An Overview of the Drug Discovery Process

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Drug Discovery Process:
Preclinical (Target to Proof-of-Concept)
Clinical (Proof-of-Concept to Completion of Phase III)
14 years and 2 billion CHF to develop one drug

Overview of drug development process

- 10,000 compounds in beginning
- 1,000 compounds in *in vivo* testing
- 10 compounds *in clinic*
- 1 new medicine

~14 years

Cumulative cost per Pharmaceutical

~2 billion USD
Increasing R&D Costs per Drug

Total Capitalized Cost per Approval

Drug Discovery and Development

- Target Review
- CSP
- sPoC

Discovery:
- Target Discovery & Validation*
- Assay Development
- Hit Finding (LMW)
- Protein Design (Biologics)
- Lead Optimization
- Clinical Candidate Selection

Preclinical:
- GLP Profiling for Toxicity and Pharmacokinetics
- Compound Scale-up and Formulation
- Obtain Regulatory Approval

Phase I Clinical / PoC Study

Clinical Development:
- Phase II, III Clinical Trials
- Registration

Launch:

Post-Launch Activities

*Target validation continues through PoC readout

CSP: Candidate Selection Phase
LMW: Low Molecular Weight
PoC: Proof-of-Concept Study
sPoC: Selected for Proof-of-Concept Study
Drug Discovery and Development at Novartis

*Pipeline Progression and Governance: Early Development*

Marker of Pipeline Progression:
- sPoC
- ISA
- FIH
- PoC Readout

Primary Governance:
- TRTD Board (IMB)
- ISA Board
- TRTD Board (IMB)

Note: DADB is responsible for project from inception to PoC
Drug Discovery and Development at Novartis

Pipeline Progression and Governance: Clinical Development

Marker of Pipeline Progression
- DDP: Development Decision Point
- FDP: Full Development Decision Point
- SDP: Submission Decision Point

Primary Governance
- IMB: Innovation Management Board

DDP: Development Decision Point
FDP: Full Development Decision Point
IMB: Innovation Management Board
SDP: Submission Decision Point
Project Teams

A Project has a single team whose leadership and membership changes as the Project’s needs change.

- Discovery
- Preclinical
- Phase I Clinical / PoC Study
- Clinical Development

Team Focus:
- Discovery: Research
- Preclinical: Proof-of-Concept
- Clinical Development: Development

Project Team Leader:
- Discovery: Research
- Preclinical: Translational Medicine Expert
- Clinical Development: Global Program Head
A Project has a single team whose leadership and membership changes as the Project's needs change.

**Team Focus**
- **Discovery**: Research
- **Preclinical**: Proof-of-Concept
- **Phase I Clinical / PoC Study**: Development

**Project Team Leader**
- Research: Research
- Translational Medicine Expert: Translational Medicine Expert
- Global Program Head: Global Program Head

**Reports To**
- DADB
- DADB
- IMB / IFB

**Team Membership**
- Discovery: Cross-functional team whose membership varies based on project needs; participants may include representatives from QDC, MAP, CPC, DMPK, TS, and OA.
- Preclinical: Cross-functional early development team (~8-8 members) whose participants include representatives from TM, PCS, TRD, NAP, DMPK, DA, and additional NIER representation as needed for the project.
- Clinical Development: Eight-member team with representation from Medical, Regulatory, Marketing, TRD, PCS, TM, and Research.

**Major Responsibilities**
- Discovery: Identify 1-4 molecules to develop for disease indication.
- Preclinical: CSP → sPoC
- Clinical Development: To develop and register a commercially successful product and to grow and maintain it until transitioned to the Global Brand Team.
Current Status of Drug Discovery:
Few new drugs are approved each year from all Pharma

FDA-approved Drugs*

High Throughput Screening
New technologies seem not to have helped
Human Genome Project Completed

* Drugs defined as ‘New Molecular Entities’ (NMEs) - a term which is applied by the Food and Drug Administration to both new pharmaceutical and immunological agents
**Does not include Biologics
Source For NMEs: Nature Reviews Drug Discovery 7, 107-109 (February 2008)
Building a Robust Biological Therapeutic Pipeline

Number of novel molecules in clinical trials

* As of October 2010. For molecules with multiple indications, phase of lead indication was counted.
Source: EvaluatePharma; TPP; Novartis pipeline data
2010 Pipeline Progress

New Molecular Entity Portfolio

Positive Proof-of-Concept Trials
Small (Chemical Actives) vs Large (Biologics) Entities
Biologics and Chemicals Are Different

Antibody (300x bigger than traditional Chemicals)

Traditional Chemical Drugs
Key Differences between Antibodies and Low Molecular Weight Chemical Drugs

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Antibody</th>
<th>LMW drug</th>
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| **Drug Characteristics** | • Parenteral administration  
  • Dosed weekly-monthly  
  • Physician administered | • Often orally administered  
  • Dosed hourly to daily  
  • Self administered |
| **Target**       | • Extracellular mechanisms  
  • Good at protein interactions | • Any druggable target  
  • Enzymes/receptors/channels |
| **Side effects** | • Specific action  
  • Low off target toxicity | • Less specific  
  • Can inhibit multiple mechanisms |
Antibodies Offer Specific Advantages Over Traditional Chemical Drugs

<table>
<thead>
<tr>
<th></th>
<th>Small Molecules</th>
<th>Antibodies</th>
</tr>
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<tbody>
<tr>
<td>Clinical success rate</td>
<td>5%</td>
<td>24%</td>
</tr>
<tr>
<td>Specificity for target</td>
<td>Varies</td>
<td>Very High (100 × &gt; sm. Mol.)</td>
</tr>
<tr>
<td>Threat from generics</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Delivery</td>
<td>Oral</td>
<td>Injectable</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Usually daily</td>
<td>Weekly or less frequent</td>
</tr>
<tr>
<td>Size of molecule</td>
<td>Very small (500Da)</td>
<td>Large (150kDa)</td>
</tr>
<tr>
<td>Cost to produce</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Molecular targets of FDA approved drugs</td>
<td>248</td>
<td>18</td>
</tr>
<tr>
<td>Risk of side effects</td>
<td>Varies</td>
<td>Usually well tolerated</td>
</tr>
<tr>
<td>Accessible targets</td>
<td>Intra- and extra-cellular</td>
<td>Extra-cellular and secreted proteins</td>
</tr>
</tbody>
</table>
When Are Antibodies Better Than Chemical Therapeutics?

1. Getting to inaccessible targets

2. Great specificity, without the significant, unpredictable, off-target toxicities of LMW drugs
Steps to Developing an Antibody Therapeutic

- Antibody Engineering
- Production Development
- Manufacturing
- Pre-clinical Testing
- Clinic
Building A Robust Biological Therapeutic Program

Steady Growth of Biologic New Molecular Entities

Biologics Constitute >25% of NME Drug Candidates

NMEs

0 5 10 15 20 25 30

2004 2008

Biologics:
- Antibodies
- Oligonucleotides (e.g., siRNA)
- Proteins/Peptides

LMW Compounds
Building A Robust Biological Therapeutic Program

Steady Growth of Biologic New Molecular Entities

Biologics Constitute >30% of NME Drug Candidates

Biologics NMEs

2004 2005 2006 2007 2008 2009

LMW Compounds
TUR Opportunities in Drug Discovery
Synthesis and purification steps.

Choice of solvents, reagents and purification techniques

- Solvent selection could be the simplest way to green a Med Chem process

- Use a less toxic solvent with less environmental impact...and use less of it.
# Solvent Selection Guide

**Preferred**
- Water
- Acetone
- Ethanol
- 2-Propanol
- 1-Propanol
- Ethyl acetate
- Isopropyl acetate
- Methanol
- Methyl ethyl ketone
- 1-Butanol
- t-Butanol

**Useable**
- Cyclohexane
- Heptane
- Toluene
- Methylcyclohexane
- Methyl t-butyl ether
- Isooctane
- Acetonitrile
- 2-MethylTHF
- Tetrahydrofuran
- Xylenes
- Dimethyl sulfoxide
- Acetic acid
- Ethylene glycol

**Undesirable**
- Pentane
- Hexane(s)
- Di-isopropyl ether
- Diethyl ether
- Dichloromethane
- Dichloroethane
- Chloroform
- Dimethyl formamide
- N-Methylpyrrolidinone
- Pyridine
- Dimethyl acetate
- Dioxane
- Dimethoxyethane
- Benzene
- Carbon tetrachloride

A ‘use this instead’, rather than ‘don’t use’ philosophy.

Solvent Selection

– Safer for the scientist: less toxic, carcinogenic, mutagenic etc.

– Safer for the process: less flammable, lower emissions, less chance of peroxide formation. etc.

– Less harmful to the environment: lower potential to deplete ozone, less ecotoxic, derived from renewable resources.
Principles of Green Chemistry.

Ø Prevention
Ø Less Hazardous Chemical Syntheses
Ø Designing Safer Chemicals
Ø Safer Solvents
Ø Design for Energy Efficiency
Ø Use Renewable Feedstocks
Ø Reduce Derivatives
Ø Catalysis
Ø Design for Degradation
Ø Real Time Analysis for Pollution Prevention
Ø Inherently Safer Chemistry for Accident Prevention
Ø Atom Economy