Indoleamine 2,3-dioxygenase (IDO) is a tryptophan catabolic enzyme that modifies inflammation and drives immune escape in many cancers. Small molecule inhibitors enhance the efficacy of chemotherapy, radiotherapy, and cancer vaccines in preclinical models (1,2), but IDO has yet to be genetically validated as a cancer therapeutic target. We have recently determined that IDO−/− mice are resistant to skin and lung carcinogenesis and metastasis (3,4). Extended survival was associated causally with decreased T cell suppression by Gr1+CD11b+ MDSCs and decreased levels of IL-6, which was needed to support MDSC development and metastasis. Unexpectedly, there was also a notable angiogenic defect in the lungs of IDO−/− mice even in the absence of malignancy (4). In other work, we established that genetic deletion of T cells could restore cancer susceptibility in IDO−/− mice. These studies firmly validate IDO as a cancer target and deepens insights into how this nodal inflammatory modifier licenses progressive cancer.

Investigations of IDO effector pathways suggest a role for mTOR control (5). One recognized IDO effector is the stress kinase Gcn2, which detects uncharged tRNA produced by tryptophan catabolism. However, Gcn2 deletion did not phenocopy cancer resistance like IDO deletion, implying other effector pathways. We determined that IDO activation blocked mTOR and the TCR regulatory kinase PKC-theta and stimulated autophagy. Tryptophan relieved these effects but not so potently as the experimental clinical drug 1-methyl-D-tryptophan (D-1MT, aka indoximod or NLG8189). The ability of D-1MT to relieve mTOR blockade but not Gcn2 activation by IDO may explain this drug’s peculiar mechanism of action along with its low clinical toxicity, when compared to risks of IDO inhibition itself (6).

In ongoing work, we are also investigating IDO2 function using a genetically deficient mouse strain constructed in the laboratory. No defects are observed in the absence of stimuli, however, IDO2 deficiency reduces severity in models of contact hypersensitivity and autoimmune arthritis. Ongoing cancer studies of IDO2 in mice and clinical settings will be presented.

References
5. Metz et al. (2012). OncoImmunology, in press.