Illuminating the Druggable Genome (IDG)

NCATS Advisory Council and CAN Review Board Meeting
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Illuminating the Druggable Genome

Shedding Light on the Dark Corners of the Genome
IDG Team

Chairs
• Christopher Austin, NCATS
• Griffin Rodgers, NIDDK

Coordinators
• Aaron Pawlyk, NIDDK
• Christine Colvis, NCATS

Project Team Leaders
• Yong Yao, NIMH (Tech Dev)
• Jean C. Zenklusen, NCI (KMC)

Project Scientists
• Ajay Pillai, NHGRI
• Margaret Sutherland, NINDS

External Scientific Panel
• Rommie Amaro, UCSD
• Andrew Hopkins, Univ. Dundee
• Peter Sorger, Harvard
• Dwight Towler, UT Southwestern

Working Group Members
• Mehdi Mesri, NCI
• Ravi Ravichandran, NCI
• Matt Reilly, NIAAA
• Antonio Noronha, NIAAA
• Dwayne Lunsford, NIDCR
• Kris Bough, NIDA
• Iddil Bekirov, NIDDK
• Colin Fletcher, NHGRI
• Zorina Galis, NHLBI
• Anne Zajicek, NICHD
• Miles Fabian, NIGMS
• J. Randy Knowlton, NCI
• Enrique Michelotti, NIMH
• Corinne Silva, NIDDK
• Gurusingham Sittampalam, NCATS
• Bobbi Gardner, NCATS
• Margaret Sutherland, NINDS
• Katerina Tsilou, NICHD
• Xin (Jean) Yuan, OPA
The IDG Challenge

The druggable genome

10% drugged

3,000 genes in the druggable genome – 90% not exploited!

Nature Reviews Drug Discovery, 2002

Box 1: Guidelines for oral bioavailability: the ‘rule-of-five’

The ‘rule-of-five’ analysis by Lipinski et al. shows that poor absorption or permeation of a compound occurs more likely when there are more than five hydrogen-bond donors, the molecular mass is more than 500 Da, the lipophilicity is high (expressed as LogP > 5), and the sum of nitrogen and oxygen atoms is more than 10. These rules, more appropriately described as guidelines, do not cover drugs that are derived from natural products, for which other absorption mechanisms are involved.

Clearly, published data on the oral bioavailability of existing drugs could be used as a method for defining the properties of viable drugs; however, our approach using the rule-of-five allows predictions to be made. In practice, the number of targets identified by applying the rule-of-five filter differs little from that obtained solely by literature analysis of all known drugs, whether orally active or not.
IDG - Pilot Phase (August 2014-August 2017)

IDG Pilot Phase Goals:
• Develop ability to identify, classify, and **prioritize understudied proteins** (G-protein coupled receptors, ion channels, protein kinases, & nuclear receptors)
• Demonstrate **scalability of technologies** needed for large-scale illumination

Knowledge Management Center (FY14-16)
• Integrate existing data and make it searchable through a single portal
• Define current state of knowledge/ignorance
• Prioritize proteins for illumination

Scalable Technology Adaptation (FY14-16)
• Medium- to high-throughput, scalable assays to explore function of protein families
• New tools to facilitate experiments at needed scale

Strong interest from pharma. Seven pharmaceutical companies attended our consortium meeting in March 2016
IDG - Implementation Phase Funding Opportunity Announcements

Coming this fall

1) Expand the informatics tools developed in the pilot phase to include additional data and allow users to access a wide range of information on sets of proteins;

2) Elucidate the function of understudied proteins from key druggable protein families; and

3) Disseminate the IDG-generated resources and data to the greater scientific community.