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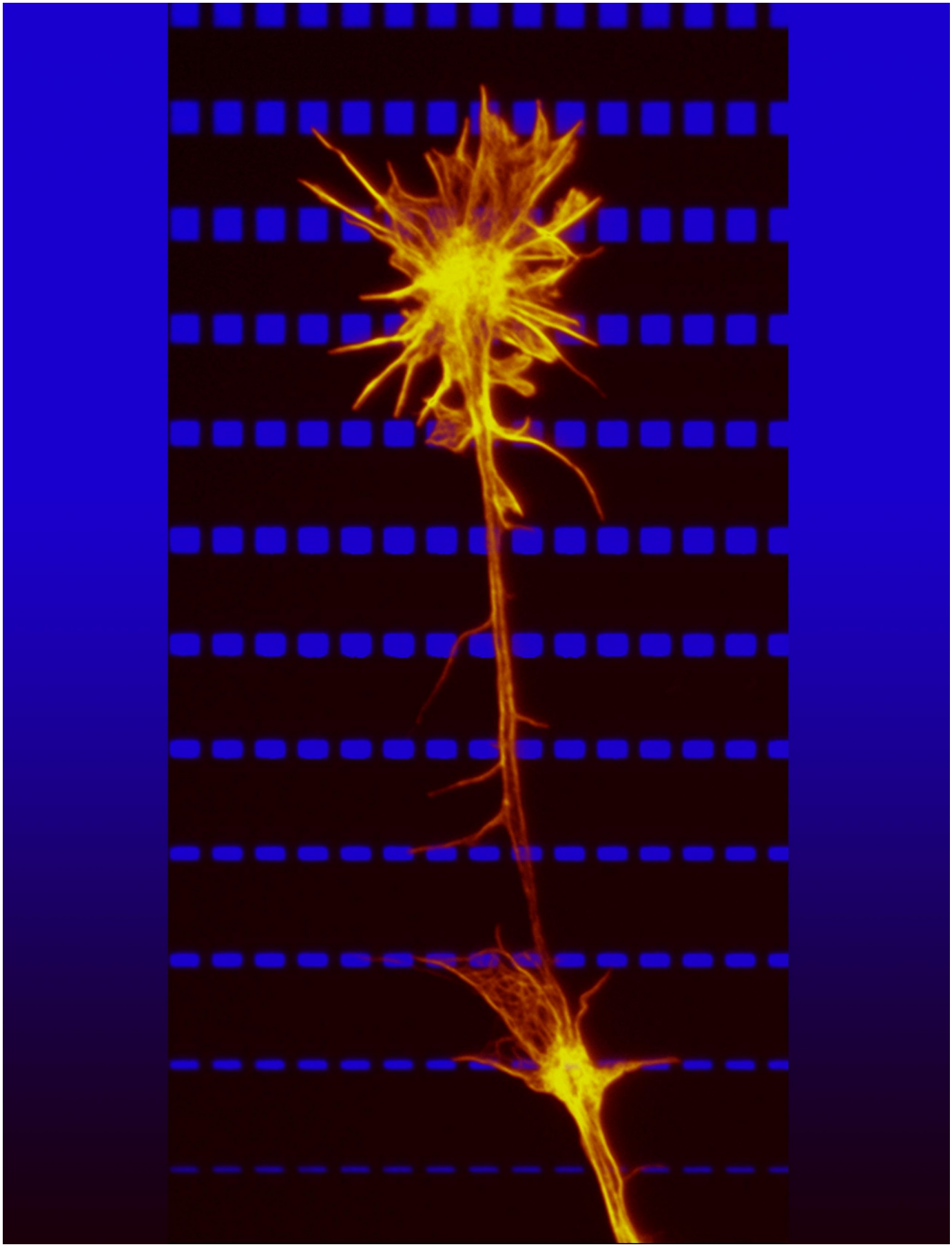
How axons find their way

The visual world has a spatial structure that is reflected in the brain. A neural map in the visual centre of the brain represents the spatial relationships between different points in the visual field. How do nerve cell connections manage to correctly arrange themselves during development to form a neuronal pendant of the environment? A group of researchers led by Prof. Dr. Martin Bastmeyer from the Institute of Zoology at the Karlsruhe Institute of Technology (KIT) is investigating how a complex network of molecular landmarks guides fully grown retinal axons to the correct point in the visual centre map. The researchers use chickens as model organism to simulate the mechanisms involved in axonal pathfinding and target recognition in cell cultures and computer simulations.

We are able to perceive things thanks to a complex architecture of interconnected nerve cells in our brain. This architecture is meticulously arranged and structured. The visual environment is represented topographically in the sense that light stimuli, which act on two neighbouring sensory cells in the retina, are transferred in a spatially correct manner into the brain: the information arrives in two neighbouring areas of the brain's visual centre. Researchers refer to the representation of information that is transferred from retinal cells into the brain as a neuronal "map". But how is this map produced? How do the nerve cells in the developing eye know where the target areas in the brain are located? "A generally accepted hypothesis is that a large number of molecules are found both on the surface of growing axons and on the surface of cells located in the target area, and that these molecules fit together like a lock and key," said Prof. Dr. Martin Bastmeyer from the Institute of Zoology I at KIT. "The interactions between these molecules determine the path of the retinal axons."

Growth and repulsion

The experimental basis for this hypothesis was laid in the 1990s when Bastmeyer worked at the Max Planck Institute for Developmental Biology in Tübingen where Prof. Dr. Friedrich Bonhoeffer had previously carried out groundbreaking investigations on the guidance of retinal axons. Researchers in Bonhoeffer's laboratory also discovered that ephrins are axonal guidance molecules. Ephrins are molecules arranged on the surface of nerve cells. They can bind to specific receptors located on other neurons, for example at the tip of axons. Once a key has found its correct lock, molecular processes inside a growing axon either induce or prevent the growth of the axon. This process can be described in very simple terms as follows: an axon from the retina with a high concentration of ephrin receptors on its surface grows into the brain where it finds its target area in the place where a gradient of inhibitory ephrins is arranged on nerve cells. Since the axon has many receptors and is therefore very sensitive, it is rejected by cells that have a high concentration of ephrins on their surface. However, the axon will establish contact with cells carrying a low number of ephrins on their surface.

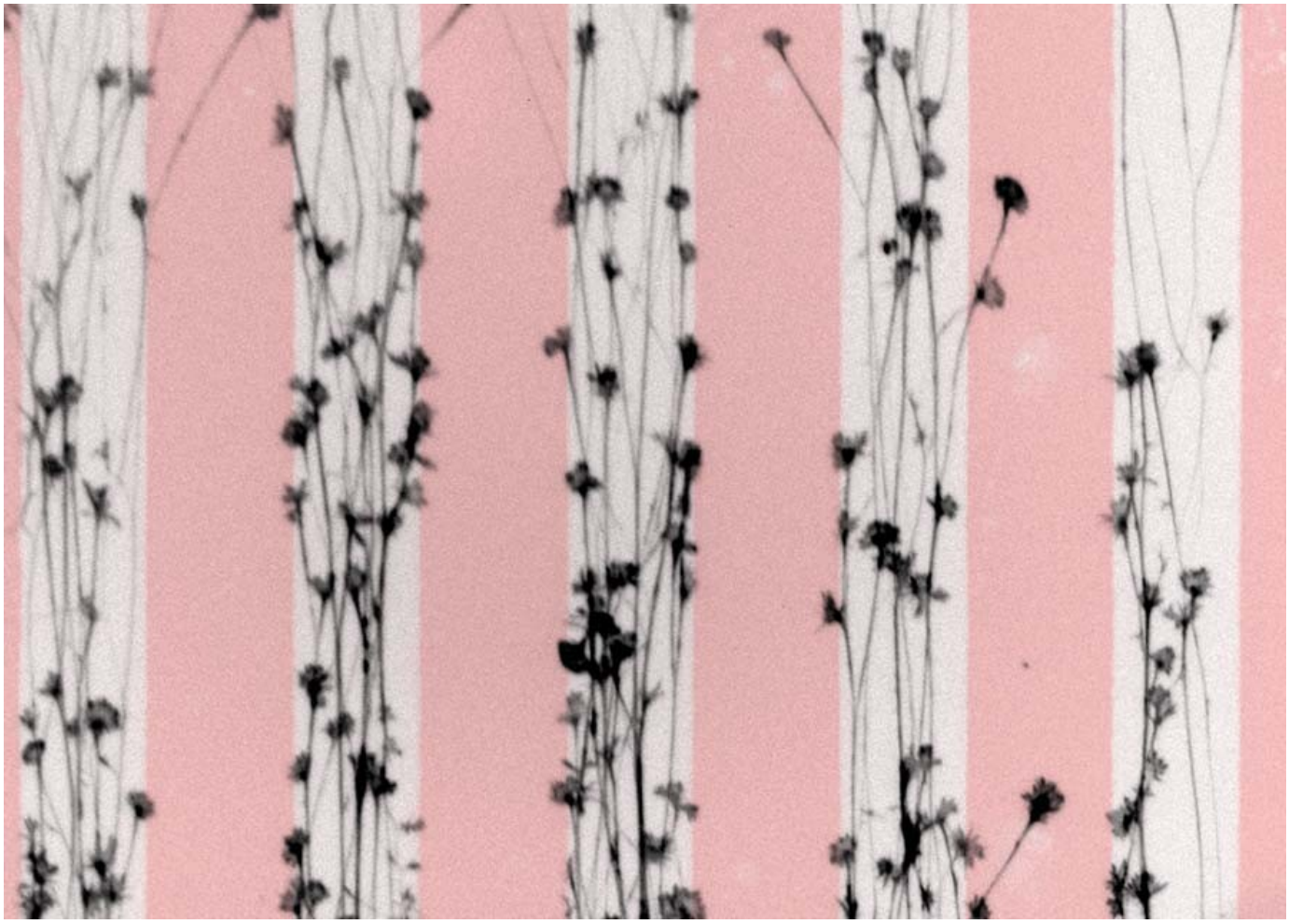


If a gradient of ephrin (blue) is printed on a surface, then retinal axons grow into this gradient and stop at a distinct zone on the gradient.

This is very simplified model because brain neurons have more than one type of ephrins. In addition, the axons and target cells possess both ephrins and ephrin receptors on the surface, and ephrins can

also act as receptors, thus making all the different processes more complex. However, the model also clarifies an important basic idea: "We assume that axons depend on the steepness of the ephrin and ephrin receptor gradients in order to find their distinct targets," said Bastmeyer. The concentration of the molecules in the retina and in the visual centre in the brain varies considerably, and these spatial variations need to somehow correspond with each other. During axon outgrowth, the stop reaction depends on the combination of local ephrin concentration and the amount of ephrin encountered. Bastmeyer's research group is using two complementary approaches to investigate this issue.

Molecular patterns in vitro and in silico



In simple stripe assays, retinal axons prevent high ephrin (red) concentrations.

"We divide the complex system into manageable partial systems in cell cultures," explained Bastmeyer. The Karlsruhe researchers use different methods to create a molecular environment with accurately defined and heavily simplified ephrin distributions (for example, stripe patterns consisting of ephrins, or linear gradients of ephrins and ephrin receptors). They then expose chicken axons to this environment and monitor their outgrowth. The researchers are also developing computer models that simulate the outgrowth and stop processes in cell culture dishes. The model axon is equipped with different combinations of ephrins and receptors and exposed to an ephrin pattern in a simulated environment. Experiments in vitro (cell culture) and in silico (computer) complement and cross-fertilise each other. Findings obtained with simulated tests can lead to theoretical predictions on the growth of real axons and can also be tested in vitro. In a reverse process, cell culture findings can be used to adapt parameters in the computer model.

Besides investigating the pathfinding of retinal axons, Bastmeyer and his team are also investigating how axons find their targets in the olfactory system of zebrafish. They are interested in topics such as mouse neurogenetics and the neuronal development of zebrafish. "Here in Karlsruhe, we are part of a very fertile interdisciplinary environment," said the biologist highlighting that his group is working with polymer chemists, physicists and other biologists in the "Centre for Functional Nanostructures (CFN)" excellence cluster. For example, Bastmeyer's research group benefits from the know-how and experience of other colleagues in the development of three-dimensional growth structures in cell cultures. And in turn, they offer their know-how to other research groups. "I believe that excellent research is best achieved in cooperation with other disciplines," said Bastmeyer.

Further information:

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