Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Developing novel cancer therapeutics that inhibit the enzyme PKB

1. Summary of the impact

Protein kinase B (PKB), also known as AKT, is an enzyme in the PI3 kinase/mTOR intracellular signalling pathway, which is found to be deregulated in many forms of cancer. Professor David Barford's team at the ICR solved the crystal structure of PKBβ using innovative protein engineering and licensed six international pharmaceutical companies with reagents to enable them to begin PKB drug discovery programmes. The ICR also initiated its own PKB drug discovery programme: two series of inhibitors were developed that were licensed to AstraZeneca and Astex and are now both in clinical trial. The ICR's work helped to establish PKB as a valid cancer therapeutic target. The ICR is involved in clinical research studies of multiple PI3 kinase and PKB inhibitors, and this research has led to the definition of useful clinical pharmacodynamic biomarkers.

2. Underpinning research

Professor David Barford (ICR faculty member, UoA5) and his team published the results of research, conducted between 1999 and 2002, in collaboration with a team at the Friedrich Miescher Institute, on the crystal structure of the enzyme PKBβ (also known as AKT2, (Yang et al, 2002, Nat. Struct. Biol. 9, 940-944)). PKB was known to be a key enzyme in the PI3 kinase/mTOR signalling pathway and is overexpressed, mutated and amplified in certain cancers and as such it was a potential target for anti-cancer drugs. Before the Barford team published the crystal structure of PKBβ, the development of inhibitors of PKB had been hindered by the lack of protein structural information.

Using the Barford crystal structure information, ICR Cancer Therapeutics teams led by Dr Michelle Garrett (ICR Faculty), Professor Paul Workman (ICR Faculty), Dr Ian Collins (ICR Faculty) as lead chemist and Dr Suzanne Eccles (ICR Faculty), began an in-house drug discovery research programme in 2002, which in 2003 became a collaboration with the UK company Astex Pharmaceuticals, and used their virtual screening technology and high throughput crystallography technology. The programme aimed at finding ATP competitive inhibitors of PKB.

Two fragment hits from the PKB virtual screen were elaborated using structure-based design and chemistry based on the Barford protein structure information. The chemistry research was a collaboration between the ICR and Astex Pharmaceuticals with Collins taking a lead role for the ICR, which undertook half the medicinal chemistry research on this project. The majority of the biological research studies were undertaken at the ICR, and these helped to validate PKB as a potentially useful oncology target. Each of the two hits led to the identification of a lead chemical series, and a number of publications resulted (Refs 1-4). One chemical series (Refs 2-4) was licensed to AstraZeneca. The second series was retained by Astex Pharmaceuticals; this chemical series is distinct from the first as it has a broader specificity and inhibits other AGC kinases, which could contribute to anticancer activity (Ref 1). In particular it has potent Rho kinase activity and a biologically distinct profile.

The ICR and its partner institution The Royal Marsden NHS Foundation Trust (RM) has also contributed to the PKB field through its clinical research. The first PKB inhibitor to enter the clinic was the Merck product (MK-2206), an allosteric inhibitor; the ICR and the RM were involved in the Phase I studies of this compound (Ref 5). The ICR led the way in developing clinical pharmacodynamic biomarkers for monitoring target engagement and the response of patients to PKB inhibitors (Ref 5). These biomarkers measure if the target is being inhibited, demonstrating 'target engagement'. This research included the establishment of a novel method for monitoring PKB target engagement in hair (eyebrow) follicles and platelet rich plasma (PRP) as surrogate tissues, and was successfully implemented in multiple clinical trials (ref MK2206 trial, e.g. NCT00670488). Subsequently, both the hair follicle and PRP PD assays have been applied to Phase I clinical trials of multiple PI3 kinase and PKB inhibitors, including AZD5363 and AT13148,

which both arose from the ICR PKB drug discovery programme.

3. References to the research

All ICR authors are in bold and ICR team leaders/Faculty are in bold and underlined.

1. **Yap TA, Walton MI,** Grimshaw KM, **Te Poele RH, Eve PD, Valenti MR, de Haven Brandon AK, Martins V, Zetterlund A, Heaton SP, Heinzmann K,** Jones PS, Feltell RE, Reule M, Woodhead SJ, Davies TG, Lyons JF, **Raynaud FI, Eccles SA, Workman P,** Thompson NT, **Garrett MD**. 2012, AT1348 Is a Novel, Oral Multi-AGC Kinase Inhibitor with Potent Pharmacodynamic and Antitumor Activity, Clin Cancer Res. 18, 3912-3923. (http://dx.doi.org/10.1158/1078-0432.CCR-11-3313)
2. **Caldwell JJ**, Davies TG, **Donald A, McHardy T, Rowlands MG, Aherne GW, Hunter LK, Taylor K, Ruddle R, Raynaud FI**, Verdonk M, **Workman P, Garrett MD, Collins I**. 2008, Identification of 4-(4-aminopiperidin-1-yl)-*7H*-pyrrolo[2,3-*d*]pyrimidines as Selective Inhibitors of Protein Kinase B through Fragment Elaboration, J Med Chem. 51 (7), 2147-2157. (http://dx.doi.org/10.1021/jm701437d)
3. **Yap TA, Walton MI, Hunter LK, Valenti M, de Haven Brandon A, Eve PD, Ruddle R, Heaton SP, Henley A, Pickard L, Vijayaraghavan G, Caldwell JJ,** Thompson NT, **Aherne W, Raynaud FI, Eccles SA, Workman P, Collins I, Garrett MD.** 2011, Preclinical Pharmacology, Antitumor Activity, and Development of Pharmacodynamic Markers for the Novel, Potent AKT Inhibitor CCT128930, Mol Cancer Ther. 10, 360-371. (http://dx.doi.org/10.1158/1535-7163.MCT-10-0760)
4. **McHardy T, Caldwell JJ, Cheung KM, Hunter LJ, Taylor K, Rowlands M, Ruddle R, Henley A, de Haven Brandon A, Valenti M,** Davies TG, Fazal L, Seavers L, **Raynaud FI, Eccles SA, Aherne GW, Garrett MD, Collins I**. 2010, Discovery of 4-amino-1-(*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)piperidine-4-carboxamides As Selective, Orally Active Inhibitors of Protein Kinase B (Akt), J Med Chem. 53 (5), 2239-2249. (http://dx.doi.org/10.1021/jm901788j)
5. **Yap TA,** Yan L, Patnaik A, Fearen I, **Olmos D,** Papadopoulos K, **Baird RD**, Delgado L, Taylor A, Lupinacci L, **Riisnaes R, Pope LL, Heaton SP**, **Thomas G**, **Garrett MD**, Sullivan DM, **de Bono JS,** Tolcher AW. 2011, First-in-Man Clinical Trial of the Oral Pan-AKT Inhibitor MK-2206 in Patients With Advanced Solid Tumors, J Clin Oncol. 29 (35), 4688-4695. (http://dx.doi.org/10.1200/JCO.2011.35.5263)

Quality Indicators

Selected research grant support

1. Workman – "Cancer Research Campaign Centre for Cancer Therapeutics", 2001-2006, £22.5M, programme grant which included the PKB project
2. Workman – "Cancer Research UK Centre for Cancer Therapeutics", 2006-2011, £30.5M, programme grant which included the PKB project
3. Garrett – "PK/PD Analysis for AT13148 Development", Cancer Research UK Drug Development Office, 2012-2014, £157k; [additional funding related to AT13148 from CRUK DDO: 2009-2013, total £34k]

Prizes

1. American Association of Cancer Research Team Science Award 2012 for the team's (involving 16 ICR Faculty members) tremendous impact in preclinical and clinical studies relating to cancer therapeutics, which included the highly promising inhibitors of PKB/AKT. (http://www.aacr.org/home/scientists/scientific-achievement-awards/scientific-award-winners/team-science-award-.aspx)

4. Details of the impact

The ICR has made a major impact on the international search for inhibitors of PKB, a key signalling enzyme and a major target for the development of cancer therapeutics. This is a significant impact in enabling a number of pharmaceutical companies to advance their research programmes for the development and commercialisation of novel drugs. Currently seven novel PKB inhibitors are in clinical trial (ClinicalTrials.gov), two of which are from the joint ICR and Astex PKB drug discovery programme.

Impacts on health

Two distinct drugs discovered by ICR and Astex Pharmaceuticals are progressing through clinical trials in the UK and overseas; patients are benefiting by being able to participate in these trials.

ICR has discovered two series of PKB inhibitors in a collaborative research programme with Astex Pharmaceuticals. As a result, one series was licensed in a commercial agreement with AstraZeneca and the lead drug, AZD5363, is currently undergoing clinical trials at RM, The Christie (Manchester), the NKI (Netherlands) and in Japan, involving a total of over 400 patients (ClinicalTrials.gov Identifiers: NCT01226316, NCT01353781, NCT01625286, NCT01692262, NCT01895946) [1]. The ICR has led on the first trial of AZD5363 and Dr Udai Banerji (ICR Faculty, from 2007) gave an oral presentation at AACR 2013, summarising its exciting potential in the clinic and reporting for the first time clinical responses in patients whose tumours had *PIK3CA* and *AKT* mutations. This highlights the fact that this drug has potential applications in a wide range of solid tumours including breast and gynaecological cancers. Results of the first Phase I clinical trial of AZD5363 have reported both partial responses and stable disease in patients harbouring mutations in PIK3CA or AKT1. This therefore identifies these mutations as potential predictive biomarkers of response for AZD5363. The clinical development candidate from the second series, AT13148, which is being developed by Astex Pharmaceuticals, has biological properties distinct from other PKB inhibitors and could be useful in a different patient group. This drug is also in clinical trial at RM (ClinicalTrials.gov Identifier: NCT01585701, estimated enrolment 40 patients) [2].

Worldwide, clinical trials of PKB inhibitors are being facilitated by the ICR's work to define useful biomarkers and make protocols generally available.

The ICR was a key site in the first clinical studies of the Merck inhibitor MK-2206 (Research Ref 5 above) (ClinicalTrials.gov Identifier: NCT00670488) through its identification of clinical pharmacodynamic (PD) biomarkers to monitor PKB inhibition, thus facilitating all PKB programmes worldwide. In some cases these PD markers also have utility in trials of other drugs, such as PI3K inhibitors. Protocols have been made available for these biomarker assays. Companies that have licensed the protocols (for a fee) include Quintiles and Boehringer Ingelheim. So far, six international pharmaceutical companies have cited this key publication (Research Ref 5 above) in work describing their PKB inhibitor programmes (data from Web of Science) [3, 4].

Impacts on commerce

Two distinct drugs discovered by ICR and Astex Pharmaceuticals are being commercially developed.

The drugs AZD5363 and AT13148, derived from chemical series discovered by the ICR and Astex Pharmaceuticals, are being developed by AstraZeneca and Astex Pharmaceuticals, respectively. Both are in clinical trial. This has a commercial benefit to both these companies by adding to their development pipeline and therefore increasing shareholder value.

Results of the first Phase I clinical trial of AZD5363 have reported partial responses in patients harbouring mutations in *PIK3CA* or *AKT1*. This highlights the fact that these drugs have potential single agent activity in solid tumours. Multiple clinical trials of combinations of AZD5363 are currently ongoing and in planning to maximize its potential in a wide range of cancers.

As stated above, the international PKB drug discovery effort has been facilitated by the ICR's structural biology and pharmacodynamic biomarker studies. In addition to the benefit to patients, this has also had commercial impact, as a number of pharmaceutical companies have added PKB programmes to their pipelines. For example, since 2008 GSK has made a major investment into developing PKB inhibitors as novel therapeutics. Its lead product, GSK2110183, progressed into Phase II clinical trials in 2009.

Industry is investing in pre-clinical research and clinical research to develop PKB inhibitors in the UK (including at the ICR and RM) and overseas.
AstraZeneca and Astex Pharmaceuticals are investing in the clinical research of AZD5363 and AT13148 respectively by conducting clinical trials. These drugs are based on the chemical series discovered by the ICR. Companies such as GSK that have cited the ICR's underpinning research are investing in clinical research worldwide (ClinicalTrials.gov lists several GSK2110183 clinical trials eg: NCT01428492, NCT01531894, NCT01532700 and NCT01653912), and seven novel PKB inhibitors are now being developed.

5. Sources to corroborate the impact

[1] http://investor.astx.com/releasedetail.cfm?ReleaseID=663984

[2] http://investor.astx.com/releasedetail.cfm?ReleaseID=663805

[3] Sommer EM et al. 2013, Elevated SGK1 predicts resistance of breast cancer cells to Akt inhibitors, Biochem J. 452, 499-508. (http://dx.doi.org/10.1042/BJ20130342)

[4] Modur V et al. 2013, Evidence-Based Laboratory Medicine in Oncology Drug Development: From Biomarkers to Diagnostics, Clin Chem. 59 (1), 102-109. (http://dx.doi.org/10.1373/clinchem.2012.191072)