Research at the Intersection of Translational Science and Women’s Health

Joni L. Rutter, PhD
Director
National Center for Advancing Translational Sciences

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National Center for Advancing Translational Sciences

An Overview
Thousands of Diseases

Disability-adjusted life years (DALYs) for diseases are INCREASING over time

Despite more tools and technologies

We are trending in the wrong direction
The Public Health Challenge

10,000 Diseases

and only 5%

Have Treatments or Cures

Time from early development to the medicine cabinet takes 10-15 years.

9 out of 10

Promising therapeutic candidates that enter clinical trials fail.
Translational Problems in Drug Development

- The percentage of drugs entering clinical trials resulting in an approved medicine is less than 12%
  - 55% fail due to lack of efficacy
  - 28% fail due to toxic effects in humans
- Average time to develop a drug takes 10-15 years
- Average cost to develop a drug to market, including cost of failures is $2.6 billion
- Current tools used for drug development involving 2-D cell culture and animal models do not always predict human response
- “One size fits all” approach

Drug Failure Modes

- Efficacy
- Safety
- Strategic
- Commercial
- Operational

Arrowsmith and Miller, Nature Reviews Drug Discovery, Volume 12, 569 (2013)
Cook et al., Nature Reviews Drug Discovery, Volume 13, 419 (2014)
NCATS’ MISSION

Turn research observations into health solutions through translational science
NCATS is Re-engineering the Translational Pipeline

NCATS is advancing translational science by addressing long-standing bottlenecks in the translational pipeline so that new treatments reach people faster.

Operational
“One size fits all” approach
- Adaptive clinical trial design, master protocols
- N of small CTs, basket/umbrella trials
Low enrollment and diversity in clinical trials
- Enhanced community engagement efforts (TIN, CEAL, telehealth)

Administrative/Workforce Dev
Administrative burden for study start-up
- Streamlined business and regulatory processes (SMART IRB)
Shortage of qualified translational investigators
- Training and career development best practices (CTSA K, T, R25, DPI)

Scientific
Insufficient tools and technologies to predict toxicity and efficacy of new drugs
- Platform-based Tissue/Organ on chips; 3D biofabrication
- Gene targeted therapies
- AI/ML drug development (ASPIRE)
Incompatible databases to advance data science
- Data, interoperability and integration (Translator, N3C, GARD, RARESource)

Examples of Solutions

Pre-clinical

Clinical
NCATS Vision: Three Audacious Goals

More Treatments

Five-Fold Increase in Number of Diseases with Treatments

All People

Dramatically Increase Inclusivity Across Every Area We Support

More Quickly

Enable Diagnostics and Therapeutics to Reach People Twice as Fast
Key NCATS Approaches

Understanding what’s similar across diseases to spur multiple treatments at a time

Developing models that better predict a person’s reaction to a treatment

Enhancing clinical trials so the results more accurately reflect the patient population

Leveraging real-world data and data science approaches to address public health needs
Translational Science is the field that generates scientific and operational innovations that overcome longstanding challenges along the translational research pipeline.

**Prioritize initiatives that address unmet needs**

**Produce crosscutting solutions for common and persistent challenges**

**Emphasize creativity and innovation**

**Leverage cross-disciplinary team science**

**Enhance the efficiency and speed of translational research**

**Utilize boundary-crossing partnerships**

**Use bold and rigorous research approaches**

**Advance diversity, equity, inclusion and accessibility in research**
NCATS’ Budget At-a-Glance

Clinical and Translational Science Awards Program
Funds nationwide network of research institutions with consortium-wide resource centers and collaborative initiatives

All Other NCATS Activities
Supports intramural and extramural programs including drug repurposing, diagnostics, ethics and training

Stimulates transformative efforts and platform approaches through the Cures Acceleration Network

Enables patient-centric innovations for studying, treating and diagnosing rare diseases

Reflects Fiscal Year 2023 Enacted Appropriations
NCATS Budget: $923,323,000
Specific Efforts in Translational Science for Women’s Health

Drugs and Medical Devices: Adverse Events and the Impact on Women’s Health
CTSA Program: Premier National Network Speeds Health Solutions

- Develop, demonstrate, and disseminate innovations that turn science into health faster
- Promote impactful partnerships and collaborations
- Address health disparities
- Provide a national resource for the rapid response to urgent public health needs
- Promote training and career support
- Nurture the field of translational science

Clinical and Translational Science Awards Primary Institutions

January 2023
Local strengths enable nimble, rapid, and robust responses to national public health challenges.
CTSAs and Women’s Health Research

CTSA Pilot Awards Promote Women’s Health Research

• The Clinical and Translational Science (CTS) Pilot Award Program provides modest research support for new and innovative research projects to CTSA academic institutions
  • These provide valuable preliminary data to investigators planning more comprehensive studies and research applications.
• 11% of pilots (82 of 751) were solely focused on women’s health research with an additional 4.3% (32) partially studying women’s health, such as:
  • expanding knowledge about and evaluating services for incarcerated pregnant and postpartum women
  • improving cardiovascular risk prediction in women
  • an integrated smoking cessation and breastfeeding program to reduce cancer disparities
CTSAs and Cross-cutting Women’s Health Research

Pain and Opioids

• The Trial Innovation Network (TIN) is an NCATS CTSA initiative that provides clinical trial infrastructure for the HEAL Pain Management Effectiveness Research Network (ERN) to speed scientific solutions to stem the national opioid public health crisis and improve pain management.

• The ERN program leverages the infrastructure of the TIN to support clinical trials that compare the effectiveness of existing non-addictive pain therapies as well as existing or novel approaches for pain prevention and management.

• Women’s Health studies include:
  • One clinical trial seeking to address opioid overprescribing after cesarean delivery
  • A clinical trial determining the effectiveness of perioperative ketamine for prevention of post-mastectomy pain syndrome
  • ERN trials identifying better ways to manage chronic pain, a condition more prevalent in women.
Towards a National Health Data Ecosystem: National COVID Cohort Collaborative (N3C)

The N3C data enclave is the largest collection of real-world COVID-19 data in the United States

- Sites: 77
- Persons: Over 17 million
- COVID+: Over 7 million
- Rows of data: 22.1 billion
- Clinical observations: 1.7 billion
- Publications and preprints: Over 117
- Google citations: Over 1,000
- Informs public health questions
  - Long-COVID risk
  - mAB effectiveness across variants
  - Paxlovid use

https://covid.cd2h.org/dashboard/
NCATS N3C Dashboard

EHRs * CMS * Vaccine Data * Viral Variant Seq
Updated every 2 weeks
Using the National COVID Cohort Collaborative (N3C) to Study the Impact of COVID-19 on Pregnancy

- The National COVID Cohort Collaborative (N3C) is being used to study COVID-19, identify potential treatments, and further validate existing therapies.

- The Pregnancy Clinical Domain Team aims to leverage N3C data to gain insights into pressing COVID-19 questions around pregnancy.
  - These include understanding the incidence, timing, and severity of COVID-19 in pregnant women and the associated maternal and infant outcomes.

- One group used N3C to develop The Temporal Events Detector for Pregnancy Care (TED-PC) algorithm (Lyu et al., 2022; PMID: 36315520)
  - TED-PC can determine the gestational week of clinical events in Electronic Health records (EHR) during pregnancy
  - TED-PC will be able to help evaluate the impact of COVID-19 on pregnancy.
Findings from N3C: Sex Differences in Severe Outcomes in Patients with COVID-19

- Researchers evaluated association of comorbidities, inflammatory biomarkers, and severe outcomes in over 570,000 adult patients admitted for COVID-19 at hospitals or emergency rooms in 2020 and 2021.

  The top four fatal comorbidities in both sexes among patients hospitalized for COVID-19, were the same (moderate to severe liver disease, renal disease, metastatic solid tumor, and myocardial infarction) but women had a higher magnitude of risk than men. Similarly, abnormal levels of several proteins (including c-reactive protein (CRP), ferritin, procalcitonin, and NT proBNP, as well as increased neutrophil and platelet counts) were significantly associated with death in both sexes, with the association being stronger in women than men.

- PMID: 36224551 (Yoshida et al., 2022).
N3C Examples of Impact

- “Without the opportunity for CTRs to participate in N3C, rural Americans would be largely missing from a significant national health database.”

- Guidelines for HIV patients changed due to N3C analyses (CDC recommendations)
- Transplant guidelines changed due to N3C analyses (Canada)

Higher hospitalization and mortality rates among SARS-CoV-2-infected persons in rural America – “Rural Penalty”
Revolutionizing Drug Development Approaches

*PhRMA, Biopharmaceutical Research Industry Profile, 2016*

Need for new technologies and better predictive tools across the translational pipeline
Better predictive models

3D Bioprinted skin tissue

Multi-organ chip

Lung chip

Precision Medicine You-on-a-chip

- Identify & test biomarkers
- Reduce trial risk
- Hone patient selection
- Explain variable treatment response

Courtesy of Marc Ferrer, NCATS, Dan Tagle, NCATS, and Gordana Vunjak-Novakovic, Columbia
Modeling the Entire Female Reproductive Hormone System

Teresa Woodruff, Ph.D Northwestern University on the ovaries; Joanna Burdette, Ph.D. (UIC), on the fallopian tubes; Julie Kim, Ph.D. (Northwestern), on the uterus; and Spiro Getsios, Ph.D. (Northwestern), on the cervix and vagina. Beth Sefton, Ph.D., at Northwestern, coordinates the work – TEAM SCIENCE!
3D Organoids

Generation of scaffold-free 3D endometrial organoids from human primary endometrial cells. (A) Endometrial epithelial and stromal cells were isolated from premenopausal endometrial tissues with benign pathology. Both stromal and epithelial cells were seeded into 1.5% agarose 3D Petri Dishes™ at a 1:3 ratio by volume and maintained in sex hormone-free medium for 7 days before downstream experiments. (B) Estradiol (E2) and testosterone (T) were added in a stepwise manner to the 3D cultures to mimic the levels of E2 and T during the follicular phase of a menstrual cycle. T levels were consistently higher (3 nM) in the polycystic ovarian syndrome hormone profile. After 14 days of normal hormone treatment, endometrial organoids were stained with (C) hematoxylin and eosin, (D) trichrome stain to detect collagen (blue), and (E) periodic acid-Schiff staining to stain mucosal substances (eg, mucins, glycoproteins; bright pink). Scale bar in inset of (E) is 10 μm.
“This work is a remarkable advance for understanding female biology, and it will fill an important gap,” said Janine A. Clayton, M.D., ORWH director. “It’s a perfect example of how considering sex as a biological variable can help us develop individualized treatments and learn more about how females may metabolize drugs differently from males.”

Teresa Woodruff, Ph.D Northwestern University on the ovaries; Joanna Burdette, Ph.D. (UIC), on the fallopian tubes; Julie Kim, Ph.D. (Northwestern), on the uterus; and Spiro Getsios, Ph.D. (Northwestern), on the cervix and vagina. Beth Sefton, Ph.D., at Northwestern, coordinates the work – TEAM SCIENCE!
Using 3-D Tissue Bioprinting and Tissue Chip to Improve Health in Pregnancy

- 3-D bioprinted interface tissue model that can mimic inflammation during pregnancy is being developed.
- Up to 1,000 drug compounds that may reduce spontaneous preterm birth will be screened.
- [1UH2TR004117-01](#)
The Maternal-Fetal Interface on a Chip aims to reproduce the structure, function, and responses of the fetal-maternal tissue interface (FMI), mimicking health and inflammation.

Reducing inflammation at the FMI could help maintain pregnancy and prevent spontaneous preterm birth.

The goal is to offer a personalized FMI model to test potential treatments and streamline clinical trials.

One study tested the effect of maternal exposure to cadmium (Cd), an environmental toxin, and found significant cell death in maternal cells, but minimal effect on fetal cells. [PMID: 34391970](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8595660/)

Physiological Changes under Prolonged Microgravity: Chips in Space

- **Early response (<3 weeks)**
  - Neurovestibular disturbances
  - Sleep disturbances
  - Bone demineralization
- **Intermediate (3 weeks to 6 months)**
  - Bone resorption
  - Muscle atrophy
  - Cardiovascular deconditioning
  - GI disturbances
  - Hematological changes
- **Long Duration (greater than 6 months)**
  - All of the above, and…
  - Declining immunity
  - Renal stone formation
  - Reverts to normal upon return to Earth
Tissue Chips and Digital Twins: Technology and Platform Development on the Horizon

RCTs with prognostic digital twins overcome the limitations of external control arms

Precise Medicine You-on-a-chip
- Identify & test biomarkers
- Reduce trial risk
- Hone patient selection
- Explain variable treatment response

NASA’s Artemis 3 mission: Landing humans on the moon

By Elizabeth Howell last updated November 16, 2022
NASA plans to land humans on the moon in 2025, for the first time in more than 50 years.

Artist’s conception of SpaceX’s Starship on the moon. Starship was selected to be NASA’s human landing system for Artemis 3. (Image credit: SpaceX)
Towards New Approach Methodologies: Human Cell-Based Physiological Systems for Women’s Health

- Assess changes in metabolic activity of specific cell types
- Effects of exposure to hormonal treatment or chemical substances on aspects of reproduction and fertility
- Studies of diseases, causes, and adverse events occurring during pregnancy such as pre-eclampsia, infertility or preterm birth, endometriosis and infertility
- Allows the co-culture of different cell types under normal and disease states of the female reproductive tract and changes occurring during conception and pregnancy
Small Molecule Therapeutics to Prevent Breast-to-Brain Metastasis

- Triple-negative (30%) and HER2+ (34%) breast cancers are more likely to metastasize to the brain.
- Many therapeutic agents effective against breast cancer can’t be used to treat brain metastases, because they cannot cross the blood-brain barrier.
- NCATS investigators are collaborating with researchers at the University of Manitoba, Winnipeg, to develop high-throughput screening approaches to identify molecules for treating breast-to-brain metastasis (Mark Henderson, 1ZIATR000405).
  - Developed the only current hematogenic HER+/ERα+ breast-to-brain metastasis human cell model.
  - Screened over 6,500 compounds, including about 2,500 cancer drugs.
  - Identified a mechanism by which metastatic breast cancer cells use resident brain cells to avoid being killed by drugs that target the HER2 receptor.
NCATS Has a Home for Rare Diseases

NCATS develops new ways to understand and treat rare diseases.

RESOURCES to educate, engage and empower the rare diseases community.

FUNDING to accelerate medical research across rare diseases.

DATA-DRIVEN SOLUTIONS to shorten the diagnostic journey and lower the economic burden.
NCATS Study Suggests People with Rare Diseases Face Significantly Higher Health Care Costs

Individual medical costs for people with a rare disease are 3–5 TIMES greater than for those who do not have a rare disease. The medical costs of rare diseases have been underestimated.

Yearly direct medical costs estimated at around $400 BILLION are similar to those of cancer, heart failure, and Alzheimer’s disease.

Rare diseases are collectively common, affecting an estimated 25–30 MILLION people in the United States.

Source: The iDeaS Initiative: Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems
Developing and Streamlining Delivery Approaches

1) Somatic Cell Gene Editing – (SCGE)
   1) NIH Common Fund Program
   2) Moving to clinical studies for second phase
   3) Toolkit – data on performance of delivery technologies

2) Accelerated Medicines Program® – Bespoke Gene Therapy Consortium (BGTC)
   1) Enhancing vector manufacturing
   2) Enhancing gene expression
   3) Regulatory playbook

3) Platform Vector Gene Therapy – (PaVe-GT)
   1) Single AAV vector as a platform for multiple therapeutic genes
   2) Testing ability to increase efficiency to clinical trial start-up
Advancement of Women in Biomedical Careers

- The Women Scientists Advisors (WSA) group within the Division of Preclinical Innovation (DPI) developed a new initiative in 2022.
- Women scientists from DPI engage with the external Bethesda/DC-area community, particularly students in grades K-12.

For grades 6-12, there are:
- Panel discussions
- 1-on-1 “speed chatting” activities with opportunities for students to ask scientists about their careers, navigating higher education, how their science contributes to day-to-day life, and overcoming challenges.

For students in K-5 there is:
- “Translational Science in Action” role playing games, developed by WSA, where students pretend to be scientists approaching various scripted problems and learn science is about teamwork, curiosity, and persistence.

This initiative increases visibility of women scientists, encourages development of students’ scientific literacy while showing that science and scientists are relatable and anyone can have a job in science.
Strategic Planning Process: Stakeholder Engagement

Getting organized

Initial stakeholder engagement

Build an outline and draft

Gather feedback on draft plan

Finalize plan and initiate rollout plans

Strategic Plan rollout and implementation

Start: November 2022

Target for rollout: Late 2023/Early 2024

Initial stakeholder engagement

Director’s Presentation

- Overview of NCATS, Translational Science principles, audacious goals
- Icebreaker questions

Staff Meetings and Public Roundtables

- Discussion guided by questions to get different groups’ perspectives

RFI/ Written input

- Focused questions to gain additional insight from individuals and/or groups
Thank You!

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