Open Access

& GSK's Published PKIS

Literature Presentation
Anne Kornahrens
21 May 2013

General | RCUK Policy | University position on OA | The OA spectrum | Green OA | Funding & APCs

Am I affected? | Data | Help | Misc

+ I'm not currently funded by RCUK. Does this apply to me?

+ Are the open-access publishing rules the same for work funded by the Department of Health as for work funded by Research Councils?

− If you are a DPhil student who is funded by a research council and you publish work before submitting your thesis does it have to be OA?

Yes.

+ Are theses subject to research funder Open Access policies?

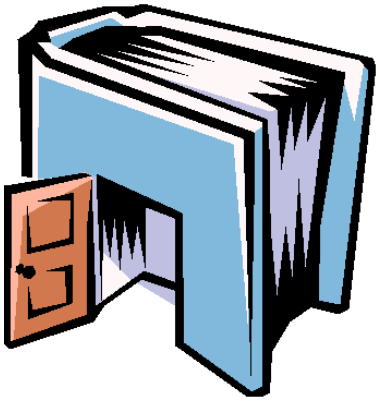
+ Many science/medicine research groups will publish a number of papers from one piece of work. Will this new policy result in longer papers and will the publishers charge more for longer papers with more data attached?

+ If someone is an AHRC-funded doctoral student but this is not tied to a specific piece of work, does this make all their publications RCUK-funded for the purposes of this exercise?

Open Access

"Open-access (OA) literature is digital, online, free of charge including for those who do not have personal or institutional subscriptions to journals, and free of most copyright and licensing restrictions. What makes it possible is the internet and the consent of the author or copyright-holder."

From Open Access Oxford



- Two routes for achieving OA:
  - Green OA: self-archiving, meaning authors publish in any journal and then self-archive a version of the article for free public use in their institutional repository a central repository (such as Oxford Research Archive (ORA), Europe PMC, the ESRC Research Catalogue, or ArXiv). It is subject to copyright or other restrictions that may be set by the journal
  - Gold OA: publishing in an open access journal that provides immediate OA to all of its articles on the publisher's website, possibly necessitating an Article Processing Charge (APC)

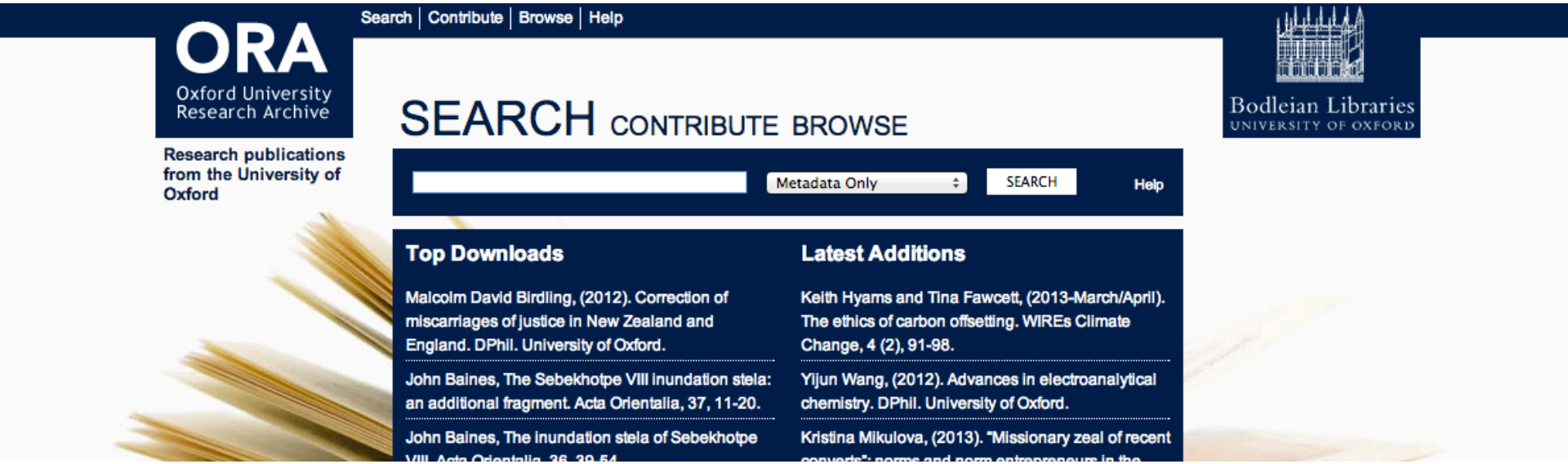
Open Access at Oxford

- The Working Group on Expanding Access to Published Research Findings ('Finch Group') was set up in October 2011 to examine how UK-funded research findings can be made more accessible.
- The Government announced on 16 July 2012 that it accepted the recommendations of the Working Group
- From 1 April 2013, the new Research Council UK policy on Open Access has come into effect
- Requires that peer-reviewed research articles that are publicly-funded achieve satisfactory open-access levels
    - Both "gold" and "green" routes are acceptable, though Oxford recommends "green"
    - Can deposit in ORA only if journal allows
    - RCUK is funding OA efforts through block funds, mostly to cover APCs
    - Support use of Creative Commons license to allow easier access to published work within the framework of copyright laws.

Ref: Open Access Oxford, *Statement on Open Access at the University of Oxford* **11 March 2013** (http://creativecommons.org)

Oxford Research Archive

- Established in 2007, the Oxford Research Archive contains research publications and other research output produced by members of the University of Oxford.
- Includes copies of journal articles, conference papers, working papers, theses, reports and other types of scholarly research publications. The full text of many of these items is freely available.



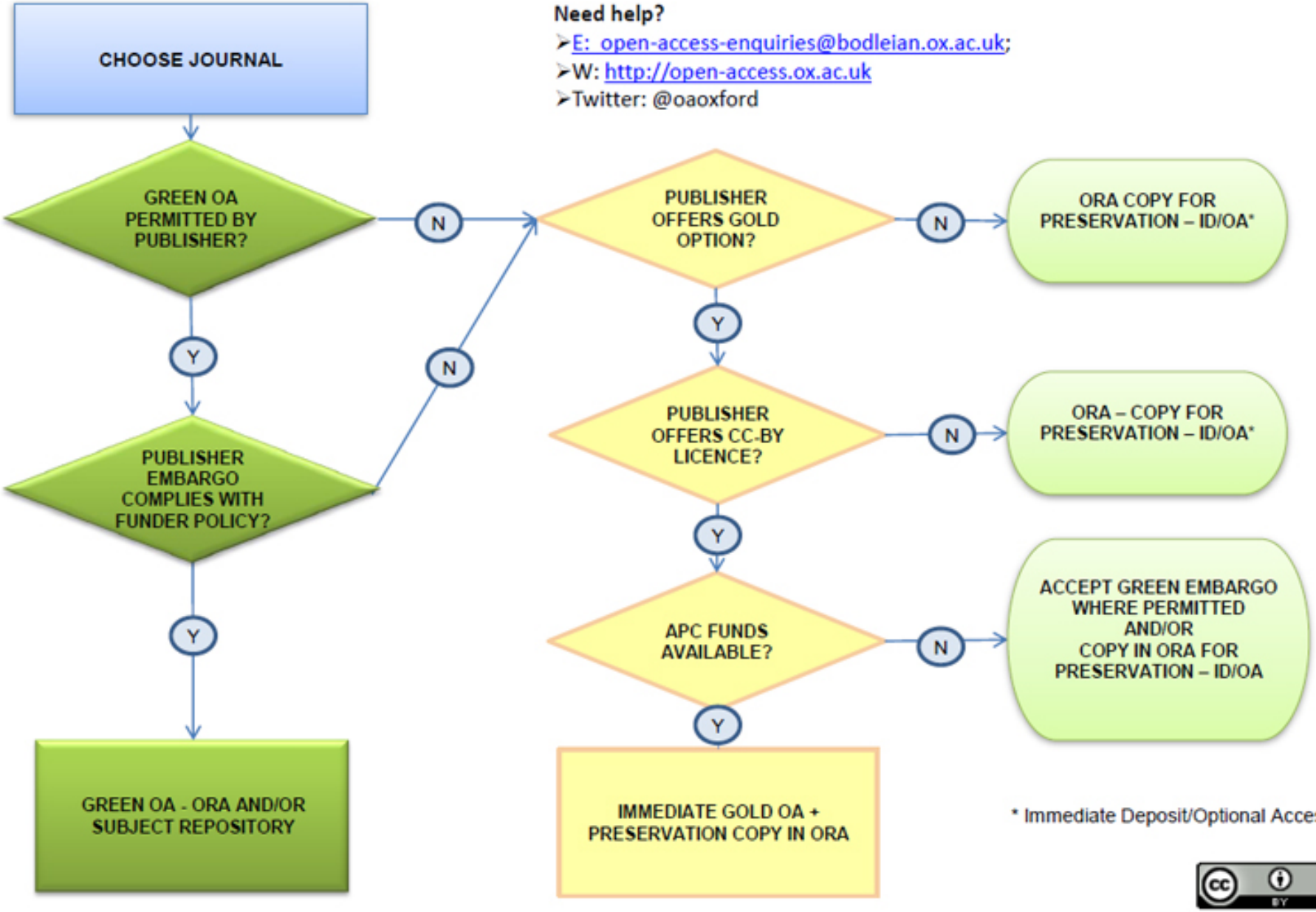
Researcher Decision Tree – 'Green' or 'Gold'?

How to meet the UK Research Councils' requirements on Open Access

open access oxford
Expanding the possibilities

Need help?

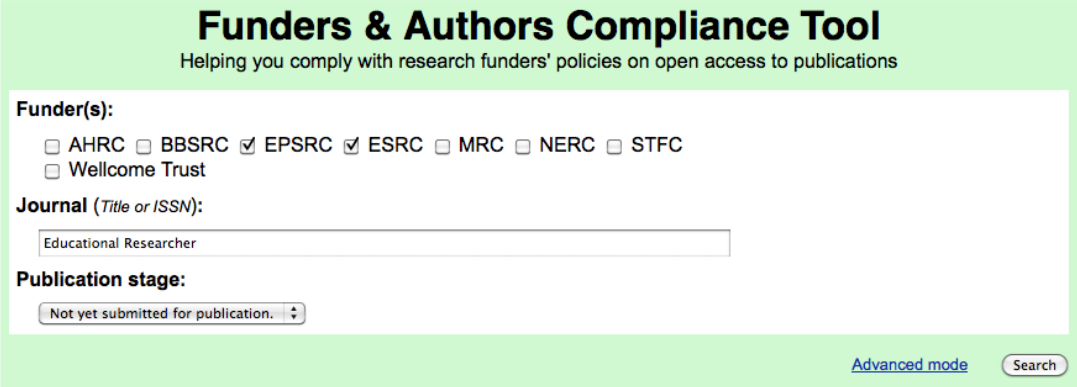
- E: open-access-enquiries@bodleian.ox.ac.uk;
- W: http://open-access.ox.ac.uk
- Twitter: @oaoxford



* Immediate Deposit/Optional Access

Case Study

- Consult “Gold or Green” rules
- Check journal compliance (http://www.sherpa.ac.uk/fact/) and determine embargo period (maximum 6 months for EPSRC)
- Can pay for “gold” route (immediate OA, for about £8000-16000)
- Instead, use Creative Commons Attributions License (depending on publisher)
- Apply for APC funds from OA Block Grant
- Also put into Oxford Research Archive



http://openaccess.ox.ac.uk/wp-uploads/2013/05/Ed-Res-Case-study_Open-Access.pdf

OA Issues

- Loss of commercial revenue to publishers through sale of reprints – (especially significant for some biomedical journals)
- Unwillingness of third-parties to allow their material to be reproduced in research papers that are licensed using CC BY;
- More easily enabling misattribution, misquoting, misrepresentation, plagiarism, or otherwise referencing material out of context, which may be damaging to the interests of authors.
- Concern that researchers will be encouraged to publish in cheaper journal
  - Oxford pushes for continued freedom to publish where you choose

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Expand Subject Tree

Subjects › Chemistry › Organic Chemistry

Browse results: Found **14**

Listing **1** - **14** of **14**

ARKIVOC - Online Journal of Organic Chemistry

Journal

ISSN/EISSN: 15517004 15517012
Publisher: Arkat USA Inc
Subject: Organic Chemistry
Country: United States **Language**: English
Start year 2000
Publication fee: No --- Further Information

Open Access Chemistry Journals

Broader Context

"Drug discovery resources in academia and industry are not used efficiently, to the detriment of industry and society. Duplication could be reduced, and productivity could be increased, by performing basic biology and clinical proofs of concept within open access industry-academia partnerships."

- Lack of understanding of disease mechanisms and issues of competition lead to less efficient drug discovery!
- Argument for drug target validation performed in a "precompetitive environment"
- Example of a partnership towards Epigenetic signaling—Structural Genomics Consortium (SGC), the Universities of Oxford and Toronto, the US National Institutes of Health (NIH) Chemical Genomics Center, GlaxoSmithKline and a network of academic collaborators—systematically generating the chemical probes based on extensive number of protein families

Aled M Edwards, Chas Bountra, David J Kerr & Timothy M Willson. Open access chemical and clinical probes to support drug discovery. *Nature Chemical Biology* **5**, 436 - 440 (**2009**)

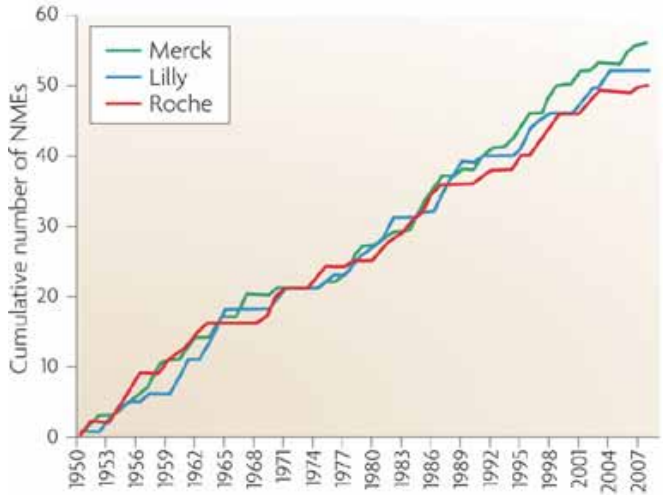
GSK Published Protein Kinase Inhibitor Set

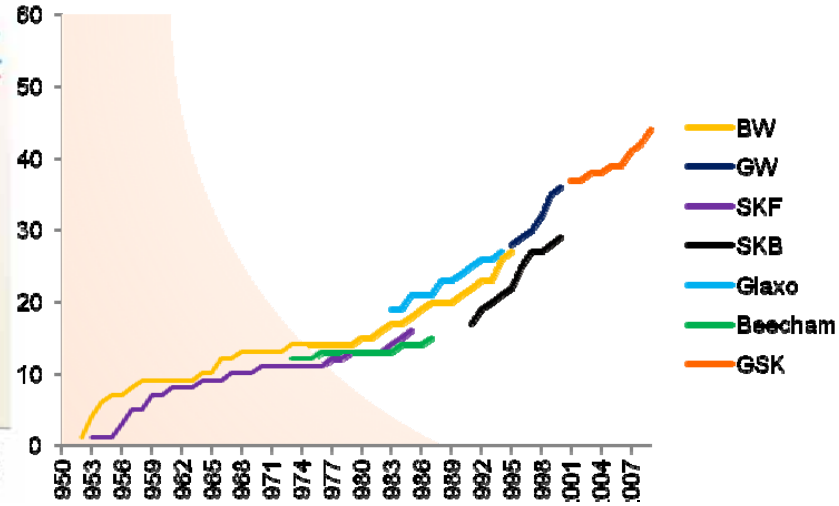
- GSK has made 367 compounds available to academic investigators
- Data on these bioactive molecules through ChEMBL
- Researchers must make their findings publicly available
- To enable better collaborations and more research into the kinome (classically known and “orphan” targets)
  - Previous research done with the SAME targets (<10% of genome) when there are many without known activity/ markers
- Database will be expanded as further compounds and additional screening data are added

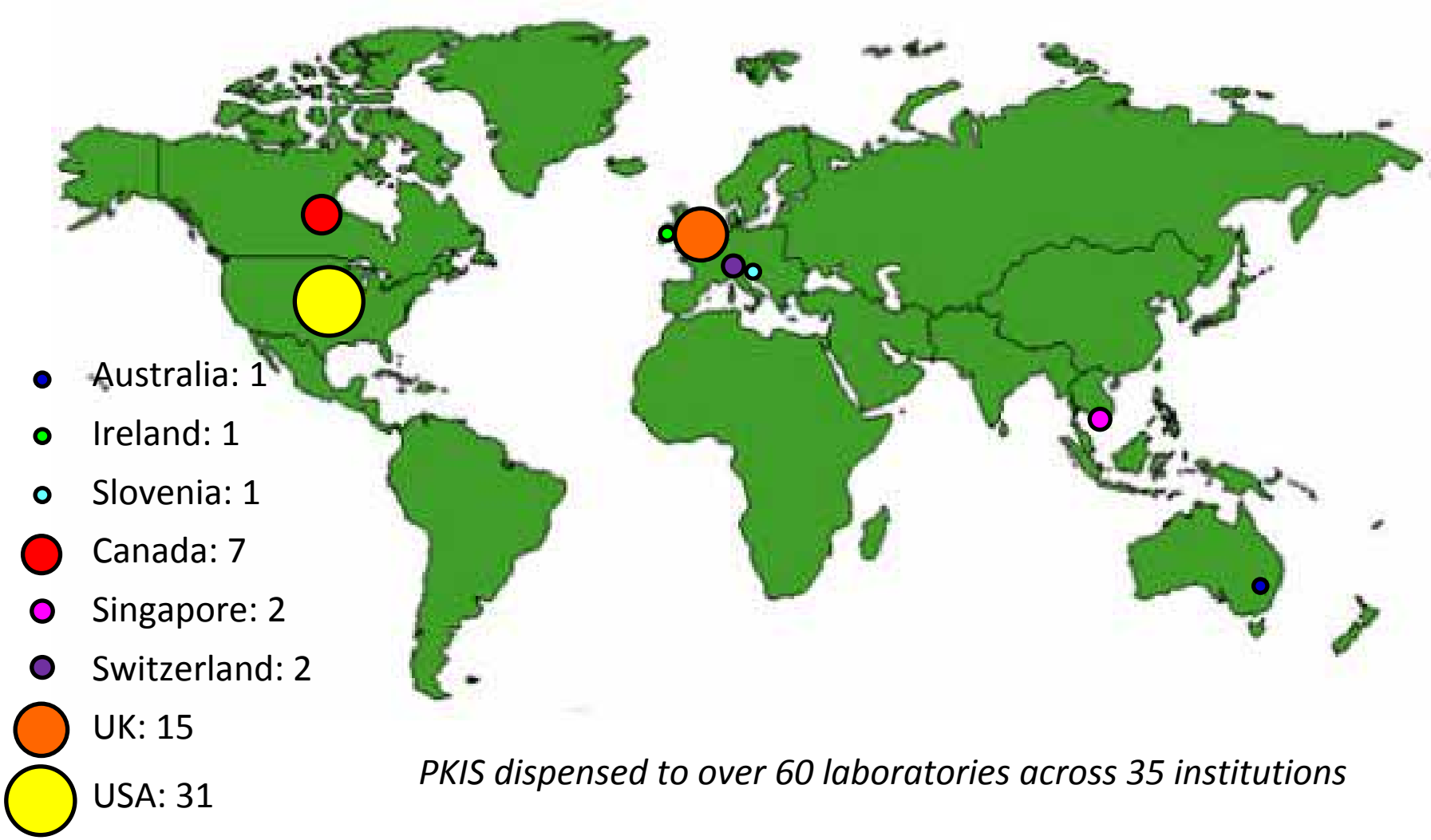
David Drewy and Bill Zuercher, The Published Kinase Inhibitor Set: A resource to develop probes for the untargeted kinome, *2nd RSC Symposium on Chemical Biology for Drug Discovery*

Goals

- Chemical probes freely available to the scientific community
- Precompetitive publicly-funded endeavor for the benefit of society
- Identification of new molecular targets for drug discovery







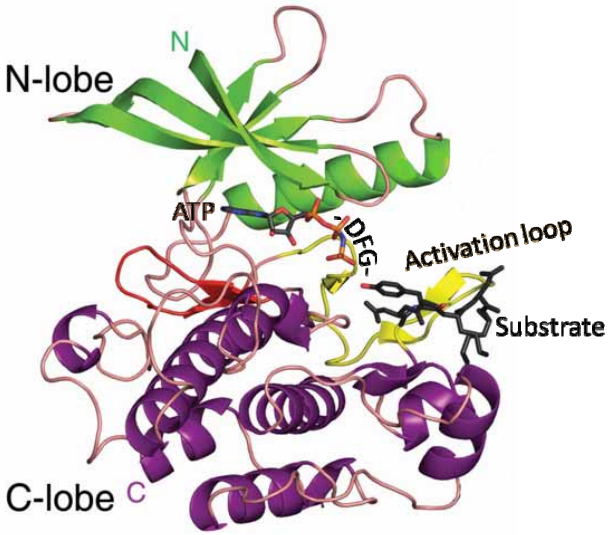
PKIS dispensed to over 60 laboratories across 35 institutions

PKIS Library

- GSK has 2 marketed drugs based on kinases and >100 publications describing 1000s of compounds

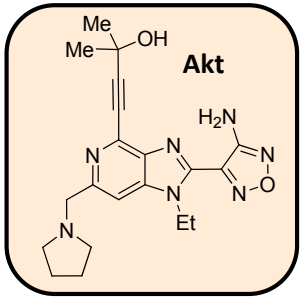
- Compound selection
  - Must be published and materially available in house
  - Removed clinical compounds
  - Reduced over-representation of kinases and chemotypes
  - Maximized potential for broad kinome coverage

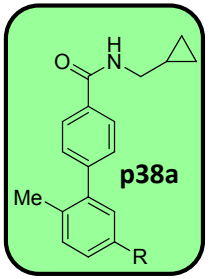
- Initial activity results
  - NANOSYN Microfluidics Assay
  - Activity-based assay performed at UNC
  - Dual assay at 1.0 and 0.1 μM



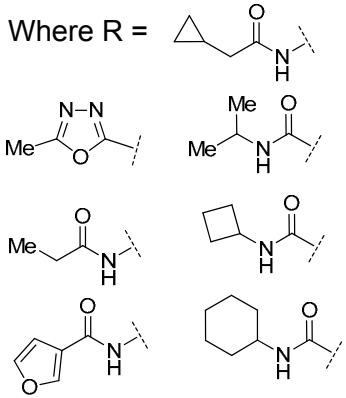
cAMP-dependent protein kinase (PKA)

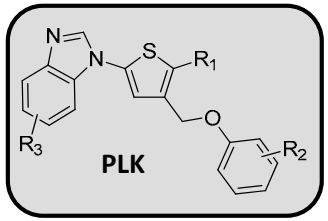
Exemplars from set





Where R =





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

<u>Kinase</u>

Akt1: 6 nM

Akt2: 200 nM

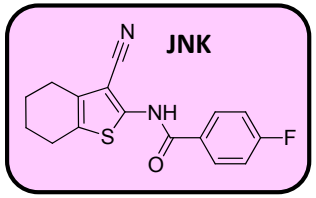
Akt3: 22 nM

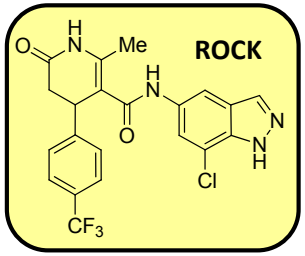
<u>Cellular proliferation</u>

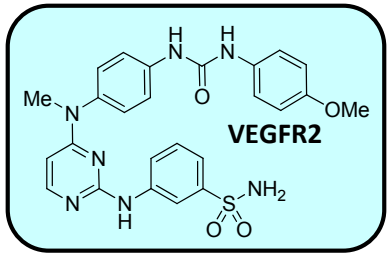
LNCaP: 0.3 μM

HLF: > 30 μM

- p38α IC_{50} values range from 100 nM to 10 μM
- Cellular activity and pharmacokinetic properties described



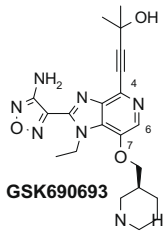


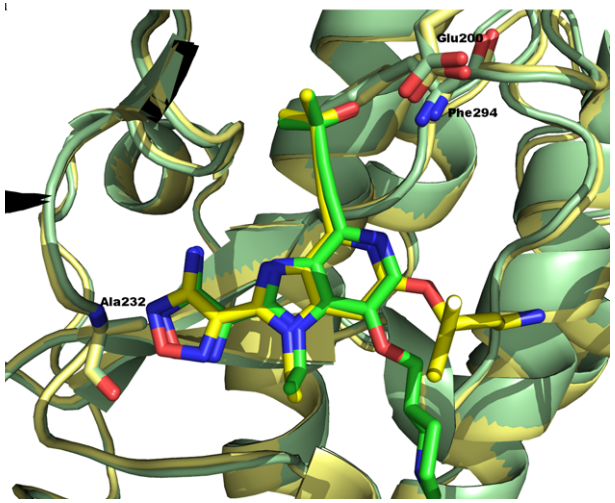


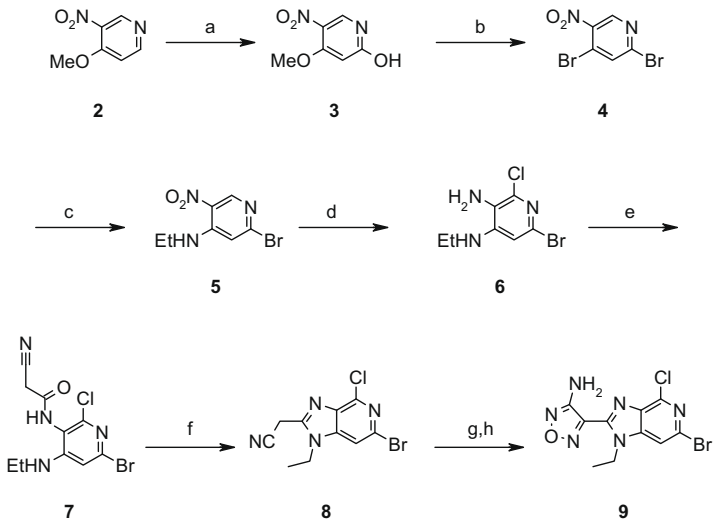
Akt: *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1508.
p38α: *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428.
PLK: *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1018.
JNK: *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1296.
ROCK: *J. Med. Chem.* **2007**, *50*, 6.
VEGFR2: *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3519.

AKT Inihibitor

- GSK690693 developed and underwent clinical trials as intravenous (iv) agent





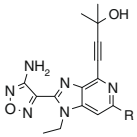


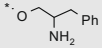
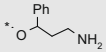
Scheme 1. Reagents and conditions: (a) KO^{t}Bu, ^{t}BuOOH, NH_3, THF, 70%; (b) $POBr_3$, MeCN, 66%; (c) $EtNH_2$, MeOH, THF, 95%; (d) $SnCl_2$, HCl, 60%; (e) cyanoacetic acid, EDC, NMM, DMF, quant.; (f) AcOH, 100 °C; (g) $NaNO_2$, AcOH, 85%; (h) NH_2OH, Et_3N, H_2O, 51%.

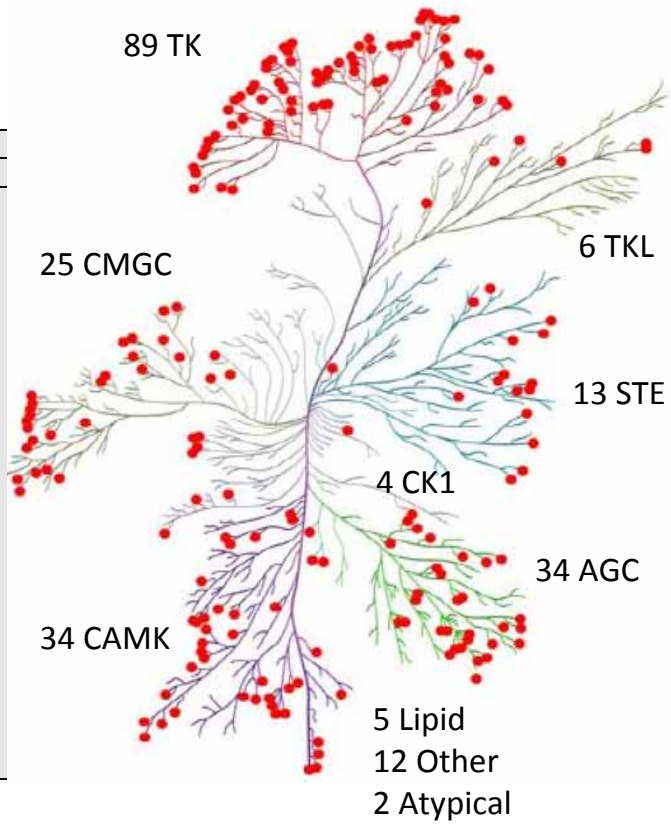
Bioorganic & Medicinal Chemistry Letters 19 (2009) 1508–1511

Activity Studies

Table 1
SAR for C-6 side chain modifications; compounds **14**–**33**[c,d]



Entry	R	Kinase (IC_{50} nM, [K_i^*])[15]				Cellular activity (IC_{50} nM)		
		Chirality	AKT1	AKT2	AKT3	GSK3β[a]	BT474[b]	LNCaP[b]
GSK690693	–	–	2 [1]	13 [4]	9	138	69	21
14	$-CH_2NH_2$	–	6	63	70	1020	806	296
15	$-(CH_2)_2NH_2$	–	4	25	NT	4000	1090	2020
16	$-(CH_2)_3NH_2$	–	3	40	30	13,200	3520	4720
17	$-CH_2NHCH_3$	–	3	16	NT	303	439	201
18	$-CH_2N(CH_3)_2$	–	2	25	NT	375	357	114
19		–	6	200	22	2700	1250	313
20	$-O(CH_2)_2NH_2$	–	5 [6]	40 [39]	43	1140	1080	497
21	$-O(CH_2)_3NH_2$	–	16 [115]	200 [646]	NT	30,000	7120	3180
22	$-O(CH_2)_4NH_2$	–	63	316	NT	30,000	20,000	6160
23	$-O(CH_2)_2NHCH_3$	–	12	79	NT	2600	3190	896
24		R	8	50	NT	400	860	220
25		S	13	63	NT	1210	4860	560
26		R	3	20	17	1110	2100	124
27		S	5	20	49	1040	3440	176
28		R	0.6 [0.2]	10 [2]	3	80	742	20
29		S	3	20	NT	310	1500	101
30		R	1 [0.4]	25 [5]	1	40	35	27
31		S	3 [3]	25 [17]	NT	190	124	68
32		S	2 [0.2]	16 [1]	NT	41	1	5
33		R	4 [1.9]	50 [105]	65	1570	224	85



GSK PSIK Issues

- Lack of interest, inertia
  - Many more compounds out there and much more biological data available
- Risk of leaking projects
  - Needs to be maintain in public domain
  - Use only published material
  - Limited by competitiveness and secrecy
- Need more probes and assays
  - Frequently targeted to the relatively few proteins that have already been the focus of industrial drug discovery efforts
  - Probes are nonselective, inadequately characterised and used inappropriately by the research community
- Combine the innovation of academia with infrastructure of industry
  - Chemical probes are not widely available because they are difficult to produce without access to skilled medicinal chemists
- Two examples each a specific type of activity-possibility for a broader effect?