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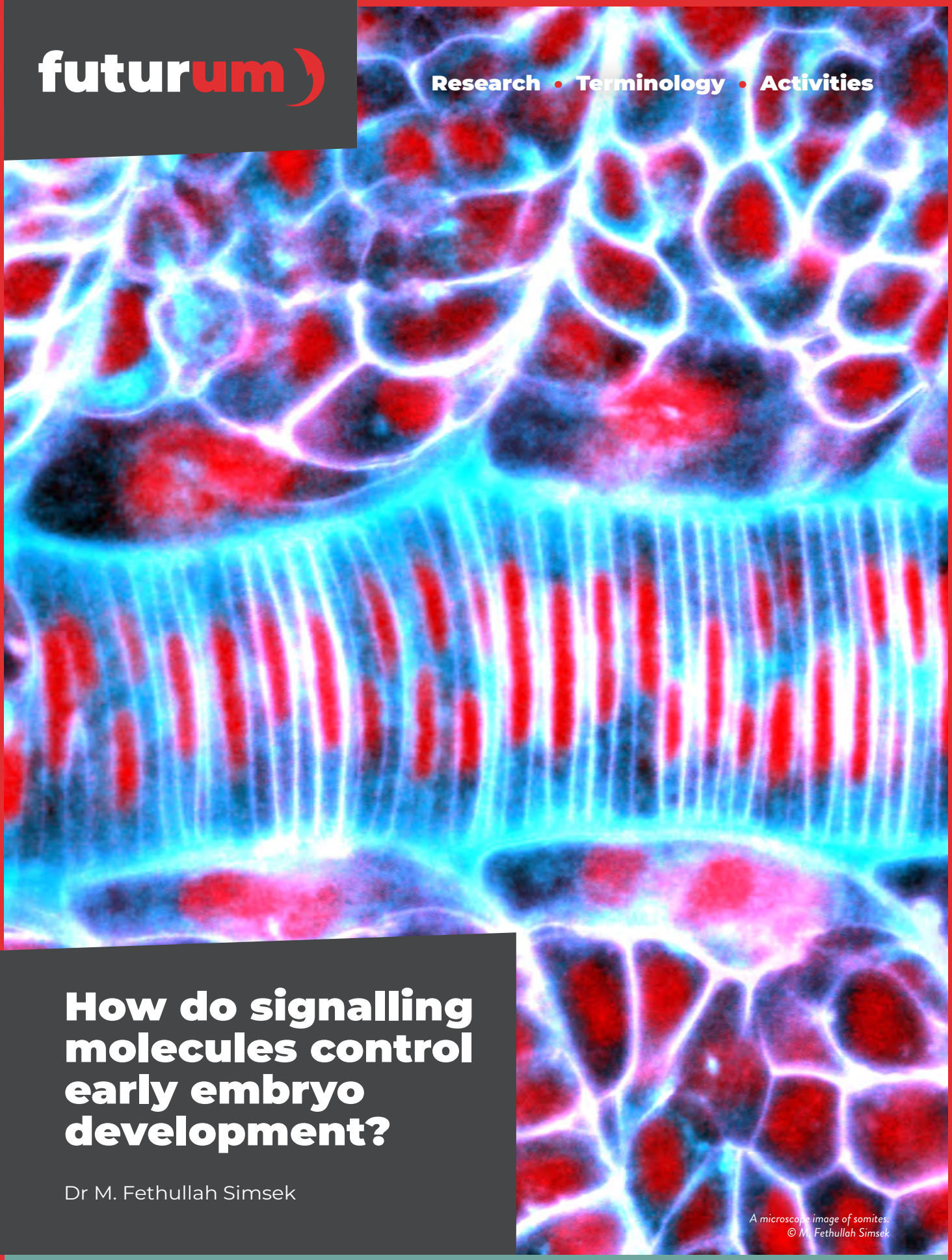

A microscope image of somites.
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How do signalling molecules control early embryo development?

Dr M. Fethullah Simsek

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How do signalling molecules control early embryo development?



Cells are the builders and foundational building blocks of all living organisms. Many animals contain billions to trillions of cells, which all begin as a single fertilised egg cell developing into an embryo. At **McMaster University** in Canada, **Dr M. Fethullah Simsek** is studying how cells communicate through signalling molecules known as morphogens. By observing genetically modified zebrafish embryos with a microscope, he has discovered how to control segmentation in vertebrate embryos.



Dr M. Fethullah Simsek

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Field of research
Developmental biology

Research project
Studying the role of morphogen gradients during embryo development

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PROFILE

Talk like a ...

developmental biologist

Diffusion — the movement of particles from a region of high concentration to a region of low concentration

Embryo — an organism at its early developmental stages

Fibroblast growth factor (FGF) — a morphogen that controls somite formation, as well as the development of the heart, inner ear, eyes and other parts of the body

Morphogen — a signalling molecule that spreads from localised source cells in an embryo to instruct other cells how to develop

Morphogen gradient — the variation in concentration of a morphogen, the strength of which controls how cells will develop

Signalling molecule — a chemical in an organism that instructs a cell to respond in some way

Somite — a repeated temporary tissue structure found in vertebrate embryos

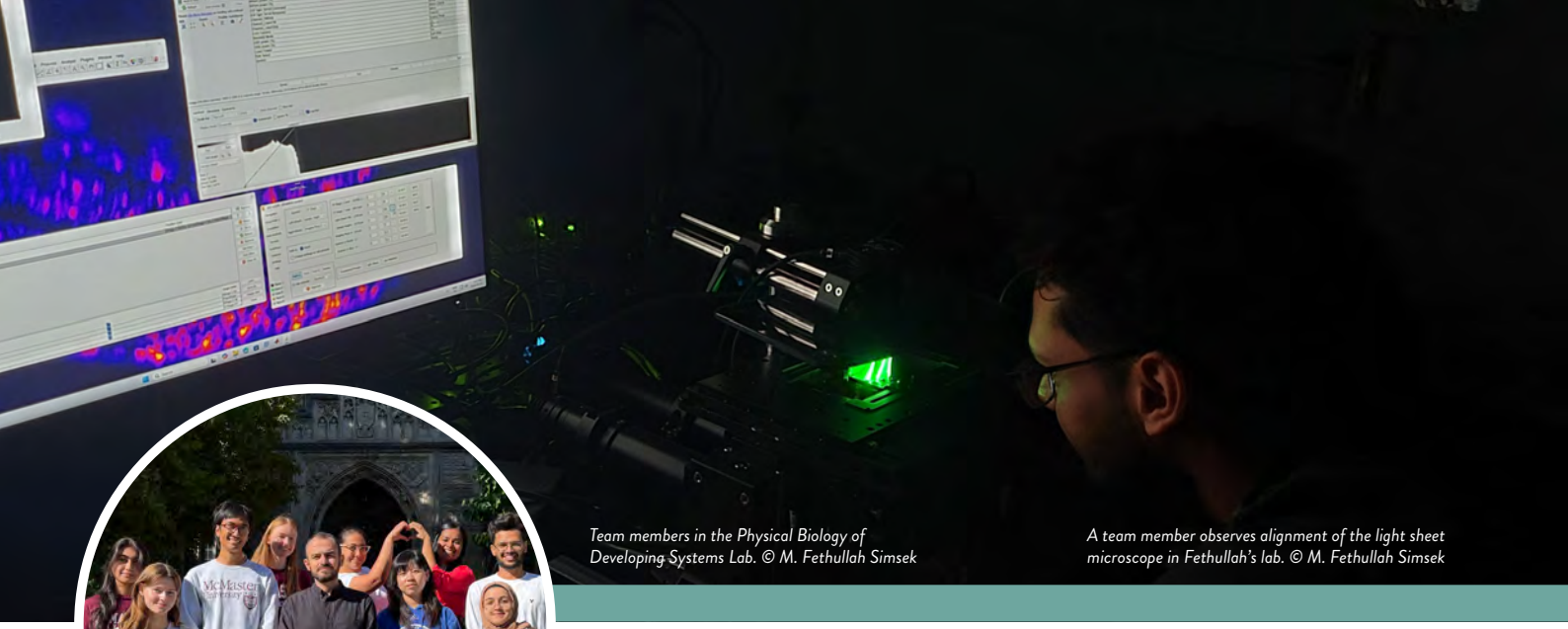
Receptor — a protein in a cell membrane that recognises a specific signalling molecule

How does a single fertilised egg cell develop into a complex whole organism? Biologists have been exploring this question for centuries, and while we now know a lot about developmental processes, there are still many mysteries that remain.

At McMaster University, Dr M. Fethullah Simsek and his team of developmental biologists are studying how signalling molecules known as morphogens control tissue segmentation during early embryo development.

How do morphogens control embryo development?

"After being released by a source cell, a morphogen will diffuse through the embryo, resulting in gradually decreasing signals – known as a morphogen gradient," explains Fethullah. This means the concentration of the morphogen will be stronger closer to the source cell and weaker further away in the embryo. "Cells in the embryo that have receptors to sense that morphogen's signals will develop in different ways, depending on the level of signal they receive." Cells close to the morphogen source will receive stronger signals than those further away, and so will develop into different functional cells as the embryo grows.



Team members in the Physical Biology of Developing Systems Lab. © M. Fethullah Simsek

A team member observes alignment of the light sheet microscope in Fethullah's lab. © M. Fethullah Simsek

How does FGF influence embryo development?

Fethullah and his team are studying a morphogen known as fibroblast growth factor (FGF), which controls body segmentation during development in vertebrates. Embryos contain temporary blocks of tissues (known as somites), whose formation is determined by the FGF morphogen gradient. "Somites mark many positions for other cells, acting like road exit signs," explains Fethullah. "For example, the location of the nervous system, circulatory system and limbs are all informed by somites."

How does Fethullah study FGF signalling?

Fethullah uses quantitative microscopy techniques to understand the role of FGF in embryo development. "In our lab, we try to keep everything intact and image specimens with precision," he says. "This approach is different to classical biochemistry studies, which take the juice out of cells to measure molecular levels and see how molecules are chemically interacting." 'Keeping everything intact' means working with whole embryos, and Fethullah uses zebrafish as his model organism.

There are many advantages to using zebrafish to study developmental biology. They lay hundreds of eggs at a time, which all develop into embryos and larvae at the same pace. Their eggs are transparent, so scientists can observe the cells as the embryo develops. And they share 80% of their proteins with humans, which means research findings from zebrafish can help us learn about human development.

After genetically modifying zebrafish to express fluorescent proteins, Fethullah's team chemically fixes eggs at different stages of development. They then observe the embryos under the microscope and measure how molecules in the embryo change over time and in space. "We combine our insights from our measurements with computer modelling of morphogen diffusion and chemical reactions," he says.

Together with his graduate school colleagues, Fethullah previously developed a live microscopy technique to study cell membranes, and his current team is now expanding this to image whole live zebrafish embryos. By taking thousands of microscope images per second and observing fluctuations caused by fluorescent proteins, the team will be able to determine how quickly morphogens are diffusing through the embryo and whether their diffusion is actively controlled by cells.

What has Fethullah discovered?

"A key observation we made was about embryo segmentation," says Fethullah. "To develop repeating structures in embryos requires the cells to know both what time it is and where they are located." Previously, scientists had discovered proteins in unsegmented tail tissue of chicken embryos (known as segmentation clocks) rhythmically increasing and decreasing to control the timing of somite segmentation. While all tail cells were exposed to these proteins, only a particular group were segmenting at a given time. The strength of the FGF signal (which depends on where a cell is located on the morphogen gradient) was known to change this location. "But the missing piece was 'How does the embryo *really* decide to segment?'," says Fethullah.

"During my previous work in the Özbudak Lab, we showed that the FGF morphogen gradient should also increase and decrease to convince cells to segment," continues Fethullah. "The segmentation clock proteins let that happen by swiftly pushing the FGF signal down. Cells can then compare with their neighbouring cells to precisely know both the time and place to make boundaries."

Having uncovered the dynamics of FGF signalling, Fethullah used inhibitor drugs to suppress the FGF signal in zebrafish embryos, then washed out the drug, then applied it again in periodic pulses. "This let us make somites in mutant embryos that were segmented at any place we wanted!" he says. Fethullah and his team have now developed a 3D-printed device controlled by open-source electronics and a syringe pump which allows them to automatically create patterns of segmented somites along embryos.

What are the applications of this work?

FGF signalling plays a key role in embryo development, meaning that if something goes wrong with the process it can have devastating impacts on the growing organism. "Our work will open new ways to timely diagnose birth defects and to develop cell therapies to alleviate diseases caused by developmental problems," concludes Fethullah. "Like we simplistically reconstituted segmentation using drug pulses, knowing the dynamics of FGF signalling will enable scientists to engineer therapeutic tissues from single cells by precise genetic programming and chemical treatments.

Developmental biology

with Dr M. Fethullah Simsek



A microscope image of a zebrafish embryo.
© M. Fethullah Simsek

Talking *points*

Knowledge

1. What is a morphogen?
2. What is a somite?

Comprehension

3. How do morphogen gradients control embryo development?
4. How does fibroblast growth factor (FGF) influence somite segmentation?
5. Why are zebrafish good model organisms for studying development?

Application

6. How do you think Fethullah's technique of using microscopes to image live zebrafish embryos will help the team learn more about FGF signalling?
7. How do you think scientists could use Fethullah's findings to treat developmental problems in humans?

Analysis

8. Why is it important to understand how morphogens control embryo development?

Evaluation

9. To what extent do you agree that it is important to conduct experiments with animals to learn more about human development? Why?

Activity

Imagine that scientists have successfully used Fethullah's research to create a technique that allows them to diagnose and treat birth defects in human embryos. You are a science journalist, and you have been tasked to write a news report about this groundbreaking new technology.

Your report should explain Fethullah's research that underlies the technology (from his article) and how this has been expanded to diagnose and treat birth defects in humans (from your answer to question 7).

As a journalist, you would have the opportunity to interview Fethullah and other people (e.g., scientists, doctors, parents). What questions would you ask them about the research, the technology and their implications? Write a list of interview questions for your interviewees and imagine how they would answer these.

Write your news report using clear and accessible language to explain the science to a general public audience who do not have background knowledge about topics such as morphogens and somites. It should include quotes from your imagined interviews and should have an engaging heading and introduction to capture readers' attention.

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