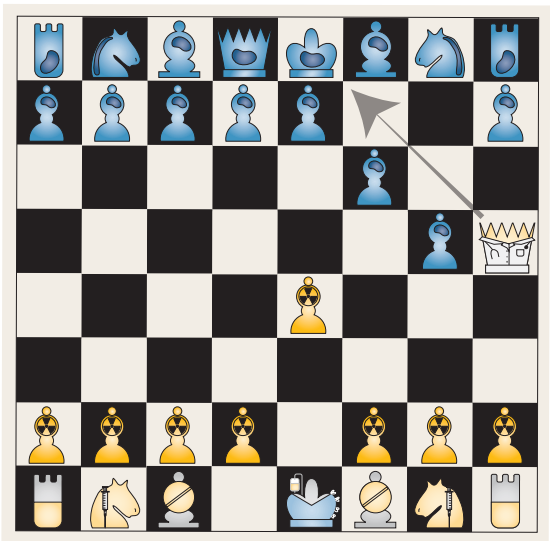
Predicting cancer's next move

I don't know about you, but I think the oncology field has reached a frustrating crossroads. We have undoubtedly made great strides in combating this myriad of diseases over the past half century, but the general feeling from the community seems to be that we are not entirely sure of the next steps to take and how to best integrate the humongous amount of information we get, let alone how to get out of the rut we are in regarding new trial designs, economic challenges and the complexity of heterogeneity—to name but a few of the key challenges.

There is no doubt about it, cancer is a clever disease. It is always multiple steps ahead of us. So, if we are to beat cancer, we have to think like cancer. I'll compare it to a game of chess. World class players win by thinking at least 15 steps ahead of their next move, and by predicting their opponents tactics well in advance. It seems that what we are doing in the fight against cancer is more a one-step reactive approach to its next move. No wonder we feel like we are losing this game!

The many hundreds of pathways and networks a cancer cell has at its disposal to divert and diversify when faced with a roadblock, can be analogized to the underground system. Blocking a pathway with a targeted agent would be similar to closing the Victoria line on the London underground; how do people get to their final destinations? Well, they choose the District line, Circle line, get a bus or different train. In other words, although there is a temporary inconvenience, we soon find another route. When using targeted therapies or even dual combinations, we are barely causing the equivalent of a partial closure on the Victoria line. Apart from exceptional poster child examples, such as imatinib in chronic myeloid leukaemia, in which cancer is relatively 'simple' in its hard-wired adaptation, we are not even close to being ahead of the game.



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This is where Systems Biology and rapid learning for precision oncology will come to the fore. These approaches are starting to become the standard of care at leading cancer centres that use inventive network-based statistical modelling to hypothesise the putative driver networks for a given tumour. While this initiative is still in its infancy—and we still have a long way to go—I believe in the long term we'll be able to generate a several-steps-ahead strategy. In this issue of the journal, Shrager and Tenenbaum (pp. 109–118) elegantly discuss the emerging paradigm of rapid learning for precision oncology. Notably, they comment that—except for the prices of drugs—costs of panomic technologies, computational algorithms and molecular models of cancer are decreasing. But, while these new technologies reduce in cost and seem to have an improved efficiency over time, the drug development arena shows the opposite trend of becoming clunkier, less efficient and more expensive. Undeniably, with the availability of so many more treatment options, increased patient subgroups and our continued appreciation of the complexity of the disease, drug development testing with the traditional clinical trial format is suboptimal, as this is now a completely different ball game compared with the old days when only a few options were available. While this scenario increases the cost of drug development to some extent, it is not the only reason for such a negative trend. Obviously, profitability is an understandable and, to some extent, justifiable element at play, but we have to admit that the current drug development and clinical trial system is woefully inadequate and has become overly complex, with too much bureaucracy that has stifled flexibility and innovation—essential attributes that must be retained if we are to tackle cancer.

We have to revise our existing paradigm of developing drugs and only approving them if they meet their primary end points as monotherapies before they are then tested as combinations. As we are now acknowledging that the only way forward is to use a cocktail of drugs, why are we hell bent on demonstrating efficacy of monotherapies for them to be approved, when we know their main or only forte will be when these agents are used as combinations? It is like building a car with only the frame and getting this approved before you've added all the engine components and wondering why you have to

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Competing interests
The author declares no competing interests.

go back to the drawing board. Likewise, we also need to think about assessing maintenance therapy in animal models and start to test whether a single drug or combination therapy is the best approach long before it reaches the clinic. Careful preclinical work in conjunction with Systems Biology and rapid learning for precision oncology could save millions in money downstream in terms of conducting ill-conceived clinical trials.

But, is it enough to charter the trajectory of a tumour's molecular profile over time? Not really, as this is not predicting cancer's next move. It certainly lays the foundations for a better knowledge base than we've had in the past and is the right next step ahead, but we have to do so much more. For instance, we should be encouraging more preclinical research that tests as a matter of course multiple drug combinations (similar to the clinical situation) in conjunction with mechanisms of resistance assessment. More attention should be paid in preclinical and clinical research to address why positive phase I and II studies often lead to disappointing phase III trial results. Excluding the crossover effect in terms of a lack of overall survival benefit in late-stage trials, the disparity between early phase and late phase results need to be carefully considered, including more assessment of toxic effects—both on target and off target.

Another aspect that deserves closer attention is designing therapies that monopolise a 'trickling' rather than 'sledge hammer' approach. Cancer is not only clever but subtle, and seems to wreak vengeance more successfully when a therapy obliterates the tumour quickly in the first instance. In such situations, the resulting resistant clones that return seem to be even stronger and appear as quickly if not more quickly than the timeframe of their supposed eradication. In other words, when our treatment approaches seem to succeed almost immediately, this should be a warning that the resistant clones may also return more rapidly too. I suspect a metronomic approach for combination therapy might also have utility here and should be investigated more extensively earlier in the drug development pipeline. Another issue in preclinical research is that therapies tested *in vitro* that kill cancer cells, and thus seem suitable candidates for further development, do not actually kill cancer. Many unsuccessful therapies in the clinic are still capable of killing cells in a test tube, but not the disease within a higher, more complex, organism. How we should best tackle this hurdle is something that requires better community engagement about the approaches to studying cancer.

Conflicts of interest are also an important issue in oncology. A classic example is the approval and testing of a drug in a clinical trial sponsored by the same company that makes the drug. Would not a better approach be for an independent clinical trials organization (as a default) to oversee the trial design and set up, and then enlist the help of multiple industry partners that all have the appropriate agents in question, so the offering is already more dynamic from the outset? If this were the case, the independent clinical trials organization would assess all the data and make all of it publicly available, which is currently not the case. Of course, this is a huge undertaking that would take years to get off the ground (and admittedly would be unpopular for a number of obvious reasons). Nonetheless, it might also alleviate some of the red tape and bureaucracy that is rife in clinical trial design, as well as alleviating the conflicts of interest issue.

It is impossible to cover all the problems and provide all the solutions in a two-page editorial, but perhaps at least some suggestions have been offered for how we should start to think about things differently in order to win this game! If we are smart, like cancer, we can win, but we have a long way to go yet.

doi:10.1038/nrclinonc.2014.4