

Challenges and Opportunities....

Venture Philanthropy Strategies Used by Patient Organizations to Support
Translational Research – A Workshop

Forum on Neuroscience and Nervous System Disorders
October 3, 2008

Dennis Choi



Drug Development is Faltering

- Despite burgeoning knowledge and exponential increases in R&D spend, drug registrations have *fallen*
 - Increasing development program duration and complexity
 - Falling success rates in Phase I and II: the “efficacy wall.”
 - 32 NAS in 1979 driven by < \$2B; 29 NAS in 2006 driven by >\$50B
- Investment cost per successful drug launch has escalated sharply in recent years
 - \$1.7B per launch cited by FDA in 2004 “Critical Path” white paper (Bain & Co), a 55% increase over the preceding 5 years
- Many Pharma company market caps have fallen sharply (Dec 2000-present: PFE (293->127); MRK (215->67; BMY (140->40; LLY (103->48); AZN (92->37)

Nervous system drug development especially challenging

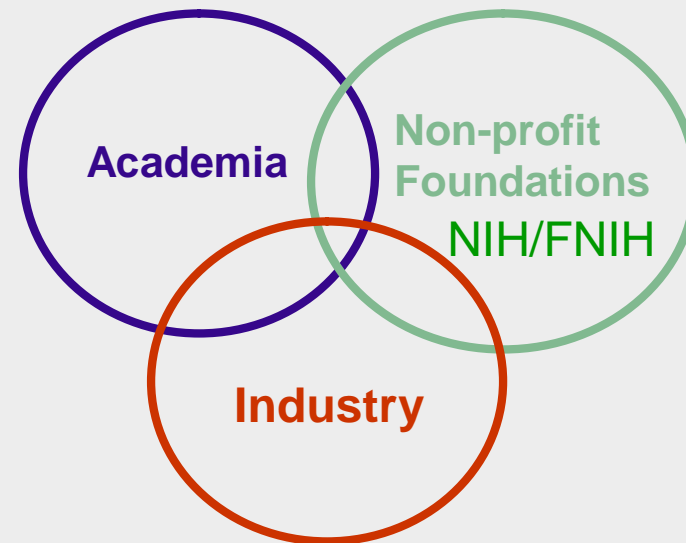
- Complexity of CNS biology
 - Plethora of expressed targets
 - 80% all genes are expressed in brain
 - Vast target heterogeneity
 - Most genes expressed in <20% brain cells
 - Dynamic changes on both short and long time scales
- Prominent limitations of animal models!
- Blood-brain barrier
- Trials often difficult
 - population heterogeneity
 - lengthy treatment may be needed
 - placebo effects, noisy readouts
- è empirical approach to identifying efficacy and toxicity
- è many parallel shots: need large testing bandwidth

New Partnerships: Academia, Foundations, NIH, and Industry

Linear model



Partnership model in "precompetitive space"



Disease Foundations: Transitioning from academic funding agencies to non-profit therapeutic companies

- Focus shifting from academic funding to the proactive discovery, development, and delivery of therapies.
- Systematic analysis of visible pipelines, gap analysis.
- Identifying, supporting, and disseminating relevant technologies.
- Virtual in-house discovery programs, milestone-driven partnerships and outsourcing contracts.
- Defensive IP protection to keep key technologies widely available.
- Prospective development of biomarkers and trial strategies.
- Development of clinical trial networks.
- Early attention to potential regulatory or reimbursement hurdles.
- Recruitment of industry partners for late development and commercialization.

Target engagement – need to assess directly

- May well not follow from comparing human plasma PK or even CSF PK to animal data, due to species differences in:
 - access to brain tissue (eg due to BBB or PGP behavior)
 - access to intracellular or subcellular compartments
 - molecular target affinity
 - occupancy–response functions
- Efforts aimed at identifying and implementing suitable human biomarkers for target engagement should be concurrent with preclinical lead optimization.
- Field progress depends on distinguishing causes of failures.
 - **failure of implementation** (dose or molecule) vs **failure of concept?**

BACK UP SLIDES