DBMR Prize for Innovative Research Idea 2024

CAR T cells secreting synthetic proteins engaging solid tumors

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Chimeric antigen receptor (CAR) T cells have changed the treatment landscape of hematological malignancies. Still, antigen escape, reduced immune cell fitness, heterogeneous target antigen expression, and resistance through tumor and tumor microenvironment (TME) remain persistent barriers for CAR T cells in the quest against solid tumors. Recently, we generated a CAR T cell aiming at mesothelin able to secrete a T cell engaging molecule (TEAM) targeting not only pancreatic adenocarcinoma (PDAC) but also its TME. We could show the superiority of this CAR T cell construct in multiple ex-vivo and in-vivo model systems.
Considering the various modification options of such a CAR T cell construct, we will use synthetic single-domain proteins such as 'Designed Ankyrin Repeat Proteins' (DARPins) being integrated to be secreted by a CAR T cell. DARPins are not only small in size and stable, they have recently been approved for clinical use.
Taking advantage of the experience from earlier work in the lab of Dr. Maus (MGH, Harvard, MIT), I will generate CAR T cells targeting different types of solid tumors secreting synthetic proteins recruiting cells of the adaptive and innate immune system to increase the therapeutic use and efficacy of CAR T cells in solid tumors.

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Establishing the minor spliceosome as an innovative therapeutic target for breast cancer

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Dysregulated splicing is a well-recognized cancer hallmark, as such the spliceosome has emerged as a new frontier for cancer therapeutics. In a recent study, I found that cancer specifically employs a specialized spliceosome called the minor spliceosome (MiS) to splice the genes that drive cancer hallmarks and to increase cell plasticity. While I extensively established this concept in prostate cancer (PCa), my preliminary data strongly suggests that overactivity of the MiS is a broadly applicable oncogenic principle with potential implications for breast cancer (BCa), another prevalent and hormone-dependent tumor type. Additionally, my preliminary data indicates that blocking MiS activity induces a BRCAness phenotype in BCa and thus sensitizes towards DNA targeting treatments such as radiation or PARP inhibitors in BCa. Nevertheless, our understanding of how minor intron splicing contributes to BCa biology, heterogeneity and complexity of resistance is still lacking. Therefore, I propose to leverage my expertise in cancer biology and MiS to systematically study the role of minor intron splicing in BCa and to ultimately establish the MiS as an innovative vulnerability in genetically distinct molecular BCa subtypes that could be exploited as mono or combination therapy.

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The role of mitochondrial energy metabolism in adrenal hyperandrogenism: mechanisms and clinical implications

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The role of mitochondria in steroid synthesis is well established, but the specific effects of mitochondrial energy metabolism on adrenal androgen production are largely unknown. My preliminary data in an adrenal cell model show that defects in oxidative phosphorylation and mitochondrial pyruvate transport lead to adrenal hyperandrogenism. I propose that mitochondrial energy metabolism plays a critical role in directing adrenal steroidogenesis toward androgen excess that needs to be further elucidated. I will use the established H295R cell model to perform an in-depth analysis of steroid output, metabolic flux dependencies and transcriptional adaptations. In parallel, I will evaluate adrenocortical steroid profiles in children with primary mitochondrial disease (PMD) to characterize the occurrence of adrenal hyperandrogenism. This proposal aims to determine the impact of mitochondrial metabolism on adrenal androgen production, to define metabolic vulnerabilities for future treatment of hyperandrogenic diseases, and to establish the rationale for testing adrenocortical function in children with PMD.