Shawn Demehri, MD, PhD

The focus of **the Demehri laboratory** is to determine the role of the immune system in regulating the early stages of cancer development in order to harness its anti-tumor potential for cancer prevention and treatment. To date, several cancer immunotherapies have been developed with proven efficacy against late-stage cancers; however, the role of the immune system in preventing the early development of cancer remains uncertain. The research in the Demehri laboratory is focused on identifying the immune mechanisms that drive an immune activation sufficient to prevent cancer formation from pre-cancerous lesions. This approach raises a great opportunity to discover novel immune pathways that can be leveraged in cancer prevention and therapy.

Demehri Laboratory

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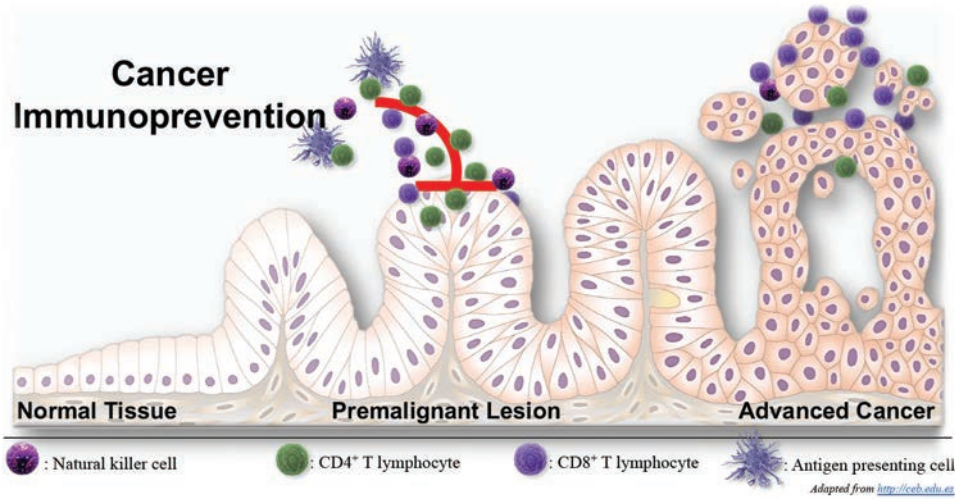
The field of cancer immunology has made substantial advances in recent years by deciphering the role of the tumor infiltrating CD8+ cytotoxic T lymphocytes (CTLs) in attacking cancer cells, which have led to promising new cancer immunotherapeutics. The current immunotherapeutic approaches, however, are largely designed to boost the anti-tumor immune response that has already formed against late-stage metastatic cancers. Therefore, the current cancer immunotherapies like immune checkpoint blockade, which rely on a pre-existing CTL infiltrate in the tumor for their effects, are proven ineffective to treat cancers that frequently lack a significant anti-tumor immune infiltrate, especially during the early in-situ phases of their development. In order to expand the potential of cancer immunotherapy, our laboratory studies the pathways that lead to immune system activation against early phases of cancer development. Devising a mechanism to activate the immune system against early-stage cancers has clear immunopreventive implications by directly blocking the cancer promotion and immunotherapeutic benefits by potentiating the immunity against late disease.

To pursue this goal, our laboratory studies the role of alarmins, damage-associated molecular patterns (DAMPs)/stress signals, commensal viruses, carcinogens, and aging-associated factors in regulating early cancer development. The major areas of research in our laboratory are:

1) Mechanisms of CD4+ T cell activation against cancer. Our laboratory has studied the mechanism of thymic stromal lymphopoietin (TSLP) in evoking tumor suppression. TSLP is an epithelial-derived cytokine that plays a central role in stimulating CD4+ T helper 2 (Th2)-mediated allergic diseases like atopic dermatitis and asthma. We have shown that high TSLP levels establish a dominant anti-tumorigenic immune environment preventing cancer promotion. Currently, our team investigates the detailed mechanism of TSLP anti-tumor function against solid cancers and examines its application for the treatment of pre-cancerous skin and breast lesions in patients.

2) Mechanisms of natural killer (NK) cell recruitment and activation against cancer. NK cells are known for their potent anti-tumor properties. However, their role in controlling cancer development in vivo remains unclear. Our laboratory utilizes an NK cell-specific activating ligand to determine the combination of signals necessary to activate NK cells against early stages of carcinogenesis and to identify the mechanism of anti-tumor immunity mounted



Immune Regulation of Early Cancer Development.

by the activated NK cells to block cancer promotion and progression.

3) The impact of commensal viruses-immune system interplays on the homeostasis of the organs exposed to environmental carcinogens. We aim to determine how the immune system's control of commensal virome regulates the homeostasis of the virus-colonized tissues. Through this effort, we aim to realize the beneficial functions of commensal virome for the prevention and treatment of cancer and other chronic diseases that affect humans.

4) Mechanisms of cancer promotion by the immune system. Although immune cells can mount anti-tumor immunity against cancer, they are also implicated in promoting cancer development in chronic inflammation. Our laboratory studies the initiating mechanisms of cancer-prone chronic inflammation development in the skin, pancreas, colon and liver, which are the major organs affected by chronic inflammation and its cancer sequela.

Selected Publications:

Hasegawa T, Oka T, Son HG, Oliver-García VS, Azin M, Eisenhaure TM, Lieb DJ, Hacohen N, **Demehri S**. Cytotoxic CD4+ T cells eliminate senescent cells by targeting cytomegalovirus antigen. *Cell*. 2023 Mar 30;186(7):1417-1431.e20.

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Li K, Li T, Feng Z, Huang M, Wei L, Yan Z, Long M, Hu Q, Wang J, Liu S, Sgroi DC, **Demehri S**. CD8(+) T cell immunity blocks the metastasis of carcinogen-exposed breast cancer. *Science Advances*. 2021 June 18; 7(25): eabdB936.

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