

# CURRENT SCIENCE

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EDITORIAL

## Cancer Research: Collaboration and Collegiality

Cancer biology is a complex field. Despite decades of intense research, the war on cancer may well extend far into the 21st century and, maybe, even beyond. The search for new targets for attack by chemotherapy is currently an intensely competitive field of research. An increasingly sophisticated range of tools are being deployed, in an area where the view from the trenches appears grim. Issues of toxicity, efficacy and resistance seem to quickly dull the promise of new drug leads. Evolution by natural selection can be a double edged sword, which favours the hardier, more adaptable tumour cells to score over their normal counterparts. The handful of molecules that emerge into the clinic, after years of development, are often priced so steeply that few can afford the exorbitant costs of treatment, that often offers only a temporary reprieve. The problems of new drug development are encountered in all human disease. As regulatory processes become more rigorous, new molecular entities that appear promising often fall by the wayside. The pharmaceutical industry is research intensive, with few companies having the deep pockets necessary for long term investment. Molecules often fail in the final steps of the drug development process, when a significant proportion of the research and development costs have already been incurred. Unsurprisingly, companies factor in the continually rising costs of research while pricing any successful molecular entity that emerges as a marketable drug.

Having often been urged by naïve peer review committees at government agencies to push basic, academic research in chemistry and biology towards 'drug design', I received, with some enthusiasm, a notice for a public lecture arranged by the Indian Academy of Sciences. The talk, delivered with great elegance, by Ashok Venkitaraman, a distinguished cancer biologist from Cambridge, described the promise of a broad interdisciplinary approach towards identification of specific targets, which would open the road towards a new generation of cancer chemotherapeutics. Molecular oncology, genetics, cellular and structural biology appeared to merge seamlessly, in this strategy to subdue cancer. The elegance and sophistication of new approaches that integrate chemistry and biology, 'chemical biology', sometimes obscures an old cautionary note that was once familiar in the research laboratories of pharmaceutical companies: 'Success in the laboratory does not always translate into success in the

marketplace.' Drug research requires a hugely organized effort, with effective collaboration between scientists with widely differing backgrounds. Venkitaraman highlighted this essential feature by first quoting Andrew Grove, a cofounder of Intel and later its CEO: 'Success breeds complacency. Complacency breeds failure. Only the *paranoid* survive.' While this may be true in the harshly competitive world of high technology, Venkitaraman suggested that Grove's dictum might be modified for the arena of drug research: 'Only the *collegiate* survive'. I was struck by the word 'collegiate'. It seemed to convey, eloquently, the need for cooperation and collaboration within an interdisciplinary team. Shared goals, complementary skills and collective responsibility seemed to be described by a single word. I could not help wondering if collegiality might indeed be the single most important quality necessary for success, in a modern, interdisciplinary research environment in almost any field of science.

Thinking about collegiality, I turned, almost inevitably, to sports and the London 2012 Olympics. As I write it is clear that the Indian contingent will return with a handful of medals, all won in individual events. Our performance in the team events, notable among them tennis and hockey, was singularly disappointing. Most regrettably, the tennis stars displayed a remarkable lack of collegiality, while newspaper reports suggested that the hockey team had several individualists who had scant regard for team strategies. While individual brilliance and commitment served lone performers well, the team sports demanded a collaborative effort, which floundered in the absence of collegiality. Science is increasingly resembling a team sport. In most areas of modern science teams of researchers with diverse specializations are required to address the major issues of interest. 'Big science', exemplified by the hunt for the Higgs boson by the physicists or the large genomics programs in biology, requires collaborative efforts on a scale never seen before. Hundreds of authors and institutional affiliations are listed on published papers in the areas of particle physics and genomics. These are, of course, extreme examples of collaborative efforts. However, even a cursory glance at any of the major journals of science will reveal very few papers which do not list many authors; testimony to the fact that modern science requires organized teams in order to succeed in a complex and competitive environment. Multiauthor

papers, on an average, appear to attract greater attention than the contributions of lone scientists, suggesting that multidisciplinary articles may have a greater impact as measured by the metrics commonly used to quantitatively assess scientific output. Successful collaboration requires a great deal of understanding and mutual respect between the researchers involved. If these conditions are not met, unpleasantness and controversy follow. Sharing of credit also implies a sharing of responsibility for the published results of a scientific study. This is often rendered difficult by the nature of research, where highly focused specialists contribute to a specific aspect of a multidisciplinary study and invariably rely on the expertise of collaborators to ensure the correctness of results and interpretations, that lie outside their areas of competence. Collegiality and trust become essential ingredients of a successful collaboration. In concluding his overview of the new approaches to finding the next generation of cancer chemotherapeutics, Venkitaraman emphasized the virtues of a specific target driven approach that might then be attacked by the proverbial 'magic bullet'.

Cancer research, in recent times, has provided an excellent example of a target driven strategy in the development of Gleevec (Glivec), as a means of treating a relatively common form of blood cancer, chronic myeloid leukemia (CML). The drug is in the news in India, where non-governmental organizations have led a legal battle against the patent protection sought by Novartis on its best selling product. The issue has been in the courts since 2007 and is expected to be decided by the Supreme Court in the very near future. A judgement against Novartis would legitimize the production of cheap generics by Indian companies, dramatically reducing treatment costs which may run as high as \$40,000 to \$98,000 annually ([swissinfo.ch](http://www.swissinfo.ch), 12 March 2012). With estimated annual sales revenues of \$4.7 billion from Gleevec, Novartis is indeed keen to avoid competition from cheap generics. The original rejection of a Gleevec patent in 2006 has been challenged. The Supreme Court's verdict is likely to have far reaching implications for the pharmaceutical industry in India and for the difficult arena of affordable health care. Pharmaceutical companies which invest heavily on research and development jealously guard successful molecules by evolving protection strategies beyond the date of expiry of the original patent. 'Evergreening' is an accepted industry strategy, whereby minor modifications of an existing molecule or formulation are used to file secondary patents, thereby extending the lifetime of monopoly protection. Gleevec's primary patent was never filed in India in the pre-TRIPS era and the secondary patent is the subject of the present dispute. The pharmaceutical industry, more than any other, illustrates the difficulty of finding means 'to balance innovation and access' (Sampat, B. N. *et al.*, *Science*, 2012, **337**, 414).

The science behind Gleevec highlights the pivotal role that basic biological understanding of a disease process may play in developing therapeutics. The key events

in understanding the underlying molecular aberrations in CML may be traced to cytogenetic work in the 1950s, that established chromosomal abnormalities, eventually leading to the identification of the 'Philadelphia chromosome' in the 1970s. Over a decade was to pass before a gene was identified as a 'likely molecular culprit' in CML. Not long afterword the gene product was identified as a tyrosine kinase, an enzyme which initiates a signalling cascade, promoting cell proliferation, a characteristic of cancer. By 1990 a target for inhibition, a specific tyrosine kinase, was at hand. By this time, a growing body of structural information suggested that, contrary to prevailing opinion in the pharmaceutical industry, these enzymes may indeed be good targets for attack. The 2009 Lasker-DeBakey Award for Clinical Medical Research recognized the work of Brian Druker, Nicholas Lydon and Charles Sawyers for 'converting a fatal cancer into a manageable chronic condition'. Gleevec was the agent of management. Having developed a cell based laboratory assay for assessing the enzyme activity, Druker turned to Lydon – a researcher at Ciba-Geigy (later Novartis) – who dug into the company's vaults of compounds. Together with Sawyers, clinical trials were soon conceived for the most promising molecule, finally christened as Gleevec (Pray, L. A., *Nature Education*, 2008, **1**(1)). The Gleevec story, like many others in drug research, includes the development of resistance to a successful product, as cancer cells learn to evade attack by presenting an altered target. A structural understanding of the new target has already permitted development of a modified molecule, this time by Britsol Myers Squibb, *Sprycel*, which targets Gleevec resistant cancers. The story of Gleevec is an example of a rare success in the war on cancer (<http://www.lasker-foundation.org/awards/2009>). Drug development to combat CML has required contributions from many diverse disciplines and has been made possible by a fundamental understanding of the molecular basis of the disease. This success is a consequence of a readily identifiable target in the case of CML. Unfortunately, targets are hard to identify and attacking the wrong targets can be a fruitless exercise.

Listening to the Academy lecture on cancer research and reading about Gleevec, reinforced a growing feeling that only a broad interdisciplinary assault on the many problems of biomedical research can lead to results that can be effective in improving health care. Such an approach may require academic laboratories in India to examine ways of creating a new ethos that promotes collaborative research. Academic institutions and partners in industry may do well to ponder on another of Andrew Grove's prescriptions: 'A corporation is a living organism; it has to continue to shed its skin. Methods have to change. Focus has to change. Values have to change. The sum total of these changes is transformation.' Replacing paranoia by collegiality may indeed be the way forward.

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