pRED: Transformative medicines for future generations

Mike Burgess, Head of pRED

The future of medicine is personalised
Roche Investor Day 2012
Roche Group
Unique diversity of approaches

Academia & Industry

Over 150 partners

Independent Centers for Research and Early Development

Genentech
Roche
Chugai

Worldwide Execution

Global Product Development
Manufacturing
Commercialisation

Roche Diagnostics
pRED snapshot: Focus on transformative medicines guided by patient needs

Established 2009
pRED established in context of Genentech integration

pRED Discovery and Translational Areas (DTAs)/Functions
• Neuroscience, Metabolism, Cardiovascular, Oncology, Virology
• Small and Large Molecule Research, Development, Non-Clinical Safety, Informatics

pRED Employees\(^1\): \(~2150\)
Global reach through 6 strategic/operational centers in Switzerland, Germany, UK, US and China

Pipeline
32 NMEs in Early Development to Phase 2

\(^1\) post restructuring 2012
pRED development pipeline
Rich and balanced portfolio

### Phase 0
**EIH enabling**
- NME 1
- NME 2
- NME 3
- NME 4
- NME 5
- NME 6
- NME 7
- NME 8
- NME 9

### Phase 1
**Safety & Tolerability**
- RG7116 Her3 MAb  
  *solid tumors*
- RG7155 CSF-1R MAb  
  *solid tumors*
- RG7304 Raf & MEK dual inh.  
  *solid tumors*
- RG7388 MDM2 ant  
  *solid tumors*
- RG1662 GABRA5  
  *cogn. disorders*
- RG7314 V1 receptor antag  
  *autism*
- RG7129 BACE inh  
  *Alzheimer’s*
- RG7685 GIP/GLP-1 dual ago  
  *T2 diabetes*
- RG7795 TLR7 agonist  
  *HCV*

**Proof of Concept/Mechanism**
- RG7112 MDM2 ant  
  *solid & hem tumors*
- RG7167 CIF/MEK inh  
  *solid tumors*
- RG7212 Tweak MAb  
  *oncology*
- RG7256 BRAF inh (2)  
  *melanoma*
- RG7356 CD44 MAb  
  *solid tumors*

### Phase 2
**LIP enabling**
- RG7686 Anti-glypican Mab  
  *liver cancer*
- RG7160 EGFR MAb  
  *solid tumors*
- RG1450 gantenerumab  
  *Alzheimer’s*
- RG7090 mGluR5 antag  
  *FXS, TRD*
- RG1578 mGluR2 antag  
  *depression*
- RG1577 MAO-B inh  
  *Alzheimer’s*
- RG4929 11 beta HSD inh  
  *metab. diseases*
- RG1512 P selectin MAb  
  *ACS/CVD*
- RG7227 danoprevir  
  *HCV*
- RG7790 setrobuvir  
  *HCV*

**Status as of June 30, 2012**
**pRED development pipeline**

80% of pRED molecules being developed with companion diagnostics (CDx)

### Phase 0
**EIH enabling**

- NME 1
- NME 2
- NME 3
- NME 4
- NME 5
- NME 6
- NME 7
- NME 8
- NME 9

### Phase 1
**Safety & Tolerability**

<table>
<thead>
<tr>
<th>Project</th>
<th>Indicator</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG7116</td>
<td>Her3 MAb</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG7155</td>
<td>CSF-1R MAb</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG7304</td>
<td>Raf &amp; MEK dual inh</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG7388</td>
<td>MDM2 ant</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG1662</td>
<td>GABRA5</td>
<td>cogn. disorders</td>
</tr>
<tr>
<td>RG7314</td>
<td>V1 receptor antag</td>
<td>autism</td>
</tr>
<tr>
<td>RG7129</td>
<td>BACE inh</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>RG7885</td>
<td>GIP/GLP-1 dual ago</td>
<td>T2 diabetes</td>
</tr>
<tr>
<td>RG7795</td>
<td>TLR7 agonist</td>
<td>HCV</td>
</tr>
</tbody>
</table>

### Phase 1
**Proof of Concept/Mechanism**

<table>
<thead>
<tr>
<th>Project</th>
<th>Indicator</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG7112</td>
<td>MDM2 ant</td>
<td>solid &amp; hem tumors</td>
</tr>
<tr>
<td>RG7167</td>
<td>CIF/MEK inh</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG7212</td>
<td>Tweak MAb</td>
<td>oncology</td>
</tr>
<tr>
<td>RG7256</td>
<td>BRAF inh (2)</td>
<td>melanoma</td>
</tr>
<tr>
<td>RG7356</td>
<td>CD44 MAb</td>
<td>solid tumors</td>
</tr>
</tbody>
</table>

### Phase 2
**LIP enabling**

<table>
<thead>
<tr>
<th>Project</th>
<th>Indicator</th>
<th>Therapeutic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG7686</td>
<td>Anti-glypican Mab</td>
<td>liver cancer</td>
</tr>
<tr>
<td>RG7160</td>
<td>EGFR MAb</td>
<td>solid tumors</td>
</tr>
<tr>
<td>RG1450</td>
<td>gantenerumab</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>RG7090</td>
<td>mGluR5 antag</td>
<td>FXS, TRD</td>
</tr>
<tr>
<td>RG1578</td>
<td>mGluR2 antag</td>
<td>depression</td>
</tr>
<tr>
<td>RG1577</td>
<td>MAO-B inh</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>RG4929</td>
<td>11 beta HSD inh</td>
<td>metab. diseases</td>
</tr>
<tr>
<td>RG1512</td>
<td>P selectin MAb</td>
<td>ACS/CVD</td>
</tr>
<tr>
<td>RG7227</td>
<td>danoprevir</td>
<td>HCV</td>
</tr>
<tr>
<td>RG7790</td>
<td>setrobuvir</td>
<td>HCV</td>
</tr>
</tbody>
</table>

- **Project with CDx available/in development**
- **Project without CDx**

Status as of June 30, 2012
Delivering a sustainable and differentiated portfolio
Translating science into transformative medicines

1. Understanding disease biology

**EXAMPLES**

**Hepatitis B**
- Established translational animal model for liver infection
- Determined gene expression profile reflecting cure

⇒ *Enabling cure of chronic Hepatitis B infection*

**Oncology**
- MDM2 a relevant target in 50% of all cancers
- Understanding of highly complex biology enabled development of pharmacodynamic biomarkers and MDM2 inhibitors

⇒ *Drugging ‘undruggable’ targets*
Delivering a sustainable and differentiated portfolio
Translating science into transformative medicines

Understanding disease biology

Expanding therapeutic modalities

Proprietary CrossMab technology
- Industry-leading platform for bi-specific monoclonal antibodies

Expansion of druggable targets with peptides
- Multi-agonistic ('swiss army knife' type) first-in-class compounds
- Cell-penetrating stapled peptides

DNA-encoded library technology
- Supersensitive and fast
- >10 billion compounds in screen (i.e. 5x small molecule library)

Potential radically novel platforms for 2015+
- Highly targeted alpha radio-immunotherapy for cancer
- Cell-killing tumor-targeted fusion proteins

1 with Aileron  2 with Areva  3 with National Cancer Institute
Delivering a sustainable and differentiated portfolio
Translating science into transformative medicines

Understanding disease biology
Expanding therapeutic modalities
Driving biomarker approach

Intensify collaboration
• Over 100 projects with Roche Diagnostics

Evolve the paradigm in oncology
• 3 studies utilizing novel predictive biomarker-based selection criteria already in phase 1

Push beyond single biomarkers and beyond the cancer cell
• Negative symptom schizophrenia
• Fragile X syndrome
• Type 2 diabetic patients with increased risk for cardiovascular events
• Chronic hepatitis B
**Translating science into transformative medicines**

**Putting it all together – Example (RO5429083)**

### Understanding disease biology

**New biology**
- Novel and multifactorial mode of action (phagocytosis of tumors)

### Expanding therapeutic modalities

**Unconventional antibody generation**
- Function-first technology delivered antibody against unique epitope

### Driving biomarker approach

**Innovative phase 1 design**
- Prospective patient selection;
- Parallel clinical imaging arm guides dose selection

*Potential to become standard of care across multiple solid and hematological tumor indications*
# pRED key elements of future success

**Sustained future growth – building new medicines**

| Applied scientific excellence | • Focus on best-in-industry neuroscience and oncology portfolios. Extend virology and cardiovascular/metabolism  
|                              | • Protect/expand/innovate franchises and platforms (e.g. bispecific antibodies, stapled peptides, brain shuttle) |
| Integrated PHC strategy      | • Drive implementation/expansion of PHC\(^1\)  
|                              | (80% of projects developed with CDx; ~100 patent applications related to PHC/CDx) |
| External network with tangible output | • Access new platform technologies  
|                                | • New portfolio opportunities  
|                                | • Identify biomarkers and support PHC strategy |
| Increased agility by optimized set-up | • Focus on core capabilities  
|                                      | • Complement internal capabilities by harnessing external network  
|                                      | • Flexibility to allocate funding to key portfolio assets |

\(^1\) PHC: Personalized Healthcare  CDx: Companion Diagnostics
pRED: Highlights with focus on Neuroscience

Luca Santarelli M.D.,
Head of CNS Research and Translational Area

The future of medicine is personalised
Roche Investor Day 2012
**Mechanism-based drug discovery for personalised therapy**

**Therapeutic areas of focus**

**Psychiatry**  
Schizophrenia and Depression

**Neurodevelopmental disorders**  
Fragile X, down syndrome and autism

**Neurodegeneration**  
Alzheimer’s and Parkinson’s

Leading glutamatergic approaches aimed at specific neural circuits

Recent advances in genetics allow to target the disease pathophysiology

Intervene at an early disease stage, co-develop molecular DX to identify patients
**Broad biomarker platform to enable PHC**

*Essential for early diagnosis or to select patients with optimal risk/benefit*

<table>
<thead>
<tr>
<th>Type of BM</th>
<th>Examples from clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td><strong>Gantenerumab:</strong> phase 2 dosing based on ApoE4 genotype</td>
</tr>
</tbody>
</table>
| Protein    | **Gantenerumab:** prodromal Alzheimer’s patients are selected based on CSF Aβ/Tau levels  

**Bitopertin:** CFHR1 levels are tested as a potential response predictor in schizophrenia |
| Imaging    | **Bitopertin:** GlyT-1 PET tracer enables dose selection  

**Gantenerumab:** amyloid PET imaging shows proof of mechanism and enables dose selection; MRI used to monitor Alzheimer’s disease progression |
| Phenotype  | **mGlu2/5:** monoamine-resistant phenotype defines treatment-resistant depression  

**Bitopertin:** predominant negative symptoms as a high-need subset in schizophrenia |

ApoE4=apolipoprotein E genotype 4, CSF=cerebrospinal fluid, CFHR1=complement factor H-related protein 1, GlyT-1=type-1 glycine transporter, PET=Positron Emission Tomography, MRI=Magnetic resonance imaging
Mechanism-based drug discovery for personalised therapy

Therapeutic areas of focus

**Psychiatry**
Schizophrenia and Depression

Leading glutamatergic approaches aimed at specific neural circuits

**Neurodevelopmental disorders**
Fragile X, down syndrome and autism

Recent advances in genetics allow to target the disease pathophysiology

**Neurodegeneration**
Alzheimer’s and Parkinson’s

Intervene at an early disease stage, co-develop molecular DX to identify patients
Schizophrenia and depression: World-leading expertise in targeting the glutamatergic system

**Depression**
- mGluR2 antagonist
  - RG1578 P2

**Schizophrenia**
- bitopertin (GlyT1 inh)
  - P3
- mGluR5 PAM preclinical

GlyT-1 = type-1 glycine transporter, mGluR2/5 = metabotropic glutamate receptor2/5, PAM = positive allosteric modulator
Adapted from Sanacora et al, Nature Reviews Drug Discovery 2008
Addressing untreated symptoms in schizophrenia

Symptoms severity

Ability to function

Current treatment start

Adolescence  Adulthood  Elderly

Positive

Negative

Cognitive
Bitopertin phase II proof-of-concept study

Recruited 320 patients in EU/US/JP

**Patient population & design**
- Predominant negative symptoms, stabilised on antipsychotics (add-on)
- 8-week treatment

**Results**
- Significant reduction in negative symptoms* (PANSS-NSFS)
- Significantly greater improvement of negative symptoms* (CGI-I)
- Trend in functional improvement (PSP)

**Potential biomarker discovered in phase II**
- Hypothesis for biomarker validated in phase III
- *In vitro* diagnostic assay in development at Roche Dx

---

*PP population; PANSS-NSFS=PANSS-negative factor symptoms score; CGI-I=Clinical Global Impression-Improvement; PSP=personal and social performance scale; CFHR1=complement factor H-related protein 1
Bitopertin phase III program

Two indications, consistency with phase II

Three studies – SUNLYTE, FLASHLYTE, DAYLYTE:
- 6 months treatment
- Negative symptoms
- Extension within protocol

Three studies – NIGHTLYTE, MOONLYTE, TWILYTE:
- 3 months
- Partial responder
- Extension within protocol

- Synergy in recruitment at clinical sites: reduced risk of rater inflation/deflation
- Creates broad safety database
- Patient recruitment globally (EU, US, JP)
- High unmet medical need in both indications

Primary end-point read-out

Patient populations with negative symptoms very consistent between Phase II and III

Schizophrenia symptoms distribution

Phase III

Phase II

Negative

Positive

Disorganised

Hostility/Excitement

Anxiety/Depression

60%

50%

40%

30%

20%

10%

0%
Mechanism-based drug discovery for personalised therapy

Therapeutic areas of focus

Psychiatry
- Schizophrenia and Depression

Leading glutamatergic approaches aimed at specific neural circuits

Neurodevelopmental disorders
- Fragile X, down syndrome and autism

Recent advances in genetics allow to target the disease pathophysiology

Neurodegeneration
- Alzheimer’s and Parkinson’s

Intervene at an early disease stage, co-develop molecular DX to identify patients
Neurodevelopmental disorders
Diseases affecting growth & development of the brain

**Large unmet medical need**
No disease modifying therapies, partially efficacious symptomatic therapy

**Emerging science**
Insights into the molecular pathophysiology of NDDs from genetics

**Tractability**
Quantum leap in the understanding of key targets and ways to develop therapies
The genetics of autism point to synaptic dysfunction

Defects in:

- Molecules that orchestrate **synaptic development** (neurexins and neuroligins)
- **Scaffold proteins** essential for excitatory synapse development (Shank3, contactin)
- **Signal transduction** at the synaptic level (mTOR pathway)
- Regulation of **gene expression** relevant to synaptic function (MECP2, FMRP)

*MECP2=methyl CpG binding protein 2, **FMRP=Fragile X mental retardation protein*
Targeting synapses and circuits for therapeutics

The bridge between genes and behavior

Genes → Cells/Synapses → Circuits → Behavior

- mGluR5 ant. RG7090 Fragile X
- GABAa5 NAM RG1662 Down Syndrome
- V1 receptor ant RG7314 Autism
Clinical programs in neurodevelopmental disorders

Phase I and phase II studies

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Fragile X Syndrome</th>
<th>Down Syndrome</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule</td>
<td>mGluR5 antagonist (RG7090)</td>
<td>GABRA5 negative allosteric modulator (RG1662)</td>
<td>V1 receptor antagonist (RG7314)</td>
</tr>
<tr>
<td>Phase</td>
<td>Phase II</td>
<td>Phase Ib</td>
<td>Phase I</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Efficacy, safety &amp; tolerability</td>
<td>Safety &amp; tolerability</td>
<td>Safety &amp; tolerability</td>
</tr>
<tr>
<td>Status</td>
<td>FPI Q2 2012</td>
<td>FPI Q4 2011</td>
<td>FPI Q3 2011</td>
</tr>
</tbody>
</table>
Mechanism-based drug discovery for personalised therapy

Therapeutic areas of focus

**Psychiatry**
- Schizophrenia and Depression

**Neurodevelopmental disorders**
- Fragile X, down syndrome and autism

**Neurodegeneration**
- Alzheimer’s and Parkinson’s

Intervene at an early disease stage, co-develop molecular DX to identify patients
Programs in Alzheimer’s disease (AD)
Multiple targets based on pathophysiology model of AD

AD=Alzheimer’s disease, MAO-B=Monoamine oxidase-B, BACE=Beta-secretase 1
AD starts ~20 years before overt clinical symptoms

Targeting treatment at an early stage for best efficacy

Our strategy

• Enroll patients with prodromal Alzheimer’s disease: before symptoms onset or dementia
• Identify patients based on a diagnostic biomarker
• Choose dosing that has demonstrated plaque removal
Gantenerumab
Anti-amyloid monoclonal antibody for prodromal and mild to moderate AD

- Fully human IgG1 with low potential for immunogenicity
- High avidity towards aggregated Aβ, i.e. oligomers/fibrils/plaques *in vitro* and *in vivo*
- Conformational epitope recognition likely contributes to high binding affinity to Aβ plaques

Amyloid Precursor Protein (APP)

- **soluble APP**
- **β site**
- **(BACE-1)**
- **α site**
- **γ-cleavage site**
- **Presenilin 1/2**
- **Gantenerumab**
- **Aggregation**
- **Oligomers**
- **Inflammation neuron loss**
- **Plaques**

**CELL MEMBRANE**

Aβ domain

**soluble Aβ (1-40, 1-42)**

IgG1=immunoglobulin G1
# Unique profile of gantenerumab

<table>
<thead>
<tr>
<th>Gantenerumab characteristics</th>
<th>Level of evidence</th>
<th>Importance</th>
<th>Effect on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully human antibody</td>
<td>Molecular</td>
<td>Less likelihood of producing anti-drug-antibodies</td>
<td>Efficacy and safety</td>
</tr>
<tr>
<td>No substantial elevation of peripheral Aβ</td>
<td>Preclinical and Clinical</td>
<td>Higher availability for entering brain and binding to amyloid</td>
<td>Efficacy</td>
</tr>
<tr>
<td>High avidity Aβ amyloid binding <em>in vivo</em></td>
<td>Preclinical</td>
<td>High degree of plaque binding per peripheral exposure (AUC)</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Quick target engagement</td>
<td>Clinical</td>
<td>Significant amyloid reduction observable already after 6 months</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Engages effector cells for amyloid removal</td>
<td>Preclinical and clinical (PET analysis)</td>
<td>Elicits phagocytosis of Aβ plaques</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>
**Gantenerumab reduces brain amyloid in patients with AD**

Compelling data from phase I imaging study

Reduction in 11C-PIB* standard uptake value ratios (SUVR) indicating brain amyloid removal

*11C-PIB=Positron Emission Tomography (PET) tracer 11C-labeled Pittsburgh Compound-B specifically binds fibrillar amyloid-beta plaques

**Patients received 2-7 i.v. infusions of gantenerumab q4w
Diagnostic strategy for prodromal and pre-symptomatic AD

Non-specific memory decline
MCI* ~13.6m est. in 2024

Specialized cognitive test

Amnestic MCI: 42% of total MCI

Molecular/imaging test

Prodromal AD: 50% of amnestic MCI

*MCI: Mild Cognitive Impairment

In MCI*, low cerebrospinal fluid (CSF) Tau/Aβ identifies patients with prodromal AD

CSF Tau/Aβ used for patient recruitment in gantenerumab Phase II/III trials

Ongoing development of Aβ42 & Tau companion diagnostic assays

SCarlet RoAd study expanded to pivotal size
PHC strategy for patient identification

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Prodromal Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase/Study</td>
<td>Phase II/III SCarlet RoAD</td>
</tr>
<tr>
<td># of Patients</td>
<td>N=770</td>
</tr>
<tr>
<td>Design</td>
<td>2-year subcutaneous treatment</td>
</tr>
<tr>
<td></td>
<td>- <strong>ARM A</strong>: Gantenerumab 225 mg sc</td>
</tr>
<tr>
<td></td>
<td>- <strong>ARM B</strong>: Gantenerumab 105 mg sc</td>
</tr>
<tr>
<td></td>
<td>- <strong>ARM C</strong>: Placebo</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Change in Clinical Dementia Rating scale Sum of Boxes (CDR-SOB) at 2 yrs</td>
</tr>
<tr>
<td>Status</td>
<td>FPI Q4 2010</td>
</tr>
</tbody>
</table>

- 150 study centers in 19 countries, trial recruiting well
- FDA offered to review Phase II/III protocol through SPA process
- Data expected in 2015