Delighting in Detail

“In science most of the time things don’t work in the way you think they will. You can do an experiment, expect a result and then what happens is the complete opposite. This is what I love about science,” says Dr Guadalupe Sabio Assistant Professor in the Spanish National Centre for Cardiovascular Research, Madrid.

Dr Sabio stores every experimental result away, explained or not, ready to recall to explain exactly how and where interactions fit together in the complicated world of cell signalling.

“Data can be like a dough; you need to put it down to rest. Very often we need more information to make sense of our results. So you have to take time to think about where it can fit in. I always want to know the answer. Even if I stop an experiment, if I haven’t been able to explain it it’s always there. I keep thinking about it and eventually things fit together,” she says.

Finding results, challenging hypothesis, sharing ideas and putting putting pieces in place to solve pathways is Dr Sabio’s joy: “You have to be open in science, sometimes you have a result you just cannot explain and then several years later another person will see something and then you realise it’s the reason why your result has happened.”

Dr Sabio leads a lab exploring the role of stress kinases in diabetes, liver cancer and heart disease. She completed her PhD in 2005 between the Medical Research Council Protein Phosphorylation Unit at the University of Dundee and the University of Extremadura after winning multiple fellowships from the European Molecular Biology Organisation, the University of Extremadura and the Spanish Ministry of Education.

Sharing results sparks ideas

“When I was doing my PhD in Dundee it was a very big lab and we all got together on Friday or Saturday in the afternoon and we’d talk about the week, what we did, our results in the lab, everyone had their own project but they were all related to kinases and everyone knew so much about their field it was amazing, I loved my time there. It was a wonderful opportunity for me and I used my time there to learn the most that I could.”

Her PhD research revealed the redundant role of p38-gamma and p38 delta kinases and found that both can phosphorylate the same proteins. She continues to work on isoforms of these p38 stress kinases today.

“My lab is trying to understand the role of the p38 pathway in metabolism and in diseases like hepatocellular carcinoma, diabetes and heart failure. We are looking at kinase activation from a physiological point of view. We have long known that the pathway described years ago isn’t quite right - if we can explain it it will help to tell us what the molecular targets are of disease,” says Dr Sabio.

Using knockout mice they’ve found that sometimes the lack of p38 kinases hyperactivates rather than downregulates the pathway, Dr Sabio explains: “We now know, for example,

that p38 is mainly activated by one of the MAPKK family of kinases. This tells us that the pathway can be regulated by other proteins or by the level of expression. This is not the type of cell signaling that we are used to. It was a surprise, so now we are trying to understand the mechanisms of the pathway."

Ongoing collaboration with clinicians is helping to explain if what they see in mice is mimicked in people with the same conditions, Dr Sabio explains: "For example we are trying to see where our kinases are hyperactivated in obesity and in atherosclerosis. We try to correlate what we find in mice with humans so we work very closely with medical doctors."

Learning new skills in the US

In 2005 Dr Sabio began a post-doc at the Howard Hughes Medical Institute at the University of Massachusset's medical school. There she worked on signalling related to type 2 diabetes in Dr Roger Davis's lab.

On looking for her next move post-PhD she says: "I didn't have any doubts that I wanted to stay in academia. What I learnt in Dundee was how to work with kinases and how to research *in vitro* in cells but I wanted to translate that to mouse models to work in diabetes and other diseases. There were few opportunities for me in England or here in Spain then I realized that in the USA there are so many opportunities. So I thought about the kind of work I wanted to do and found the perfect place to do it. I wrote to Roger and told him I loved what he was doing and I wanted to work there."

Simply asking, visiting and learning about the lab was enough to secure a job there. It gave Dr Sabio the chance to apply everything she had learnt about kinases *in vivo* to animal modes *in vitro*.

Dr Sabio originally trained as a vet but made the switch to medical research because she was frustrated by the lack of certainty over potential treatment outcomes and the guessing involved in diagnosing an animal.

The science of certainty

"In my first years of university I spent each summer in a veterinary clinic and that's when I realized that most of the time when you work as a vet you can't know all the answers. You have to think, 'this could be this' or 'it could be that' and I don't like that uncertainty. You have to decide on treatment without having the answer – without knowing that it would work. I wanted to be sure of the treatment and I wanted to be sure about what would happen to the animal so I decided that I wanted to be a scientist because then I could find out how things would work and solve problems that way," she says.

"Being a vet has shaped the way I think and approach problems, I thinks it complements my peers. Most are biologists and they think in a different way. I'm grateful because the two approaches work together. As I vet I learnt less biology but know more about disease, it is complementary."

Training as a vet does have another advantage though: “In science a lot of things can go wrong, I always have in my mind that I have a second back up plan – the ability to be a vet. Research can be frustrating, the process in the postdoc can be more tricky than PhD for example. In the PhD your supervisor will more or less give you a project that should work. In the postdoc if a project is going well it helps to think, ok I do have a back-up plan if this really doesn’t work-out.”

It did work-out for Dr Sabio and in 2009 when family circumstances brought her back to Spain she won a Ramón y Cajal funding award to join a biotechnology lab. In 2011 she became Assistant Professor and moved to the cardiovascular institute.

Dr Sabio’s success in Spain is testament to her hard work and thorough approach: “I didn’t do my PhD or postdoc in Spain, I’d been away for a long time but I won a European Research Council grant, started in a new post and now I’m running a lab.”

Building a bigger picture

Having oversight of lots of people’s work and experimental results is what Dr Sabio enjoys most about being the lab’s Principal Investigator, she says: “You are able to connect results between experiments even if people are not working on similar projects. We are all looking at p38 so sometimes you find an answer to one question in another project that you thought was not as important. You think that the project is going to be interesting for another reason and then it surprises you, I like that element of science.”

Helping the people who work for her to be successful is important too: “I think if I can create and teach new people to think about science and to work in this field there will be more of us approaching the same questions in different ways. I would love in years to come to collaborate with PhD students that go out from here. I’d consider that a huge achievement.”

But the best part of her job Dr Sabio says, is the chance to talk about science: “The thing I really like the most is discussing science. To talk with students, to share and explore ideas, to find out what students think, to hear their hypothesis to argue them out, I could do this forever. I think it’s the reason I don’t like it when an experiment turns out the way that you thought it would because then you don’t have a chance to try to explore why it’s different. My job doesn’t stop when I leave the lab, I’m always thinking about it. Sometimes we never have the final word about what is happening inside cells.”

Final word

“I like to find the answers to things, to small things, for me I always feel that I’m interested in everything, I’d like to work in every part of science. When I moved to the cardiovascular centre and I started to learn about the heart, for me this was not a problem because what I like is to ask ‘what is this protein doing?’. It’s the same to ask what is this protein doing in diabetes? What is it doing in the heart? Or in liver cancer? To be the scientist who discovers a new substrate of a kinase and to understand what it is doing that would be the best. If I know the model of the kinase I know I can figure it out,” Dr Guadalupe Sabio.

Career Highlights

2010: European Research Council Starting Independent Researcher Grant
2010: Loreal-Unesco Spain
2012: Impulsa award of Science, Principe de Girona – awarded by the King of Spain to the best research investigator in Spain under 35 years old.
2014: Premio Asociación Extremeña de Alcorcón
2014: Siete Estrellas Award Comunidad de Madrid – the Madrid community gives this award to women important in the community.
2014 & 2015: Selected as one of the ten most important female scientists in Spain
2015: Patented *P38 inhibitors for the treatment and prophylaxys of liver cancer*
2016: Young investigador award Investigador SEBBM-Biotools

Top Publications

Dr Guadalupe Sabio picks her top three papers and tells us why she has chosen each one.

p38 and δ promote heart hypertrophy by targeting the mTOR-inhibitory protein DEPTOR for degradation.
Nature Communications 2016 Jan 22;7:10477. doi: 10.1038/ncomms10477. IF: 11.47
González-Terán B, López JA, *Rodríguez E, Leiva L*, Martínez Martínez S. Jiménez Borreguero LJ, Redondo JM, Vázquez J, Sabio G

"This paper was a challenge because I have never worked in the heart before and this was all new for me. We show that p38γ and p38δ are key regulators of heart growth during postnatal development and by hypertrophy-inducing stimuli. We demostrate that p38γ/δ phosphorylate DEPTOR which leads to its degradation and mTOR activation. Hearts from mice lacking p38γ/δ are smaller, have high levels of DEPTOR, low activity of the mTOR pathway and reduced protein synthesis. We found then a new substrate for this kinases and we demonstrate with mice models using inhibitors and AVVs this molecular pathway in vivo."

p38γ and p38δ reprogram liver metabolism by modulating neutrophil infiltration.
EMBO Journal 2016 Feb 3. pii: e201591857. PMID:26843485 IF: 10.43
*González-Terán B, Matesanz N, Verdugo M*A, Sreeramkumar V, Hernández-Cosido L, *Bernardo E, Leiva-Vega L, Rodríguez E*, Torres JL, Perez S., Ortega L, Cuenda A, Nogueira R, Hidalgo A, Miguel Marcos M, Sabio G

"This was the first project that I started in my lab and it was quite difficult to achieve because it combined basic science and also translational science. We found that p38γ and p38δ are highly expressed in liver of obese patients with steatosis. We demonstrated that mice lacking p38γ/δ in myeloid cells are resistant to diet-induced fatty liver, hepatic triglyceride accumulation and glucose intolerance. This protective effect is due to defective migration of p38γ/δ-deficient neutrophils to the damaged liver. We further show that neutrophil infiltration in wild-type mice contributes to steatosis development. We combined

basic with translational science to try to go forward with our research and to improve the impact of our results."

A stress signaling pathway in adipose tissue regulates hepatic insulin resistance.
Science 322: 1539-1543 IF: 30
Sabio G, Das M, Mora A, Zhang Z, Jun JY, Ko HJ, Barrett T, Kim JK, Davis RJ (2008

"This paper is quite special for me because was the first one I published as a postdoctoral researcher. In in we show that JNK1 in adipose tissue can control liver steatosis and insulin resistance in the liver. This was an important finding, providing evidence of functional crosstalk between tissues, showing how the lack of a protein in one tissue affects metabolism in another tissue."

Dr Guadalupe Sabio's Lab Website

This profile was written by Hazel Lambert of sciencestory.com

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