Harnessing therapeutic modalities to translate our excellence in science and biology

Jean-Jacques Garaud, M.D., Global Head of pRED
Roche Pharmaceuticals

pRED mission and organisation

A Focus on Therapeutic Modalities

- Small molecules
- New generation antibody technologies
- Peptides
- SiRNA
The pRED mission

Science and patients: our focus, our passion

Translate understanding of disease biology in the clinical setting

Leverage technologies and capabilities to develop new compounds to Lifecycle Investment Point (LIP)

Deliver on individual patient needs through the implementation of PHC strategies

pRED’s global reach

Tapping into global innovation

major pRED Centers

major pRED Sites
Roche Research & Early Development has delivered
Six transitions to late-stage over 2007-2009

- Dalcetrapib
- Aleglitazar
- Taspoglutide
- GA101
- B-RAF antagonist
- Gly T-1 inhibitor

pRED: Further improving productivity
Enhancing effectiveness and innovation

**Improved innovation capacity**
- Research and Early Development combined (Translational research)
- Accessing external innovation (e.g. Singapore TM hub, Harvard stem cell)

**Improved focus and processes**
- Focus on less programs but with optimal resources
- Sites consolidated (closure of Palo Alto)
- Processes optimized through technology enhancement and outsourcing

**Recruitment of key leadership**
pRED potential transitions to lifecycle management (LIP = Lifecycle Investment Point)

Only NMEs shown
Does not include line extensions, backup programs

pRED mission and organisation

A Focus on Therapeutic Modalities

Small molecules
New generation antibody technologies
Peptides
siRNA
Three critical steps for innovation in drug discovery and early development

We know what to target (Understanding disease, new pathways, Biomarkers, PHC)

We have a powerful multiplier (Therapeutic Modalities)

World-Class skills in Translational Medicine (PoM and PoC)

- Small Molecules
- Therapeutic Proteins
- RNA Interference
- Peptides
- Therapeutic stem cells

Strong progress in small molecule discovery

Attrition for safety reasons dramatically reduced

Outstanding medicinal chemistry capabilities + Industry-leading safety based attrition rates in Phase 0 and 1

% of projects terminated for safety reasons

Source: internal analysis
MDM2 antagonist (RG7112) induces apoptosis

*Nutlins: a novel approach to cancer therapy*

- p53 is a major tumor suppressor protein that induces apoptosis in tumors
  - MDM2 naturally inhibits the activity of p53
  - Nutlins prevent MDM2 from inactivating p53
- Nutlins represent a breakthrough in cancer drug research
  - small molecule that specifically blocks the interaction between the two proteins

- **Roche is the leader in the field**
- RG7112 currently in late Phase 1
- Companion diagnostics in co-development with Diagnostics (p53 chip & MDM2 expression)

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Enhancing antibody performance

<table>
<thead>
<tr>
<th>Naked Antibodies</th>
<th>Antibody inhibits or activates signaling</th>
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<tbody>
<tr>
<td>Armed Antibodies</td>
<td>Antibody specifies delivery of drug</td>
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<tr>
<td>ADCC enhanced Antibody</td>
<td>Antibody recruits immune effector cell and induces cytotoxicity</td>
</tr>
<tr>
<td>bi-specific Antibodies</td>
<td>Bi-specific antibody binds to two different targets in different cells</td>
</tr>
<tr>
<td>bi-specific Antibodies</td>
<td>Bi-specific antibody binds to two different targets and enhances specificity</td>
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</table>
GA101: a glycoengineered, type II anti-CD20 antibody

Enhanced ADCC and direct cell induction

Mossner E., et al., Blood, Mar 2010
GA101 B-CLL data presented at ASH, December, 2009

GA201

Anti-EGFR glycoengineered antibody for enhanced ADCC

- A potential breakthrough in cancer therapy
  - opportunity to treat k-ras mutant tumors
- Will allow to demonstrate the utility of glycoengineering antibodies
- Roche could become the leader in ADCC–enhanced antibody therapy

Gerges C., et al., Presentation at AACR Meeting, April 2009; Abstract 5476
Data on file, Roche
Next generation of antibodies
A leadership position in protein engineering

Glycoengineered for enhanced ADCC
Type II epitopes for direct cell induction

Bi-specific 2+1 valency
Tissue targeted cytokines
ScFv diabody-cytokine

Bi-specific 2+2 valency
Targeted siRNA
Targeted peptides
BBB-penetrating antibodies

Example of an engineered antibody linked to a cytokine
Superior efficacy of Roche tumor-targeted IL-2 vs. competitors

Roche data on file

Y2R: A novel anti-diabetic peptide associated with significant weight loss

- PYY and GLP1 are natural drivers of weight loss (and diabetes resolution) in bariatric surgery
- Y2R is targeted to be a first in class (SC) weekly injectable PYY analogue
  - a novel PEGylated, Selective, Truncated Peptide Analog of PYY_{3-36}
- Could be used in monotherapy or in combination with GLP-1

Anti-diabetic effect of Y2R in leptin receptor deficient db/db mice

Y2R preserves the islets & insulin content

data submitted to ADA, June 2010
Roche investment in RNA Therapeutics

One of the biggest efforts in our industry

The Promise
- Specific gene activity can be down-regulated by interrupting protein synthesis
- Can address virtually every target – including previous “undruggable” target
- Well-suited for personalised medicine

The Hurdle
- Safe and targeted delivery into the right tissue, right cell, right part of the cell

Our Commitment
- Landmark technology deal with Alnylam in 2007
- Investment in siRNA delivery (Mirus, Tekmira)

Focusing on safe and targeted delivery of siRNA

Leveraging new technologies to enable a breakthrough

Our efforts:

<table>
<thead>
<tr>
<th>Method</th>
<th>In vitro</th>
<th>In vivo</th>
<th>Pre-clinical</th>
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<tbody>
<tr>
<td>Liposomal delivery systems</td>
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<tr>
<td>Polymers and Biopolymers</td>
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</tr>
<tr>
<td>Dynamically PolyConjugates (DPC)</td>
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<tr>
<td>Antibodies</td>
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<td>siRNA small molecule conjugates</td>
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<tr>
<td>Cell-penetrating peptides</td>
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<td>Receptor ligands</td>
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<td>Peptides</td>
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Our target: First program into man by end of year
Our distinctiveness
Innovation and excellence in science

Unparalleled expertise in molecular biology

Multiple therapeutic modalities

Differentiated medicines

Small Molecules
Therapeutic Proteins
RNA Interference
Peptides
Therapeutic stem cells