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PEOPLE & IDEAS

Judith Agudo: Beware of your inner self-immune attack

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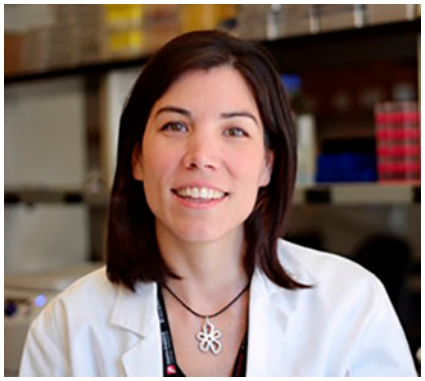
Judith Agudo studies the mechanisms that adult and cancer stem cells use to evade the immune response with the goals of engineering autoimmunity- and allograft-resistant stem cells and improving the response of cancer stem cells to immunotherapy.

The everyday of a third grader is full of surprises. They can learn about tints and shades and what an antibiotic is on the very same day. How, by inadvertently leaving an uncovered Petri dish next to an open window, Alexander Fleming discovered penicillin—synthesized by the mold that contaminated the bacteria plate—was a story that stuck in Judith Agudo's head. Her mom is positive that's probably when Judith first genuinely thought about becoming a scientist, as she burst open the front door shouting, "Mom, I want to save millions of lives like Fleming did." A couple of decades later, Judith is on the right track.

Born and raised in a working-class neighborhood near Barcelona, Spain, Judith pursued a degree in biology and a PhD in biochemistry and molecular biology at the Autonomous University of Barcelona. Her thesis focused on regenerative medicine for the treatment of diabetes—Judith found a potential target, VEGF, for preventing β cell mass loss during type 2 diabetes. However, she realized that for type 1 diabetes, which is an autoimmune disorder, no regenerative approach would be successful without neutralizing the self-immune attack. Thus, she switched gears to immunology for her postdoctoral training. Judith obtained a Fulbright fellowship in 2010 and moved to New York to join the lab of Dr. Brian Brown in the Immunology Institute at the Icahn School of Medicine at Mount Sinai. There, she investigated how microRNAs regulate innate immunity. Judith also engineered a model to study T cell function in vivo, which has one of the coolest names heard in science: JEDI (Just EGFP Death Inducing). The JEDI mice generate $CD8^+$ T cells that recognize and kill any EGFP-expressing cell type; thus, one can deplete specific cell populations in the body or investigate how T cells interact with tissue stem cells. Judith depleted a rare population in the heart, $Hcn4^+$ cells, and showed their function in cardiac conduction and pacemaking (1). Thanks to this model, she also clarified that not all tissue stem cells are immune privileged—only those that are quiescent can escape immune detection (2). These findings prompted Judith to ask whether quiescence is also a requirement for cancer stem cells to evade T cell recognition. With this idea in mind, she set up her own her lab at one of the most prestigious cancer institutes across the world, the Dana-Farber Cancer Institute (DFCI), in 2017. Judith is currently an assistant professor in the Department of Cancer Immunology and Virology at DFCI and in the Department of Immunology at Harvard Medical School. We chatted with Judith to learn more about her journey and future endeavors.



Judith Agudo. Photo courtesy of Albert Ruzo.

What drew you to the study of the immune evasion mechanisms of adult and cancer stem cells?

My PhD work focused on regenerating β cells for the treatment of diabetes. However, I soon realized that without halting the autoimmune attack, no regenerative approaches would be successful. This prompted me to explore the mechanisms of autoimmunity. I enjoy working on technology development, so I engineered a mouse model to investigate immune responses against almost any cell type (1). I was then curious to know if stem cells, so often utilized in regenerative medicine, could resist an autoimmune attack. If they could, the tissue could potentially regrow once the immune attack subsides. Otherwise, it would be destroyed. This drove my interest in studying how healthy stem cells evade the immune system (2). Afterward, I became interested in what happens when stem cells become cancerous and how cancer stem cells interact with the immune system (3).

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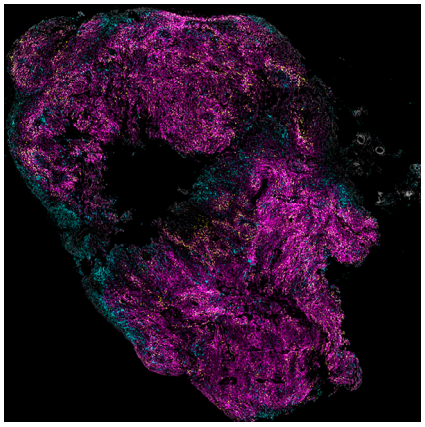

Immunofluorescence image of murine 4T07 breast carcinoma. 4T07 cells express mCherry (magenta) and the cell cycle reporter mVenus-p27K (yellow). CD11c is depicted in cyan. Image courtesy of Pilar Baldominos from the Agudo lab.

What are you currently working on, and what are the research lines you would like to open?

Currently, my lab works on two main topics: understanding how cancer stem cells evade the immune system to improve responses to immunotherapy, and engineering stem cells and stem cell–derived tissues to achieve immune ignorance so they can survive autoimmunity or allograft transplantation. As for my future research, I usually follow the biology that I discover, so it's hard to predict where exactly I will go next. I'm interested in cancer and autoimmunity and how stress and aging influence them; thus, I think the crosstalk between stress, aging, stem cells, and immune cells could come next.

You said you follow the biology you discover wherever it goes?

Yes, I'm inherently a curious person by nature. As a mentor, I try to promote a dynamic environment with lots of scientific discussions and freedom to explore ideas, no matter how wild they may sound, so you could easily find my lab members testing crazy hypotheses.

So, there's nothing that stops you...

Well... Okay, let's be honest. Money is an issue, everybody knows, and time is another one. We use complex mouse models, so this makes our research both time-consuming and expensive, and we also face the pressing need to publish our results quickly while maintaining high quality. I do my best to provide my lab members with enough resources so we can overcome whatever hurdle we find in our way.

With the intrinsic limitations that accompany the generation of complex animal models, every major development in your field must surely be celebrated. Is there any advancement you are particularly impressed with?

Immunology is a large field, and as an immunologist I work at the interface between two other fields: tumor immunology and regenerative medicine. Cancer immunotherapy is undoubtedly the most thrilling advancement in recent years. And in regenerative medicine and diabetes, I am particularly impressed by the recent success of the transplantation of stem cell–derived pancreatic islets in a patient with type 1 diabetes. That is, in my opinion, the most exciting recent development in these fields.

Pushing forward projects at the intersection of different fields requires having expertise in all of them, which is challenging. What is your secret?

I collaborate. Collaborations are one of my favorite aspects of science. Working with others is a great opportunity to learn new things and discuss ideas to push your own research much further. We are, for instance, part of the JDRF New England team—a multidisciplinary team with a common goal, which is to make transplantation of stem cell–derived islets a reality. It's exciting and rewarding. I love feeling that I can bring something different to the table and that I have the expertise and support of other researchers working toward the same aim.

Any other secrets or advice you would like to share with us for building a successful research career?

I'm still an assistant professor, and I just got published my first manuscript as an independent principal investigator, so I can't yet consider myself successful [enough] to give advice on this regard. But I can share some tips about how to succeed in the transition from postdoc to getting a faculty position. Having—and being able to communicate—a clear and concise vision of what you would like to study is crucial. Not too broad, not too narrow. As for building a lab and a research program, I would tell you what I was once told by Dr. Miriam Merad, who was my co-supervisor when I was a postdoc: "It's not a speed race but a marathon." This has helped me a lot in moments when experiments fail and projects are stuck or don't move fast enough. It also helped me during the lockdown due to the COVID-19 pandemic, where things and the world just abruptly stopped.

Was the pandemic the biggest challenge you have faced in your career so far?

The pandemic was a challenge, for me and for everybody, but not the biggest challenge so far. The constant battle between spending time with my kids and working is. I love my job: I enjoy mentoring my students, and I love the excitement of new scientific findings. If I did not have a family, I think I'd be always working! But I have three children: an 8-yr-old, a 6-yr-old, and a 3.5-mo-old baby. I also love being a mother, and I decided to have kids to enjoy them too, so it's

The Agudo lab members, collaborators, and significant others celebrating the acceptance of the work led by first-author Pilar Baldominos in *Cell*. Photo courtesy of Alice Bertocchi.

very important for me to spend time with them every day. That inner fight can sometimes be exhausting.

Is there anything you would like to change in academia if you could?

I would make it more inclusive. Scientists should be more committed to diversity and inclusion. There's a lot of talking about it and there are new efforts from institutes. These efforts are sometimes honest but other times are just to check the box. We need more training and awareness, and we need to get everybody—including the established old professors—to be part of this work.

You are very passionate about this...

There's so much going on in the world: racism, loss of reproductive rights, climate change, etc., and academia does not escape from injustice. If I were not a scientist, I would be involved in activism.

References

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