Molecular Cancer Therapeutics

Discovering and Developing PI3 Kinase Inhibitors for Cancer: Rapid Progress through Academic-Biotech-Pharma Interactions

Florence I. Raynaud and Paul Workman

Commentary on:
Florence I. Raynaud, Suzanne A. Eccles, Sonal Patel, Sonia Alix, Gary Box, Irina Chuckowree, Adrian Folkes, Sharon Gowan, Alexis De Haven Brandon, Francesca Di Stefano, Angela Hayes, Alan T. Henley, Letitia Lensun, Giles Pergl-Wilson, Anthony Robson, Nahid Saghir, Alexander Zhyvoloup, Edward McDonald, Peter Sheldrake, Stephen Shuttleworth, Melanie Valenti, Nan Chi Wan, Paul A. Clarke, and Paul Workman. **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 2009;8:1725–38.

In this paper, we reported for the first time detailed pharmacological and therapeutic properties of the pan-class I PI3 kinase inhibitory drug GDC-0941, which is now completing phase I clinical trials and being developed by Genentech/Roche. This drug is the culmination of a ten year research program exemplifying the value of drug discovery partnerships between academia and industry. At the initiation of the project, that was initially a research collaboration between our group at the Institute of Cancer Research, Cancer Research UK, Ludwig Institute of Cancer Research, and the Yamanouchi Pharmaceutical Company, PI3 kinase-inhibitory drugs were unprecedented and the approach was generally viewed as high risk by industry. This article demonstrates how major improvements in properties were achieved by progressing from our useful chemical probe compound PI-103 (1, 2) through two more advanced inhibitors (PI-540 and PI-620) to the eventual clinical drug GDC-0941 (see also ref. 3)—research carried out in the collaboration between our Institute and the biotech start-up Piramed Pharma that was founded based on our earlier progress.

GDC-0941 is a pan-class I PI3 kinase drug that inhibits p110α, β, γ and δ at low nanomolar concentrations, but not the class II, III, or IV isoforms, including mTOR, or a wide range of other kinases. Our paper reports potent anticancer activity across a panel of tumor cell lines, demonstrates and quantifies the PI3 kinase pathway inhibition required, and describes the improved drug-like properties of GDC-0941 compared to the earlier compounds, especially enhanced pharmacokinetic exposures. This translates into superior antitumor activity in human tumor xenografts genetically addicted to the PI3 kinase pathway, as shown here by results in the PTEN null U87MG glioblastoma and the *PTEN* and *PIK3CA* mutant IGROV-1 ovarian carcinoma models, with accompanying evidence of proof-of-mechanism biomarker modulation.

The discovery and development of PI3 kinase inhibitors is critically important because of the high proportion of human cancers with oncogenic abnormalities in the PI3 kinase pathway. In particular, the *PIK3CA* gene encoding the p110α PI3 kinase isoform is the most commonly mutated kinase in the human genome and the frequency of loss or epigenetic silencing of the *PTEN* gene encoding the opposing phosphatase makes it the second most common tumor suppressor in human cancer after p53. These genetic findings coupled to target-validating results with chemical probes like PI-103 (2, 4) have led to the current major interest in PI3 kinase inhibitors for cancer treatment (5).

As GDC-0941 and other PI3 kinase inhibitors now progress through clinical trials, some key questions have emerged that are currently being addressed. What are the best predictive biomarkers of therapeutic activity, e.g. *PIK3CA*, *PTEN*, *HER-2* and *RAS*? What are the pros and cons of different PI3 kinase isoform selectivity profiles?

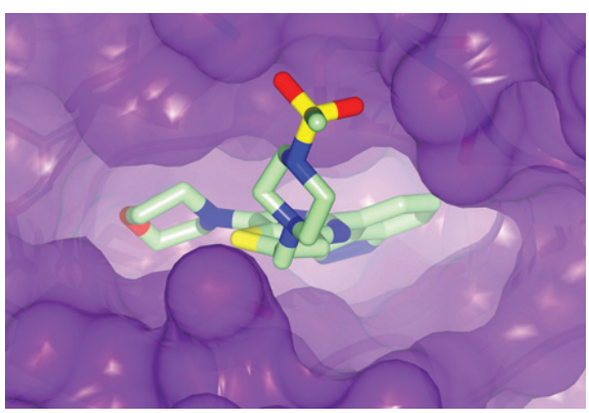

Figure 1. Crystal structure of GDC-0941 bound to human p110γ (PDB code 3dbs; see ref. 3).

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And what are the best drugs for use in combination? We discuss these issues in Shuttleworth et al. (5).

Disclosure of Potential Conflicts of Interest

The authors are employees of the Institute of Cancer Research, which has a commercial interest in PI3 kinase inhibitors and operates a rewards to inventors scheme. Paul Workman received a commercial grant from Yamanouchi (now Astellas), Piramed Pharma. He is Scientific founder of Piramed Pharma (acquired by Roche) and of Chroma Therapeutics. Intellectual property on PI3 kinase inhibitors was licensed to Piramed and Genentech (both acquired by Roche). Dr. Workman is a consultant or serves on the advisory board of Piramed Pharma, Chroma Therapeutics, Novartis, Wilex and Nextech Ventures.

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