第 **897** 回 千葉県がんセンター研究所集談会

演題：TARGETING THE TGFB AXIS TO TACKLE RESISTANCE TO CANCER THERAPIES

演者・所属：**Rosemary J. Akhurst PhD.**

Helen Diller Family Comprehensive Cancer Center and Department of Anatomy, University of California, San Francisco, CA, USA.

日 時 ： 令和 **7** 年 **4** 月 **18** 日（金）午後 **3** 時 **30** 分～午後 **5** 時 **00** 分

場 所 ：千葉県がんセンター旧事務研修棟 **2** 階大会議室

要 旨 ：

TGF-β has long been known to have a variety of activities on tumor cells and cells of the tumor microenvironment, including tumor suppressive and tumor progressing processes, dependent on cell type and stage of tumorigenesis. Utilizing the mouse skin model of chemically induced carcinogenesis, our lab has investigated these mechanisms and the utility of targeting TGF-β signaling for cancer therapy in cutaneous SCC and other tumor types. As tumors progress, becoming invasive and metastatic, they show elevated levels of TGF-β and TGF-β signaling. Moreover, many existing cancer therapies including chemotherapy, radiation and immunotherapy, further potentiate TGF-β signaling to drive a cancer stem-like state that resists therapy. I will discuss recent data showing how the stem cell signaling networks are rewired as epithelial cells transition from normal keratinocytes, through the benign tumor state to malignant carcinomas, and the close association between TGFB1 and stem cell markers in papillomas and carcinomas but not in normal tissue.

I will also describe efforts to target TGF-β ligands for cancer therapy and barriers to success, as well as ongoing studies to target activation of latent TGF-β within the tumor using an antibody to anti-αvβ8 integrin. Tumor responses to TGF-β blockade in combination with immune checkpoint blockade therapy are influenced by the tumor mutation load, CD4+ T cell content, and by germline genetic variants or modifier genes. High mutation load tumors respond better to combinatorial immunotherapy due to a higher neoantigen load on the tumor cell. CD4+ T cells play a critical role in therapeutic responses to TGF-β blockade as TGF-β drives CD4+ T cell polarization towards Tregs, Th2 and Th17 cells at the expense of Th1 help T cells, that promotes tumor progression. Moreover, αvβ8 integrin is enriched on Tregs where is activates TGF-β to suppress the cytotoxic T cell responses and drive tumor progression. Finally, I will demonstrate the activity of a germline TGF-β genetic modifier in conferring resistance to immunotherapy, offering further drug targets to enhance immunotherapy responses, and emphasizing the importance of personalized approaches to TGF-β blockade therapies for cancer.