New Era for the Treatment of Cancer and Genetic Diseases

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Gene Therapy

Initial Strategy: Transfer of genetic material into cells to treat inherited genetic diseases

- First successful trial in 1990 at the NIH for Severe Combined Immune Deficiency (SCID)
    - Delivery of adenosine deaminase (ADA) gene via a viral vector to restore protein function in a 4 year old female

- Early clinical trials in 1990s resulted in setbacks due to
    - Inflammatory responses to vectors
        - In particular adenoviral vectors (AV)
    - Malignancies caused by insertional activation of oncogenes
        - In particular retroviral vector murine leukemia virus (MLV)

Numerous advancements in viral vector development, T cell activation, manufacturing and targeting specific diseases led to current successes in gene therapy

Advancements resulted in novel cancer therapies

Engineering of lymphocytes to target and kill cancer cells

One approach is through the use of CAR T-cell therapy

- Patient undergoes apheresis
- T cells are isolated and genetically modified by a viral vector to express a chimeric antigen receptor (CAR) resulting in CAR T-cells
- Cells are expanded and infused back into the patient
- CAR T-cells find and attack the cancer cells
  - Cells continue to propagate and destroy cancer cells

First Gene Therapy Approval – CAR T-cell Therapy

Novartis CAR T-cell therapy Kymriah™ (tisagenlecleucel)

Approved in 2017 for children and young adults with B-cell acute lymphoblastic leukemia (ALL)

- CD19 is the most ubiquitous expressed protein in B lymphocyte lineage
  - ➢ CD19 is down-regulated in differentiated plasma cells
  - ➢ CD19 expression is maintained in B-cell malignancies
  - Patient undergoes apheresis
  - T cells are extracted off-site, transduced with a lentiviral vector for the expression of antigen binding domain (anti-CD19) in T cells - CTL019
  - Cell expansion, quality assessment prior to patient infusion

Future of CAR T-cell Therapy

- Regulating CAR T-cell persistence
- Moving beyond hematologic malignancies to solid tumors
- Identification of target antigens
- Targeting multiple cell surface markers
- Use of check point inhibitors with CAR T-cell therapy

Genome Editing - Gene Therapy Approach

CRISPR technology (Clustered Regularly Interspaced Short Palindromic Repeats)

Background: Bacteria have a built-in gene editing system in response to invading pathogens, viruses. Portion of the virus is cut and retained by the bacteria to recognize and defend against future viral attacks.

2012 Scientific Development of CRISPR genome editing

Viral vectors to express Cas9 nuclease and single guide RNA for knocking out gene expression

- First clinical studies in US for beta-thalassemia and sickle cell
- Several clinical studies are underway in China for genetic diseases and cancer (HPV)