New Small Molecule Therapies in Rheumatoid Arthritis

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Disclosures

• Pfizer
• Astellas
• Lilly
• Pharmacyclics
• Abbott
• Sanofi
• Regeneron

• Gilead
• Vertex
• Johnson & Johnson
• Celgene
• Principia
• Galapagos
• GSK
Cytokine Signaling Pathways Involved in Inflammatory Arthritis

- Rheumatoid factor and other autoantibodies
- Interleukin-4
- Interleukin-6
- Interleukin-10
- Interferon-γ
- Interleukin-12
- Interferon-γ
- Interleukin-1, and interleukin-6
- TNF-α

- Synovium
- Plasma cell
- B cell
- CD4+ T cell
- CD11
- CD69

- OPGL
- Osteoclast
- Fibroblast
- Chondrocyte

Production of metalloproteinases and other effector molecules
Migration of polymorphonuclear cells

Erosion of bone and cartilage
Human Kinome: More than 400 Kinases

Different Kinase Pathways can be Exploited for Therapeutic Purposes in RA\textsuperscript{1-10}

Small Molecule enzyme Inhibitors

- JAK- Inhibition
- SYK-Inhibition
- PDE4-Inhibition
- BTK-Inhibition
- PI3K-Inhibition
- Tyrosine Kinase Inhibition
  - C-FMS
  - C-KIT
Binding of cytokine receptors activates JAK signalling pathways

- Rapid membrane to nucleus signalling:
  - Cytokines bind trans-membrane receptors that are associated with JAKs
  - Binding activates JAKs
  - JAKs phosphorylate receptors
  - STATs bind to receptors
  - JAKs phosphorylate STATs
  - STAT translocate to the nucleus
  - STATs bind DNA and activate transcription to produce proteins that mediate immune responses/inflammation


JAKs activate STATs, which then act as transcription factors

JAK, Janus kinase; P, phosphate; STAT, signal transducer and activator of transcription.
Activation of JAK/STAT Signaling by Cytokines in RA

The JAK/STAT signalling pathways

- There are four JAK family members: JAK1, JAK2, JAK3, and TYK2

### Example of cytokines that signal through JAK/STAT combinations

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>STAT</th>
<th>JAK</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ-chain cytokines(^2)</td>
<td>1, 3, 5, 6</td>
<td>JAK1, JAK3</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>1, 3, 5</td>
<td>JAK1, JAK2</td>
</tr>
<tr>
<td>IL-10, IL-22</td>
<td>1, 3, 5</td>
<td>JAK1, TYK2</td>
</tr>
<tr>
<td>IL-12, IL-23</td>
<td>3, 4</td>
<td>JAK2, TYK2</td>
</tr>
<tr>
<td>IL-6(^{†}), IL-11</td>
<td>1, 3, 5</td>
<td>JAK1, JAK2, TYK2</td>
</tr>
<tr>
<td>EPO, TPO, GM-CSF</td>
<td>5</td>
<td>JAK2, JAK2</td>
</tr>
</tbody>
</table>

**JAKs mainly work in pairs within the cell and signal via JAK/STAT combinations**

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Small Molecule enzyme Inhibitors

- JAK- Inhibition
  - Tofacitinib
  - Baracitinib
  - VX-509 (Decernotimib)
  - Ast015k
  - Galapagos
# Tofacitinib Phase 3 studies: Overview

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>ORAL Solo(^1) (N=610)</th>
<th>ORAL Sync(^2) (N=792)</th>
<th>ORAL Scan(^3) (N=797)</th>
<th>ORAL Standard(^4) (N=717)</th>
<th>ORAL Step(^5) (N=399)</th>
<th>ORAL Start(^6) (N=952)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>6 months</td>
<td>12 months</td>
<td>24 months</td>
<td>12 months</td>
<td>6 months</td>
<td>24 months</td>
</tr>
<tr>
<td><strong>Background treatment</strong></td>
<td>None</td>
<td>Non-biologic DMARDs</td>
<td>MTX</td>
<td>MTX</td>
<td>MTX</td>
<td>None</td>
</tr>
<tr>
<td><strong>Feature</strong></td>
<td>Monotherapy</td>
<td>Background DMARDs</td>
<td>X-ray</td>
<td>Active control (adalimumab)</td>
<td>TNFi failure</td>
<td>mTSS scores with monotherapy</td>
</tr>
</tbody>
</table>


DMARD, disease-modifying anti-rheumatic drug; IR, inadequate responder; mTSS, modified total Sharp score; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.
EFFICACY

Background DMARD studies
ACR20 Response Rates at Primary Time Point – Phase III Background DMARD Studies

1044/Scan-24-month, MTX background, X-ray evaluation of joint damage
1046/Sync-12-month, various background non-biologic DMARDs
1064/Standard-12-month, MTX background, adalimumab active control
1032/Step-6-month, MTX background, TNF-inadequate responders

MTX, methotrexate

Pfizer Inc. Advisory Committee Briefing Materials: Available to General Public. 9th May 2012:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302960.pdfuller
EFFICACY

Monotherapy study
ACR20, ACR50, ACR70 Response Rate (%) (NRI, Comparisons to Placebo), 1045/Solo Study

1045/Solo, 6-month, monotherapy (n = 610)

*p≤0.05; ** p<0.01; *** p<0.001, compared to placebo

NRI, non-responder imputation

Pfizer Inc. Advisory Committee Briefing Materials: Available to General Public. 9th May 2012: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM302960.pdffuller
RADIOGRAPHIC OUTCOMES
ORAL Start: \( \Delta \) mTSS at Month 6 – co-primary endpoint

**p<0.001; ***p<0.0001 vs MTX; Full analysis Set
Fleischmann R et al. Presented at ACR 2012; Washington, DC, November 10–14; Presentation 2486

BID, twice daily; LS, least squares; MTX, methotrexate.
ORAL Step: Study design

Inadequate responders to ≥1 TNFi (N=399)

2:2:1:1 randomisation

Baseline

Month 3

Month 6 study end

Co-primary efficacy endpoints

- ACR20 response (month 3)
- Mean change in HAQ-DI from baseline (month 3)
- Rate of achieving DAS28-4(ESR)<2.6 (month 3)

Tofacitinib 5 mg BID + MTX

Tofacitinib 10 mg BID + MTX

Placebo + MTX

Placebo + MTX

Tofacitinib 5 mg BID + MTX

Tofacitinib 10 mg BID + MTX

ACR, American College of Rheumatology; BID, twice daily; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.

ORAL Step: ACR20 primary endpoint

ACR20 (Month 3)

- Placebo + MTX
- Tofacitinib 5 mg BID + MTX
- Tofacitinib 10 mg BID + MTX

Patients (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (n)</th>
<th>ACR20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX</td>
<td>32/131</td>
<td>24.4</td>
</tr>
<tr>
<td>Tofacitinib 5 mg BID + MTX</td>
<td>55/132</td>
<td>41.7</td>
</tr>
<tr>
<td>Tofacitinib 10 mg BID + MTX</td>
<td>64/133</td>
<td>48.1</td>
</tr>
</tbody>
</table>

*p≤0.05; ***p<0.0001 vs placebo at month 3 (unadjusted)

ACR, American College of Rheumatology; BID, twice daily; MTX, methotrexate.

SAFETY
Side-effects of JAK inhibition with tofacitinib

- Most common (≥2%) adverse events reported during the first 3 months (placebo-controlled) in Phase III studies were:¹
  - Upper respiratory tract infections, headache, nasopharyngitis, diarrhoea, nausea, urinary tract infection, hypertension, dyspepsia, oedema, peripheral, blood creatine phosphokinase increased, arthralgia, and RA
- Treatment with tofacitinib was associated with an increased incidence of neutropenia (<2,000 cells/mm³)
  - A dose-dependent mean decrease in ANC, which reached a plateau within 3 months of treatment, was observed in RA patients treated with tofacitinib¹
  - Confirmed decreases in ANC below 1,000 cells/mm³ occurred in 0.07% of patients treated with tofacitinib²
- Confirmed decreases in lymphocyte counts below 500 cells/mm³ occurred in 0.04% of patients treated with tofacitinib during the first 3 months of exposure²

## Incidence Rates for Serious Adverse Events: All Doses of Tofacitinib

<table>
<thead>
<tr>
<th>Duration of tofacitinib exposure (months)</th>
<th>IR/100 pt-yrs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.28 ± 3.47</td>
</tr>
<tr>
<td>0–6</td>
<td>10.77 ± 3.77</td>
</tr>
<tr>
<td>6–12</td>
<td>10.44 ± 3.77</td>
</tr>
<tr>
<td>12–18</td>
<td>12.14 ± 3.64</td>
</tr>
<tr>
<td>18–24</td>
<td>10.43 ± 3.29</td>
</tr>
<tr>
<td>24–30</td>
<td>10.03 ± 2.86</td>
</tr>
<tr>
<td>30–36</td>
<td>8.46 ± 2.38</td>
</tr>
<tr>
<td>36–42</td>
<td>7.34 ± 2.10</td>
</tr>
<tr>
<td>&gt;42</td>
<td>8.82 ± 2.55</td>
</tr>
</tbody>
</table>

### Notes
- The most common serious AEs were infections and infestations, musculoskeletal and connective tissue disorders, and injury, poisoning and procedural complications.
- The IR for mortality* was 0.276 (0.198, 0.385)

*within 30 days of receiving last dose of study medication

Bars indicate 95% confidence limits. IRs are per 100 pt-yrs. Phase 2, Phase 3 and LTE data as of 10 April 2013. N, number of patients exposed to tofacitinib, n, number of patients with events.
Incidence Rates for Serious and Non-serious Herpes Zoster: All Doses of Tofacitinib

- 39 patients permanently discontinued study treatment due to HZ
- Serious HZ* was reported in 35 patients (IR: 0.276 [0.199, 0.385])
  - 34/35 events resolved, 1/35 events resolving
- Multidermatomal HZ (n=6), ophthalmic HZ (n=6) and HZ oticus (n=1) were reported rarely
- There were no cases of visceral dissemination of HZ

*Require hospitalisation or meeting other SAE criteria
Bars indicate 95% confidence limits. IRs are per 100 pt-yrs. Phase 2, Phase 3 and LTE data as of 10 April 2013
Safety Conclusions

- The pattern and rate of serious AEs and AEs of special interest observed in patients with RA following >12 000 pt-yrs of overall exposure to tofacitinib was stable across time intervals.
- No new risks were identified compared with previous reports.
- Longer-term follow-up, observational research and pharmacovigilance activities will further characterize the safety profile of tofacitinib in RA.
Small Molecule enzyme Inhibitors

- JAK- Inhibition
  - Tofacitinib
  - Baracitinib
  - VX-509 (Decernotimib)
  - Ast015k
  - Galapagos
Baricitinib (LY3009104; INCB28050)

• Baricitinib is an oral, reversible inhibitor of JAK1 and JAK2
  – *In-vitro* potency (IC$_{50}$)
    • JAK1 and JAK2 ~ 2 - 5 nM
    • TYK2 ~ 53 nM
    • JAK3 ~ 560 nM (JAK3 sparing)
• Baricitinib is currently being developed for the treatment of RA and other autoimmune disorders
Randomized, Double-Blind, Placebo-Controlled Trial on Background MTX

Patients and Investigators remained blinded during Parts A and B

Part A (12 weeks)
- Baricitinib 1 mg QD (N=49)
- Baricitinib 2 mg QD (N=52)
- Baricitinib 4 mg QD (N=52)
- Baricitinib 8 mg QD (N=50)

Part B (12 weeks)
- Baricitinib 2 mg QD (N=50)
- Baricitinib 4 mg QD (N=49)
- Baricitinib 8 mg QD (N=48)

Extension Study
- Baricitinib 2 mg BID (N=61)
- Baricitinib 4 mg QD (N=61)
- Baricitinib 4 mg QD (N=50)
- Baricitinib 4 mg QD (N=49)

0 Week

Primary Endpoint

12 Weeks

24 Weeks

128 Weeks
Safety and Efficacy Baricitib 24 weeks
Genovese MC. et. al. ACR 2012

Week 12

Week 24

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg</th>
<th>2 mg</th>
<th>4 mg</th>
<th>8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>57</td>
<td>54</td>
<td>63</td>
<td>73</td>
<td>63</td>
</tr>
<tr>
<td>ACR50</td>
<td>31</td>
<td>35</td>
<td>40</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>ACR70</td>
<td>12</td>
<td>23</td>
<td>20</td>
<td>24</td>
<td>28</td>
</tr>
</tbody>
</table>

*p < 0.05
**p < 0.01
***p < 0.001 vs placebo
MRI study of Baricitib 24 weeks
Change in Total Damage Score
Peterfy. et. al.

12 Weeks

24 Weeks

P value Top: Wilcoxon rank-sum test
P value Bottom: ANCOVA as prospectively defined in SAP
Small Molecule enzyme Inhibitors

- JAK- Inhibition
  - Tofacitinib
  - Baracitinib
  - VX-509 (Decernotinib)
  - ASP015k
  - Galapagos
VX-509 is an oral, selective Janus Kinase 3 (JAK3) inhibitor

JAK3 associates only with the common gamma chain receptor subunit
- Exclusively involved in immune function and shared by receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
- Both JAK1 and JAK3 inhibitors will prevent signaling by these cytokines.

JAK3 selectivity may have advantages over other JAK inhibitory approaches
- Selective inhibition of JAK3 will not affect JAK1 signals mediated by other JAK1 pairs controlling a diverse set of physiologies
- Selectivity against JAK2 avoids impact on hematopoietic and growth factor signaling pathways (e.g. erythropoietin)

Phase II MTX-IR Study Design

Patients

- Age 18–80 years with active RA
- CRP > ULN
- SJC/TJC ≥6 of 66/68 joints
- Stable dose of MTX
- ≤20% for whom 1 TNF inhibitor failed

Primary assessments

SJC, swollen joint count; TJC, tender joint count; MTX, methotrexate
ACR Responses at Week 12

ACR Response (%)

\[ \Delta 50\% \]

Placebo (n=71)
VX-509 100 mg QD (n=71)
VX-509 150 mg QD (n=72)
VX-509 200 mg QD (n=72)
VX-509 100 mg BID (n=72)

*P<0.05; **P<0.01; ***P<0.001; P values vs placebo.

Nonresponder imputation
# Most Common Infections†

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (n=71)</th>
<th>100 mg (n=71)</th>
<th>150 mg (n=72)</th>
<th>200 mg (n=72)</th>
<th>100 mg (n=72)</th>
<th>All VX-509 (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>2 (2.8)</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>4 (5.6)</td>
<td>3 (4.2)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Upper resp tract infection</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>3 (4.2)</td>
<td>3 (4.2)</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (4.2)</td>
<td>1 (1.4)</td>
<td>3 (4.2)</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>4 (5.6)</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>0</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>6 (2.1)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>3 (4.2)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (1.4)</td>
<td>0</td>
<td>4 (5.6)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0</td>
<td>2 (2.8)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
<td>4 (1.4)</td>
</tr>
</tbody>
</table>

†Occurring in ≥1% of VX-509 subjects
Small Molecule enzyme Inhibitors

- JAK- Inhibition
  - Tofacitinib
  - Baracitinib
  - VX-509 (Decernotinib)
  - ASP015k
  - Galapagos
Introduction

- ASP015K is an oral immunosuppressant that acts by inhibiting Janus Kinase (JAK), a critical element in gamma-chain dependent cytokine signaling.

- *In vitro* kinase activity suggests that ASP015K has greater selectivity for JAK3 as compared to JAK1, JAK2, and TYK2.

- The pharmacokinetic profile of ASP015K supports its use as once daily dosing
  - $T_{\text{max}}$ 1.5~4 hrs
  - Terminal $t_{1/2}$ between 7 to 13 hrs

JAK=Janus kinase; $T_{\text{max}}$=time to maximal concentration; $t_{1/2}$=half life; TYK=tyrosine kinase.
Primary Endpoint: ACR20 Response at Week 12
DMARD-IR patients not on MTX

* p<0.05; ** p<0.01, based on normal approximation to binomial distribution for difference in proportions.
ACR20 Response at Week 12
MTX-IR patients on MTX

<table>
<thead>
<tr>
<th>Dose</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=72)</td>
<td>44.4%</td>
</tr>
<tr>
<td>ASP015K 25 mg (n=66)</td>
<td>43.9%</td>
</tr>
<tr>
<td>ASP015K 50 mg (n=78)</td>
<td>61.5%*</td>
</tr>
<tr>
<td>ASP015K 100 mg (n=84)</td>
<td>46.4%</td>
</tr>
<tr>
<td>ASP015K 150 mg (n=78)</td>
<td>57.7%</td>
</tr>
</tbody>
</table>

Dose-response p-value = 0.201
*p<0.05
ACR20 Response at Week 12 by Region (Pre-specified Analysis)

**United States**
- Placebo: 50.0%
- ASP015K 25 mg: 54.2%
- ASP015K 50 mg: 61.8%
- ASP015K 100 mg: 60.6%
- ASP015K 150 mg: 35.7%

**Europe**
- Placebo: 28.1%
- ASP015K 25 mg: 51.6%
- ASP015K 50 mg: 53.8%
- ASP015K 100 mg: 56.3%*
- ASP015K 150 mg: 27.6%

**Latin America**
- Placebo: 75.0%
- ASP015K 25 mg: 61.5%
- ASP015K 50 mg: 84.6%
- ASP015K 100 mg: 47.1%
- ASP015K 150 mg: 53.8%

*\( p<0.05 \)
Small Molecule enzyme Inhibitors

- JAK- Inhibition
  - Tofacitinib
  - Baracitinib
  - VX-509 (Decernotinib)
  - ASP015k
  - Galapagos
Efficacy and Safety of GLPG0634, a Selective JAK1 Inhibitor, After Short-Term Treatment of Rheumatoid Arthritis: Results of a Phase 2a Trial

- Double-blind, placebo-controlled phase 2a proof-of-concept trial of 91 patients with active RA
- Single center in Moldova; study duration 4 wks
- 3 treatment arms
  - GLPG0634 200 mg QD (n = 12)
  - GLPG0634 100 mg BID (n = 12)
  - PBO (n = 12)
- Patients continued stable background therapy of MTX, low-dose steroids and/or NSAIDs

<table>
<thead>
<tr>
<th></th>
<th>PBO (n = 12)</th>
<th>100 mg BID (n = 12)</th>
<th>200 mg QD (n = 12)</th>
<th>Pooled (n = 24)</th>
<th>Pooled vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>33.3</td>
<td>91.7</td>
<td>75.0</td>
<td>83.3</td>
<td>(P &lt; 0.01)</td>
</tr>
<tr>
<td>DAS28 (change)</td>
<td>-0.30</td>
<td>-2.81</td>
<td>-2.23</td>
<td>-2.52</td>
<td>(P &lt; 0.0001)</td>
</tr>
<tr>
<td>CRP (change, mg/L)</td>
<td>21.9</td>
<td>-13.8</td>
<td>-35.1</td>
<td>-24.4</td>
<td>(P &lt; 0.0001)</td>
</tr>
</tbody>
</table>

SAFETY AND EFFICACY OF GLPG0634, A SELECTIVE JAK1 INHIBITOR, IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS OF A 4-WEEK PHASE IIA DOSE RANGING, MULTI-CENTER TRIAL

• Double-blind, placebo-controlled phase 2a proof-of-concept trial of 91 patients with active RA

• Multinational study duration 4 wks

• 5 treatment arms
  – GLPG0634 300 mg QD (n = 22)
  – GLPG0634 150 mg QD (n = 15)
  – GLPG0634 75 mg QD (n = 22)
  – GLPG0634 30 mg QD (n = 15)
  – PBO (n = 17)

Generalizability to all JAK Inhibitors?

- Efficacy?
- Safety?
Enzyme Inhibitors

- JAK- Inhibition
- SYK-Inhibition
- PDE-4-Inhibition
- BTK-Inhibition
- PI3K-Inhibition
- Tyrosine Kinase Inhibition
  - (FMS/c-kit)
  - (c-kit inhibitor)
Spleen Tyrosine Kinase (SYK)\(^{1-6}\)

Small-Molecule Enzyme Inhibitors

- JAK-Inhibition
- SYK-Inhibition
- PDE4-Inhibition
- BTK-Inhibition
- PI3K-Inhibition
- Tyrosine kinase inhibition
  - C-FMS
Kinase Inhibitors

- JAK-Inhibition
- SYK-Inhibition
- PDE-4-Inhibition
- BTK-Inhibition
- PI3K-Inhibition
- Tyrosine Kinase Inhibition
  - cFMS
  - c-kit inhibitor
Bruton’s Tyrosine Kinase (BTK)
Kinase Inhibitors

- JAK-Inhibition
- SYK-Inhibition
- PDE-4-Inhibition
- BTK-Inhibition
- PI3K-Inhibition
- Tyrosine Kinase Inhibition
  - cFMS
  - c-kit inhibitor
Phosphoinositide 3-kinase
Summary

- Intra-cellular kinase pathways can be exploited for therapeutic purposes in the treatment of RA and other autoimmune diseases.

- The current targets with the greatest excitement include:
  - JAK
  - SYK
  - BTK
  - PI3K

- Human trials are necessary to fully understand the potential risks and benefits of these approaches.

- Impossible at this point to generalize either response or side effect profiles based on the selectivity of compounds in a class.