Translational Research through Public-Private Partnerships

65th Annual Bohan Lecture

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Drug Focused Translational Research
Translational Research Defined by the Clinical Problem

Breast Cancer

Clinical Problem

Clinical Trials

Drug Treatment

Laboratory Research

Solution
Breast Cancer Cells Die!
The Lock and Key

Drug Targets and Drugs

Drug (Key)

Drug Target (Lock)
The Role of Academia in Drug Discovery and Development
• One in 5000 to 10,000 compounds become an approved drug
• Costs to discover, develop and commercialize a new drug today exceeds $1.2B
• Regulatory requirements continue to increase, decreasing the effective patent life of a drug
• Days of “blockbuster” drugs may be over
• Investment in R&D exceeds profits from sales
• Reimbursement environment is becoming increasingly restrictive
Do or Die Time – R&D chiefs agree that big pharma’s fully integrated business model has one more chance to deliver.
Rare and Neglected Diseases Landscape

- Over 7000 human diseases
- Historically, 300 human diseases of interest to the pharmaceutical industry due to prevalence and commercial potential

- Rare Diseases
  - *Over 6000 diseases considered rare by The Orphan Drug Act*
  - *Orphan Drug Act defines rare diseases as a prevalence of less than 200,000 US patients*

- Neglected Diseases
  - “Conditions that inflict severe health burdens on the world’s poorest people”
July 6, 2010

FOCR Town Hall Meeting


- HHS Secretary Sebelius presented as keynote speaker
- Panel discussion with NIH Director Collins and FDA Commissioner Hamburg moderated by Richard Gephart
- Four panels representing academia, government, industry and disease philanthropy
- Held at Kauffman Foundation
Our Strategy
KU School of Pharmacy ranked in top 4 based on NIH funding
Research led to commercialization of several products, however, none of these drugs were not evaluated in patients at KU!
Basic and clinical researchers separated by 40 miles
Kauffman Foundation research on technology commercialization has defined best and worst practices
Drug development identified as economic development priority for Kansas
Cancer biology research programs were relatively weak within KU, strength came from Stowers Institute for Medical Research
Our Translational Research Strategy

- Establish
  - Translational research processes
  - Demonstrate translational research success
  - Leverage to build basic research through recruitment of eminent scholars and rising stars

- Internal and external messaging
  - Focus on innovative solutions rather than imitating big pharma
  - Focus on unmet medical needs, i.e., rare and neglected diseases, pediatrics
  - Achieve end-to-end translation through collaboration

- Balanced project portfolio
  - Novel and repurposed drugs
  - Not just cancer!
Partnerships with Industry, Academia, Government and Disease Philanthropy

Medicinal Chemistry

Molecular Biology

Integration with Technology Transfer

Regional and State Economic Development

Pharmaceutical Chemistry

Regulatory Science

Clinician Scientists

Drug Discovery, and Development Guidelines

Industry Experienced Drug Discovery and Development Experts

Leveraging Regional Drug Development Assets

Underpinning Major University Translational Research Priorities

Public Policy

Translational Research “Village”
Empowered Teams Define Project Plans

Drug Discovery Program
From Target Validation through Identification of Development Candidate

**DECISION #1**
Identification of Chemical Leads by High Throughput Screen (HTS)
- GO
- NO GO

**DECISION #2**
Identification of Chemical Leads Based on In Vitro Screens
- GO
- NO GO

**DECISION #3**
Selection of Chemical Leads for Evaluation in Cell/Mouse Model
- GO
- NO GO

**DECISION #4**
Selection of Development Candidate for Clinical Proof of Concept
- GO
- NO GO

- Combinatorial Chemistry Design and Synthesis/SAR Medicinal Chemistry Analysis Analoging (1-10 mg)
  - ~$1,200 Per Week
- Hit Identification and Validation
- HTS Primary Screen ~$50,000 - $500,000
- In Silico Secondary Validation of Hits on Targets and Specificity
- Key Crystallography & Target Computed Interaction

- Aqueous Solubility Screen ~$200/Compound
- Caco-2 Absorption Screen ~$500/compound
- Metabolic Stability Screen ~$500/Species
- Ames Screen ~$1,500
- H&PG Screen ~$2,000

- Development & Validation of In Vitro Cancer Model ~$25,000
- In Vitro Proof of Concept Rodent Model ~$30,000
- Preclinical Pharmacokinetics in Rodent ~$50,000
- Synthesis of Chemical Leads for In Vitro Proof of Concept (~$100,000)

- In Vitro Pharmacology/Receptor Binding Profile ~$50,000
- Non-GMP In Vitro Pharmacology in Rodent ~$35,000
- Non-GMP In Vitro Toxicology in Rodent ~$35,000
- Synthesis of C-GMP Drug Substance (~$500,000)
- Non-GMP Pre Formulation Characterization of Bench Scale Drug Substance

**Study Begins**
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80
- 90
- 100
- 110
- 120

**Number of compounds**
- 100,000
- 30
- 18
- 4
- 1
- 1
- 1
- 1
Industry, academia, government, disease philanthropy collaborations
Public-Private Partnerships
The Valley of Death

The Formidable Barrier to Translation

Scientific Proof of Concept

Too Applied for NIH
Too Risky for Industry

Commercial Proof of Concept

The Valley of Death

Government Funding

Private Sector Funding

R&D Funding

Time

Rx
The Valley of Death

Funding Gap Ranges from $1.5M to $6M

-Federally Funded Basic Research

Drug Discovery

Preclinical Drug Development

"Too Applied for NIH" and "Too Early for Pharma"

Clinical Drug Development (Pharma Funded)

FDA Review, Approval, Launch (Pharma Funded)
Bridging the Valley of Death through Collaboration

Federally Funded Basic Research

Academia KU!

Biotech Innovative Pharma Models

Drug Discovery

Preclinical Drug Development

Clinical Drug Development (Pharma Funded)

FDA Review, Approval, Launch (Pharma Funded)

Disease Philanthropy Foundations

Venture Philanthropy

NIH TRND CTSA

Philanthropy Foundations

NIH TRND CTSA

Biotech Innovative Pharma Models
news release

For immediate release

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The Leukemia & Lymphoma Society and The University of Kansas Cancer Center Advance Novel Drug to Clinic in 13 Months

White Plains, NY And Kansas City, KS – In only 13 months, a team of researchers and drug developers at The University of Kansas Cancer Center, Ontario Cancer Institute, The Leukemia & Lymphoma Society (LLS), and Beckloff Associates Inc. have advanced a promising new therapy for leukemia into a Phase I clinical trial.
Drug Repurposing

De novo drug discovery and development
- 10–17 year process
- <10% overall probability of success

Target discovery
- Expression analysis
- In vitro function
- In vivo validation; for example, knockouts
- Bioinformatics

Discovery & screening
- Discovery
  - Traditional
  - Combinatorial chemistry
  - Structure-based drug design
- Screening
  - In vitro
  - Ex vivo and in vivo
  - High throughput

Lead optimization
- Traditional medicinal chemistry
- Rational drug design

ADMET
- Bioavailability and systemic exposure (absorption, clearance and distribution)

Development
- Must start clinical testing at Phase I (Phase II for cancer)

Registration
- United States (FDA)
- Europe (EMEA or country-by-country)
- Japan (MHLW)
- Rest of world

Drug repositioning
- 3–12 year process
- Reduced safety and pharmacokinetic uncertainty

Compound identification
- Targeted searches
- Novel insights
- Specialized screening platforms
- Serendipity

Compound acquisition
- Licensing
- Novel IP
- Both licensing and novel IP
- Internal sources

Development
- May start at preclinical, Phase I or Phase II stages
- Ability to leverage existing data packages

Registration
- United States (FDA)
- Europe (EMEA or country-by-country)
- Japan (MHLW)
- Rest of World
One Key Opens Multiple Locks

Drug Repurposing

Drug (Key)

Drug Target (Lock)
An Example - Ciclopirox Olamine

- Indication: mild-moderate fungal nail infection
- Marketed in gels, creams, shampoos, and lacquers for topical administration
- “Key” fits a newly discovered “lock” in acute myeloid leukemia pathway
- Goal to administer drug to patients orally
Bench to Bedside in 13 Months

- First clinical trial in relapsed and refractory acute myeloid leukemia patients
- First trial approved by Health Canada (Canadian “FDA”)
- Capitalized on existing data generated by innovator company
- 24 patients have received ciclopirox olamine to date
- Discovery licensed to biotechnology company who will open trials in the US

13 Months

$1.5M
The Learning Collaborative

Capitalizing on Strengths

- Defining new role of academia
- National leadership in medicinal and pharmaceutical chemistry
- Bench to bedside translation in drug repurposing
- Successful public-private partnerships
- Recruited pharma experience

- > $60M invested annually in basic blood cancer research
- Therapy Acceleration Program home to 60 active projects
- World wide network of blood cancer experts
- Established several commercial partnerships
- Recruited pharma experience

- Focus on rare and neglected diseases
- Industrial scale HTS, medicinal chemistry, and bioinformatics capabilities
- Successful collaborations with academia and industry
- Recruited pharma experience
Exit Strategies

- Multidisciplinary, multiorganizational teams
- TLC defines and executes project plan
- Define path(s) to exclusivity
- LLS leads licensing effort targeting their network of commercial partners
- Thought leaders well positioned for Phase II
2009
- Nanotax® Phase I Trial (Crititech Inc) ★
- SR-13668 Phase 0 Trial (Mayo Clinic)
- Ciclopirox Olamine Phase I Trial (Ontario Cancer Institute, LLS)

2010
- Captisol-Enabled Melphalan (Cydex) in BMT ★
- Pre-IND Meeting with FDA on Pediatric Cardiovascular Drug

2011
- Pediatric Anticancer Drug PK/PG Trial (CMH) ★
- Auranofin Clinical Proof of Concept Trial (KU, NHLBI, OSU) ★
- Tigecycline Clinical Proof of Concept Trial (KU, OCI, UCLA, MSK) ★
- Hydroxyurea for Sickle Cell Anemia (PTN) ★

2012
- Pediatric Cardiovascular Drug Pivotal Bioavailability (Silvergate)
- Pediatric Anticancer Drug Product Bioavailability Trial (Silvergate)
• **Stevens et al**\(^1\)
  
  » 125 medical schools studied  
  » Study spans 40 years  
  » Medical school research conducted led to registration of 153 drug products  
  » Forty of the 153 drug products were hematology and oncology products  

• **University of Kansas**  
  
  » Eight hematology and oncology products advanced to clinical trials over 2009-2011  
  » An additional two drug products entering clinical trials in 2012

\(^1\) NEJM 2011 364(6):535-551