

SCIENCE'S TOP BREAKTHROUGH OF 2013

Every year the editors of *Science* have an intense discussion to identify the top scientific breakthrough of the year. This year the winner is cancer immunotherapy. This nascent field is just taking baby steps but it is a paradigm shift in the way cancers are treated. The target here is the body's immune system and not the tumour. The story begins in the late 1980's when French researchers discovered a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4 (CTLA-4). Then an American scientist, James Allison found that these receptors actually inhibit T cell activity. He wondered whether blocking the blocker — the CTLA-4 molecule — would set the immune system free to destroy cancer. In 1996, he demonstrated that antibodies against CTLA-4 destroyed tumours in rats. Pharma companies initially were wary of this new approach, so a tiny company Medarex in Princeton developed the drug. Finally it was bought over by Bristol-Meyers-Squibs for more than \$ 2 billion. For the first time, they demonstrated that any treatment had extended life in advanced melanoma in a randomized trial. Nearly a quarter of participants receiving these antibodies survived at least 2 years.

Meanwhile, a biologist in Japan discovered a molecule expressed in dying T cells, which he called programmed death 1 (PD-1), and which he recognized as another brake on T cells. An oncologist in John Hopkins urged Medarex to develop anti PD-1 antibodies. The results of anti PD-1 antibodies in patients with drug refractory cancers were astounding. However oncologists are still trying to understand how they work and what they do. Some tumours actually grow before shrinking and some tumours continue to shrink even when antibodies have been stopped. Another therapy is called chimeric antigen receptor therapy, or CAR therapy — a personalized treatment that involves genetically modifying a patient's T cells to make them target tumor cells. For physicians accustomed to losing every patient with advanced disease, these therapies bring a hope they couldn't have dreamed of a few years ago. (*Science 20 December 2013*)

CLARITY

Another of the top breakthrough's listed in science is a new imaging technique called CLARITY. It stands for **C**lear, **L**ipid-exchanged, **A**natomically **R**igid, **I**maging/immunostaining compatible, **T**issue **h**Ydrogel. It is used on biopsies or post-mortem samples to study highly detailed pictures of the protein and nucleic acid structure of organs,

especially the brain. First a series of chemical treatments are applied so that the lipid content of the sample is removed, while all of the original proteins and nucleic acids are left in place. The aim is to make the tissue transparent so that a detailed microscopic analysis of the protein scaffolding may be done. The imaging is done using immunostaining with fluorescent tags. An example of a discovery made through CLARITY imaging is a peculiar 'ladder' pattern where neurons connected back to themselves and their neighbors, which has been observed in animals to be connected to autism-like behaviors. Scientists predict CLARITY will be a powerful tool to study neurological disorders with a 3 dimensional perspective. (*Science 20 December 2013*)

HYPOTHYROIDISM STILL RAMPANT

A nation-wide study to evaluate the prevalence of hypothyroidism has revealed that hypothyroidism affects 11% of Indians as compared to less than 2% in UK and less than 5% in USA. Ever since India adopted the universal salt iodization program in 1983, there has been a decline in goiter prevalence in several parts of the country, which were previously endemic. In 2004, a WHO assessment of global iodine status classified India as having 'optimal' iodine nutrition, with a majority of households (83.2% urban and 66.1% rural) now consuming adequate iodized salt. India is supposedly undergoing a transition from iodine deficiency to sufficiency state. This study was a cross-sectional, multi-centered epidemiology study conducted at eight sites in India: Bangalore, Chennai, Delhi, Goa, Ahmedabad, Hyderabad, Kolkata and Mumbai. The prevalence of previously undetected hypothyroidism was 3.47%. Those who self-reported to be hypothyroid, a significant proportion (28%) still had a high TSH indicating inadequate treatment. The emergence of Kolkata as the worst affected city was unanticipated, particularly as the city was established to be iodine replete over a decade back. It appears that thyroid disorders in India are not confined to the conventional iodine-deficient sub-Himalayan zone but also extend to the plain fertile lands. A possible etiological role of cyanogenic foods acting as goitrogens which interfere with iodine nutrition has been previously suggested as well as increasing exposure to thyroid disruptors including industrial and agricultural contaminants. However this study was done only in adults and limited to urban areas. More studies in children are warranted. (*Indian J Endocr Metab. 2013;17:647-52*)

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