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Picured left to right: David Mullins, PhD, Assistant Professor of Microbiology and Immunology at the Geisel School of Medicine at Dartmouth and Member of the Norris Cotton Cancer Center; Eleanor Clancy-Thompson, JMNMF RSA Recipient; Dr. Mark Israel, Professor of Medicine at the Geisel School of Medicine at Dartmouth and Director of the Norris Cotton Cancer Center at Dartmouth.

SUMMARY: Modulation of the CXCR3 Chemotactic Axis to Enhance T cell-mediated Infiltration and Eradication of Metastatic Melanomas

Immunotherapies are one of the most promising treatments for metastatic cancers. The development of melanoma-specific vaccines has been partially successful, demonstrating that tumor-specific immune cells ($CD8^+$ T cells) are stimulated and increased in blood circulation. However, to kill tumors, the vaccine-induced T cells must leave circulation and infiltrate the cancer lesions. We've shown that vaccine-induced $CD8^+$ T cells may not efficiently infiltrate established primary or metastatic tumors. Our lab is investigating the mechanisms that drive T cell infiltration of melanoma, in hopes of finding new therapies that the clinical efficacy of immunotherapy.

To leave circulation and infiltrate cancerous lesions, T cells use a system of chemical detectors called chemokine receptors (CCRs) to detect problems in the body. Inflammed tissues, including newly-arising tumors, release chemical messengers (chemokines) that can be detected by T cells using their CCRs. Therefore, we would expect T cells to detect tumors via their CCRs, then leave circulation and infiltrate the tumors. We have shown that one particular CCR molecule, called CXCR3, is vital for T cell infiltration of melanomas. CXCR3 detects specific "danger" chemokines (CXCL9, CXCL10, and CXCL11) produced in inflamed tissues. However, we've also observed that T cells, even those with CXCR3, are excluded from more advanced tumors. This suggests to us that late-stage tumors may fail to produce the danger chemokines that normally attract $CD8^+$ T cells through CXCR3

Therefore, our hypothesis is that CXCR3 expression on T cells, plus CXCR3-specific chemokine production in the tumor microenvironment, are both required for the infiltration of T cells into metastatic melanoma lesions. We propose to evaluate the cellular and molecular mechanisms that regulate chemokine production in metastatic melanoma, and to evaluate a new approach that may restore chemokine production and T cell infiltration, thereby allowing immune-mediated eradication of late-stage melanomas; if effective, the proposed therapeutic approach is readily-translatable to clinical trials.

In terms of clinical therapy of metastatic melanoma, we already have vaccines that can induce or expand tumor-specific T cells with CXCR3. Our work could provide the second half of the equation by restoring chemokine production in tumors, thus enhancing the clinical efficacy of current immunotherapy methods. This therapy makes use of the endogenous immune response, rather than relying on a drug that is toxic and needs continuous administration. Improving the functionality of the immune system and using it to fight cancer would provide a therapy to all patients, even those with unresectable metastatic disease.