CNS Drug Development
(What is a “drug target”?)

a conversation to stimulate thinking

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Outline

• A little bit about me
• CNS drug development
• What is a drug target?
• If we only knew the pathological basis of disease we could fix it
• Why is pharmacology important?
• What do we want/need to know to put something into humans?
• It’s the best time to be in science...
A little about Sam Kongsamut

- Ph.D. (Neuropharmacology) – Univ Chicago; Postdocs – Cornell, Yale
  - R&D: Discovery → Development → Clinical Development → 2 Marketed Products
  - Management (portfolio, people)
  - External (open) Innovation / Business Development

Rudder Serendip (2012-present):
- Consulting in Neuroscience & Aging + other areas
- Universities and Foundations
- Biochron Therapeutics
- Neurotrope BioScience Inc.
- NSF iCorps, ELAB NYC
- Rutgers CTEC Entrepreneurship Mentor
- Launch NJ Life Sciences Hub
- Institute for Life Sciences Entrepreneurship
- RISE Associate, Drew University
US New Drug Development Process

Preclinical
- Genomics
- Proteomics
- New Target Identification
- High Throughput Screening
- Computational Methods
- Medicinal Chemistry
- Preclinical Testing
- Pharmacology
- Efficacy Prediction

Clinical
- IND filing
- 30 day wait
- Phase 1 Clinical (Safety)
- Phase 2 Clinical (Efficacy)
- Phase 3 Clinical (Side Effects & Long Term Use)
- Supplementary Reporting and Review
- FDA Approval Process
- FDA Approval
- NDA/BLA Submission
- Supplemental Reporting
- Supplementary Reporting
- Phase 4

Nonclinical
- Pharmacology
- Safety Pharmacology
- Toxicology
- DMPK: Drug Metabolism & Pharmacokinetics
- Chronic Toxicity
- Carcinogenicity
- Reproductive Toxicity
- Additional Genotoxicity
- Special Toxicity

Time Required
- (7-17 Years)

Cost
- $2-5 billion+

Scale-up and Process Development
- Analytics, Pharmaceutics and Formulation Development
- Medical Education and Marketing

High Throughput Screening
- Computational Methods
- Medicinal Chemistry
- Preclinical Testing
- Pharmacology
- Efficacy Prediction

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Supplemental Reporting
- Phase 4
CNS Drug development

Why is it so difficult?

Crossing the Blood Brain Barrier
Understanding of brain function
Redundant mechanisms and feedback loops
Neurodevelopmental abnormalities
Compensatory mechanisms
Acute vs chronic effects
Trial and error
What is a drug target?

Phenotypic screen – behavioral models
Molecular targets
Cloning of the human genome
Dictionary vs language – can you learn a language by studying the dictionary?
Disease pathology (up/downregulation)
    humans vs. animal models
Mechanistic vs. pathological models
If we only knew the pathological basis of disease, we could fix it.

- Lysosomal storage disorders (ERT)
  - many CNS symptoms
- Diabetes (insulin – successful?)
  - Alzheimer’s as T3D?
- Huntington’s disease
- Sickle Cell Anemia
Why is pharmacology important?

Pharmacodynamics
Pharmacokinetics

What the drug does to the body vs. what the body does to the drug
Benefit risk - everything is toxic
potency vs efficacy
Agonist or antagonist
Allosteric modulators
Pharmacokinetics – ADME
Structure Activity Relationships
What do we want/need to know to put something into humans?

Investigational New Drug application (IND)

Safety, safety, safety (first do no harm)
Benefit risk
Therapeutic index
Chronic treatment
CMC – we tend to take this for granted
It’s the best time to be in science
We know more than ever

Change in R&D model from big company to small company

Innovation occurs best in a resource-scarce environment
**JOBS Workshop: Drug Development in Biotechnology**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:30 – 9:45AM</td>
<td>Introduction and Purpose of the Symposium – Janet Alder</td>
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<td>9:45 – 10:15</td>
<td>Overview of the Pharmaceutical Industry – Larry Wennogle</td>
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<td>10:15 – 10:25</td>
<td>Questions/Discussion</td>
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<td>10:25 – 10:55</td>
<td>Technologies for discovery of new drug candidates – Mary Konsolaki</td>
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<td>10:55 – 11:05</td>
<td>Break</td>
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<td>11:05 – 11:35</td>
<td>CNS Drug Development (What is a “drug target”) – Sam Kongsamut</td>
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<tr>
<td>11:35 – 12:05PM</td>
<td>Clinical Development of a Pharmaceutical Agent for Food and Drug Administration (FDA) approval – Ira Daly</td>
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<tr>
<td>12:05 – 12:35</td>
<td>The story of Entresto – Novel therapy for Heart Failure - Randy Webb</td>
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<td>12:35PM</td>
<td>Working lunch will be served</td>
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<td>1:00 – 1:30</td>
<td>Funding the Pharmaceutical and Biotechnology Industry – Ben Bowen</td>
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<td>1:30 – 2:00</td>
<td>Break out groups – Attendee will break out into small ~6 person groups to develop a plan to organize a biotech company designed to develop pharmaceuticals. (More specific instructions will be supplied.)</td>
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<tr>
<td>2:00 - 2:30</td>
<td>The long and winding road to a marketed drug – Ron Steele</td>
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<td>2:30 – 3:00PM</td>
<td>General Discussion including answers to questions submitted in advance of the symposium by participants.</td>
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<td>3:00 – 4:00PM</td>
<td>Mixer</td>
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