

Professor Wrighton's Assignment

- A. **Investments:** What are the most important and appropriate opportunities for enhanced federal investments in research and education?
- B. **Impact:** What would be the potential impact of these investments...that will stimulate innovation and enhance competitiveness?
- C. **Accelerators:** How can we accelerate returns on investments made in basic research?
- D. **Value:** What specific areas of fundamental research are of greatest value?

Some Investments and Payoffs

Target Identification

- A. **Investments:** Expand on Human genome project: a national phenotype collection tied to patient populations with genotypes, Investment in eBiology - systems biology
- B. **Impact:** Improved efficiency of disease associations, expect improved national health, could drive national standards for record keeping and epidemiology
- C. **Accelerators:** Human Genome/pharmaco-omics project(s) accelerated with addition of and competition from the private sector. Go beyond traditional technology-base companies. Consider ways to involve records standardization (Insurance, Social Security and Medicare)
- D. **Value:** Rapid and standard phenotyping, database standards, better targets, cheaper/better trials (enriched populations), personalized medicine

Some Investments and Payoffs

Lead Identification – Small Molecules

- A. **Investments:** Pre-competitive generation of massive chemical diversity. US resource
Predictive approaches for molecular association (next gen virtual screening)
Develop new technology for discovery of drugs with non-traditional mode of action, eg, allosteric binder, disrupt traditional non-drugable targets (eg, protein-protein interactions).
Reconstitute complex cascades for drug discovery assays.
- B. **Impact:** Higher success and lower cost; difficult targets may find new therapies; possible utility in other fields
- C. **Accelerators:** Basic research advancing fundamental understanding of chemical diversity (chemo informatics) and molecular basis of interactions; national project to drive investment
- D. **Value:** Methods for megadiversity, step-fold changes in crystal structure, protein folding, computational methods to predict molecular behavior in complex systems

Some Investments and Payoffs

Target Validation through Candidate Selection

- A. **Investments:** Methods for faster production of genetically engineered models. Improved methods for humanizing rodents. Improved methods for tissue selective inducible gene knock-in/knock-out
 - Models for chronic human degenerative diseases (eg, Alzheimers, plaque rupture models of athero, osteoarthritis, etc.)
 - Translation biomarkers – soluble and imaging biomarkers, methods for multiplexed fingerprints of biomarkers
- B. **Impact:** Rapidly couple preclinical with clinical efforts
- C. **Accelerators:** Bench to Bedside – Industry-Academic Partnerships
- D. **Value:** Faster selection of mechanisms with highest potential, high responder populations for cheaper/faster development

Some Investments and Payoffs

Target Validation through Candidate Selection (cont'd)

- A. **Investments:** Current systems are contrived (eg, signaling network instead of pathway), low throughput and relatively undiscerning. An enhanced understanding of how biological systems interact with novel molecules in a predictive fashion is needed. Sophisticated issues such as role of lipid rafts (surface biology)
- B. **Impact:** Could expect better efficiency and improved selection of drugs likely to succeed with fewer late surprises
- C. **Accelerators:** System biology and interfacial/surface biology. Reconstitute biological systems in smallest scale possible; capture diversity
- D. **Value:** Impact on toxicology is a major upside since it is often classified as “idiosyncratic”

Some Investments and Payoffs

Biological Therapeutics

- Transformational improvements in production (COGS decrease by 10-100X) and breakthrough delivery methods.
 - Better/broader tissue distribution (eg, RNAi, antisense).
 - New approaches that enable more reliable specific interaction with intracellular targets.
 - New approaches to overcoming immunogenicity (stealth technology).
- A. Novel ways to decrease dose frequency or increase duration of action.

Some Investments and Payoffs

Phase I

- A. **Investments:** (Improved) Non-invasive methods to measure drug levels and their action against target throughout the body, but especially in tissue of interest

Cost effective methods to reliably measure tens to hundreds of analytes over a large dynamic range (100's to 10000's)

- Extension/improvements in omics (genomics, proteomics, lipidomics, metabolomics, toxicomics)

- B. **Impact:** Fewer failures to test the hypothesis

- C. **Accelerators:** Broad access to consented patient samples

- D. **Value:** Highly reliable pharmacodynamics

Some Investments and Payoffs

Phase II

- A. **Investments:** Improved methods for measuring the action of drugs
- Methods to predict and assess patient variability
 - Enhanced clinical trial designs using innovative statistical methods coupled with broad profile of markers of drug action (pharmacodynamic markers)
- B. **Impact** Non-invasive Methods to assess (Patho)Physiology
- Cost effectiveness and broadly applicability is ultimate goal
- Methods to identify patients (fore runner of personalized medicine)
- Patients who will respond (who to treat)
 - Patients who will not respond (avoid side effect risks)
 - Potential for eBiology (Genotyping and Systems Biology/Phenotyping)
- C. **Accelerators:** Precompetitive consortia for biomarker panels/methods
- D. **Value:** Understanding dose-exposure-effect with high confidence in PII (Enhanced trial design)

Some Investments and Payoffs

Phase III (and beyond)

All of the Ph I and Ph II investments/payoffs

A. **Investments:** Methods that assess/ensure compliance

- Not taking medicine as directed accounts for 25-50% loss of effectiveness in many, if not most indications

B. **Impact:** Improved efficacy and national health (efficacy guarantee)

C. **Accelerators:** Technology for confirming exposure

D. **Value:** Disease lacking patient palpable symptoms (HTN, etc.)