Why society needs researchers

Robert S. Chapkin, M.S., Ph.D.

Program in Integrative Nutrition & Complex Diseases
Texas A&M University

Center for Translational
Environmental Health Research

Why we do research?

- **Without a deep understanding of fundamental facts it is difficult, and often impossible, to make progress in understanding a problem, e.g., disease state.**

- **It is often necessary to work in teams. This structure is designed to bring the expertise of chemists, physicists, engineers, computer scientists, mathematicians, and biologists to bear on a complex problem, e.g., cancer.**

- **Industry has successfully conducted research in this manner for years. Academia is lagging far behind.**

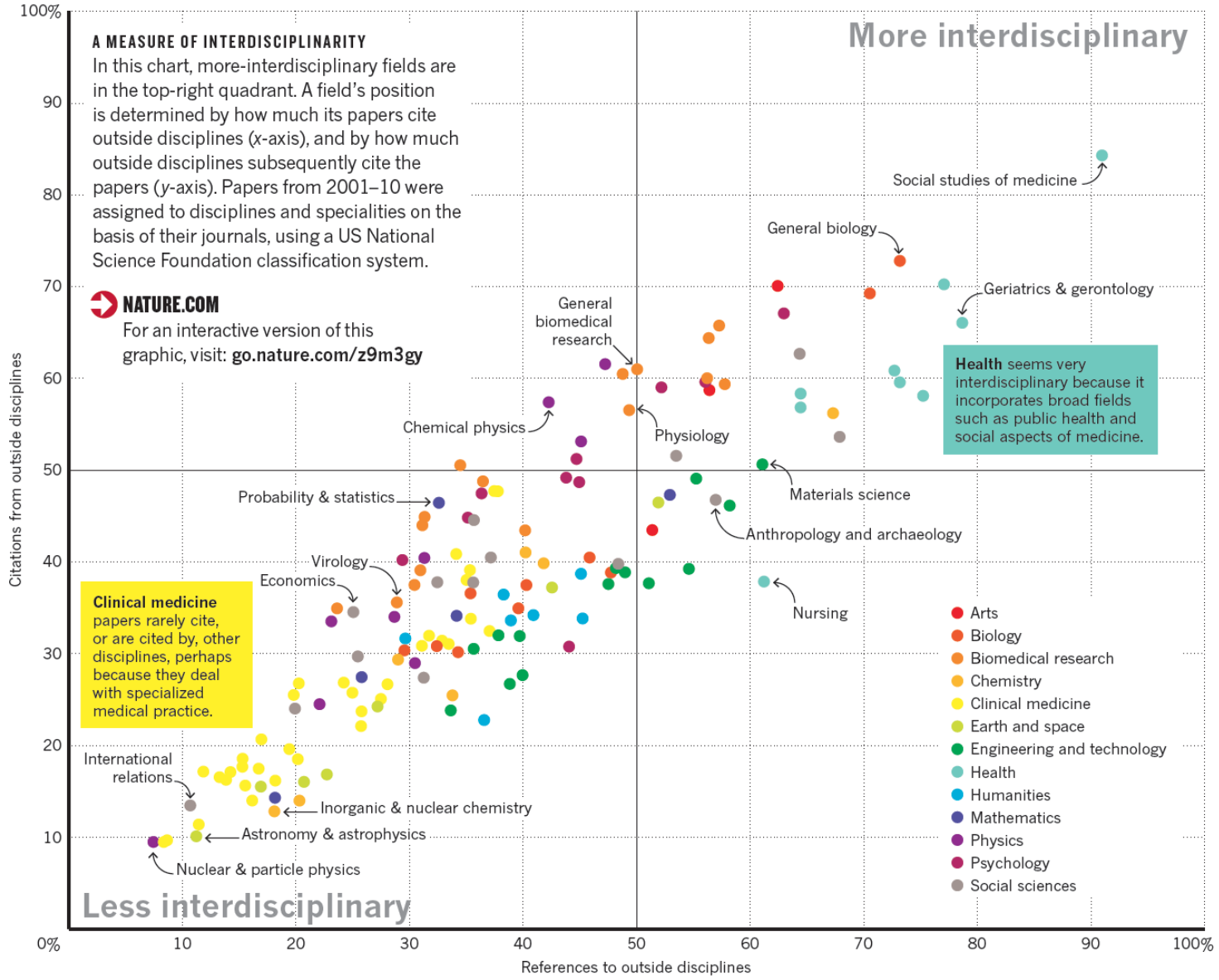
Toward a more pluralistic mindset

- **The winner-takes-all approach to science can lead to the loss of creativity.**
- **Often the greatest breakthroughs in science have come precisely from researchers who challenged the accepted truths of their discipline.**
- **Narrow-minded approaches to funding and publishing can stifle innovation.**
- **A pluralistic approach needs to be undertaken to ensure open-minded quality control.**

At Texas A&M University, we do BIG SCIENCE

Transdisciplinary research: A vision for integrating silos

3 Some fields are more interdisciplinary than others ...

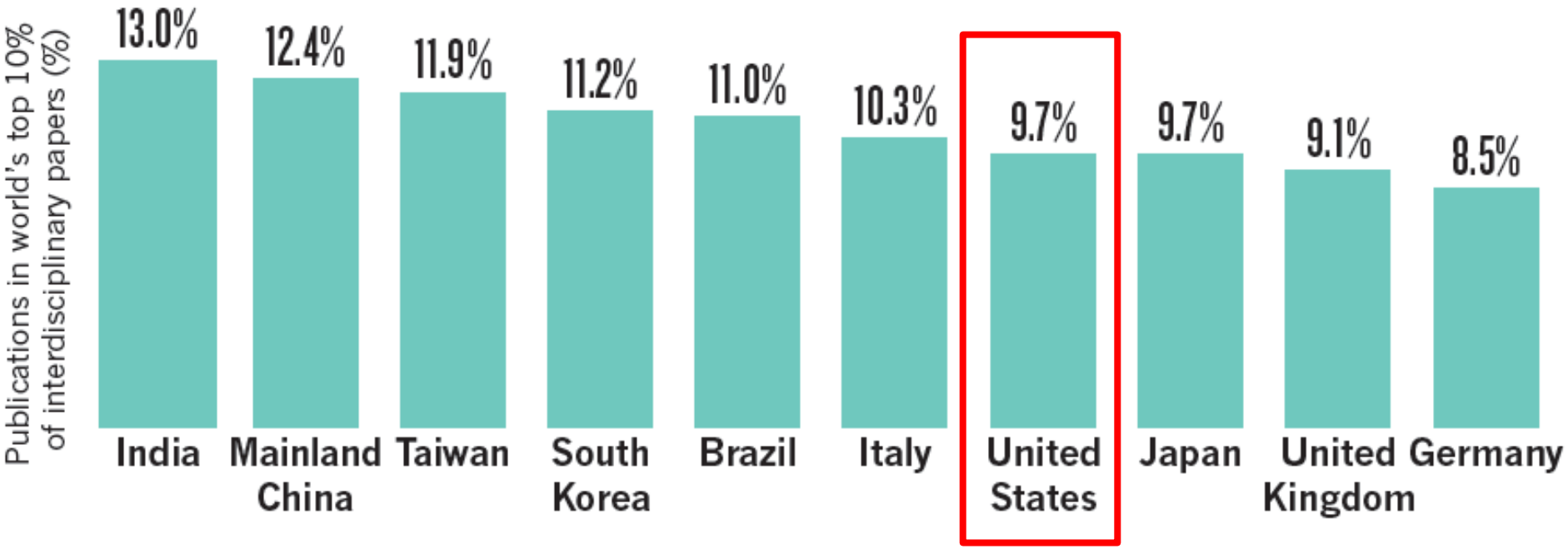


Van Noorden, Nature 525:306, 2015

4 ... and so are some countries

MOST INTERDISCIPLINARY COUNTRIES

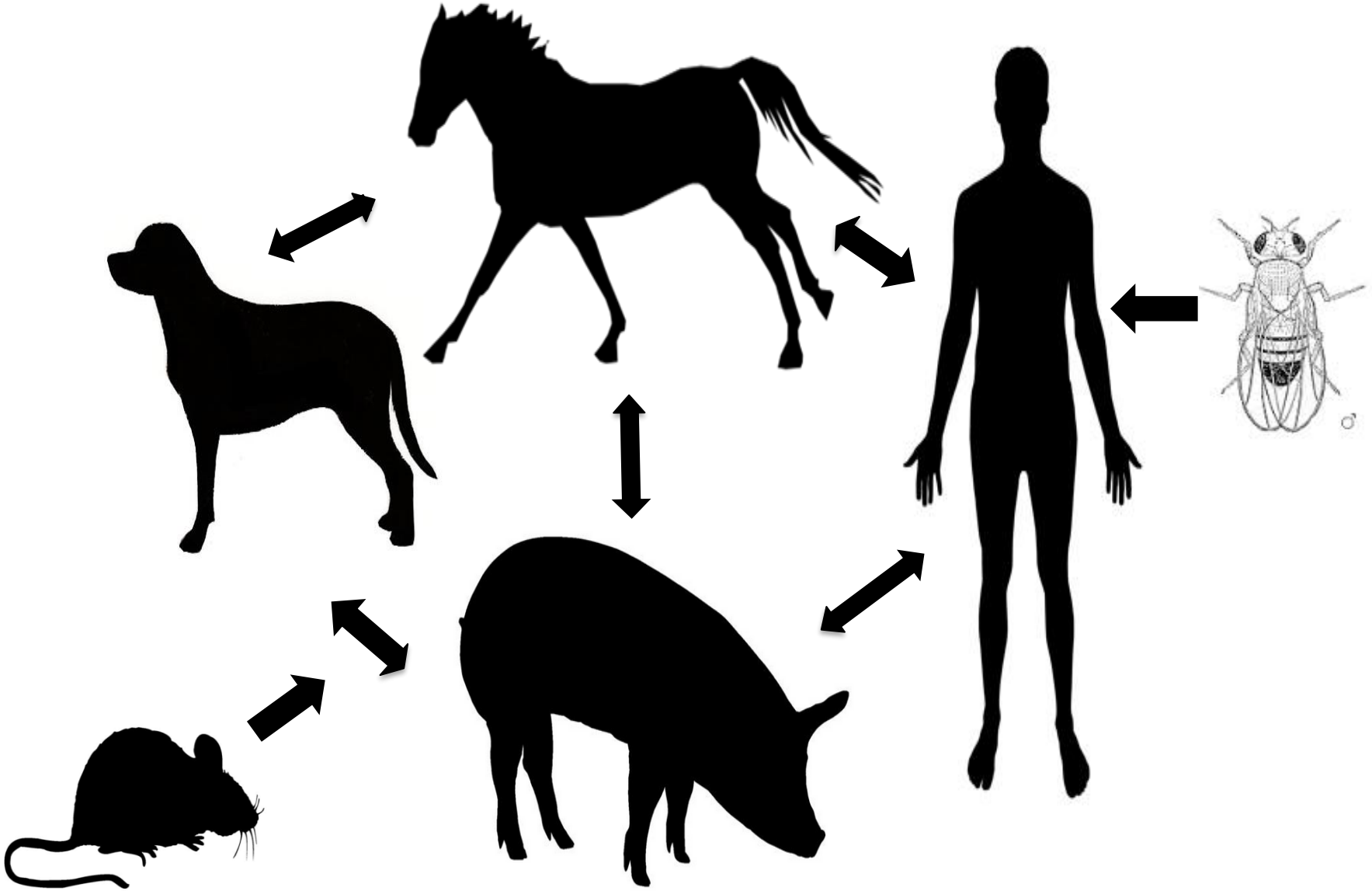
A 2015 study by researchers with the publisher Elsevier defined interdisciplinary papers as those that reference journals that are rarely cited together. The report looked only at countries that routinely publish more than 30,000 papers per year to find the 'most interdisciplinary' countries for 2013.



Van Noorden, *Nature* 525:306, 2015

Scientists must work together to save the world. A special issue asks how they can scale disciplinary walls.

ONE HEALTH
TEXAS A&M UNIVERSITY



Disappearing Silos

Chapkin lab research: Molecular basis for cancer prevention by dietary & microbial bioactives

Program in Integrative Nutrition & Complex Diseases

Center for Translational Environmental Health Research

Center for Translational
Environmental Health Research

CHAPKIN LAB

PROGRAM IN INTEGRATIVE
NUTRITION & COMPLEX DISEASES

NCI Outstanding Investigator Award Recipients

NCI's Outstanding Investigator Award supports accomplished leaders in cancer research, who are providing significant contributions toward understanding cancer and developing applications that may lead to a breakthrough in biomedical, behavioral, or clinical cancer research. Below are profiles of the most recent NCI Outstanding Investigator Award recipients.

Molecular Basis for Dietary Chemoprevention

Research on Arylhydrocarbon Receptor (AhR) and Gut Health

Diet

Dietary AhR ligands

Data Analysis

AhR diet →

Microbiota & Metabolites
AhRm

Metabolite Modeling

Metabolite Identification

AhR agonist / antagonist characterization

AhR diet →
AhRm

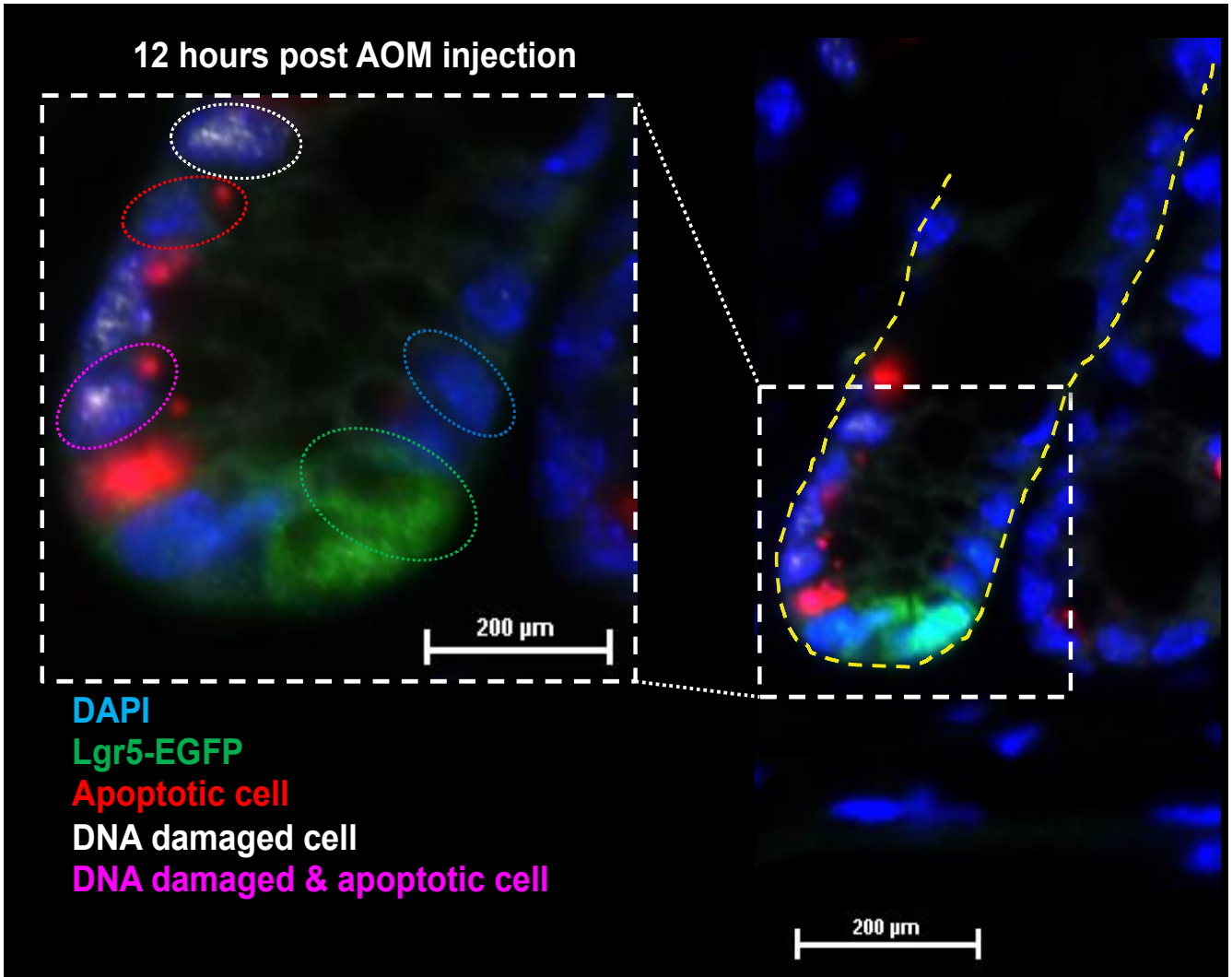
Colon

Colon stem cells

Chronic Inflammation

Cancer

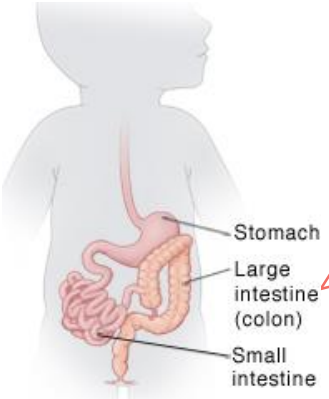
Use of diet/microbial bioactive molecules to target DNA damaged stem cells

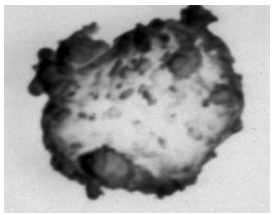


Host-Microbe Interactions in the Human Gut

What components in the diet/exposome affect intestinal microbiota?

Early Life Exposures & Developmental Reprogramming





Exfoliated Cells

Intestinal Microbiome (genetic diversity)

Human Genome (epigenetic variation)

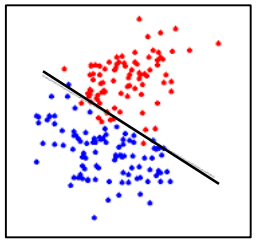
Human-Microbial Cross-talk

Bacterial Components & Metabolites

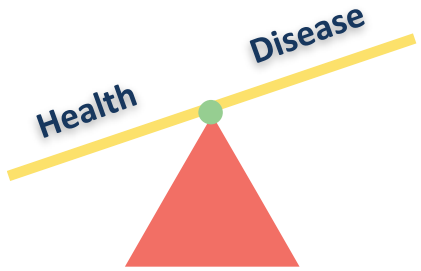
Which bacteria and their genes are involved in the interaction?

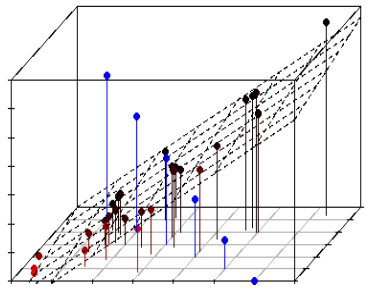
Which human genes are involved and respond to bacterial signals?

Data Integration/ Multivariate Analysis



Classification





Prediction

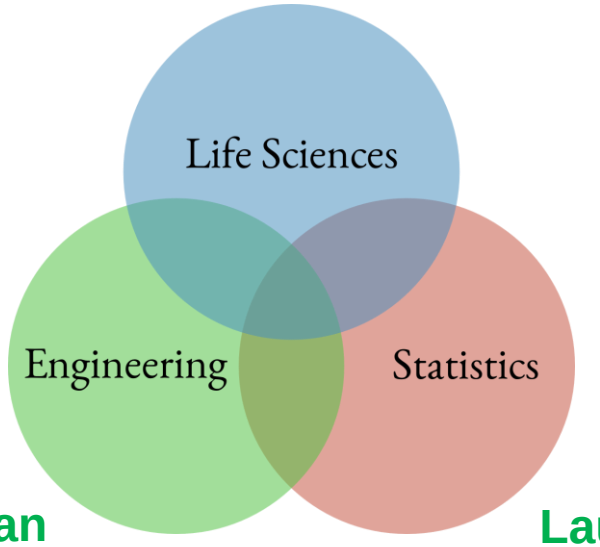
Schwartz *et al. Genome Biology* 2012, **13**:r32
http://genomebiology.com/2012/13/4/r32

Genome Biology

RESEARCH Open Access

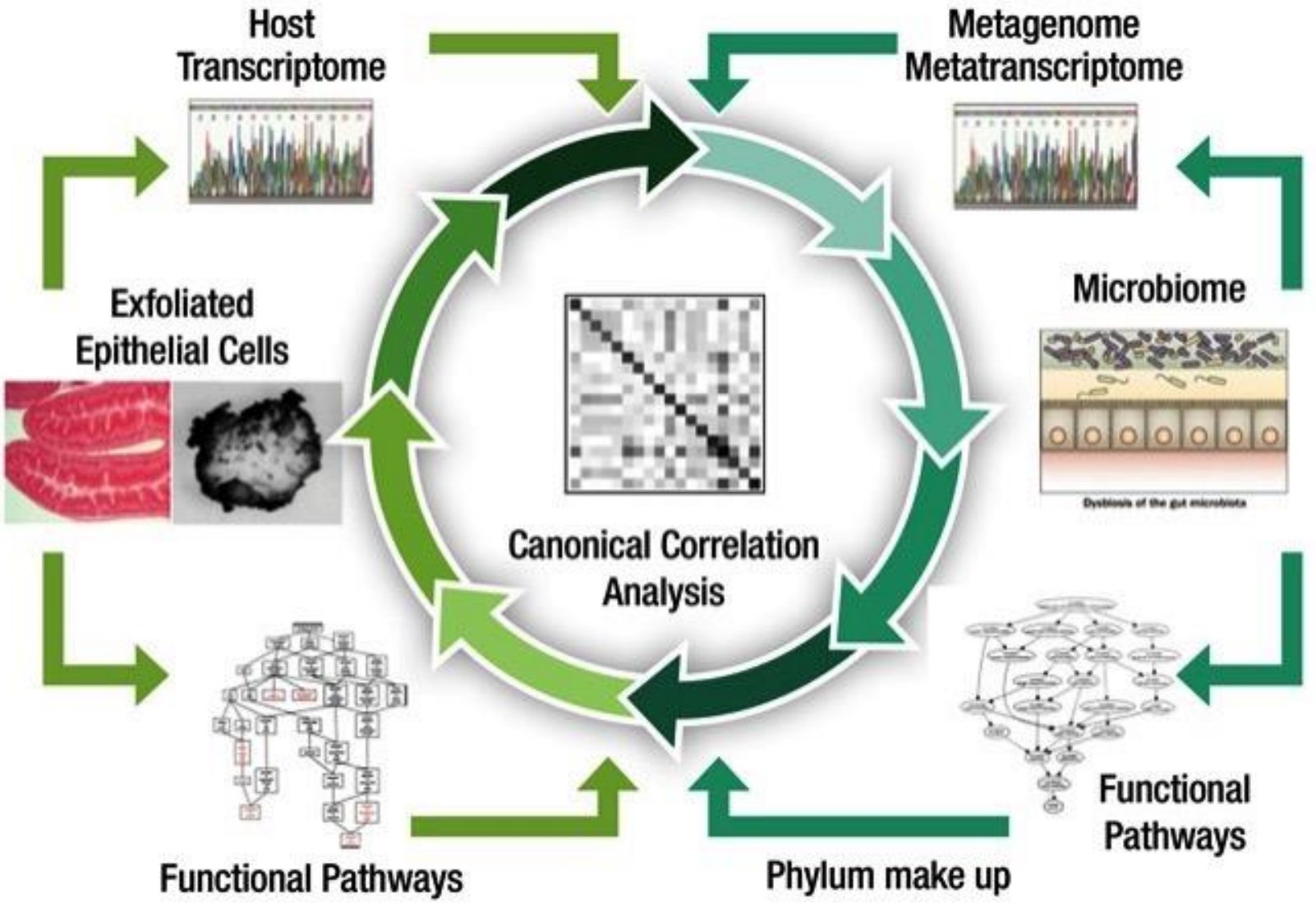
A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response

Scott Schwartz[1,2], Iddo Friedberg[3,9], Ivan V Ivanov[4,5], Laurie A Davidson[1,4], Jennifer S Goldsby[4], David B Dahl[2], Damir Herman[6], Mei Wang[7], Sharon M Donovan[7] and Robert S Chapkin[1,3,8*]



Ivan Ivanov Sharon Donovan Laurie Davidson Scott Schwartz

Sparse Canonical Correlation analysis of host and microbiome data sets

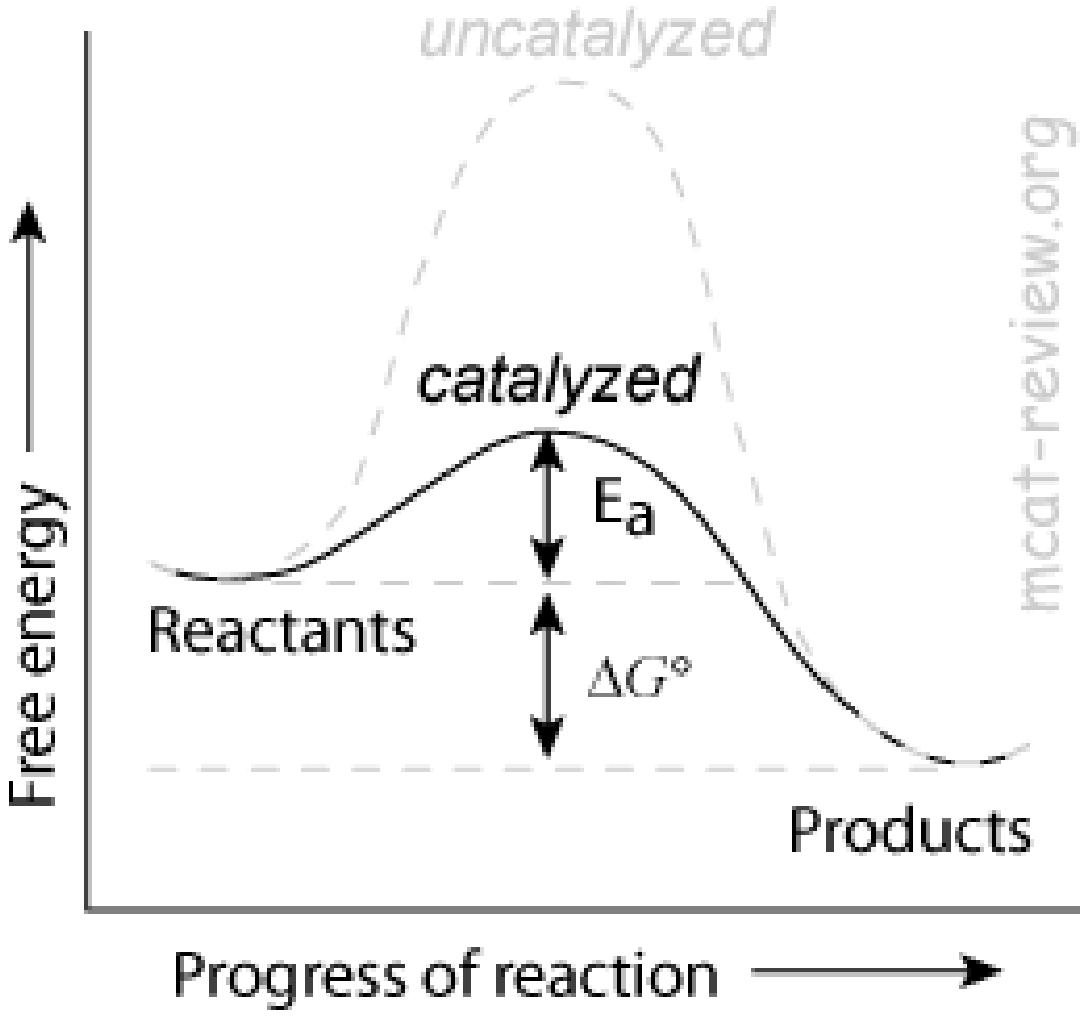


Systems Biology

- Modeling, at the molecular level, the dynamic relationships between diet and host/microbial molecules which regulate colon cancer and developmental biology of the intestine.

- Diagnostic mRNA, histone code, long non-coding RNAs and microRNA expression patterns to assess “phenotypic flexibility”.

I see myself as a catalyst……



CPRIT Training in Cancer Prevention and Patient Survivorship

Center for Translational Environmental Health Research

NIH P30 ES023512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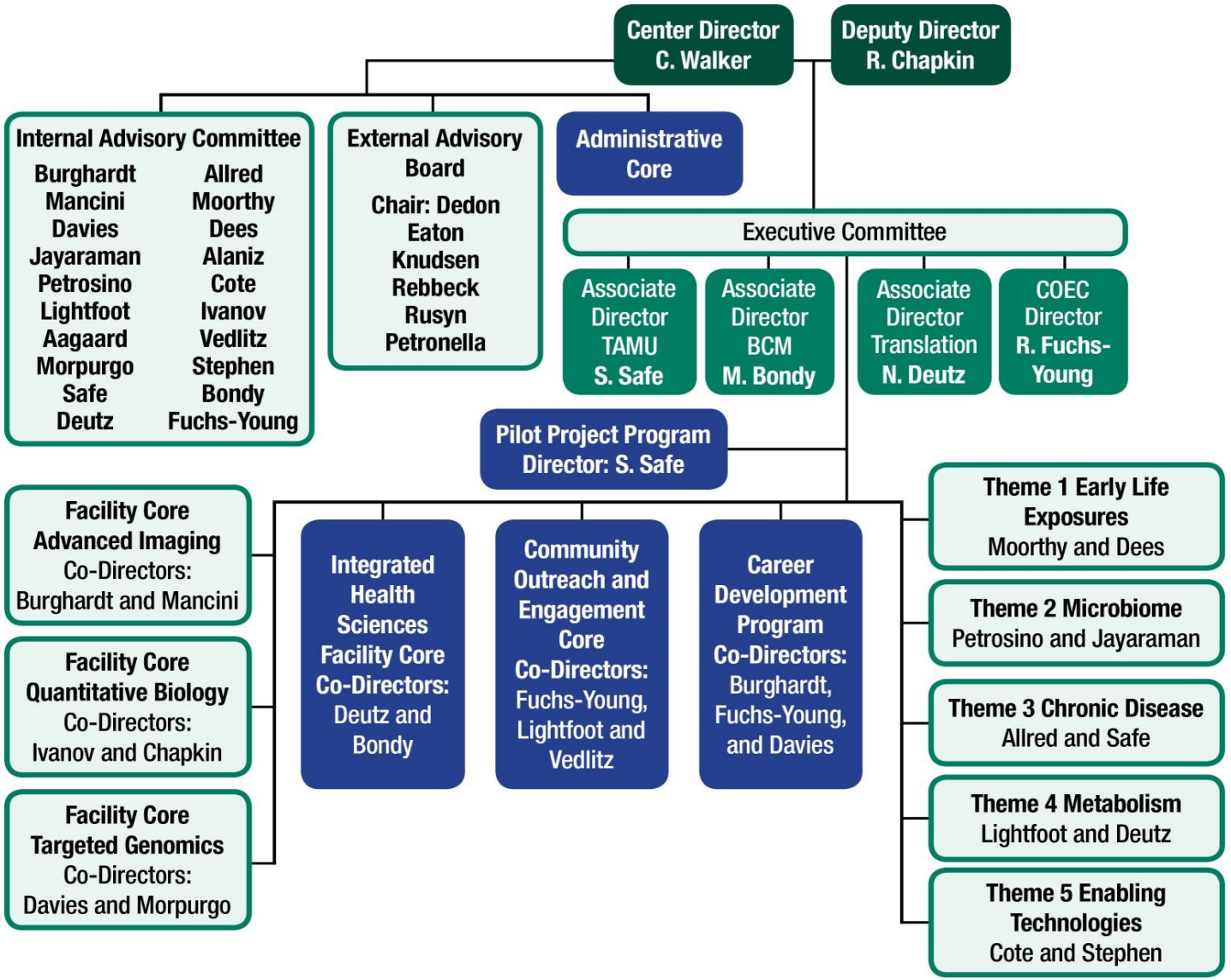
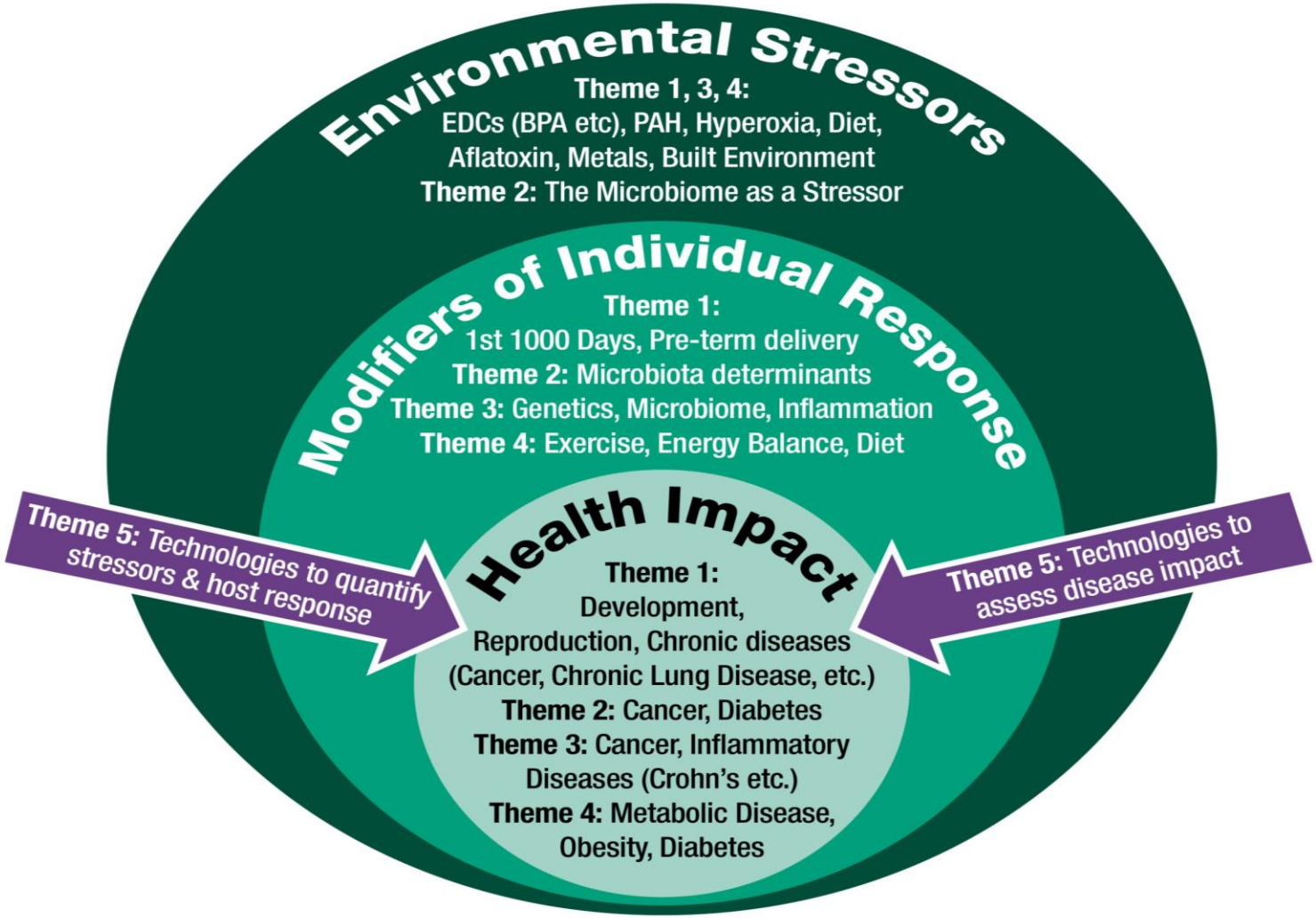
Mexico
Cuba
Puerto Rico
Guatemala
Caribbean Sea

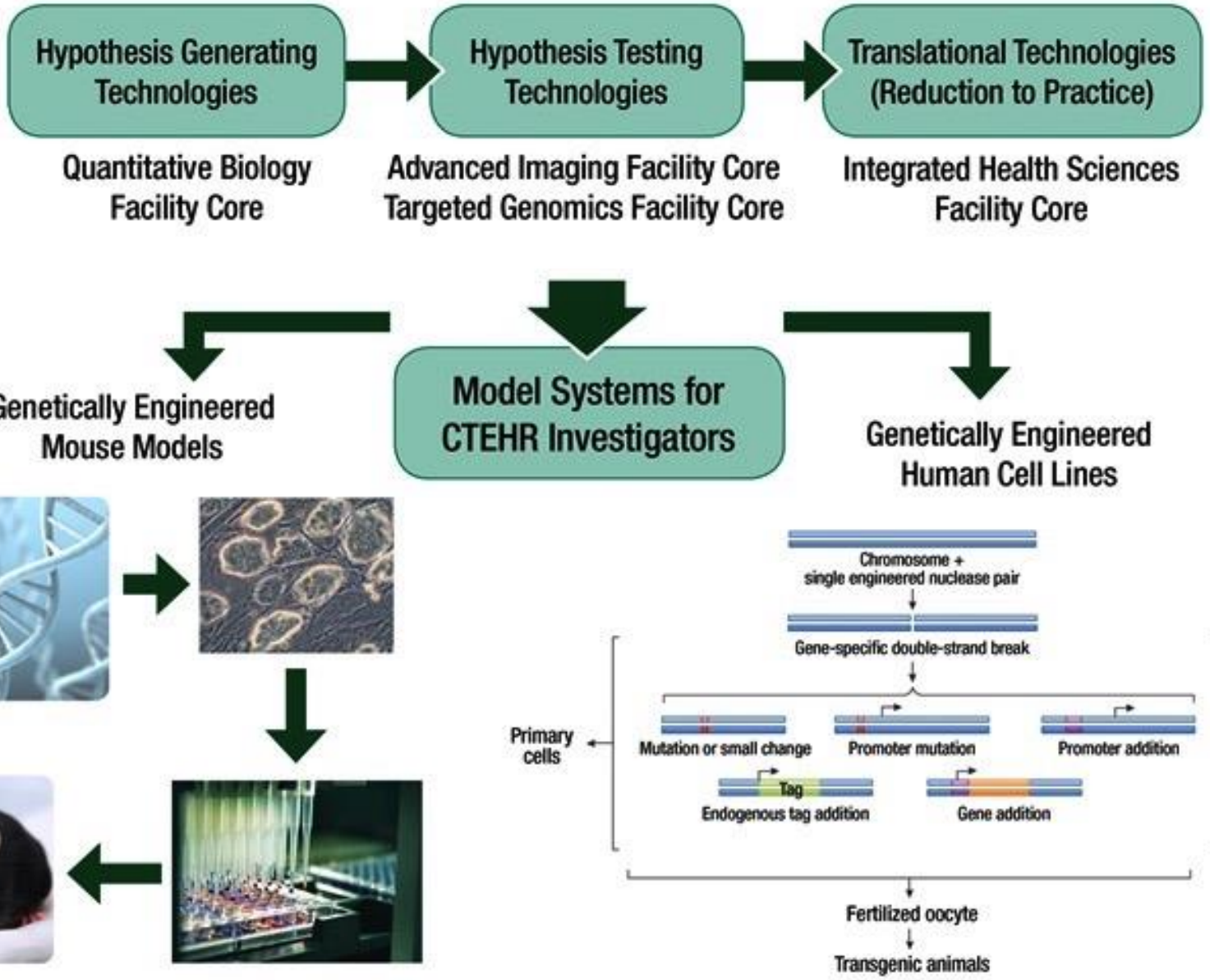
CTEHR Organizational structure



CTEHR research focuses on environmental stressors, modifiers of individual exposure/response and human health outcomes



An integrated discovery pipeline for environmental health sciences research



Little Science

Graduate Students: Need to ask the right questions

- **You are at the beginning of your career -> developing critical thinking skills.**
- **Pay careful attention to what your experiments are really telling you.**
- **Learn how to differentiate between authentic data vs artifact. Essential to establish “controls”, so you can determine what is worth investigating further.**
- **Pay attention to negative results.**
- **Learn from your mistakes.**


You Dun
Goofed Up

Biomarker development: Prudence, risk, and reproducibility

Edward R. Dougherty

A recent report regarding comments by Janet Woodcock, FDA drug division head, states, "Based on conversations Woodcock has had with genomics researchers, she estimated that as much as 75 per cent of published biomarker associations are not replicable. 'This poses a huge challenge for industry in biomarker identification and diagnostics development,' she said" [1].

Bioessays 34: 277–279,


RE-
DO!

How to choose a research area

- **Read the scientific literature.**
- **Attend conferences and seminars.**
- **Join a research society.**
- **Brainstorm ideas with peers.**
- **Define focused questions in the research area.**
- **Ensure the research area is fundable.**

Sivakumar, ASCB Newsletter, June 2016

What is the secret to a successful career in science?

- **See yourself as an explorer (take risks, try to do new things, be prepared for failure).**
- **Embrace the paradox, this often leads to more exciting discoveries.**
- **Communicate your “out of the box” ideas with others.**
- **Ask significant questions, “think small, talk big”.**
- **Don’t expect linearity, opportunities for unexpected findings will open up.**
- **Show your enthusiasm, appreciate your colleagues.**
- **Teach, mentor and have high standards.**

Walter, ASCB Newsletter, June 2016

A look into the future

Understanding the fundamentals of research

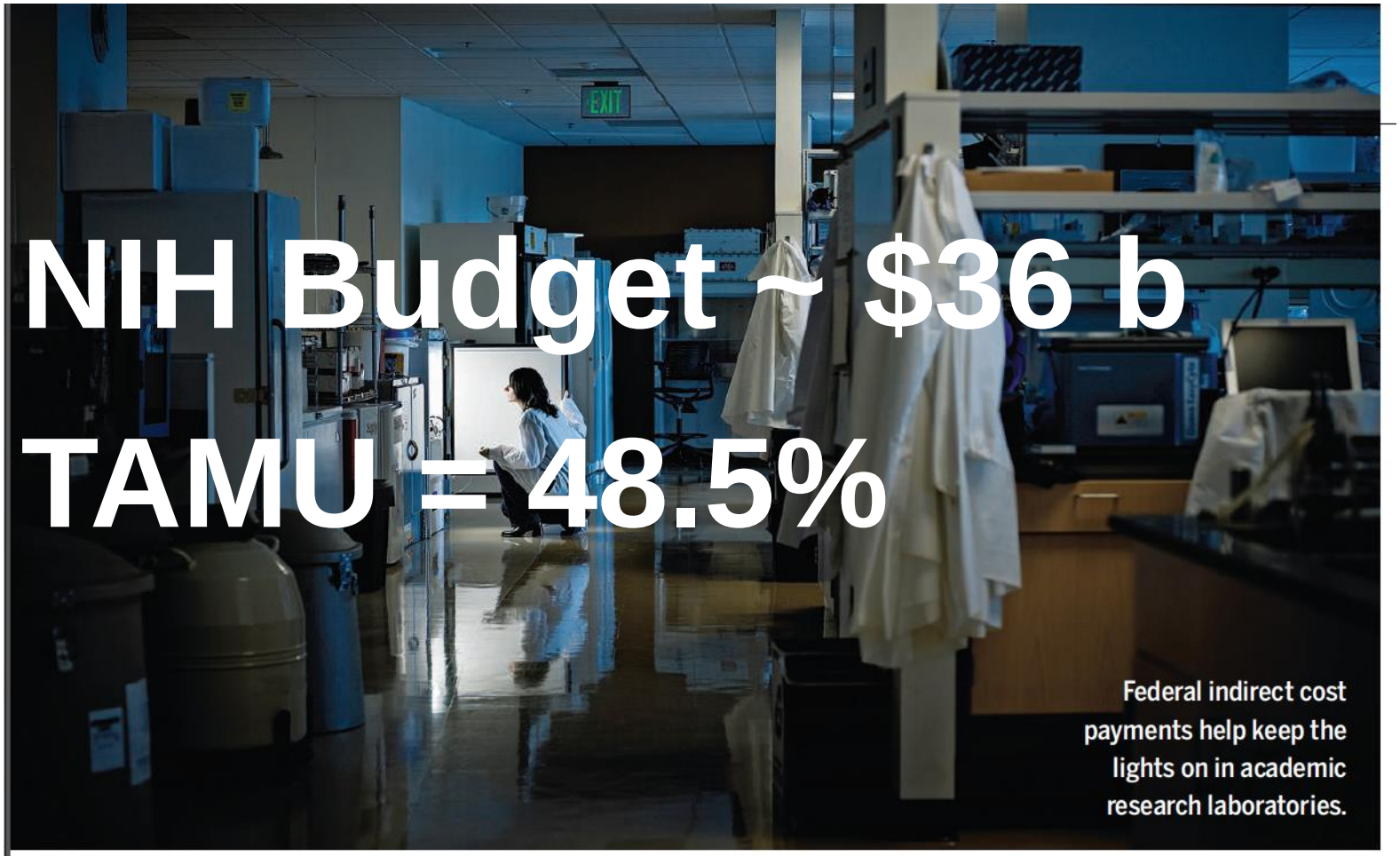
- **First you get the money, then you do the research.**
- **The government is dropping the ball. Science (NIH and NSF) and related funding is at a 50 year low.**
- **Start Up Scholar is a funding platform for educational projects for students in higher education that aims to connect donors with college students.**

NIH must support broadly focused basic research

The National Institutes of Health, to its detriment and that of society at large, appears to be veering away from its traditional mission of broad, species-diverse research. Image courtesy of Carnegie Institution for Science.

In the expansive view of NIH research, all biological systems whose properties make them worthy of current study are synergistic partners with mammalian and human systems, not competitors.

Spradling, PNAS 113:8340, 2017



NIH Budget ~ $36 b

TAMU = 48.5%

Federal indirect cost payments help keep the lights on in academic research laboratories.

BIOMEDICAL RESEARCH

NIH overhead plan draws fire

White House wants to reduce indirect cost payments to universities from 28% to 10% of NIH's research spending

Kaiser, *Science* 3565:893, 2017

Submitting an NIH grant: Required Files

Cover Letter (not required, but highly recommended)
Project Summary/Abstract – No more than 25-30 lines
Project Narrative 2-4 sentences layman's terms

Specific Aims – 1 page limit (purpose, rationale, hypotheses, significance, expectations, impact, solution to a problem, innovation, long term goal)
Introduction to Application (for resubmission/revision only)

Research Strategy– 12 page limit (aims, introduction, review of relevant literature, preliminary data, research design, expected outcomes, potential problems & alternative strategies, timeline, future directions)

Protection of Human Subjects – if applicable
Vertebrate animals – if applicable
Select Agent Research – if applicable
Consortium – if applicable
Letter or Support
Resource Sharing Plan
Facilities and other resources
Equipment
Biosketch 4 pages (include active and completed support).
Budget – Modular budget
Budget justification - Personnel justification only required for modular budgets

Purpose of the Award

• Provides funding to support investigator-initiated research on a discrete, specified, circumscribed project

• Investigator-initiated research, also known as unsolicited research, is research funded as a result of an investigator submitting a research grant application to NIH in an investigator's area of interest and competency

Details

• NIH's most commonly used grant program
• No specific dollar limit unless specified in FOA
• Generally awarded for 3 to 5 years
• Utilized by all NIH Institutes and Centers

• A comprehensive list of Guidelines for Reviewers is available at http://grants.nih.gov/grants/peer/reviewer_guidelines.htm

1. Significance

Strengths

•

Weaknesses

•

OVERALL IMPACT

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria.

An application does not need to be strong in all categories to be judged likely to have major scientific impact.

If all the specific aims are achieved, what would the project contribute to this field and how significant/important is this contribution?

- Significance assumes success of the specific aims.
- Premise pertains to the strength of the scientific foundation upon which the objectives of the study are built. Is the current project based on sound scientific knowledge or concepts?
- Focus on the importance of the proposed work in the field, NOT the importance of the disease or condition (e.g., child obesity, probe development) being studied.
- Direct relevance to human health is not required. Significance can be related to the basic/ fundamental, mechanistic, technological, translational, clinical and public health contributions.

2. Investigator(s)

Strengths

•

Weaknesses

•

If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training?

If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)?

If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Does the investigative team have the collective expertise to lead the project, do the work and interpret the results?

- Assess evidence of appropriate expertise for the proposed project.
- Assess evidence of or potential for successful project management and execution.
- Investigator independence should not be considered.
- For Multi-PI applications, you should address each Principal Investigator and the leadership plan.

3. Innovation

Strengths

-

Weaknesses

-

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?

Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?

Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

4. Approach

Strengths

-

Weaknesses

-

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?

Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (exclusion) of children, justified in terms of the scientific goals and research strategy proposed?

Overall Impact:
The likelihood that a project will have a sustained and powerful influence on science (and/or clinical practice and/or technological developments?)

Overall Impact	High	Medium	Low
Score	1 2 3	4 5 6	7 8 9

Evaluating Overall Impact:
Consider the 5 criteria: significance, investigator, innovation, approach, environment (weighted based on reviewer's judgment)

e.g. Applications are addressing a problem of high importance in the field. May have some or no technical weaknesses.

e.g. Applications may be addressing a problem of high importance in the field, but weaknesses in the criteria bring down the overall impact to medium.

e.g. Applications may be addressing a problem of moderate importance in the field, with some or no technical weaknesses

e.g. Applications may be addressing a problem of moderate/high importance in the field, but weaknesses in the criteria bring down the overall impact to low.

e.g. Applications may be addressing a problem of low or no importance in the field, with some or no technical weaknesses.

5 is a good medium-impact application, and the entire scale (1-9) should always be considered.

Littermate controls
Cre controls
Randomization
Power calculations
Appropriate (n)
Male and female
Inclusive reporting

Precise Identification
Contamination
Infection
Culture conditions
Passage number

Validation
Sensitivity
Specificity

Towards Reproducible Research

Quantify reproducibility
for Scientists & Journals
Discuss reproducibility
Value reproducibility
Reward reproducibility

Comprehensive methods
Source of all reagents
Appropriate statistics

Drucker, *Cell Metabolism* 24:348, 2016

RIGOR AND TRANSPARENCY IN NIH & AHRQ GRANT APPLICATIONS

Purpose

The purpose of this notice is to inform the research community of new updates to grant applications and reviews that will enhance the reproducibility of research findings through increased scientific rigor and transparency.

Background

NIH defines scientific rigor as *the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation, and reporting of results.*

Scientific rigor also includes transparency in reporting full experimental details so that others may reproduce and extend the findings.

The **four areas** deemed important for enhancing rigor and transparency and apply to the full spectrum of research, basic to clinical, are:

1. The scientific premise forming the basis of the proposed research,
2. Rigorous experimental design and unbiased results,
3. Consideration of relevant biological variables, and
4. Authentication of key biological and/or chemical resources.

NIH expects the applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods. Robust results are obtained by using methods designed to avoid bias and can be reproduced under well-controlled and reported experimental conditions.

Subscribe to Peer Review Notes: www.csr.nih.gov/prnotes

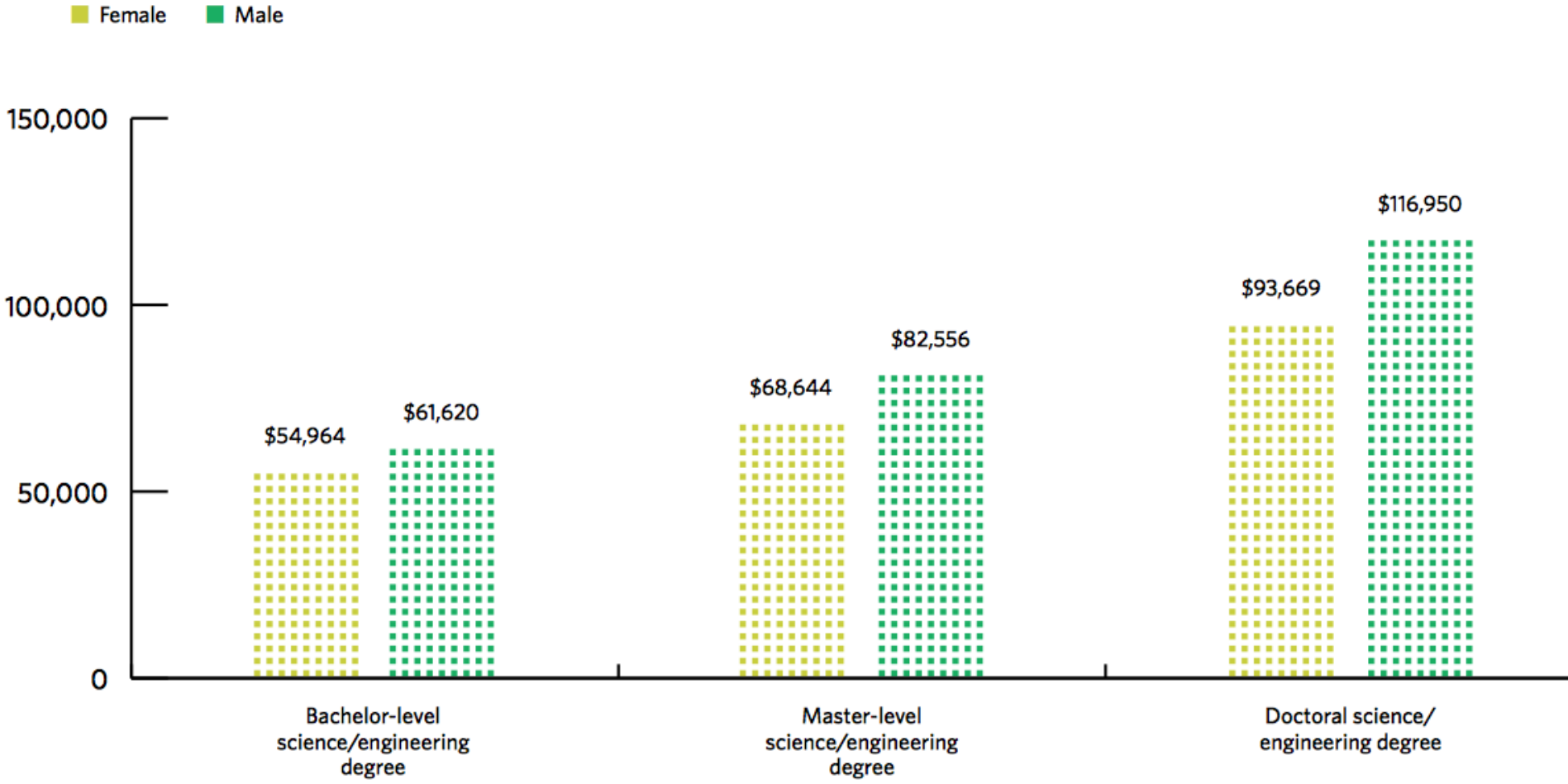
Send comments or questions: PRN@csr.nih.gov

Center for Scientific Review
National Institutes of Health
U.S. Department of Health and Human Services

Congratulations on a job well done!

You are contributing to the generation of new knowledge.

AVERAGE COMPENSATION IN U.S.



Holy grail: tenure track faculty position

Professor Emeritus

Full Professor

Associate Professor

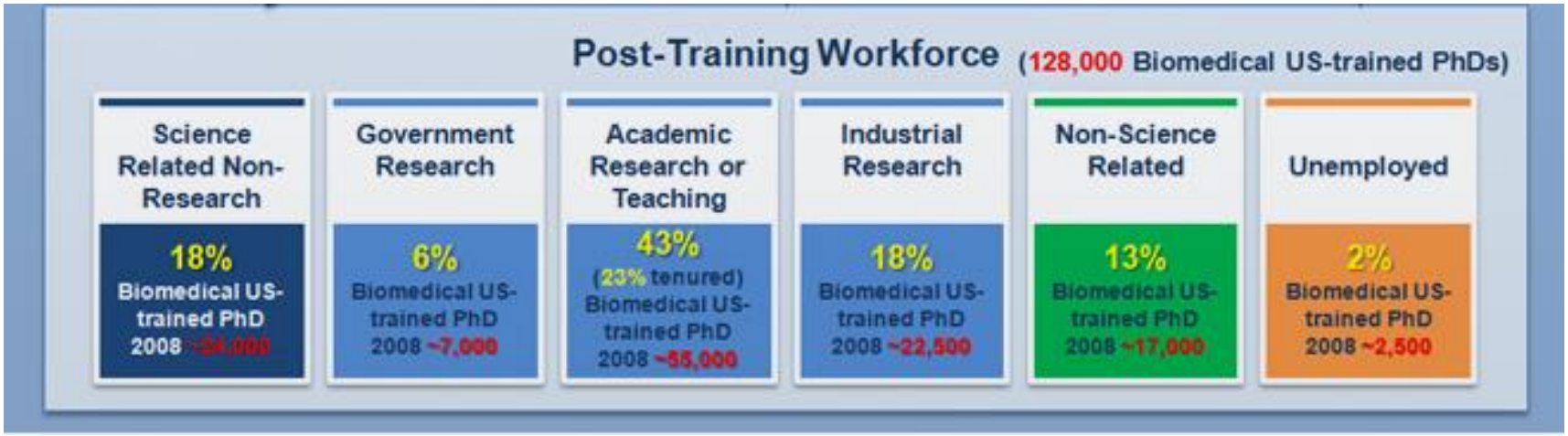
Tenure

Assistant Professor

Post-doc

PhD graduate

Snapshot of PhD Workforce (NIH study; published 2012)



http://acd.od.nih.gov/Biomedical_research_wgreport.pdf

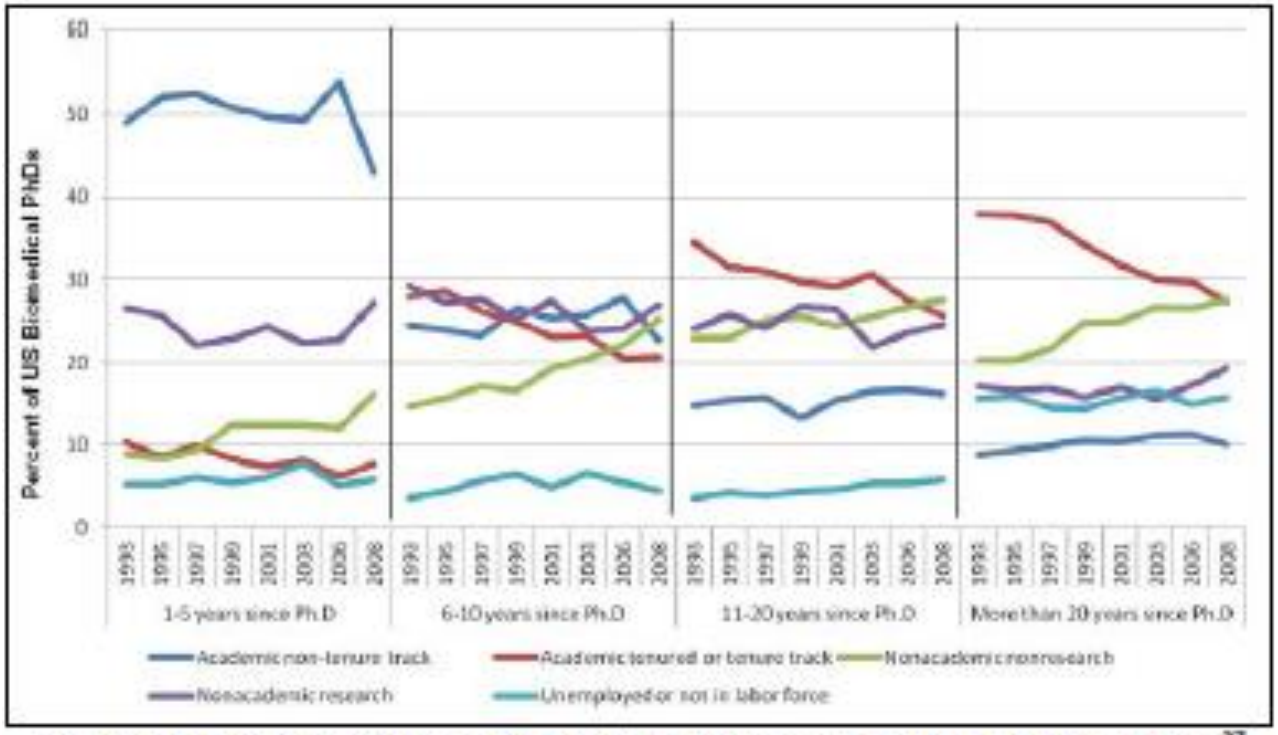


Figure 11: U.S. Trained Biomedical PhD employment, by Years Since Degree[27]

http://report.nih.gov/investigators_and_trainees/acd_bwf/Phd_Workforce_category.aspx

- Only 20% of US grad students in STEM will land tenure-track position within 4-6 years of completing Ph.D (Science, 2012)
- 50,000 students earn PhD in US (highest number ever recorded)
- Between 2005 and 2009, American universities conferred 100,000 doctoral degrees, but only 16,000 new professorships,

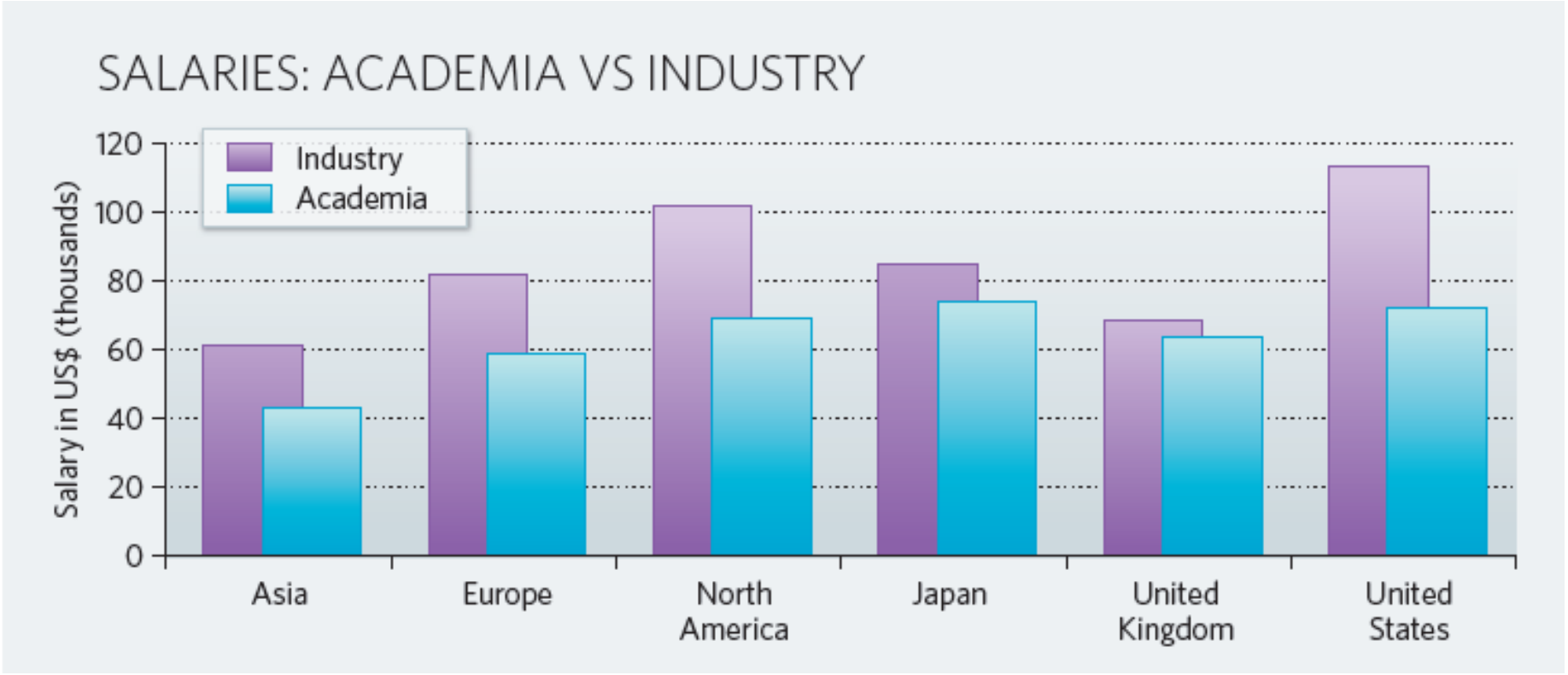
NON-TENURE

- For the last 30 years, number of non-tenure track faculty positions have increased significantly
- Non-tenure track positions = higher teaching loads and does not guarantee salary; renewable contracts
- Less pressure; can still have a strong research component and opportunities for professional growth
- Types: short-term block visitors, lab instructors, continuing, part-time faculty, temporary position to tenure-track
- Place in department and evaluation dependent on individual department

Why look beyond academia?

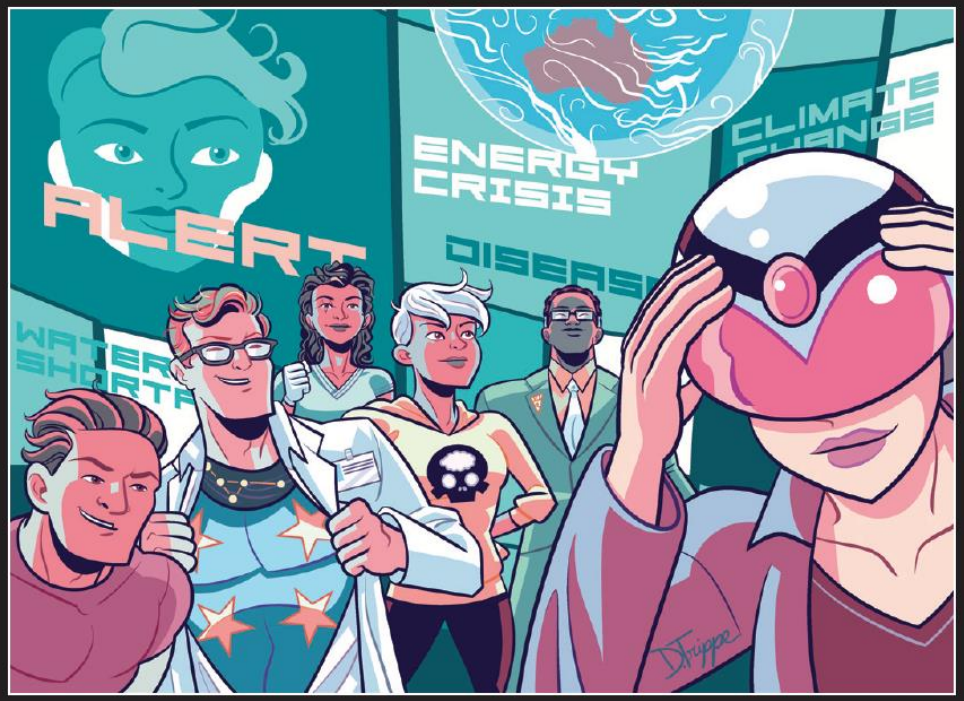
Is Private Sector Right for You?

- structure
- money
- product/project driven; direct, tangible impact
- problem focus
- time to do technical work
- priorities can change quickly and projects can be dropped quickly
- not having to write grants (varies on maturity of company)
- little freedom in research
- research projects are more team oriented, as you may only see or control a small part of the overall project
- less or very little publication
- less stable



Love and Money (Nature, 2010) http://www.nature.com/naturejobs/2010/100624/pdf/nj7301-1104a.pdf

Robert S. Chapkin, PhD
Title: Distinguished Professor and Deputy Director of the Center for Translational Environmental Health Research
Institution: Texas A & M University
Research: Focus on cancer prevention strategies to delineate the nuclear and plasma membrane targeted mechanisms modulating stem cell responses to exogenous (diet-derived) and endogenous (gut microbial) bioactive agents.



TEAM SCIENCE

Interdisciplinarity has become all the rage as scientists tackle society's biggest problems. But there is still strong resistance to crossing borders.

BY HEIDI LEDFORD

ILLUSTRATION BY DEAN TRIPPE

Asking for US$40 million is never easy, but Theodore Brown knew his pitch would be a particularly tough sell. As vice-chancellor for research at the University of Illinois at Urbana–Champaign in the early 1980s, Brown had been tasked with soliciting a major donation from wealthy chemist and entrepreneur Arnold Beckman, a graduate of the university. Beckman was hesitant, believing that the university should receive most of its support from the state. So Brown decided to devise a project like nothing he had ever seen before.

In 1983, he and his colleagues put together a proposal for an institute that had little chance of being funded through normal channels. It would defy the powerful disciplinary cartography that defines many modern universities, bringing together members of different departments and inducing them to work together on common projects. Brown argued that it would allow faculty members to tackle bigger scientific and societal questions than they normally could.

"The problems challenging us today, the ones really worth working on, are complex, require sophisticated equipment and intellectual tools, and just don't yield to a narrow approach," he says. "The traditional structure of university departments and colleges was not conducive to cooperative, interdisciplinary work."

It was an early example of the push for interdisciplinary research that is now sweeping universities around the globe. Although Brown was not completely alone — the interdisciplinary Santa Fe Institute in New Mexico was founded around the same time — he was advocating crossing boundaries before it

Ledford, Nature 525:308, 2015