

Editorial

Nanobyte - Perspectives and milestones in molecular biology and immuno-oncology

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IMMUNOTHERAPY OUTLOOK FOR 2019

A decade ago, we were not discussing chimeric antigen receptor-T cells, adoptive cell transfer, tumor-infiltrating lymphocytes or checkpoint inhibitors in the oncology clinic. Today, the promise of immunotherapy has moved from bench to bedside and is changing the treatment landscape worldwide. At the time of this publication, 2532 clinical trials [Table 1] were registered (and in various stages) at the national library of medicine^[1] under search terms “cancer” and “immunotherapy.” This is an exciting juncture in oncology with many unanswered questions, and much to learn and contribute across scientific and clinical disciplines.

BASIC SCIENCE BYTE: MUTATIONAL BURDEN IN “HEALTHY” TISSUE

A 2018 study reported in science showed that mutations in 14 genes that are normally associated with cancer accumulated in non-cancerous esophageal epithelium with aging.^[2,3] They observed that, among others, TP53 and NOTCH1 mutations were highly prevalent in the normal esophagus. Remarkably, NOTCH1 mutations were higher in normal than in cancerous esophageal epithelium. Based on the results, the authors hypothesized that several clones of cells harboring mutations were growing throughout body tissues, competing for resources, and keeping each other in check. They cautioned that one must be aware that the existence of mutations associated with cancer did not imply the existence of cancer. Furthermore, the study re-emphasized the need to understand the role of spontaneous mutations in physiology and pathophysiology in the absence of any obvious external mutagen.

A TRIBUTE TO TWO PIONEERS OF IMMUNO ONCOLOGY

In 1987, Susumu Tonegawa (born in 1939) was awarded the Nobel Prize in Physiology and Medicine for his discovery of the genetic basis of antibody diversity.^[4,5] From humble beginnings, he pursued his education in Chemistry at the University of Kyoto during the post-World War II era turmoil. He was fascinated by the research in Molecular Biology unraveling in the 1950s and '60s. He began his doctoral research on SV40 in the United States and subsequently joined the Basel Institute of Immunology, Switzerland, where he was at the forefront of the new and hot field of Molecular Immunology. Restriction enzyme technology and Southern blotting were allowing researchers like Tonegawa in the early 1970s to pursue the question of a genetic role in the variability of immunoglobulin (IgS).

Fast forward a few decades the Nobel Prize in Physiology and Medicine 2018 was awarded to Tasuku Honjo and James P. Allison for their “discovery of cancer therapy by inhibition of negative immune regulation.”^[6] Honjo (born 1942), also a chemist by training, was fervently studying Ig class-switching (to produce Ig isotypes) in the 1970s. His academic journey began at Kyoto, Japan and came full circle as he returned to Kyoto after several years and made the groundbreaking discovery of the protein programmed cell death-1 (PD-1) in the 1990s. In the early 2000s, Honjo and his team showed in animal models that PD-1 inhibition allowed T cells to target and destroy cancer cells.

Tasuku Honjo, currently, continues research in understanding the basic mechanisms of Ig class switching. Concurrently, Susumu Tonegawa, after unraveling the genetic recombination mechanism of antibodies,

Table 1: National library of medicine clinical trials database results

Terms	Search results*	Entire database**
Synonyms		
Immunotherapy	2532 studies	3510 studies
Immunomodulatory agent	40 studies	65 studies
Immunomodulator	37 studies	163 studies
Immune modulators	22 studies	40 studies
Immunotherapeutic agent	14 studies	21 studies
Biological response modifiers	7 studies	13 studies
Immunomodulating agent	4 studies	12 studies
Immune regulators	4 studies	7 studies
Immunological therapy	4 studies	4 studies
Immune mediators	3 studies	15 studies
Biomodulators	1 studies	3 studies
Immunologically directed therapy	1 studies	1 studies
Cancer	2532 studies	65,620 studies
Neoplasm	2375 studies	57,466 studies
Tumor	943 studies	14,694 studies
Malignancy	145 studies	2838 studies
Oncology	40 studies	1019 studies
Neoplastic syndrome	9 studies	548 studies
Neoplasia	8 studies	564 studies
Neoplastic disease	--	19 studies
-- No studies found. *Number of studies in the search results containing the term or synonym. **Number of studies in the entire database containing the term or synonym		

went on to study other challenging unanswered questions in immunology and neuroscience, and he continues to do so today at the Massachusetts Institute of Technology, United States.

As the field of molecular biology and immuno-oncology rapidly advance in today's world, we owe much to the insightful and relentless work of those who were undeterred by geographical, technological, and socio-political hurdles as they pushed our boundaries of knowledge.

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