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Our research focuses on anti-tumor antibodies that target tumor cells via ADCC (antibody-dependent cellular cytotoxicity). ADCC is an Fc-dependent mode of action (MoA) by which antibodies mediate tumor cell lysis and phagocytosis by innate effector cells, including NK cells and macrophages. The clinically-approved ADCC-competent antibodies Rituximab, Daratumumab and Obinutuzumab have achieved moderate to high response rates in patients. However, most patients ultimately relapse and require additional treatments or succumb to the disease. Only a small number of patients on ADCC-competent antibody therapies remain tumor-free for decades. Tumor-specific T cells and antibodies have been detected in these patients, which suggests that the ADCC-competent antibodies induced immunological memory against tumor antigens (the vaccinal effect). However, the mechanism of this vaccinal effect is under-explored and more effort is needed to identify pathways or genes that can modulate the vaccinal effect.

Several recent studies demonstrated that the vaccinal effect can be achieved in murine models by enhancing the ADCC activity or by combining ADCC-competent antibodies with immune modulatory agents. Our exploratory research is focused on identifying and characterizing factors that modulate immune cell activation (i.e., enhance the vaccinal effect) as well as tumor cell-intrinsic molecular features that impact the cell's sensitivity to ADCC-competent antibodies. To identify such genes, we use a combination of cellular and molecular analyses, syngeneic mouse models, and in vivo functional genomics screens. Understanding the response of tumor cells to antibodies with Fc-dependent MoA has the potential to improve the efficacy of antibody therapeutics and identify rational combination partners. Furthermore, by dissecting the mechanism of immune effector cell activation by ADCC-competent antibodies, we hope to achieve long-term immunological memory and durable response in patients.

Selected Publications

Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases.
Chen YN, LaMarche MJ, Chan HM, Fekkes P, Garcia-Fortanet J, Acker MG, Antonakos B, Chen CH, Chen Z, Cooke VG, Dobson JR, Deng Z, Fei F, Firestone B, Fodor M, Fridrich C, Gao H, Grunenfelder D, Hao HX, Jacob J, Ho S, Hsiao K, Kang ZB, Karki R, Kato M, Larrow J, La Bonte LR, Lenoir F, Liu G, Liu S, Majumdar D, Meyer MJ, Palermo M, Perez L, Pu M, Price E, Quinn C, Shakya S, Shultz MD, Slisz J, Venkatesan K, Wang P, Warmuth M, Williams S, Yang G, Yuan J, Zhang JH, Zhu P, Ramsey T, Keen NJ, Sellers WR, Stams T, Fortin PD.
Nature. 2016 Jul 7;535(7610):148-52.

Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers.
Hoffman GR, Rahal R, Buxton F, Xiang K, McAllister G, Frias E, Bagdasarian L, Huber J, Lindeman A, Chen D, Romero R, Ramadan N, Phadke T, Haas K, Jaskelioff M, Wilson BG, Meyer MJ, Saenz-Vash V, Zhai H,

Myer VE, Porter JA, Keen N, McLaughlin ME, Mickanin C, Roberts CW, Stegmeier F, Jagani Z.
Proc Natl Acad Sci U S A. 2014 Feb 25;111(8):3128-33.

CD44posCD49fhiCD133/2hi defines xenograft-initiating cells in estrogen receptor-negative breast cancer.
Meyer MJ, Fleming JM, Lin AF, Hussnain SA, Ginsburg E, Vonderhaar BK.
Cancer Res. 2010 Jun 1;70(11):4624-33.

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