Testing new models of research funding: One Brave Idea

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Disclosures

- Revenue from gene testing in cardiomyopathies
- Patents for cardiotoxicity testing in zebrafish
- Patents for drug discovery in zebrafish
- Novartis
- Atlas Ventures
- ArrayBioPharma
- The Medicines Company
- Synthon
- Biogen Idec
- Sanofi
- Merck
- Pfizer
- Vertex
- AHA/Verily/Astra Zeneca
- Academic self-interest
One Brave Idea™: AHA/Verily/Astra Zeneca

- $75M for a single investigator
- 3 month/3 stage timeline
  - 250 words
  - 10 pages
  - Shark tank
- No constraints on use of funding
- Distinctive reporting structure

One Brave Idea™
Central Organization/CEO/CSO/CIO
Overall scientific strategy and direction
  › Core data science
  › Day to day operations/Project management
  › Scientific, reporting, financial and legal accountability
  › Incubator and other partnership development and maintenance
  › Cross-functional collaborative teams to maximize project velocity/efficiency
  › Lean and nimble
Scientific thought leaders - ad hoc advisors
Idea(s)

• Redefining coronary heart disease: at the edge of wellness
  • Redefinition of CHD in dynamic and quantitative biological terms
  • Identify new and much earlier true endophenotypes
  • Establish empiric approaches to moving from deep to broad

• New disease genes, new environmental contributors
  • New therapeutic approaches or new therapies
  • New preventative strategies

• Testing new approaches to research execution and funding
• Contributing to a new ecosystem for discovery and care
Personnel: Initial core team

AHA/AZ/Google

Euan Ashley
Lazlo Barabasi
Elazer Edelman
Mike Gaziano
David Grayzel
Calum MacRae
Chris O’Donnell
Fritz Roth
Ramachandran Vasan
Phenotype is limiting in multiple areas of biomedical science

- Static or limited dynamic range
- Almost all aggregates
- Unidimensional with no organizing metadata

Few if any conditioning variables ever measured

Most medical data
The phenotype gap

Published Genome-Wide Associations through 07/2012
Published GWA at p≤5X10⁻⁸ for 18 trait categories
NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

Genome
Transcriptome
Proteome
Connectome
Physiome

Timescale
Dependent

Exposome

All clinical phenotypes

10⁹
10¹⁶
10²⁰
10⁶⁹
10⁴
Moving beyond legacy phenotypes

Unstructured
18th century
Semi-subjective and duplicative
Lack of standardization
Cross sectional and static
No metadata

High threshold for innovation
Tied directly to implementation evidence base

EKG
Specific metabolites
Microbiome
Microcirculation confocal imaging
Adipose tissue mapping
Thermography
Everything else
• Comprehensiveness
• Organizing metadata across datasets and models: perturbations and timescales
• New datasets-shared across biological models
• A computable molecular/cellular/physiologic ‘physical exam’
Linking clinical and basic science

- Mapping relationships across species
  - Genome
  - Phenome
  - Perturbations

- Multiple ‘omics
  - Cell biology, physiology
  - Environmental and drug responses

- Multiple dimensions improve specificity

- Shared phenotypic lexicon
  - ‘Mechanistic’ phenotypes in all species
  - ‘Co-clinical’ modeling: real time application

Clinical Genomics

Extant systems/network biology
Most of what we know about CHD has emerged from a focus on the latter 15-20 years of the disease.

CHD represents many different disorders which resemble each other most in their later stages.

- Identifying new translatable markers of the very earliest stages of CHD
- Define new underlying causal factors for CHD,
- Develop technologies for population detection,
- Move towards new therapies and preventative strategies

Libby et al.

Generic
Different underlying forms of CHD
New ways to detect different forms of CHD
Scaling to general population for screening and disease Rx
New pathways in atherosclerosis?

- Preclinical phenotypes
  - Discrete genetics

- Core genes
  - LDLR, ApoB, PCSK9

- Extant biology predictions
  - HTN
  - T2DM
  - Cognitive decline
A generalizable approach for phenotype discovery

Phenotype and perturbation discovery
Cells to organisms

Validation in kindreds and genotyped cohorts

New causal pathways
Perturbation/phenotype discovery

Democratization of phenotyping
Large simple trials
Orthogonal phenotypes: scalability by design

• Rapid cycle development
  - Plug and play
  - Flexible bioengineering and computational infrastructure
  - Benchmarking technologies
  - Developing our own technologies
  - Rigorous biologic insight for positioning
  - Stimulus identification

• Disease-enriched populations
  - Large numbers of subjects
  - Large proportion already genetically defined
  - Active Precision Medicine efforts

• Based in outpatient clinic
  - Physician encounter occupies <20% time spent on site
  - Integrating genomics and care reinvention
  - Mapping onto existing disease framework
  - Controlled environment: stimulus-response pairs

• Efficient scaling to population cohorts
  - FHS
  - Million Veterans Program
  - Verily, Microsoft, AHA My Research Legacy

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Funding mechanism considerations

- PPG format
- Venture fund: ‘for profit’ vs ‘not for profit’
- Discrete commercial entity
- Closed end vs sustainable

- Additional partners and fundraising
  - Industrial/Foundations/Philanthropy
  - Focused on alignment: Pharma/Tech/Biotech/Device/Retail/other
  - In-kind resources
  - Governance

- Partnerships with traditional funders
  - Joint investments: shared returns
  - Federal and international cohorts-fee for service
  - Training mechanisms
  - Infrastructure development
Structural features of program

• Administrative
  • Central core with fiduciary, legal and reporting responsibility
  • Renewable engagement of scientific team members and SAB
  • Flexibility to continue to engage/disengage based on science
  • Executive board with oversight

• Highly goal directed
• Objective go/no go metrics for each funding component
  • Scientific rigor
  • Alignment with goals of program
• Efficient funding cycles-<6 weeks

• Indirect costs
• Intellectual property
**Core infrastructure**

Ideation & initial development

- Traditional science
- AHA/AZ/Verily
- Commercial entities
- Patients
- General public
- Crowdsourcing

Selection

Fabrication

Prototyping

Initial human testing

Initial clinical testing & validation

Population studies

- BWH
- MIT
- BWH
- PHS
- FHS
- MVP
- AHA
- AZ
- VLS
- AHA
- VLS
- Global Partners

Core Translational Program

Informatic and computational backbone

Fundamental biology, drug discovery, pharmacology

Education and training: lay and professional

Active engagement of public, government, potential additional funding
Initial science strategy

• Core data science
• Balanced portfolio
  • Early initiation of low risk/high yield
    • Exposure quantitation
    • Extant atherosclerosis cell biology
    • Population science with existing data
  • Prioritization of high risk/high return projects
    • Early basic science
    • Foundation for later implementation
  • Developing criteria for moving to scale
• Internal and external RFAs
  • ‘Quality, price and performance’
  • Testing the structure of the program
• Optimization of teams for projects
  • Members
  • Locations
• Exploring partnership mechanisms
Culture

- Emphasis on alignment and engagement
- Diversity-personnel, ideas etc
- Building community engagement for the long haul
- Balancing comprehensiveness and utility-the academic conundrum

- Rigorous metrics including effect size
- Active cross-fertilization between projects within OBI
  - 20% rule or equivalent: rewarding multi-disciplinarity/engagement
- Teaming across groups to advance goals
- Team member development
  - Maintenance of long term fundability for investigators
  - Development of orthogonal skills for all team members
Reappraisal in new funding context

• Creating and testing approaches to:
  • Team science
  • Data accessibility
  • Science process-planning, budgeting, execution
  • Academic-private partnerships
  • Public-private partnerships

• Communication
  • Engagement across entire program: channels
    • Scientists/Funders
    • Project management
  • Regular videoconferencing: I2 based solutions
  • Shared dashboards-metrics

• Publication

• Sociology
• Economics
• Process
• Sustainability or otherwise-by design
Partnership models

• Direct investment in the original project
• In-kind collaborations

• Joint investment in specific projects with shared risk/reward
  • e.g. a real world clinical trial
• Joint investment in communal projects
  • Data escrow or other strategies to overcome the long-term issues with ‘de-identification’
• Joint investment in external RFAs
  • e.g. In specific population cohorts to test/validate new phenotypes
• Training and education
Physical location

One Brave Idea™
Science Innovation Center

Start-up companies to lease space and collaborate with One Brave Idea Team

MIT and BWH Next Generation Phenotyping Center

Start-up Translational Incubator with Brigham & Women’s Hospital

CVD Clinical Innovation Programs from Brigham and Women’s Hospital
Information content drives integration and ‘learning’

Areas of potential transformation
- Timing and resolution of care delivery, research and education
- True scalability
- Value as well as its measurement and attribution
- New partnerships across multiple areas: devices, delivery channels, etc,
- Biomedicine as learning platform: knowledge generation/implementation
- Basic or Translational science/Hybrid trials/Real world randomization

Orthogonal data streams
- Devices
- Response dynamics
- Real-time stratification
- Continuous audit
- Adaptive optimization
  - Cost/Risk
  - Virtual/Physical
- Care networks
The real driver for new models of funding

- Disruptive partners/competitors with deep pocket: PBMs, eHR companies, Global IT Players, VCs, Pharma, Banks, Real Estate, Supermarkets etc
- New revenue models
  - ACO, pay per click, subscription, added services
  - Renewed focus on knowledge generation, knowledge management and knowledge transmission
  - Different transaction types: direct to patient, educational, research premium
  - Lower cost larger markets
- Failure of many AMCs
- Emergence of small number of ‘global’ networks

New workflow
New data streams
New delivery systems
Summary

• Information content is a core problem in biomedicine
  • Overcoming entrenched legacy phenotypes
  • Overcoming lack of comprehensiveness
  • Actively balancing broad (fewer metadata) vs deep (lower scale) phenotyping
• New models of funding are required that align all of the potential partners
  • Complement traditional biomedical science funding models
  • Directly associated with data sources
• Convergence of care and discovery
  • Data management, data science and decision support
  • Trajectories - across health and disease
  • Funding

• We need systematic approaches to acquiring the right information content
  • New earlier, orthogonal and more granular data and new data gathering tools
  • Eliminating non-biological silos
  • Structured perturbations-translatable by design to models-to allow integration
• Quantitative learning health systems-generalizable rules
Acknowledgements

- Andreas Werdich, Daniela Panakova, Albert Kim, David Milan, Jordan Shin, Stephanie Eby, Andrea Giokas, Ian Jones, Khaled Sabeh, Matt Killeen, Jeff Winterfield, Shannon Coy, Eva Plovie, Adrian Low, Amy Ronco, Amy Doherty, Ward Capoen, Chris D’Amato, Ming Sum Lee, Jason Becker, Tomas Andersen, Tim Kamerzell, David White, Anne-Karin Arndt, Micah Burch, Akiyoshi Ogimoto, Brittney Mikell, Adrian Haber, Patrick Sips, Manu Beerens, Gabe Musso, Micah Burch

- Steve Chelko, Angeliki Asimaki, Andre Kleber, Jeff Saffitz, Dan Judge
- Bob Murphy, Garret Fitzgerald and LIPIDMAPS
- Fritz Roth, Euan Ashley, Dave Grayzel, Chris O’Donnell, Mike Gaziano, Laszlo Barabasi, Vasan Ramachandran, Mark Huffmann
- Randy Peterson
- Jon and Kricket Seidman, Mark Fishman

- NHLBI, NIGMS, NINDS, Leducq, MDA, BHF, Harvard Stem Cell Institute, Burroughs Wellcome Fund, AHA/Verily/AstraZeneca