Best Science for the Most Neglected

From patient needs to implementation of new treatments

Discovery and Lead Optimisation Programs:
A Future Generation of Drugs for Neglected Diseases

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Advinus’ Business Model

Drug Discovery in Partnership

Internal Drug Discovery

Contract Services

Drug Discovery

Pharma Drug Development Center

Partners
- Merck
- J&J
- Novartis
- DNDi

Data Funding

IP

Licensing

Pay-out

Services

Fee-for-service

Idea to IND filing
- 35 months

> 80 clients

80 clients
Drug Discovery & Development at Advinus

METABOLIC DISORDERS: Type 2 Diabetes, Obesity, Dyslipidemia

INFLAMMATION: RA, Asthma/COPD, Psoriasis

NEGLECTED DISEASES: Leishmaniasis, Dengue, Malaria

Early Stage Discovery Collaboration

Out-licensing post Proof-of-Concept

Advinus Core Strengths

Value creation through internal and collaborative research
Drug Discovery & Development Processes: Key Decision Points

Focus
- Potency & Selectivity
- Druggability
- Quality Drug Candidate

Key activities
A. DMPK
- In-vitro screening
  - Permeability, Metabolic stability, P-450 inhibition/induction
- In-vivo screening
  - Bioavailability, biopharm evaluation, PK, PK/PD & Prediction in humans

B. In-vitro & Exploratory Toxicology
- In-vitro geno & cellular toxicity & safety pharmacology & mini toxicology in rodents

C. Physico-chemical Characterization
- Form selection, solubility, stability
Background on Advinus and its policy for social responsibility for neglected disease and short outline of the lead optimization process as most of the audience doesn’t know well this part of the R&D process.

Activities developed since 2007 in Advinus to tackle Kala Azar (tox, pharmacokinetic, chemistry…). It won’t be necessary to explain the existing limitations with current treatments therapies but only to remind that NCEs are still needed to really improve case management of Kala Azar patients.

Importance of partnerships illustrated through collaboration with CDRI, Anacor …

Main outcomes with the lead compound from the Nitroimidazoles series that meets the criteria for pre-clinical candidate.
Visceral Leishmaniasis (VL) Lead Optimization Strategy

**Screening** → **Hit Expansion** → **Lead Optimization**

- Reiterative cycles of medicinal chemistry
- Parallel assessment of DMPK Tox and Potency
- Pharmaceutical chemistry
- GLP Toxicology
- Drug Candidate

**CDRI - Advinus**

**TB Alliance** → **Lead to Candidate**

**IRD** → **Anacor** → **Institut Pasteur Korea**
Nitroimidazoles and a Clinical Candidate

- Nitroimidazole series was initially being investigated by TB Alliance to develop a drug for the treatment of tuberculosis - collaboration with Dr. Brian Palmer, University of Auckland, New Zealand
- Representative compounds from nitroimidazole series were screened at Swiss Tropical Institute against L. donovani (axenic model) followed by additional screening at the London School of Hygiene and Tropical Medicine (LSHTM); and Central Drug Research Institute (CDRI)
- DNDI-VL-2001 emerged as a lead candidate after performing a series of in vitro and in vivo studies safety, efficacy, and pharmacokinetic studies
DNDI-VL-2001: Summary

- In vitro efficacious with IC50 in < 50 nM
- In vivo efficacy demonstrated in mice and hamsters following oral dosing
- Adequate PK properties in mouse and hamsters
  - Dose related increase in systemic over a 80-fold dose range (6.25 to 500 mg/kg)
  - No enantiomeric interconversion in vivo in mouse
  - No inhibition of major CYP450 (except CYP2C19 with IC50 < 1 µM), not a potential issue for this class of compounds
- Exploratory toxicology study – 25, 50, 200 and 500 mg/kg (repeated once daily dosing for 5 days in mice)
  - All doses well tolerated, no clinically meaningful changes in clinical chem.
- Ames-negative (mini-Ames test)
- hERG binding, IC50 = 5.6 microM, not a potential issue
- Pan-labs screen: No concern for any off-target activities
- At present, process optimization to synthesize the DNDI-VL-2001 is ongoing and the IND enabling toxicology studies are projected to be initiated in 1Q 2011.
Advinus’ Role in Lead Selection

- Several nitroimidazoles, with desirable in vitro potency were screened for metabolic stability in mouse, hamster, and human liver microsomes
- The pharmacokinetics of over 10 compounds were characterized in mice to enable compound selection
- VL-2001 emerged as a preferred candidate for development
- VL-2001 is a racemate compound. Several studies were performed to ensure
  - Lack of chiral interconversion in vivo
  - Metabolic stability/intrinsic clearance of racemate and individual enantiomers
  - In vitro efficacy in L.donovani (Amastigote, Macrophage model) of racemate and both enantiomers
  - 7-Day exploratory toxicology study in mice
- Based on the results of in vitro and in vivo studies, VL-2001 – racemate is selected for further development
**DNDI-VL-2001: Key Characteristics**

*In vitro (L. donovani)*
- IC$_{50}$ = 0.01 µM
- CC$_{50}$ = 96 µM
- SI > 1000

Solubility (µM) < 10
% Metab in 30 min:
- HLM = 14, MLM = 21, HamLM = 51

CL$_{intra}$ (mL/min/g liver):
- HLM = 0.6, MLM = 0.8, HamLM = 2.5

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<tr>
<th>Compound</th>
<th>Dose regimens</th>
<th>Mean ± SD % Inhibition</th>
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<td></td>
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<td>Day 12</td>
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<td>Day 35</td>
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<td>Day 50</td>
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<tr>
<td>DNDI-VL-2001</td>
<td>50 mg/kg x 5, once daily</td>
<td>95 ± 3 (n=4)</td>
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<td></td>
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<td>99 ± 1 (n=3)</td>
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<td>50 mg/kg x5, once daily</td>
<td>86 ± 14 (n=5)</td>
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<td>72 ± 25 (n=5)</td>
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<td>25 mg/kg x10, once daily</td>
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<td>99 ± 1 (n=5)</td>
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<td>98 ± 1 (n=2)</td>
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<td>25 mg/kg x5, once daily</td>
<td>65 ± 40 (n=5)</td>
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<td>63 ± 40 (n=4)</td>
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<td>Miltefosine</td>
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Ongoing Discovery program: Thiazoles Series

Compounds from IPK
In vitro activity in micromolar range Resynthesized & confirmed the activity

Designed focused library around these compounds

Achieved very low nanomolar active compounds Metabolically unstable

Focused modification to improve met stability

Achieved metabolically stable/low intrinsic clearance compounds with acceptable activity In vivo studies are in progress
Thiazoles: Back-Up Series

• Aminothiazole series emerged as a promising series based on HTS performed by Institut Pasteur Korea for in vitro activity

• Good Structure-Activity-Relationship in the thiazole series; however, compounds had poor metabolic stability
  – Modifications to improve metabolic stability resulted in amidothiazole series

• Several compounds with good in vitro activity and metabolic stability have been identified

• Additionally, compounds will be identified based on results from the in vivo efficacy and pharmacokinetic studies

• Target to identify a back-up clinical candidate by 2nd half of 2011
Issues for Developing Countries

- Access to resources
- Access to and availability of skills
- Access to information
  - intellectual property (patented and non-patented)
- Establishing appropriate infrastructure
- Establishing appropriate culture to support innovation
- Budget to support R & D
- Being invited to the table
- Considered only for Phase II and III clinical trials & manufacturing
What is Needed?

- Change in mindset – from “we are here to help” to “how can we do it together” leveraging each other strength keeping the common goal in mind
- Change in mindset – from spending majority of R & D money on clinical trials to high risk innovation to POC (more shots at the goal)
- Change in mindset – regarding compromising IP for commercially important areas
- More companies to follow GSK’s and Novartis’ example and commitment
- A fundamental shift in focus - from just finding money for R & D to efficient use of the money
- Change in mindset – innovation can and does happen in developing countries
The Tata Nano Story

The idea took birth on a rainy day in 2002 ...

- Two Wheeler is very often used by families in India who cannot afford a car
- Very unsafe, especially in the rainy season

There was an unfulfilled need for a...

- Safe
- Affordable
- All weather alternative

Mr. Tata made a remark that a Rs 1 lakh car (~$2000) could make a 4 wheeler within the reach of such families, and make them realize their dream.

This remark however, became the target price for the Tata Motors team.
The Product concept went through several cycle of changes and refinements starting from a clean sheet.

CONCEPT DEVELOPMENT & FINALIZATION

- 2003
- 2004
- 2005
- 2006
- 2007
Could Tata Motors have developed this car using GM or Ford’s model?
VL-2001: Preclinical Development Plan

- The time lines are going to be frozen on 29-Nov during Denis’s visit.

- We will send you a Gantt chart on the finalized plan on 30-Nov.