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## **Why is man smarter than the mouse?**

*Stem cells in the human brain produce far more nerve cells than corresponding cells in mice. Jürgen Knoblich, a researcher at the Vienna Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) found out what mechanisms are responsible, and why the orientation of the cells plays a role.*

The rapid evolution of brain size, and in consequence intelligence, is a distinctive feature in the evolution of mammals. Although the genes of mice and humans are more than a 90% match the cerebral cortex of a mouse has around eight million nerve cells (neurons) while in humans there are more than 15 billion - a significant difference.

Nerve cells are produced in the brain of the embryo from stem cells which continuously divide, each division producing a nerve cell and another stem cell, providing an inexhaustible supply for reproduction. Why stem cells in humans are able to produce far more nerve cells than in the mouse is explained by the recent work of IMBA scientists.

### **Researchers can control the direction of cell division**

It has long been known that stem cells can divide into different spatial planes, the daughter cells are then either up and down or left and right. According to current doctrine the direction of division of stem cells defines whether new nerve cells or only new stem cells are produced.

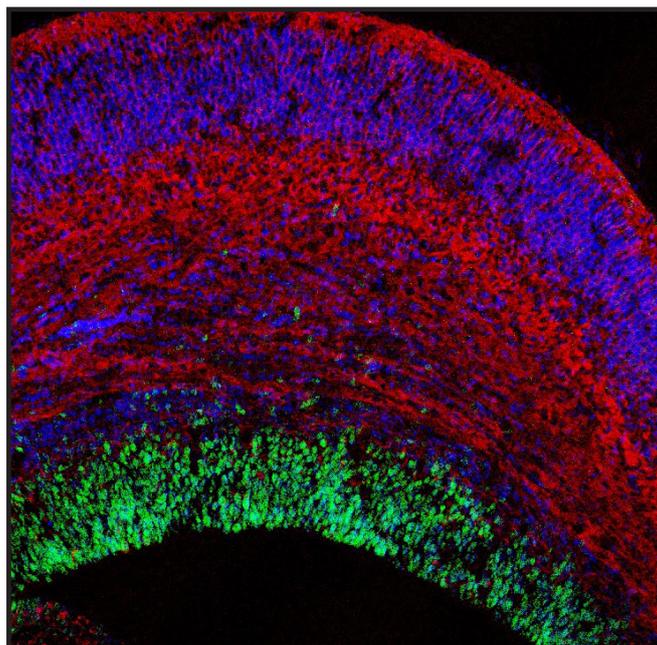
IMBA's Jürgen Knoblich had doubts about this model and determined to finally clarify the issue. Together with his postdoctoral fellow Maria Pia Postiglione he bred mice in which the direction of division of the stem cells can be controlled. The genetic trick is based on the protein „Inscuteable“ which works like a switch for the direction of division: cells divide horizontally with „Inscuteable,“ vertically without the protein.

Studies of the mice with the genetic switch disproved the textbook wisdom: nerve cells are actually generated in both vertical and horizontal divisions, however far more in the latter case. If a mouse has more of the „Inscuteable“ protein there are more horizontal divisions and so more nerve cells. The IMBA scientists see this mechanism as being responsible for the tremendous proliferation of nerve cells in the human brain.

### **„Detour“ in nerve development leads to larger brain**

Higher organisms reproduce nerve cells through a „detour“, horizontal division initially creating a stem cell and an „intermediate progenitor“. This cell no longer has stem cell properties but can still divide, on average once in the mouse, so that two nerve cells are generated per horizontal stem cell division, this „indirect neurogenesis“ also being controlled by the „Inscuteable“ protein.

Indirect neurogenesis is therefore the key to the development of larger and more intelligent brains. Lower organisms such as fish only use direct



*"Section through the cerebral cortex of a mouse, stem cells can be seen glowing in green, mature nerve cells in red; cell nuclei for both types of cell are shown in blue." Foto IMBA*

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neurogenesis and have accordingly fewer nerve cells. Indirect neurogenesis was developed and continually refined in the course of evolution. In humans the „intermediate progenitors“ are already much more complex and divide more frequently than in the mouse, so that compared to rodents, humans have a plethora of nerve cells.

Whether mice without the „Inscuteable“ protein are dumber than their counterparts due to fewer nerve cells cannot yet be determined, whether an artificially induced overproduction of the protein leads to more intelligent animals equally so.

## ***Does “Inscuteable” make man human?***

“Far more interesting however is the role played by „Inscuteable“ in humans” says Jürgen Knoblich, “It probably also regulates the number of neurons in our own bodies by activating indirect neurogenesis, the evolution of the protein and its function may have contributed to the enormous enlargement of the human brain.”

Another research result supports this hypothesis: the division pattern of the “intermediate progenitors” closely correlates with the level of intelligence, and this pattern only appears in primates, including humans, so without „Inscuteable“ we would certainly not be what we are.