The Maus Lab 411-BB

Volume 2 Issue 1

April 2022

Maus lab and collaborators ski day at Wachusett, March 2022

Catch Up With the CAR-Tologists

It has been an eventful four months for the Maus Lab and the CIP since you've last heard from us! We presented 8 abstracts at the ASH conference in December and had 5 primary research articles accepted for publication! You can read about two of them, published in Nature and Blood Cancer Discovery, in this issue. The 3rd was a retrospective study on using anakinra to treat CAR T cell patient toxicity and was published in the Journal of Immunotherapy for Cancer. The 4th on CAR T cells specially engineered to optimize targeting of CD70, a new target antigen for acute myeloid leukemia (AML), was accepted for publication in *Cancer Cell* and will be highlighted in our next issue of the 411-BB. Our 5th publication demonstrated a differential T cell response in people receiving the Pfizer vs. Moderna COVID-19 vaccines. This work was published in Clinical Infectious Diseases. We also had our inaugural Maus lab ski day at Wachusett mountain and were joined by our collaborators from the Manguso and Sen labs. It was a fun and rejuvenating day had by all!

Current Lab Members

Marcela Maus, MD, PhD
Stefanie Bailey, PhD
Trisha Berger, PhD
Amanda Bouffard
Diane Brunett
Korneel Grauwet, PhD
Lu Huang, PhD
Michael Kann
Tamina Kienka
Felix Korell, MD
Adam Kuo
Rebecca Larson, PhD
Mark Leick, MD
Grace Martin
Markus Mergen
Merle Phillips
Diego Salas-Benito, MD, PhD
Emily Silva
Harrison Silva
Marc Wehrli, MD, PhD

Immune Monitoring Lab
Kathleen Gallagher, PhD
Charlotte Graham, MD, PhD
Eva Elder
Elba Gonzalez
Kathleen Ho
Katelin Katsis

In this issue

DiP in the CIP: News Updates

Honors and Awards

- Marcela made the list of highly cited researchers for 2021, meaning she had multiple publications in the top 1% of papers cited in the field. Such an amazing accomplishment! Congratulations to Marcela and all the the lab members, current and alumni, who made this possible!
- Marcela is also currently the top-rated expert in CAR T cell therapy in the world on ExpertScape
- Mark Leick, MD, won an Emerging Generation (E-Gen) award, which recognizes post-MD, pre-faculty physician-scientists who are meaningfully engaged in immersive research. Congrats, Mark!
- Felix Korell, MD, won an ASH abstract achievement award for his abstract at the American Society of Hematology annual meeting. Congrats, Felix!
- The lab had 4 abstracts accepted for presentation at the AACR annual meeting in New Orleans, including two abstracts for oral presentations: one by Mike Kann, a senior research technician in the lab, and the other by Nick Haradvhala on our collaboration with the Getz and Wu labs and IBM.
- Harry Silva, a technician in the lab, was accepted into a PhD program at UNC-Chapel Hill and will be joining the Biological and Biomedical Sciences Program this fall. Congratulations, Harry!
- In December, Tamina Kienka took his preliminary qualifying exam for the Harvard Immunology PhD program and is now officially a PhD candidate. Congratulations, Tamina!
- At the Irving Family Foundation Cancer Immunology Innovation Retreat, Stefanie Bailey, PhD received the achievement award and Mark Leick, MD received the mentorship award. Congrats to you both!

Lab Members

- In January, we welcomed Merle Phillips as a new PhD graduate student to the lab. Merle is a member of Harvard's Biological and Biomedical Sciences Program. Welcome, Merle!
- We also bid farewell to Andrea Schmidts, MD, a postdoctoral fellow in the lab who is starting her own lab in Germany at the Technical University of Munich. Andrea is an incredible scientist and colleague. She will be greatly missed. Congrats and best of luck in your new endeavor, Andrea!
- The Immune Monitoring lab also welcomed Charlotte Graham, MD, PhD as a new postdoctoral fellow from the United Kingdom. Welcome, Charlotte!

Grants

- Stefanie Bailey, PhD was awarded an ASGCT Career Development Award—a one-year fellowship to support her transition to independence. Congrats, Stef!
- Diego Salas-Benito, MD, PhD was awarded a CRIS OutBack Fellowship Programme award, which supports 3 years of cancer research abroad for physician-scientists from Spain. Congrats, Diego!

Member Spotlight: Mark Leick, MD

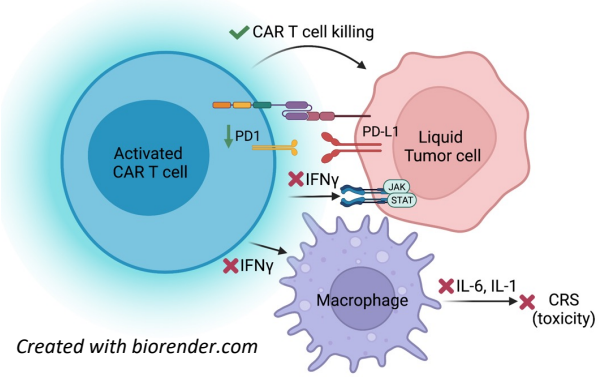
Mark grew up in Tucson, AZ and completed his undergraduate degrees in bioengineering, biochemistry, and molecular biology before going to Georgetown for medical school. He did his residency in internal medicine at Johns Hopkins before matching into the joint medical oncology fellowship at MGH/DFCI. During his first year of fellowship, he developed an interest in bone marrow transplantation (BMT) and cellular therapies and joined the Maus lab with a focus on AML and examining FDA-approved CAR T cell products. He now splits his time between the lab and caring for BMT and CAR T patients. His goal is to become an independent physician-scientist investigator with a clinical focus in cellular therapies/BMT and a research focus on developing novel cell therapies and investigating the limitations of existing cell therapies.

Mark's favorite thing about the Maus lab is, "Our substantial diversity in a myriad of ways including geographical, cultural, academic, culinary, and athletic. We routinely have members hailing from every continent (well—not Antarctica, yet!) with a variety of academic training levels from newly minted high school graduates to seasoned post-doctoral fellows. The breadth of knowledge across these domains ensures a rich academic, cultural, and humanitarian experience and makes it a joy to be a part of the lab!" Mark has won numerous awards for his work in the clinic and lab, for his science and for his mentorship. He also recently had a first author publication accepted in *Cancer Cell*.

Can a CAR Still Run Without IFNγ?

IFNγ release is often used to measure T cell activation and is classically thought of as essential for T cell function during an immune reaction. Logically, it has also been assumed that IFNγ is needed for CAR T cells to function properly. However, high IFNγ in a patient's blood following CAR T cell treatment is also associated with toxicity in the form of cytokine release syndrome (CRS). In preclinical models, IFNγ release from CAR T cells causes other immune cells, such as macrophages, to release several other cytokines, which results in massive inflammation. We predicted that blocking CAR T cell release of IFNγ would prevent the further release of cytokines associated with CRS and that IFNγ may not be necessary for CAR T cells to kill cancer cells. In a study led by Stefanie Bailey, PhD (a postdoctoral fellow in the lab) and published in *Blood Cancer Discovery*, we tested this hypothesis by knocking out IFNγ in CAR T cells or using an antibody specific to IFNγ to block its function. We then assessed if CAR T cells still kill leukemia cells or induce cytokine release from macrophages.

Without IFNγ, CD19-targeting CAR T cells were still able to kill a variety of leukemia and lymphoma cells in preclinical models but did not induce the same macrophage activation and cytokine release as CAR T cells with functional IFNγ. In fact, the macrophage activation was reduced to a greater extent than when CAR T cells/macrophages were treated with tocilizumab (the standard treatment given to patients with CRS). Additionally, CAR T cell lacking IFNγ expression had lower levels of PD-1, a molecule that can suppress CAR T cell function when it binds to PD-L1 expressed on tumor cells and other cells within the tumor microenvironment. However, this finding did not hold true for CAR T cells targeting solid tumor cells, which required IFNγ to properly kill. This suggests that targeting IFNγ in patients receiving the currently approved CAR T cell products for leukemia or lymphoma could prevent these unwanted toxicities without affecting how the CAR T cells "run".



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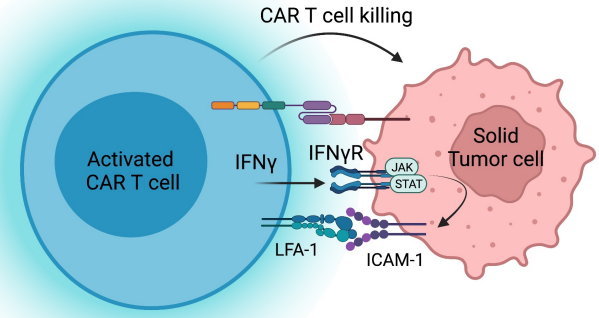
What Makes Solid Tumors Put on the CAR Brakes?

One of the major limitations of CAR T cell therapy their use in solid tumors. While CAR T cells are effective in treating liquid tumors, they have yet to be approved for use in solid tumors. We aimed to explore what makes solid tumors resistant to targeting by CAR T cells. In a study led by Rebecca Larson, PhD (a graduate student in the lab) and published in *Nature*, we performed a CRISPR screen in glioblastoma tumor cells to ask which genes when knocked out prevent CAR T cell killing. In the tops genes enriched within tumor cells that survived being mixed with CAR T cells was the IFNγ receptor (IFNγR) and its downstream signaling molecules Jak1 and Jak2.

We confirmed that knocking out IFNγR, Jak1 or Jak2 prevented CAR T cell killing of glioblastoma cells and found that this was dependent on upregulation of ICAM-1, an adhesion molecule expressed by tumor cells binds to LFA-1 on T cells. This interaction increases CAR T cell binding to tumor cells, allowing for efficient killing. Without IFNγ signaling, tumor cells do not upregulate ICAM-1 and therefore are resistant to CAR T cell killing. This was not only true for glioblastoma, but also for other solid tumor cells targeted by CAR T cells specific to other tumor antigens, suggesting this could be a pathway universally required for solid tumor killing by CAR T cells. In line with the study on IFNγ above, the same finding did not hold true for liquid tumor cells, which did not become resistant to CAR T cell killing when IFNγ signaling was knocked out. This study identified a unique mechanism used by solid tumor cells to resist CAR T cell therapy and suggests that enhancing CAR T cell binding to solid tumor cells will improve their function.



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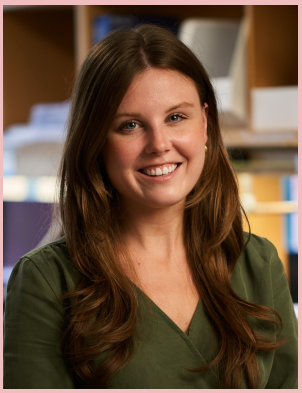
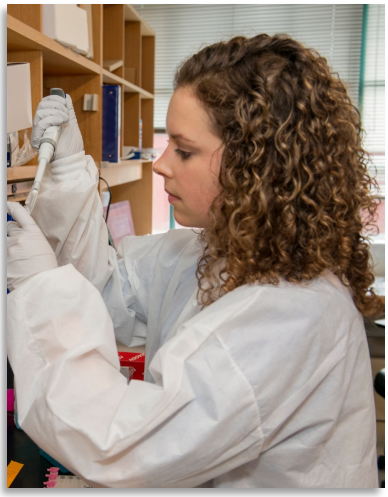
Cruising Past the Finish Line: Congratulations, Dr. Larson!



The newly minted Rebecca Larson, PhD defended her thesis on March 24, 2022. Becca is a member of Harvard's Immunology graduate program and has been in the Maus lab since 2017. During this time, Becca has contributed as an author on an amazing 18 publications for the lab, including her recent first author author publication in *Nature* (highlighted in this issue). In addition to being a skilled scientist, Becca is an incredible leader in the lab and a true team player. She will no doubt be an accomplished scientist, wherever her future career path takes her. In the words of one of her fellow lab member, "We will all be working for Becca some day!"

Congratulations, Dr. Larson! We are so proud of you!!

CAR-eer Track: Angela Boroughs, PhD



Angela was born in DC, grew up in Johannesburg, South Africa, and did her undergraduate studies at the University of Cape Town. She then attended Harvard for her PhD studies in Immunology and completed her thesis work in the Maus lab, focusing on how different costimulation domains affect regulatory CAR T cell function and conventional CAR T cell transcriptional pathways. She is now a senior scientist at ArsenalBio in San Francisco where she leads a group of scientist and research associates studying logic-gated and armored CAR T cells for solid tumors. Her career goal is to develop cell therapies that will bring more cures and increased quality of life to cancer patients. For her, this means looking for ways to have more say on the science and strategies pursued preclinically in biotech.

When asked what her favorite thing about the Maus lab was, she said "The scientific background I gained from discussions with Marcela and others in the lab was extremely helpful from day one in biotech. Marcela also taught me how to focus on the most important pieces to move a project forward. These days, it is critical for me to see the fastest path from problem to solution and coordinate the people and resources needed to come together and make it happen. I also think working in collaborations across labs helped me learn about leading and motivating scientists around a common goal. And I still use some of Marcela's calendaring tips to manage my busy schedule!"

CAR-ing Together: Supporting The Maus Lab

Thanks to the generosity of our donors, we've been able to develop multiple novel cell therapies, of which the first few have now entered clinic, and we hope many more will follow. Our mission is to develop cutting-edge cell therapies to effectively treat patients with cancer. Your donations have enabled us to remain steadfast in that mission. We are enthusiastically working to develop the next generation of CAR T cells and combination immunotherapies to improve patient outcomes.

With your help, we can make a difference in the lives of cancer patients who are in need of more treatment options. Contributions to the Cellular Immunotherapy Program help us develop new ideas, translate our findings to patients, and train the next generation of scientists and physicians to carry out our mission. Click here to donate.