years). Our human cohort also does not have sufficient BC cases (n=2) for cancer studies. We can overcome those limitations by using preclinical mouse models. There is a long track record of modeling BC using rodents by our group [36–43] and others [44,45], including hormone-induced BC [45]. Male rats co-treated with estradiol and testosterone developed ER+ tumors (100% incidence) while tumors were not detected with either estrogen or testosterone treatment alone [46]. Mouse aging is accelerated by a factor of 70 compared to humans, and hormone regulation of breast development is similar in mice and humans. Therefore, given that an individual will pursue TT for >50 years, starting between 16 and 20 until >80 years old, we consider mouse models an excellent methodology to understand the effects of TT on BC development. Aim 1 will use 1) MMTV-Cre Pik3ca$^{f/wt}$ mice [44] that model human sporadic BC harboring the most common *PIK3CA* mutation and develop ER+ tumors [47], and 2) K14-Cre Brca1$^{f/f}$p53$^{f/f}$ mice [39] that model human germline *BRCA1* mutation and develop ER- tumors [47]. Aim 1 will study 5 arms of mice: female controls, females receiving TT, oophorectomized female controls, oophorectomized females receiving TT, and male controls. Oophorectomy study arms will allow us to assess the effect of TT in combination or in the absence of endogenous estrogen on BC development, and determine if the aromatization of testosterone to estradiol plays an important role in driving BC risk. We will compare the BC incidence of female mice receiving TT with two points of references—female and male control mice. This will clarify whether transmasculine BC risk is closer to cisgender females or males, thus enabling clinicians to better manage their transmasculine patients' BC screening.

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Aim 1 significance and contribution. Aim 1 will help us to estimate the BC risk in both the general transmasculine population and those with a genetic predisposition in the short term as we await population-wide BC risk data that will take decades to collect. Understanding transmasculine BC risk will empower transmasculine people to make informed decisions about pursing TT so that the benefits of TT outweigh cancer risk. Leveraging on our findings, future studies can be designed to refine the clinical recommendations for TT. For example, individuals with a genetic predisposition or a strong family history of BC may benefit from receiving TT doses sufficient to maintain well-being while avoiding attaining testosterone levels comparable to cisgender men.

By understanding transmasculine BC risk, and whether that risk is closer to cisgender females or males, clinicians will be empowered to create personalized cancer surveillance strategies for their transmasculine patients. It can be emotionally distressing for transmasculine individuals to undergo screening for female cancers because of the discordance between their gender identity and their natal genitalia. Combined with a lack of evidence-based screening guidelines and a reluctance to undergo female health screening, transmasculine individuals are at higher risk for delayed diagnosis and worse outcomes than their cisgender women. Patients are more likely to adhere to their cancer surveillance plan if they are involved in the planning, thus avoiding delayed diagnosis.

Lastly, Aim 1 will also allow us to understand how the biology of transmasculine BC (exposed to TT) may be different from that of cisgender women. Transmasculine individuals are currently excluded from BC clinical trials because of their TT use. The completion of Aim 1 will accelerate progress toward closing the knowledge gaps regarding to what extent TT affects BC biology and risk, paving the way for transgender patients to participate in research and clinical trials, an essential aspect of addressing discrimination, and reduce their healthcare disparities.

A2. Background, rationale, and significance of Aim 2.

There are no treatment guidelines for transmasculine BC patients. Oncologists, like Dr Wulf, face unique challenges when managing the BC treatment for transmasculine patients [15]. It is unclear whether the patient can continue TT while being treated for BC as no one knows how TT affects the efficacy of the BC drugs. When postmenopausal cisgender women are diagnosed with BC, the standard of care is to discontinue postmenopausal hormone replacement therapy. With no study comparing the risks and benefits of continuing TT during cancer treatment, most clinicians have erred on the side of caution by recommending transmasculine patients to cease TT during treatment [48]. The discontinuation of TT is undesirable as it greatly affects the transmasculine patients' emotional wellbeing and compounds their cancer-induced emotional distress. Given this conflict, research about whether TT affects the efficacies of BC treatment is critical to support these difficult clinical decisions. A large study with over 200,000 female and >2000 male BC cases reported that even after adjusting for age, stage, and tumor biology, cisgender men had a 43% greater chance of death from BC than cisgender women [49], suggesting that cisgender male BC is more aggressive. Such aggressive disease may potentially occur in transmasculine individuals receiving TT. If we fail to understand how TT interacts with breast tumors and treatment, we will lack the knowledge to properly treat transmasculine BC patients, leading to poorer BC prognosis in this population. Aim 2 will investigate whether the continuation of TT during BC treatment affects a successful outcome. The completion of Aim 2 will accelerate progress toward developing a transgender-specific clinical plan to manage and treat transmasculine BC.

Aim 2 rationale. We will use the same mouse models to investigate whether continuing TT affects the treatment outcomes when using alpelisib (PIK3-inhibitor), olaparib (Poly(ADP-ribose) Polymerase (PARP)-inhibitor), or paclitaxel (microtubule stabilizer, non-nucleoside-based chemotherapy). In the design of this aim, we consider that the effect of TT on tumor initiation may be different from the effect of TT on an established cancer that requires treatment, and that the effects of TT on ER+ BC may be different from *BRCA*-related ER- BC. We chose to use alpelisib and olaparib as they are treatments with known efficacies in our mouse models (see preliminary data D and E in section C2). Alpelisib is a FDA-approved second-line treatment for *PIK3CA*-mutant BC [50]. Clinical trials are underway to move PI3K inhibitors into first-line therapy (NCT01872260). We will also investigate if TT affects combination therapy of 1) alpelisib with fulvestrant (selective ER degrader) which is the current standard of care [50,51]; and 2) alpelisib and letrozole (aromatase inhibitor) to determine if blocking the aromatization of testosterone enhances the efficacy of alpelisib whereby circulating estradiol is reduced. Cell lines generated from our tumors respond to fulvestrant *in vitro* (see preliminary data E). Olaparib is a FDA-approved first-line adjuvant treatment for *BRCA1/2*-related metastatic BC [52–54]. Paclitaxel is chosen to evaluate the effect of TT on a chemotherapy whose mechanism of action is independent of the disease causing mutations in our mouse model. We also designed our studies using immune-competent mice as sex hormones can have direct impact on the cells in the tumor microenvironment, including the innate immune system [55].

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Aim 2 significance and contribution. The discontinuation of TT during BC treatment affects the transmasculine patients' emotional wellbeing and body image. Data on how TT affects BC prognosis will enable clinicians to have informed discussions with their patients about TT use after BC diagnosis and during BC treatment. This is critical to support the management and successfully treat BC in of transmasculine patients, and reduce disparities. Our preclinical findings combined with molecular investigations (see section A3) will support the development of better strategies to treat BC in transfeminine individuals and cisgender men and women, hence reducing BC mortality.

A3. We will investigate the mechanism of TT on AR mediated transcriptional programs in breast development and carcinogenesis, and response to BC treatment.

Testosterone exerts most of its effects via its nuclear receptor, AR. Despite molecular advances, including the development of AR modulators to treat BC, androgen signaling in BC remains incompletely understood. A recent review by Dai and Ellisen talked about how preclinical studies have yielded conflicting evidence about whether AR serves as a tumor suppressor or an oncogene in BC [56]. Raths *et al*. recently published a single-cell atlas of TT-exposed normal breast tissues as a resource to study androgen signaling in the human breast [57]. Therefore, in addition to addressing the clinical needs regarding BC in the transmasculine population, this proposal will also conduct mechanistic studies to investigate the effect of testosterone on breast development, carcinogenesis, and treatment response. As mentioned earlier, mouse models are highly suitable for this work because the hormone regulation of murine breast development is similar to humans. The molecular insights gained from completing this proposal will not only impact our understanding of transmasculine BC, it will also shed light on the constituents of the AR signaling pathway that may be targeted as prevention or treatment for cisgender male and female BC.

AR is expressed on normal breast tissue [58], breast cancer cells [59], and the cells of the tumor microenvironment [57,60]. Approximately 90% of ER+ BC express AR, while only 25% of ER- BC are AR+ [61–63]. Dr. Jia [co-I] was among the first to investigate the role of AR in ER+ BC [64]. In general, the testosterone-AR complex regulates downstream mRNA expression in BC cells that affect cellular proliferation [64–67], promote metastasis [67,68], and cause resistance to therapies [69,70]. Dr. Jia and others also showed that the binding of testosterone to AR alters microRNAs (miRNAs) in prostate cancer [71–73] and BC [70,74–78]. Studies investigating testosterone regulating miRNAs in normal mammary glands has never been done before. MiRNAs are small non-coding RNAs, a class of master regulatory molecules that control the expression of hundreds of target mRNA transcripts leading to major shifts in epithelial cell architecture and function [79–82]. MiRNAs either have their own promoter elements or are embedded in their host genes, resulting in them being co-regulated or regulated in the same manner as their host genes [83]. Drs. Slack [co-I] and others reported that miRNAs can modulate oncogenes [84,85], function as tumor suppressors [86,87], and are associated with cancer treatments outcomes [88–90]. As such, studying mRNA and miRNAs in conjunction with AR signaling is important in this proposal to obtain a comprehensive understanding and fill knowledge gaps of how TT regulates mammary gland development, affects carcinogenesis, and response to BC treatment.

A4. Our proposal will gain fundamental new insights about BC risk, improve clinical management of BC in transmasculine patients, and potentially discover novel therapies to treat BC in transgender and cisgender people.

Transgender people are the fastest growing group in the LGBTQ community. We need to start understanding the cancer risk attributable to TT now because the prevalence of individuals receiving TT will rapidly increase in the coming decades. Approximately 23% of transgender individuals in the US are between 13 and 24 years old [91], and this young population will increase the demand for specialized cancer care as they age. We need to understand the effect of TT on cancer treatment so that clinicians are ready to manage TT during BC treatment in transmasculine patients.

The NIH listed transgender health as an area of research priority (NOT-MD-19-001). Our proposal is responsive to PAR-21-322 Basic Research in Cancer Health Disparities. National organizations including the American Society of Clinical Oncology released statements committed to prioritizing transgender health research, calling for more funding, and reducing transgender health disparities [92]. We will utilize BC mouse models to understand the effect of TT on cancer risks and cancer treatment. In addition, this proposal will investigate the effect of TT on AR mediated transcriptional programs (mRNA and miRNA expression) on breast development, carcinogenesis, and BC treatment. MiRNA-based therapeutics—a novel class of drugs—are rapidly evolving. Therefore, investigating how the testosterone-AR complex modulate miRNAs and their downstream genes is important for understanding transmasculine BC as well as open new avenues for the prevention or treatment of cisgender BC.

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B. INNOVATION

The current understanding about the effects of TT on BC risk and treatment is minimal. *This work represents a substantive departure from the status quo by: 1) investigating BC risk in the unique transmasculine population where no such study has ever been done before; 2) using transgenic mouse models to study transmasculine health outcomes; 3) understanding the effect of TT on ER+ and ER- BC development and treatment; and 4) gain fundamental insights into testosterone-AR signaling regulation of mRNAs and miRNAs in mammary glands and tumors exposed to TT.*

The new horizons achievable after the completion of this proposal include: 1) using similar mouse models to understand the impact of gender-affirming hormone therapy on the risk and treatment outcomes of other hormonally-driven cancers such as prostate and ovarian; 2) advancing evidence-based transgender care; 3) establishing transgender oncology as a new medical subspecialty; and 4) developing miRNA-based therapeutics for BC treatment.

Our proposal uses preclinical studies to pave the way for future clinical studies that will address the unmet clinical needs of BC risk and treatment concerns of the medically underserved transmasculine community. This work will not only have implications for transmasculine individuals, but will also serve as a model to develop better strategies to treat BC in transfeminine individuals, cisgender men, and cisgender women. This work will increase our understanding of sex hormones and cancer biology, as well as demonstrate the potential of developing miRNA-based therapeutics for BC. This proposal will contribute to our long-term goals of reducing cancer disparities for the transgender community.

C. APPROACH

C1. Aim 1: Determine the effect of TT on ER+ and ER- BC development.

Preliminary data A. The Wulf lab established MMTV-Cre Pik3ca$^{fl/wt}$ mice that develop ER+/AR+ tumors and K14-Cre Brca1$^{f/f}$p53$^{f/f}$ mice that develop ER-/AR+ tumors [36–40,42] (Fig 2). The mice have been back-bred onto a pure FVB/N background and are currently operational. These mice develop BC with minimum 50% tumor incidence by 7 months and >80% penetrance at 18 months [36,38].

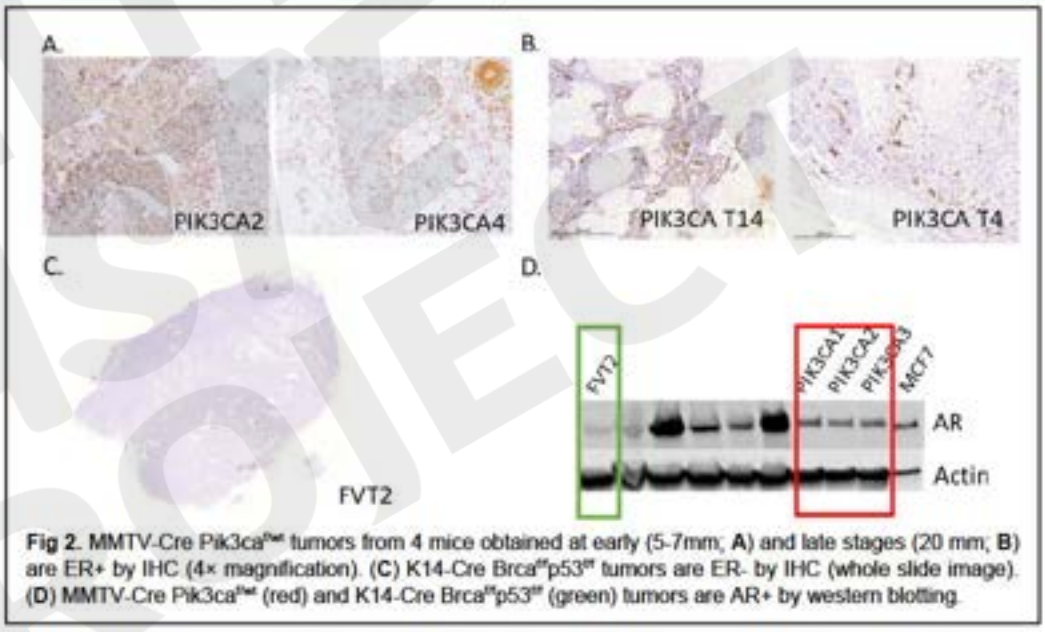

Fig 2. MMTV-Cre Pik3ca$^{fl/wt}$ tumors from 4 mice obtained at early (5-7mm; **A**) and late stages (20 mm; **B**) are ER+ by IHC (4× magnification). (**C**) K14-Cre Brca$^{f/f}$p53$^{f/f}$ tumors are ER- by IHC (whole slide image). (**D**) MMTV-Cre Pik3ca$^{fl/wt}$ (red) and K14-Cre Brca$^{f/f}$p53$^{f/f}$ (green) tumors are AR+ by western blotting.

PIK3CA^{mut} is the most common activating mutation in human sporadic BC (25-40%) [47]. Our mouse model contains a knock-in dormant *Pik3ca^{H1047R}* copy conditionally activated in mouse mammary glands upon Cre-mediated recombination [93–95]. Tumors from these mice maintain ER expression throughout progression (Fig 2A and 2B). We chose the MMTV-Cre line because 1) MMTV-driven Cre-mediated recombination is specific for mammary glands; 2) MMTV-Cre recombinase activity in the murine mammary gland is detected as early as age 3 weeks; and 3) the Cre-lox activation is permanent [94,95]. Since Cre-recombinase-mediated insertion of *Pik3ca^{H1047R}* is complete at the start of our experiments at age 6 weeks, any potential modulation of MMTV activity by subsequent experimental procedures such as oophorectomy or TT will not affect the study's outcome.

The K14-Cre Brca1$^{f/f}$p53$^{f/f}$ mouse model is driven by loss of *Brca1* induced by tissue-specific knock-out via the K14-activated Cre-recombinase which models human germline *BRCA1* mutation [36–38]; 70-80% of these murine tumors are ER- and these tumors are frequently used in triple negative breast cancer studies [96]. Germline *BRCA1^{mut}* is an established hereditary BC risk factor whereby ≈70% of female *BRCA1/2^{mut}* carriers will develop BC by age 80 [29]. Therefore, not only will this model allow us to understand the effect of TT on ER- BC development, it will also will inform the extent to which TT affects the penetrance of the *BRCA1^{mut}* gene leading to BC development.

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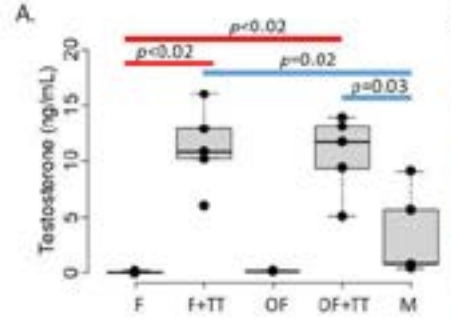
Preliminary data B. We completed the first round of pilot study investigating the effect of TT on ER+ BC incidence using MMTV-Cre Pik3ca$^{f/wt}$ mice. This first round of pilot consisted of 25 healthy mice: female mice (n=4), oophorectomized female mice (n=6), female mice receiving weekly 400 µg s.c. of testosterone cypionate starting at 8 weeks of age (n=5) [97,98], oophorectomized female mice receiving testosterone cypionate (n=5), and male mice (n=5). Normal testosterone levels for male mice are 3 to 11 ng/mL and <0.5 ng/mL for female mice [98,99]. Our TT regimen successfully raises the testosterone levels of female mice to >3 ng/mL, comparable to male mice (Fig 3A). TT-treated mice developed hypertrophic nipples after >8 weeks of TT (Fig 3B), displaying phenotypic changes associated with TT. Upon histological evaluation, those nipples were highly keratinized (Fig 3C). Fig 3D displays the number of mice that reached study endpoint. All female controls were euthanized at ~35 weeks due to largest tumor reaching 10 mm. Remaining mice were euthanized at study endpoint of 48 weeks.



D.

Study arm	Mice reached endpoint, n	Mice bearing tumors	Tumors/total mammary glands, n
F (n=4)	4	4/4	17/40
F+TT (n=6)	3	1/3	1/30
O (n=5)	4	3/4	5/40
O+TT (n=5)	4	2/4	6/40
M (n=5)	2	1/2	4/20

Fig 3. (**A**) Serum testosterone levels in female (F), oophorectomized female (OF), and male (M) mice after 4 weeks of weekly TT or vehicle measured using an ELISA assay. TT-treated mice had significantly higher testosterone levels than controls. (**B**) Examples of mice who received 12 weeks of TT with hypertrophic nipples compared to a female control. (**C**) Example of highly keratinized nipples from a female mouse treated with TT for 35 weeks. (**D**) Table summarizing tumor incidences for the first pilot. Female controls were euthanized 13 weeks earlier than the rest of the mice.

Mice have 10 mammary glands and each tumor is considered an independent event. Therefore, Fig 3D also shows the total number of mammary glands—i.e., potential carcinogenic events—and the number of tumors detected at necropsy. Tumor incidences in females receiving TT and oophorectomized females receiving TT were significantly lower than female controls (both p<0.001). There was no difference in tumor incidences between oophorectomized females receiving TT and oophorectomized controls (p=0.63). This pilot showed that TT-treated mice develop tumors later than controls, and that oophorectomy increases the lag time to tumor development. Based on this pilot, we hypothesize that TT increases the lag time to ER+ tumor development and does not increase ER+ BC incidence compared to female controls. Only 2 out of 5 males reached study endpoint of 48 weeks, with one male developing 4 tumors. Due to small sample size, we did not perform comparison analysis with males. In our experience, tumor development in the male mouse can happen in this genotype but remains rare (<2%). Comparing tumor incidences of TT-treated mice with males is of clinical significance. The study by de Blok *et al.* [17] indicate that transmasculine BC risk remains closer to cisgender females than cisgender males. We hypothesize that transmasculine BC risk is higher than that of cisgender men (0.12%) [15]. Therefore, even though transmasculine individuals identify as men or non-binary, they will require BC surveillance.

The effect of TT on *BRCA*-related ER- BC development remains to be determined. Since *BRCA*-related ER- BC is also likely driven by sex hormones [30–32], we similarly hypothesize that TT increases the lag time to ER- tumor development and does not increase ER- BC incidence compared to female controls. We also hypothesize that the increased lag time to breast tumor development in TT-treated female mice is similar for both mouse models compared to their respective female controls. We need larger sample sizes to obtain a definitive conclusion regarding the effect of TT on BC risk when compared to both female and male controls. Since February 2023, we embarked on a second pilot by repeating the first pilot with the same 5 arms of 5 mice each. Our second pilot will complete by December 2023. This R01 will allow us to further expand this work using larger sample sizes to clarify the effect of TT on BC development.

Preliminary data C. Dr. Jia has expertise in studying AR signaling in prostate cancer using chromatin immunoprecipitation-sequencing (ChIP-seq), RNAseq, and miRNA profiling [71,100–102]. Prostate cancer growth and progression depends on androgen-induced AR signaling. Although treatment of advanced prostate cancer via surgical castration leads to initial response and remission, resistance eventually develops, demonstrating that

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AR activity remains critical for prostate tumor growth even in androgen-deprived conditions. Using ChIP-seq and RNA-seq, Dr Jia showed that androgen-independent AR binding events lead to reprogramming of AR-mediated gene expression and drive castration-resistant prostate cancer growth [101]. In another study, miR-193a-3p was identified as a key player in metastatic prostate cancer [71]. ChIP-seq analysis confirmed that miR-193a-3p is an AR target gene and functional validation demonstrated that miR-193a-3p targets AJUBA and promotes prostate cancer cell migration [71]. The same profiling technologies demonstrated that PARP-2 is a key component in AR-mediated transcription through interacting with the pioneer factor FOXA1 in prostate tumorigenesis [102].

Dr. Heng piloted H3K27Ac profiling via FiTSeq [103] using 8 transmasculine breast tissues. The low cellularity of normal breast lobules compared to tumors resulted in only 4 out of 8 patients with sufficient DNA yield for FiTSeq. FiTSeq was successfully carried out for 3 out of 4 patients (Fig 4). For future work, we will triple the amount of normal human breast tissue to achieve sufficient amounts for RNASeq and FiTSeq. Given Dr. Jia's technical expertise and that Dr. Heng had successfully conducted pilot FiT-Seq on transmasculine breast tissues, we are confident that ChIP-seq on mouse breast tissue will be feasible.

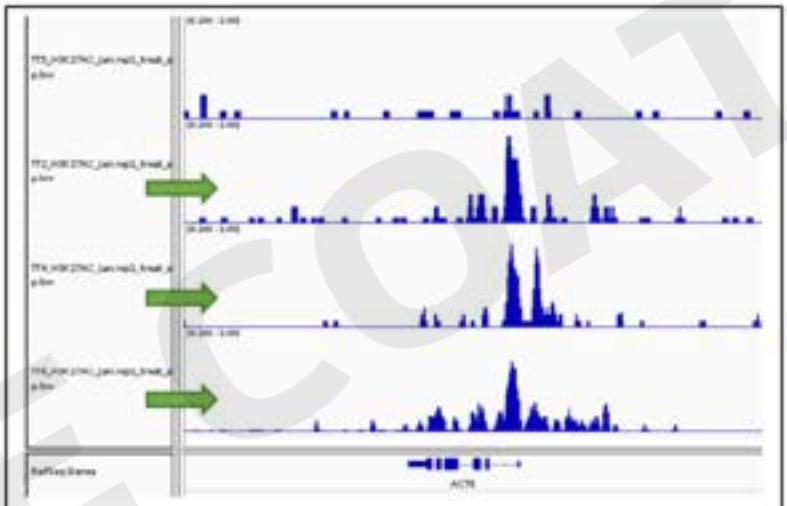

Fig 4. Adequate amounts of DNA were extracted from 4 out of 8 transmasculine breast samples. FiTSeq of H3K27ac was successful for the bottom 3 samples (arrows).

Research Design. ***Mouse population and sample size.*** The study design will be identical for both MMTV-Cre Pik3ca$^{fl/wt}$ and K14-Cre Brca1$^{f/f}$p53$^{f/f}$ mouse models. For each mouse model, we will have 5 arms of 50 mice each: 1) female controls, 2) female mice receiving TT, 3) oophorectomized female controls, 4) oophorectomized female mice receiving TT, and 5) male controls. Aim 1 will have 250 mice per model; a total of 500 mice (see power calculations below).

Surgery, testosterone administration, and blood collection. Mice reach puberty at 4-6 weeks old, hence our design mimics post-puberty TT. At 7 weeks old, healthy female mice will undergo oophorectomy or sham. At 8 weeks, mice will begin weekly 400 µg s.c. of testosterone cypionate [97,98] or sesame oil vehicle in a total volume of 20 uL and continue indefinitely. Fig 3A shows that our TT regimen successfully raises the testosterone levels of female mice to >3 ng/mL, comparable to male mice.

Aim 1.1. Tumor incidence at a predefined time point, expected outcomes, statistics, and power calculation. Thirty of 50 mice per arm will be randomly selected for euthanasia at 10 months. Euthanasia at a prespecified endpoint allows for the comparison of the number of tumors between the different arms after a defined period of TT. Mammary glands and tumors from these 10-month-old mice will be harvested—a subset will be frozen for molecular work, the others will be fixed in formalin for histology-type assays. Based on our preliminary data B, MMTVCre Pik3ca$^{f/f}$ female controls developed an average of 4 tumors/mice while females receiving TT will develop an average of 1 tumor/mice. Therefore, we hypothesize that at 10 months, the tumor incidence is lower in both *Pik3ca^{mut}* and *Brca1^{mut}* female mice receiving TT compared to female controls. We will consider a 50% difference in the number of tumors between the study arms biologically meaningful. We power this study for the primary comparison of interest between females receiving TT and female controls. A size of 30 mice per arm will give us 80% power (two sided α=0.05) to detect an effect size of 0.7 (Cohen's d) using two-sample t-test (pwr.t.test, pwr package, R). Cohen's d of 0.7 corresponds to comparing 120 tumors from 30 female controls developing an average of 4 tumors versus 15 tumors from 30 females taking TT developing an average of 0.5 tumors, and with the common standard deviation (s.d) of 2.5 in each group. In practice, we will analyze the data using ANOVA model with post-hoc mean comparisons corrected for multiple testing, if we reject the null hypothesis of equal means in the groups.

Aim 1.1 Tumor-free survival, expected outcomes, data analysis, and power calculation. The remaining 20 mice per arm will be monitored for tumor development. Should tumors arise, they will be measured with calipers 3x a week. Female controls of both mouse models achieve a minimum of 50% tumor incidence by 7 months. The endpoint for these mice is euthanasia when a tumor reaches 10 mm, or, if multiple tumors arise, when the

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combined tumor burden reaches 20 mm. Mice that have not reached endpoint by that time will be euthanized at 18 months and censored. All mice will be weighted and inspected by a complete necropsy at euthanasia. Endpoint tumors will be harvested—largest tumor will be spilt to be frozen and fixed in formalin, all other tumors will be fixed in formalin. Metastatic disease, if any, will be recorded. Survival will be measured in days. From experience, we expect female controls to achieve tumor incidence of >80% and male controls to have a BC incidence of <1% by 18 months [36,38]. Male BC in our *Brca1^{mut}* mouse colony is extremely rare (1 case since 2009). Male *Pik3ca^{mut}* BC frequency is higher (<2%) than in male *Brca1^{mut}* mice, but still remains much less frequent than their female counterparts.

We hypothesize that TT increases the lag time to tumor development compared to female controls. We also hypothesize that increased lag time to breast tumor development in TT-treated female mice is similar for both mouse models. Based on preliminary data B, we expect the median time to euthanasia for MMTVCre *Pik3ca$^{f/wt}$* females receiving TT to be 12 months compared with 9 months for female controls. Hence, we will consider it biologically meaningful if there is at least 30% difference in median tumor-free survival between females receiving TT versus female controls. We will use the log-rank test and Kaplan-Meier curves to compare tumor-free survival between the study arms.

Histological evaluation. Mammary glands and tumors will be embedded in paraffin to create tissue blocks for histology and will be reviewed by Dr. Baker (co-I) for tumor morphology. We will perform immunohistochemistry (IHC) for ER, progesterone receptor (PR), AR, and Ki-67, and p-AKT to ascertain sex hormone receptor status, proliferation, and PI3K pathway activation. Given the known effects of sex hormones on tumor immunology [55], we will perform multiplex immunofluorescence staining using Opal™ assay (Akoya Biosciences) to assess the tumor microenvironment including cancer-associated fibroblasts (e.g. vimentin, platelet-derived growth factor receptor A, and alpha smooth muscle actin), tumor-associated macrophages (e.g F4/80) [43], and CD8+ infiltrates. This will allow us to capture potential tumor microenvironment modulatory effects of TT in the breast. The slides will be digitized and quantitated as a 0–100% continuous estimate of expression using QuPath or inForm® software [104]. We have experience with quantitative image analysis [62,63,104] and the Opal™ assay [9,43]. Marker expression comparisons between the 5 study arms will be performed using ANOVA. With a minimum of 12 samples per group, we will have 86% power (α=0.05) to detect an effect size of 0.5 (pwr.anova.test). If a marker is statistically significant at $p<0.05$, we will perform post hoc testing between the groups and correct for multiple hypothesis testing using Tukey's HSD method.

Aim 1.2. Molecular assays to investigate effect of TT. For each mouse model, we will profile mRNA using RNASeq and screen for 352 miRNAs using Mirxes ID3EAL™ miRNA Cancer Panel on 3 mammary glands and 3 endpoint tumors from female controls and females receiving TT. We focus on the comparisons of those 2 study arms as the effect of TT in the breast is our main clinical interest. If tumor incidences in the oophorectomized mice arms (controls and TT-treated) show significant differences, we will also perform mRNA and miRNA profiling on those samples.

For RNASeq, raw data will processed by the Molecular Biology Core Facilities at Dana-Farber Cancer Institute using Visualization Pipeline for RNAseq (VIPER) [105] then normalized using *voom* [106] prior to differential expression analysis using limma [107]. Continuous gene expression values will be treated as dependent variables, and TT as binary factor in a full factorial model. Benjamini-Hocheberg FDR method will be used to correct for multiple testing. The ID3EAL™ miRNA Cancer Panel is a highly sensitive qPCR-based assay that screens for 352 miRNAs frequently associated with oncogenes, tumor suppressor genes, and pathways involved in various types of cancers [108,109]. We decided to use the ID3EAL™ technology because the ID3EAL™ panel is superior to smallRNASeq in detecting low abundant miRNAs [110], and that qPCR remains the gold standard for miRNA detection. ID3EAL™ panel assays will be conducted at the Detection Unit, Precision RNA Medicine Core Facility, BIDMC, whereby Dr Heng is Director of the Unit, and Dr Slack is the co-Director of the Core. Dr. Heng has statistical and computational biology expertise to lead the analyses for RNASeq and miRNA data [47,111–113].

To determine which genes are directly regulated by AR, we will perform AR ChIP-Seq to map global AR binding sites in normal and tumor tissues. We will use the ChIP-seq workflow previously established by the Jia Lab [71,100–102]. TT-altered mRNA and miRNAs within 50Kb of AR binding sites are considered as direct AR targeted genes. We will perform pathways and gene set enrichment analysis to determine the role of TT in BC development. In the MMTV-Cre Pik3ca$^{f/wt}$ ER+ model, we will additionally perform ER ChIP-Seq to examine global ER binding, to determine what extent TT impacts ER-mediated transcription or AR activation alters the genomic distribution of ER, which may mechanistically explain how TT lengthens the lag time to ER+ tumor development. In the ER-K14-Cre Brca1$^{f/f}$p53$^{f/f}$ model, we will investigate whether AR activates Wnt and HER2 pathways through

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transcriptional induction of Wnt7b and HER3 as previously described by others [67] and Dr Jia [114]. Dr. Jia will lead the AR signaling and ChIP-Seq part of the work.

Functional validation. Results will be functionally validated using our already generated Pik3ca$^{f/wt}$ and Brca$^{f/f}$p53$^{f/f}$ murine tumor cell lines (Fig 2D) and standard biochemical approaches. We will use a hypothetical example to briefly describe how we will perform functional validation. If data show that females receiving TT have reduced ER+ cancer incidence, and that miR-326 is upregulated in tumors from females receiving TT compared to female controls, we will first use cell lines to confirm that miR-326 expression is increased in the presence of testosterone. Next, to understand the molecular mechanism of miR-326 as a tumor suppressor, we will identify a candidate downstream target gene (e.g. *AKT2*) for further analysis. We will screen the mRNA and protein expression of *AKT2* using mimics/silencers of miR-326 as well as +/- testosterone. We will confirm the inhibitory role of miR-326 on breast cancer cell proliferation using cell cycle analysis, colony formation assay, and cell viability (MTT) assay.

Potential problems and alternative strategies. Should our findings demonstrate that testosterone is protective against BC whereby TT lowers BC incidences compared to female controls, that finding will be important for the transgender and medical community in two ways: 1) TT does not increase BC risk in the general population, and 2) TT does not increase BC risk in *Brca^{mut}* carriers.

If we discover that tumor incidences in oophorectomized female mice receiving TT are higher than oophorectomized female controls, we will investigate whether the aromatization of exogenous testosterone in nongonadal tissues is a significant mechanism by which TT may drive breast tumorigenesis. In postmenopausal cisgender women, cisgender men, and transmasculine individuals who had oophorectomies, estradiol is produced in nongonadal tissues via the aromatization of testosterone [115]. This aromatization pathway is clinically targeted by aromatase inhibitors, such as letrozole, to treat and prevent BC in postmenopausal women [116,117]. In transmasculine individuals who had oophorectomies but continue to receive TT, the conversion of excess exogenous testosterone to estradiol may be a significant factor in modulating their BC risk. We will investigate the effect of letrozole in reducing BC incidence by comparing tumor incidence in TT-treated oophorectomized female mice with or without letrozole. There will be 4 arms of mice per model (n=30 mice/arm): 1) oophorectomized female mice receiving TT treated with letrozole; 2) oophorectomized females treated with letrozole; 3) oophorectomized females receiving TT treated with vehicle; and 4) oophorectomized females treated with vehicle. We do not need to include non-oophorectomized mice as aromatase inhibitors such as letrozole are only clinically indicated to treat or prevent BC in postmenopausal women. The study design will be similar to Aim 1.1, whereby mice will be randomized to be concurrently given daily oral vehicle (10% N-methyl-pyrollidone (NMP)/90% polyethylene glycol (PEG300)) or oral letrozole (0.015 mg; 150 µL of 1 mg/kg letrozole in 10% NMP/90% PEG300) [118] and continue indefinitely.

Based on observations in humans [17], we expect females receiving TT (with or without oophorectomy) to have higher BC incidences compared to male mice. That will be a clinically important finding, and reiterate the importance of managing cancer risks of transmasculine patients based on their biological sex, and not their gender expression. In this case, we will investigate if AR blockade with bicalutamide reverses the testosterone effect. It is possible that TT may induce other malignancies in these mice. We will monitor and assess the biological significance of those different pathologies. Should a high incidence of competing non-breast malignancies make the study of *BRCA*-related BC impossible, we will use the MMTV-Cre Brca1$^{f/f}$p53$^{+/-}$ strain, in which the MMTV promoter ensures selective removal of *Brca1* from more developed precursor cells [32]. That strain is cryopreserved in the Wulf laboratory.

C2. Aim 2: Determine the effect of TT on treatment outcomes for ER+ and ER- BC.

Preliminary data D. In a separately funded study, we investigated the effect of gender-affirming estrogen therapy on *BRCA1*-related ER- BC treatment outcome**.** We implanted viable fragments of female K14-Cre Brca1$^{f/f}$p53$^{f/f}$ murine tumors into healthy recipient mice (*n*=184): female controls, male controls, male castrated controls, males receiving estrogen, and castrated males receiving estrogen (Fig 5A). When the tumors reached 5 mm, mice receiving estrogen were first randomized to stop or continue estrogen. Then, mice in all arms were randomized to receive olaparib treatement or vehicle (Fig 5A). Mice were euthanized when their tumor reached 20 mm. All mice that did not receive olaparib had a median survival of 14 days, validating olaparib's efficacy and the stability of our tumor model. Only olaparib treated arms are reported hereafter. Female control mice receiving olaparib have the longest median tumor-specific survival times (*n*=17; 103 days). Male controls (*n*=16; 75 days) had significantly shorter survival than female controls (*p*=0.031). Survival times for males that stopped estrogen or males that continued estrogen were significantly shorter than females (all *p*<0.01; Fig 5B). Males that stopped

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estrogen also had significantly shorter survival than male controls (p=0.013; Fig 5B). Castrated males that stopped estrogen were also significantly shorter than females (p<0.01) and male controls (p=0.025; Fig 5C). Survival for male castrated mice that continued estrogen was also shorter than female and male controls, but did not achieve significance (p=0.19 and p=0.918; Fig 5C). There was no tumor-specific survival difference between male mice that stopped estradiol versus continued estradiol during olaparib treatment (p>0.05).

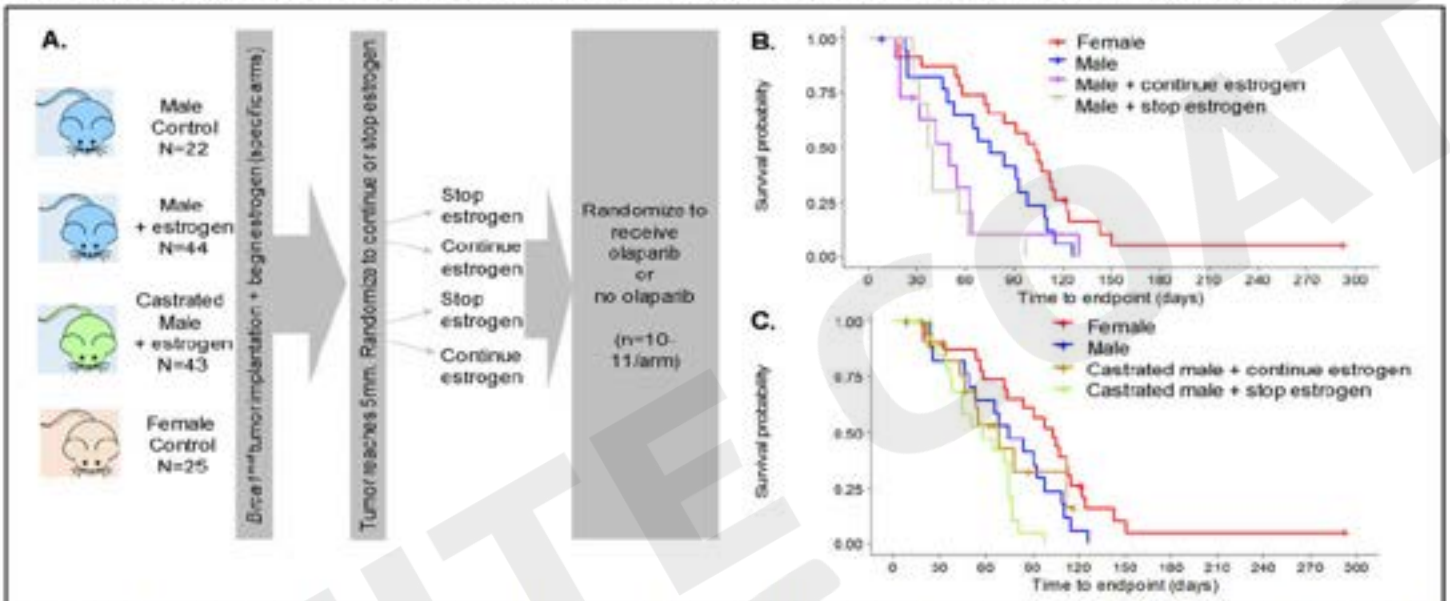

Fig 5. (**A**) Study design using cross-sex mouse model to understand the effect of continuing estrogen therapy during BC treatment with olaparib in transfeminine individuals. (**B**) Kaplan-Meier curves showing that the tumor-specific survival for male mice who stopped (n=10; 39 days) or continued (n=10; 50 days) their estrogen therapy during olaparib treatment was significantly shorter than female mice (n=17; 103 days; p<0.01). Males that stopped estradiol also had significantly shorter survival compared to male controls (n=16; 75 days; p=0.013). (**C**) Castrated male mice that stopped estrogen therapy during olaparib treatment (n=19; 58 days) had worse survival than females (p<0.01) and male controls (p=0.025). Castrated male mice that continued estrogen therapy also had shorter survival (n=10; 68 days) than females and males, but did not reach significance (p=0.19 and p=0.918).

In summary, when the same tumor was treated with olaparib, females had better outcomes then males, regardless of castration status or estrogen regimen during olaparib treatment. This indicates that sex at birth affects the olaparib treatment outcome for *BRCA1*-related BC. The data also indicate that despite estradiol supplementation leading to worse outcomes, there is no need for transfeminine individuals who are already taking estradiol to cease estradiol during olaparib treatment. Molecular analysis of the tumors is underway to understand the hormonal effects on the tumors and interaction with olaparib treatment. This independent study demonstrated the feasibility of implanting a female murine *Brca1*^{mut} breast tumor into syngeneic male and female recipients, and validated our pre-clinical approach to study the effect of cross-sex hormones on BC treatment outcomes. Our team has the expertise and ability to conduct Aim 2 studies.

Preliminary data E. Our MMTV-Cre Pik3ca^{Wt} tumor is sensitive to alpelisib (Fig 6A and B) and responsive to fulvestrant (Fig 6B). We also have published *in vivo* preclinical studies demonstrating our experience with administering fulvestrant [119] and paclitaxel [120].

Research Design. ***Mouse population and sample size.*** There will be 6 treatment studies: 1) alpelisib, 2) alpelisib plus letrozole, 3) alpelisib plus fulvestrant (for *Pik3ca*^{mut} tumors), 4) olaparib (for *Brca1*^{mut} tumors), 5) paclitaxel (for both tumor models). We will require a total of 840 FVB/N mice for this aim (n=140 per tumor type x 6 treatments). We have banked tumors ready for *in vivo* implantation [36-42] into healthy syngeneic FVB/N mice recipients. Our re-implantation success rate is >95% [32].

Aim 2.1. Study design, procedures, expected outcomes, and power calculation. For each treatment study, there will be 5 arms of mice: female

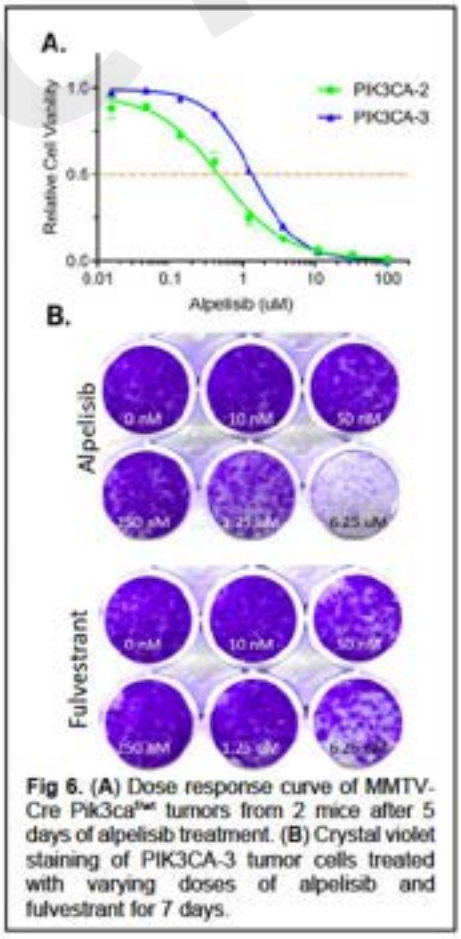

Fig 6. (**A**) Dose response curve of MMTV-Cre Pik3ca^{Wt} tumors from 2 mice after 5 days of alpelisib treatment. (**B**) Crystal violet staining of PIK3CA-3 tumor cells treated with varying doses of alpelisib and fulvestrant for 7 days.

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controls (n=20), females receiving TT (n=40), oophorectomized female controls (n=20), oophorectomized female controls receiving TT (n=40), and male controls (n=20). Female mice in the oophorectomy arm will have their ovaries removed at 7 weeks. We will implant banked female murine *Pik3ca*^{mut} or *Brca1*^{mut} tumor fragment into 8 weeks old mice (Fig 7). If feasible, we will implant tumors exposed to TT collected during Aim 1 or from preliminary data B (*Pik3ca*^{mut} tumors only). Arms slated to receive TT will begin weekly 400 µg s.c. testosterone cypionate [97,98].

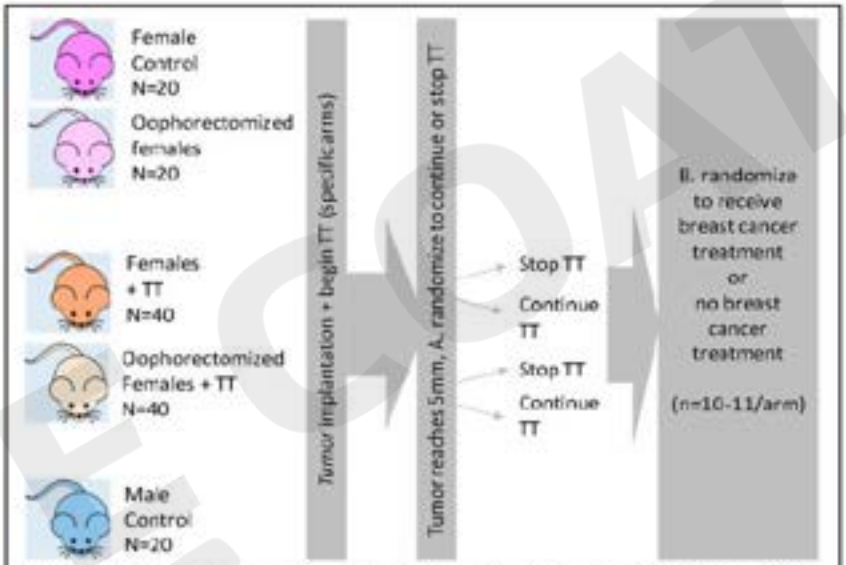

Fig 7. Study design for Aim 2 to understand the effect of continuing TT during BC treatment.

Upon tumor growth to 5 mm, mice on TT will first be randomized to either continue or discontinue TT during drug treatment. Mice will then be randomized to either receive BC treatment or vehicle (Fig 7). Daily alpelisib (30 mg/kg via oral gavage using 0.5% methylcellulose/0.2% Tween® 80 as vehicle) [39], letrozole (1 mg/kg via oral gavage using 10% NMP/90% PEG300 as vehicle) [118], and olaparib (50 mg/kg via intraperitoneal injection using PBS as vehicle) [39] are administered until either complete remission is achieved or until tumors meet requirements for euthanasia. Fulvestrant is administered at 200 mg/kg twice per week via s.c. using 2% DMSO/30% PEG300/2% Tween® 80 as vehicle [119]. Paclitaxel is administered 10mg/kg weekly via i.p using 10% DMSO, 40% PEG300, 5% Tween 80, 45% saline [120]. Tumor growth and time to 20 mm will be recorded. Endpoint tumors are harvested. With each arm size of 20 mice, we can determine a difference in median treatment-related survival of 30 days with α-error of 0.05 and β-error of 0.2. We will use the log rank test and Kaplan-Meier curves to compare treatment survival between the study arms.

We do not expect TT to accelerate tumor growth. We expect no difference in median treatment-survival between 1) female mice that continued TT during BC treatment versus female controls; and 2) female mice that continued TT versus female mice that stopped TT during BC treatment. Preliminary data D demonstrated that male mice have poorer olaparib treatment outcomes than females (Fig 5B). We expect female mice, irrespective of oophorectomy status and/or received TT, to have better survival outcomes compared to male mice.

Aim 2.2. 10-day treatment study. If TT affects any of the treatment outcomes, we will set up 10-day treatment studies of those treatments and study arms of interest. We expect to focus on 2 arms (n=5 mice/arm) that are of clinical interest: tumors from female mice that continued TT and treated for BC and female controls treated for BC. We will implant tumors, let the tumors grow to 5mm, treat for 10 days, and harvest the tumors.

Tumor-intrinsic and tumor-extrinsic alterations attributable to TT. The 10-day treated tumors will be reviewed by Dr. Baker, and IHC will be conducted for ER, PR, AR, and p-AKT (PI3K pathway activation). Next, we will determine whether the effect of TT is via tumor-intrinsic or tumor-extrinsic factors. For tumor-intrinsic parameters, we will evaluate tumor morphology, grade, proliferative index (Ki67 IHC), and apoptotic index (caspase 3 (CASP3) by western blotting). For tumor-extrinsic parameters, we will assess the tumor microenvironment using the Opal™ assay to investigate if this is related to anti-tumor immunity, including CD8+ infiltration, or pro-tumorigenic with increased presence of tumor-associated macrophages.

Molecular work and functional validation. Using the 10-day treated tumors, we will similarly perform ChiP-Seq, RNASeq, and screen for miRNAs as described in Aim 1 to understand the effect of TT in drug-treated tumors at the molecular level. Results will be functionally validated using our generated tumor cell lines (Fig 2D) and standard biochemical approaches. Our functional validation strategy is as described previously in section C2.

Potential problems and alternative strategies. AR activation can be pro-mitogenic through activation of the PI3K pathway. It is possible that testosterone counteracts the efficacy of alpelisib to treat *Pik3ca*^{mut} tumors in

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male controls and females that continue TT. This will be a clinically important finding. In that case, we may consider excluding alpelisib and treat these *Pik3ca*^{mut} tumors with fulvestrant or letrozole only. We will consider using RLY-2608, a new PIK3-inhibitor (Relay Therapeutics) that preferentially binds to mutant PI3Kα at the H1047R site, in lieu of alpelisib in Aim 2. In the event whereby we are able to implant tumors exposed to TT (from Aim 1 or preliminary data B) for Aim 2, but there is high failure implantation rate of those tumors in FVB female recipients, we would stipulate that TT induces immunological changes that lead to tumor rejection. We will test that by implanting TT-exposed tumors in immune deficient NOD scid gamma mice.

If we find that the effect of TT on drug treatment outcome is attributable to the tumor microenvironment, we will confirm that finding using immune-deficient mouse models. For example, should TT-exposed tumors treated with olaparib display higher numbers of pro-tumorigenic tumor-associated macrophages, we will repeat that experiment in NOD scid gamma mice which cannot mount an effective pro-tumorigenic tumor-associated macrophage response. Should we find that TT-related treatment outcomes in immunocompetent mice cannot be replicated in immune-deficient animals—indicating involvement of the tumor microenviroment—we will focus our transcriptomic data analysis on mechanisms linked to the tumor microenvironment. If TT-related treatment outcome differences persist in immune-deficient mice, then we would focus our transcriptomic studies on tumor-cell intrinsic mechanisms.

Our preliminary study (Fig 5) showed an unexpected effect of sex at birth on olaparib treatment outcome. Male mice had poorer survival than females, irrespective of hormone manipulations. In this Aim 2, we will pay close attention to whether this holds true when *PIK3CA*^{mut} tumors are treated with alpelisib or paclitaxel. Should we detect a systematic sex-dependent, hormone-independent, effect on treatment outcomes, we would attribute the differences in treatment response to immune repertoire or sex chromosomes. Such findings would be clinically meaningful and pursued in separate future projects.

D. TIMELINE

This proposal will take 5 years to complete. Benchmarks for success for each aim are in Fig 8.

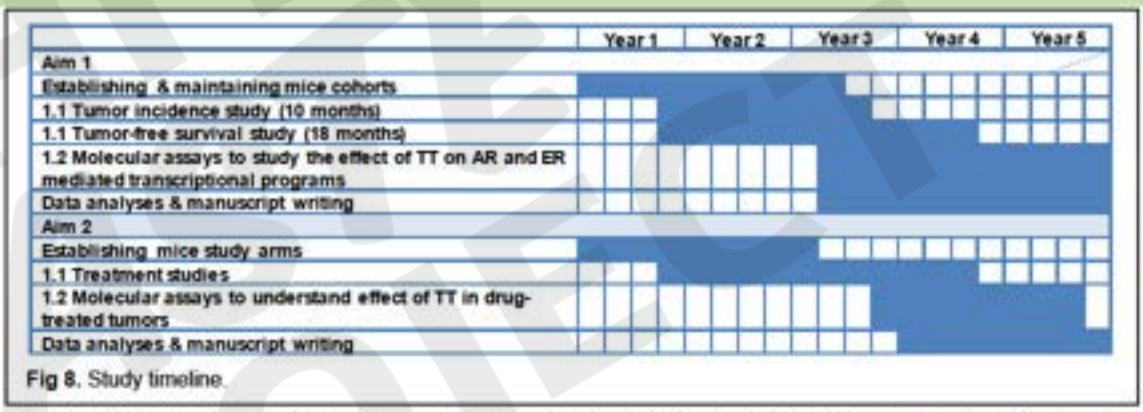

Fig 8. Study timeline

E. STUDY TEAM

The successful completion of this proposal requires the following expertise: transgender health, clinical oncology, cancer biology, preclinical mouse models, pathology, medical image analysis, microRNAs, and sex hormone signaling. We assembled a synergistic team to produce an outcome greater than that could be achieved by independent efforts. Dr. Heng is a scientist with expertise in transgender health, computational biology, and wet-lab techniques. She will lead the molecular assays and data analyses. Dr. Wulf is a breast oncologist who has been conducting pre-clinical mouse studies involving PARP and PIK3 inhibitors for >15 years. She will lead the animal work. Dr. Baker is a breast pathologist. Dr. Jia has expertise with AR and ER signaling and ChIP-Seq technology. Dr. Slack is a miRNA expert.

F. FUTURE DIRECTIONS

The success of our proposal will support new hypothesis to understand the role of sex hormones in hormonally driven cancers, and explore novel cancer therapeutics for cancer. Strategies used in Aim 1 will support the initiation of prospective human studies to study disease risks in the transgender people. Increased understanding of gender-affirming hormone therapy will pave the way for transgender patients to participate in research and clinical trials. Aim 2 will contribute to the development of BC treatment strategies for both transfeminine individuals and cisgender people as well as serve as a blueprint to investigate how sex hormones affect the treatment outcomes of diseases. Should we observe sex-dependent, hormone-independent, effect on BC treatment outcome, the next R01 application will investigate the influences of sex in modifying the pharmacokinetics and pharmacodynamics of the drugs investigated in Aim 2. New knowledge arising from these future studies will improve disease management and treatment for both transgender and cisgender general population, and improve global health.

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PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	❍ Yes	● No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.		
Are Human Subjects Involved	❍ Yes	● No
Is the Project Exempt from Federal regulations?	❍ Yes	❍ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8	
Other Requested Information		

WHITE COAT WASTE PROJECT

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Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

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VERTEBRATE ANIMALS

Approval from the BIDMC IACUC Committee on Animal Research will be through the current protocol 052-2020 (PI Wulf).

For simplicity, we purposefully excluded Aim 1 details regarding breeding, the necessary number of offspring required to fill the study arms, and the estimated number of redundant offspring after genotyping.

Mice for Aim 2 will be purchased from JAX to fill the study arms.

Aim 1: Detailed description of proposed used of animals

This research entails the generation of arms of mice for two different tumor types:

A. K14-Cre BRCA1f/fp53f/f on the FVB background. This strain of mice is currently operational in the Wulf lab. We will generate 4 arms of 50 females each and one arm of 50 males (total 250 mice).

Arm 1: female + sham surgery

Arm 2: female + testosterone treatment (TT) + sham surgery

Arm 3: female + oophorectomy

Arm 4: female + TT + oophorectomy

Arm 5: male, observation only

B. MMTV-Cre PIK3CAf/wt on the FVB background. This strain of mice has been generated in the Wulf lab. We are using the FVB.129S6-Gt(ROSA)26Sortm1(Pik3ca*H1047R)Egan strain from JAX and Tg(MMTV-cre)4Mam/J from JAX. These mice are developing mammary tumors starting at age 5 months. We will generate 4 arms of 50 females each and one arm of 50 males (total 250 mice).

Arm 1: female + sham surgery

Arm 2: female + testosterone treatment (TT) + sham surgery

Arm 3: female + oophorectomy

Arm 4: female + TT + oophorectomy

Arm 5: male, observation only

Thirty mice of each arm will be euthanized at age 10 months for incidence study and transcriptomic work using CO_2. All others (n=20/arm) will be followed to euthanasia endpoint.

Total N= 500 mice; 400 female, 100 male. Pain Category D

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Aim 1: Surgical procedures and treatment

Oophorectomy: Oophorectomy will be done at 7 weeks. It will be done under isoflurane anesthesia using an established protocol. Make a single midline dorsal incision (0.5 cm). Incision should be made in the lower back, directly below the bottom of the rib cage. Gently free subcutaneous connective tissue from the underlying muscle on each side using blunt forceps. Locate ovary under the thin muscle layer and make a small incision (less than 1 cm) on each side to gain entry to the peritoneal cavity. Hold securely the edge of the incision with tooth forceps and retract the ovarian fat pad surrounding ovaries with blunt forceps to expose oviduct. Identify and replace ovaries back into the abdominal cavity for sham operations. Perform a single ligature around the oviduct (0.5 cm for mice from ovary) to prevent bleeding following removal of ovary. Remove ovary by gently severing the oviduct, using sterile, small scissors. Replace uterus and remaining part of the oviduct back into the abdominal cavity. Suture muscle layer. Wound closure is with Vetbond, analgesia with Meloxicam. Allow animal to recover for a week prior to starting TT.

Tumor development: Mice will be observed for development of tumors 3x a week. We will record date of tumor onset and measure tumor size using calipers.

Endpoint: Euthanasia endpoint is a combined tumor burden of maximal 2 cm, or euthanasia criteria per our tumor policy scoring system. Data will be collected on date of onset, and tumor growth as measured by calipers. All tumors will be banked.

Testosterone treatment: 400 µg/mice. Testosterone cypionate will be diluted in 20 uL mineral oil and injected subcutaneously weekly starting age 7 weeks.

Aim 1: Justification

We will need a total of 500 genetically modified animals.

Given the details of the transgender hormone treatments, we will require 640 females and 100 males. This aim addresses breast cancer risk in female to male transition, and hence the imbalance, we need more females to start with.

For simplicity, we purposefully excluded details regarding breeding, the necessary number of offspring required to fill the study arms, and the estimated number of redundant offspring after genotyping. We will require more animals than listed to achieve the gender ratios in the study arms. Redundant offspring will be used for other unrelated research studies or euthanized.

Aim 1 tumor incidence statistical consideration: For each model, 30 out of 50 mice per arm will be randomly selected to be euthanized at age 10 months. Based on our experience, female controls for both mouse models achieve minimum tumor incidence is 50% by 7 months and >80% by 18 months. We will consider a 50% difference in the number of tumors between the study arms biologically meaningful. We power this study for the primary comparison of interest between females receiving TT and female controls. A size of 30 mice per arm will give us 80% power (two sided α=0.05) to detect an effect size of 0.7 (Cohen's d) using two-sample t-test (pwr.t.test, pwr package, R). Cohen's d of 0.7 corresponds to comparing 120 tumors from 30 female controls developing an average of 4 tumors versus 15 tumors from 30 females taking TT developing an average of 0.5 tumors, and with the common standard deviation (s.d) of 2.5 in each group. In practice, we will analyze the data using ANOVA model with post-hoc mean comparisons corrected for multiple testing, if we reject the null hypothesis of equal means in the groups.

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Aim 1 tumor-free survival statistical consideration: The remaining 20 mice per arm will be observed for the natural progression of tumor development. The endpoint for these mice is euthanasia when a tumor reaches 10 mm, or, if multiple tumors arise, when the combined tumor burden reaches 20 mm. Observation will be terminated at 18 months. Mice that have not reached endpoint by that time will be euthanized and censored. Survival will be measured in days. By 18 months, we expect female controls to achieve tumor incidence of >80%.

Based on our Preliminary Data B, we expect the median time to euthanasia for females receiving TT to be 12 months compared with 9 months for controls. There is no evidence that TT accelerates the development of *BRCA1*-related ER- BC. We also hypothesize that increased lag time to breast tumor development in TT-treated female mice is similar for *Brca1*^{mut} mice as well. Therefore, we will consider it biologically meaningful if there is 30% difference in median tumor-free survival between females receiving TT versus female controls. We will use the log-rank test and Kaplan-Meier curves to compare tumor-free survival between the study arms.

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Aim 2: Detailed description of proposed used of animals

This research entails the generation of arms of mice for 6 treatment plans: 1) alpelisib, 2) alpelisib plus letrozole, 3) alpelisib plus fulvestrant (for *Pik3ca*^{mut} tumors), 4) olaparib (for *Brca1*^{mut} tumors), and 5) paclitaxel for both tumors. For each treatment regimen, we will need 140 FVB mice

We will establish 5 arms and implant the relevant tumor at 8 weeks:

Arm 1: female (n=20)

Arm 2: female + testosterone treatment (TT) (n=40)

Arm 3: female + oophorectomy (n=20)

Arm 4: female + TT + oophorectomy (n=40)

Arm 5: male (n=20)

Once the tumor reaches 5mm, mice in Arm 2 and 4 will be randomized to stop or continue TT. Then mice in all arms will be randomized to whether they receive the drug treatment or vehicle. For each treatment regimen, we will have final cohorts of 20 mice in 7 arms whereby there is a female control arm for each TT modality (none, discontinued, continued).

All mice will be followed to euthanasia endpoint, and euthanized using CO_2.

Total N= 840 mice; 720 female, 120 male. Pain Category D

Aim 2: Surgical procedures and treatment

Oophorectomy: Oophorectomy will be done at 7 weeks. It will be done under isoflurane anesthesia using an established protocol. Make a single midline dorsal incision (0.5 cm). Incision should be made in the lower back, directly below the bottom of the rib cage. Gently free subcutaneous connective tissue from the underlying muscle on each side using blunt forceps. Locate ovary under the thin muscle layer and make a small incision (less than 1 cm) on each side to gain entry to the peritoneal cavity. Hold securely the edge of the incision with tooth forceps and retract the ovarian fat pad surrounding ovaries with blunt forceps to expose oviduct. Identify and replace ovaries back into the abdominal cavity for sham operations. Perform a single ligature around the oviduct (0.5 cm for mice from ovary) to prevent bleeding following removal of ovary. Remove ovary by gently severing the oviduct, using sterile, small scissors. Replace uterus and remaining part of the oviduct back into the abdominal cavity. Suture muscle layer. Wound closure is with Vetbond, analgesia with Meloxicam. Allow animal to recover for a week prior to starting TT.

Tumor implantation: Banked murine tumors will be implanted into 7 weeks old mice. The procedure for tumor implantation has been established in our laboratory. Briefly, fragments of live tumor (*Brca1*^{mut} or *Pik3ca*^{mut}) will be implanted syngeneically into the mammary fat pad under isoflurane anesthesia.

Tumor development: Mice will be observed for development of tumors 3x a week. We will record date of tumor onset and measure tumor size using calipers.

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Endpoint: Euthanasia endpoint is a combined tumor burden of maximal 2 cm, or euthanasia criteria per our tumor policy scoring system. Data will be collected on date of onset, and tumor growth as measured by calipers.

Testosterone treatment: 400 µg. Testosterone cypionate will be diluted with mineral oil and 20 uL of working solution will be given weekly via subcutaneous injections starting age 7 weeks. Half of the mice in Arm 2 and 4 will be randomized to stop TT once tumor reaches 5 mm.

Alpelisib treatment: 30 mg/kg. Stock solution will be diluted with 0.5% methylcellulose/0.2% Tween® 80 and 100 µL of working solution will be given daily via oral once tumor reaches 5 mm.

Letrozole treatment: 1 mg/kg. Stock solution will be diluted with 10% N-methyl-pyrollidone/90% polyethylene glycol and 150 µL of working solution will be given daily via oral once tumor reaches 5 mm.

Fulvestrant treatment: 200 mg/kg. Stock solution will be diluted with 2% DMSO/30% PEG300/2% Tween® 80 and 100 µL of working solution will be given twice a week via subcutaneous injections once tumor reaches 5mm.

Olaparib treatment: 50 mg/kg. Stock solution will be diluted with phosphate buffered saline and 200 µL will be given daily via intraperitoneal injections once tumor reaches 5 mm.

Paclitaxel treatment: 10mg/kg. Solution will be prepared using 10% DMSO, 40% PEG300, 5% Tween 80, 45% phosphate buffered saline and given weekly via intraperitoneal injections once tumor reaches 5 mm.

Aim 2: Justification

We will need a minimum of 852 FVB recipients for tumor growth, 840 for the randomizations above, and at least 12 mice to generate seeder tumors from previously frozen, banked specimens. Given the details of the gender affirming hormone treatments, we will require substantially more females than males. This aim addresses breast cancer treatment in transmasculine individuals (i.e., female to male transition), and hence the imbalance in gender.

Aim 2 Survival statistical consideration: Twenty mice of each cohort will be observed for breast cancer progression, the endpoint for euthanasia is the development of a breast tumor that reaches 10 mm, or, if multiple tumors arise, if the combined tumor burden reaches 20 mm. At this endpoint, mice will be euthanized and a complete necropsy will be undertaken. Survival will be measured in days. With each arm size of 20 mice, a tumor incidence of 80% (re-implantation efficacy), we can determine a difference in median treatment-related survival of 30 days with α-error of 0.05 and β-error of 0.2. For each treatment regimen study, we will determine the median treatment survival statistics (log rank). Outcomes will be documented, analyzed using the log rank test, and displayed according to Kaplan Meier.

Veterinary Care

The animals shall be housed and cared for in the BIDMC Animal Research Facility (ARF) within the Center for Life Sciences (CLS), which is a fully AAALAC accredited facility which has a current Public Health Service Animal Welfare Assurance Number (A3153-01). As such, the facility adheres to the policies and procedures outlined in the PHS Policy on Humane Care and Use of

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Laboratory Animals. An O.P.R.R. approved animal facility, Transgenic Mouse Facility, and ES cell knockout facility are provided by BIDMC's ARF. The animal floors are secured 24 hours a day. Animals will be monitored daily by the research team, as well as the animal care staff. Problems requiring veterinary care shall be brought to the attention of the full-time supervisor of the animal care facility. An attending veterinarian, Dr. Barbara Garibaldi, oversees the animal research facility (ARF), and her staff provides 24-hour coverage for the animals.

Procedures for limiting discomfort, pain, and injury to animals

Animals will be inspected daily. Behavior of mice will be monitored and inspected for evaluation of pain and distress. If/when any animal displays a hunched posture or weight loss of greater than >20% of its body weight, or remains motionless even when the cage has been moved will be considered to be in distress.

Impaired breathing, sunken eyes, hunched posture, matted fur and anorexia will also be considered to be a sign of discomfort. Any mice with visible tumors will be monitored on a daily basis for signs of discomfort and distress. We will adhere to our institutional tumor policy. Any animal judged to be in distress will be euthanized by CO^2 inhalation.

For our cancer studies, a strict tumor propagation policy will be followed. Specifically, mice bearing tumors will be observed daily to assess their physical condition, including weekends and holidays. We will ensure that the tumor burden will not exceed 2 cm in diameter. Tumors will be inoculated at only one site on an animal. We expect that multiple tumors can occur spontaneously in mutant animals. The tumor(s) will not be allowed to become ulcerated or necrotic. The tumor(s) will not be allowed to significantly interfere with the movements of the animal, especially its ability to obtain food and water, ability to bear its own weight and prevent the animal from regaining normal posture if placed on its back. If the tumor(s) cause(s) the animal apparent distress the mouse will be euthanized.

Euthanasia

Animals shall be euthanized using CO_2 inhalation, consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association and then we will collect tissues sufficient to assure the animal will not recover (e.g. liver). In our facility this is done with a "Smartbox" device. Mice will be followed for a maximum of 36 months before being euthanized. Any mice showing signs of distress or discomfort prior to this time will be sacrificed by euthanasia.

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Multiple Leadership Plan

1. Leadership team. In the proposed future scope of work, all components of the study will be conducted at the Beth Israel Deaconess Medical Center (BIDMC) under the leadership of Drs. Jan Heng and Gerburg Wulf (MPI). Dr. Heng will serve as the Contact PI. They bring together complementary areas of expertise and a track record of collaboration.

Dr. Jan Heng, PhD, is an Assistant Professor in the Department of Pathology, BIDMC and Harvard Medical School. She is a breast cancer translational scientist who has inter-disciplinary expertise in transgender health, cancer epidemiology, omics, computational biology, and medical image analysis. She will lead the molecular assays and data analyses.

Dr. Gerburg Wulf, MD PhD, is an Associate Professor in the Department of Medicine, BIDMC and Harvard Medical School. She is a breast oncologist in the Division of Hematology/Oncology at BIDMC and is the main oncologist who manages transgender oncology cases. She is also an outstanding scientist who has been conducting basic and pre-clinical breast cancer research involving PARP, PIN1, and PIK3 inhibitors for >15 years. She has a strong successful record in translating her pre-clinical studies into national clinical trials. She has leadership roles in early phase clinical trials investigating agents to treat metastatic breast cancer. She will lead the animal work.

Drs. Heng and Wulf bring together unique skill sets that will complement one another and ensure success in accomplishing the project aims. Drs. Heng and Wulf participated equally in the preparation of the current proposal. They plan to maintain this equal partnership in the conduct of the work and management of finances if the proposal is funded.

2. Leadership roles. Dr. Heng will oversee all work, including experimental design, laboratory assays, data analyses and supervising the research assistant and postdoctoral fellow. Dr. Wulf will contribute to experimental design, and animal work. Together, Drs. Heng and Wulf will direct, and implement the proposed study. They will also present findings at scientific meetings and prepare results for publication.

3. Track record of successful collaboration. The PIs' synergistic expertise is evidenced by a strong track record of collaboration for the past 6 years—9 publications with five in transgender health. Another two more transgender publications are in preparation.

4. Communication strategy. Both investigators are faculty at BIDMC. Their offices are adjacent to each other which facilitates daily communication, and their laboratories are on the same floor (Dana 5). The close proximity of the study investigators and their lab space allows the team to meet in-person for project updates. Drs Heng, Wulf, postdoctoral fellow and research assistant, will have weekly in-person meetings to discuss and direct the project, and monitor and review progress, with Dr. Heng taking meeting notes. The PIs' team and collaborators will meet monthly in-person or via zoom to discuss progress, data analyses and manuscript drafts.

The team will also use these meetings to resolve any potential conflicts that may arise. If a potential conflict develops, arising out of or relating to the interpretation, performance or breach of the terms of the grant (including but not limited to science, budget, personnel, progress reports, authorship), the involved the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the appropriate departmental and research administrators will meet together with them and attempt in good faith to settle the matter. If the administrators fail to resolve the disagreement within ten (10) business days after the meeting with the involved PIs/Co-Investigators, then the research administrator shall in writing refer the matter for resolution to the Department Chair(s) and VP of Research Administration, who have the final internal authority to settle the disagreement. Finally, review by an independent external party may be sought by the VP of Research Administration, with the full understanding that the advice and/or decision of such is final and hence binding on all parties.

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Cancer Center

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

May 10, 2023

To the Reviewing Committee,

Re: Letter of Support for Dr. Yu Jing Jan Heng

I write this Letter to express my strongest support for Dr. Yu Jing Jan Heng's application titled, "Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes". Dr. Heng is submitting this proposal together with Dr. Gerburg Wulf as MPIs.

I am the Shields Warren Mallinckrodt Professor at Harvard Medical School in the Beth Israel Deaconess Medical Center (BIDMC) Department of Pathology and Director of the BIDMC Cancer Research Institute and Director of the HMS Initiative for RNA Medicine. In my lab, I primarily undertake research involving RNA therapeutics in cancer. I have contributed discoveries of the first human microRNA, *let-7*, and demonstrated its tumor-suppressing qualities. My research also extends to the discovery of additional novel small RNAs in development, cancer, aging, and diabetes, as well as identifying the next generation of targets in cancer. I received my BSc from the University of Cape Town, South Africa. I then completed my PhD in molecular biology at Tufts University School of Medicine, followed by a postdoctoral fellowship at HMS.

I have been collaborating with Drs. Heng and Wulf since 2020. Leveraging on breast cancer clinical trials, some led by Dr. Wulf, we are analyzing pre-treatment plasma microRNAs as potential biomarkers to predict response to breast cancer treatment (lead by Dr. Heng). We are also collaborating on a Massachusetts Institute of Technology (MIT)-BIDMC joint project to identify microRNAs associated with olaparib resistance in breast tumors. For this current proposal, we will collaborate to understand how testosterone therapy modulates sex hormone signaling in murine mammary glands and breast tumors, and whether microRNA plays a role in that modulation. This proposal has clear innovation and translational scientific merit. The findings will have important implications for clinical transgender care and addresses the healthcare disparities of the transgender community.

Drs. Heng and Wulf are true innovators in pioneering breast cancer studies for the transgender community. I am excited to participate in this important and timely research endeavor. Please do not hesitate to communicate with me if I can provide any additional helpful information.

Sincerely,

Frank J. Slack, Ph.D.
Professor of Medicine and Pathology
BIDMC/Harvard Medical School
Director, BIDMC Cancer Research Institute
Director, HMS Initiative for RNA Medicine
Director, BIDMC ncRNA Core Facility

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Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

May 4, 2023

Dear Jan,

Re: Letter of support

I write this letter of support for your R01 application titled, "Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes". I am pleased to collaborate with you and Dr. Gerburg Wulf on this proposal. I am excited to continue our long-standing working, productive relationship for the past seven years.

I am a breast pathologist at Beth Israel Deaconess Medical Center (BIDMC) and Assistant Professor of Pathology at Harvard Medical School (HMS), Boston, MA. I trained in anatomic and clinical pathology at Massachusetts General Hospital and received my subspecialty fellowship in breast pathology at BIDMC. I served as the primary breast pathologist at the University of Chicago (2013-2016) before returning to BIDMC and HMS in 2016. During my training and practice as a breast pathologist, I have obtained the expertise to microscopically evaluate the broad spectrum of breast diseases.

We have co-published numerous manuscripts related to breast cancer. I am part of the multidisciplinary transgender breast care working group that you assembled at BIDMC. I am the lead pathologist on the Transgender and Testosterone Therapy use research cohort that you are the PI. Our transgender research efforts have led to four published manuscripts and four conference abstracts (1 oral, 4 posters). I believe your Proposal will generate important knowledge for transgender health, especially in addressing breast cancer disparity in transmasculine individuals.

I will support the histopathological review of the mice breast tissues. I will evaluate the quality of immunohistochemistry markers of interest. I will contribute to data interpretation, and the writing and reviewing of manuscripts. Therefore, I have the necessary qualifications and expertise to support this application. My office is located on the ground floor of the same building where your office is located. I will participate in bi-weekly team meetings with you and the team via zoom or in person. I look forward to continue our working relationship with you to understand how testosterone therapy affects breast cancer risk and prognosis in transmasculine individuals.

I wish you the best of luck with this application.

Yours sincerely,

Gabrielle M Baker, MD
Breast Pathologist, Beth Israel Deaconess Medical Center
Assistant Professor of Pathology, Harvard Medical School
330 Brookline Avenue, Sherman 165
Boston, MA, 02215

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BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

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Li Jia, Ph.D.
Assistant Professor of Surgery
Harvard Medical School

Director of Urology Research
Brigham and Women's Hospital

May 4, 2023

RE: Letter of Support for Drs. Yu Jing Jan Heng and Gerburg Wulf

Dear NIH Study Section Review Committee:

I am the Director of Urology Research at Brigham and Women's Hospital and Assistant Professor of Surgery at Harvard Medical School. I am writing this letter to confirm my support for this proposal, "Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes" submitted by the MPIs.

The research focus of my laboratory has been on AR-mediated transcriptional regulation in prostate cancer. My lab has developed an integrated pipeline to perform genome-wide analyses for AR DNA binding and AR target gene regulation using next-generation sequencing technology along with CRISPR gene editing approach. I believe that these novel genomic approaches and my expertise on AR signaling can be perfectly applied on your proposed studies. Importantly, I have previously studied the role of AR in breast cancer (Peters et al, Cancer Res 2009) and revealed AR binding to the estrogen responsive element in breast cancer cells. In this project, I will contribute my sex hormone receptor signaling expertise to understand how testosterone therapy modulates murine mammary glands and breast tumors.

I am happy to serve as a co-investigator in this project. To achieve your research goals, I will work closely with you to understand your specific needs, help design the appropriate experiment workflow, and analyze the data. I am looking forward to sharing my expertise and working with you on this exciting project.

Sincerely,

Li Jia, Ph.D.

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Beth Israel Deaconess Medical Center

Harvard Medical School

Director, Preclinical Murine Pharmacogenetics Facility, Cancer Genetics Program

Member, Cancer Center

Associate Member, Cancer Research Institute

John G. Clohessy, PhD

Beth Israel Deaconess Medical Center

330 Brookline Ave, CLS 402 • Boston, MA 02215 USA

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Assistant Professor, Division of Genetics Department of Medicine

June 2, 2023

Dr. Yu Jing Jan Heng, Ph.D. (Contact PI)
Dr. Gerburg Wulf, M.D. Ph.D.
Harvard Medical School,
Beth Israel Deaconess Medical Center
330 Brookline Ave, Dana 517B
Boston MA, 02215

Re: Letter of Collaboration

Dear Jan and Gerburg,

I am delighted to write this letter outlining our collaborative efforts on your project to investigate the role of gender-affirming testosterone therapy on breast cancer risk and treatment outcomes and in support of your upcoming R01 resubmission.

The Preclinical Murine Pharmacogenetics Facility that I direct here at Beth Israel Deaconess Medical Center and Harvard Medical School, is ideally suited to assisting you in designing and implementing the *in vivo* mouse experiments that you are planning. As you know, our core has extensive expertise in cancer biology across a variety of models including breast cancer biology and genetics and can facilitate your work in a number of areas. These include the administration of hormonal therapies as well as advising and training your staff in monitoring and analyzing mice for tumor development in your models. In addition, my staff are expert in delivering such services and we will be very happy to work with you to meet your needs.

We have already established productive collaborative efforts with you over the last number of years around the area of gender-affirming therapies, as demonstrated by co-authorship in your recent manuscript. I am thrilled to be able to collaborate with your team on this project as we believe strongly that there is a critical need to understand how hormonal therapies impact cancer risk and outcome for transgender communities. As our labs and offices are in close proximity to one another at BIDMC, we are in an excellent position to collaborate and join forces.

I look forward to an exciting and productive collaboration.

Yours sincerely,

John G. Clohessy, Ph.D.

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Dana-Farber Cancer Institute

Zachary T. Herbert, M.S.

Director
Molecular Biology Core Facilities
Lead Scientist
Dana-Farber Cancer Institute

Research Associate
Department of Medicine
Harvard Medical School

450 Brookline Avenue
Boston, MA 02215
617.632.3082

Date: May 12, 2023

Dr. Yu Jing Jan Heng
Assistant Professor of Pathology
Harvard Medical School
Beth Israel Deaconess Medical Center 3
30 Brookline Ave, Dana 517B
Boston, MA, 02215

Subject: Letter of Support

As the Director of the Molecular Biology Core Facilities (MBCF) at Dana-Farber Cancer Institute (DFCI), it is my pleasure to collaborate with you and to provide support services necessary for successfully undertaking your project entitled "Gender-Affirming Testosterone Therapy on Breast Cancer Risk and Treatment Outcomes" Our work with you over the last five years collecting expression profiling data using both RNAseq and microarray technologies has been successful, resulting in three publications.

The MBCF is equipped with cutting edge instrumentation for genomic scale research and our sequencing platform includes an Illumina NovaSeq, two Illumina NextSeq500s, three Illumina MiSeqs, and one Illumina MiniSeq that operate seven days per week to facilitate rapid turnaround time. The MBCF also specializes in a diverse array of sample preparation services for a number of NGS applications such RNAseq, ChIPseq, smRNAseq, ATACseq, methylation profiling, exome sequencing, and more. Sample library preparation for large scale projects using standardized protocols is performed on one of our Biomek i7 liquid handling systems capable of processing hundreds of samples within a week.

The MBCF will provide bioinformatics support for RNAseq and ChIPseq using internally developed pipelines, for alignment, gene quantification, peak calling, and generation of publication ready figures such as heatmaps, PCA plots, etc. Customized in-depth analysis such as alternative splicing and integration of datasets generated from different NGS applications through our collaboration with the Computational Biology and Bioinformatics group at DFCI. All of the data generated by the MBCF are made easily available to collaborating investigators and is backed up in the MBCF data archive forever.

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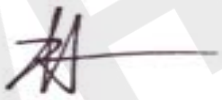
I will be happy to participate in the design of your studies, provide quality control for your samples, perform the sequencing studies and provide my input for the analysis and interpretation of the data. I look forward to working with you again on this upcoming project!

Sincerely,

Zachary T. Herbert, MS



Lead Scientist
Director, Molecular Biology Core Facilities
Dana-Farber Cancer Institute

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Data Management and Sharing Plan

The plan for sharing materials, data, and related resources will adhere to the latest NIH Grant Policy Statement.

A Types and amount of scientific data expected to be generated in the project:

- *In vivo* data
  - Tumor burden, tumor weight, tumor volume, date of euthanasia/death
- Histological data
  - H&E morphological evaluation of mammary glands and tumors
  - Immunohistochemistry, multiplex immunofluorescence of specific markers of interest
- High-throughput data
  - RNASeq, miRNA screening, and ChIP-Seq of mammary glands and tumors
- Molecular work to conduct functional validation
  - PCR, western blotting, ELISA, etc.

B. Scientific data that will be preserved and shared and the rationale for doing so:

- All data described in A will be preserved in our institute's secure Research drive.
- RNASeq and ChIP-Seq data will be deposited into GEO as required.
- Metadata, other relevant data, and associated documentation:
  - Detailed methods outlining the collection of each scientific data generated with this work will be provided in our publications as supplementary protocols. Specifications about instruments and technologies used to produce this data will also be reported in the publications.
- Related Tools, Software, and/or Code:
  - Rscript files for data analysis
- Standards:
  - Community standard file formats will be used to save our data: excel sheets, word documents, .jpegs or .qptiff for whole slide images or microscopy

C. Data Preservation, Access, and Associated Timelines

- RNASeq and ChIP-Seq data will be deposited into GEO as required. GEO is a database supported by NCBI with long-term access. Datasets are available under an open access policy. Unique identifiers associated with the data will be referenced in the corresponding publications.
- Scientific data will be shared as soon as possible. Scientific data included in published manuscripts will be made available at the time of publication. All final peer-reviewed manuscripts that arise from this proposal will be submitted to the digital archive PubMed Central. All other scientific data will be made available no later than the end of the award.
- Data will be preserved and available for at least 5 years. Raw data, intermediate data, and the code/software/tools used to develop the published or submitted dataset will be shared at the time of data submission or publication and for at least 5 years.
- We will continue to maintain a policy that actively promotes new research collaborations that make use of the comprehensive observational data collected during this study.

Access, Distribution, or Reuse Considerations

- There are no use limitations associated with the scientific data generated in this study. There are no ethical or legal issues that can have an impact on data sharing. No personal data will be published in this project.
- Whether access to scientific data will be controlled:
- Data in GEO is publicly available.

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- We are willing to share banked mice tissues with other groups that might be interested in other aspects of transgender biology. For example, our collaborators at the Harvard/MIT Broad Institute are analyzing ovarian tissues obtained from pilot studies to understand the effect of testosterone therapy on reproductive function.
- For this proposal, protections for privacy, rights, and confidentiality of human research participants are not applicable.

Oversight of Data Management and Sharing:
The Principal Investigators for this project, Drs. Heng and Wulf, will ensure that this Data Management and Sharing (DMS) Plan is followed. The institutional official Andi Hernandez, will be responsible for oversight of compliance with the accepted DMS Plan. Compliance will be evaluated annually during the award period and progress towards the plan's DMS activities will be included in the annual Research Performance Progress Report (RPPR) submitted to the NCI Project Officer. At the project conclusion, the final progress report will summarize how the DMS objectives were fulfilled and provide links to the shared dataset(s).

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NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

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Authentication of Key Biological and/or Chemical Resources Chemicals:

Standard chemicals and/or reagents will be purchased from US vendors. Drugs for the treatment of animals are purchased from vendors in the US. The drugs that we use have FDA-approval for use in humans. For animal treatments, we will purchase generic drugs. On-target efficacy and purity will be double-checked in the laboratory through pharmacodynamics established for the respective drugs.

- Testosterone
  - Testosterone Cypionate will be purchased from MedVet #103810.
- Letrozole
  - Letrozole (CGS 20267) will be purchased from Novartis Pharma.
- Alpelisib
  - Alpelisib (BYL-719) will be purchased from MedChemExpress HY-15244.
- Fulvestrant
  - Fulvestrant (ICI 182780) will be purchased from MedChemExpress HY-13636.
- Olaparib
  - Olaparib (AZD2281) will be purchased from Adooq Bioscience A-10111.
- Paclitaxel
  - Paclitaxel will be purchased from MedChemExpress HY-B0015.

Antibody reagents will be validated using pilot studies, positive and negative controls, and evaluation by a board-certified pathologist. Should the following antibodies fail to work, we will explore different antibodies to identify the best antibody for the assay. Depending on the results of our proposal, additional antibodies will be used, and similarly validated prior to assay.

- Mouse antibodies for immunohistochemistry
  - Estrogen Receptor will be purchased from Abcam #ab32063
  - Progesterone Receptor will be purchased from Invitrogen (PR-AT 4.14) #MA1-410
  - Androgen Receptor will be purchased from Abcam #ab133273
  - Ki67 will be purchased from BioCare Medical #CRM326
  - p-AKT will be purchased from Cell Signaling (Ser473) #9271
  - Caspase 3 will be purchased from Abcam #ab13585

- Mouse strains
  - K14-Cre BRCA1f/fp53f/f on the FVB background
    - This is our own mouse line and operational in our animal facility.
    - >99% purity for FVB/N status by Charles River.
    - Juvekar, A. *et al.* Phosphoinositide 3-kinase inhibitors induce DNA damage through nucleoside depletion. *Proc. Natl. Acad. Sci. U. S. A.* **113**, E4338-E4347.
  - MMTV-Cre PIK3CAf/wt on the FVB background
    - This mouse line was generated by breeding MMTV-Cre male mice from JaX 003553 with *Pik3ca*^{H1047R} female mice from JaX 016977
    - These mice are operational in our animal facility
    - Adams, J. R. *et al.* Cooperation between Pik3ca and p53 mutations in mouse mammary tumor formation. *Cancer Res.* **71**, 2706–2717 (2011).

- Opal Assay (multiplex immunofluorescence)
  - Opal 7-Color Automated IHC Kits (NEL821001KT)
  - Leica Bond reagents as required

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