Institution: The Institute of Cancer Research

Unit of Assessment: UoA1

Title of case study: Developing inhibitors of the PI3 kinase enzymes as novel therapeutics

1. Summary of the impact

The PI3 kinase (PI3K) enzymes play a significant role in AKT-mTOR intracellular signalling, a key pathogenic pathway in many cancers. The ICR has discovered first-in-class inhibitors of class I PI3K and these are now being commercially developed by Genentech and are in clinical trials, having demonstrated clinical safety, as well as target inhibition and antitumour activity. To accelerate the commercial development of its PI3K inhibitors, the ICR founded the spin-out company Piramed Pharma, which was subsequently acquired by Roche for a total of $175million. The ICR's published research and its development of a tool compound has underpinned the worldwide effort by pharmaceutical companies to develop these novel cancer therapeutics.

2. Underpinning research

The PI3K drug discovery project was initiated in 1999 as a collaboration between the ICR, the Ludwig Institute (Mike Waterfield), the Imperial Cancer Research Fund (ICRF) (Peter Parker) and Yamanouchi Pharmaceuticals (now Astellas). Professor Paul Workman (ICR Faculty) was the overall ICR project leader and the overall cancer drug discovery lead in the project. The chemistry was initially carried out by Yamanouchi, but when they exited the collaboration in 2001 the chemistry leadership was provided at the ICR by Dr Ted McDonald (ICR Faculty). The majority of the biology research also took place at ICR. By 2001, the collaborative research project had led to the discovery of three series' of class I PI3K inhibitors including the pyridofuro-pyrimidines, as represented by PI-103, a potent inhibitor of class I PI3K and mTOR, which has subsequently been used worldwide as a valuable tool to probe the potential of PI3K inhibitors pre-clinically (Ref 1). Work led by Workman showed proof of concept for anti-tumour activity in animal models with PI-103, supported by biomarker evidence of target engagement. Subsequently, PI-103 provided the basis for compounds with improved pharmaceutical properties (increased solubility and reduced rates of metabolism).

After the collaboration with Yamanouchi terminated in 2001, the ICR, the Ludwig and ICRF formed the spin-out company Piramed Pharma in 2003 in order to accelerate the research on their novel PI3K therapeutics. Further research work involved medicinal chemistry, pharmacokinetics, mechanistic and pharmacological studies and *in vivo* tumour efficacy studies at the ICR led by Workman, Sue Eccles (ICR Faculty) and Paul Clarke (ICR Senior Scientific Officer), with Piramed Pharma taking on chemical syntheses and enzyme inhibition screening assays. The chemistry was led jointly by the ICR (McDonald) and Piramed Pharma. This research led to the discovery of a number of inhibitors including PI-728 (GDC-0941), which was the first class I-selective PI3K inhibitor to enter Phase I clinical trials worldwide. (Refs 2, 3).

The ICR played a key role in developing pharmacodynamic biomarkers of response to PI3K inhibitors and taking these into the clinic. The team have demonstrated the predictive value of PTEN loss and PI3KCA mutation and are now evaluating these in cancer patients (Refs 1, 3).

Clinical research studies have been conducted on the candidate therapeutic inhibitor GDC-0941 under the leadership of ICR faculty member Professor Johann de Bono (ClinicalTrials.gov: NCT00876122 and NCT01437566). The drug is well tolerated at doses leading to PI3K target modulation, and clinical responses have been observed in breast cancer, ovarian cancer, GIST, multiple myeloma and melanoma (Ref 4). There is evidence that GDC-0941 and the MEK inhibitor GDC-0973, in combination, show antitumour activity in prostate, melanoma, pancreatic and lung cancer. Laboratory research at the ICR has also demonstrated that PI3K inhibitors could have utility in glioma (Refs 1, 5). Clinical studies with a next generation compound derived from PI-103, GDC-0980, has also been evaluated in patients by ICR Faculty member Professor de Bono with this drug demonstrating antitumour activity against mesothelioma.
The importance of the ICR's drug discovery research work is evidenced by its receipt of the AACR

Team Science award in 2012, where the PI3K project is specifically named as an example of research excellence (American Association for Cancer Research press release March 22nd 2012). Also, the research of the ICR team was recognised by the journal Molecular Cancer Therapeutics (MCT) in its 'Best of MCT – 10 years' review (MCT 2011, 10 (11), 2009-2212; 2017-2018). One of the ICR PI3K papers (Ref 3 below) was recognised as a key publication for its high patient impact factor as judged by MCT's editorial board and a panel of peer-review experts. Professor Workman was also named 'Entrepreneur of the Year' by The Royal Society of Chemistry in 2012, partly for his work on PI3 kinase inhibitors and the founding of Piramed Pharma.

3. References to the research

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

1. **Raynaud FI, Eccles S, Clarke PA, Hayes A, Nutley B, Alix S, Henley A, Di-Stefano F, Ahmad Z, Guillard S, Bjerke LM, Kelland L, Valenti M, Patterson L, Gowan S, de Haven Brandon A,** Hayakawa M, Kaizawa H, Koizumi T, Ohishi T, Patel S, Saghir N, Parker P, Waterfield M, **Workman P**. 2007, Pharmacologic Characterization of a Potent Inhibitor of Class I Phosphatidylinositide 3-Kinases, Cancer Res. 67(12), 5840-5850. (http://dx.doi.org/10.1158/0008-5472.CAN-06-4615)
2. Folkes AJ, Ahmadi K, Alderton WK, **Alix S**, Baker SJ, **Box G**, Chuckowree IS, **Clarke PA**, Depledge P, **Eccles SA**, Friedman LS, **Hayes A**, Hancox TC, Kugendradas A, Lensun L, Moore P, Olivero AG, Pang J, Patel S, Pergl-Wilson GH, **Raynaud FI**, Robson A, Saghir N, Salphati L, Sohal S, Ultsch MH, **Valenti M**, Wallweber HJA, Wan NC, Wiesmann C, **Workman P**, Zhyvoloup A, **Zvelebil MJ**, Shuttleworth SJ. 2008, The Identification of 2-(1*H*-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine (GDC-0941) as a Potent, Selective, Orally Bioavailable Inhibitor of Class I PI3 Kinase for the Treatment of Cancer, J Med Chem. 51 (18), 5522-5532. (http://dx.doi.org/10.1021/jm800295d)
3. **Raynaud FI, Eccles SA**, Patel S, **Alix S, Box G**, Chuckowree I, Folkes A, **Gowan S**, **de Haven Brandon A, Di Stefano F, Hayes A, Henley AT**, Lensun L, Pergl-Wilson G, Robson A, Saghir N, Zhyvoloup A, **McDonald E**, **Sheldrake P**, Shuttleworth S, **Valenti M**, Wan NC, **Clarke PA, Workman P**. 2009, Biological properties of potent inhibitors of class I phosphatidylinositide 3-kinases: from PI-103 through PI-540, PI-620 to the oral agent GDC-0941, Mol Cancer Ther. 8 (7), 1725-1738. (http://dx.doi.org/10.1158/1535-7163.MCT-08-1200)
4. Moreno Garcia V, Baird RD, Shah KJ, Basu B, **Tunariu N,** Blanco M, Cassier PA, Pedersen JV, Puglisi M, **Sarker D,** Papadatos-Pastos D, Omlin AG, Biondo A, Ware JA, Koeppen H, Levy GG, Mazina KE, **de Bono JS**. 2011, A phase I study evaluating GDC-0941, an oral phosphoinositide-3 kinase (PI3K) inhibitor, in patients with advanced solid tumors or multiple myeloma, J Clin Oncol ASCO Annual Meeting Abstracts. 29 (15_suppl), 3021.
5. **Guillard S, Clarke PA, te Poele R, Mohri Z, Bjerke L, Valenti M, Raynaud F, Eccles SA, Workman P.** 2009, Molecular pharmacology of phosphatidylinositol 3-kinase inhibition in human glioma, Cell Cycle. 8 (3), 443-453. (http://dx.doi.org/10.4161/cc.8.3.7643)

Selected research grant support

1. De Bono – "First clinical evaluation of a phosphoinositide 3-kinase (PI3K) inhibitor for the treatment of advanced prostate cancer", Medical Research Council 2007-2010, £461k
2. Workman – "Cancer Research Campaign Centre for Cancer Therapeutics", 1999-2001, £5.31M, programme grant which included the PI3 kinase project
3. Workman – "Cancer Research Campaign Centre for Cancer Therapeutics", 2001-2006, £22.5M, programme grant which included the PI3 kinase project
4. Workman – "Cancer Research UK Centre for Cancer Therapeutics", 2006-2011, £30.5M, programme grant which included the PI3 kinase project
5. Workman – "Cancer Research UK Centre for Cancer Therapeutics", 2011-2016, ~£33.5M, programme grant which included the PI3 kinase project

4. Details of the impact

ICR research has made a major contribution to the international search for inhibitors of the key lipid

signalling enzymes known as the PI3 kinases (PI3Ks), which have a critical involvement in cancer. ICR's research programmes in this area have had strong impacts on health and on commerce, arising not only from the novel therapeutics developed in the ICR drug discovery programme, but also from the influence of its research outcomes on the advancement of research programmes by pharmaceutical companies.

Impacts on Health

The discovery of the tool compound PI-103 which has been made available worldwide and has contributed to drug discovery programmes internationally.

Over 25 PI3 kinase inhibitors are now in clinical trial sponsored by over 15 companies (ClinicalTrials.gov). Patients are benefiting by being able to participate in these trials. The tool compound PI-103, discovered by the ICR and its collaborators, has been a valuable resource that has supported this international drug discovery effort. Currently, 10 chemical vendors supply this compound (Pubchem, NCBI). Eighteen international pharmaceutical companies have subsequently cited the publication describing this compound (Research Ref 1 above), indicating that it has facilitated drug discovery programmes (data from Web of Science).

The discovery of the novel therapeutic GDC-0941

The ICR and its collaborators, working with the company that they formed, Piramed Pharma, discovered the PI3K inhibitor GDC-0941, which was licensed to Genentech in 2006 and then, in 2009, became the first selective class I PI3K inhibitor to enter Phase I clinical trials [1]. The ICR has played a key role in the clinical development of GDC-0941 together with its partner The Royal Marsden NHS Foundation Trust (RM) (Research Ref 4 above). Since 2008, 4 clinical trials have been completed, involving over 150 patients, and 8 trials are ongoing with an estimated enrolment of 1146 patients [2]. The drug is now in Phase II trials in 27 different countries. GDC-0941 has already demonstrated clinical efficacy (Research Ref 4 above). Patients are benefiting by being able to participate in these clinical trials.

The development of the novel therapeutic GDC-0980

Genentech licensed GDC-0941, the compound that the ICR and its collaborators discovered, and then, in collaboration with Piramed Pharma, went on to develop the dual class I PI3K/mTOR inhibitor GDC-0980, based on the same chemical scaffold as PI-103 and GDC-0941 [3]. GDC-0980 is therefore a direct result of ICR's research. It should also be noted that the tool compound PI-103, discovered by the ICR and its collaborators, is a combined inhibitor of class I PI3K and mTOR; the ICR exemplified the value of this dual activity in their work on this molecule (see Research Ref 1 above). When the first clinical candidate, GDC-0941, was created, the team improved the solubility and decreased the metabolism seen with PI-103, and also removed the mTOR activity. In the case of GDC-0980, the mTOR activity has been reinstated, building on ICR's initial research findings with PI-103.

GDC-0980 began clinical trials in 2009 and is now showing promising clinical activity in Phase II clinical trials. As of 2013, 1 clinical trial involving more than 100 patients is nearing completion, with this drug having antitumour activity in mesothelioma. 8 trials are ongoing worldwide with an estimated enrolment of over 900 patients [4]. Patients are benefiting from being able to participate in these trials.

Stimulation of the international drug discovery effort to find PI3 kinase inhibitors through publication of results.

ICR's PI3K drug discovery programme led to a number of publications showing results in biology models and identification of possible biomarkers. This has had a worldwide impact as it has stimulated other PI3K drug discovery programmes in the pharmaceutical industry. Over 40 different commercial companies have cited the ICR's work (Research Refs 1-3 above, data from Web of Science), showing the impact that the ICR has had on international drug development. Over 25 PI3K inhibitors are now in clinical trial sponsored by over 15 companies. Patients are benefiting from being able to participate in these clinical trials.

Impacts on commerce

Formation of the company Piramed Pharma and its sale to Roche.
The ICR, with its collaborators, formed the company Piramed Pharma in 2003 to accelerate development of its novel PI3K inhibitors. Piramed was sold to Roche in 2008 for $160 million, plus a milestone payment of $15 million on the commencement of Phase II trials, providing a very satisfactory return to the investors [5]. The scale of the financial investment made by Roche in acquiring Piramed Pharma illustrates the major commercial impact of this spin-out company established by the ICR.

The compounds GDC-0941 and GDC-0980 are part of the Genentech development pipeline.
Genentech has created shareholder value by adding the compounds GDC-0941 and GDC-0980 to its development pipeline. GDC-0941 was discovered by the ICR and its collaborators, and GDC-0980 resulted directly from ICR's research.

International pharmaceutical companies have added shareholder value by adding PI3 kinase inhibitors to their development pipelines.
The ICR and its collaborators have facilitated the international effort to identify PI3K inhibitors through the discovery of the tool compound PI-103 and the publication of their results and identification of possible biomarkers. There are 254 clinical trials of PI3K inhibitors listed on the NIH clinical trials database ClinicalTrials.gov. These clinical trials have included patients with a wide range of cancers and unmet medical needs.

Development by Roche of PI3K delta inhibitors
ICR's collaboration with Piramed Pharma identified selective PI3K delta inhibitors based on the same scaffold as GDC-0941. One factor influencing the acquisition of Piramed Pharma by Roche was the access it provided to the PI3K delta programme [6], indicating that this programme was of commercial value. Roche has continued to carry out research on these specific PI3K delta inhibitors. This work has resulted in compounds that are being developed by Roche for treatment of rheumatoid arthritis [6, 7].

5. Sources to corroborate the impact

[1] Shuttleworth SJ et al. 2011, Progress in the Preclinical Discovery and Clinical Development of Class I and Dual Class I/IV Phosphoinositide 3-Kinase (PI3K) Inhibitors, Curr Med Chem. 18, 2686-2714 (http://dx.doi.org/10.2174/092986711796011229)

[2] ClinicalTrials.gov search GDC-0941 (http://clinicaltrials.gov/ct2/results?term=GDC-0941&Search=Search)

[3] Patent: Publication No: WO/2008/073785, International application No: PCT/US2007/086533. PHOSPHOINOSITIDE 3-KINASE INHIBITOR COMPOUNDS AND METHODS OF USE, (http://patentscope.wipo.int/search/en/WO2008073785)

[4] ClinicalTrials.gov search GDC-0980 (http://clinicaltrials.gov/ct2/results?term=GDC-0980&Search=Search)

[5] www.roche.com/media/media_releases/med-cor-2008-04-15.htm

[6] Sutherlin DP et al. 2012, Potent and selective inhibitors of PI3Kδ: Obtaining isoform selectivity from the affinity pocket and tryptophan shelf , Biorg Med Chem Lett. 22 (13), 4296-4302. (http://dx.doi.org/10.1016/j.bmcl.2012.05.027)

[7] Safina BS et al. 2012, Discovery of movel PI3-kinase δ specific inhibitors for the treatment of rheumatoid arthritis: taming CYP3A4 time-dependent inhibition, J Med Chem. 55 (12), 5887-5900. (http://dx.doi.org/10.1021/jm3003747)