

Cells with a future

Stem cells are our body's all-rounders. They are the source of all tissue types. This makes them particularly valuable in drug development as well: they can be used to simulate entire organs and even to model diseases. Bayer researchers are seeking new treatment approaches using what are termed induced pluripotent stem cells.



Clean work: experiments with living cells, like those being conducted here by laboratory technician Wibke D'Acquisto, require sterile conditions.



Insights of a new kind: work with so-called induced pluripotent stem cells and cells derived from those stem cells allows Bayer researchers such as Dr. Heidrun Ellinger and Dr. Nils Pfaff, for example, to test the effects of drug candidates on specific cellular functions or to simulate genetic diseases in Petri dishes.

The heart muscle cells in the Petri dish are beating, one beat a second. The wafer-thin cell layer is functioning just like the fully developed organ. However, these cells were not taken from a human heart but originated in human skin. Using a biological trick, it is now possible to reprogram the body's fully developed cells, so-called adult cells, back to the stem cell state and then specialize them into heart muscle cells. "These all-rounders, called induced pluripotent stem cells or iPSCs for short, can theoretically develop into any cell type and consequently any tissue, similarly to embryonic stem cells," explains Dr. Nils Pfaff, a molecular scientist at Bayer HealthCare Global Drug Discovery. The thin cell matrix of heart muscle cells is a valuable research material in Bayer's laboratories. Pfaff and his colleagues in Wuppertal are using it to investigate whether certain active substances are capable of disrupting the heart rhythm, as this would be a life-threatening adverse effect of any potential drug. iPSCs can also be transformed into liver-like cells. Research teams worldwide are therefore investigating their use in early metabolism and toxicology studies of potential drug candidates.

Induced pluripotent stem cells can be specialized into different types of cells

A few years ago, the reprogramming of mature or adult body cells triggered a revolution in the world of research. Until then, a cell's developmental pathway in the body was considered to be firmly fixed: although the entire genome is present in every cell, mature skin or nerve cells are no longer able to access all parts of it. "Embryonic stem cells, on the other hand, have access to other specific regions of the genome, allowing formation of all cell and tissue types," says Pfaff. Due to their origin, however, human embryonic stem cells raise ethical and moral concerns, and the production of these stem cells and their use for research purposes is banned in some countries. Bayer is likewise not active

in research with human embryonic stem cells. In recent years, therefore, researchers worldwide intensively sought alternatives – and came up with the technology to derive iPSCs from mature cells of the body.

These all-rounders are already helping drug research. "We are finding clues to new starting points for treatments – for

4 inserted genes

ensure that skin cells are reprogrammed into induced pluripotent stem cells.

Source: EuroStemCell

example, for patients with particular genetic diseases," continues the molecular scientist. Using iPSCs, researchers can produce organ cells that show particular disease manifestations. "With this sophisticated technology, diseases can be simulated in the Petri dish, as can genetic predispositions to diseases and their effects," says Pfaff. Alternatively, iPSCs can be produced with genome alterations, thereby simulating patients with genetic defects and diseases. "There was previously no way of obtaining these specific cell types," says Pfaff. "By testing substances in the diseased cells, we are able to develop new treatment approaches and also to test the effects of potential drug candidates," adds Dr. Herbert Himmel, a physician at Bayer HealthCare Global Drug

Discovery. "We can study the effects these compounds have on ion channels and electrical excitation in the heart." This does not yet work for large-scale screening, as it is not possible to produce enough cells. The experts are nevertheless working on standardization and improvement of production. "iPSCs are an invaluable source of human cell material," explains Dr. Heidrun Ellinger, a toxicologist in the Cell Biology department.

A gene cocktail allows the reprogramming of adult skin cells to iPSCs

To produce induced pluripotent stem cells, adult skin cells, for example, are treated with a special gene cocktail. Blocked, inactive genome regions become accessible again and the cells end up assuming stem cell status. In a second step, the researchers add certain additives such as growth factors at a particular development stage and for a set period of time. In this way, the iPSCs are steered onto the desired developmental pathway. "Similar processes also take place in the embryo in the womb," says Pfaff. "We are now trying to simulate these steps in the Petri dish." Various differentiation protocols have been developed, describing possible combinations of additives for producing heart or liver cells, for example. The currently known protocols only allow production of immature organ cells without the properties of adult organ cells, however. Bayer's experts are therefore working on optimizing the process.

"With cardiomyocytes derived from induced stem cells, indications as to whether drug candidates may pose a risk to heart function in patients are obtainable at an early stage," explains Himmel. "Some substances affect ion channels in the cell membrane. This may alter electrical excitation in the heart and cause arrhythmias." On the basis of the results, Himmel can assign the active substances to risk classes before they are tested in animal models or test subjects. In this way, iPSCs offer a chance to further improve risk predictions of potential drug candidates. Therefore, iPSCs have major potential in toxicology in particular.

Cell experiments can improve risk predictions for drug candidates

The liver plays a key role in this respect, as most drugs are metabolized there. Real liver cells from patients cannot be propagated in the laboratory, however. This limits test series. "Furthermore, liver cells differ considerably from patient to patient," says Ellinger. She is therefore focusing on hepatocytes, which account for around 80 per cent of the volume of the liver. The Bayer experts are investigating whether hepatocytes derived from iPSCs are also suitable for early testing of adverse effects of potential drug candidates. The advantage with iPSCs is that hepatocytes could be newly produced at any time. Tests in animals and humans remain essential, however. "In the liver, as in other organs, many different cell types work together and it is

Producing and using pluripotent stem cells

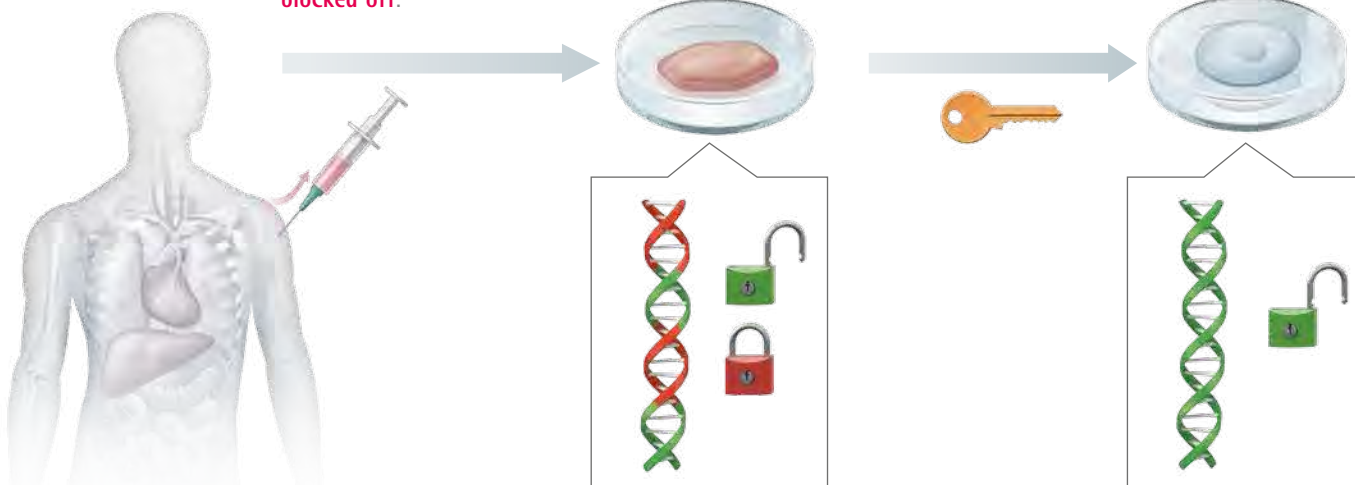
Induced pluripotent stem cells – iPSCs for short – can be used to produce different types of the body with their characteristic properties. These are very valuable for research into active substances and diseases as well as for regenerative medicine.

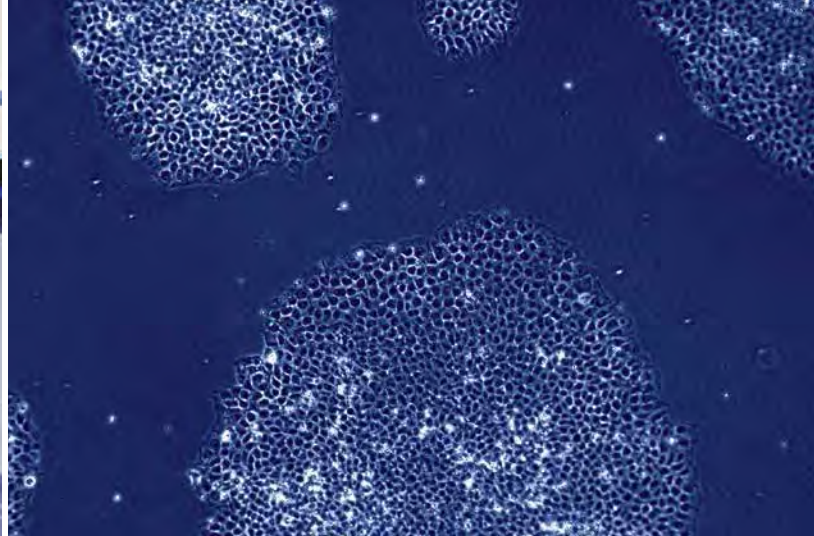
Biopsy

Skin cells are harvested. Even though they contain the entire genome, they have access only to **certain segments**. Other areas are **blocked off**.

Reprogramming

A special gene cocktail makes the blocked-off genome segments **accessible again**. An induced pluripotent stem cell can therefore use the entire genome.





Invaluable material: induced pluripotent stem cells – the photo on the right shows what a group of cells looks like under the microscope – divide frequently and with the addition of specific factors can be converted into various cell types such as liver cells. Dr. Asifqbal Kadari and Dr. Heidrun Ellinger test these transformation processes and are aiming to further optimize them.

not yet possible to simulate physiological interactions between them under cell culture conditions," says the toxicologist. The continuous improvement of in vitro testing methods, however, may also allow further reduction of the animal experiments required in the development of a new drug.

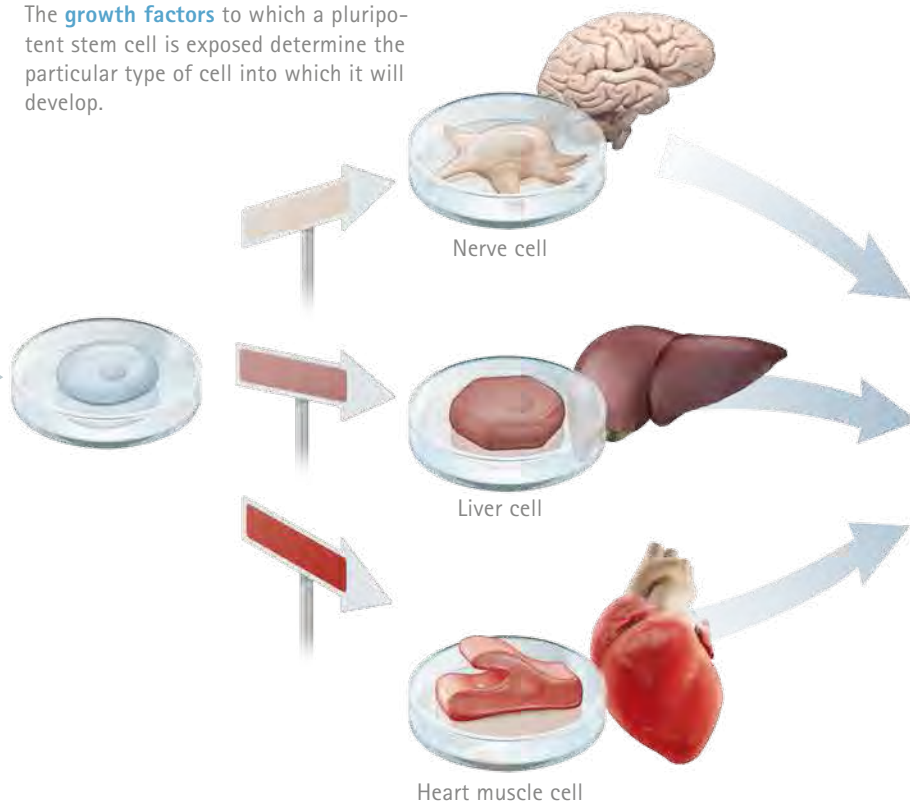
iPSCs are already a major addition to drug research. In addition, iPSCs may also have a promising future in regenerative medicine. "In the long term, for example, it might be possible to

remove diseased cells from patients, repair them in the pluripotent state after reprogramming and then transplant differentiated cells back into the body," explains Pfaff.

www.research.bayer.com/stem-cells
 More information on this subject

Differentiation

The **growth factors** to which a pluripotent stem cell is exposed determine the particular type of cell into which it will develop.



Hope for the future of medicine

Cell cultures produced by this means have great potential in active substance research and drug development, in disease research and also, in the long term, in regenerative medicine.

