Cancer research: in need of introspection


Tata Memorial Centre

The cancer research landscape globally seems to be dominated by an almost missionary zeal towards unraveling more and more biological (genomic, epigenomic, transcriptomic, etc) information for every single tumour and therapeutic intervention envisaged around this framework. This unbridled enthusiasm was initially ignited by the discovery of the human genome at the turn of this century and later fuelled by a series of discoveries about genetic alterations in human cancer cells and their associated pathways of carcinogenesis and tumour progression. This research has yielded a very large amount of 'omics' data for practically every cancer type and their many histological subtypes. The seductive nature of these thrilling discoveries satisfied an innate scientific curiosity to understand cancer in terms of pure mathematical reductionism. Almost simultaneously, initial successes of some targeted therapies (eg, imatinib for a single-mutation driven cancer) led researchers to naively believe that cancer could be conquered after all, and this conquest was only a matter of time.

Publication of each piece of mutational information in high-impact journals, particularly if it seemed actionable, resulted in a frenzy among research groups to contribute to this molecular revolution. Whereas each molecular discovery with its attendant promise of a potential therapeutic target appeared thrilling, and a victory for funding opportunities, the hype has unfortunately neither translated into a meaningful understanding of the malignant process nor to a substantial therapeutic gain when tested in an appropriately conducted clinical trial.[1] These revelations must now make us question the approach of treating a complex problem such as cancer by targeting only a single or a few altered pathways. However, notwithstanding the high cost and potential adverse effects of targeted therapies, political interventions, including the use of terminologies such as personalised or precision medicine, have refuelled attention in this direction. The societal pressure from a public enamoured with these announcements and sensational case stories in the lay press have forced some cancer centres to offer genetic portfolios for every single patient and seek funding, philanthropic support, and partnership with industry. These centres are fully cognizant that these portfolios might have very little to offer in terms of meaningful benefit in clinical outcomes for most of their patients.[2]

Perhaps the greatest fallout in the current climate of omics-driven research is the progressive discouragement of a free-thinking environment to foster alternative innovative ideas. Before the omics era, several path-breaking discoveries and inventions were developed, which are still applicable to most cancer patients.[3] In a desperate measure, time-tested statistical methodologies are being modified, with excitement generated by meaningless gains in progression-free survival of a few weeks. A 2–3% improvement in overall survival seems to have become the outer limit of our intellectual expectation. Technological advances in cancer management for both diagnostics and therapeutics are also growing at a rapid pace. Modern technologies (eg, robotic surgery and proton radiotherapy) are being embraced with enthusiasm, with all centres wanting to adopt new technologies just because the other centre has, disregarding the scientific rigour that they need before adopting them in routine clinical practice.[4]

This situation is particularly challenging to lower-to-middle income countries, where limited material and human resources for research require judicious allocation.[5] The dilemma of whether to follow omics-driven cancer research or pursue novel hypothesis-driven and cost-effective innovative research is a considerable one. However, having a relatively large number of patients does offer opportunities to do investigator-initiated research with clinically relevant endpoints.[6] Some of these trials have already translated to potentially practice changing work.[7,8]

Genomic and molecular test profiling have invaded the lay public domain in some low-to-middle income countries, which due to their exorbitant cost, unrealistic expectations, and absence of good clinical evidence, pose a formidable challenge to policy makers and leading cancer and health experts in these regions. There is an urgent need worldwide for an honest appraisal as to whether current research and therapeutic strategies are appropriate and whether the resources available are being optimally used in a meaningful way.[9] We need to decide if even the basic

principles of cancer mechanisms and their attendant research so firmly embedded in our minds are flawed and need revision.

Tata Memorial Centre in Mumbai, India, is about to celebrate its 75th anniversary. The centre has chosen this anniversary to host an international conference (Tata Memorial Centre Platinum Jubilee, Feb 26–28, 2016). The conference's theme is of challenging existing dogmas and debating the currently entrenched versus contrarian viewpoints in cancer research and treatment. We hope the discussion that emerges from this conference might reveal some revolutionary approaches as to how we perceive and treat cancer today and lead to a commonly accepted resolution in the future.

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1 Le Tourneau C, Delord JP, Goncalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol* 2015; **16:** 1324–34.
2 Joyner MJ, Paneth N. Seven questions for personalised medicine. *JAMA* 2015; **314:** 999–1000.
3 Mittra I. Why is modern medicine stuck in a rut? *Perspect Biol Med* 2009; **52:** 500–17.
4 Brada M, Bortfeld T. Proton therapy: the present and the future. *Semin Radiat Oncol* 2013; **23:** 75–76.
5 Sullivan R, Badwe RA, Rath GK, et al. Cancer research in India: national priorities, global results. *Lancet Oncol* 2014; **15:** 213–22.
6 Jalali R. Conduct of clinical trials in developing countries. *Lancet* 2007; **370:** 562.
7 D'Cruz AK, Vaish R, Kapre N, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med* 2015; **373:** 521–29.
8 Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol* 2015; **16:** 1380–88.
9 Aran D, Sirota M, Butte AJ. Systematic pan-cancer analysis of tumour purity. *Nat Commun* 2015; **6:** 8971.

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