Combination of epigenetic modifying agents and gamma delta T lymphocytes for immunotherapy of solid cancers

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Experience:

Dr. Tsai received her medical degree at National Taiwan University (NTU) and completed Internal Medicine residency and Pulmonology fellowship at NTU Hospital. Subsequently, Dr. Tsai received her PhD and postdoctoral training in a cancer epigenetics laboratory at Johns Hopkins University School of Medicine. Following her research training, Dr. Tsai joined the faculty of Graduate Institute of Toxicology at NTU College of Medicine. She also resumed her clinical practice as attending physician in the Department of Internal Medicine at NTUH. The patient-care experiences and medical knowledge learned over the years laid a strong foundation for Dr. Tsai to conduct biomedical research with high clinical relevance and implications. Dr. Tsai's past and current research achievements include molecular and cellular mechanisms of two DNMT1 inhibitors, 5-aza-2'-deoxycytidine and 5-azacitidine (*Cancer Cell 2012*), interactions of DNA methyltransferases in maintaining cancer-specific DNA methylation across major genome features (*Genome Research 2017*), as well as potentiating effects of epigenetic therapy for γδ T-based cellular immunotherapy in lung cancer (*Nature Communications, 2021*), among others. Dr. Tsai has received several prestigious institutional and national research awards in the field of cancer epigenetics. She also holds two provisional patents on novel diagnostic and therapeutic strategies in cancer. Dr. Tsai is now the deputy director of NTUH Center for Frontier Medicine and help facilitate clinical development of cellular immunotherapy in cancer.

Market Needs:

Despite the advances in multimodality cancer therapeutics, cancer remains a global health threat and accounts for nearly 10 million deaths worldwide in 2020. Among all cancers, lung cancer is the leading cause of cancer death. Each year, 2.2 million people in the world are newly diagnosed as lung cancer,and approximately half of them have advanced diseases ineligible for curative surgical treatments. Similarly, about 15000 people are diagnosed as lung cancer in Taiwan and 46% of them have stage IV diseases. Most patients with advanced diseases who receive targeted therapy, chemotherapy, or checkpoint inhibitors will eventually develop resistance to the treatment. These patients are potentially eligible for the adoptive transfer of autologous or allogeneic γδ T cells in combination with epigenetic therapy as developed by our team, which represent a tremendous market opportunity. In addition, our therapy can also be applied in other solid cancers and thus may account for annual revenues of 5-10 billion NT dollars.

Our Technology:

γδ T cells, a distinct subset of T cells that sense molecular stress signals from pathogen-infected or transformed cells, can display broad tumor-targeting capabilities in a major histocompatibility complex (MHC)-independent manner. We developed a novel therapeutic strategy by combining a DNA demethylating agent and the adoptive transfer of patient-derived γδ T cells to combat cancer. We developed an novel expansion protocol for clinical-grade expansion of γδ T cells in vitro, and discovered that the addition of DNA demethylating agent enhances the immune synapse formation between lung cancer and γδ T cells, thereby significantly enhancing γδ T-mediated killing of cancer cells. In addition, we identified an immune synaptic-cytoskeletal gene signature for patient stratification to maximize the benefits of γδ T-based therapy. The findings were published in *Nature Communications* in April 2021 with a provisional patent on file.

Strength:

Our γδ T-based therapy has several strengths:

1. We developed a reliable clinical-grade expansion protocol of γδ T cells suitable for clinical uses in patients.
2. DNA demethylating agents have been approved by the US FDA for the treatment of hematological malignancies. Repurposing of these drugs in combination with γδ T-based therapy can significantly reduce the development time and costs.
3. The mechanism of action of this combined epigenetic and γδ T therapy is different from all existing cancer treatments and may be uses in patients who failed multiple conventional therapies.
4. Our therapy is suitable for either autologous or allogeneic adoptive transfer since γδ T cells target cancer cells in an MHC-independent manner. Therefore, patients have more options in terms of donor selection and better chances for a successful therapy.

Competing Products:

In Taiwan, development of γδ T-based cellular therapy are mostly still in the preclinical phase. There is no competing product on the market yet. Our team leads the field in terms of γδ T cell expansion, the strategy of epigenetic priming, and gene signature for patient selection. In the world, there are several companies that are specialized in the development of γδ T-based cellular products, such as GammaDelta Therapeutics (UK), Adicet Bio (US), etc. Most companies are still in the preparatory process to launch clinical trials in patients.

Intellectual Properties:

US provisional patent: **Tsai HC**, in CT, Huang TC, Weng RH (2021) METHOD FOR TREATING CANCER, Patent Number: 63/139820

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