NIH - Industry Pilot Program:
*Discovering New Therapeutic Uses for Existing Molecules*

APRIL 16, 2013
CHRISTINE COLVIS, PH.D.

NCATS
NCATS Mission

Catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.
Background:
Drug rescue and re-purposing are valuable approaches to speed the development of new drugs and diagnostics.

**NIH-Industry Roundtable: Exploring New Uses for Abandoned and Approved Therapeutics**

Opportunities:
- Enhance NIH-industry partnerships in order to de-risk new concepts for therapeutic indications
  - Serve as a clearing house for discontinued compounds, biologics and data
  - Identify projects addressing compelling health needs
  - Establish template partnership agreements
Goal:
To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

The pilot initiative will:

- Match candidate Agents from 8 pharmaceutical partners with innovative ideas for new indications from the biomedical research community.

  - **NIH provides**: template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), Funding Opportunity Announcements, review, funding, and oversight

  - **Pharmaceutical partners provide**: compounds, biologics, in kind support, and pertinent data

  - **Academic researchers provide**: deep understanding of disease biology, new concepts to test, and access to appropriate patient populations
NCATS: Therapeutics Discovery Pilot
NCATS: Therapeutics Discovery Pilot

58 Agents made available for this pilot program by 8 pharmaceutical company partners*

• AbbVie (formerly Abbott)
• AstraZeneca
• Bristol-Myers Squibb Company
• Eli Lilly and Company
• GlaxoSmithKline
• Janssen Pharmaceutical Research and Development, LLC
• Pfizer
• Sanofi

*listed alphabetically
Criteria for Agent Inclusion

- Undergone significant R&D, including safety testing in humans
- Well characterized MoA
- Most have been in Phase I or Phase II for original indication(s)
- Safety profile understood
- Ready for Phase IIa studies for unexplored new uses
- Commitment to supplying material
Phase Ib and Phase IIa definitions for this program

- Phase Ib trials are defined as studies usually conducted in the target patient population to establish feasibility (e.g., target engagement, pharmacodynamics/pharmacokinetics (PD/PK), optimal dosing of the Agent) for a Phase IIa proof of concept trial.

- Phase IIa proof of concept trials are defined as studies designed to explore new hypotheses and to assess whether the Agent demonstrates an early signal of efficacy in the targeted patient population, typically 150 subjects or less. In addition to clinical benefit, Phase IIa trials also include assessments of safety, tolerability, and PD/PK response of the Agent.
Launched May 3, 2012
MEMORANDUM OF UNDERSTANDING

- Template MOU

CONFIDENTIAL DISCLOSURE AGREEMENTS

- AbbVie (formerly Abbott)
- AstraZeneca
- Bristol-Myers Squibb Company
- Eli Lilly and Company
- GlaxoSmithKline
- Janssen Pharmaceutical Research & Development, L.L.C.
- Pfizer Inc.
- Sanofi

COLLABORATIVE RESEARCH AGREEMENTS

- AbbVie (formerly Abbott)
- AstraZeneca
- Bristol-Myers Squibb Company
- Eli Lilly and Company
- GlaxoSmithKline
- Janssen Pharmaceutical Research & Development, L.L.C.
- Pfizer Inc.
- Sanofi
## Sample from the Table of Compounds and Biologics

<table>
<thead>
<tr>
<th>Code Number &amp; Link to More Information</th>
<th>Mechanism of Action</th>
<th>Original Development Indication(s)</th>
<th>Route of Administration Formulation Available (CNS Penetrant*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVE5530 canosimibe</td>
<td>Acyl-coenzyme A:cholesterol O-acyltransferase (ACAT) inhibitor Cholesterol absorption inhibitor</td>
<td>Hypercholesterolemia</td>
<td>Oral</td>
</tr>
<tr>
<td>SSR149744C celvarone</td>
<td>Anti-arrhythmic, Vaughan Williams Class I to IV</td>
<td>Maintenance of sinus rhythm in atrial fibrillation patients Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator</td>
<td>Oral</td>
</tr>
<tr>
<td>PF-05416266 senicapoc (ICA-17043)</td>
<td>Calcium-activated potassium channel blocker (KCa3.1), intermediate-conductance</td>
<td>Sickle cell disease Asthma</td>
<td>Oral</td>
</tr>
<tr>
<td>ABT-639</td>
<td>Calcium channel, voltage-gated (Cav3.2, T-type) blocker</td>
<td>Pain</td>
<td>Oral (Yes)</td>
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<tr>
<td>CP-945598 otenabant</td>
<td>Cannabinoid receptor 1 (CB1) antagonist</td>
<td>Obesity</td>
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<tr>
<td>LY2828360</td>
<td>Cannabinoid receptor 2 (CB2) agonist</td>
<td>Osteoarthritis pain</td>
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<td>AZD1981</td>
<td>Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2)/prostaglandin D2 (DP2) receptor antagonist</td>
<td>Asthma Chronic obstructive pulmonary disease</td>
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<td>SSR150106</td>
<td>Chemokine receptor antagonist (TNFα release)</td>
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<td>AZD2423</td>
<td>Chemokine (C-C motif) receptor 2 (CCR2) antagonist</td>
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### Mechanism of Action

Chemokine (C-C motif) Receptor 2 (CCR2) antagonist  
http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59  

### Overview

AZD2423 is a potent orally bioavailable non-competitive, negative allosteric modulator of the CCR2 chemokine receptor. CCR2 is a receptor for monocyte chemoattractant protein MCP-1 (CCL2) and the closely related proteins MCP-2 (CCL8), MCP-3 (CCL7), and MCP-4 (CCL13). Human CCR2 exists as two forms, CCR2a and CCR2b, which differ at their C-termini by alternative splicing. Evidence obtained from studies on leukocytes suggests that MCP-1 binds preferentially to CCR2 and mediates monocyte chemotaxis. Studies have implicated MCP-1-mediated monocyte infiltration in pain and a range of inflammatory diseases. AZD2423 has been developed for the oral treatment of neuropathic pain and chronic obstructive pulmonary disease (COPD).

In preclinical studies, AZD2423 inhibited MCP-1 induced calcium mobilization and chemotaxis of THP-1 cell line with an IC$_{50}$ of 4 nM. The AZD2423 affinity for CCR2 in human whole blood, measuring MCP-1 induced L-selectin shedding from monocytes, was the same. AZD2423 is highly selective (> 500-fold) for CCR2. AZD2423 demonstrated robust analgesia in two rodent models of neuropathic pain and a pain model of joint destruction against heat, mechanical and weight-bearing endpoints. A significant (> 500-fold) drop-off in potency was observed for several pre-clinical species (rat, mouse, dog, marmoset). Consequently several tool compounds have been used for most in vivo pharmacology studies; a tool CCR2 antagonist inhibited neuronal excitability in rat neuropathic models to heat, mechanical and electrical stimuli either via systemic administration or via administration directly to the spinal cord.

### Safety/tolerability

A comprehensive safety assessment package has been performed on AZD2423 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and dog. Identified target organs for toxicity are liver and cardiovascular function.

In healthy volunteers, AZD2423 has been studied at single doses of up to 60 0mg and in multiple ascending doses of up to 300 mg once daily for up to 14 days. Gastrointestinal side effects, (nausea and vomiting), determined a single dose MTD of 300 mg and multiple dose MTD of 150 mg. In patients (COPD and neuropathic pain) multiple doses up to 150 mg (pain) and 100 mg (COPD) for 28 days have been generally well tolerated.

### Additional Information

AZD2423 has been studied in several Phase 2a studies. Doses of up to 150 mg for 4 weeks have been tested examining its potential effects in pain and COPD. In the COPD study, treatment with AZD2423 (100 mg) was associated with a decrease in the number of monocytes in peripheral blood. This effect was observed within 1 week after start of treatment, was sustained over the 4-week treatment period, and is consistent with the mechanism of action, as was the observed increase in CCL2, the endogenous ligand.

### Suitable for and exclusions

Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. Mycobacterium tuberculosis screening should be performed to exclude patients with latent tuberculosis until more information has been gained on the potential risk with CCR2-antagonists regarding host defense.

Proposals for studies in COPD, ophthalmology or dermatology are not of interest.

### Clinical trials

http://clinicaltrials.gov/ct2/results?term=AZD2423

### Publications

None
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<td>MoA 1</td>
<td>Hypercholesterolemia</td>
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<td>Rheumatoid arthritis</td>
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<tr>
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<td></td>
<td>Chronic obstructive pulmonary</td>
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Impact of Crowdsourcing

The diagram shows the number of applications for individual compounds across different indications. The indications are labeled as:
- Indication A
- Indication B
- Indication C
- Indication D
- Indication E
- Indication F

The x-axis represents individual compounds, and the y-axis represents the number of applications. Each bar is color-coded to correspond with the different indications.
Importance of Template Agreements

- 8 Industry partners

- Crowdsourcing

- Template agreements
  - Save time and resources
  - Make a crowdsourcing program possible
Template agreements

• Agreements developed de novo can take months or more than a year to develop
• Crowdsourcing would not be possible without the template agreements
• On behalf of our research community, NIH worked with each pharma partner to develop template Confidential Disclosure Agreements and Collaborative Research Agreements
Future Plans?

If the pilot is successful, the program may be expanded to include additional pharmaceutical or biotechnology company partners, Agents, and new therapeutics discovery projects.
TDP Team Page 1 of 2

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Vicki Maurer
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