

## A mouse as a key to human diseases

**For the first time a human immune system has been re-created in a mouse on the basis of haematopoietic stem cells. The research was carried out under the direction of Dr Markus Manz of the Institute for Research in Biomedicine (IRB), Bellinzona, and the results published in Science. This ground-breaking study presents scientists with an animal model replicating the human immune system, in such a way as to be applicable to the field of infectious diseases, but also in oncology. Experimentation with drugs and vaccines used to treat serious human viruses may well have reached a turning point.**

Biomedical research has for many years endeavoured to reconstruct the human immune system within another living organism. Researchers have long aspired to achieve a simple system, easy to manipulate in vivo, to study some of the diseases affecting man and to screen drugs and vaccines. The dream has now come true, and we owe it to a team of IRB biologists headed by Markus Manz. The findings were published in the prestigious journal Science in April of this year. *"To grasp the significance of this achievement - explains Antonio Lanzavecchia, director of the Institute - just bear in mind that the HIV virus, which causes AIDS, attacks only human cells. Therefore we simply have no ideal experimental model to help us along". "It's very straightforward: - adds Elisabetta Traggiai - we took a newborn mouse deprived of its immune system and we inoculated its liver with stem cells obtained from human blood. The human stem cells divided and differentiated in the mouse to generate the*



The mouse with human immune system obtained by IRB researchers.

*type of cell that constitutes the human immune system".* The immune systems of mice and men are quite similar, a good enough reason for us to take a number of human cells, inoculate them into a mouse, and then observe the mouse to investigate pathologies affecting human beings. *"Our models are still far from perfect - declares Markus Manz - yet we have been able to ascertain that a mouse's immune response is not dissimilar from a man's: we injected the mouse with the human vaccine against tetanus and the animal reacted by producing tetanus-specific anti-bodies. Also, when we infected the mouse with a human virus we observed a specific response mediated by T-lymphocytes".* From now on, mice with a human immune system can be used both to construe the evolution of a disease and to locate new treatments. This breakthrough will help us speed up the testing process and obtain results that, though based on an animal model, may turn out to be closer to man than ever before. Finally, this research programme also shows the Institute's success in building partnerships with other research ventures in the same field in Ticino. Indeed the publication bears the imprint of four institutes of the area: besides the IRB's, that of the Regional Hospital in Bellinzona, the Cantonal Institute of Pathology, and the Cantonal Institute of Microbiology.

### The Institute for Research in Biomedicine (IRB)

Set up in 2000 in Bellinzona (Switzerland), the Institute accommodates some sixty researchers working in nine separate teams. The IRB contributes to the advance of research in biomedicine by studying the founda-

tions of immune defence mechanisms. IRB's research topics range from cell and function issues in immune response, to molecular infection processes and innate and acquired

immunity. Other areas of scientific inquiry include certain mechanisms of cellular biology and the structure of proteins. IRB is also home to some fifteen researchers of the Oncology Institute of Southern Switzerland ([www.iosi.ch](http://www.iosi.ch)). Under Antonio Lanzavecchia's leadership, the IRB has distinguished itself, in the short time span since its foundation, as one of the best research centres for immunology.



## Applications: infectious and tumours

Scope for application in the short term is considerable. First, mice represent an ideal tool to study human immune system development. This implies that pharmacological products that target the human immune system, i.e. immunosuppressants or immunostimulators, could be directly tested *in vivo* before undergoing clinical trials. Second, mice can be used to study human reactions to infections that specifically attack the human immune system (e.g. HIV). Third, they might be a valuable tool for the generation of human monoclonal antibodies. And finally, they might serve as an *in vivo* model for human tumours such as leukemias.

### ■ From concept to realisation

To obtain mice with a human immune system, researchers used an immuno-deficient mouse, in other words a mouse genetically unfit to develop its own immune system. The peculiarity of its condition consists in the absence of two genes that are crucial for the generation of B and T cells in the immune system (the RAG1 and RAG2 genes) and of a receptor required for the growth of the NK 'natural killer' cells (gamma common chain). The newborn babies of such a mouse were inoculated with some human stem cells (CD34+) removed from the blood of a human umbilical cord. Stem cells are undifferentiated cells that may be found in any tissue of our body. They are not fully grown and they are capable of long-term self-renewal. They spring into action when the need arises, and can replace any ageing or damaged tissue cells. Researchers at the IRB used the blood of the umbilical cord because it contains haematopoietic-type

### A world première

A mere few months after the 'creation' of a modified mouse, fresh progress can be reported at the IRB in the long-standing fight against cancer and serious infectious diseases. IRB researchers, working jointly with other universities, have devised a method to obtain cells generating human monoclonal antibodies, to be used in the field of infectious diseases, among others. The antibodies against the SARS virus that this research has discovered are 100 to 1,000 times more powerful than antibodies produced so far by applying traditional techniques. Hence, the aim will be to use the new method to turn out antibodies able to neutralise other viruses. It is hoped that one day they may be employed also in the fight against cancer. This major discovery was published by the prestigious scientific journal, *Nature Medicine*.



Elisabetta Traggiai, Markus Manz and Laurie Chicha from the IRB.

stem cells, which can form all the types of blood cells in the body, including those of the immune system (B, T and NK cells). Researchers proceeded to single them out, cleanse them and lastly inject them into the liver of a newborn mouse lacking its own immune system. So, the mouse genetically unequipped to produce its own immune system resorted to the available immature human cells to create one. And because these parent cells had their origin in a human being, the immune system that took shape in the mouse was of a human kind. *"It is hard to believe that a human system may settle down in the organism of a mouse"* - agrees Elisabetta Traggiai - *"yet the evidence points that way: two months since the transplant into the mouse, we have observed fully-fledged human cells capable of reacting to human viruses and vaccines"*.

### For further details:

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### References:

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