The Role of Industry in Clinical Research

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February 2, 2016

Disclosures

- Clinical trial investigator: Edison Pharmaceuticals (EPI-743), Raptor Pharmaceuticals (RP-103)
- Consultant: Mitokyne, Amicus Therapeutics
- DSMB member: Biomarin (BMN 165, BMN 701), Ultragenyx (UX003, UX007)
- Stock options: Natera, Glycomine

Learning Objectives

- Understand the types of funding opportunities that are available for industry-academic clinical research
- Describe the types of relationships that may occur between industry and academics in the setting of clinical research
- Be aware of the ethical issues that are pertinent to industry-academia interactions, as well as methods of mitigation

Bayh-Dole Act

- Non-profits, including universities, and small businesses may elect to retain title to innovations developed under federally-funded research programs
- Universities are encouraged to collaborate with commercial concerns to promote the utilization of inventions arising from federal funding
- Universities are expected to file patents on inventions they elect to own

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Bayh-Dole Act

- Universities are expected to give licensing preference to small businesses
- The government retains a non-exclusive license to practice the patent throughout the world
- The government retains march-in rights.

Slide courtesy of Dr. Mildred Cho

Industry-Academia Funding

- Grants
  - SBIR
  - STTR
- Investigator-initiated research
- Clinical trials
- Academic training grants/fellowships
- Other

SBIR/STTR Program Goals

- Meet Federal research and development needs
- Increase private-sector commercialization of innovations derived from Federal R&D funding
- Stimulate technological innovation
- Foster and encourage participation in innovation and entrepreneurship by socially and economically disadvantaged persons

https://www.sbir.gov/about/about-sbir

SBIR/STTR Program History

- Created by Roland Tibbetts at the National Science Foundation and made into Federal program by Ronald Reagan in 1982
- SBIR programs awarded >$40 billion
- Grants to ~450,000 engineers and scientists
- 11 Federal agencies participate

https://www.sbir.gov/about/about-sbir

Small Business Innovation Research (SBIR)

SBIR Mission and Program Goals

The mission of the SBIR program is to support scientific excellence and technological innovation through the investment of Federal research funds in critical American priorities to build a strong national economy.

The program's goals are four-fold:

- Stimulate technological innovation.
- Meet Federal research and development needs.
- Foster and encourage participation in innovation and entrepreneurship by socially and economically disadvantaged persons.
- Increase private-sector commercialization of innovations derived from Federal research and development funding.

https://www.sbir.gov/about/about-sbir

Small Business Technology Transfer (STTR)

https://www.sbir.gov/about/about-sttr

Small Business Technology Transfer (STTR)

- Joint venture opportunities for small business and nonprofit research institutions
- Small business must formally collaborate with a research institution in Phase I and Phase II
- Bridges the gap between basic science research and commercialization of resulting inventions

https://www.sbir.gov/about/about-sttr

STTR Three-Phase Program

- Phase I – establish technical merit, feasibility and commercial potential (budget ≤$225,000, 6 months)
- Phase II – continue R&D efforts with funding based on Phase I results and merit (budget ≤$1.5 million, 2 years)
- Phase III – small business pursues commercialization (not funded by STTR program)

SBIR/STTR Comparison

Requirements	SBIR	STTR
Application form	Electronic grant application package	Electronic grant application package
PI requirements	51 percent or greater of the PD/PI's time is spent in the employ of the small business concern.	Minimum 10 percent effort on project; total percent effort, including effort at academic institution, cannot exceed 100 percent.
Time	Phase I—normally not to exceed six months Phase II—normally not to exceed two years	Phase I— normally not to exceed one year Phase II—normally not to exceed two years

https://www.niaid.nih.gov/researchfunding/tool/pages/sbirsttrcomp.aspx

SBIR/STTR Comparison

Requirements	SBIR	STTR
Maximum award (total costs) – can be exceeded with justification	Phase I—$225,000 Phase II—$1.5 million	Phase I—$225,000 Phase II—$1.5 million
Subcontracts including consultants	Guidelines say not to exceed 33 percent in phase I or 50 percent in phase II.	Required subcontract of at least 30 percent to academic partner; total subcontracts (including that with the academic partner) and consultants cannot exceed 60 percent.
Performance site	Grant funds must be used entirely in U.S.; part of research must take place in company-controlled research space.*	Grant funds must be used entirely in U.S.; part of research must take place in company-controlled research space and part in that of academic partner.*

https://www.niaid.nih.gov/researchfunding/tool/pages/sbirsttrcomp.aspx

SBIR Participating Agencies

- Department of Defense
- Department of Energy
- Department of Health and Human Service
- National Aeronautics and Space Administration
- National Science Foundation
- Department of Agriculture
- Department of Commerce
- Department of Education
- Department of Homeland Security
- Department of Transportation
- Environmental Protection Agency

STTR Participating Agencies

- Department of Defense
- Department of Energy
- Department of Health and Human Service
- National Aeronautics and Space Administration
- National Science Foundation

SBIR/STTR Funding

- Federal agencies with extramural R&D budgets exceeding $100 million are required to allocate 2.8% to SBIR program
- Federal agencies with extramural R&D budgets exceeding $1 billion are required to reserve 0.3% for small business STTR awards

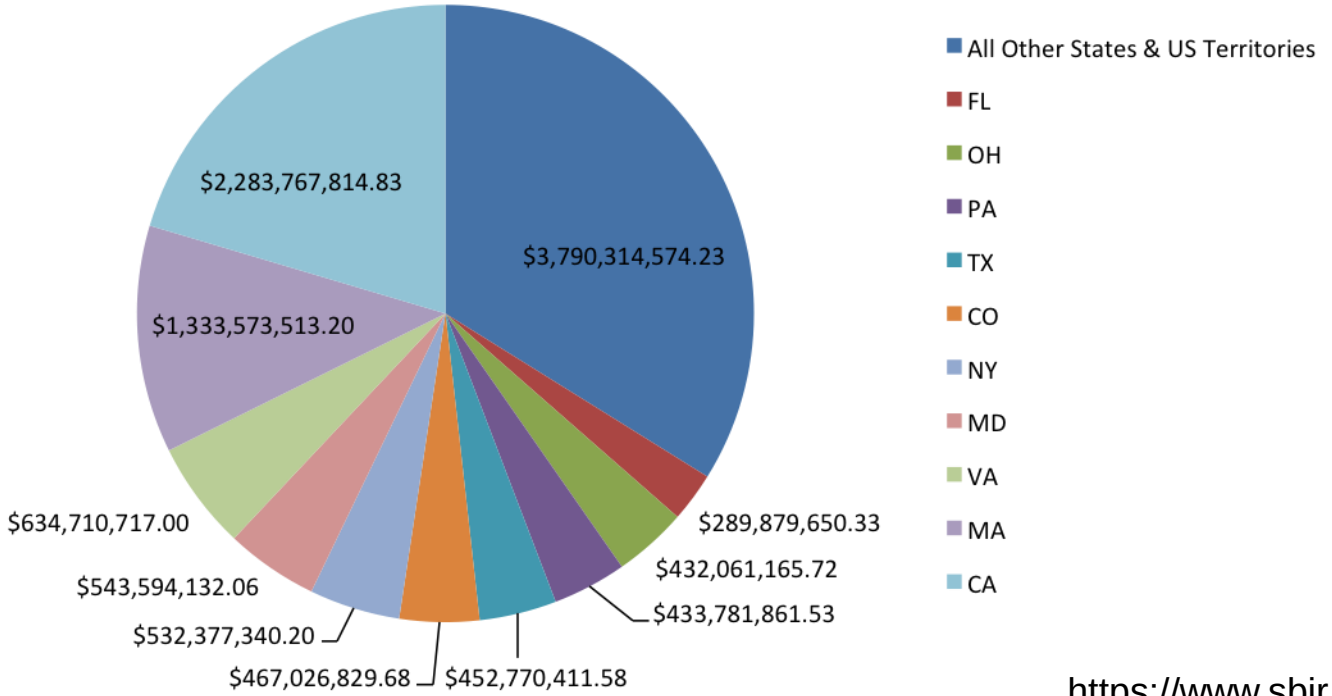
SBIR/STTR Budgets FY2015

- DHSS/NIH - $797 million
- National Science Foundation - $176 million
- Department of Defense - $1.07 billion
- Department of Energy - $206 million
- NASA - $180 million

https://www.sbir.gov/about/about-sbir

SBIR Funding Past 4 Years

Top total award dollars went primarily to 10 states:
CA, MA, VA, MD, NY, CO, TX, PA, OH and FL



https://www.sbir.gov/about/about-sbir

Investigator-Initiated Research

- Clinical studies/small clinical trials
- Observational studies
- Diagnostic test development
- Specific disease targets
- Basic research
  - *In vitro* experiments
  - Animal studies

Clinical Trials

- Sponsor initiated
- Principal investigator, co-PI, sub-investigator
- Clinical trial protocol established
- Investigator's Brochure
- Schedule of events
- Data safety monitoring board
- Contract between sponsor and university

Company	Drug	Indication	Trial Design	Primary Outcome	Enrollment
Edison	EPI-743	Leigh syndrome	Phase 2B RDBPC	NPMDS 1-3	30
Raptor	RP-103	Mitochondrial disease	Open-label	NPMDS Quality of life	32
Reata	RTA 408	Mitochondrial myopathy	Phase 2 RDBPC	Exercise testing	52
Stealth Peptides	MTP-131	Mitochondrial myopathy	Phase 1/2 RDBPC	Adverse events, vitals, lab tests	36
Santhera	Idebenone	MELAS	Phase 2A RDBPC	Cerebral lactate	21
Cardero	(-)-epicatechin	Becker muscular dystrophy	Phase 1/2A Open-label	Muscle function and strength	10
Wellstat	PN401	Mitochondrial disease	In development	-	-
Mitobridge	In development	-	-	-	-

Molecular Genetics and Metabolism 105 (2012) 91–102

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Initial experience in the treatment of inherited mitochondrial disease with EPI-743

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ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder

Brendan Lee, MD, PhD[1,2], George A. Diaz, MD[3], William Rhead, MD, PhD[4], Uta Lichter-Konecki, MD[5], Annette Feigenbaum, MD[6], Susan A. Berry, MD[7], Cindy Le Mons[8], James A. Bartley, MD[9], Nicola Longo, MD, PhD[10], Sandesh C. Nagamani, MD[1], William Berquist, MD[11], Renata Gallagher, MD, PhD[12], Dennis Bartholomew, MD[13], Cary O. Harding, MD[14], Mark S. Korson, MD[15], Shawn E. McCandless, MD[16], Wendy Smith, MD[17], Stephen Cederbaum, MD[18], Derek Wong, MD[18], J. Lawrence Merritt II, MD[19], Andreas Schulze, MD, PhD[6], Gerard Vockley, MD, PhD[20], David Kronn, MD[21], Roberto Zori, MD[22], Marshall Summar, MD[5], Douglas A. Milikien, MS[23], Miguel Marino, PhD[15], Dion F. Coakley, Pharm D[24], Masoud Mokhtarani, MD[24], the UCD Consortium and Bruce F. Scharschmidt, MD[24]

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

STEATOHEPATITIS/METABOLIC LIVER DISEASE

Ammonia Control and Neurocognitive Outcome Among Urea Cycle Disorder Patients Treated With Glycerol Phenylbutyrate

George A. Diaz,[1] Lauren S. Krivitzky,[2] Masoud Mokhtarani,[3] William Rhead,[4] James Bartley,[5] Annette Feigenbaum,[6] Nicola Longo,[7] William Berquist,[8] Susan A. Berry,[9] Renata Gallagher,[10] Uta Lichter-Konecki,[11] Dennis Bartholomew,[12] Cary O. Harding,[13] Stephen Cederbaum,[14] Shawn E. McCandless,[15] Wendy Smith,[16] Gerald Vockley,[17] Stephen A. Bart,[18] Mark S. Korson,[19] David Kronn,[20] Roberto Zori,[21] J. Lawrence Merritt, II,[22] Sandesh C.S. Nagamani,[23] Joseph Mauney,[24] Cynthia LeMons,[25] Klara Dickinson,[3] Tristen L. Moors,[3] Dion F. Coakley,[3] Bruce F. Scharschmidt,[3] and Brendan Lee[23]

Other Industry Grant Types

- Charitable donation
- Patient organization grant
- CME meeting support
- Travel awards
- General grants
  - Equipment
  - Educational funding

BETTER HEALTH THROUGH GENETICS™

ACMGF Awards

- Genzyme Fellowship Award
- Pfizer/ACMG Foundation for Genetic and Genomic Medicine Fellowship Award
- Horizon Pharma Award
- Signature Genomics Award
- Richard King Trainee Award
- David L. Rimoin Lifetime Achievement Award in Medical Genetics

ACMG FOUDATION AWARDS

In an effort to promote professional research and education in the field of medical genetics, the ACMG Foundation for Genetic and Genomic Medicine has partnered with numerous Corporate Partners, Genzyme Corporation, Pfizer and Signature Genomics, a PerkinElmer Company, to establish two annual awards. These generous partners share ACMG Foundation for Genetic and Genomic Medicine's mission *Better Health Through Genetics*™. The award recipients demonstrate leadership in their field through cutting edge research, development of research guidelines or the recruitment and training of clinicians.

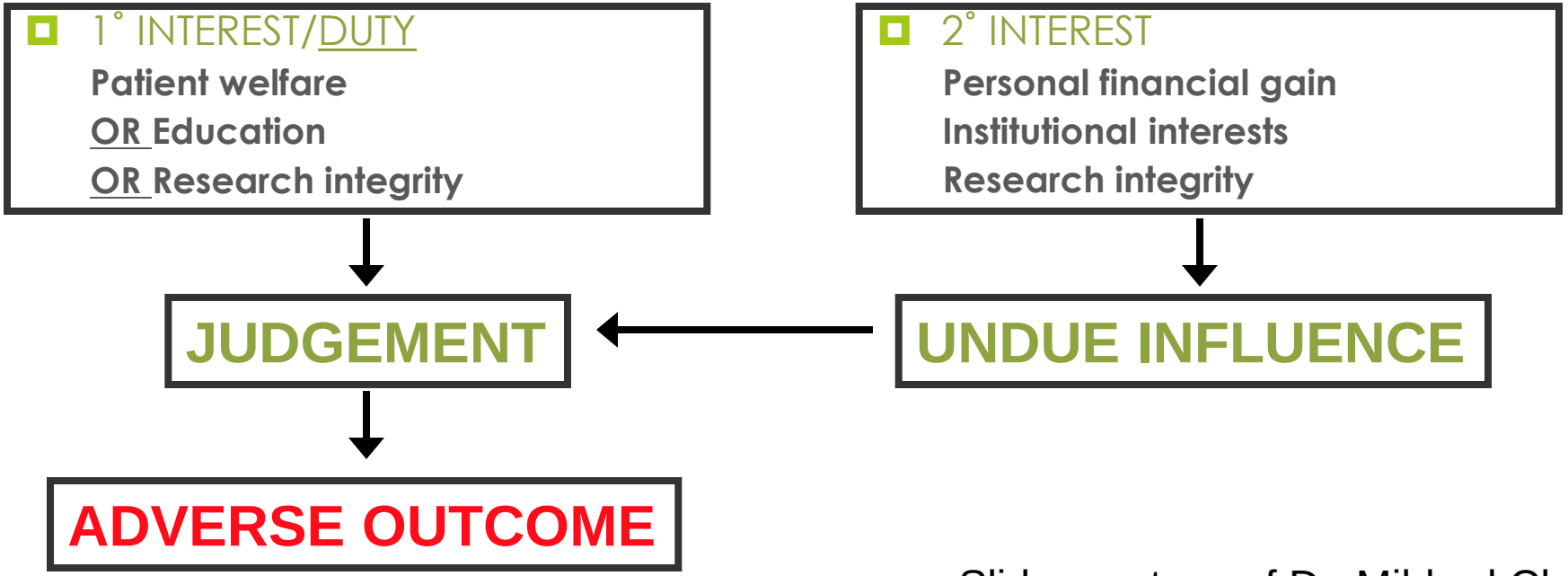
To apply or obtain more information, please click on the links below.

- Genzyme/ACMG Foundation for Genetic and Genomic Medicine Fellowship Award
- Pfizer/ACMG Foundation Clinical Genetics Combined Residency for Translational Genomic Scholars Fellowship Award
- ACMG Foundation for Genetic and Genomic Medicine David L. Rimoin Award

Relationships

- Clinical trial investigator
- Data safety monitoring board member
- Consultant
  - Formal
  - Informal
- Investigator-initiated study investigator
- Emergency IND

What is a conflict of interest?



Slide courtesy of Dr. Mildred Cho

Financial conflicts of interest

- What are financial interests for biomedical researchers?
  - having external sponsorship of research
  - being a paid consultant for a sponsor of research
  - being an employee or board member of a sponsor of research
  - testing a technology for which the researcher holds a patent and would receive royalties
  - having stock in a company sponsoring their research

Slide courtesy of Dr. Mildred Cho

Duties in research

- Designing study
- Enrolling subjects
- Analyzing & interpreting data
- Serving on DSMB
- Reviewing and editing publications
- Developing clinical guidelines
- Serving on advisory committees for regulatory approval

Slide courtesy of Dr. Mildred Cho

Mitigating COI

- Federal and state policies
  - Disclosure
  - Prohibition of financial interests
- Professional society guidelines
  - Disclosure
  - Prohibition of financial interests
- Institutional conflict of interest committees
  - Disclosure
  - Prohibition of financial interests
  - Oversight, mediation

Slide courtesy of Dr. Mildred Cho

Mitigating COI

Disclosure	publication of 2˚ interest
Mediation	blind trust (2˚), oversight (1˚)
Abstention	recusal from 1˚ interest
Divestiture	removal of 2˚ interest
Prohibition	permanent withdrawal from 2˚ interests

(Thompson, 1993 NEJM 329:573-576)

Slide courtesy of Dr. Mildred Cho

STANFORD INDUSTRY INTERACTIONS POLICY

Home
Policy
FAQ's
Letters of Agreement, Educational Activities
Resources
Contact Information

SEE ALSO

"DoResearch" Conflicts of Interest Information & Forms

Policy https://med.stanford.edu/coi/siip/policy.html

Policy and Guidelines for Interactions between the Stanford University School of Medicine, the Stanford Hospital and Clinics, and Lucile Packard Children's Hospital with the Pharmaceutical, Biotech, Medical Device, and Hospital and Research Equipment and Supplies Industries ("Industry")

Date of implementation: October 1, 2006
Revised as of July 1, 2014

Purpose of Policy

The purpose of this policy is to establish guidelines for interactions with Industry representatives throughout the Stanford University Medical Center (SUMC), which is composed of the Stanford School of Medicine, Stanford Hospital and Clinics and the Lucile Packard Children's Hospital. Interactions with Industry occur in a variety of contexts, including marketing of new pharmaceutical products, medical devices, and hospital and research equipment and supplies on-site, on-site training of newly purchased devices, the development of new devices, educational support of

Health Professionals

SYSTEMATIC EVIDENCE REVIEWS & CLINICAL PRACTICE GUIDELINES

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Current Guidelines & Reports

Systematic Evidence Reviews

Guideline Archive

Expert Panel Members

Guideline Executive Committee Policy for Managing Potential Conflicts of Interest and Relationships with Industry

The Guideline Executive Committee (GEC) for the CVD Panels and Working Groups (P/WG) has established the following approach to manage relationships with industry (RWI) and other potential conflicts of interest (COI). The GEC comprises a GEC chair and the chairs and co-chairs of the 6 P/WGs.

Voting: A P/WG Co-chair without RWI/COI associated with the matter being decided shall oversee the voting on evidence statements and recommendations, including their grading. P/WG members with RWI/COI may participate in discussions after orally identifying their RWI/COI, but shall recuse themselves from voting on guideline evidence statements or recommendations. Recusals will be documented.

Reporting of RWI and COI: Each P/WG member shall orally disclose relevant RWI/COI at meetings/teleconferences of each P/WG of which she/he is a member. All relationships with industry and other entities starting from the time of the first P/WG meeting in September 2008 shall be disclosed.

Members of P/WG should avoid adding RWI/COI. If relevant relationships are added, P/WG members shall disclose them orally to the P/WG at the next meeting/teleconference. Although the names of those who vote for or against an evidence statement or recommendation will not be recorded, the names of those who recuse themselves on each vote will be recorded and will be published with the panel's final published document.

All P/WG members shall list their RWI/COI when reports from the P/WG are presented, released or published. Journal guidance for reporting RWI/COI shall be followed for journal publications.

http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/conflict-of-interest-policy

Grants & Funding

Grants Policy

- Policy & Guidance
- Compliance & Oversight
- Research Involving Human Subjects
- Office of Laboratory Animal Welfare (OLAW)
- Animals in Research
- Peer Review Policies & Practices
- Guidance for Reviewers
- Intellectual Property Policy
- Acknowledging NIH Funding

Intellectual Property Policy

Division of Extramural Inventions & Technology Resources (DEITR) in the NIH Office of Extramural Research

Regulations

Inventions arising from federally funded research projects are required to be reported to the government agency that funded the project, per the Bayh-Dole Act (the Patent and Trademark Law Amendments Act). The Act permits businesses (large and small) and nonprofits (including universities) to retain ownership of the inventions made under federally funded research and contract programs, while also giving the government the license to practice the subject invention. In turn, the organizations are expected to file for patent protection and to ensure commercialization upon licensing for the benefit of public health. Read the regulations at Bayh-Dole Act (37 CFR 401).

Related Resources

- Contact Us
- iEdison Module
- Invention Reporting website

http://grants.nih.gov/grants/intell-property.htm

Summary

- Interactions between industry and academic institutions are common in clinical trials and other forms of clinical research
- Various types of grants/funding mechanisms in place
- Relationships between university faculty and industry may be formal or informal, and include participation as investigators in clinical trials, investigator-initiated research, DSMB participation and consulting
- Ethical issues related to COI are important considerations

Suggested Reading

- Angell M. Industry-sponsored clinical research: a broken system. JAMA 300:1069-71, 2008
- Thompson DF. Understanding financial conflicts of interest. New Eng J Med 329:573-6, 1993
- Laterre PF, Francois B. Strengths and limitations of industry vs. academic randomized controlled trials. Clin Microbiol Infect 21:906-9, 2015
- Miller JE et al. Clinical trial registration, reporting, publication and FDAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. BMJ Open 12:e009758, 2015
- Rawal B, Deane BR. Clinical trial transparency update: an assessment of the disclosure results of company-sponsored trials associated with new medicines approved in Europe 2012. Curr Med Res Opin 31:1431-5, 2015