"To do science it is essential to be proactive and not wait for your project to progress on its own"

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Dr. Jacky Goetz works on intravital imaging and biomechanical forces during the progression of tumors.

Jacky Goetz graduated in pharmacology and cell biology from the University of Strasbourg in France and moved to Canada to work at Ivan Robert Nabi's laboratory, at the University of Montreal and later at the University of British Columbia. In 2007 he received his doctorate from the University of Montreal and the University of Strasbourg. During his post-doctorate, Jacky Goetz moved to Miguel Ángel del Pozo's laboratory at the National Center for Cardiovascular Research (CNIC) to study the

microenvironment of the tumor. Afterwards, he joined Julien Vermot's laboratory at the Institute of Genetics and Molecular and Cellular Biology (IGBMC). In 2012, he won the Young Scientist Award from the French Society for Cell Biology, in 2020 the Grand Prix de Cancérologie de la Fondation Del Duca (Académie des Sciences) and the Prix Ruban Rose Avenir 2020. In 2013, he founded his own research group, "Tumor Biomechanics", in Strasbourg to work on intravital imaging methods and biomechanical forces during the progression of tumors. Currently is the Coordinator of the NanoTumor program (Programme Fédérateur Aviesan, 2020-2022).

- *Your work is currently directed at digging deeper into the metastasis processes. Can you explain what your main areas of work are? ?*

During the past five or six years, in the laboratory we have been researching the different steps that occur in the process of tumor metastasis in different animal models. In addition, we have developed emerging technologies to analyze metastasis using very high image resolution.

In this sense, we have been pioneers in the development of a technique, in collaboration with our colleagues in Heidelberg, called intravital correlative electron microscopy. Thanks to this technique we can observe how tumor cells promote metastasis and, thus, understand how this very harmful process is really happening.

In the same way, we are also **interested in understanding how the mechanical forces work**, which is related to the work I did in Madrid during my first post-doctorate, and how these mechanical forces affect metastasis.

However, while at the CNIC I was working primarily on the mechanical forces that come from the extracellular matrix for surrounding tumors, now we are primarily investigating forces generated by fluids, such as blood flow that only affect circulation.

In summary, the main project is to understand how blood flow affects tumor metastasis formation, and we know that it does in many different ways.

Finally, something that is related to this last question is that tumors generate and share very small vesicles, nanoscale vesicles, in the blood. This is something that happens in many other diseases, especially inflammatory pathologies, but we are interested in the context of cancer progression. And we know that tumors generate vesicles. That’s why we are really interested in how they feed themselves so that these vesicles reach distant organs, far from those tumors, and prepare the microenvironment to promote metastasis.

And this matters to us in many ways. One angle is microscopy because, when we started the project, there wasn’t a good model, no good approach to track these little vesicles, because they are so small. My laboratory is focused on understanding how they behave in the blood flow, because we think that this is the key step in the way in which they diffuse in the body.

Furthermore, we have established a new animal model, the zebrafish embryo, which allows us to track these vesicles in the animal at very high speeds in the blood flow. And in doing so, we have understood a little more about how they stop in specific vascular regions and how they can prepare the initiation of subsequent metastases.

- *This is probably the most important challenge in cancer treatment. How can metastasis be stopped before it starts?*

The idea of stopping metastasis before it occurs is something that can be done in animal models, but in patients it will be very difficult because it is very hard to find patients who have a primary tumor with metastasis in very early stages.

The main objective of my team is to understand the fundamental mechanisms that are at the base of metastasis. By doing so, we could identify new therapeutic targets that are definitely safe. For

example, in the work we did on blood flow and metastasis, **we identified on the surface of the tumor cell some receptors that are involved in stabilizing the tumor cell within the blood vessels**. And we have identified a new variation that allows them to leave the circulation and form metastases. And this is something we could target to inhibit this metastasis process.

And there is another thing that we discovered when we looked at the impact of blood flow on tumor metastasis, which is that the blood flow is actually capable of indoctrinating the blood vessels; that is, it basically makes the endothelial cells that make these blood vessels reactive to blood flow when there is a tumor cell. And, when this happens, we have shown that the vascular microenvironment is involved in a process we call endothelial remodeling. This process expels cells from the vasculature.

And when we dissect this a bit more, we identify the molecular mechanism of this **endothelial remodeling that is partially** driven by a signaling pathway that is very well known, VEGFR, involved in angiogenesis. We have now seen that the early stages of vascular remodeling can be inhibited with the classic drugs available on the market and alter metastasis.

However, applying it to a human patient is a very delicate matter in this phenomenon of early metastasis. On a clinical level, we would be more interested in targeting the already established metastasis, in order to find ways to kill the established metastasis, although this is not exactly what we are studying in my laboratory.

- *In an idealistic scenario, would it be possible to predict if this tumor will suffer metastasis?*

Predicting this is very complicated. Of course there are ways to prevent metastasis from starting. For example, one way to do this would be through extracellular vesicles, since they affect the ability of these tumors to share and spread extracellular vesicles, and the amount of metastasis they generate can be considerably reduced.

But this is something that is very complex because, although it is true that tumors can metastasize when you do experiments in mouse models, some tumors, even if they are of the same cell lineage, would metastasize and, in other mice, they would not.

So there is a combination of many different factors that triggers metastasis

- *You currently lead your own group. Do you still have time to do research in the laboratory? ?*

Running a laboratory involves learning to do many things in a short time. If you want to continue researching and doing science, you have to be able to do it in a short and fast way because most of the things that you deal with are not scientific 'per se'.

In my opinion, the best option to be able to continue doing science is to identify the people who work with you with whom you can do science and basically, they will be the ones who will research and bring science closer to you.

Unfortunately, at least at my level, I can no longer do that research work. And I miss it, like for example when the CNIC was here because I was the person who did the experiment and promoted the project and analyzed the results.

That is why, recently, I went to work in **Sydney** (Australia) for a while to go back to the laboratory a bit and get away from the team a bit. Thankfully I knew it was being run by people I trusted in France. I took a little time to do some experiments. And it was a lot of fun and interesting. In my opinion, it is essential not to be too far away from science for too long because the real science, the one I refer to, is doing experiments.

- *Why did you decide to go back to the laboratory for awhile?*

Going back to the laboratory also gives you an idea of what you can ask for and expect from the people who work on your team because, sometimes, being a laboratory manager, all the students of any team in the world will tell you that “my boss is crazy because he asked me to do this and this in one week”.

And it's not just because we want things to go fast, it's more because we lose track of the reality of what it really means to run an experiment and analyze all the work. So when you go back to the lab you realize that sometimes it is not a good idea to go so fast.

- *And as a laboratory manager, can you mentor young researchers and students?*

I **was lucky to have a very good mentor**. In a way, she was good because she was always pushing me a lot, in a good way. She always pressured me to find, for example, better and more precise analyses, encouraging me to do more experiments, to make sure everything was correct. She taught and trained me to be able to summarize a set of data, which I had acquired for weeks, basically always trying reconstruct the different pieces of a puzzle and do this work regularly. And I think this is essential. This is what allowed me to come here to Madrid and gain a lot of autonomy. I was working with **Miguel** [Del Pozo], he was very good at allowing me to work, but I didn't necessarily ask him for so much help in terms of tutoring because I already knew how to work and he gave me the freedom to do it which, in my opinion, was very beneficial for me because later, you reach a different stage and you can create your own project.

In that phase you only need help for some parts of the projects, financially or to obtain help from a technician, and basically let the project move forward

- *Which qualities should a good mentor have??*

One quality that I think I have, and that comes from my own mentoring experience, is how to stimulate people. I'm pretty sure most of my researchers will say just the opposite, which is the worst of me.

In my opinion, to do science it is essential to be proactive and not wait for your project to progress on its own. And that's what I try to get my students to do. It's your baby, it's your project, you're working on your specific scientific question, and if you have that little passion that all scientists have, you want your project to move fast and be well done. And, for this, you must make additional efforts.

I would like to spend more time on individual discussions with my students. This is one of the main drawbacks of being too busy when you have other responsibilities that take you away from the real world in the lab. If I could change anything, this is something I would have to focus on and would certainly have to make more time for.

- *it possible to identify when a research is “different” from others?*

Yes, you definitely can, although I don't have that much experience because I'm still young; but you can **definitely distinguish which students have that passion**. You can sense it in the way they talk about science and how they listen to your own project because they come up with questions, sometimes very naïve ones, but you can tell they are interested. One of the things I like to ask the students who come to my lab is something very simple: is there something in science, related to our projects that you would love to work on or that you knew about beforehand? I don't find many students who come up with specific questions and say yes, I am really interested in this because I have been reading a lot about this bacterial disease, etc. There are few who have this sensibility. But at the same time, it doesn't mean that the others are not good scientists: some just may be shy or may not have enough experience to know what they could be working on. That is why you must be sensitive to this type of profile because you can find many good students among young people who do not necessarily know where they want to go yet.

- *Do you remember the moment you decided you wanted to be a scientist?*

I recently celebrated my **40th anniversary** with many friends and we talked a bit about the past. And even today I can identify exactly when I became interested in science.

I was 17 years old and in high school in biology class studying the 3D structures of proteins using software and playing with 3D structures of molecules. When I got home I told my parents "today I have done something that has changed my life." It was that moment. Until that day I didn't know that I was interested in biology, that I knew I wanted to become a scientist.

In regards to what you are really interested in doing or what the main scientific question you want to ask is, I think that, in my case at least, it is mainly related to the first laboratory experiment that you enjoyed at the university.

And for me it is my work on glioblastoma, on how they evolve, how they form, how they become invasive. I was watching tumor cell migration and this kind of thing. Whatever I do, I always come back to these kinds of questions: how do tumors become invasive, how do they become metastatic.

- *You also dedicated yourself to scientific dissemination. Why do you think it is important?*

When I l**ived in Vancouver (Canada) I was a columnist for a French monthly newspaper**. I had a lot of freedom to choose the topics and I loved that. I chose a topic freely and wrote about it; I really enjoyed doing that. In fact, I still love writing and reading a lot about science. However, when I came back to Europe, to France, I contacted several newspapers, but it was a lot more difficult to do it.

- ***Dr. Jacky Goetz taught the '*Multiscale Tracking of Metastasis In Vivo*' seminar invited by Dr. Miguel Ángel del Pozo.***