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## Cell pharmacy

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Prof. Dr. Micha E. Drukker

## Cell Pharmacy



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Bij ons leer je de wereld kennen

# Cell Pharmacy

Inaugural Lecture by

**Prof. Dr. Micha E. Drukker**

On the acceptance of his position as Full Professor  
with the teaching mandate Stem cell research for drug development  
at Leiden University  
on Friday 18 November 2022



**Universiteit  
Leiden**



## Preface

Mevrouw de Rector Magnificus, zeer gewaardeerde toehoorders,

Respected guests, family members, and dear colleagues,

After 25 years of scientific journey, I am proud and privileged to stand before you today as a new professor at Leiden University. I believe in the University's ambition to discover how stem cells can cure disease. A revolution in bio-pharmaceutical sciences and medicine is upon us. We will make stem cell drugs.



## Introduction

I would like to announce today an ambitious vision for Leiden University. I call it the “cell pharmacy” (illustration 1). My role is to lead stem cell research using cutting-edge scientific knowledge and research facilities to turn the “cell pharmacy” vision into reality.

My vision is that, in the future, patients will have access to replacement organs and tissues in case of illness<sup>1-4</sup>. For example, type I diabetes patients will be able to “shop” for pancreatic islets that will be made from stem cells entirely in the laboratory. In diabetes, for the replacement of islets have

been damaged. This “shop” is a metaphor for a technology that will revolutionize the treatment and cure of numerous illnesses.

I would like to emphasize the idea of cure. Today, numerous health problems are treated to relieve symptoms; as an example, I will use diabetes once more: patients are treated by insulin, but this doesn't cure the disease. Only the replacement of islet beta cells made from stem cells can free patients from monitoring blood glucose level and injecting insulin. Because insulin injection has many limitations this will dramatically increase their health.

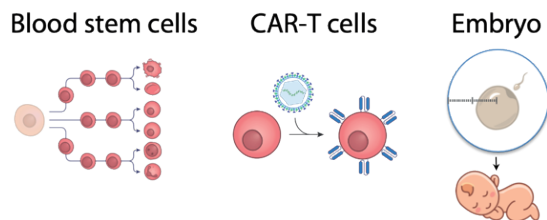
There are numerous additional exciting possibilities. Thousands of syndromes could potentially be cured using stem cells. For example, spinal cord injuries and nerve problems. Also, well-known diseases including Parkinson's disease, and cardiac infraction. The principal idea is the same: using cells as drugs to cure disease, and in Leiden University we are devoted to this goal.

## The living drugs

I have already introduced the key idea of this lecture; namely, that cells will become drugs. It is important to discuss what this means. From an overarching perspective, there are three main types of drugs: there are small molecule drugs, like antibiotics and aspirin, as the model in my hand shows. These are the drugs presently in pharmacies. The second type of drug are large biomolecules that are made of peptides and proteins. I would like to show a model of an antibody that is used in cancer therapy. These drug types are established domains in the industry and research institutes like our Center for Drug Research.

The third type of drug, the one which my research focuses on, is very new - drugs that are made of living cells. Relative to small molecules and to biomolecules, the size of a cell is roughly the size of this hall. Because cell therapies are comprised of billions of cells, the relative size of cell drugs will be roughly the size of the city of Leiden. This leads to

significant challenges in the safe production of stem cell drugs which will live in the body for many years, as I will explain. It is important to mention that bone marrow transplantation and cancer immunotherapy using T cell are proven powerful cell cures (Illustration 2). Even in vitro fertilization is a type of cell therapy for infertility. The lecture today will take you on a journey about how we will accomplish the development of totally new types of cures using special cells called pluripotent stem cells.



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### Pluripotent stem cells

As the name implies, pluripotent stem cells are unique because they are the only cells that are all capable – namely, having the potential to produce all the organs, tissues, and cells in the human body (Illustration 3 next page).

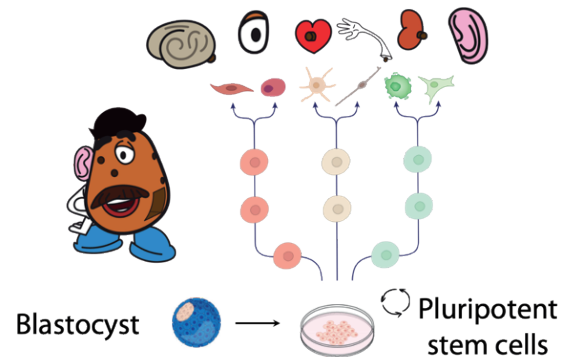
Classical animal anatomy and modern human embryology taught us a very important fact - the embryo does not contain a human figurine. Instead, mouse and human embryos contain a group of roughly 100 uncommitted cells at a stage called the blastocyst<sup>5</sup>. These cells undergo metamorphosis, a process that we call “differentiation”<sup>6</sup>. Stem cells were given this name because they gradually diversity into branches of cell types that give rise to the body.

Brilliant classical embryology and molecular experiments revealed growth factors can maintain mouse pluripotent cells as undifferentiated cells<sup>7</sup>. Subsequently, two sensational developments took place. First, human embryonic stem cells were made for the first time in 1998 based on knowledge of mouse growth factors<sup>8</sup>.

This seminal discovery ignited the idea of totally new stem cell cures, which were previously not possible due to

limitations of tissue transplantation technology. For example, we can't obtain dopaminergic neurons from donors to treat Parkinson patients. However, the new technology showed the promise to differentiate dopaminergic neurons from human embryonic stem cells. It also demonstrated that we can rapidly grow any amount of pluripotent stem cells in the lab. In 1998 I was fortunate to be one the first PhD students that had the access to human embryonic stem cells. I seized the opportunity of a PhD with Prof. Nissim Benvenisty at the Hebrew university, which was fundamental for my career in stem cell therapy.

It was during my PhD that I developed an approach to solve gaps towards stem cell cures, and at the same time conduct basic research in stem cells. Before telling you more about our research, I would like to speak about the second pioneering discovery of induced pluripotent stem cells.



### Induced pluripotent stem (iPS) cells

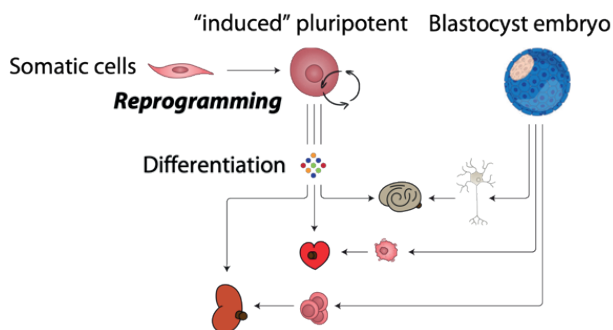
In 2006, Prof. Shinya Yamanaka from Kyoto University published a technique to reset adult cells to pluripotent stem cells<sup>9</sup>. He discovered a cocktail of proteins that can literally send adult cells back in time to their “embryonic origin”, in a process named “reprogramming” (Illustration 4).

The importance of this invention is enormous. Our idea is that “cell pharmacy” will be established based on skin cells, or

a few drops of blood, or even cells in urine by reprogramming them into iPSCs. Then brain cells, pancreatic islets, or any other tissue type will be differentiated for therapy.

This technology has two critical advantages. First, it allows to produce individualized, or as we like to call it, “personal” iPS cells for any person, to match her or his own immune system. Its literally creating personal tissues in the laboratory. It means that immunosuppressant drugs will not be necessary to prevent graft rejection, as with human embryonic stem cells<sup>10</sup>. I published the rejection mechanisms of human embryonic stem cells during my PhD<sup>11-15</sup>, and Prof. Yamanaka found a way to overcome the rejection.

The second implication is that ethical issues about use of embryos for producing embryonic stem cells, are completely removed by making of iPS cells. Thus, reprogramming technology, allows, in principle, to make any tissue type without immunological and ethical complications. The explanations so far set the grounds for explaining our research in Leiden university.



### Discovering new differentiation mechanisms of iPS cells

In Leiden University, we believe that a significant challenge for the cell pharmacy vision is to discover how to effectively “direct” the differentiation of iPS cells to specific types of cells. I think of differentiation as our personal “miniature” big bang. What we observe in the universe is an increase in complexity from basic particles, to molecules, stars, planets and living

organisms. My view is that in analogy each of us is the outcome of a similar process where simple building blocks give rise to our highly sophisticated bodies by a dramatic increase of complexity. It is an amazing thought that the molecules that are coded in the nucleus of pluripotent cells have an output, which is every one of us!

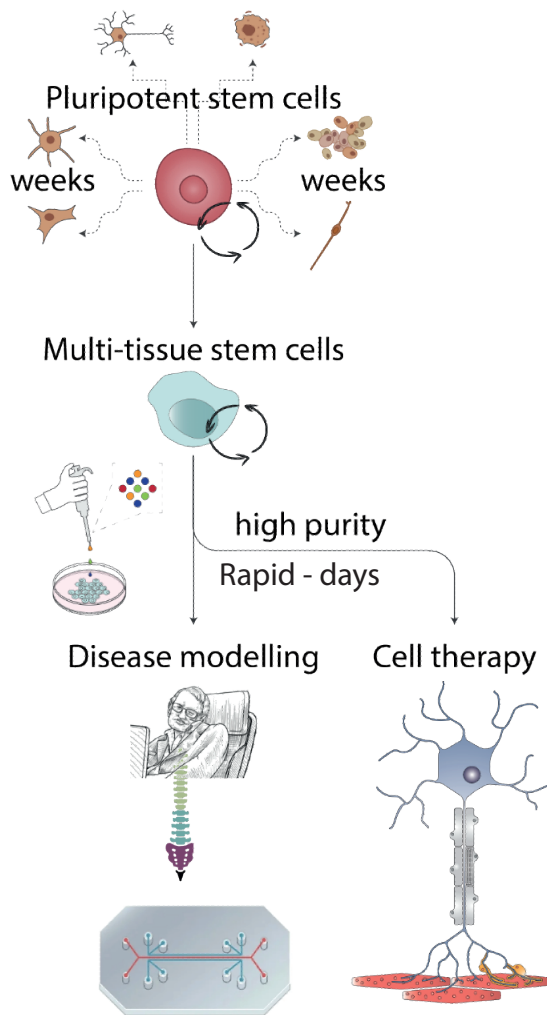
We developed a novel approach to make the differentiation more effective. I explained earlier that scientists discovered ways to propagate undifferentiated pluripotent stem cells. On top of that scientists discovered protein growth factors that can direct the differentiation towards specific types of cells using so called “differentiation protocols”<sup>16-19</sup>. Protocols are basically the specific order and timing that iPS cells are exposed to differentiation factors (illustration 5).

The challenge with current differentiation protocols is that often they have low efficiency and produce unwanted cell types<sup>20</sup>. This is a problem because we should avoid transplanting cell mixtures, for example, it would be very risky to transplant impure neurons for in brain disorders. Also, because current differentiation protocols have many complicated steps and take several weeks, errors and failures are common.

In my lab in Leiden University, we developed a new approach that generate pure cell types at a short time thereby reducing risk and failure rates. We aim to discover new types of stem cells that can differentiate only to subsets of tissues. Simply put, we develop new ways to propagate cells below the hierarchy of pluripotent cells to proliferate as multi tissue stem cells.

We published patents for this technology, and we expect exciting publications soon. What I can say now, is that our approach is very effective for producing pure neurons of the peripheral nervous system. These are the motor and sensory neurons by which we sense and activate muscles. We have also very good indications that this technology will enable us to produce other cell types, which so far have been very difficult to differentiate from iPS cells, including immune cells.

Among the key advantages of this new stem cell technology, is reduction in the duration of differentiation



protocols from weeks to days. Moreover, we found that the new types of stem cells are potentially much safer because significantly lower risk of making cell masses following transplantation in mice <sup>21-23</sup>.

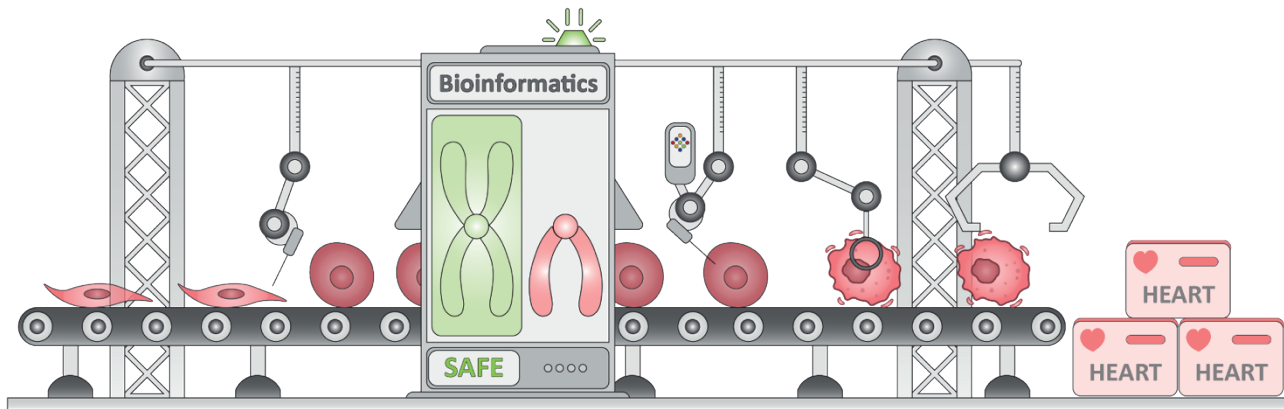
It is important to mention that differentiation technologies have an additional paramount medical application to model disease and develop drugs. Thanks to iPS cell technology, scientists can produce iPS cells from specific patients affected by genetic disorders and differentiate them in the lab to tissues relevant for the disease <sup>24-29</sup>. The idea is to develop drugs directly using disease relevant human cells without using animals. For example, iPS cells have been produced from ALS (Amyotrophic lateral sclerosis) patients and differentiated to motor neurons that are affected in ALS. This led to discovery of a promising drug candidate for ALS which is now in a clinical trial. I believe that our approach of making new types of stem cells can also facilitate these efforts. Therefore, we intend to produce multi tissue stem cells from patients for drug development purposes.

In the coming months the research directions of cell therapy and drug development using multi-tissue stem cells will grow dramatically in our laboratory. We intend to transplant them in animal models of nerve injuries, perhaps even spinal cord injuries models. We also collaborate with Leiden University Medical Center (LUMC) on implementing new stem cells in organ-on-a-chips, where different differentiated cells mimic complex tissues in a sick person.

#### IPS cell safety and affordability

The second project in our lab at Leiden University focuses on contributing to the safety and reducing production cost of stem cell therapies. Growing stem cells in the lab is certainly not a natural process, and cells always bear risk of making tumors, especially if they proliferate extensively. Thus, we need to de-risk stem cell therapies. Also, cell production in clear rooms is enormously expensive. To illustrate, I am currently spending approximately half a million Euros per cell line in Munich for production of iPS cells for one individual <sup>2</sup>. This is due to the sterility and quality standards necessitating the use of special clean rooms called GMP (Good manufacturing practice) facilities.





We intend to develop solutions by collaborations that we established recently with the Medicines Evaluation Board of the Netherlands, called the CBG (College ter Beoordeling van Geneesmiddelen), and with a company in the Leiden Bioscience Park called MIDA Biotech<sup>30</sup>. To spearhead these collaborations, we established in the university a group of computational scientists called “bioinformaticians”. They work together with wet lab experts to analyze the entire genomes of stem cell products to identify risky mutations as Illustration 6 shows. The bioinformaticians also analyze all the genes that are expressed in thousands of single cells using a technique called “transcriptomics”. This helps identifying cell types and potential impurities.

With the Medicines Evaluation Board we create a new software pipeline that will be directly implemented in the assessment of new stem cell drugs. This software will also be used for other types of advanced therapies, such as gene editing, and gene therapy with our colleagues at the LUMC.

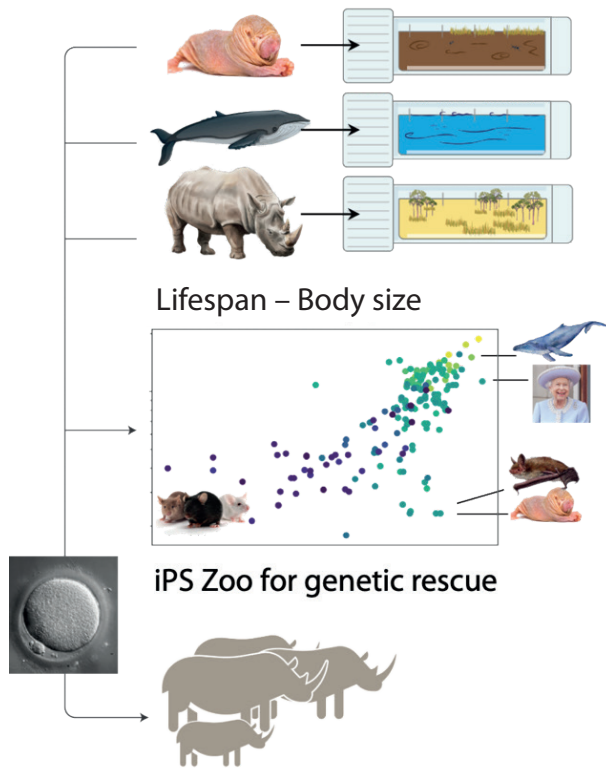
With the startup MIDA biotech we aim to improve the affordability of clinical grade iPS cells<sup>30</sup>. Together with MIDA, we won a prestigious European innovation council grant to develop a new device for production of personalized iPS cells with high clinical safety. It will provide three solutions. 1. It will circumvent the use of expensive clean rooms by producing the iPS cell in miniaturized devices, called microfluidics.

2. It will de-risk iPS cells by integrating a safety assessment software in the device. 3. It will be customized to manufacture personalized iPS cells for reducing the chance of immune rejection. Collectively, I believe these projects will be among the forefront of Leiden University vision of the cell pharmacy for stem cell therapy safety.

### Cellular longevity – rejuvenation

The final chapter of my lecture is about basic science<sup>31-34</sup>. Curiosity-driven science is a foundation of human discovery. We have a unique project in the lab that uses stem cells from different species for discovering the regulation of lifespan<sup>35</sup>. If we discover such mechanisms, we could probably enhance the survival of differentiated stem cells after transplantation.

The hypothesis that we are testing is that cells of long-living species live longer than cells of short-living species. This idea sparked the interest of the John Templeton foundation, which recently awarded us 1 million euros to pursue lifespan research using a new iPS cell Zoo concept. We currently produce stem cells from species of different lifespans including whales, apes, lions, bats, rodents, and more. Using sophisticated bioinformatics we analyzed the genomes of roughly 200 mammal species including the human. Quite strikingly, we have promising results, indicating a mechanism of cellular endurance that is highly correlated to the lifespan of



mammals. You can see in the illustration the yellow and green spots, which indicate a conserved mechanism in long living species including exceptionally long living bats, naked mole rat, whales, and people <sup>36-39</sup>.

We have another idea which is to recreate the species that are becoming extinct - like in the movie, Jurassic Park. We collaborate on this project with an international team of veterinarians and scientists who develop iPS cell differentiation protocols of oocytes and sperm. Together with the Naturalis Biodiversity Center in Leiden, we are now making initial plans for establishing a bank of stem cells for this purpose of genetic rescue.

To demonstrate the feasibility of a frozen animal stem cell bank, we adapted the reprogramming technology to endangered species. For example, my lab recently published reprogramming of precious biopsies of the northern white rhino, which is the rarest animal on the planet. Only two specimens remain alive today <sup>36</sup>.

We work hard so in several years differentiation will produce sperm and eggs of the northern white rhino in the dish <sup>39</sup>. Taken together, iPS cell zoo, is a new horizon of stem cell research for human regeneration, and animal regeneration.

#### Address to students and concluding remarks

Dear students, and dear students of the Bio-Pharmaceutical Sciences association Aesculapius. The vision of cell pharmacy will become a reality only through your uncompromised dedication and hard work. To prepare you to the challenge, we have developed new courses and will be creating further education programs dedicated to your cutting-edge education on innovative stem cell drugs. Cell drugs is a one-in-a-century historical innovation in Bio Pharmaceutical sciences, and I firmly believe that by educating you thoroughly about the challenges that this new field brings, you will become the leaders of cell drug innovations in the future. I am committed to this task. If you work hard, you have a bright future in accomplishing the cell pharmacy vision!

To finish, I would like to say that I believe that great rewards are waiting for those who rise to difficult challenges. This requires volumes of values and strength of character. I have faith that Leiden University is giving scientists the freedom to follow their research ambitions, knowing that support, advice, collegialism, tradition and pursuit of enlightenment is precious, and serving a cradle for the progress of humanity. I am proud of establishing the vision of the "cell pharmacy" in Leiden university. I am confident that we will be successful.

## Acknowledgements

I would like to dedicate this lecture to the memory of my late grandmother Anna Rosa (Ans) Van Dam and my grandfather Max Drukker, who during their pursuit of MD and PhD degrees in the University of Amsterdam, were persecuted and deported to concentration and death camps because they were Jewish citizens of the Netherlands. They survived the atrocities, but majority of their families have not.

I would like to thank my beautiful and beloved family, Inbal my wife, and children Lotem, Omer and Didin. I would also like to thank my parents, Abraham Drukker, and Esther Drukker, who are present here today, and this special occasion may serve to dim their pain over those who perished in the holocaust. I would like to thank my parents-in-law, Rina Regev, and Mati Regev, for their long-lasting support, who give Inbal and me endurance in our cross-continent scientific journey.

I would like to thank my mentors, colleagues, and friends. Especially, I would like to thank Prof. Nissim Benvenisty from the Hebrew University <sup>40-42</sup>, and Prof. Irving Weissman from Stanford University <sup>43-45</sup>, who were and still are my most important and devoted advocates. I would also like to extend special acknowledgments to my colleagues in Leiden University, especially Prof. Bob van de Water and Prof. Hubertus Irth for their outstanding support, and colleagues at the Leiden University Medical Center (LUMC) lead by Prof. Ton (A.J.) Rabelink. On this occasion, I would like to thank my friends around the globe who support me enormously in this scientific journey.

Lastly, I would like to thank my lab members, the Labbies, for pursuing science at the highest standards, and pushing forward despite numerous setbacks. It's a genuine pleasure pursuing research in your company.

Ik heb gezegd.

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### Additional reading - Book Chapters

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## PROF. DR. MICHA E. DRUKKER



Prof. Micha Drukker is an expert in stem cell research for clinical applications. He gained his Ph.D at the Hebrew University before becoming a postdoctoral scholar at Stanford University Medical School in the lab of Prof. Irving Weissman. He received tenure as a group leader and head of the induced pluripotent stem (iPS) cell core facility at the Helmholtz Center in Munich in 2012 and 2018. Drukker became a full professor in Leiden University within the Leiden Academic Center for Drug Research (LACDR) in 2020. Prof. Drukker and his team investigate induced pluripotent stem (iPS) cells. They study how the flow of genetic information and the architecture of the nucleus determine the proliferation and differentiation. On the application side, they develop methods to produce personalised lab grown tissue grafts. A special focus of his group is motor neurons, mechanisms of neurodegeneration, and development of stem cell drugs to treat neurodegeneration. In addition, Prof. Drukker promotes the creation of an iPS cell “Ark” to build a bank of stem cells and tissues for future conservation biology.



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