October 2022

Swifty Foundation 2022 Impact Report

Updates on 2019 Co-funded Projects

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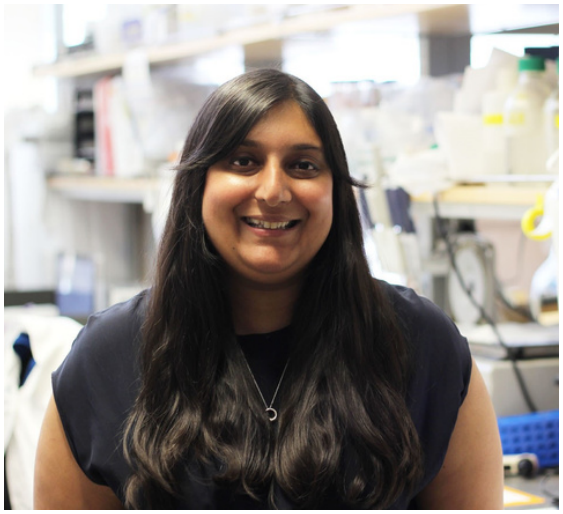
Targeting TGFb Dependencies in Group 3 Medulloblastoma

Zulekha Qadeer, PhD
The University of California, San Francisco
Young Investigator Grant

Dr. Zulekha Qadeer is now in the third and final year of her Young Investigator Grant. Her final report will be available after receipt and review in March 2023.

Progress Update

Neurons are nerve cells that populate the brain and are responsible for transmitting chemical signals to regulate several human functions. Medulloblastoma (MB), occurs when these neurons start to proliferate uncontrollably. Developing nerve cells, known as neural stem cells, can transform and get 'stuck' at a certain stage in brain development.



Recent work has identified alterations in distinct developmental pathways, TGFβ, in aggressive group 3 medulloblastoma. The functional significance of this pathway and how it cooperates with other cancer driving events, such as MYC amplification, is currently unclear. Our studies have focused on using a novel humanized model for MB utilizing induced pluripotent stem cells (iPSC) differentiated to neuroepithelial stem cells (NES), the presumptive cell of origin for MB. These cells have been genetically engineered to express MYC and/or TGFβ pathway effectors identified to be altered in Group 3 MB patients. Excitingly, we have validated that the combination of MYC and TGFβ pathway effectors accelerated tumorigenesis when injected into the brain of mice with some TGFβ pathway effectors causing tumor growth alone. We have utilized these cells as a platform to test out clinically relevant TGFβR1 inhibitors and found that MYC may be promoting drug resistance in these cells. We are now analyzing gene expression and epigenetic profiling from NES lines driven by MYC and TGF pathway effectors to identify new targetable genes and pathways that can overcome intrinsic resistance of Group 3 MB. Using our unique models, we hope to generate critical information on the mechanisms that drive Group3 MB with important therapeutic relevance.

Future Plans

In Year 3, our priority is to further decipher the mechanism(s) of drug resistance mediated by MYC and the TGFb pathway through in NES cells identified from our analyses with a focus on KDM2B.

Dr. Qadeer's findings were recently published in the Journal of Experimental Medicine.

Targeting Symmetric Division in Pediatric Cancers

Rosalind Segal, MD/PhD
Dana-Farber Cancer Institute
Innovation Grant

Final Report Summary

A protein called Eya1 has important functions in tumor formation and growth in medulloblastoma, a common brain tumor in children. In fact, decreasing the amount of Eya1 has been shown to reduce the number of deaths in mice with these tumors. We developed a compound, DS38, based off a known drug called benzbromarone, that works against EYA proteins. We found that this compound is better at interrupting Eya1 functions that benzbromarone in both mice and human tumors. Our data suggests that DS38 can increase the life of mice with medulloblastoma tumors. Therefore, our updated results show that this compound can be used to develop a new treatment for pediatric medulloblastoma by interrupting Eya1 functions.

Significance

The Sonic hedgehog (SHH)- subtype of medulloblastoma constitutes about 30% of medulloblastomas. Treatment for these cancers have not altered radically over the years, and new therapies are needed. Single cell sequencing indicates the haloacid dehalogenase (HAD) phosphate Eyes Absent 1 (Eya1) is a consistent feature that can be detected in every individual SHH-MB cancer cell, making the protein a potential avenue for developing selective therapies for these cancers.

Reduced levels of Eya1 expression have decreased mortality rates in mouse SHH-medulloblastoma models. We have previously found that Eya1 is critically involved in the normal development, promoting symmetric division of cerebrellar granule cell precursors, the cells of origin for SHH-subtype medulloblastoma. Benzarone derivatives have been suggested as allosteric EYA-inhibitors in past studies. Here, we developed and assessed novel benzarone derivatives and found a dervative, DS38, with enhanced inhibitory activity not only in mouse, but in human cells. We also found that DS38 may be used to develop a therapy to inhibit the growth of Sonidegib-resistant SHH-MB tumors. Our results show an exciting new avenue for developing therapeutics for pediatric SHH-medulloblastoma via inhibition of EYA phosphatases.

Dr. Qadeer's findings were published in the scientific journals Neuron; Developmental Neuroscience; and Neuro-oncology Advances.