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Pictured Left to Right: David W. Mullins, PhD, Assistant Professor of Microbiology and Immunology, Geisel School of Medicine; Matthew Alexander, JMNMF RSA Award Recipient; Mark Israel, PhD, Professor of Medicine, Geisel School of Medicine & Director, Norris Cotton Cancer Center; and, William R. Green, Chair of Microbiology and Immunology, and Director of the Center for Biomedical Research Excellence in Immunology at the Geisel School of Medicine.

SUMMARY: Vemurafenib-mediated modulation of the melanoma microenvironment (MME) to enhance tumor infiltration and eradication by $CD8^+CXCR3^+$ T cells.

Cancer therapy has been revolutionized by the discovery and development of small-molecule inhibitors, drugs that specifically block mutated forms of proteins found in cancer cells but not in normal cells. The mutated proteins blocked by these inhibitors are important for delivering growth and pro-survival signals to the tumor cells, and their blockade induces cancer cell death and tumor regression. Vemurafenib is one such inhibitor effective against melanomas harboring a specific mutation in the BRAF protein, a mutation found in roughly half of patient melanomas. Vemurafenib treatment induces tumor regression in the majority of patients treated with it, although resistance to the drug typically develops within a year. Thus, it is important to understand the mechanisms of Vemurafenib's action in order to develop therapeutic approaches that circumvent drug resistance.

It has recently been characterized that in tumors from patients treated with Vemurafenib, there is a large influx of T cells, a type of immune cell that is capable of killing cancer cells. Further, the degree of T cell infiltration in the tumor correlates with the degree of tumor regression. This raises the strong possibility that Vemurafenib mediates tumor regression by not only inhibiting mutant BRAF growth signaling, but also by recruiting anti-tumor T cells into the tumor. We are interested in understanding how Vemurafenib mediates enhanced T cell infiltration of melanomas, as harnessing the power of the immune system to fight cancer has great potential to augment existing therapies.

T cells home to different sites in the body using a system of molecules called chemokines and chemokine receptors. Chemokine receptors are on the surface of T cells, and they recognize and direct the T cell towards chemokines, molecular beacons produced at sites of infection or damage in the body. Cells can express many different chemokine receptors, though our lab has shown that the ability of T cells to infiltrate melanomas depends on a particular chemokine receptor called CXCR3, which recognizes the chemokines CXCL9, 10, and 11. We hypothesize that Vemurafenib causes T cells to home to the tumor by stimulating the production of CXCL9, 10, and 11 at the tumor site, thereby generating a signal at the tumor site that attracts T cells with CXCR3 on their surface. We also hypothesize that CXCR3 is required for Vemurafenib-mediated T cell infiltration of melanoma and subsequent control of tumor growth. We are employing mouse models of melanoma as well as human melanoma cell culture systems to address these questions.

We believe these observations are readily translatable to clinical therapies; in particular, vemurafenib-stimualted changes to the tumor environment that enhance T cell infiltration could represent a window of opportunity to synergize Vemurafenib treatment with immunotherapy. Vaccination protocols already exist that generate large populations of CXCR3-expressing, anti-tumor T cells, and this could potentially be combined with Vemurafenib treatment to substantially augment the anti-tumor effect of Vemurafenib and improve patient outcomes.