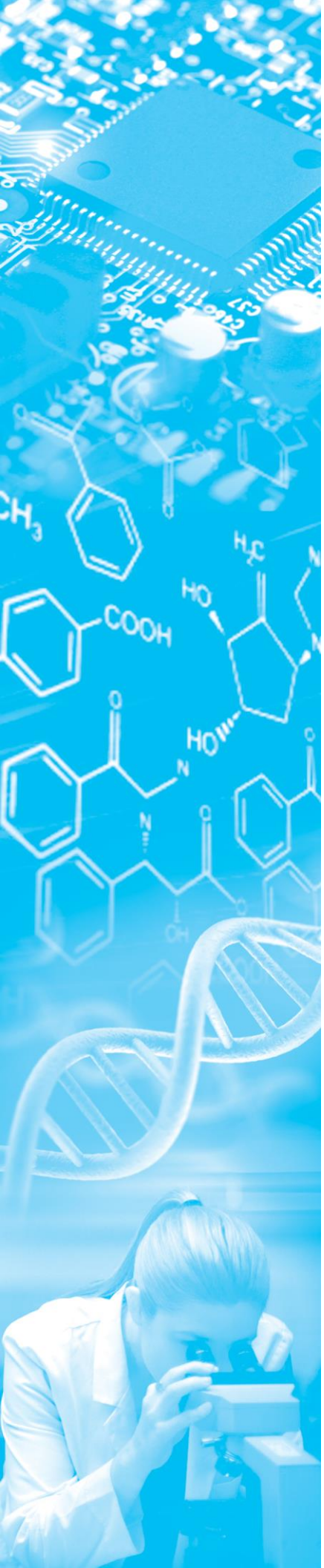

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Genetically Modified Natural Killer Cells for Immunotherapy

Immunotherapy has made significant progress over the last decade and today there are multiple immuno-oncology therapies available to patients. Although there are other avenues of cancer treatment such as chemotherapy or radiation therapy, the adverse events, recurrence of malignancies and lack of specificity associated with these traditional therapies are driving researchers and health professionals to search for advanced therapeutic options such as immunotherapy. The global oncology immunotherapy market alone is predicted to reach a total value of US$118.8 billion by 2025. One type of immunotherapy that is gaining prominence is the application of Natural Killer (NK) cells as agents of cell-based therapies. Currently, multiple treatments applying NK cells are going through clinical trials and some of them have produced promising results. Although NK-cell based immunotherapies have demonstrated efficiency against different ailments in clinical studies, they are still lacking in safety, specificity and efficiency. One of the major concerns in the development of an efficient immunotherapy is mispairing of T cell receptor (TCR) chains. Researchers at NSU developed a novel technology to bypass this issue posed by currently used immunotherapy strategies. This invention can be implemented to develop genetically modified (GM) NK cells, which selectively target antigens in complex with Major Histocompatibility Complex (MHC), thus offering a more efficient therapeutic option for treatment of cancer and other diseases.

Technology

This technology is an immunotherapeutic method that implements T cell receptor (TCR) gene transfer to modify NK cells. The innovative strategy genetically modifies NK cells to express antigen-specific functional TCR complexes. The technology allows researchers to retarget these NK cells towards various cell surface antigens, including tumor-associated antigens (TAA). This unique approach enables the therapy to overcome challenges resulting from mispairing of TCR α and β chains. In addition, it provides MHC-restricted antigen-specific cytotoxicity to the NK cells. These modified NK cells are suitable for being used with different therapies such as immunotherapy, T cell receptor gene therapy, and adoptive therapy. As this technology can be used to develop GM NK cells that can target different antigens, the therapeutic application of this immunotherapy is not restricted to the treatment of cancer. Owing to this versatility, the technology can produce reprogrammed NK cells suitable for treatment of cancer, graft versus host disease, viral infections, and autoimmunity.

Application

- This novel technology can be used to produce NK cells that target tumor-associated antigens (TAA) or melanoma-associated antigens. Therefore, it can be used as a therapeutic agent in cancer immunotherapy.

- In addition to targeting TAA, these GM NK cells can target viral infections, autoimmunity and graft versus host disease. Hence, the therapeutic application of this immunotherapy is not limited to oncology.

Advantages/Benefits

- As these modified NK cells possess MHC-restricted antigen-specific cytotoxicity, this mode of immunotherapy will have superior specificity compared to other similar treatments.
- Can be applied in the treatment of multiple diseases including cancer, viral infections, graft versus host disease and autoimmunity.
- Overcomes the issues faced by other immunotherapies owing to mispairing of TCR α and β chains and hence can be more efficient.

Status of Development

- NSU researchers successfully generated GM NK cell lines expressing TCR
- Ability of these GM NK cells to detect specific antigens and induce killing of targeted cells were validated through functional assays
- Repeated dosing of GM NK cells demonstrated efficacy in killing tumor in an *in vivo* experiment using NOD/SCID mouse model

Intellectual Property Status – PCT submitted in January 2018.

Information on Inventors

Adil Duru - Dr. Adil Duru is an Assistant Professor at NSU's Cell Therapy Institute. Dr. Duru also serves as a Clinical Research Assistant Professor of Biomedical Sciences at NSU's Dr. K.C. Patel College of Allopathic Medicine. His current research at NSU's Cell Therapy Institute focuses on cancer immunotherapy and is conducted in collaboration with colleagues from Karolinska Institutet.

Dr. Tolga Sutlu – Dr. Tolga Sutlu is a Senior Researcher at Sabançi University's Nanotechnology Research & Application Center in Turkey. Dr. Sutlu's research group focuses on developing novel methods of cancer immunotherapy and gene therapy.

Dr. Batu Erman – Dr. Erman is currently an Associate Professor at the College of Engineering and Natural Sciences in Sabançi University in Turkey. His research interests include molecular mechanism of signal transduction and gene activation in the mammalian immune system.

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