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Editorial

Cancer and immunity – The contributions of Thomas Starzl☆

Thomas Starzl (1926–2017), the father of modern organ transplantation, was an exceptional clinician scientist, who published more than 1600 publications in professional journals, 4 books, and more than 100 textbook chapters in a research career spanning nearly 70 years, starting as a 23-year-old second-year medical student at Northwestern University. He was at the forefront of almost all major advances made in organ transplantation over the last 65 years, which formed the bulk of his published work. His contributions to understanding the interplay of drug-induced immunosuppression needed for organ transplantation and cancer, admittedly a small part of his contributions, form the basis of this review. The award of the Nobel Prize in Physiology or Medicine for 2018 to James P. Allison and Tasuku Honjo, for their discovery of cancer therapy by inhibition of negative immune regulation, bought the subject of cancer and immunology to the forefront again. However, the concept of immunological control or lack thereof, permitting the genesis, growth, and spread of cancer, was enunciated by the pioneer of the cellular basis of immunology, Macfarlane Burnett (Nobel Laureate 1960),[1] and the high occurrence of malignancies in the rare spontaneous immune deficiency states was already becoming known in the 1960s.[2,3] As Thomas Starzl was carrying out his early experimental and clinical work on drug immunosuppression for kidney and liver transplantation, he predicted presciently[4] in 1964 the risk of development of de novo cancers in these patients. By 1968, Starzl team from Denver reported[5] five cases (3 of their own and 1 each from Minneapolis and Edinburgh) of malignant lymphoma developing after renal transplantation with drug immunosuppression. Thomas Starzl also encouraged Israel Penn to start an informal tumor registry at Denver,[6] which started collecting and collating data from transplant centers throughout the world informally. By 1972, Israel Penn and Thomas Starzl[7] reported on 75 chronic survivors of organ transplantation who subsequently developed malignant tumors. Epithelial tumors were seen in 44, the most common being of skin followed by several other organs. However, there were 32 mesenchymal tumors, mainly lymphomas. Many characteristics of these lymphomas, now called posttransplantation lymphoproliferative disorder (PTLD), would be elucidated by the Pittsburgh group,[8] where Starzl had moved from Denver in 1980. With the recognition of Epstein-Barr virus as the causative agent in most PTLD cases, the transplant pathology group, under his supervision, made fundamental contributions to understanding the underlying molecular basis of its pathogenesis.[9] They also noted that the incidence of tumors was 80 times greater than that in the average population in a comparable age. Israel Penn moved to the University of Cincinnati, in 1982, and the registry, now called Cincinnati Tumor Transplant Registry, carried out the work of collecting and collating the tumor burden after organ transplantation and immunosuppression, from voluntary submission by transplant programs globally. After his death, in 1999, the Israel Penn International Tumor Transplant Registry carries out this important legacy of Drs Starzl and Penn, continuing to advance this field and provide an Internet-based free consulting service. As the number of transplanted organs grew exponentially, it was also becoming clear that apart from the de novo malignancies, transmission of donor malignancy also occurred in those cases where donor was having what was presumed to be having early localized malignancy in a nondonated organ. This revived the concept of immunological surveillance hypothesis for malignancy.[10] Liver transplantation was becoming established, and one of the earlier indications was localized hepatocellular carcinoma (HCC). However, the high rate of recurrence of the original malignancy after successful transplantation dampened the initial enthusiasm. The imaging and other staging modalities were not as refined as today, and Starzl[11,12] continued to do liver transplantation in stage II and III HCC, laying the ground work for the currently accepted indications for such treatment. In the cases with recurrence of HCC after liver transplantation, he demonstrated that the tumor doubling time is reduced significantly with immunosuppression.[13] If the drug-induced immunosuppression could cause malignancy to appear and spread, could reducing or stopping immunosuppression help in controlling this malignancy? This concept, now well accepted, was strongly emphasized by Starzl from the beginning.[14] His 1984 article on the reversibility of PTLD by reducing immunosuppression remains a classic and the most widely cited one on the subject.[15]

Dr Starzl leaves a rich legacy, his last published article appearing in 2017,[16] when he was 90, but still with a vigorous inquiring mind. He remains a role model of what a perfect scientist-clinician should be.

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Amitabh Gautam
Department of Surgery, Section of Transplant Surgery, Boston University School of Medicine, Robinson 4400, 72 E Concord St, Boston, MA 02118, United States
E-mail address: agautam@bu.edu.

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