

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

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NCATS

# NCATS: New Therapeutic Uses Pilot

## 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 will:*

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

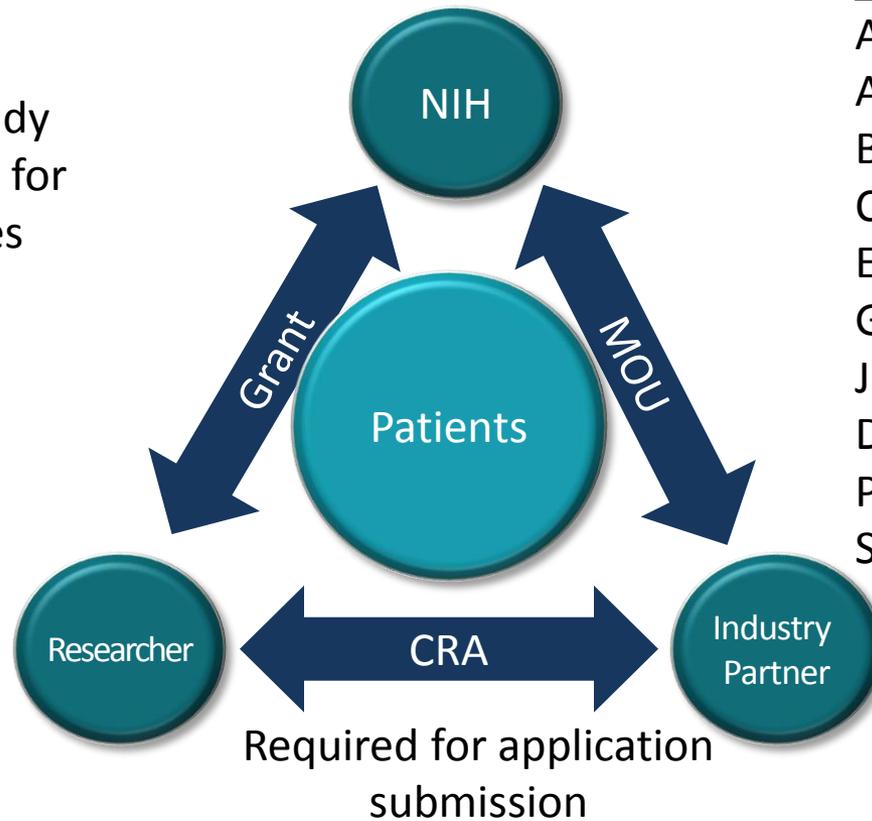
# NCATS: New Therapeutic Uses Pilot

## 58 Agents

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

## 8 Companies

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



Propose Phase 1b & 2a trial

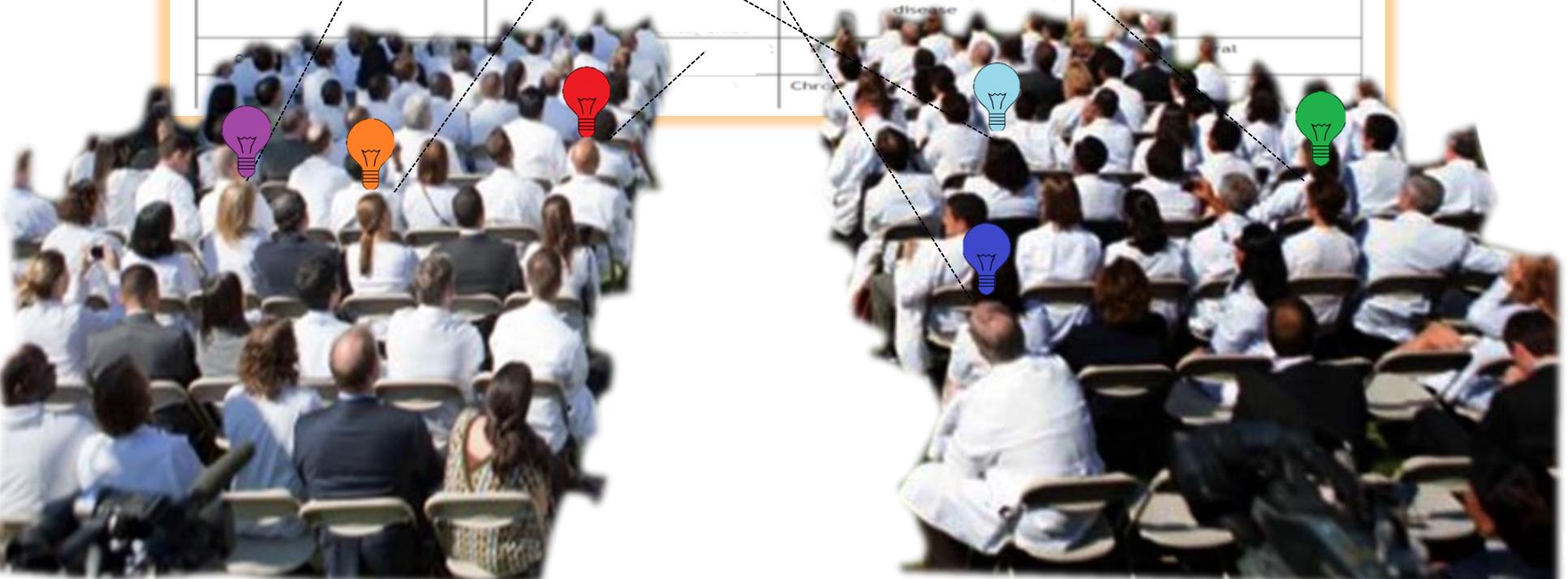
# Sample from the Table of Compounds and Biologics

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

<b>AstraZeneca</b>	<b>AZD2423</b>
<b>Mechanism of Action</b>	Chemokine (C-C motif) Receptor 2 (CCR2) antagonist <a href="http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59">http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59</a> <a href="http://www.ncbi.nlm.nih.gov/gene/729230">http://www.ncbi.nlm.nih.gov/gene/729230</a>
<b>Overview</b>	<p>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).</p> <p>In pre-clinical studies, AZD2423 inhibited MCP-1 induced calcium mobilization and chemotaxis of THP-1 cell line with an IC<sub>50</sub> 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 <i>in vivo</i> 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.</p>
<b>Safety/tolerability</b>	<p>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.</p> <p>In healthy volunteers, AZD2423 has been studied at single doses of up to 600 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.</p>
<b>Additional Information</b>	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.
<b>Suitable for and exclusions</b>	<p>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.</p> <p>Proposals for studies in COPD, ophthalmology or dermatology are not of interest.</p>
<b>Clinical trials</b>	<a href="http://clinicaltrials.gov/ct2/results?term=AZD2423">http://clinicaltrials.gov/ct2/results?term=AZD2423</a>
<b>Publications</b>	None

# The Table of Compounds and Biologics

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant <sup>†</sup> )
Compound 1	MoA 1	Hypercholesterolemia	Oral
Compound 2	MoA 2	Maintenance of sinus rhythm in atrial fibrillation patients Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator	Oral
Compound 3	MoA 3	Sickle cell disease Asthma	Oral
Compound 4	MoA 4	Pain	Oral (Yes)
Compound 5	MoA 5	Obesity	Oral (Yes)
Compound 6	MoA 6	Osteoarthritis pain	Oral (Yes)
Compound 7	MoA 7	Asthma Chronic obstructive pulmonary disease	Oral
		Chro	Oral

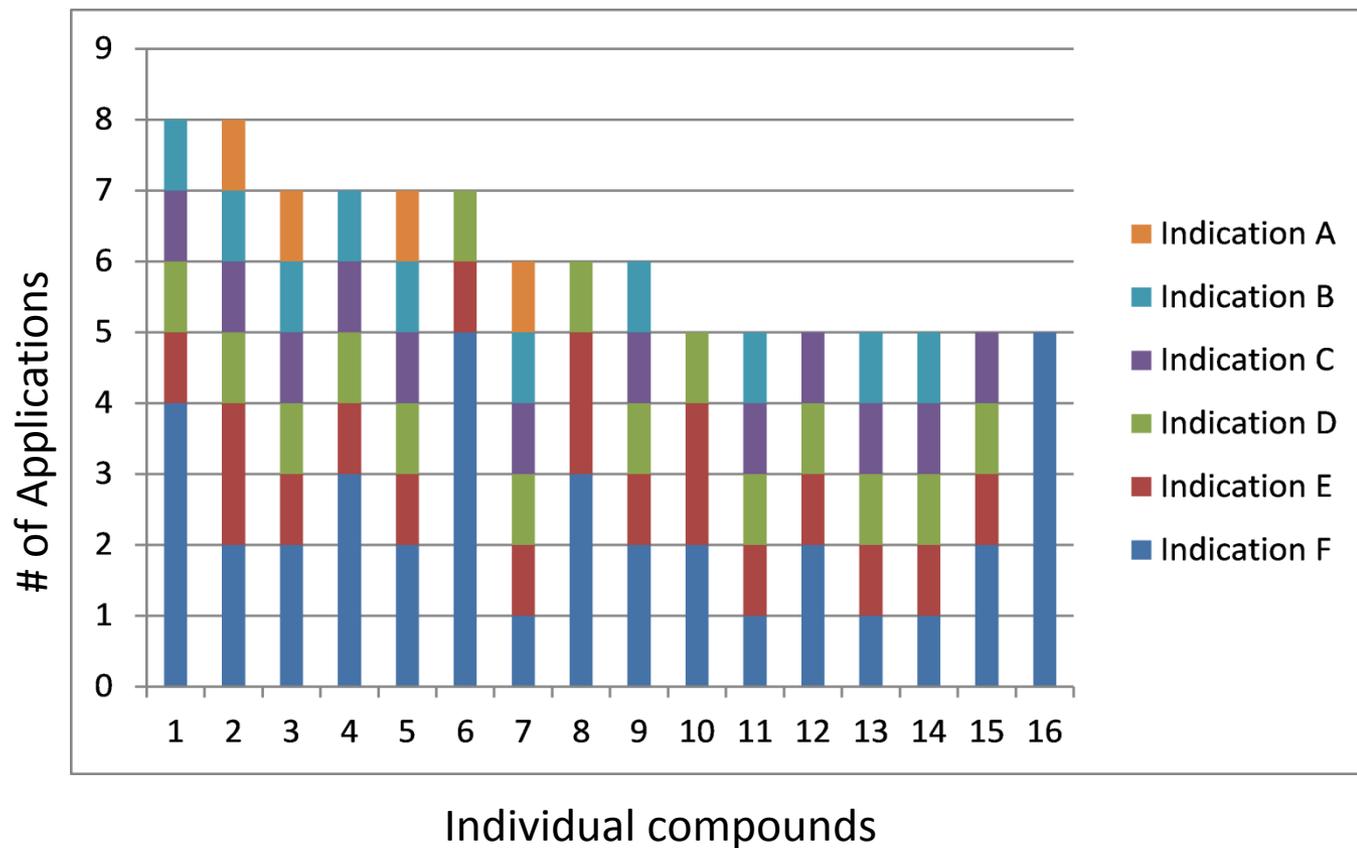


# The Table of Compounds and Biologics

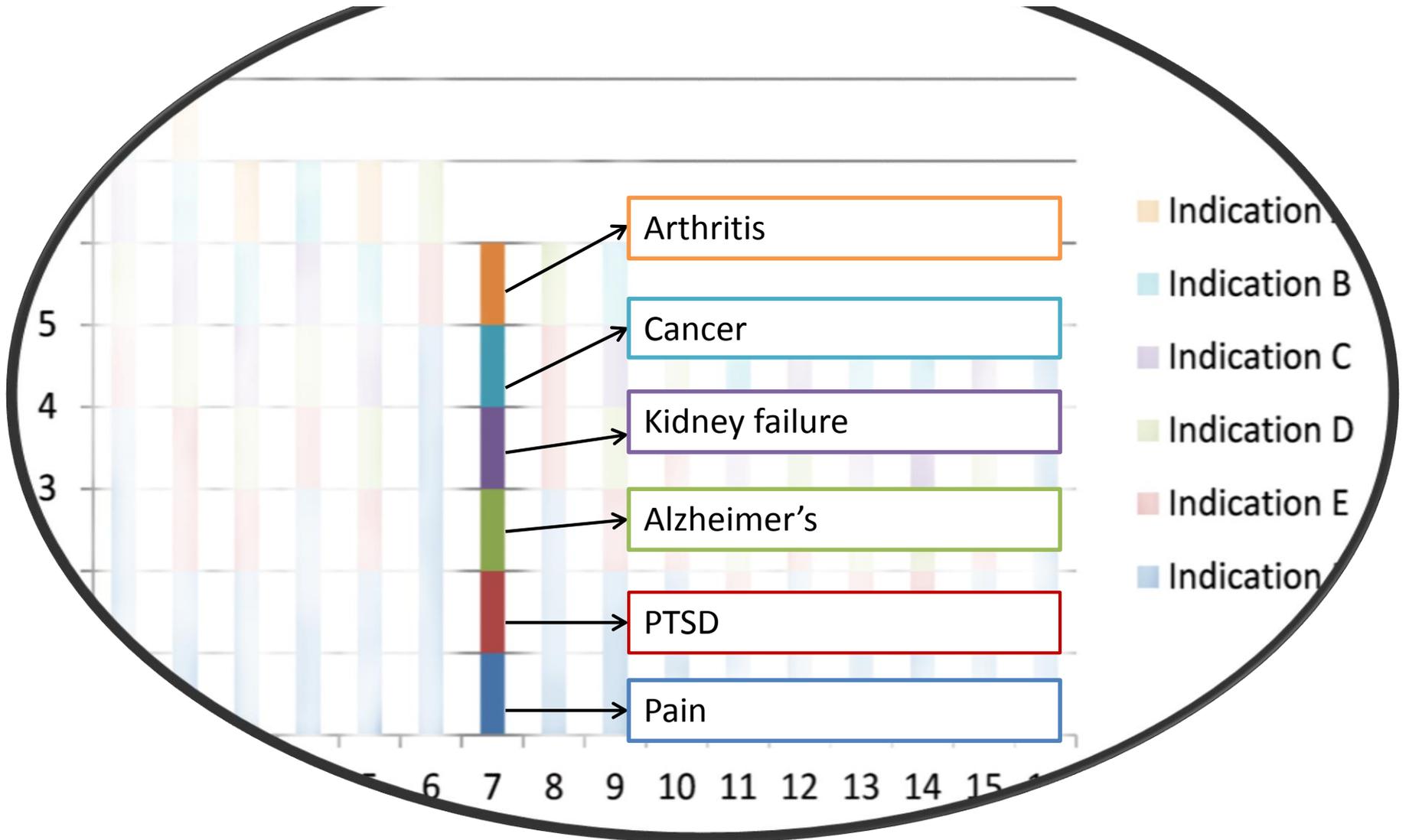
Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant <sup>†</sup> )
Compound 1	MoA1	Hypercholesterolemia	Oral
Compound 2	MoA2	Maintenance of sinus rhythm in atrial fibrillation patients Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator	Oral
Compound 3	MoA3	Sickle cell disease Asthma	Oral
Compound 4	MoA4	Pain	Oral (Yes)
Compound 5	MoA5	Obesity	Oral (Yes)
Compound 6	MoA6	Osteoarthritis pain	Oral (Yes)
Compound 7	MoA7	Asthma Chronic obstructive pulmonary	Oral
		Chronic	



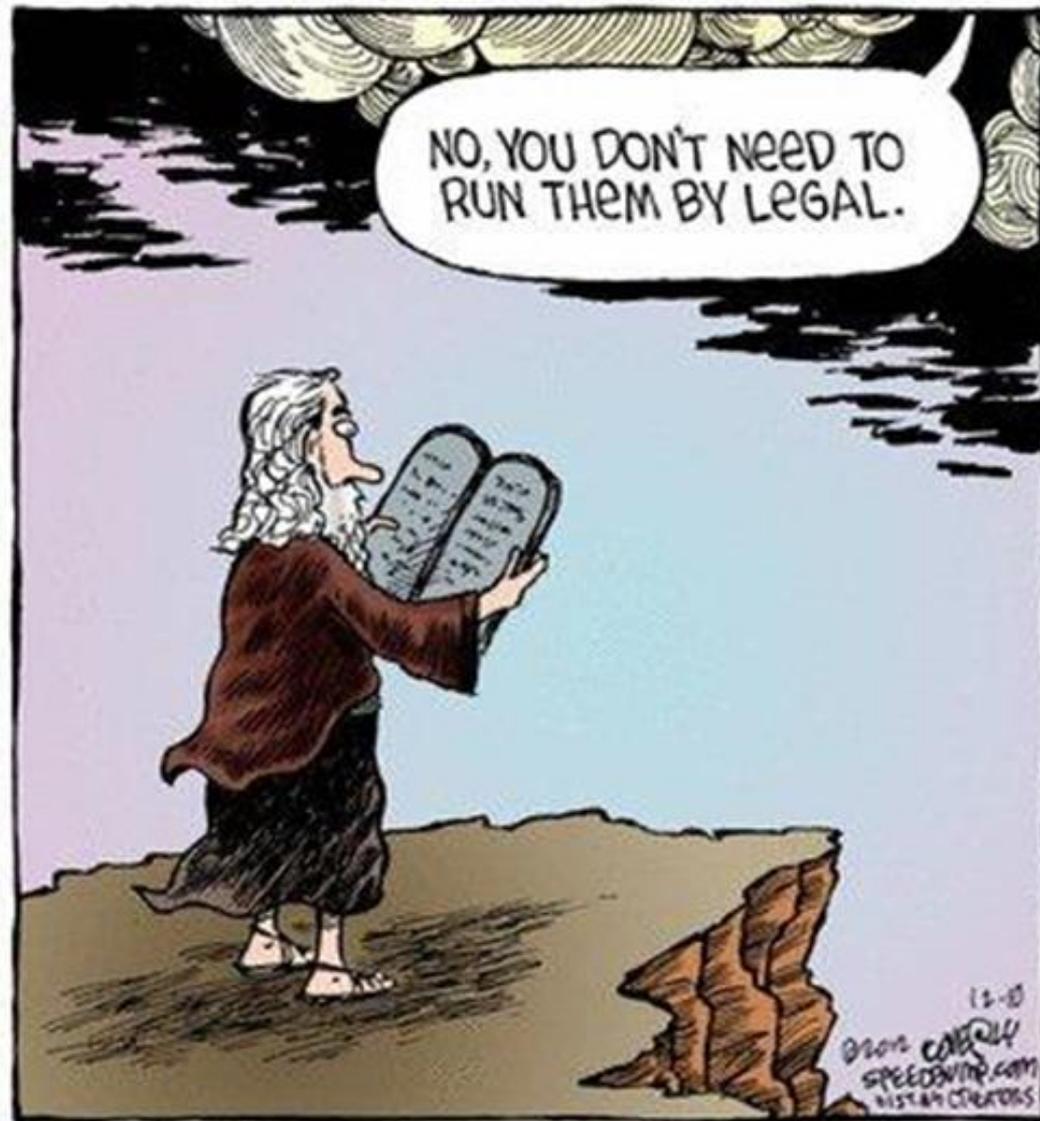
# Impact of Crowdsourcing



# Impact of Crowdsourcing



# 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), Lymphangiomyomatosis (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

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