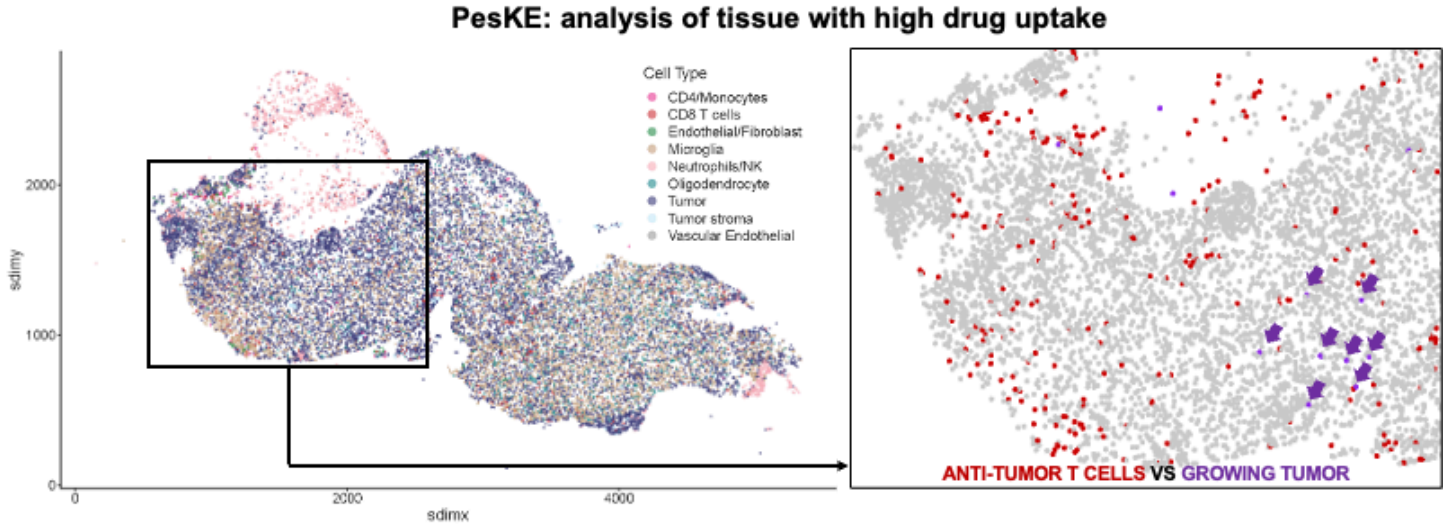
Duke Brain Tumor Center Researchers Present:
2025 Progress Report for the Knox Martin Foundation Regarding KMF Funded Clinical Trials

PesKE Trial: With the support of the Knox Martin Foundation, we completed the PesKE clinical trial in 2024 (NCT04937413) and identified a potential new treatment approach for patients with glioblastoma. This trial was designed to evaluate if a drug (evolocumab) entered tumors and made them more visible to anti-tumor immune cells (T cells).

We found that increasing amounts of drug correlated with increasing visibility of tumor cells. In the tissue where drug levels were highest, we saw very high levels of anti-tumor T cells dispersing throughout, including next to areas of rapidly growing tumor. Representative images of tumor tissue analysis are included below.

On the left, we characterize all the cells that were detected in tissue (tumor cells, immune cells and supporting cells). On the right we specifically identify areas of rapidly growing tumor (purple arrows), surrounded by anti-tumor T cells (shown in red). This pattern is not normally observed in aggressive tumors like glioblastoma, which often contain very few immune cells.



The funding from KMF made it possible to extensively characterize the tumor tissue of patients who received the drug. With this support, we determined that the drug could increase the visibility of tumors to anti-tumor T cells. We now will work on ways to increase the overall amount of drug that can get into tumors. Studies like PeSKE are the first step in re-thinking the way we develop new treatments for glioblastoma, where we first really understand the effects of drugs before spending more time and effort testing them in clinical trials. We will be formally reporting our results via a journal publication, with a pre-print currently available online for public review: https://www.medrxiv.org/content/10.1101/2024.06.19.24309192v2

TILs Trial: Regarding the TILs project generously funded by KMF, we have been optimizing methods for expanding immune cells from human tumors while investigating the factors that determine why some tumors successfully yield TILs while others do not. We have generated a substantial amount of data through single-cell and spatial sequencing of RNA, T cell Receptors (TCR) and proteins from these tumors. Currently, we are compiling these findings into a publication that will describe the differences between tumors that generated TILs and those that did not. This work will play a critical role in assembling the necessary application package for FDA submission, a key requirement before we can initiate a human clinical trial.

There are a couple of bottlenecks preventing us from advancing this TIL approach to a clinical trial, which we will outline below:

1. Antibody Manufacturing
   One of the antibodies we identified as highly effective in enhancing TIL functionality against tumor cells is produced by a Korean company. While they have provided material for our laboratory studies, they are unwilling to supply or authorize its use in brain tumor clinical trials. To overcome this limitation, we have identified a group capable of manufacturing the antibody for us at a cost. We are exploring different options of alternative suppliers for this antibody including a local company and a research group in Melbourne, Australia who might do this collaboratively at a smaller cost. Securing additional funding will allow us to produce this reagent for use in the planned human trial. Manufacturing this antibody is a critical next step in advancing the project, and we anticipate that this work will accelerate progress toward preclinical IND-enabling studies required by the FDA for clinical trial approval, contingent upon the timely production and validation of the new antibody.

2. TIL Sorting
   Another necessary step is sorting the TILs to isolate those that specifically recognize and target tumor cells from immune cells that lack this capability. This process requires a high-quality cell sorter, and we are currently assessing whether our existing funding is sufficient to support its purchase. Given the need to maintain financial stability and ensure staff salaries for the next few years, I am reluctant to allocate funding for the sorter unless we have a surplus of at least $300K beyond secured salaries.

FLIRT Trial: Recruitment for this study remains ongoing, though the rate of accrual has slowed. We believe this is due to the highly specialized patient population that is required for this complex type of study. To increase the potential pool of eligible patients, we have onboarded multiple other centers in 2024, including Stanford University, and UC San Diego. We are also actively engaging with other high-volume academic centers to see if they would be able to join the trial.

Further, we are performing ongoing review of our enrollment criteria to ensure that we can include as many potential participants as possible. We hope that these changes will result in more patients coming on study in 2025, and for us to begin to perform preliminary analysis on the outcomes of patients receiving fluoxetine/temozolomide.

In summary, we have successfully concluded one clinical trial and are actively continuing work on the second, with actions underway to boost enrollment and increase the speed of progress. This work would not be possible without the support of the whole team at the Knox Martin Foundation, for which we remain incredibly grateful.