

Immunotherapy and Prevention

Mission:

Create and implement a national strategy to discover and evaluate novel immunotherapies that, in the short term, increase the cure rate in cancer patients and eventually provide the opportunity to develop immune-based approaches that prevent cancers of all types. A subset of immune-responsive cancers, such as lung and melanoma, and their premalignant lesions will be targeted, as well as a subset of cancers where immunotherapies have yet to be routinely successful, such as prostate, ovarian, brain and pancreatic cancers, and their premalignant lesions. Some of these cancers are high-risk because of genetic susceptibility (e.g., ovarian) and provide synergistic opportunities (e.g., develop biomarkers) with other recommendations of the Blue Ribbon Panel. In addition, a specific focus on a subset of pediatric tumors will be included since pediatric tumors are unique in their origins and biology.

To accelerate advances in immunotherapy for cancer treatment and prevention, we propose to develop a comprehensive program that would include constructing an immune atlas similar to The Cancer Genome Atlas (TCGA), cataloging the genetic, epigenetic, and inflammatory pathways for each of several tumor types and their precursor lesions, together with a translational program that provides rigorous testing of novel immunotherapies that overcome fundamental obstacles to successful treatment. Critical to this program is the revealing of antigens that can be recognized by the immune system and the development of vaccines or engineered immune cells to target these antigens. **The overriding goals are:**

- **To activate and redirect our own immune systems to attack and kill all cancers.**
- **To develop anti-cancer vaccines as potent as current polio, diphtheria, and rubella vaccines that will protect future generations from developing cancer.**

Key Concepts:

1. Our immune system has the intrinsic potential to recognize cancer cells as “foreign” and kill them.
2. The key cell that mediates immune surveillance against cancer is called a T lymphocyte or “effector T cell”, which becomes activated to kill the cancer cell by recognizing those components in tumor cells that distinguish them from their normal counterparts. T cells can be stimulated or engineered to recognize unique molecular features of tumor cells.
3. Orchestrating the destruction of cancers that escape normal immune surveillance relies both on the ability to direct T cells to recognize the tumor as foreign and to overcome a disabling, immunosuppressive tumor microenvironment. The extended application of immunotherapy to treat a broad range of cancers will require the identification of novel tumor antigens, the ability to target T cells to recognize these antigens, and strategies to disrupt the immunosuppressive properties in the tumor microenvironment.
4. The interaction between the immune system and cancer reflects a fundamental principle that is applicable to all or nearly all tumor types.

5. The elimination of cancers “before” they develop and become malignant is an aspirational goal. As in cervical cancer, where vaccination against human papilloma virus has virtually eliminated the disease, the development of cancer vaccines to stimulate the T cell to recognize that cancer cells are foreign will **prevent** cancer.

Where we are now (successes and challenges of immunotherapy)?

We know what is possible! The success rates of first generation cancer immunotherapies, such as checkpoint inhibitors, genetically engineered T cells, and new immune activators, have improved remarkably over the last 10 years, resulting in durable, long term survival, and in some cases cures, for a subset of patients with advanced cancers such as melanoma, blood, and lung cancers. For many such patients, these life-saving drugs were their last hope years ago, and we are delighted to hear them and their families tell their stories today. However, the numbers of patients who benefit from these drugs are too few. Indeed, only 10-20% of these patients respond long-term to current immunotherapies. Furthermore, patients with many other types of cancer, such as ovarian, breast, pancreatic, brain, and prostate cancer in adults, as well as most pediatric cancers, have a brief or non-existent response to currently available immunotherapies. The challenge therefore is to increase efficacy, both in terms of the percentages of patients and the types of cancer that derive a benefit from immunotherapy.

Cancer prognosis is correlated with the presence of effector T cells in tumor sites. Hence, the ultimate goal for all approaches to treating cancer is getting activated effector T cells into the tumor to maximize anti-cancer T cell activity and improve prognosis. Although less data are available, T cells are likely the main effector cells in preventing all forms of cancer, including those that arise from viral infection and those that are due to genetic changes in normal tissue.

The immune system can be educated to prevent cancer. A few vaccines are approved for preventing virally-induced cancers (cervical and liver cancers). A long term goal of this initiative is to develop vaccine approaches that can prevent most forms of cancer that are not caused by viruses. To achieve this goal, we will also need to identify antigens that arise from the earliest genetic changes that initiate cancers, develop novel vaccine approaches that can produce T cells that recognize these antigens, and identify early signals within developing tumors that are barriers to T cell function at precancer sites.

In addition, cells of the immune system, particularly T cells, can be redirected to recognize and kill cancer cells by genetically engineering them to express receptor molecules that sense tumor antigens. These engineered T cells, when transferred back to patients, have been highly successful in treating certain blood cancers. Nonetheless, for most cancers, we know little about what antigens can be safely and effectively targeted to discriminate between cancer and normal tissues. To improve engineered T cell therapies, we will need to identify antigens or antigen combinations that are unique to cancer, develop receptors and circuits that allow targeting of these antigens, and improve our ability to optimize the efficacy and safety of these cellular therapeutics.

Hence, this moonshot program is focused on two key actionable, patient-based strategies that must be rapidly advanced in order to ensure maximal progress against all cancers in all individuals. The first is development of robust cancer immunotherapies, especially vaccines and engineered T cells that target relevant antigens that distinguish cancers and their premalignancies. The second is development of approaches to overcome an obstructive, immune-suppressive tumor environment. In short, we must learn how to **both strengthen T cell immunity - either through immunization or engineering -- and concurrently how to disrupt a hostile tumor microenvironment that prevents T cell activation and infiltration into premalignant or cancerous tissue.**

Recommendation 1: Cancer Moonshot Clinical Trial Immunotherapy Network

We are in an extraordinary period of opportunity, with the advent of unique technologies, including imaging, genomics, proteomics and ability to manipulate and analyze large datasets that can change the way we conduct and evaluate clinical interventions. The therapeutic potential of the adaptive immune system has not been effectively exploited due to two major barriers, our failure to identify unique cancer cell antigens that can be targeted by T cells, and the presence of an underlying immune-suppressive environment that surrounds the tumor and begins forming as early as the first premalignant change – barriers that only recently have been appreciated as the first immunotherapies have entered the market.

There are two kinds of cancers - those that tend to be sensitive to activated T cells (e.g., melanoma, kidney, bladder, and lung) and those that resist being controlled by activated T cells (e.g., prostate, ovary, breast, pancreas, and brain cancers). We must find answers soon to the following 2 questions by studying patients with these cancers.

- 1) Why do a minority of patients who have melanoma (e.g., President Jimmy Carter) or lung cancer respond to therapeutics like checkpoint blockade?
- 2) Why do cancers like prostate, pancreas, and ovarian cancer rarely respond to T cell activation checkpoint blockade or other immunotherapies?

We believe that success will depend on understanding each tumor's unique microenvironment consisting of cancer proteins and immune-suppressive pathways, as well as efficient and effective translation of pre-clinical studies into patients. This will **require a nationwide infrastructure to facilitate immunotherapy trials**, which may include a limited number of patients, but should be conducted as part of a larger clinical database to allow pooling of data, comparative analyses, and rapid implementation of combination therapies across a whole spectrum of therapies (i.e. immunotherapies, cell-based therapies— as well as small molecules— and more conventional targeted cancer therapies such as oncogene inhibitors and radiation (e.g., impact of heat, cryo-electron microscopy, ultrasound) that may engage and activate immunity as a consequence of immunogenic cell destruction). This will require the assembly of a national database that includes these trial data, as well as details of cancer histology, tumor antigens, markers of immune suppression, patient demographics, and clinical outcomes (i.e. the immune atlas described below). This is best accomplished via a coordinated effort of clinicians and scientists with a keen appreciation of the importance of collaboration.

We propose to **create a robust national clinical trials network** to overcome the barriers to cancer elimination present in many tumors.

Approach:

Create and implement a national strategy to discover and evaluate novel immunotherapies to produce cures both in patients with cancers where immunotherapy has demonstrated success, such as in lung cancer, renal cell cancer, and melanoma patients, and in patients with advanced cancers for which immunotherapy has demonstrated little success thus far, such as prostate, ovarian, pancreatic and brain cancer patients who currently have little hope for long-term survival. To accelerate advances in immunotherapy, we propose the “Cancer Moonshot Clinical Trial Immunotherapy Network” to take advantage of a standardized baseline protocol (including drug treatments, tissue acquisition, and biomarker interrogation) embedded into the broader community (both academic and industry) to test novel immunotherapies efficiently and with a deep understanding of how pathways work and influence each other, as well as additional fundamental obstacles to success. Specific areas that are burgeoning or would benefit from a more concerted effort include senescent cells and molecular signaling methodology.

The Network will focus on:

1. Tumor and premalignant lesion target identification
2. Tumor and premalignant lesion microenvironment to identify immune- suppressive signals (and mechanisms of checkpoint signaling, such as T cell metabolism) that prevent T cell activation and entry into premalignant and malignant lesions
3. Testing of new combinations of checkpoint and immune enhancers informed by these biomarker studies. Developing animal models appropriate for these immune studies.
4. Developing and testing cancer vaccines informed by target identification
5. Developing and testing therapeutic T cells engineered to recognize identified disease target antigens and to overcome immunosuppression

Our central premise is that we have **uncovered only the tip of the iceberg** in immunotherapy treatments, and that human studies using newly developed interdisciplinary, cutting edge, technologies are key to further advancements. Success will be recognized by the development of new combination immunotherapy treatments that increase the success of current immunotherapies today in more patients with many different cancers and lead to vaccines and cell therapies that can be employed for treatment and prevention of cancer, and therapeutic cures.

Recommendation 2: The Cancer Immunity Atlas (TCIA)

Critical to achieving benefit from immunotherapy for all patients with cancer and to developing vaccine approaches that prevent cancer in future generations is the creation of a comprehensive, dynamic and easily searchable database that aggregates multiple datasets to describe the immunological profile of human cancer and its premalignant lesions as well as the genetic and environmental factors that can influence cancer immunity. TCIA data will provide insight into cells that affect immune response but the Atlas will not test hypotheses. These data

should be linked to patient demographics and outcomes. The resulting biology is expected to engage technology and pharmaceutical companies. The data should be gathered from the proposed Clinical Trial Immunotherapy activity as well as from the external cancer research community and freely accessible to all researchers and to the general public.

Scope: The long-term goal should be to include all human cancers and their premalignant lesions (solid, liquid), with a special focus on pediatric cancers, but the project should begin by concentrating on at least two major adult and 2 major pediatric cancers and their associated premalignancies. At least one adult cancer type should be a cancer where immunotherapy has proved efficacious: melanoma, NSCLC, bladder, breast cancer (TNBC), colorectal cancer (MSI^{hi}). At least one adult cancer should be a cancer where responses are poor (CRC- MSI^{lo}, prostate, pancreatic). Including cancer types that have responders to currently employed immunotherapies and cancers that have non-responders to these same immunotherapy drugs will provide many opportunities to compare the differences in tumor micro-environments across cancers of the same and different sites of origin and biology. A set of pediatric cancers should include a responder and non-responder to a therapy as recommended by the Pediatric Oncology Working Group.

- Initial workflow should include the complete annotation of 1000 tumors in each indication using archival specimens. These data will serve as a general resource and training set for subsequent efforts, similar to that of The Cancer Genome Atlas (TCGA). Use of archival samples will accelerate population of the TCIA database.
- The highest priority and greatest value dataset, however, will be to collect and annotate biomarker data using paired samples from patients prior to and following treatment with approved immunotherapies (currently, anti-PD-L1/PD-1; anti-CTLA4 agents).
- Actual choice of indication(s) for the initial training set will be influenced by the availability of sample collections that will permit the planned analyses (see below). This decision can be made after consideration by the steering committee and its advisors.
- A next step would be the analysis of the evolution of cancer from premalignant to metastatic disease focusing on the cancer cell-immune system interactions.
- Similar analyses could be performed using samples from patients prior to and after treatment with adoptively transferred T cell therapies (currently in clinical trials).

Content: Data for each tumor and patient should include all relevant information. The TCIA database should be constructed using an open source, flexible structure that will permit the entry and relational searching of all forms of data ranging from sequence to imaging information. Priority should be given to the following:

- Tumor RNAseq, from bulk tissue and single cell
- Patient exome sequence for SNP identification
- Mutant neo-epitope discovery (in coordination with the Antigen Discovery and Tumor Microenvironment program)
- Cancer-testis, differentiation antigen, overexpressed shared antigens, viral antigen discovery

- TCR usage
- Microbiota (gut, lung, skin)
- Multiplexed IHC/IF analysis of tumor sections
 - T cell infiltrates
 - Myeloid/monocytic cell infiltrates
 - Stromal architecture
 - metabolism
- Radiologic imaging
- Treatment and medical history
- Non-oncology pharmaceutical history
- Geographic residence
- Patient demographics, including age, gender and ethnicity
- Mutational status for common cancer susceptibility genes (e.g. deleterious mutations in BRCA, p53, PALB2, mismatch repair genes, and others)

Technology development: TCIA should promote the development of new technologies and computational methods to support its mission and that would contribute to the emerging database. These can include:

- Radiologic imaging methods
- Nuclear medicine imaging methods: new metabolic probes, immunoPET
- Quantitative imaging of cell distribution and function in biopsy samples
- Cross-referencing to TCGA datasets
- Facile approaches to T cell epitope identification and TCR diversity
- Single cell transcriptome analyses in unprocessed tissue
- Multiplexed in situ hybridization transcriptome analyses
- Multiplexed morphological-immunohistochemical-molecular analyses in fixed tissue