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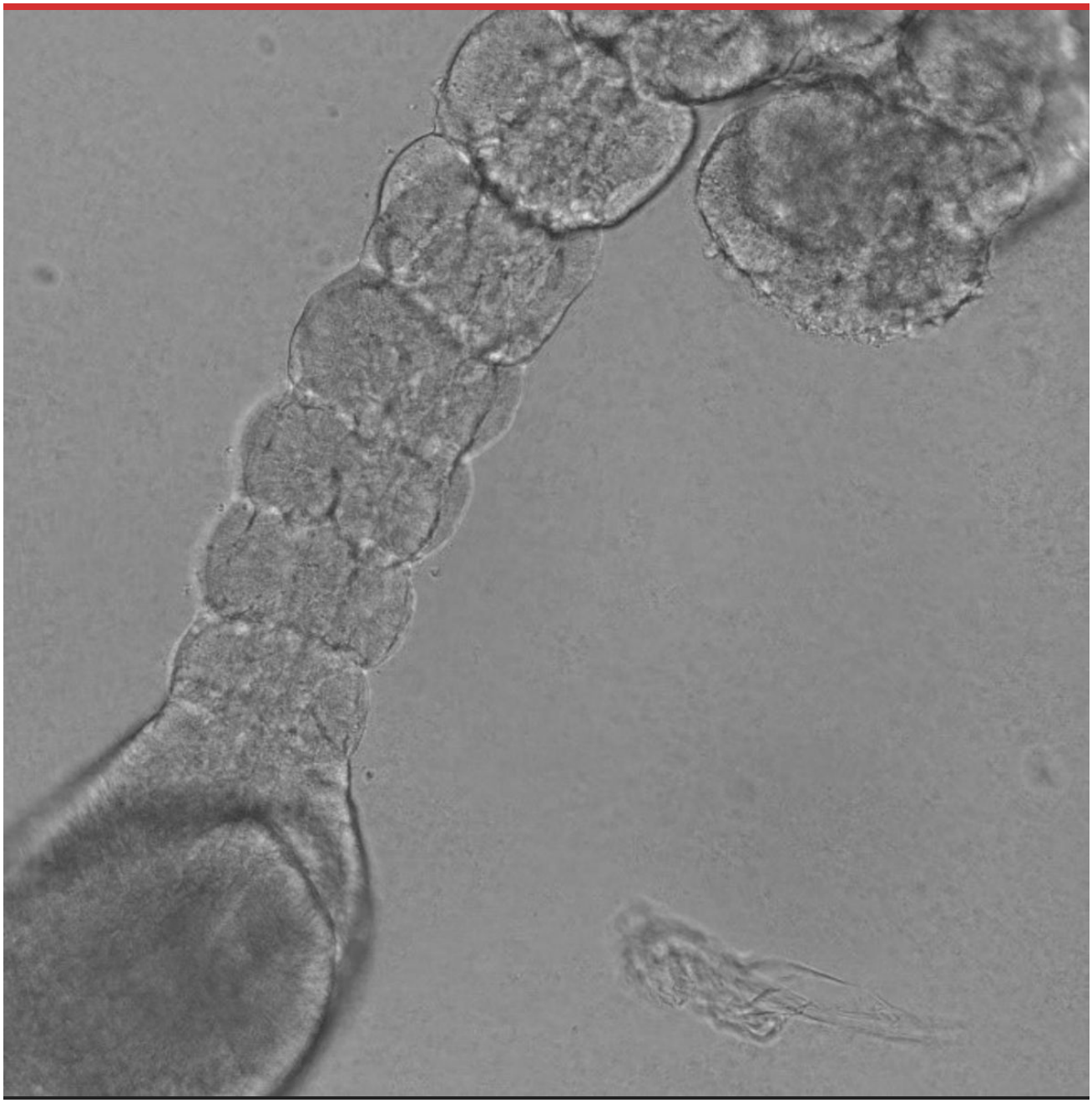

Reconstructing How the Spine Takes its Shape

Marina Sanaki-Matsumiya figured out how to grow human somites in a dish through a process that mirrors the tissue's development in the embryo.

Nele Haelterman, PhD
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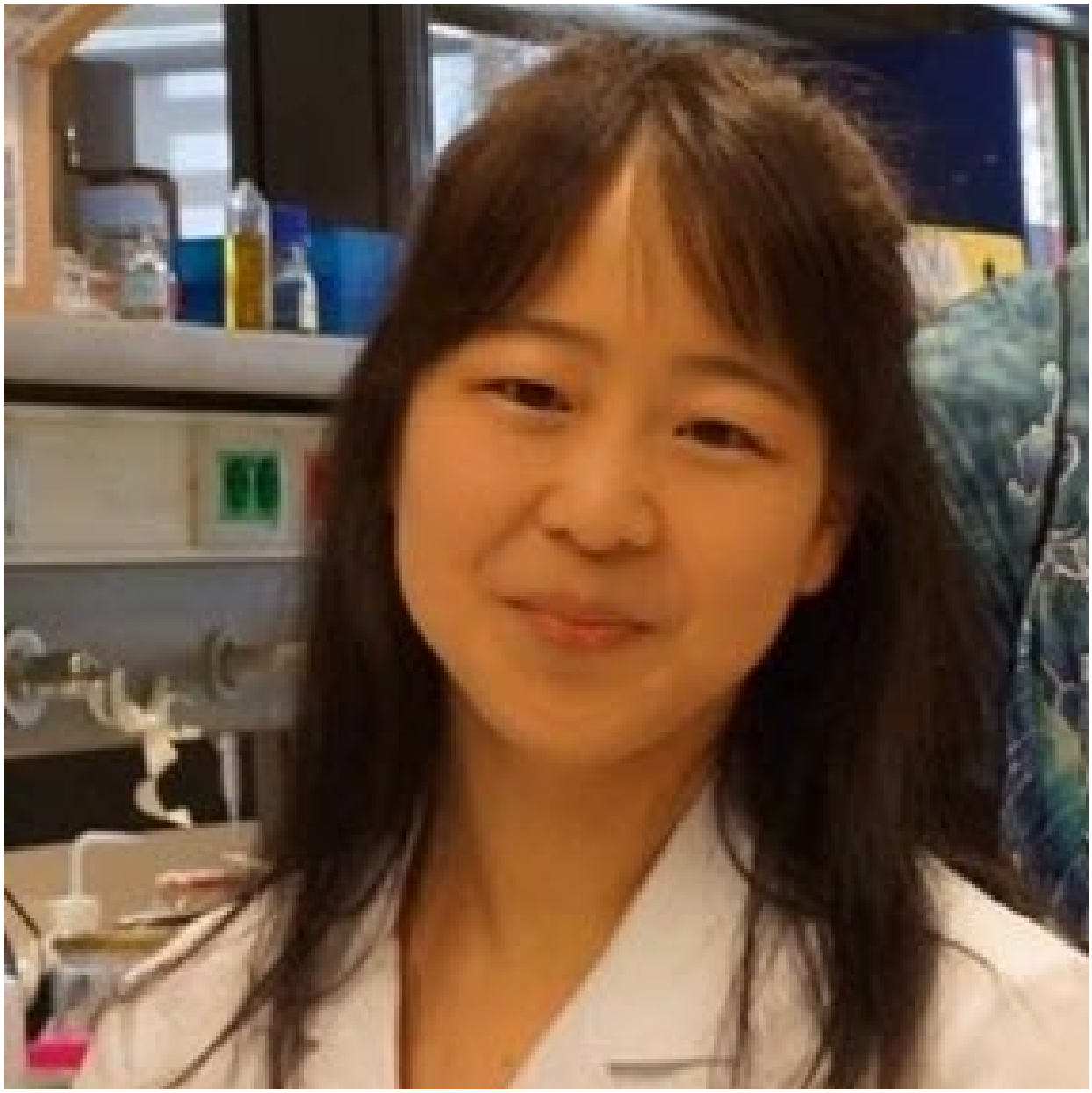
For as long as she can remember, Marina Sanaki-Matsumiya wanted to understand the mechanisms shaping the bones that form our skeletons. Born with a genetic skeletal disease, the developmental biologist first established an in vitro model to study the transient mouse embryonic tissues called



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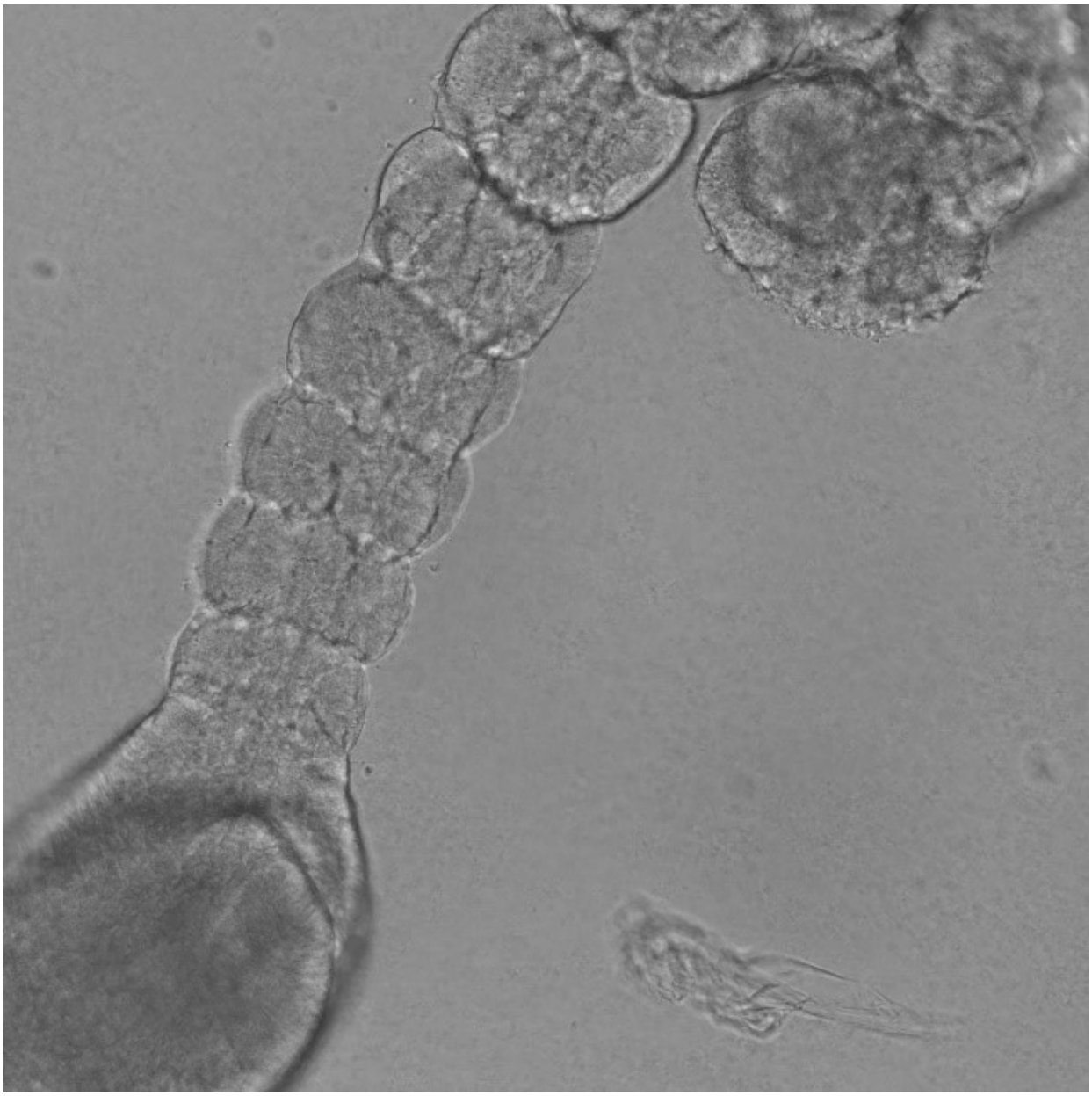
somites that form the spine.[1] She then joined Miki Ebisuya's laboratory at the EMBL campus in Barcelona as a postdoctoral fellow to continue this work with human induced pluripotent stem cells (iPSCs).[2] In a recent *Nature Communications* study, Sanaki-Matsumiya described how to create human somite organoids, or somitoids, that mimic the tissue's development in vivo.

Why is there a need to study human somite formation in vitro?

Somitogenesis is a complex developmental process that sends waves of gene expression changes at precise intervals, called the segmentation clock, through the presomitic mesoderm to bud off somites at the anterior end of the tissue. We study somitogenesis in model organisms, such as mice, chicks, and zebrafish, but, while the overall process is very similar, there are some important differences. Because somite formation takes place during embryogenesis, we cannot study how this tissue

develops in humans, or how mutations that cause skeletal diseases in humans affect the process. This is why we wanted to develop an in vitro model that would mimic somite formation and differentiation in humans.



Scientists developed human organoids that mimic how and when somites bud off from the presomitic mesoderm. Courtesy of Marina Sanaki-Matsumiya, EMBL-Barcelona.

How do you grow somitoids?

We start by culturing human iPSCs and form aggregates in U-bottom well plates. We then change the basal medium for an induction medium that will trigger the aggregates to differentiate into presomitic mesoderm, and then we coat the oval-shaped aggregates in Matrigel™ to support their growth. At this moment, the tissues self-organize and form an anterior-posterior axis. This is also when the segmentation clock genes are induced, so we can see oscillatory waves of gene expression that go from the posterior to the anterior end of the tissue. When these waves reach the anterior end,

it induces a population of cells to epithelialize, pinching off a somite. This process takes about five to six hours in our human somitoid, but it only takes two to three hours in mice, so the timing of this process is quite different between species. On average, every aggregate will form about 10 somites.

What part of this process challenged you the most?

The hardest part of this project was to optimize the protocol. We spent more than two years varying every single step and reagent, but we still could not see the somites develop. The last reagent I changed was the basal medium that we grow the organoids in. I tried different commercial brands, but none of them worked. Finally, I went back to the homemade medium I used during my PhD to grow somite-like tissues from mouse embryonic stem cells (ESCs). Even though this basal medium has the same composition as its commercial counterpart, only the one we made ourselves supported somitogenesis. So, you really have to be persistent. It takes a lot of time to develop the protocol, and there are many different aspects that you can change.

What are your next steps for this project?

Now that we have created an in vitro model that recapitulates human somitogenesis, our goal is to better understand the mechanisms that regulate the segmentation clock and its timing. To do this, we plan to create a “somitoid zoo”, using the same protocol to create somitoids from mice, rabbits, cows and others. We have ESCs and iPSCs from many species, obtained through wonderful collaborators, and we want to better understand the mechanisms underlying somitogenesis and how that differs between different organisms. Our lab also studies spondylocostal dysostosis, a skeletal disease that affects the spine and ribs. We are trying to identify the genes that cause this condition through whole genome sequencing and plan to develop somitoid models using iPSCs from patients to better understand what goes wrong during skeletal development.

References

1. M. Matsumiya et al., “ES cell-derived presomitic mesoderm-like tissues for analysis of synchronized oscillations in the segmentation clock,” *Development,* 145(4):dev156836, 2018.
2. M. Sanaki-Matsumiya et al., "Periodic formation of epithelial somites from human pluripotent stem cells,” *Nat Commun,* 13(1):2325, 2022.

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