editorial

Keith Blundy

# Pathways and targets—opposite approaches to success?

Becoming involved in the world of cancer drug discovery from technology transfer some 10 years ago, I was immediately struck by the clash of paradigms, that is, new molecularly targeted therapeutic approaches based upon our growing genetic description of the disease, were emerging at the expense of the historic functionally based (largely cytotoxic) molecule discovery. Let us be provocative for a moment, are these approaches really that different in terms of the molecule discovered and is there perhaps a 'third way' to marry the best of both approaches, rather than to stay firmly in one camp or the other? Do we always need to describe fully a drug's mechanism if it has the desired effect?

Rationally, a molecule is as targeted (specific) as your ability to measure its activity, *in vitro* and *in vivo*. Specificity (and selectivity) depends also on what the state of biochemical and physiological knowledge dictates is therapeutically relevant (and, hence, what you decide to measure pharmacodynamically). Both the ability to measure certain pharmacodynamic events and the deemed relevant physiology change with the status of our knowledge about pathways and target biology in general and therefore a targeted therapy may be classified as selective or non-selective at different points in time? Is an hsp90 inhibitor a molecularly targeted selective agent, or a cytotoxic with a known mechanism of action (a 'neocytotoxic', [1])?

As a newcomer to drug discovery, one of the first questions that occurred to me was, is it really logical to expect a molecule to enter the bloodstream, locate a single (intracellular) target and have no/limited effects on any other relevant physiology? With the molecularly targeted paradigm, this is what we aim to achieve and are we then by design setting ourselves up for failure or, at least, to compromises (witness the emergence of 'multi-targeted inhibitors' in the kinase field). Of course, there are exceptions where a structurally 'novel' target is created through mutation, for example *bcr/abl* fusions and Gleevec in CML, but given that these targets are only a small proportion of cancer driver mutations, is there not room for a more holistic approach through functional based screening (that discovers molecules that modulate the pathway or function) supported by appropriate biochemical mode of action and selectivity screening that as a minimum demonstrates a differential effect on tumour cells over normal? Would such a 'third way' not lead us to molecules for which we have a similar amount of knowledge as to selectivity, specificity and so on, as the wholly targeted approach but just be discovered from the opposite starting point to a biochemical target based HTS? Recent evidence points to the success of this type of approach in the discovery of molecules with new molecular mechanisms [2] and also in finding agents against pathways that have previously been difficult to drug (e.g. in the pathways regulating response to oxidative stress [3]). Furthermore, in a world where we believe new breakthrough medicines come from exploring new mechanisms of action, it is interesting to note that functional screening has been more successful in this respect than the target based approach [2].

Yes, perhaps history is littered with past unsuccessful deconvolution campaigns from cell based and functional screens, but as technologies to measure the molecular mode of action *in vivo* continue to develop, the functional/pathway approach seems worth its place at the table with biochemical screening. Indeed, within CR-UK we have recently had considerable success in

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deconvoluting such screens and discovering new molecular targets and potential drugs.

A prerequisite for this 'third way' is the need to bring intensified biological pathway knowledge to the approach and this is where academic drug discovery can play a bigger part in providing the biology to build successful pathway/functional screens and in understanding and explaining the mode of action of the outputs (hits). At CR-UK we are increasingly looking at these types of approaches based on world class biology inputs (see article on Targeting Senescence in this issue).

In addition to thinking deeply about the best approach to discover new therapeutics, we also need to assess from the outset how the molecule will be used clinically. Given the wealth of new cancer agents in development worldwide (>500) a key question for all concerned is what is the right balance of activity in generating new molecules against ever more targets versus the effort required to assess how these would be used clinically. For example, should we be investing more in assessing combinations and potential synthetic lethalities in the early stage of discovery, in the pre-clinical and in the clinical setting and developing new ways to do this efficiently? The I-Spy2 trial is an example of the latter [4]. With tumour heterogeneity and a rapidly mutating cancer cell population, developing multiple different combination regimes that can be substituted, will become essential if we are to kill tumour cells and not just halt growth temporarily. Therefore, without some rebalancing of effort towards pre-clinical and clinical testing and a change in the way we set out to discover and use new cancer drugs, we will struggle to test and consequently use all the molecules we already have or those we produce in future?

As many have written, this is a golden age in cancer drug discovery and one in which we have realised that detailed biological understanding of the disease is key. Two things should follow from this – academia has a vital role to play both in discovery and in the clinic and secondly, it is not the paradigm by which you operate discovery, but how intelligently we use the biological knowledge to discover the most therapeutically effective molecules whether their mechanism is fully revealed or not.



## References

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