

The human genome: realising pharmaceutical opportunities

**Summary of the 2006 Annual Forum Lecture
delivered by Dr Tim Rolph, Discovery Site Head,
Pfizer Global R&D Sandwich Laboratories, on 6 March 2006
to an audience of Forum Members, Academy Fellows and guests**

Defining the opportunity

Dr Rolph began by exploring the extent of the 'druggable' space in the human genome, which provides exploitable targets for developing either novel small molecule drugs or biologicals as drugs.

The starting point in quantifying this for small molecules (a collaboration between Pfizer and Inpharmatica) is the number of genes (and their protein products) targeted by the current generation of drugs – a total of 170 genes. These drugs are commonly characterised as being 'Rule of 5' (Ro5) compliant, denoting common features, for example in terms of maximum molecular weight, lipophilicity and propensity for H-bonding. In addition, there are 740 other gene targets for which chemical lead compounds are currently available; assuming that other members of the homologous gene families will share similar properties as drug targets adds approximately another 2000 gene candidates. Extrapolating to other proteins with similar physical-chemical features (e.g. transmembrane helices) to the core group identifies a further 500 gene candidates and yet another 100 can be added by searching the protein structure databases for structural analogies (e.g. ligand binding pocket).

An equivalent calculation for the total number of targets for biologicals can be made, giving a total of around about 5,000 potential gene targets that could be hit by either a small molecule or a biological agent. This is the 'druggable' genome, representing 20% of the total human genome.

In considering the extent to which these drug targets intersect with disease, data were drawn from mouse gene knockout models, where the phenotype is consistent with human disease, and from the Medline database of human gene-disease associations. It was concluded from this scoping work that approximately half of the theoretical molecular targets would be therapeutically relevant – representing a substantial opportunity for developing novel treatments. In the near term, it is anticipated that biological agents will become increasingly important (because fewer of their opportunities have already been explored) and that finding new small molecules will increasingly rely on expanding the search for compounds into the Ro5 fringe.

Pfizer has made some successful attempts to expand the search for small molecules, and two detailed case studies were presented:

1. Maraviroc – CCR5 antagonist

Genetic and genomic studies have shown that a deletion in the CCR5 chemokine antagonist cell surface receptor is associated with resistance to HIV infection, leading to the hypothesis that a small molecule binding to CCR5 would block HIV binding via gp120. More than 500,000 compounds were tested in high throughput

screening based on displacement of a cognate ligand, but the initial hit selected as a lead compound was found not to possess antiviral activity.

In a chemical modification programme, antiviral activity was conferred by substitutions to reduce lipophilicity, and antiviral potency was increased by conformational restriction to reduce the scope for structural rotation. However, problems of concomitant cardiac potassium channel (hERG) blockade (associated with QT prolongation), and unpredictable variability in circulating drug level because of an interaction at cytochrome P450 with other antiretroviral therapies, required further modification of compound lipophilicity and basicity – a strategy to find outlier molecules at the edge of Ro5 space. The net result was an optimum balance of desirable pharmacokinetics and improved antiviral potency without hERG effects.

Approximately 1,000 analogues were tested in the process of converting the initial lead from high throughput screening into the final choice, Maraviroc, an outlier in the Ro5 space, whose tight binding to the CCR5 receptor is consistent with a prolonged antiviral effect as monotherapy. The compound optimisation strategy lasted approximately three years and illustrates the necessity for combining high throughput chemistry, biology and drug metabolism in order to succeed in the Ro5 fringe. Pharmacokinetics is as important as pharmacology in lead selection. Pivotal clinical trials are now being completed and it is expected that registration approval will be sought by the end of 2006.

2. Torcetrapib – modulation of cholesterol ester transfer protein activity

Genetic linkage studies demonstrated that cholesterol ester transfer protein (CETP) deficiency is associated with raised HDL and decreased LDL concentration and, potentially, protection against atherosclerosis. CETP mediates reverse cholesterol transport and excretion but represents a difficult target for modulation by a small molecule: as it is not an enzyme it has no transition state; its substrates are conformationally-flexible and present in high concentrations; and protein-protein interactions are generally difficult to influence with a Ro5 compliant molecule.

The initial lead identified by high throughput screening was optimised to produce a larger, more lipophilic compound with higher potency, torcetrapib. Surprisingly – and highlighting the power of serendipity – the mechanism of action of torcetrapib was found to be different from that originally assumed, an enhancement of CETP affinity for HDL rather than a blockade of lipid binding. Human studies showed additive changes in lipoprotein concentration on combination with a statin. However, torcetrapib represents a major drug delivery challenge because of its lipophilicity and insolubility. This problem arose because of the emphasis on increasing potency in lead selection rather than also attending to optimisation of drug-like properties. The insolubility challenge has been addressed (in collaboration with Bend Research) by spray-dried dispersion onto a polymer, which enhances oral bioavailability by acting as a reservoir in the gut. This technology is now seen to be broadly applicable to a range of structurally diverse insoluble compounds.

Thus, torcetrapib was rescued by formulation technology and is now in Phase 3 trials in fixed dose combination with a statin. A large clinical development programme – 25,000 subjects and \$800 million investment – illustrates the further challenge to demonstrate efficacy with regard to both disease endpoints and mortality.

Two additional case studies were presented to exemplify Pfizer approaches to expanding the biological space:

Inhaled insulin

By 2025 it is expected that there will be approximately 350 million Type 2 diabetics worldwide (a 70% increase compared to 2003). Glycaemic control in Type 2 diabetes is currently sub-optimal because of 'treatment inertia' – a failure to advance therapy when required, including delaying the introduction of insulin. The availability of inhaled insulin overcomes some of the existing barriers to insulin use, avoiding the problems of injection and the inconvenience of coordinating administration with mealtimes. Clinical studies during the development of inhaled insulin (collaboration between Pfizer, Nektar Therapeutics and Aventis/Sanofi) show good absorption, rapid onset and sustained activity, and patients report high satisfaction with the efficacy outcome.

This pioneering work on insulin also helps to define the more general applications of the inhaled route for biologicals that will capitalise on the improved understanding from genomics of the biological space. For example, there is potential for inhaled cytokines, growth factors and appetite control peptides.

Macugen – anti-angiogenesis RNA aptamer

Reduction of VEGF activity in retinal blood vessels inhibits angiogenesis in age-related macular degeneration. VEGF165 is the isoform most responsible for pathological choroidal neovascularisation. The synthetic oligonucleotide Macugen (discovered by Eyetech Pharmaceuticals, jointly developed with Pfizer), which was identified by library screening, specifically binds to VEGF165, preventing binding to its receptor. Macugen is PEGylated to prolong its duration of action.

A clinical study, VISION, compared Macugen with standard photodynamic therapy: Macugen achieved significant reduction in loss of vision and halved the progression to severe vision loss.

In summarising the lessons learned from these four compelling case studies, Tim Rolph concluded that there are major opportunities for novel medicines as a result of genomics research – and real progress is being made now in drug R&D. It is equally important for industry to apply its expertise across a broad range of other technologies (e.g. in pharmaceutical formulation) as well as the 'omics' technologies. Studies in toxicology and pharmacokinetics must accompany the attempts to optimise pharmacology in compound lead selection.

The example from angiogenesis showed that more than 30 years has elapsed between the initial hypothesis about the importance of angiogenesis in disease and the demonstration of Macugen proof of principle. Drug discovery and development is a complex enterprise and it will take significant time to realise the opportunity afforded by knowledge of the human genome. And, as the Chairman of the Forum Barry Furr noted in his summing up, while the era of genomics is still in its infancy, what is clear is that the application of genomics knowledge needs considerable intellectual input, it cannot be automatic.

Among topics raised in general discussion were:

- *Value of animal models* – There had been a time when industry was tempted to assume that in vitro studies with cloned receptors would provide sufficient information for target validation and drug discovery in

many cases but the critical role of in vivo pharmacology in the drug R&D process has again now been reinforced.

- *Value of academic collaboration* – Industry continues greatly to appreciate the contribution from university researchers across a broad front. For example, in understanding drug targets at the mechanistic level (particularly in the absence of genetic linkage studies), in understanding the determinants of toxicology (such as the relevance of cell signalling pathways) and in using fundamental research advances to develop new high throughput screens.
- *The current place of the Ro5* – Will it survive when the druggable genome universe has been successfully exploited? As the originator of the concept of Ro5, Pfizer is well placed to judge if it will have continuing relevance – certainly researchers are becoming much more sophisticated in optimising small and not-so-small molecules.
- *Prioritisation of drug opportunities* – History teaches that pharmaceutical companies are not very good at estimating future returns on their investment. Pfizer assumes that, within reason, development of novel therapy for many diseases might offer a similar economic return. In this context, Pfizer also attempts to maximise the potential for serendipity – and this requires a strategy of addressing many targets rather than excessive early selection of priorities.

Dr Robin Fears, March 2006

Notes:

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