MAYO CLINIC

2023 Stewardship Report

Philanthropy at Mayo Clinic

Respectfully presented to Desert Mountain CARE

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Thank You

On behalf of Mayo Clinic, thank you for your long-standing philanthropic partnership. Thanks to you, we are advancing critical cancer research that will bring hope and healing to patients from across the Valley and around the globe.

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Research Updates

Adoptive T-Cell Clinical Trial for Multiple Myeloma

T-cell redirection therapies are revolutionizing the treatment of blood cancers. T-cells are part of the immune system and play an important role in protecting humans from viral infections and cancer. In order for cancer cells to progress, they must find a way to evade T-cells. Over the last 10 years, we have found that we can redirect T-cells so they recognize cancer cells as foreign invaders.

Previously, we developed a culture system that is able to amplify naturally occurring tumor-fighting T-cells without artificial manipulation. We believe this will result in safer therapies with longer effects, and we shared with you our plans for an adoptive T-cell therapy trial that will be the first investigator-initiated clinical trial to use immune effector cells manufactured in-house at our Phoenix campus.

We submitted an investigational new drug application to the Food and Drug Administration. We obtained the necessary approval and subsequently obtained Institutional Review Board (IRB) approval for the clinical trial and enrolled the first patient in June 2022. We have completed accrual to the first three dose levels without any dose-limiting toxicities, accruing one patient per dose level. The first and third patients have not progressed, while the second patient has progressed and moved on to treatment with CAR-T cells. We are preparing to start enrollment in the final dose cohort.

In order to have single patient cohorts we needed to close the protocol after each patient was treated. Although this has slowed accrual, it has allowed us to be certain that no dose-limiting toxicities developed during the first month following treatment.

During the next year, we expect to complete accrual of the study, which will require six patients. Because we will not need to close the study after each patient, we expect a faster accrual and hope to see positive responses. Additionally, we will begin planning for the next phase of clinical trials in ovarian cancer.

“We are very grateful for the support from this award, which will help us accelerate progress in the treatment of patients with multiple myeloma, and hopefully all patients with cancer.”

—Leif Bergsagel, M.D.
David F. and Margaret T. Grohne Professor of
Novel Therapeutics for Cancer Research

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Predicting Metastatic Potential of Cutaneous Squamous Cell Carcinoma Using Gene Expression

Our research team has sequenced and analyzed intermediate to high-risk cutaneous squamous cell carcinoma cases to identify a gene expressional profile (GEP) that predicts metastasis. We used the identified genes to create a risk score with a cutoff that is highly effective in predicting metastasis in the initial cohort.

To validate our results, we successfully developed a second generation of our initial GEP panel using Nanostring barcode technology, and an additional 250 samples have been identified. Tissue is currently being requested and extracted and is undergoing Nanostring sequencing for validation analysis. Preliminary review of the sequencing data on 117 cases shows that our assay can differentiate metastatic potential. Further validation is ongoing. Additionally, using the high-risk cases identified in both the initial and validation cohorts, a machine learning platform has been generated to stratify squamous cell carcinoma. Clinical studies with dermatopathologists are underway.

As we look to next steps, we will focus on validating our current findings and optimizing our panel based on initial results. Although identifying a sufficient number of cases that meet inclusion criteria is a challenge, we have adequate samples to complete the work, and we are preparing a manuscript outlining these results.

The team is able to properly identify the outcome of more than 90% of patients with high-risk skin cancer. For example, if our test is negative, the risk of the disease recurring or spreading is less than 5%, and if the test is positive, the risk of disease spread is greater than 90%. Those individuals at low risk can forgo unnecessary, costly and morbidity-generating procedures, and those at high risk can receive more aggressive treatment.

In the near future, we will be able to better stratify over 250,000 individuals diagnosed annually in the U.S. with at-risk squamous cell carcinoma. Currently, squamous cell carcinoma in the skin accounts for as many deaths as melanoma. With the implementation of our genetic assay, we hope to reduce the number of deaths from squamous cell carcinoma of the skin and more appropriately manage patients.

“Thank you for your continued support of our work to identify skin cancers at risk of spreading and shortening someone’s life. Our work has been able to move forward at lightspeed thanks to your generous gift.”

—Aaron R. Mangold, M.D.
Division Chair, Clinical Dermatology
Associate Professor of Dermatology

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Targeting advanced metastatic prostate cancer with a novel Fn14 inhibitory compound

This study is designed to assess the effectiveness of the Fn14 inhibitory compound against aggressive variant prostate cancer (AVPC) metastasis. AVPC is often considered a “cold” tumor, due to the reduced or complete lack of T-cell infiltration, either because of the missing tumor-associated antigens, lack of T-cell activation, or local immunosuppression.

Studies have shown that tumor-associated macrophages are mainly responsible for the immunosuppression observed in AVPC, but the mechanism remains unclear. To date, we have shown that a subpopulation of myeloid cells within the tumor microenvironment expresses high levels of Fn14. In tumor cells, activation of Fn14 induces chemotherapy resistance and survival, but in myeloid cells, activation of Fn14 results in the secretion of the immunosuppressive cytokines, including IL-6 and IL-10, potentially resulting in a shift of immune cell phenotype to an immunosuppressive function.

In addition, co-culturing of Fn14-expressing myeloid cells with T-cells suppressed T-cell proliferation and function in a murine model. Importantly, we showed that inhibition of TWEAK binding to Fn14 for activation by a novel Fn14 antagonist compound (K784-2278) suppressed TWEAK-induced IL10 expression in myeloid cells. We are currently assessing the systemic pharmacokinetics, pharmacodynamics and efficacy across multiple xenograft models (PDXs) derived from patients with prostate cancer and then integrating this PK-PD-efficacy model with human systemic PK data to predict a dosing regimen that will provide adequate systemic exposure of the Fn14 inhibitor (K784-2278) in human PCa tumors. We have shown that K784-2278 suppressed the invasion and survival of a highly aggressive human prostate cell line model in vitro KM3j7 as compared to the parental DU145.

Our team is currently working with the IRB to obtain and collect AVPCs to generate more relevant human primary-derived cell models for the in vivo testing of the Fn14 inhibitor. We anticipate approval by late summer/early fall of 2023, which will help us complete the in vitro and in vivo assessment of the Fn14 inhibitor across relevant human prostate lines.

Our next steps include:

1. Examine the cytokines induced by TWEAK-Fn14 in myeloid cells that promote an immunosuppressive T-cell function.
2. Assess Fn14 expression across prostate cancer tissues, including AVPC from the Mayo Clinic Tissue Repository Biobank.
3. Assess the systemic pharmacokinetics, pharmacodynamics and efficacy across multiple xenograft models (PDXs) derived from patients with prostate cancer and then integrate this PK-PD-efficacy model with human systemic PK data to predict a dosing regimen that will provide adequate systemic exposure of the Fn14 inhibitor (K784-2278) in human PCa tumors.

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Thank You

Health care is undergoing transformation like never before — and philanthropy is essential to driving that transformation. We are honored by your exceptional support as we innovate and revolutionize cancer care for people everywhere.

"If we excel in anything, it is in our capacity for translating idealism into action."

— Charles H. Mayo, M.D.

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