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Our research focuses on understanding how therapies targeting the immune system cause cancer cell death. Clinically-approved immune-oncology (IO) therapies have demonstrated dramatic efficacy in some patients' tumors, but our appreciation of the critical components driving response and resistance to these therapies is incomplete. Studies have shown that the targets of IO therapies are receptors expressed on multiple immune cell types, and some co-inhibitory receptors have several known ligands. However, investigating how these receptors function via immune-immune and tumor-immune interactions is challenging: experimental models do not reflect the diverse cell populations present in the tumor microenvironment (TME), and the technologies commonly used to assess clinical specimens are unable to capture the complexity of the TME.

Recent advances in molecular pathology - particularly genome and transcriptome profiling, and multiplex imaging analyses - may be used to shed light on the TME in situ. We aim to extend the impact of these technologies to further elucidate the fundamental nature of immune-immune and immune-tumor interactions. Untangling the complex biology of checkpoint expression and interactions will not only add to our understanding of TME biology, but also inform clinical development and strategy in the area of immunotherapy.

Selected Publications**Studying clonal dynamics in response to cancer therapy using high-complexity barcoding.**

Bhang HE, Ruddy DA, Krishnamurthy Radhakrishna V, Caushi JX, Zhao R, Hims MM, Singh AP, Kao I, Rakiec D, Shaw P, Balak M, Raza A, Ackley E, Keen N, Schlabach MR, Palmer M, Leary RJ, Chiang DY, Sellers WR, Michor F, Cooke VG, Korn JM, Stegmeier F.

Nat Med. 2015 May;21(5):440-8.

Detection of circulating tumor DNA in early- and late-stage human malignancies.

Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, Bartlett BR, Wang H, Luber B, Alani RM, Antonarakis ES, Azad NS, Bardelli A, Brem H, Cameron JL, Lee CC, Fecher LA, Gallia GL, Gibbs P, Le D, Giuntoli RL, Goggins M, Hogarty MD, Holdhoff M, Hong SM, Jiao Y, Juhl HH, Kim JJ, Siravegna G, Laheru DA, Lauricella C, Lim M, Lipson EJ, Marie SK, Netto GJ, Oliner KS, Olivi A, Olsson L, Riggins GJ, Sartore-Bianchi A, Schmidt K, Shih IM, Oba-Shinjo SM, Siena S, Theodorescu D, Tie J, Harkins TT, Veronese S, Wang TL, Weingart JD, Wolfgang CL, Wood LD, Xing D, Hruban RH, Wu J, Allen PJ, Schmidt CM, Choti MA, Velculescu VE, Kinzler KW, Vogelstein B, Papadopoulos N, Diaz LA Jr.

Sci Trans Med. 2014 Feb 19;6(224):224ra24.

Detection of chromosomal alterations in the circulation of cancer patients with whole-genome sequencing.

Leary RJ, Sausen M, Kinde I, Papadopoulos N, Carpten JD, Craig D, O'Shaughnessy J, Kinzler KW, Parmigiani G, Vogelstein B, Diaz LA Jr, Velculescu VE.

Sci Transl Med. 2012 Nov 28;4(162):162ra154.

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