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A Nobel Prize-worthy pursuit: cancer immunology and harnessing immunity to tumour neoantigens

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Summary

The field of cancer immunology stepped into the limelight this year when James P. Allison and Tasuku Honjo received the Nobel Prize in Physiology or Medicine for their discovery of cancer therapy by inhibition of negative immune regulation. Among many exciting advances contributing to the coming of age of tumour immunology as a viable clinical specialty has been the ability to progress from the initial elucidation of tumour antigens, such as the melanoma antigen, MAGE-1, to high-throughput sequencing facilitating identification of T cell epitopes from diverse tumour neoantigens. This has resulted from the convergence of expertise in tumour biology, next-generation sequencing, T cell and structural immunology, and predictive algorithms. Among many examples, immunotherapy for ovarian cancer has been one of the beneficiaries of these advances, leading to a number of recent and ongoing clinical trials.

The showbiz quote to the effect that 'it takes 40 years to become an overnight success' seems uniquely fitting to the field of cancer immunology, which on 1 October this year was shot into the spotlight when James P. Allison and Tasuku Honjo won the Nobel Prize in Physiology or Medicine for their discovery of cancer therapy by inhibition of negative immune regulation.

It should be a source of great pride to each and every practitioner of any part of immunology research that everywhere we look there are successful clinical treatments and trials on chimeric antigen receptor T cells, checkpoint blockade, other monoclonals, and tumour vaccines.[1–3] There are 53 such clinical trials currently recruiting patients in the UK alone. As with those other 'overnight successes', it has actually been nearly 40 years since the Herculean, brute-force, expression cloning and transfection studies by Thierry Boon and colleagues identified the first T-cell-recognized tumour antigen, MAGE-1 — a melanoma antigen — setting the scene for modern tumour immunology.[4]

An interesting link to those early mouse studies comes with the observation that the pipeline for elucidation of anti-tumour therapeutic T cells may be facilitated by a generic approach to humanize murine T-cell receptor anti-tumour sequences, as has been explored for MAGE epitopes.[5] A great deal is now known about tumour antigens, including potentially immunogenic neoantigens generated by mutations within tumours, with next-generation sequencing approaches playing a key role in their high-throughput identification. A major new review article considers the case of ovarian cancer antigens and particularly the cancer testis (CT) family of antigens.[6] This family comprises more than 250 antigens of altered expression, not just in ovarian cancer, but in other cancers too.

In ovarian cancer, as in several others, the extent of tumour-infiltrating lymphocytes (TIL) is a correlate of survival, but with the presence of regulatory T cells among TIL a confounder. The CT antigens have now been the subject of targeted immunotherapy strategies in some 20 clinical trials. Although the study of tumour immunogenicity was once a dark art of trial and error, the application of high-throughput sequencing, structural immunology and predictive algorithms has now elevated the field to one of precise, personalized medicine.[7] New approaches allow the calculation of tumour fitness through analysis of neoantigen immunogenicity. This algorithm rests on long investment in understanding the rules of human leucocyte antigen binding to peptide, in this case, predicted neoantigen epitopes coupled to predictions of T-cell receptor recognition. Neoantigen epitopes, like microbial epitopes, are derived naturally as a variable set of epitope clusters. Among the exciting new tools for analysis of these clusters is a tool available

through the Immune Epitope Database[8] (www.iedb.org) to facilitate easily accessible online clustering of disparate epitope data sets.[9]

One of the cell-types within tumour infiltrates that is perhaps less well understood is the tumour-associated macrophage (TAM): clearly, heterogeneity within this population and nuances in antigen presentation and innate function will influence the relationship between the tumour and immunity, but how to understand this well enough for therapeutic manipulation? A new review looks at the animal studies showing that tumour-infiltrating myeloid cells, particularly TAM, will be important targets in efforts to optimize immunotherapies.[10] The notion is that, by additional targeting of the potentially suppressive impacts of TAM on tumour immunity, it should be possible to further enhance approaches such as checkpoint blockade. Another exciting area of progress during the 'overnight success' of tumour immunology has been delivery on decades of investment in viral immunology. A new review article considers the concept of 'memory T-cell inflation' and the collateral damage from anti-cytomegalovirus (CMV) immunity in later life.[11] The article considers CMV immunity as a double-edged sword in editing anti-tumour immune responses, with evidence showing that CMV is highly prevalent in patients with a wide variety of cancers.

These are truly exciting times for the coming of age of tumour immunology and *Immunology*, one of the longest-standing journals publishing in this area, welcomes your ideas, submissions, review and research articles in this area.

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