Published Kinase Inhibitor Set (PKIS): Catalyzing chemical biology through strategic compound sets

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Justin’s Buddies: Inspiration to persevere
“There are two kinds of people and organizations in the world: eaters and bakers. Eaters want a bigger slice of an existing pie; bakers want to make a bigger pie. Eaters think that if they win, you lose, and if you win, they lose. Bakers think that everyone can win with a bigger pie.”

Drug discovery needs to change

Figure 1 | Large pharma productivity from 2005-2010. Combined FDA-approved NMEs versus R&D spending for nine large pharmaceutical companies (AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche and Sanofi-Aventis). Figures shown are in millions of US dollars. Source: FDA CDER; Bernstein1. NME includes biologicals and vaccines.
Phase II attrition is significant

→ Initial target selection is a key determinant of success

Bunnage Nature Chemical Biology 2011, 7, 335
Kinases: important, tractable drug targets

- A family of enzymes which transfer the $\gamma$-phosphate of ATP
  - $>500$ in the human genome
  - Key regulators of cellular physiology and pathology

- Conserved catalytic domain
  - Bind ATP and substrate
  - Ca. 180 different kinases have x-ray structures in PDB

- Well-precedented as drug targets
Kinase inhibitors help patients

- **Imatinib**
  - 2001
  - CML, GIST

- **Gefitinib**
  - 2003
  - NSCLC

- **Sorafenib**
  - 2005
  - Renal cell carcinoma
  - Liver cancer

- **Erlotinib**
  - 2005
  - NSCLC
  - Pancreatic cancer

- **Sunitinib**
  - 2006
  - RCC, GIST

- **Dasatinib**
  - 2006
  - CML, ALL

- **Nilotinib**
  - 2007
  - CML

- **Lapatinib**
  - 2007
  - Breast cancer

- **Pazopanib**
  - 2009
  - RCC

- **Crizotinib**
  - 2011
  - NSCLC

- **Vandetanib**
  - 2011
  - Thyroid cancer

- **Vemurafenib**
  - 2011
  - Melanoma

- **Ruxolitinib**
  - 2011
  - Myelofibrosis

- **Axitinib**
  - 2012
  - RCC

- **Bosutinib**
  - 2012
  - CML

- **Tofacitinib**
  - 2012
  - Rheumatoid arthritis
The (Orphan) Human Kinome

Inhibitors for one kinase can be useful as starting points to develop inhibitors of other kinases.

- heat map showing 203 kinases against 577 compounds
- non-selective compounds: bright vertical bands
- kinases frequently inhibited by many different compound: horizontal bright bands
Chemically Connected System: Why it works

- ATP site - conserved but **not** optimized for ATP
- large database of structures allows for:
  - greater understanding of key pharmacophores and SAR
  - improved homology models
  - novel template design

- Exploit unique features of ATP site to achieve potency and selectivity
How do we seed orphan kinome research?

- *Proposal*: Define and release an open access set of kinase inhibitors
  - ID probes or chemical starting points for probe generation
  - ID interesting phenotypic profiles/kinases for therapeutic targeting
  - Engage a diverse range of experts

- Why should we share compounds?
  - Mitigate risk: include only published compounds
  - Mitigate cost: include only materially available compounds
  - Enable an *innovative network of experts*
  - Open the door for future collaboration
GSK Published Kinase Inhibitor Set (PKIS)

- **Set design**
  - 367 inhibitors published by GSK
  - >20 chemotypes
  - At the start: limited annotation across <50 kinases

- **Availability**
  - Solutions in screening quantities available to any academic investigator
  - Investigators required to make data publicly available
  - [https://www.ebi.ac.uk/chembl/](https://www.ebi.ac.uk/chembl/)

- **Contacts**
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PKIS2

- 541 new compounds from 61 GSK publications
- Features expansion of some chemotypes and addition of new chemotypes
- series made for kinases including AKT, ALK5 (TGFBR1), CDKs, EGFR, ErbB2, GSK3beta, IKK2 (IKK beta), IKK epsilon, MSK1, P38 alpha, PDK1, PERK, PI3K beta, PLK1, bRAF (V600E), ROCK1, SYK, TIE-2, VEGFR2
PKIS Kinome Coverage (Nanosyn)

- PKIS screened at 100 nM and 1 μM
- PKIS has activity across the TKs and non-TKs
- Potent inhibitors were found more often against the TKs
- PKIS had activity on 127/131 non-TKs

367 Inhibitors

- >10 μM
- 0.1-10 μM
- <0.1 μM
Potential BRSK2 starting point

• BRSK2 expressed in brain and required for neuronal polarization; regulation of neurotransmitter release
• SAR between BRSK2 and PLK1 appears divergent (at least some differences)
Chordoma cell line screening at University College London

Overview of the screening flow using the Incucyte platform for measuring cell growth
Example plate screen: UCH1 Plate 4 (JOOB68K)

**Hits**

A4  GW680191X  
D1  GW779439X  
D4  GW780056X  
D7  GW810576X  
G3  GW784684X  
A10 GW282974X
Chordoma cell line growth inhibition

- treatment with 1 uM compound
- effect on cell proliferation obtained by imaging the cultures using the automated Capture of phase-contrast images using the Incucyte FLR imaging platform
Example: GSK571989A

100 nM

PLK1, TTK, NEK9, LOK

related compounds:
GSK579289A (plus BRSK2); GSK237701A (PDGFRα, PDGFRβ)

GSK571989A; GSK579289A; GSK237701A: UCH1 and UCH2
GSK317314A; GSK978744A; GSK326090A (also ARK5): UCH2
GW568377A: ERBB2 / EGFR chemotype

EGFR, ERBB2

GW621823A

EGFR, ERBB2, ERBB4

Related compounds:
GW282449A; GW680191X; GW784684X; GW282974X; GW576609A; GSK259178A
GSK2186269A (UCH1): series made for IGF1R

GSK2110236 (UCH2): INSR, IGF1R, IRR, LTK, TSSK1, PLK, ALK, ROS, FER, PYK2, FES

GSK2110236 (UCH2): INSR, IGF1R, IRR, LTK, TSSK1, PLK, ALK, ROS, LRRK2, FER, FES, PYK2, TSSK2, FMS
Also: GSK2163632A (UCH2)
Pilot study: PKIS against UCH-1 and UCH-2
An evolving new model

High quality chemical probes and strategic compound sets made available to academia without restriction

→

The academic community generates and publishes deeper knowledge on more targets

→

Pharma and Biotech select best targets with greater probability of Phase II success

→

Industry competes to identify the best drugs for well-validated targets

Open, precompetitive innovation

Closed, proprietary innovation

Adapted from Mark Bunnage, Pfizer
Closing thoughts

- The commercial pressure on pharmaceutical drug discovery presents an opportunity to reorganize basic research
- **sharing compounds through PKIS** is an experiment in open science to aid preclinical validation of pharmacologic targets
  - Created PKIS, a set of 367 kinase inhibitors
  - Obtained activity map vs. 220 kinases
  - Engaged 100+ collaborators (and growing)
  - PKIS2 created (541 compounds), being rolled out
  - Laid foundation for broader effort on kinome probe generation
  - Have initiated experiments with chordoma cell lines to identify active chemotypes and useful targets
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A growing list of collaborators!
Thank you! Questions?
PKIS publications

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Exemplars from PKIS

**Akt**
- Akt1: 6 nM
- Akt2: 200 nM
- Akt3: 22 nM

**Cellular proliferation**
- LNCaP: 0.3 μM
- HLF: > 30 μM

**Kinase**
- p38α IC₅₀ values range from 100 nM to 10 μM
- Cellular activity and pharmacokinetic properties described

**p38a**

**PLK**
- 10 PLK inhibitors
- Variation at 3 sites
- PLK activity from 10 nM to > 1 μM

**ROCK**

**VEGFR2**