NCATS Mission

To 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.
Exploring New Uses for Abandoned and Approved Therapeutics

Although the U.S. National Institutes of Health (NIH) has made waves with a proposed new center aimed at translational research, so far the main innovation has been to put scattered existing programs under the same roof. But this month NIH Director Francis Collins unveiled something fresh: an effort to persuade drug companies to open up their troves of abandoned drugs to academics, who would look for new uses.

NIH’s Secondhand Shop for Tried-and-Tested Drugs

NIH researchers have found new uses for several therapeutics. As for logistics, the agency has made a small start. In April, NIH’s intramural Chemical Genomics Center unveiled a public database listing all 38000 or so approved drugs along with structural data (Science Translational Medicine, 27 April, http://sciencemag.org). Researchers can apply to have the center test their cell or molecular assays against the drugs to look for “hits,” or possible biological activity.

Could pharma open its drug freezers?

The NIH wants industry to contribute old, new and experimental drugs to a systematic, collaborative approach to drug rescue and repurposing.

Double duty. NIH researchers have found new uses for several therapeutics.
Launched May 3, 2012
Goal of each project:
To identify new therapeutic uses of proprietary compounds across a broad range of human diseases in areas of medical need.

The pilot initiative:
- Matched candidate Agents from 8 pharmaceutical partners with innovative ideas for new indications from the biomedical research community.
  - NIH provided: template Confidential Disclosure Agreements (CDAs) and Collaborative Research Agreements (CRAs), and FOAs, review, funding, and oversight
  - Pharmaceutical partners provided: compounds, in kind support, and pertinent data
  - Academic researchers provided: deep understanding of disease biology, new concepts to test, and access to appropriate patient populations
NCATS: New Therapeutic Uses Pilot

58 Agents
Agents are ready for Phase 2a studies for unexplored new uses

Propose 2a trial

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

Required for application submission
FOAs for the NIH-Industry Pilot Program publish June 12, 2012

Requisite X02 Pre-application PAR-12-203

Limited Competition (UH2/UH3) RFA-TR-12-004

Limited Competition (UH3) RFA-TR-12-005
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 cellvarone</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>
</tr>
<tr>
<td>CP-945598 otenabant</td>
<td>Cannabinoid receptor 1 (CB1) antagonist</td>
<td>Obesity</td>
<td>Oral (Yes)</td>
</tr>
<tr>
<td>LY2828360</td>
<td>Cannabinoid receptor 2 (CB2) agonist</td>
<td>Osteoarthritis pain</td>
<td>Oral (Yes)</td>
</tr>
<tr>
<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>
<td>Oral</td>
</tr>
<tr>
<td>SSR150106</td>
<td>Chemokine receptor antagonist (TNFα release)</td>
<td>Rheumatoid arthritis pain</td>
<td>Oral</td>
</tr>
<tr>
<td>AZD2423 (highlighted)</td>
<td>Chemokine (C-C motif) receptor 2 (CCR2) antagonist</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Oral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AstraZeneca</th>
<th>AZD2423</th>
</tr>
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<tr>
<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 IC\textsubscript{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 (&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>
</tr>
<tr>
<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 mg 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 endogonous ligand.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td><strong>Publications</strong></td>
<td>None</td>
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# The Table of Compounds and Biologics

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<td>Hypercholesterolemia</td>
<td>Oral</td>
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<td>Compound 2</td>
<td>MoA 2</td>
<td>Maintenance of sinus rhythm in atrial fibrillation patients</td>
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<td></td>
<td></td>
<td>Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator</td>
<td></td>
</tr>
<tr>
<td>Compound 3</td>
<td>MoA 3</td>
<td>Sickle cell disease</td>
<td>Oral</td>
</tr>
<tr>
<td>Compound 4</td>
<td>MoA 4</td>
<td>Anemia</td>
<td>Oral (Yes)</td>
</tr>
<tr>
<td>Compound 5</td>
<td>MoA 5</td>
<td>Obesity</td>
<td>Oral (Yes)</td>
</tr>
<tr>
<td>Compound 6</td>
<td>MoA 6</td>
<td>Osteoarthritis pain</td>
<td>Oral (Yes)</td>
</tr>
<tr>
<td>Compound 7</td>
<td>MoA 7</td>
<td>Chronic obstructive pulmonary disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
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*Note: CNS Penetrant indicates the compound's ability to cross the blood-brain barrier.*
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<td>MoA 6</td>
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<td>Compound 7</td>
<td>MoA 7</td>
<td>Asthma, Chronic obstructive pulmonary</td>
<td>Oral</td>
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Note: MoA stands for Mechanism of Action.
Impact of Crowdsourcing

![Bar chart showing the number of applications for different individual compounds. The chart compares various indications: Indication A, Indication B, Indication C, Indication D, Indication E, and Indication F. The x-axis represents Individual compounds, and the y-axis represents the number of applications ranging from 0 to 9.]
Impact of Crowdsourcing
Top tier X02 applications identified

1st contact: applicant & company

Top tier applicants identified

CDA and CRA executed; additional info on compounds provided; full application submitted

Late September 2012
Template agreements
Template agreements

- 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
- Template agreements served as the starting point for negotiations for all of the applications
Awards issued June 18, 2013

• 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
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- 3 of 9 projects were dosing patients within 3 months of award
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- 2 of 9 projects are relevant to the Joint Council
Ghrelin in Alcoholism: Summary

- Preclinical studies support a role for ghrelin in alcoholism. Jerlhag E. and colleagues

- In alcoholic individuals, blood ghrelin levels may vary based on their alcohol use and correlate with alcohol craving. A pharmacological challenge with IV ghrelin increases urge to drink alcohol and blood ghrelin levels correlate with urge to drink. Leggio L. and colleagues

Question:
- Could antagonism of the ghrelin receptor (GHS-R1a) be a novel treatment for alcoholism?
PF-05190457

- Ghrelin receptor inverse agonist, competitive antagonist
- Original indication: Type II Diabetes
- Suitable for clinical studies up to 28 days duration in conditions/diseases of ghrelin elevation
Open

Alpha7 Nicotinic Acetylcholine Receptors Modulate Motivation to Self-Administer Nicotine: Implications for Smoking and Schizophrenia

Darlene H Brunzell*1 and J Michael McIntosh2,3

1Department of Pharmacology and Toxicology, Interdisciplinary Neuroscience Program and Institute for Drug and Alcohol Studies, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; 2Department of Psychiatry, University of Utah, Salt Lake City, UT, USA; 3Department of Biology, University of Utah, Salt Lake City, UT, USA

NIH grants DA031289 and DA023114 to DHB and MH53631 and GM48677 to JMM
JNJ-39393406

- Nicotinic acetylcholine receptor, α7 (α7nAChR) positive allosteric modulator
- Original indication: Cognitive impairment in schizophrenia
Project Plan

- Preclinical feasibility studies in rodent models
- Human clinical Phase 2a studies to detect evidence of efficacy for smoking cessation in both the broader population of healthy dependent smokers and in smokers with schizophrenia
Feedback on the Pilot

• Template agreements worked well
• Two-tiered selections process worked well
• Length of time for preparing the UH application was too short
• Pharma companies saw ideas they hadn’t previously investigated
• Overall, there is strong enthusiasm for another initiative
Notice Soliciting Compounds

Notice to Solicit Compounds for Inclusion in the NIH-Industry New Therapeutic Uses Program

Notice Number: NOT-TR-14-001

Release Date: January 27, 2014
Project Team

**NIH ICs:**
- Larry Refolo (NIA)
- Mark Egli (NIAAA)
- Joanne Fertig (NIAAA)
- Jane Acri (NIDA)
- Linda Brady (NIMH)
- Patricia Walicke (NINDS)
- Crina Frincu (NINDS)
- Rajesh Ranganathan (NINDS)
- Ron Margolis (NIDDK)
- James Witter (NIAMS)
- Barbara Mroczkowski (NCI)
- Janet Cyr (NIDCD)
- Mike Kurilla (NIAID)

**NCATS:**
- Cheryl McDonald (NHLBI)
- John Thomas (NHLBI)
- George McKie (NEI)
- Ann Zajicek (NICHD)
- Debra Lewis (FDA)
- Katherine Needleman (FDA)
- Bonnie Dunn
- Sheri Hild
- Bobbie Ann Austin
- Chuck Niebylski
- Lili Portilla