Stem Cells: Microscopic Gems of the Future?

By Wayne Zeng and Orhan Sonsöz

Preface

Motivations

Wayne:

Stem cells are very widely known as cells which can become "almost everything". The media often talks about the magical properties they have and their ability to generate the impossible. One of the first articles we encountered was a very old one about how umbilical stem cells cured lower paralysis in a middle aged woman. [1] Although this source is over 10 years old and the reliability of this can be questioned, the sheer aspect of a reliable method of curing paralysis motivated me to delve deeper into this topic.

Having later discovered that stem cells can also become nerve cells (which cannot naturally be regenerated in the human body) and that, if not rejected by the immune system, can help cure diseases such as HIV/AIDS, Alzheimer's and diabetes which inevitably inspired me to write this semester paper on these potentially game-changing cells.

Orhan:

My motivation to choose this topic was genuine curiosity. Although stem cell research isn't new to us, the progress has been outstanding in the last few years. In 2012 two scientists, John B. Gurdon and Shinya Yamanaka, won a Nobel Prize for **"**the discovery that mature cells can be reprogrammed to become pluripotent" [2] (Usually stem cells can differentiate into mature cells; these two scientists discovered the reverse process!)

The reason I find it so interesting is simple: there's a chance that we will eventually be able to defeat our human nature. It's a long way from here but still, in 50 years maybe we will be able to generate body organs out of mere cells. Then a hundred years later we will maybe be able to create clones. This could even lead to immortality. The dream of humanity, achieving something divine, living among gods, and not necessarily in the skies. Being our own creators and never having to lose someone. Even though climbing this "Stairway to Heaven" sounds very appealing, we are still just learning to crawl.

Aims and questions

- What exactly are stem cells?
- How are stem cells used nowadays?
- What can stem cells do?

Introduction

Stem cells are very unique They are "unspecialised" i.e. do not have a specific function, which may seem very ordinary at first. However, they have the potent ability to specialise into any kind of cell in an organism, from red blood cells to liver cells and even to nerve cells! They can divide like normal cells, meaning that the body has an essentially unlimited supply of stem cells for repair and growth. There are three main types of stem cells: embryonic stem cells, adult/somatic stem cells and induced pluripotent stem cells.

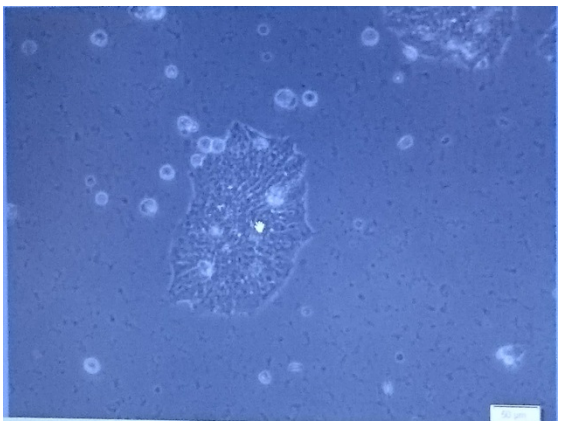

Fig. 1: A small cluster of stem cells as seen under a microscope

Stem cells are widely used in research mainly because they can model and replicate somatic processes, providing vital information that would otherwise be extremely difficult to extract during human development e.g. neurons or cardiac cells. However the biggest goal of stem cell research is to figure out how undifferentiated stem cells become differentiated. If scientists achieve this, they could generate new tissues even new organs from scratch! (See interview) [3]

Recent Events

Stem cell research is a rapidly developing area of science. As mentioned, recently a Nobel Prize has been given to two scientists who discovered that mature specialised cells can be reprogrammed to become immature cells capable of developing into all tissues of the body. Their findings have revolutionised our understanding of how cells and organisms develop.

There are also many other impressive recent events in stem cell research. One of the most difficult and life-hindering injuries is damage of the spinal cord and scientists have been trying to cure this for many years. Experiments with stem cells have already been conducted in this area; however they were not particularly successful, mainly because none of these involved regenerating a certain part of a neuron called a *corticospinal axon* which was previously believed to lack the "internal mechanisms needed to allow for regeneration". These axons are vital to animals because they enable voluntary movement in the body. In March 2016, the research team in the University of California's Medicine Department of Neurosciences reprogrammed multipotent neural progenitor cells (a type of stem cell) to develop into spinal cord and injected these into rats. Lost tissue was replaced, and most importantly,

functional synapses (spaces between neurons key in making sure that neuron-to-neuron communication is smooth) were formed, and the motion was enhanced in the rats' forelimbs. Further development in this area can potentially lead to a cure for paralysis! [4]

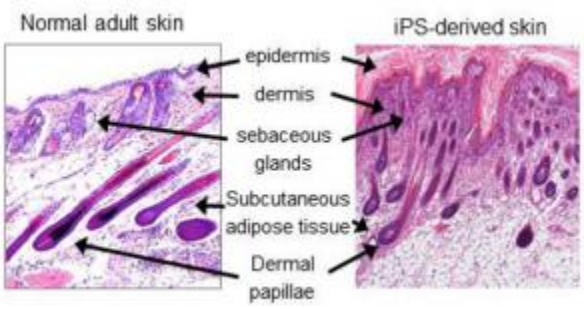

Fig. 2: Normal skin vs 3D stem-cell skin, showing the same properties and composition.

Another difficult field of genetic engineering is the generation of artificial tissue. 2D tissue is relatively easy to "imitate" compared to 3D tissue, which requires careful and precise modelling of numerous factors. Just less than a month ago (early April 2016!), Japanese scientists successfully grew 3D skin, complete with sweat glands and even hair follicles, organised in the same complex manner as the real thing! Skin is very difficult to generate because it is a very sophisticated organ serving as an insulating yet waterproof layer for our bodies, protection for organs, and getting rid of excess water, *and* it has to be quite thin and stretchy so we can move around in it. The researchers made induced pluripotent stem cells from mouse gum cells then used these to grow the necessary elements (follicles etc.) needed for functioning skin. Mice successfully incorporated the implanted 3D stem-cell skin into their nervous and muscle systems and they responded to touch in these areas, just like real skin. If implemented on humans, we could have a way to creating sensitive skin transplants for victims with burns etc. [5]

Alternative treatments

As seen above, stem cells are the alternative treatments! Current methods such as anti-retroviral therapy for HIV (see Discussion) do temporarily provide resistance to HIV growth, however they are not as stable as stem cell therapy mainly because they are not from one's own body, and that stem cells can last much longer than such treatments because they can self-multiply. Stem cell therapy from iPSCs involves your own modified cells, reducing side effects and the risk of being rejected by the immune system (if correctly applied, see Discussion).

Description of engineering technique

Human embryonic stem cells (hESCs) are a type of pluripotent stem cell (PSC; "pluri" meaning many and "potent" meaning power; cells that can perform multiple roles effectively) extracted from pre-implantation-stage embryos fertilised via in vitro fertilisation (IVF). The cells are placed in a Petri-dish containing a nutritious liquid called culture medium. If the plated cells survive this process (which is not always the case), they are moved into fresh culture dishes where they multiply again. This

process is repeated as many times as needed; cells can also be frozen when needed and stored for later use. [6]

Adult somatic stem cells are extracted in quite a different way. Most commonly, they are directly harvested from blood sources such as bone marrow, the umbilical cord when a baby is born, or a person's circulating blood. These are then nurtured in the same way as hESCs and left to multiply into large enough numbers so that they can be used for experimentation or treatment. Other extraction methods include from amniotic fluid and from differentiating iPSCs. [7]

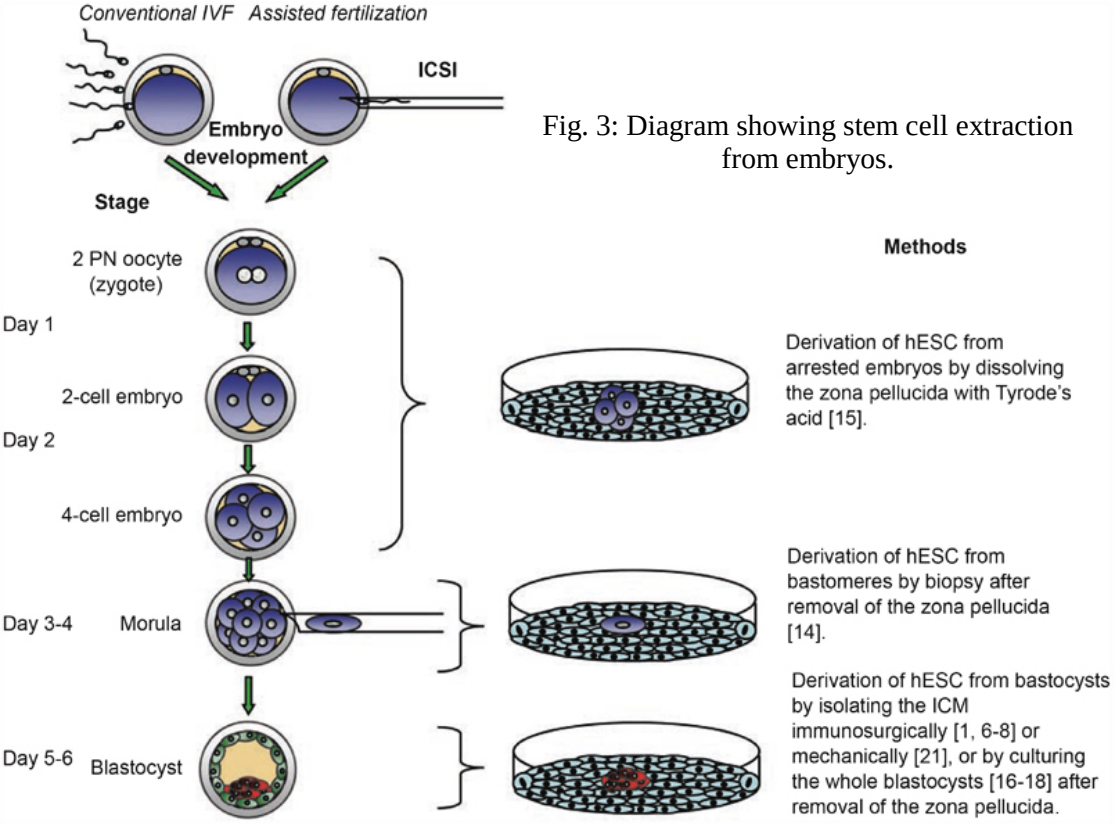

Fig. 3: Diagram showing stem cell extraction from embryos.

The last commonly used type of stem cell is "the new kid in the block"(they were only discovered in 2006; the discoverers were rewarded with a Nobel Prize [see *Preface*]), induced pluripotent stem cells (iPSCs). These are essentially mature adult cells reprogrammed to behave in a "hESC state" i.e. to express traits similar to embryonic stem cells. The huge advantage of these cells compared to hESCs is, unlike the aforementioned, iPSCs do not involve the destruction of embryos. They derive from mature cells, meaning every individual has his/her own iPSC line, reducing the chances of the immune system rejecting them. However, unlike hESCs, iPSCs are not "natural". In fact, iPSCs are produced with the help of viruses which may lead to nasty side effects such as the expression of *oncogenes* (cancer-inducing genes!). [8]

In research, stem cells are one of the most hyped ingredients in a researcher's lab. They are versatile enough for a plethora of applications and uses. Most cells are used for observation, for example if certain cells in a patient need examining but they cannot be extracted easily, scientists can extract stem cells from a patient's skin, let them differentiate into e.g. cardiac cells, and then examine these. Most of the stem cells are subjected to further experimentation. Some are genetically modified to express certain traits such as cystic fibrosis and then injected into "test subjects" (mostly mice) and the mice are carefully observed. Sometimes the stem cells are reprogrammed into other cells in order to induce a certain type of growth.

Unfortunately, there are little usages of stem cell therapy itself, simply because this engineering technique, especially with iPSCs not being technologically developed enough and hESCs having huge amounts of ethical issues. In the USA, President George W. Bush personally signed a document in 2006 making ESC research illegal (fortunately this was ban was lifted in 2009 by Preident Obama!).[9] However adult stem cells are readily used in bone marrow transplants, where an injection of adult stem cells from marrow into e.g. the heart can provide regeneration of heart tissue.[10]

Certain test experiments however have proven how potentially game-changing stem cells can be. We have seen in the introduction how stem cells can cause spinal regrowth; in the discussion we will also see many other astonishing diseases that stem cells could cure.

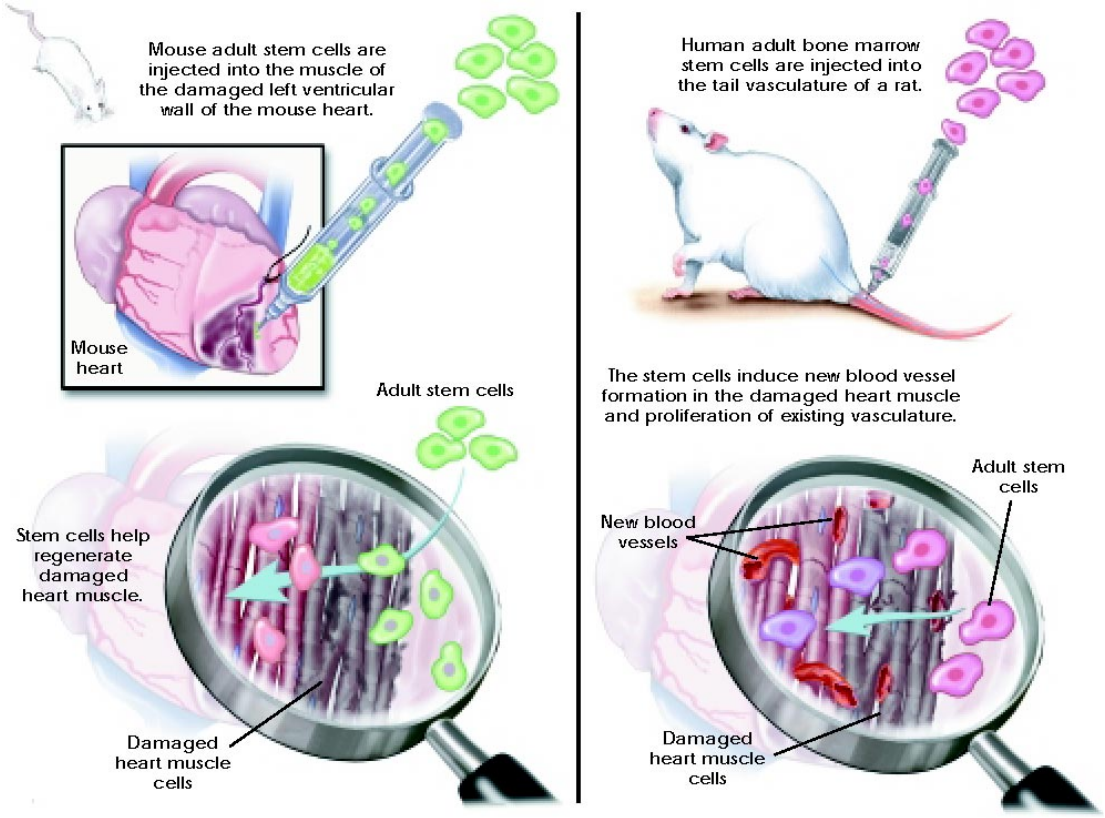

Fig. 4: How bone marrow stem cells can induce regeneration, here helping to regenerate cardiac and muscle tissues.

Discussion

Disadvantages of Stem Cell Therapy/Research

Embryonic stem cell research is controversial because the cells are derived from human embryos and for them to be obtained the embryo must be disassembled. The component cells are then grown in culture. Many believe that life begins at conception, the same reason that some people are against cloning. [11] , and a potential human being is killed in the process. Some people believe that it is important that we shouldn't mess with human life and God decides what's best for humans. Some also believe that stem cell research will eventually make it possible to clone humans, which may lead to devastating consequences

Embryonic stem cell research currently has major disadvantages and risks. Embryonic stem cells may not be accepted when used in transplants because there is no process to generate them. They are simply not something that the body produces so this can obviously be problematic. They can cause tumours when used directly from undifferentiated culture preparation. [12] Other major side effects were also sighted in an experiment in 2001 involving the insertion of foetal brain cells into the brains of Parkinson's disease patients, including writhing, twisting, head-jerking, arm-flailing, and constant chewing. [13]

The process, as we will see in the interview is very costly because it is so new to us. State of the art technology is needed in order to keep these samples alive in a homeostatic environment, and highly qualified researchers, often called in from foreign countries, are required to perform these experiments. Most people will not approve any use of their taxes to destroy human embryos in any type of medical research.

Advantages of Stem Cell Therapy/Research

Certain diseases such as vision loss, hearing loss as well as heart disease and diabetes require/lack cells generated form human embryonic stem cells. Scientist can reliably differentiate stem cells into almost any kind of somatic cell. [14]

Stem cell research can also potentially help treat medical problems like Alzheimer's disease, Parkinson's disease, and spinal cord injuries as

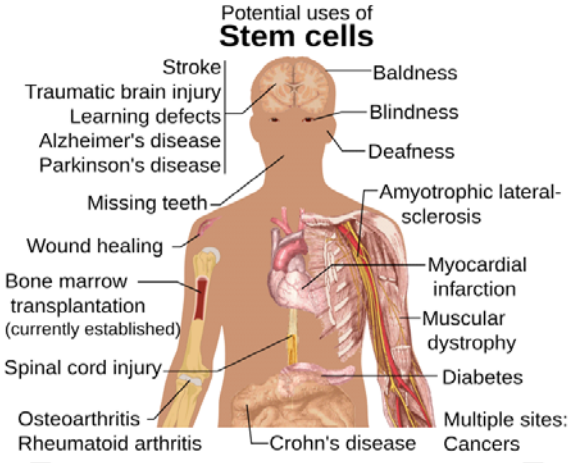

Fig. 5: The many potential uses of Stem Cells

well as being able to replace or repair damaged organs [15] as well as possibly reversing the symptoms of serious diseases like the ones mentioned above. [16] Some even believe (and even achieved results) that modified stem cells can be used for HIV resistance! Unlike antiretroviral therapy (medicine used to inhibit HIV growth) [17], your own stem cells are less likely to be rejected by the immune system and are also "long-lived" and "self renewing" as well as offering "continuous, long-term production of genetically engineered cells that are resistant to HIV infection and/or have enhanced anti-viral activity to clear infected cells" and potentially achieving a "lifelong cure".[18] Individuals can benefit hugely from this therapy, and because so many are affected by these diseases, finding a cure for them would benefit society as a whole.

Stem cells can also serve as a "test subject" that does not involve a live animal or human. New drugs can be tested on stem cell-differentiated "subjects", the side effects are then assessed to see whether they are safe enough for animal testing, then human testing. The stem cells themselves can, with the help of well replicated body conditions, very accurately simulate what would really happen if you used these drugs in an "real" organism. For example, a cancer cell line could be created to test an anti-tumour drug.Also [16]

Our Opinion

We think there are two main questions when it comes to the ethical issues. The first question is whether can you consider an embryo to be human. If yes, would you be ready to sacrifice human lives to save and improve many more?

We personally don't perceive a clump of cells as a human, and even if so, we know that science requires some sacrifice. We actually think the inhumane thing to do here is to let people suffer horribly from diseases and disorders just because you want to sleep well at night knowing you didn't kill a tiny organism which did not have any developed organs at all. However it is understandable that there is a lack of willingness in donating you own fertilised foetus to science. There are also some people that believe that we shouldn't intervene with gods work. Firstly we think that we have already crossed that line a long time ago . Secondly , we see this only as a lack of empathy on these people because if something were to happen to them or their relatives most of them would gladly "intervene with god's work "

The second question is whether it is economically effective to invest private funds as well as taxpayers' money in stem cell research, which so far has only produced what the uneducated person may interpret as "small biological advances" like small patches of artificial skin or producing mouse egg cells which only successfully hatch four percent of the time [19]. For the educated biologist, however, these advances are

huge leaps forward in the world of pharmaceuticals. The opportunity costs of stem cells are, in this sense, relatively low and I think that we will benefit more than what we spend into this research.

Summary

When we started writing this paper, we knew little about stem cells except that they apparently could "transform" into any type of cell, they have powerful healing properties and that they could be extracted from embryos. Having spent many hours researching on the internet and asking for expert help, we realised how potent and life-changing these cells can be and how big an impact stem cells could have on our day-to-day lives. Stem cells can potentially cure devastating diseases like Alzheimer's and Diabetes and provide key resistance to HIV as well as generating damaged organs, which can ultimately save many millions of lives; as soon as this industry truly takes of in the next century, companies which invest in stem cell research will earn many billions of Francs. They also help researchers across the world get a better idea of diseases like ALS (the "ice-bucket-challenge" or "Stephen-Hawking" disease) which would not be researchable, let alone curable, for them. We genuinely believe that stem cells are mankind's microscopic gems of the future.

Fig. 6: Stem cell cartoons showing the most important aspects of them as well as their controversial aspects.

APPENDIX: Includes interview and references

Documentation and pictures of research institutions visited

Interview with Dr. Matthias Müller, Chipperfield building, Novartis Campus, Basel

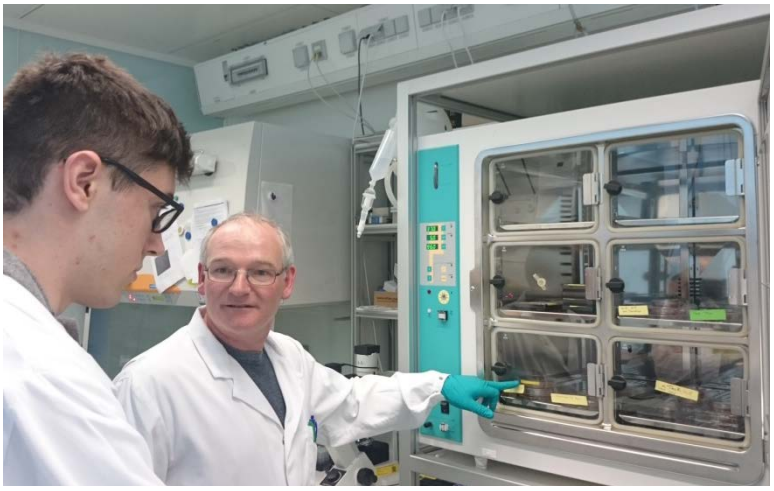

Fig. 7: Orhan and Dr. Müller looking at a stem cell incubator

On 13.04.2016, we visited Novartis, one of the world's leading pharmaceutical companies. We were shortly shown around the campus by Wayne's father before entering the Chipperfield building where the interview took place.

We were greeted by Dr. Matthias Müller, a leading scientist in stem cells and did the interview. After half an hour of asking vigorous questions, all of which were answered thoroughly, he kindly showed us around the laboratory. Unlike a normal lab, this one was fused together with the researcher's offices in a "big open space environment". This apparently speeds up communication between lab worker and office worker which is "vital in today's fast-paced society", as Dr. Müller put it.

We were then lucky enough to inspect some stem cell samples under the microscope, including undifferentiated ones, some which had differentiated into blood cells. Dr. Müller even showed us a cluster of around 60 stem cells which had differentiated into nerve cells and were working as a "mini-brain". Lastly, he allowed us to look at some neurons differentiated from modified stem cells which glowed in the dark (see cover)!

Research Questions

What kind of stem cells do you use here in Novartis? What do you use them for?

Here we mainly use embryonic stem cells and iPSCs, although sometimes we also use adult stem cells too. The stem cells are used mainly for inspecting cells we cannot

directly extract from the patient. For example, if you want to research autistic behaviour, you can extract some stem cells from the skin of the patient, cultivate them and then differentiate them into neurons for further study.

How do you extract the stem cells?

The stem cells are extracted from an early stage embryo shortly after fertilisation. This is done *in vitro* (in the glass) and the cells are then placed in a Petri dish with nutrients where they are cultivated and observed.

Do you use animals during these tests as a basis for experiments?

Yes, of course. At this stage its more mice than men. There are many health risks in using humans as test subjects. Usually we use mice as they are relatively genetically similar to humans, their genes can be easily modified and they are easy to breed and have short life cycles.

What are the ethical issues associated with stem cells?

Well an obvious one is animal testing which is always a big topic in the pharmaceutical industry. The other issue is that you are using an embryo which potentially could've been a human for scientific benefit. Personally I don't believe that this is a problem because we take embryos of such an early stage (a large cluster of cells) which, for me, is like extracting cells from an organ or something else that isn't really physically alive. Sadly the embryo is killed during this process…

Treatment questions

How is one eligible for stem cell therapy?

Usually elderly people who have e.g. cardiac difficulties or muscle pain can receive an injection of adult stem cells from a bone marrow donor. This can also be used to cure some types of Leukemia. However, stem cell therapy cannot always help the patient, for example in later stages of cancer. Embryonic and iPSC cell therapies are not readily used in hospitals because of health risk issues: all these treatments must go through strict testing before they are safe on humans.

How much does it cost for the stem cells and the research behind them?

The cost of stem-cell research is huge: all the workers, all the incubators and the sophisticated equipment… Tens of millions of Francs have been invested into this industry. And this figure will only get higher as more people become interested in stem cell therapy; as you probably know, our population is ageing and the demand for stem cell therapy will increase in the future.

Fig. 8: The "big open space environment"

Personal questions

What does a researcher's day usually look like?

Well we come into the office at 9, make a cup of coffee, drink it, make another one, and drink that too… No, on serious note it varies from colleague to colleague. This lab has all sorts of different people: technicians who do the experiments, their assistants, there are managers and coordinators like me who tell them what to do. For me for example its more computer work and organising data.

What keeps you motivated when working with stem cells?

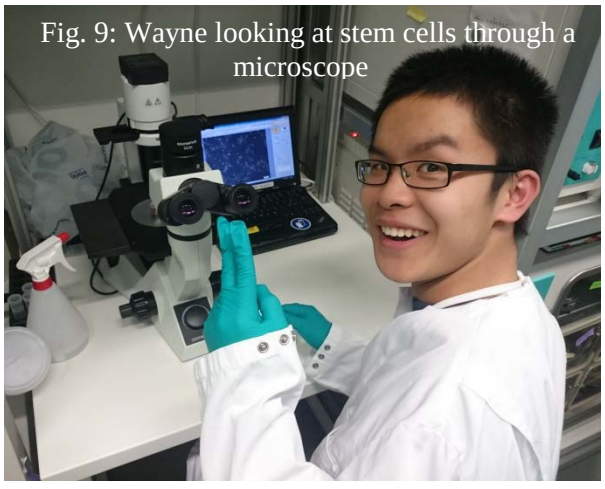

Fig. 9: Wayne looking at stem cells through a microscope

Stem cell therapy is a hot topic in the world of pharmaceuticals today. We are doing experiments which nobody has done before. We are doing this for the time. The experiments are unique and enjoyable and extremely flexible and I feel that I'm contributing to something which could change the world forever. We also have the motivation to help patients, this is clear. When you see somebody suffer from a disease, you want to help. We have the possibility here in Novartis to produce drugs and help those patients eventually through stem cell research. It's new it's exciting, it just feels right.

How do you think stem cells will change today's society? Will stem cell therapy become cheap enough for (maybe) everyday use?

As I just said, stem cells have the potential to revolutionise healthcare. Say, for example, you have heart disease and the only way of survival is a heart transplant. Now, as you probably know, heart transplants have all sorts of complications and risks associated with them, including the possibility of the immune system rejecting the organ, or not being able to find a donor at all! In the future, we could generate a heart from your own stem cells, eliminating the two said problems! Of course, I will not be able to see any of this technology in my lifetime, but you two may benefit from this!

References (All *last visited* dates are given in the form DD.MM.YYYY)

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[2] http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html (02.05.2016)

[3] http://stemcells.nih.gov/info/basics/pages/basics6.aspx (02.05.2016)

[4] https://www.sciencedaily.com/releases/2016/03/160328114619.htm (02.05.2016)

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[6] http://stemcells.nih.gov/info/basics/pages/basics1.aspx (02.05.2016, modified 05.03.2015), also http://www.nature.com/stemcells/archive/faqs.html (02.05.2016, date of publication unknown)

[7] http://stemcell.childrenshospital.org/about-stem-cells/adult-somatic-stem-cells-101/where-do-we-get-adult-stem-cells/ (02.05.2016)

[8] https://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell (02.05.2016)
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[14] http://www.medhealthdaily.com/pros-and-cons-of-stem-cell-research/ (02.05.2016)

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Publications

[11]http://www.academia.edu/178498/Rescuing_human_embryonic_stem_cell_research_The_possibility_of_embryo_reconstitution

[18] http://www.mdpi.com/1999-4915/6/1/1/pdf (02.05.2016 uploaded 12.05.2015, text is cited from this paper), and
http://www.mdpi.com/1999-4915/5/11/2898/pdf (02.05.2016 uploaded 12.05.2015)

Images

http://cdn1.medicalnewstoday.com/content/images/articles/308/308626/normal-and-ips-skin.jpg (02.05.2016 , picture of skin tissues)

http://www.nature.com/cr/journal/v17/n8/images/cr200761f1.jpg (Embryo hESC extraction)
http://stemcells.nih.gov/staticresources/images/figure4_lg.jpg (02.05.2016 ,mouse picture)

https://upload.wikimedia.org/wikipedia/commons/thumb/b/bd/Stem_cell_treatments.svg/2000px-Stem_cell_treatments.svg.png (02.05.2016)

https://popperfont.files.wordpress.com/2013/01/lookstemcells.jpg (snowman) (02.05.2016)

https://s-media-cache-ak0.pinimg.com/736x/5a/17/0e/5a170e5d71e5e06346e21da8ba839fd6.jpg (old man and baby in heaven)

The rest of the images were taken in Novartis on Orhan's smartphone, including the very cool cover photo.