Bridging The Valley Of Death In Academic Drug Discovery

A NEW PARADIGM FOR 21ST CENTURY DRUG DISCOVERY

Dennis Liotta, Ph.D.
Director
Emory Institute for Drug Discovery
Atlanta, Georgia

October 26, 2010
“Today...two-thirds of the roughly 3,000 drug compounds currently under development were engineered in biotech labs.... Just as important, they were created at half the average cost of those at pharmaceutical firms.”

*The Wall Street Journal (November 29, 1995)*

“We expect that in the future a major portion of our drug pipeline will come from collaborations with external partners.”

*Jeffrey Kindler, CEO Pfizer*

“Collaboration with others in industry, academia, government and non-governmental organisations and healthcare in general is fundamental to our strategic priorities of growing a diversified, global business and delivering more products of value.”

*Glaxo SmithKline website*
PHARMACO ECONOMICS 101

Risk

Value

Cost

Conception
Technical Feasibility
Product Development
Safety / Pre-Clinicals
Clinicals / Manufacturing
Commercialize

0%
50%
100%

Univ.
Biotech Co.’s
Big Pharma
EXAMPLES OF DISCIPLINES REQUIRED FOR DRUG DEVELOPMENT

<table>
<thead>
<tr>
<th>Target ID</th>
<th>Lead Discovery</th>
<th>Lead Development</th>
<th>Process Development</th>
<th>Form./Tox.</th>
<th>Clinical Trials</th>
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</thead>
<tbody>
<tr>
<td><strong>Target ID</strong></td>
<td>• Genetics / Genomics</td>
<td>• Structural Biology</td>
<td>• Immunology</td>
<td>• Biophysics</td>
<td>• Pathology</td>
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<tr>
<td><strong>Lead Discovery &amp; Development</strong></td>
<td>• Medicinal Chemistry</td>
<td>• Pharmacology</td>
<td>• Molecular Biology</td>
<td>• Biochemistry</td>
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<td>• Chemical Biology</td>
<td>• Microbiology</td>
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<td><strong>Process Development</strong></td>
<td>• Synthetic Methods Development</td>
<td>• Scale-up Facilities</td>
<td>• Metabolite Synthesis</td>
<td>• Analytical Chemistry</td>
<td>• cGMP Manufacturing</td>
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<td><strong>Clinical Trials</strong></td>
<td>• Clinical Trial Design</td>
<td>• Pharmacokinetics</td>
<td>• Metabolism</td>
<td>• Biostatistics</td>
<td>• Genetics / Genomics</td>
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<tr>
<td>• Physician &amp; Patients</td>
<td>• Regulatory Expertise</td>
<td>• CRO</td>
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<td><strong>Preclinical Development</strong></td>
<td>• Whole Animal Pharmacology</td>
<td>• Biostatistics</td>
<td>• Pharmacokinetics</td>
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<td>• Metabolism</td>
<td>• Formulation</td>
<td>• Drug Delivery</td>
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<td>• Toxicology</td>
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GLOBAL NETWORKS WITH MANY PLAYERS

- GOVERNMENTS
- FOUNDATIONS
- NGOs
- BIOTECH
- PHARMA
- UNIVERSITIES
- RESEARCH INSTITUTES
Identify broad-based needs that can not be adequately addressed by the commercial sector.

Develop strategic initiatives for catalyzing economic development in prioritized areas.

Actively engage in human capital development:
- Training scientists
- Training entrepreneurs

Develop infrastructure (a national informatics backbone, high tech instrumentation, professional expertise, etc.) with broad availability to the academic and commercial sectors.

Develop partnerships that facilitate scientific exchanges across borders.

Provide special incentives for startup companies.
Drug discovery research in academia provides an important complement to the discovery activities in Pharma.

The emphasis by universities on basic research provides a natural platform to identify potential therapeutics.

Research carried out in academia is not immediately dictated by the needs of the marketplace.
PHARMACO ECONOMICS 101

Conception
Technical Feasibility
Product Development
Safety / Pre-Clinicals
Clinicals / Manufacturing
Commercialize

Value
Cost

Maximum Risk Potential
Maximum Return Potential

Risk

Univ.  Biotech Co.’s  Big Pharma
### Product Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Licenses</th>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>NDA</th>
<th>Market</th>
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<tbody>
<tr>
<td>3TC (Combivir®)</td>
<td>GlaxoSmithKline/Shire</td>
<td>HIV</td>
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<td>D-FT-44C (Elvucitabine)</td>
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<td>DFC (Dexelvoltabine)</td>
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• A multidisciplinary environment staffed with experienced investigators
• State of the art bioanalytical instrumentation
• An array of computational design programs and hardware
• Fully equipped chemistry and biology labs
• Access to fully staffed rodent and non-human primate vivaria
South Africa is an excellent example of the advantages that can emerge from partnering with Developing World nations.

- **Strong research science:**
  - Research universities and institutes
  - Government research councils

- **Unique biodiversity:**
  - Cape Floristic Region
  - National Botanical Garden

- **Traditional Knowledge Systems**

“Africa’s real compound GDP growth, about 5 percent annually between 2002 and 2009, was on par with Russia’s and significantly higher than those of developed countries….. 4.5 percent until 2015, which will boost consumer spending by more than 35 percent”

– McKinsey Quarterly, June 2010
EXAMPLES OF SOUTH AFRICA’S GROWING DRUG DISCOVERY INDUSTRY

- **iThemba Pharmaceuticals** - an emerging drug discovery company whose goal is to develop novel, small molecule therapeutics to address unmet medical needs in sub-Saharan Africa. iThemba recently merged with Arvir, a start-up biotechnology company focused on providing a strategic array of affordable antiretrovirals (ARVs) and microbicides (Capresa trial) through the establishment of local capacity for API (Active Pharmaceutical Ingredient) manufacturing.

- **ACRO** - a CRO which offers clinical research services to donor-funded organizations, non governmental organizations, research institutions, pharmaceutical companies, and government institutions.

- **Aspen** - Africa’s largest pharmaceutical manufacturer and a major supplier of branded and generic pharmaceutical, healthcare and nutritional products to southern Africa and selected international markets.

- **Elevation** - a spin out biotech company from the University of the Witwatersrand and South African National Health Laboratory Service (NHLS) that is focused on the discovery and development of HIV attachment inhibitors.

- **Kapa** - founded to develop next-generation PCR reagents. Their molecular evolution technology platform is currently being used to optimize enzymes for DNA amplification, next-generation DNA sequencing, and molecular diagnostic applications.

- **Synexa** - a South African-based provider of specialized clinical trial laboratory services. This entity offers an extensive portfolio of non-routine laboratory analyses that provide a better understanding of the safety and efficacy profiles of clinical agents.
Established in partnership with the government of South Africa (National Research Foundation).

Yearlong postdoctoral and 6 month research advanced training programs in a number of disciplines including medicinal chemistry, biochemistry, computational chemistry, pharmacology, and bioinformatics. “Mini” sabbaticals are also available for more experienced individuals.

Course in fundamentals of drug discovery (science, business, and law) and career development.

15 Scholars since 2008.

Partners include SCYNEXIS, Inc. and GlaxoSmithKline, Inc. (2011).
Established in collaboration with the Innovation Fund (now a part of the Technology Innovation Agency) to help develop new life science companies in South Africa.

2 day workshop in patent law/licensing and entrepreneurship.

Weeklong Executive Education provided by Goizueta Business School (Emory University) faculty.

Mentorship from established biotechnology executives is provided to help assist the development of business plan.

Business plan competition is judged by experienced Venture Capitalist from South Africa, USA, and Europe.

Winners receives seed funding. All participants receive access to a powerful network of supportive entrepreneurs and scientists.
The collaboration is focused on inhibition of two enzymatic targets (isocitrate lyase and malate synthase) associated with latency stage of TB.
GSK pays for flights from and to the country of origin.

GSK pays for accommodations for visiting scientists.

GSK pays scientists a competitive annual salary on a pro rata basis.

Visiting scientists will spend 6 months in Tres Cantos, Spain, followed by 6 months in Moderfontaine, South Africa to complete the knowledge transfer process.
GLOBAL NETWORKS WITH MANY PLAYERS

- Governments
- Foundations
- Universities
- Recherche Institutes
- Biotech
- Pharma

- Develop Capacity Building Partnerships
- Bring New Products and Services to the Marketplace
- Become Innovation Boutiques
Roles: Execute a focused business strategy for the efficient development of both individual and platform technologies.

Opportunities

SOUTH AFRICAN PHARMA OFFERS
- Low operating costs
- Minimal marketing overhead
- Conduit for global social investment
- Dual branding opportunities
- Expedient clinical development

PROFITABILITY POTENTIAL
Developing World:
- Good ROI
- Low margins / High volumes

Developed World:
- Excellent ROI
- Spectacular margins

Both Worlds
- Opportunity for reinvestment in R&D
Leader in Medicinal and Synthetic Chemistry

www.ithembapharma.com
Overview of iThemba Pharmaceuticals

• Only small molecule Chemistry company in South Africa (and Africa)
  – Highest number of PhDs in Africa
• What do we provide?
• What is our expertise base?
• What do you gain by contracting with iThemba?
• Our track record
Location

- South Africa is GMT +2h
- Cape Town to iThemba = London to Rome
Board of Scientific Advisors

- Prof. Dennis Liotta (Emory University, Atlanta, USA; founding member and shareholder)
- Prof. James Bull (University of Cape Town, South Africa)
- Prof. Anthony G. M. Barrett (Imperial College, London, United Kingdom; founding member and shareholder)
- Prof. Erick Carreira (ETH, Zurich)
- Prof. Steven V. Ley (Cambridge University, England; founding member and shareholder)
- Dr. George R. Painter (Chimerix Inc., NC, USA)
A Few Facts

- Commenced operations: June 2008 with 4 staff
- Finance: R30M ($4M) initial investment (government), a further R19M ($2.5M) raised through collaborations
- Number of employees: 16 (10 PhDs)
- Facility: 800m$^2$ of laboratory space with state-of-the-art analytical and synthesis equipment (mg – 100g and array up to 20)
- Equipment: 400MHz NMR, Agilent LCMS and prep HPLC, Genevac, CEM discover 12 µW
Service Business

• Offer contract service (FTE or project-based)
  – synthetic organic chemistry
  – medicinal chemistry (via collaboration with AIBST)
• Top quality SAB
• Several international clients
  – repeat business
• Produce and sell novel chemical intermediates
• ‘Gold Standard’ Hit validation service
Service Business – In Vitro ADMET

• Joint service offering with the African Institute of Biomedical Research and Technology (AiBST), Harare
  – 2h by plane
• CSO Dr. Collen Masimirembwa (PhD, DPhil)
  – >8y experience with AstraZeneca Sweden
• Offer one-stop-shop for managed medicinal chemistry
  – Deal format per sample or FTE based
• WHO-TDR DMPK Center of Excellence
Our Molecular Database

• Chemical Intermediates
  – produce and sell range of molecules
Discovery Pipeline

Proposal → Screening → Hit to Lead → Lead Optimisation → Process Optimisation

- **MRCT Malaria proposals**
- **Chroma, iThemba, IPK selective macrophage accumulation**
- **MRCT (100k, TB)**
- **Chimerix (7k, TB)**
- **TB/ICL**
- **IF – TB Nitroimidazoles**
- **MRCT Collection (45k, Malaria)**
- **TB Hits (NIH/TB CoC)**
- **Chimerix (7k, Malaria)**
- **Abacavir**
- **β-Thymidine**

www.ithembapharma.com
Drug Discovery - TB

- Highly active isocitrate lyase drug candidates
  - Best validated target for persistence
- Novel nitroimidazole drug candidates
  - Currently most exciting compounds in clinic
- Collaboration with TB CoC
  - Optimize screening hits
Drug Discovery - TB

• International consortium screening campaign to identify novel starting points
  – Phenotypic screen, 100k compounds

• Signed MOU with GSK to access Knowledge Pool for Open Innovation
  – Announced by Andrew Witty (CEO)
  – Transfer of first scientist due Jan 2011
Drug Discovery - Malaria

• Screening campaign complete
  – 60k compounds
• Active compounds refined
  – Properties, opportunities, potential
• Project support requested from Medicine for Malaria Venture (MMV)
  – Selected for final review (6/60), 3 to be funded
Process Technology ARV APIs

• Abacavir; alternative synthetic route licensed from Emory and investigated by iThemba
• β-thymidine and AZT; biocatalytic process which has several advantages over the existing fermentation route and could reduce cost of AZT API production
Why iThemba?

- Competitive cost base
- Strong IP laws in South Africa
- Efficient / Outcomes driven
- Access to superlative Scientific Advisory Board
- Good cultural fit
- Moral leverage – all profits re-invested into neglected disease research
Poverty, Many People → Poor health conditions → High Morbidity & Mortality → Inadequate medication → Huge Unmet Medical Need

Poverty, Many People → Poverty, Many People

High Morbidity & Mortality → Big Need Low Commercial Value to Pharma

Big Need Low Commercial Value to Pharma → High Commercial Risk & Insufficient Return To Justify Focused Research

High Commercial Risk & Insufficient Return To Justify Focused Research → Intense Political & Moral Pressure

Intense Political & Moral Pressure

Affordability Pricing issues

Pleasing Wall Street: Pharma’s need to create >10% annual growth in shareholder value

Economic Paradigm is inconsistent
Each entity should avoid the temptation to become a FIPCO. Instead, they should focus on their strengths in the discovery/development continuum and seek partnerships with entities that possess complementary capabilities.
Yves Ribeill, PhD - President and CEO of SCYNEXIS, Inc.

Over 20+ years of international pharmaceutical experience prior to SCYNEXIS, Inc.

Member of the Scientific Advisory Committee of the World Health Organization.

Contracted with DNDi in 2006 to discover compounds for HAT (sleeping sickness).
High Throughput Screening (HTS) has become an essential component for efficient and competitive drug discovery and development.

A stand alone HTS facility without additional infrastructure to transform “hits” into clinical candidates does not represent a viable business opportunity.

The startup costs for a national HTS facility could be easily leveraged by philanthropic contributions from foundations.

The establishment of a South African High Throughput Screening Facility would create the opportunity for extracting maximum value from South Africa’s rich biodiversity from both an innovation and economic development perspective.