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

JUNE 24, 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.
**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), FOAs, 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

- NIH
- Patients
- Researcher
- Industry Partner
- CRA

Arrows indicate relationships:
- NIH to Patients: Grant
- NIH to Industry Partner: MOU
- Patients to Researcher: CRA

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
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Additional companies join; FOAs issued; Info on Agents provided

X02 applications submitted

Top tier applicants identified

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TIMING

May 3, 2012

June 12, 2012

August 14, 2012

Late September

December 17, 2012

March 2013

July 2013

2 – 3 years
MEMORANDUM OF UNDERSTANDING

- Template MOU

CONFIDENTIAL DISCLOSURE AGREEMENTS

- AbbVie (formerly Abbott)
- AstraZeneca
- Bristol-Myers Squibb Company
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COLLABORATIVE RESEARCH AGREEMENTS

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<td>AVE5530 canosimibe</td>
<td>Acyl-coenzyme A:cholesterol O-acyltransferase (ACAT) inhibitor Cholesterol absorption inhibitor</td>
<td>Hypercholesterolemia</td>
<td>Oral</td>
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<tr>
<td>SSR149744C celivarone</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>
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<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 (Yes)</td>
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<tr>
<td>ABT-639</td>
<td>Calcium channel, voltage-gated (Cav3.2, T-type) blocker</td>
<td>Pain</td>
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<tr>
<td>CP-945598 otenabant</td>
<td>Cannabinoid receptor 1 (CB1) antagonist</td>
<td>Obesity</td>
<td>Oral (Yes)</td>
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<tr>
<td>LY2828360</td>
<td>Cannabinoid receptor 2 (CB2) agonist</td>
<td>Osteoarthritis pain</td>
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<tr>
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<th><strong>AstraZeneca</strong></th>
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<td><strong>Overview</strong></td>
<td>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 pre-clinical studies, AZD2423 inhibited MCP-1 induced calcium mobilization and chemotaxis of THP-1 cell line with an IC₅₀ 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 (&gt; 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 (&gt; 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.</td>
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<td><strong>Safety/tolerability</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Additional Information</strong></td>
<td>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.</td>
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<td><strong>Suitable for and exclusions</strong></td>
<td>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.</td>
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<td><strong>Publications</strong></td>
<td>None</td>
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Crowdsourcing

The practice of obtaining needed services, ideas, or content by soliciting contributions from a large group of people and especially from the online community rather than from traditional employees or suppliers

--Merriam-Webster.com
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<td>Compound 4</td>
<td>MoA 4</td>
<td>Asthma</td>
<td>Oral (Yes)</td>
</tr>
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<td>Compound 5</td>
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<td>Obesity</td>
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</tr>
<tr>
<td>Compound 6</td>
<td>MoA 6</td>
<td>Osteoarthritis pain</td>
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</tr>
<tr>
<td>Compound 7</td>
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<td>Oral</td>
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<tr>
<td></td>
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*Note: CNS Penetrant indicates whether the compound can pass through the blood-brain barrier.*
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- CNS Penetrant? indicates whether the compound can penetrate the blood-brain barrier.
- Oral indicates the route of administration is via oral ingestion.
- Oral (Yes) indicates the compound is available for oral administration and has been confirmed to have CNS penetration.
- Oral (No) indicates the compound is available for oral administration but has not been confirmed to have CNS penetration.
- Oral (Not Available) indicates the compound is not available for oral administration.
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Impact of Crowdsourcing

![Bar chart showing the number of applications for individual compounds. The chart indicates the impact of crowdsourcing on different indications. Each compound is represented by a bar with different colors corresponding to different indications: Indication A (orange), Indication B (teal), Indication C (purple), Indication D (green), Indication E (red), and Indication F (blue). The y-axis represents the number of applications, ranging from 0 to 9, and the x-axis represents individual compounds, numbered from 1 to 16.]
Impact of Crowdsourcing

- Arthritis
- Cancer
- Kidney failure
- Alzheimer’s
- PTSD
- Pain
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Template agreements

- Agreements developed de novo can take months or years 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
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Award Stats

• 9 awards - $12.7M total for the first year
• 8 disease areas: Alzheimer’s, Alcoholism, Smoking Cessation, Schizophrenia (2), Peripheral Artery Disease (PAD), Lymphangioleiomyomatosis (LAM), Duchenne Muscular Dystrophy, Calcific Aortic Valve Stenosis
• 6 diseases in the neurosciences
• 3 relevant to NHLBI (LAM also of interest to NCI)
• 2 rare diseases
Requesting Feedback

• We are currently seeking input on administration of the NIH-Industry Pilot Program Discovering New Therapeutic Uses for Existing Molecules

• Responses to this RFI will be accepted through July 18, 2013. All comments must be submitted using the online form at the following location:
http://grants.nih.gov/grants/rfi/rfi.cfm?ID=33