First selective JAK1 inhibitor: GLPG0634 from hit to Proof of Concept

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Project Director, Medicinal Chemistry

Protein Kinase 2012
May 2012
GLPG0634
The 1st selective JAK1 inhibitor

- Introduction
- Target identification
- Hit finding to PCC
- Clinical development
  - Phase I
  - Phase II Proof of Concept
Rheumatoid arthritis (RA)
A global health issue

Disease facts

- Inflammation & destruction of joints
- Affects ~1% of population
- Typically diagnosed age 40-60
- 2-3 times more prevalent in women

Current treatments

- First line: steroids, methotrexate (MTX)
- Second line: disease-modifying biologics
  - TNFα blockers (Enbrel®, Remicade®, Humira®)
  - IL-6 (Actemra®), B & T-cells (Rituxan®, Oencia®)
  - Effective in 50-60% of MTX non-responders
New wave of RA oral therapies

Small molecule drugs in development for RA

- Easier to use (oral administration)
- Lower cost of goods
- Comparable efficacy & safety profile to biologics

<table>
<thead>
<tr>
<th>2011</th>
<th>Other biologics</th>
<th>15%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNF blockers</td>
<td>85%</td>
</tr>
</tbody>
</table>

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Galapagos: a leader in European biotech

- One of the largest biotech pipelines in Europe
- > 800 staff in pharmacology/biology, chemistry and drug development
- 400 staff fee-for-service organization in UK: discovery research activities

- Drug research & development in various therapeutic areas throughout Europe
Galapagos approach
From protein to drug

- Target identification: Find human protein responsible for disease
- Target validation
- Assay development: Identify chemical compound that binds to protein
- Screening
- Lead optimization: Develop compound into drug candidate
- Preclinical testing
- Clinical trials I, II, III: Test drug candidate
GLPG0634
The 1st selective JAK1 inhibitor

- Introduction
- Target identification
- Hit finding to PCC
- Clinical development
  - Phase I
  - Phase II Proof of Concept
Technology
Adenoviral technology

- Changes in cell health monitored via functional readouts
- 20-25 validated targets per screen
- IP on target and compound

recombinant adenovirus → human primary cell

Gene silencing or over expression

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Technology
Arrayed adenoviral libraries for KI and KD

full length cDNAs

shRNA constructs

cloned into vector

adenovirus

HTS functional screens

arrayed library

JAK1 was identified using this technology

Genome Res. 2003, 13: 2325
Nature Biotech 2002, 20: 1154
DDT 2005, 10: 1385
JAK family

- 4 family members: JAK1, JAK2, JAK3, TYK2
- Cytoplasmic tyrosine kinases
- Serve as intracellular signal transducers for many cytokines, hormones
  - interleukins, interferons, EPO, GH, OSM, LIF,…

<table>
<thead>
<tr>
<th>JAK</th>
<th>Cytokines</th>
<th>Phenotype of mouse knockout</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1</td>
<td>Gp130 cytokine, type I IFN, IFN-γ, and βc cytokines, γc cytokines</td>
<td>Perinatally lethal; neurological defects and SCID</td>
</tr>
<tr>
<td>JAK2</td>
<td>EPO, TPO, PRL, GH, IFN-γ and IL-12</td>
<td>Embryonically lethal; defective erythropoiesis</td>
</tr>
<tr>
<td>JAK3</td>
<td>γc cytokines</td>
<td>SCID</td>
</tr>
<tr>
<td>TYK2</td>
<td>Gp130 cytokines, type I IFNs, IL-12 and IL-23</td>
<td>Modest viral susceptibility, reduced IL-12 response and resistance to arthritis induction</td>
</tr>
</tbody>
</table>
JAK-STAT signalling

Ke Shuai & Bin Liu, Nature Reviews Immunology 3, 900-911
JAK inhibitors in development for RA

Three JAK inhibitors have shown clinical efficacy in RA

- rapid onset, 30-50% improvement in ACR20 over placebo
- *tofacitinib* and VX-509 administered twice-daily

<table>
<thead>
<tr>
<th>RA clinical candidate</th>
<th>JAK inhibition profile</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>tofacitinib</em></td>
<td>JAK3&gt;JAK1&gt;JAK2</td>
<td>Filed</td>
</tr>
<tr>
<td>INCB28050 <em>baricitinib</em></td>
<td>JAK1=JAK2</td>
<td>Phase II</td>
</tr>
<tr>
<td>VX-509</td>
<td>JAK3</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Different selectivity profile = opportunity to differentiate JAK inhibitors
Balancing safety and efficacy
Lessons from 24 weeks of *tofacitinib* in Phase II

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>5 mg bid</th>
<th>10 mg bid</th>
<th>15 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>59</td>
<td>49</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>ACR20 (%)</td>
<td>25.4</td>
<td>51.0</td>
<td>65.6</td>
<td>66.7</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>10.2</td>
<td>34.7</td>
<td>44.3</td>
<td>54.4</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>6.8</td>
<td>20.4</td>
<td>37.7</td>
<td>33.3</td>
</tr>
</tbody>
</table>

*tofacitinib* 24-week Phase II study

- significant, dose-dependent improvements in ACR20/50/70 response rates
- dose selection (5 mg, 10 mg bid) for Phase III studies based on efficacy data and safety: incidence of (severe) anemia, at doses of 10 mg bid and higher
- anemia is JAK2-driven side effect, apparent within 2 weeks

Potential to increase efficacy by minimizing JAK2 side effects

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1 Fleischmann et al/Kremer et al. ACR presentation (2009).
GLPG0634
The 1st selective JAK1 inhibitor

- Introduction
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- Clinical development
  - Phase I
  - Phase II Proof of Concept
Hit finding overview

JAK1 biochemical assay

Primary screen: 9,510 compounds (10 µM, single dose)
90%: focused kinase collection

Overall hit rate: 5.6%

Rescreen, D/R testing
161 actives

Spec panel - Cell tox
Cpd QC

JAK/STAT cellular assays
SAR identified > H2L

Best hit:

hJAK1 IC$_{50}$ = 65 ± 18 nM
hJAK2 IC$_{50}$ = 168 ± 7 nM
hJAK3 IC$_{50}$ = 675 ± 174 nM
hTYK2 IC$_{50}$ = 783 ± 148 nM
From H2L to LO

SAR of the phenyl was developed

Investigation on position 2

hJAK1 IC₅₀, 110 nM

Start at easy point, diversify to large variety of compounds to understand the SAR of the series
Exploration in position 2

<table>
<thead>
<tr>
<th>R</th>
<th>JAK1 IC_{50} (nM)</th>
<th>R</th>
<th>JAK1 IC_{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical Structure 1" /></td>
<td>&gt;10,000</td>
<td><img src="image" alt="Chemical Structure 2" /></td>
<td>5,740</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure 3" /></td>
<td>&gt;10,000</td>
<td><img src="image" alt="Chemical Structure 4" /></td>
<td>&gt;10,000</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure 5" /></td>
<td>&gt;10,000</td>
<td><img src="image" alt="Chemical Structure 6" /></td>
<td>2,270</td>
</tr>
<tr>
<td><img src="image" alt="Chemical Structure 7" /></td>
<td>&gt;10,000</td>
<td><img src="image" alt="Chemical Structure 8" /></td>
<td>&gt;10,000</td>
</tr>
</tbody>
</table>

Replacement of the cyclopropyl-amide on the 2-position was not tolerated
### Phenyl substitution improvement

The para-position of the phenyl was tolerant to wide range of substitutions.

<table>
<thead>
<tr>
<th>Substitution R</th>
<th>JAK1 $IC_{50}$ (nM)</th>
<th>JAK2 $IC_{50}$ (nM)</th>
<th>JAK3 $IC_{50}$ (nM)</th>
<th>TYK2 $IC_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>180</td>
<td>564</td>
<td>1,790</td>
<td>1,767</td>
</tr>
<tr>
<td></td>
<td>361</td>
<td>925</td>
<td>1,142</td>
<td>3,877</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>188</td>
<td>1,155</td>
<td>587</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>168</td>
<td>675</td>
<td>783</td>
</tr>
<tr>
<td></td>
<td>528</td>
<td>980</td>
<td>2,857</td>
<td>7,049</td>
</tr>
</tbody>
</table>
Lead optimisation

SAR

Hits

Compounds synthesized

JAK1 IC50 (nM)

Improvement of potency

Drive towards potent JAK1 compounds

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Lead optimisation
Biochemical selectivity

The series was made selective towards JAK1
ADME analysis of main series led to sub-series: good solubility, low PPB
Further optimization resulted in GLPG0634
Crystal structure of JAK2

Triazolo-pyridine series docked in JAK2 crystal structure

Nitrogen atom of the scaffold and of cyclopropylamide of the series interact with the hinge

Cyclopropyl group locates in favorable hydrophobic pocket
GLPG0634 inhibits JAK1

**JAK selectivity**

Potencies of compounds in biochemical assays*

<table>
<thead>
<tr>
<th>Compound</th>
<th>JAK1 IC(_{50}), nM</th>
<th>JAK2 IC(_{50}), nM</th>
<th>JAK3 IC(_{50}), nM</th>
<th>TYK2 IC(_{50}), nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLPG0634</td>
<td>10</td>
<td>28</td>
<td>810</td>
<td>116</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>1.3</td>
<td>1.9</td>
<td>0.2</td>
<td>23</td>
</tr>
<tr>
<td>INCB28050</td>
<td>5.9</td>
<td>5.7</td>
<td>&gt;400</td>
<td>53</td>
</tr>
</tbody>
</table>

JAK1 selectivity ratios of compounds in biochemical assays

<table>
<thead>
<tr>
<th>Compound</th>
<th>JAK2/J AK1 ratio</th>
<th>JAK3/J AK1 ratio</th>
<th>TYK2/J AK1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLPG0634</td>
<td>2.8</td>
<td>81</td>
<td>11.6</td>
</tr>
<tr>
<td>tofacitinib</td>
<td>1.5</td>
<td>0.2</td>
<td>17.7</td>
</tr>
<tr>
<td>INCB28050</td>
<td>1.0</td>
<td>60</td>
<td>9.0</td>
</tr>
</tbody>
</table>

* Biochemical assays by fluorescence read-out show higher potencies than prior radioactive assays.

GLPG0634 shows good selectivity over JAK3 and TYK2
GLPG0634 inhibits JAK1
High selectivity towards 150 kinase-panel

- Selectivity panel upstate GLPG0634
- > 50 fold selective over 175 kinases
- 25-fold over FLT3, FLT4 and CSF1R
GLPG0634 inhibits JAK1
High selectivity for JAK1 over JAK2 in cellular assays

<table>
<thead>
<tr>
<th>JAKs involved</th>
<th>Cell type</th>
<th>Trigger</th>
<th>Read-out</th>
<th>pIC$_{50}$ ± SEM</th>
<th>IC$_{50}$ (nM)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1-JAK3</td>
<td>THP-1</td>
<td>IL-4</td>
<td>pSTAT6</td>
<td>6.75 ± 0.06</td>
<td>154; 203</td>
<td>2</td>
</tr>
<tr>
<td>JAK1-JAK3</td>
<td>NK-92</td>
<td>IL-2</td>
<td>pSTAT5</td>
<td>6.46 ± 0.12</td>
<td>148; 757; 367</td>
<td>3</td>
</tr>
<tr>
<td>TYK2-JAK1</td>
<td>U2OS</td>
<td>IFNαB2</td>
<td>pSTAT1</td>
<td>6.33 ± 0.03</td>
<td>494; 436</td>
<td>2</td>
</tr>
<tr>
<td>JAK1-JAK2</td>
<td>HeLa</td>
<td>OSM</td>
<td>STAT1 reporter</td>
<td>6.01 ± 0.07</td>
<td>1,045</td>
<td>4</td>
</tr>
<tr>
<td>JAK1-JAK2</td>
<td>U2OS</td>
<td>IFNγ</td>
<td>pSTAT1</td>
<td>5.45</td>
<td>3,364</td>
<td>1</td>
</tr>
<tr>
<td>JAK2</td>
<td>TF-1</td>
<td>IL-3</td>
<td>pSTAT5</td>
<td>5.45</td>
<td>3,524</td>
<td>1</td>
</tr>
<tr>
<td>JAK2</td>
<td>BaF3</td>
<td>IL-3</td>
<td>proliferation</td>
<td>5.34 ± 0.04</td>
<td>4,546</td>
<td>3</td>
</tr>
<tr>
<td>JAK2</td>
<td>UT7-EPO</td>
<td>EPO</td>
<td>pSTAT5</td>
<td>&gt;5</td>
<td>&gt;10,000</td>
<td>2</td>
</tr>
<tr>
<td>JAK2</td>
<td>22Rv1</td>
<td>PRL</td>
<td>pSTAT5</td>
<td>&gt;5</td>
<td>&gt;10,000</td>
<td>2</td>
</tr>
</tbody>
</table>
GLPG0634 inhibits JAK1
High selectivity for JAK1 over JAK2 in human blood

Preclinical JAK profiling in human whole blood assay

Selectivity for JAK1 over JAK2
(ratio IC\textsubscript{50} values)

<table>
<thead>
<tr>
<th>Assay</th>
<th>IC\textsubscript{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1 IL6/pSTAT1</td>
<td>600</td>
</tr>
<tr>
<td>JAK2 GM-CSF/pSTAT5</td>
<td>17,500</td>
</tr>
</tbody>
</table>

rhlL-6: 10 ng/mL; pSTAT1 in CD4\textsuperscript{+} leucocytes by FACS
rhmGM-CSF: 20 pg/mL; pSTAT5 in CD33\textsuperscript{+} leucocytes
Animal pharmacokinetics for GLPG0634

<table>
<thead>
<tr>
<th>Vehicle MC 0.5% (v/v)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{AUC}_{0-24h}$ (ng.h/mL)</th>
<th>$T_{\frac{1}{2}}$ (h)</th>
<th>$\text{Cl}$ (L/h/kg)</th>
<th>$V_{ss}$ (L/kg)</th>
<th>$\text{F}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV 1 mg/kg</td>
<td>1,407</td>
<td></td>
<td>739</td>
<td>1.6</td>
<td>1.4</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>PO 5 mg/kg</td>
<td>310</td>
<td>2.2</td>
<td>1,681</td>
<td>3.9</td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>dog</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV 1 mg/kg</td>
<td>1,143</td>
<td></td>
<td>4,098</td>
<td>7.5</td>
<td>0.25</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>PO 5 mg/kg</td>
<td>1,807</td>
<td>1.5</td>
<td>13,908</td>
<td>5.2</td>
<td></td>
<td></td>
<td>67</td>
</tr>
</tbody>
</table>

GLPG0634 was well exposed in rodent and non-rodent species using 0.5% methylcellulose as vehicle
Collagen-induced arthritis rat model

- Injection of heterologous type II collagen in susceptible rat strain
- Boost injection with Coll II at day 0 and 7
- Treatment day 15
- Read-out until day 29
Therapeutic CIA rat model
GLPG0634

Shows a dose-dependent reduction in joint inflammation
Conclusion lead optimization

- GLPG0634 is a selective JAK1 inhibitor
  - JAK1 biochemical potency IC$_{50}$ ~10 nM
  - human whole blood assay and cellular models show selectivity for JAK1 over JAK2
- Highly potent in therapeutic CIA animal model
GLPG0634

The 1st selective JAK1 inhibitor

• Introduction
• Target identification
• Hit finding to PCC
• Clinical development
  ➢ Phase I
  ➢ Phase II Proof of Concept
Phase I
Trial design and safety

• Ascending single dosing and Multiple dosing
  ➢ 48 healthy volunteers: 6 subjects per groups received GLPG0634 and 2 placebo

• Safety: adverse events were mild and transient in nature.
  ➢ headaches and abdominal discomfort (including loose stools) were reported in more than one subject, over all dose groups and including placebo
  ➢ no changes in hematology parameters (including reticulocytes)
  ➢ no changes in blood biochemistry (including cholesterol)
  ➢ no signal in cardiovascular safety or vital signs
GLPG0634 clinical pharmacokinetics
Healthy volunteers

- Dose proportional PK
- Low variability (CV < 20%)
- Half life: 5-8 hours
- No food effect on capsule formulation
- Plasma exposure ≥ 50 mg
  - exceeds effective exposure in rat CIA
  - exceeds cellular IC₅₀
GLPG0634 has a unique JAK profile

JAK1 and JAK2 measured in whole blood from Phase I healthy volunteers

- JAK1 (IL-6/pSTAT1) compared to JAK2 (GM-CSF/pSTAT5)

GLPG0634 is a selective JAK1 inhibitor
Conclusion Phase I

- GLPG0634 is well tolerated in the pharmacological active dose range, with no effects on hematology or other safety markers following 10 days dosing in healthy volunteers.
- Good oral pharmacokinetics and biomarker PK/PD support a once-daily oral dosing regimen.
- Results support the initiation of a Phase II trial in rheumatoid arthritis patients.
GLPG0634
The 1st selective JAK1 inhibitor

• Introduction
• Target identification
• Hit finding to PCC
• Clinical development
  ➢ Phase I
  ➢ Phase II Proof of Concept
Phase II: Why only a 4 week trial?

_tofacitinib_ monotherapy in active RA

- Rheumatoid arthritis patients failing prior DMARD (n=264)
- Dose dependent efficacy
  - short-term efficacy (4 weeks) is maintained long-term (2 year)
- Safety and tolerability
  - infections
  - lipid elevations
  - transaminase increased
  - anemia
  - neutropenia

Ref: Kremer et Al. Arthritis & Rheumatism, 7, 2009, 1895
Riese et Al. Best Practice & Research Clinical Rheumatology, 24, 2010, 513
GLPG0634 Phase II PoC

Trial design

• Randomized, double-blind, placebo-controlled study in Moldova

• 36 RA patients with insufficient response to MTX, naïve to biologics
  ➢ 4 week treatment, oral dosing
  ➢ 200 mg QD vs. 100 mg BID vs. placebo
  ➢ all on MTX (mean: 12 mg/week), with stable low-dose steroids/NSAI Ds
  ➢ patients randomized to 12 per group
    ▪ similar demographics (mean age 49 years, 11 females per group)

• All 36 patients completed 4 weeks of treatment

Designed to give rapid evaluation of efficacy at high dose
## Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=12</th>
<th>GLPG0634 100 mg BID n=12</th>
<th>GLPG0634 200 mg QD n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA diagnosis (years)</td>
<td>5.6</td>
<td>9.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Use of NSAIDs</td>
<td>11</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>CRP at baseline (mg/L)</td>
<td>34.9</td>
<td>21.3</td>
<td>40.5</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.3</td>
<td>6.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

GLPG0634

Placebo

n=12

100 mg BID

n=12

200 mg QD

n=12
GLPG0634 efficacy: ACR20

- Achieved primary endpoint
- ACR20 scores at Day 28: 42-58% improvement over placebo

GLPG0634 is highly efficacious with rapid onset of action
GLPG0634 efficacy: C-reactive protein

- CRP: inflammation biomarker
- GLPG0634 treatment induces a rapid and lasting decrease in serum CRP to near-normal levels

GLPG0634 is highly efficacious with rapid onset of action
GLPG0634 efficacy
DAS28

Changes in DAS28 (CRP) score

% of patients achieving DAS28 remission or low disease activity

GLPG0634 is highly efficacious with rapid onset of action
## GLPG0634 safety findings

<table>
<thead>
<tr>
<th>Any treatment-related AE</th>
<th>Placebo n=12</th>
<th>GLPG0634 100 mg BID n=12</th>
<th>GLPG0634 200 mg QD n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Asthenia (weakness)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia (abnormal taste)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Somnolence (drowsiness)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
GLPG0634 safety summary

• Safe and well-tolerated
  - no SAEs on GLPG0634 treatment
  - few patients reported side-effects
  - neither anemia nor increase in LDL
  - modest decrease in neutrophils and platelets
  - no effects on blood pressure
Conclusion
GLPG0634 a potential best in class

• Hit finding to PCC
  ➢ Triazolopyridine identified as JAK1 inhibitors by HTS screening
  ➢ Identification of subseries that offer a balance of ADME properties and potency

• GLPG0634 has a unique profile
  ➢ a selective JAK1 inhibitor in biological systems
  ➢ active in preclinical models of arthritis
  ➢ well tolerated in a wide dose range in Phase I
  ➢ PK/PD profile consistent with once daily dosing

• Proof-of-Concept in rheumatoid arthritis patients achieved
  ➢ 4 weeks treatment at 200 mg/day on top of failing MTX
THANK YOU

Questions?