CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP100728

Project Title:
Development of a Synergistic Genetically Enhanced Dendritic Cell/Natural Killer T Cell Vaccine for Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
Levitt, Jonathan

Entity:
Baylor College of Medicine

Lay Summary:

Many traditional cancer treatments carry high toxicities due to lack of specificity and can cause new cancers even decades later. Instead, immunotherapy has the potential to selectively target cancer cells without damaging surrounding tissue or causing additional mutations. To be effective, immunotherapy needs to manipulate the immune system to circumvent this immune-suppression. As a result of their key role in activating tumor-specific, killer T cells, blood-derived dendritic cells (DC) have been used to expand tumor-specific immune responses in patients. However, pre-existing methods to activate these DCs have been largely insufficient, partly because therapeutic DCs are typically activated in culture before arrival at tissue-draining lymph nodes (dLNs), where they meet tumor-reactive T cells. If activated prematurely, these DCs can release T cell-specific growth factors before they are required and can be inactivated too quickly. In contrast, we describe a completely novel way to be able to activate tumor-targeting DCs only after they have sufficiently already arrived in dLNs. We accomplish this by re-engineering two cell-signaling receptors, the TLR4 and CD40 receptors, to respond to a membrane-permeant crosslinking drug, called AP1903. These receptors are “fused” in a single protein, so that one drug can activate both synergistic signaling receptors, leading to potent DC activation at the “right time” and the “right place”, after LN arrival. Our preliminary data shows that this approach can shrink and even eliminate large, aggressive pre-existing tumors. The 3 aims of this proposal are designed to optimize the use of these drug-inducible genetically enhanced DCs, to answer a key question about the relationship between DC activation level and expansion of long-lived memory T cells, and finally to convert this new vaccine approach to a portable, “off-the-shelf” vaccine. If successful, our platform will be widely applicable to a broad range of tumors and even infectious agents.