“Innovation to Impact: Beginning the Process”
ATVB/PVD, May 5, 2016

“Turning Discovery into Health:
The NIH translation paradigm”

Zorina S. Galis, Ph.D.
Chief, Vascular Biology and Hypertension Branch
National Heart, Lung, and Blood Institute
http://www.nhlbi.nih.gov/
National Institutes of Health
Zorina.Galis@nih.gov
Conflict disclosures

- No financial conflicts

**Note**: The opinions presented do not necessarily represent the opinions of the National Heart, Lung, and Blood Institute (NHLBI).
NIH’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

http://www.nih.gov/about/mission.htm
Defining “Translational research”

NIH NHLBI FY2016
Who funds US biomedical research?

Percent of total health costs: 4.5%

Major sources:
- Industry: 58%
- Federal: 33%

Dorsey ER et al.  JAMA 2010;303:137-43
Main contributors to the current paradigm of finding a cure

Dozens of ideas ("targets")
Millions of compounds

>10 yrs
>$2 billion

Academia
Biotech
Pharma

Public funds

The Valley of Death

Private funds

http://www.w3.org/2004/Talks/0612-sb-wswapps/slide33-0.html
Robert J. Lefkowitz, M.D. and Brian K. Kobilka, M.D. 2012 Nobel Prize for Chemistry for important basic scientific contributions to the field of G-protein coupled receptors (GPCRs)

NHLBI grantees: Lefkowitz since 1974, Kobilka since 1990

GPCRs are the target of the majority of currently used therapeutic agents (> 40%)

Their discoveries specifically led to the development of beta-adrenergic receptor blockers used to treat hypertension (HTN), angina, and coronary heart disease.
Pharma in the news: The “patent cliff”!

- “Drug makers face $140 billion patent ‘cliff’”
  Reuters

- “Warning: Patent cliff approaching”
  FiercePharma

- “Pharma refocuses on the patent cliff”,
  Chemistry World
How can we do more with less?
Cooperation and Efficient transitions among major stakeholders

- Understanding and aligning goals
- Understanding drivers, barriers, and strengths
- Need for “champions”
- Effectively managing transitions
Key Questions

Should public funds be spent on drug development? What is the role of NIH?

- What are the developmental/regulatory hurdles in NIH’s view?
- What is NIH doing about it?
- Is the NIH approach working?
- What could NIH do to make it better?
Role of NIH in early biomedical product development?

- Identify unmet medical needs
- Support fundamental knowledge
- Assess the best clinical evidence to inform health care decisions
- Work across the board to better serve the health needs of the patient (/tax-payer):
  - Assume risk of early funding (“de-risking”)
    - Provide assistance to the extramural inventors community
    - Assess critical development/regulatory gaps and hurdles
    - Special funding programs for early product development efforts, including critical national or local resources, à-la carte assistance
    - Create a framework to help accelerate translation

“ROI” – seek commercial development, however therapeutic value may trump potential financial return
Discovery to Development Pipeline
NHLBI Funding and Resources

- VITA, Vascular Interventions/Innovations and Therapeutic Advances
- SBIR, Small Business Innovation Research
- SMARTT, Science Moving Towards Research Translation
- GTRP, Therapy Gene Therapy Resource Program
- NCAI, NIH Centers for Accelerated Innovations

Galis, Black, Skarlatos, 2013 Circulation Research 112 (9), 1212-1218
“NHLBI is hearing you“: A biomedical product development sandbox

- NHLBI requirements:
  - Focus on specific medical conditions (what is/not included)
  - Funding mechanism: BAA w/check points (milestones-driven, “go/no go” decisions)
  - Maximum time/amount of funding

- Applicant-driven:
  - Propose project: product type, goals and milestones, allocation of effort/resources ($, time)
  - No restrictions on institutional affiliation
  - No required level of expertise/current access to resources

Vascular Interventions/Innovations and Therapeutic Advances

Managing ideas *lightly*... and the process *tightly*
SBIRs: NHLBI Office of Translational Alliances and Coordination (OTAC)

Charge: Develop and implement initiatives to enhance translation of technologies from the bench to the market

Lab to Market for Health

Contact NHLBI OTAC 301-496-2149
NHLBI SBIR-supported Products

- **CoaguChek®**: Because it’s my life
- **ThermoSuit**: The FASTEST non-invasive cooling in the world of medicine.
- **Heartsbreath™ Heart Transplant Rejection point-of-care breath test**
- **MENSSANA RESEARCH, INC.**: SERF Ablation System
- **THORATEC CORPORATION**: SARF Ablation System
- **THERMEDICAL**: Heart Transplant Rejection point-of-care breath test
Examples of various translational resources for NHLBI investigators

NHLBI and NIH

<table>
<thead>
<tr>
<th>Target ID and Characterization; Concept</th>
<th>Proof-Of-Concept</th>
<th>Preclinical</th>
<th>Ph. I</th>
<th>Ph. II</th>
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<tbody>
<tr>
<td>Selected Topic in Transfusion Medicine (R01, R21) PAR-13-025, PAR-13-026</td>
<td>Translational Program Project Grant (PO1) PAR-14-245</td>
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<td>Onsite Tools and Technology at the Point of Care SBIR/STTR HL-14-011/17</td>
<td>Gene Therapy Resources Program (GTRP)</td>
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<tr>
<td>Science Moving towards Research Translation and Therapy (SMARTT)</td>
<td>Small Business Innovation Research SBIR (PA-14-071)</td>
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<tr>
<td>NIH Research Evaluation and Commercialization Hub (REACH) Awards (U01) RFA-OD-14-005</td>
<td>Vascular Interventions/Innovations and Therapeutic Advances (VITA)</td>
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<tr>
<td>Bridging Interventional Development Gaps (BriDGs)</td>
<td>Therapeutics for Rare and Neglected Diseases (TRND)</td>
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<tr>
<td>Tissue Chip for Drug Screening</td>
<td>Discovering New Therapeutic Uses for Existing Molecules</td>
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c/o NHLBI Translational Research Working Group
Resources to help you get started with a translational research project: NHLBI repositories

(BioLINCC) https://biolincc.nhlbi.nih.gov/home/

- Clinical Trials (N > 80)
- Observational Epidemiology Studies (N >30)
- Searchable function for specimens/data of interest
- Apply directly on the website
Target discovery: “Illuminating the Druggable Genome (IDG)” NIH Common Fund

IDG Will Foster Basic Research to Enable Translation

Functionalization | Protein Prioritization | Assay Develop. | Screening | Hit to Lead | Lead Valid. | Lead Optim. | Pre-Clinical Development | Phase 1-4

IDG Tools & Technology Development Knowledge Management Center

Enhanced Basic Research Portfolio

Small Business
Pharma
NIH Translation

http://commonfund.nih.gov/idg/index
Precision medicine is an emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.

The NIH Precision Medicine Initiative will generate the scientific evidence needed to move the concept of precision medicine into clinical practice.

**NIH Request for Information** (RFI) Closes May 7th!!
Find potential collaborators and resources available within the NIH Intramural program

http://www.cc.nih.gov/translational-research-resources/index.html
“Got idea?” Find NIH funding opportunities!

Google: “NIH funding opportunities”

https://grants.nih.gov/grants/oer.htm
Clinical Research Guide for NHLBI Investigators

Preparing, submitting and managing a clinical research award can be challenging. This site is designed to guide potential investigators in organizing a clinical research application and to provide information on conducting a study and maintaining an award. Here you will find:

- An Overview of Human Subjects Research
- Pre-application Information
- Peer Review Details
- Funding Information
- Grants Oversight and Management Tips
- Closing a Study Specifically
- Toolkit Resources

ATTENTION: Specific Guidelines for Applications with Direct Costs of $500,000 or More in Any One Year

NEW requirements for Multi-site Clinical Trials will apply as of Oct 16, 2016 (to be published in April 2016)
Research Portfolio Online Reporting Tools (RePORT)

In addition to carrying out its scientific mission, the NIH exemplifies and promotes the highest level of public accountability. To that end, the Research Portfolio Online Reporting Tools provides access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and the results of NIH.

http://report.nih.gov/
Find collaborators, home for your applications, etc.

“NIH Matchmaker”

Which NIH Institute might be interested in my research?

What type of mechanism (e.g., R01, R21, etc.)?

Which Study Section is likely to review my application?

What other similar research was funded by the NIH?

Who are the PIs?

Active Awards FY2015 NIH Re-PORTER
Turning discovery into health...

WE WANT YOU!
The NHLBI webpage
www.nhlbi.nih.gov
FY 2016 NHLBI FUNDING AND OPERATING GUIDELINES
http://www.nhlbi.nih.gov/funding/policies/operguid.htm
NHLBI Strategic Visioning
http://strategicvisioning.nhlbi.nih.gov
Research Portfolio Online Reporting Tools (Re-PORTER)
http://projectreporter.nih.gov/reporter.cfm
NIH-sponsored Clinical Trials
www.clinicaltrials.gov

When in doubt…. Google it!
Basic research is essential for development of new therapeutics: Hypertension

Most cited by patents are ALL basic science studies
(n=165, Uehata et al., 1997; n=154, Halushka et al., 1999, n=113, Mullins et al., 1990)

>> Presented at CV Drug Development Think Tank, July 2014
NIH sponsored development of essential building blocks: some NCATS translational programs

<table>
<thead>
<tr>
<th>Program Name</th>
<th>Description</th>
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<tr>
<td>Clinical and Translational Science Awards (CTSAs)</td>
<td>National consortium of academic center-associated research bastions focused on the translation and the training of the next generation of academic medicine researchers</td>
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<tr>
<td><a href="https://www.ctsacentral.org">link</a></td>
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<tr>
<td>Molecular Libraries Program (MLP)</td>
<td>This program gives researchers access to the large-scale small molecule screening capacity, along with medicinal chemistry and informatics necessary to identify chemical probes to study the functions of genes, cells and biochemical pathways.</td>
</tr>
<tr>
<td>[link](<a href="http://www.ncats.nih.gov/research/reengineerin">http://www.ncats.nih.gov/research/reengineerin</a> g/ncgc/mlp/mlppc.html)</td>
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</tr>
<tr>
<td>Bridging Interventional Development Gaps (BrIDGs)</td>
<td>Previously known as the NIH Rapid Access to Intervention Development (RAID) program, was launched under its new name in October 2011. BrIDGs makes available, on a competitive basis, certain critical resources (synthesis, formulation, pharmacokinetic and toxicology services) needed for the development of new therapeutic agents.</td>
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<td><a href="http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html">link</a></td>
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<tr>
<td>Therapeutics for Rare and Neglected Diseases (TRND)</td>
<td>Program to stimulate and speed the development of new drugs for rare and neglected diseases. Research collaborations between NIH and academic scientists, non-profit organizations, and pharmaceutical and biotechnology companies are highly encouraged.</td>
</tr>
<tr>
<td><a href="http://www.ncats.nih.gov/research/rare-diseases/trnd/trnd.html">link</a></td>
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<tr>
<td>Cures Acceleration Network (CAN)</td>
<td>This program is to advance the development of high need cures and reduce significant barriers between research discovery and clinical trials.</td>
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<tr>
<td><a href="http://www.ncats.nih.gov/funding-and-notices/can/can.html">link</a></td>
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<tr>
<td>Office of Rare Diseases Research (ORDR)</td>
<td>ORDR supports and coordinates rare disease research, responds to research opportunities for rare diseases and provides information on rare diseases.</td>
</tr>
<tr>
<td><a href="http://www.ncats.nih.gov/research/rare-diseases/ordr/ordr.html">link</a></td>
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Getting started with a translational research project: other specific opportunities

- **Secondary Dataset Analyses in Heart, Lung, and Blood Diseases and Sleep Disorders (R21)** funding to investigate existing human datasets to test innovative hypotheses relevant to the NHLBI mission. Up for renewal. **Scientific contact:** Ruth Kirby, RN at Ruth.Kirby@nih.gov

- **Genetically-Triggered Thoracic and Aortic Aneurysms (GenTAC) [https://gentac.nhlbi.nih.gov/](https://gentac.nhlbi.nih.gov/)** Active Registry of clinical data and biological specimens. Apply for access directly on website or contact: Dr. Eser Tolunay, (301) 435-0560, Eser.Tolunay@nih.gov
How can we do more with less?

Understanding key barriers (and drivers) for major stakeholders

- **Academia**: tension between publishing and IP, resource fragmentation, lack of know-how
- **Biotech/Small private**: scarce resources
- **Pharma**: tension between mission and goals (profit), legacy business model, “The patent cliff”
- **Government**: multiple constituencies, “red tape,” limited reach
- **Investment/Venture**: risk adverse (!)
- **Consumer/patient**: unmet medical needs, wants personalized care, worries about cost of innovation
Enabling innovation: biomedical product development “cloud”

Offerors: academic, industry, partnership, +/- CRO
Product (offer) types: therapeutics, devices, diagnostics
Solutions for: Vascular disease, Pulmonary hypertension, Thrombotic disorders
Enablers: NHLBI, EAC, PCC
PHASE I – R41, R43
• Feasibility Study
• $225K for 6-12 months

PHASE II – R42, R44
• Full Research/R&D
• $1.5M for 2 years
• Commercialization plan required

PHASE III
• Commercialization Stage
• Use of non-SBIR/STTR Funds

Bridge and Small Market Awards
• $1 million per year for 3 years
• Supports products requiring FDA clearance/approval
• Requires matching funds

Contact NHLBI Office of Translational Alliances and Coordination (OTAC)
301-496-2149
nhlbi_sbir@mail.nih.gov

http://www.nhlbi.nih.gov/research/funding/sbir/
New type of translational program designed to address community’s concerns

<table>
<thead>
<tr>
<th>Perceived need/barrier</th>
<th>Proposed VITA feature</th>
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<tbody>
<tr>
<td>Unmet medical need: widespread disease conditions “neglected” by the industry</td>
<td>Focused on:</td>
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<tr>
<td></td>
<td>• vascular disorders</td>
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<td>• thrombotic diseases</td>
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<tr>
<td></td>
<td>• pulmonary hypertension</td>
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<tr>
<td>Many untested early concepts/ideas for medical products</td>
<td>Consider new diagnostics, therapeutic agents, or devices; repurposing</td>
</tr>
<tr>
<td>Scarcity of funding for early product concepts</td>
<td>Provide support for very/early stage development</td>
</tr>
<tr>
<td>Perceived need/barrier</td>
<td>Proposed VITA feature</td>
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<tr>
<td>--------------------------------------------------------------------------------------</td>
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<tr>
<td>Difficult career decision for academics to engage in early product development</td>
<td>Eliminate requirements regarding PI affiliation with a company</td>
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<tr>
<td>Lack of ‘know-how’ and/or local access to needed product development resources</td>
<td>Provide needed training and project support regardless of geographical localization (within US)</td>
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<tr>
<td>Diverting NIH money from funding basic research</td>
<td>Increased fiscal responsibility, Contract style (BAA): milestone-driven process, “go/no go” decisions points</td>
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</tbody>
</table>
NHLBI VITA team:

- **Division of Cardiovascular Sciences (DCVS)**, Basic and Early Translational Research (BETR)
  - Vascular Biology and Hypertension Branch (VBHB) : Zorina Galis,* Eser Tolunay,* Yunling Gao,* Cheryl McDonald,* VITA Program Director, Marc Charette, * VITA Program Director
  - Advanced Technologies and Surgery Branch (ATSB): Simhan Danthi*

- **Division of Blood Diseases and Resources** (DBDR), Thrombosis and Hemostasis Branch, Andrei Kindzelski

- **Division of Lung Diseases (DLD)**: Tim Moore

- **Division of Extramural Research Activities (DERA)**, Office of Acquisitions (OA): Keli Malkin, Janet Mattson, Jennifer Swift, Contracting Officers

(*previous industry experience)

**With input from:**
NHLBI colleagues and leadership