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INTERVIEW

The people behind the papers – J. Guillermo Sanchez and Jim Wells

During development, the gastrointestinal tract undergoes patterning along its anterior-posterior axis to define regions with distinct organs and functions. A new paper in Development derives human intestinal organoids from an individual with duodenal defects and a compound heterozygous variant in the gene encoding the transcription factor RFX6. By studying these organoids, the authors identify novel roles for RFX6 in intestinal patterning. To learn more about the story behind the paper, we caught up with first author J. Guillermo Sanchez and corresponding author Jim Wells, an endowed professor in the Division of Developmental Biology at Cincinnati Children's Hospital, USA, where he is also the Director for Basic Research in the Division of Endocrinology.

J. Guillermo Sanchez (left) and Jim Wells (right)

Jim, can you give us your scientific biography and the questions your lab is trying to answer?

JW: I received my PhD degree in Genetics from the State University of New York at Stony Brook and performed postdoctoral research at Harvard University. I became an Assistant Professor at the Cincinnati Children's Hospital Medical Center in the Division of Developmental Biology in 2002 before being promoted to Associate Professor in 2008 and full Professor in 2012. My research focuses on the processes by which gastrointestinal and endocrine organs form in the developing embryo and how they maintain systemic metabolic homeostasis. My work in developmental biology has provided the basis for the efforts to generate human cells and tissues from pluripotent stem cells (PSCs), and my lab has pioneered approaches to generate gastrointestinal (GI) tissue organoids of the oesophagus, stomach, pancreas, intestine and colon from human PSCs. We use these human organoids alongside mouse models to study congenital defects of the digestive tract, as well as digestive and metabolic diseases, such as inflammatory bowel disease and diabetes. We are also using organoids as a basis for tissue engineering efforts to generate functional tissues for transplantation.

Guillermo, how did you come to work in the lab and what drives your research today?

JGS: I joined the lab of Jim Wells in 2019 because of the amazing work his lab had pioneered on organoids derived from induced PSCs (iPSCs). Organoids are the perfect model to study patterning and disease, and the Wells lab has optimized protocols to generate multiple organs in the GI tract. The lab is now investigating specific genetic diseases that can be modelled in the organoids to understand their underlying mechanisms, and we have also been working on recombining additional components to organoids, such as vasculature and immune components.

Tell us about the background of the field that inspired your work

JGS: We started working on transcription factors that are crucial for the differentiation of enteroendocrine cells. RFX6 was one of our targets and, with the addition of the Mitchell–Riley syndrome patient-derived iPSC line, we were able to find additional phenotypes.

JW: My lab has been interested in the fundamental question of how a simple tube (the gut tube) gives rise to such diverse organs along the anterior-posterior axis. Previous studies, including our own, have used animal systems to identify some of the basic mechanisms that drive gut organogenesis. From these basic discoveries, we can now recapitulate some of the steps of organogenesis, starting with human PSCs and culminating in the formation of GI organoids. Because of this, we can now directly model human development and congenital malformations using a patient's own PSCs.

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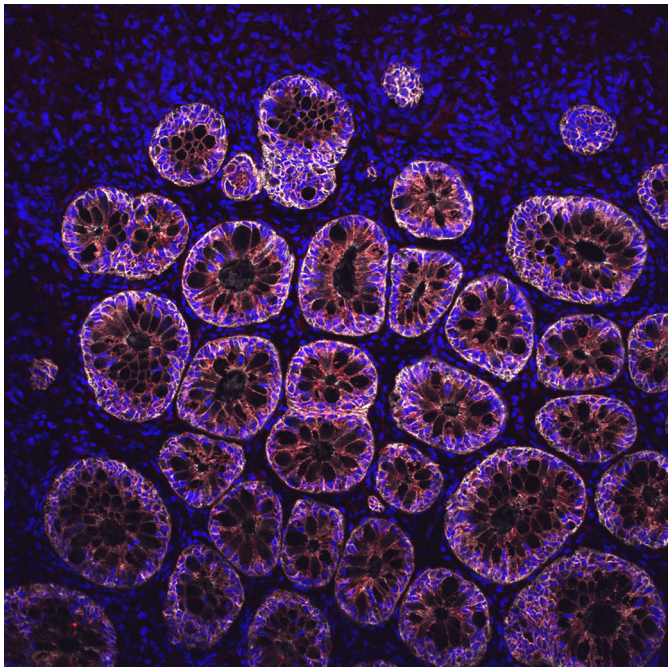

Wild-type intestinal organoid after 10-week transplant stained for nuclei (DAPI, blue), epithelial cells (CDH1, white) and intestinal epithelial cells (CDH17, red).

Can you give us the key results of the paper in a paragraph?

JGS: RFX6 is known to be key for pancreas development, but we show that it also regulates small intestine patterning and function. We find that RFX6 indirectly regulates epithelial–mesenchymal crosstalk in the early development of the midgut. RFX6 also directly regulates PDX1 expression, which maintains the duodenal identity of the tissue. Additionally, our work validates the use of iPSC-derived organoids for disease modelling.

JW: A patient with variants in the transcription factor RFX6 had malformation of the duodenum. Using PSC-derived organoids, we identified that RFX6 is one of the most upstream molecular regulators involved in the initiation of duodenal development.

When doing the research, did you have any particular result or eureka moment that has stuck with you?

JGS: At first, I thought the mispatterning of the duodenal organoids was due to the variability of *in vivo* organoid models. However, we were able to go back to the original patient biopsies and found the same expression profile in the patient biopsy, which suggested that the mispatterning was a novel phenotype.

And what about the flipside: any moments of frustration or despair?

JGS: There were a few moments of frustration, mainly in the generation of the transplanted organoids, which go through a 35-day differentiation process with an additional 10-week period of engraftment. There were a few instances when factors outside of our control (cage flooding, for example) caused us to lose our organoids.

Why did you choose to submit this paper to Development?

JGS: Development is the perfect fit for a project that combines model systems for the study of development and a transcription factor that has several key roles in organogenesis and early patterning.

JW: As a graduate student, I published my first two papers in Development. The papers published in Development are high quality, insightful and provide important advances in our understanding of mechanisms. I think it is a fantastic venue for all developmental studies across species.

Guillermo, what is next for you after this paper?

JGS: I am finishing my PhD in April and I will continue my career in academia in the lab of Nick Zachos at Vanderbilt University where I will be studying intestinal epithelial interactions with nutrients, drugs and infection.

Jim, where will this story take your lab next?

JW: From a developmental perspective, we will attempt to assemble transcriptional regulatory networks that are involved in the development of the different regions of the GI tract.

Finally, let's move outside the lab – what do you like to do in your spare time?

JGS: Outside of the lab, I like going to sporting events, trying new coffee shops, going out dancing and working out.

JW: Outdoor activities of all kinds, depending on where I am. Here there is great kayaking and every year we do a lab kayaking trip.

Reference

Sanchez, J. G., Rankin, S., Paul, E., McCauley, H. A., Kechele, D. O., Enriquez, J. R., Jones, N.-H., Greeley, S. A. W., Letourneau-Friedberg, L., Zorn, A. M. et al. (2024). RFX6 regulates human intestinal patterning and function upstream of PDX1. *Development* **151**, dev202529. doi:10.1242/dev.202529