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ORGANOIDS AS A NEW APPROACH TO MODERN MEDICINE

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1. Introduction

1.1 Presentation

The understanding of mankind's health related issues has had a drastic progression over the last centuries. Advanced technologies and developed knowledge of life itself has made possible for medicine to have a big impact on society as we know it nowadays; infections are not the main cause of death anymore, epidemics and pandemics are much better regulated, and many complex diseases have been remedied.

The discovery of penicillin a hundred years ago was a major outbreak in science, and it has been basic life necessity ever since. Although this antibacterial drug is very effective, it has reached its maximum potential in the healthcare area and is suffering from immune-resistance due to its abuse. Chronic diseases such as cancer and diabetes have not yet been as we could say "solved" and need a new approach towards developing a treatment. To do so we must look at it differently as we have done before, and that is where tailored medicine comes into play. This research paper is primarily going to be focused on organoids and its role in modern medicine.

Organoids are what could possibly be one of the most revolutionizing discoveries in the history of medicine. They are organized cell cultures derived from stem cell proliferation that can resemble the complexity of a person's specific cell tissue.

They are three-dimensional in vitro organisms that are formed by extracting stem cells from the patient and genetically engineering them so that they form the specific tissue desired. They allow for much more advanced treatment options; an example would be drug testing. By doing so we can find out how a particular patient's tissue reacts to a certain drug and determine which treatment suits them best.

It englobes many aspects of modern medicine and how it may develop, so in this review we are going to enlighten the common reader of how disease treatment and research may advance, talking from a biological standpoint.

1.2 Justification

Medicine has been studied in such a profound manner, that it has led us society have access to the knowledge of almost all aspects of life. My entire life I have been captivated by the mysteries of life, of what makes us living things. Studying biology at school has definitely empowered this feeling of attraction towards the things we can only see magnified by the school microscope.

Following my brother's footsteps, who is currently studying biomedicine in the Netherlands, I heard about personalized medicine and organoids. He had been dealing with the topic at university and told me all about it. I considered it to be so interesting and fascinating that I jumped straight to my computer to learn more about it, and after little consideration, I decided that it would be ideal for this research project.

Its broadness and complexity allow for this paper to be extent and informative, and its relation to modern medicine and how it may develop makes for a great empirical work possibility.

This review is going to be solely in English, a language I have opted since it will be of great help for the near future. The interview however, has been translated to Spanish for the comfortability of the interviewee.

1.3 Hypothesis and objectives

In this research paper there are going to be no hypothesis for the following reasons. The subject of this review is about stem cells, stem cell development, and organoids, all of which is closely monitored by specialized entities. Since it englobes human development and cells, it is illegal as an unspecialized unauthorized person to handle an experiment using human cells. Therefore, I have opted for not presenting any hypothesis, except there will be a qualitative conclusion extracted after fully understanding the topic at hand and after speaking to medical specialists.

For this project I have presented some objectives that I hope to complete after finishing.

External goals:

- Improve researching skills. This includes better internet filtering, getting the most out of a textbook, learning about efficient synthesizing, drafting a research paper, how to citate properly and more.
- Enrich vocabulary, especially of medical kind, in order to gain a much wider range of options in terms of describing an event or item.
- Manage properly the long-term responsibility of a project and control its process.
- Use my autonomy to be self-sufficient at most times and get the most out of my knowledge and capacity.

Internal goals:

- Get a hold of what medicine looks like right now and in the future.
- Learn about organoid formation, functions, types and what they will be like in a couple of years from now.
- Learn about the evolution of personalized medicine and its future.
- Take into consideration what the ethics of the subject are.

1.4 Methodology

Regarding the acquirement of knowledge for the purpose of writing about it, the methodology aspect of this paper is quite simple. Since the internet has progressed so much over the years, the information will solely be acquired from online medical reviews. The standardized protocols to follow when writing research papers have been so well established, that it is very easy nowadays to find reliable sources with very precious information.

All the information will be gathered from articles coming from reliable and double-checked sites. Specifically, the following sites will be the primary sources of information: PubMed, Google Scholar, and Sigma Aldrich. References are named at the end of this paper, using the APA system.

For the empirical aspect of this project, a structured interview will be used. This is a systematic approach for learning the interviewee's point of view in a very clear way. This will be done in the desired manner of the person at hand, being either face-to-face, by online call or just by filling the gaps, giving him or her more time to think about the answers.

The interview will be annexed to this document at the bottom of it.

2. Stem cells

Stem cells, as the name indicates, are the precursor cells. These are the ones that end up forming our cells in a process called specialization, in other words, these are the cells at the beginning of the cell lineage [1]in a multicellular organism. Within its many functions, stem cells serve as a repair system in our body, replacing damaged or diseased tissue thanks to their ability to self-renew and differentiate into the wide spectrum of cell types. Self-renewal is the process in which they proliferate [2]without losing their stemness [3]and differentiation is the process in which they specialize into a more complex cell. Some may be confused by their similarities to progenitor cells, but these are much more specific and can only differentiate into their target cell.

Cells that arise from stem cell division are called daughter cells, and can either be both unspecialized stem cells, both differentiated stem cells or one of each. Studies have yet to identify what incites which of the three will take place.

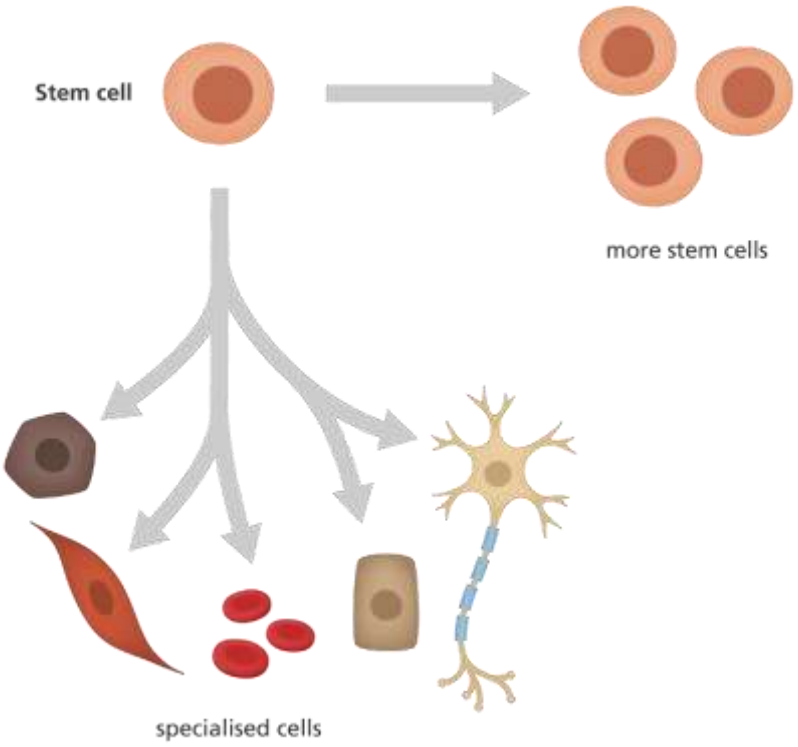

Figure 1 – Representation of cell fate of stem cells, either specialized cells or more stem cells.

[1] Developmental history of a type of cell, from progenitor to daughter cell.
[2] Duplicate indefinitely.
[3] Ability to give rise to other cells

2.1 Stem cell potency

There is a vast amount of stem cell types[4], ranging from embryonic stem cells to hematopoietic stem cells, but they all share a characteristic: the potency. Cell potency is the ability of a stem cell to differentiate into the wide spectrum of cell types. The more cell types a stem cell can specialize into, the greater the potency. In a nutshell, there are three types of potencies.

- **Totipotent stem cells**. Also called omnipotent, these are the first cells that appear as the zygote [5]starts to divide by mitosis[6] in an exponential manner (2, 4, 8, 16…).
- **Pluripotent stem cells.** Once the zygote had grown into the blastula (single-layered hollow sphere of cells), the also called embryonic stem cells appear in the form of the inner cell mass (ICM), which ends up being reorganized into the three primary germ layers of the gastrula[7]: ectoderm, endoderm, and mesoderm. This will end up forming the embryo and therefore potentially all 220 cell types of the adult human body (pluripotency).
    - **Ectoderm:** skin and nervous system.
    - **Endoderm:** gastrointestinal and respiratory tracts, endocrine glands, liver, and pancreas.
    - **Mesoderm:** bone, cartilage, most of the circulatory system, muscles, connective tissue and more.
- **Multipotent stem cells.** As the embryo starts forming the tissues, the pluripotent stem cells begin to lose their potency and end up becoming adult stem cells, which are multipotent and are found in adult human tissues in very small proportions. These are called multipotent because they can differentiate into a much narrower spectrum of cell lineages, generally appropriate to their location and tissue.

[4] Set of cells that share similar characteristics and functions.
[5] Fecundated egg.
[6] Duplicating without changing its genome.
[7] Stage in which the ICM is restructured into primary germ layers.

2.2 Embryonic stem cells (ESCs).

These stem cells appear in 3 to 5 days old embryos, where the fecundated egg is at its Blastocyst stage: a spherical structure of cells consisted of the trophoblast (outer cell mass) and the ICM, as mentioned before. This last one contains about 150 stem cells, and are the ones called pluripotent stem cells. The outer cell mass becomes the placenta [8]and the ICM essentially forms the human embryo, meaning that ECSs, being pluripotent, have the ability to develop into any tissue in our body, starting with the mesoderm, ectoderm and endoderm.

Since these cells can differentiate into potentially any of the 220 cell types, they are clinically very significant and offer a great deal of interest, presenting a wide range of medical ramifications revolving personalized and regenerative medicine. These incredibly versatile stem cells are grown by *in vitro* fertilization (IVF), creating an embryo in its first stages of proliferation and specialization. If maintained in the right conditions, these be exploited and go on to form large colonies of undifferentiated stem cells, which can later be stimulated to form the tissue of choice.

However promising this may sound, ESCs raise a lot of ethical questions owing to the fact that in the process of extraction the mammalian embryo is destroyed. Many consider that human embryos should be granted the same status as any other being (for religious, political, or social reasons), making their 'harvesting' by IVF morally unjustifiable.

2.3 Adult stem cells (ASCs).

These are found in the adult human body and in a very dispersed manner, serving as a repair system for dead or damaged tissue. Located in very small numbers at tissues, these can only proliferate into the cell types of their location, meaning that they are multipotent. ASCs are much less versatile and durable than ESCs and are much more likely to present abnormalities in an *in vitro* configuration, making them less useful in

[8] Organ that provides the embryo with oxygen and nutrients during its development.

scientific studies. On the same note, ASCs can be very difficult to find, due to that it may take years for them to take a specified role and stay quiescent [9]in the meantime.

However, these adult stem cells have already been very useful for clinical applications in transplants and are much more accepted socially because they aren't controversial ethical-wise.

Since adult stem cells are dispersed throughout our body, these can be classified depending on their location and/or function:

2.3.1 Hematopoietic stem cells

Hematopoietic stem cells (HSCs) are found in some adult red bone marrow tissues (mainly from sternum and pelvis), in the blood flow and even in the umbilical cord blood, hence are classified as adult stem cells. These come from the mesoderm layer in early-stage embryo and are responsible for haematopoiesis, which is the process in which blood cellular components are formed. Their ability to give rise to all of the different mature blood cells makes them very important in our body, since around 10^{12} blood cells are produced in a single day to maintain a steady blood flow and keep our immune system healthy. This is achieved by their extensive self-renewal capacity.

HSCs form two cell lineages, the myeloid and the lymphoid. Within the myeloid lineage, we can find cells such as erythrocytes, platelets and some white blood cells. Lymphoid cells however include strictly white blood cells, which serve in the response of the body's immune system.

[9] In a state or period of inactivity or dormancy.

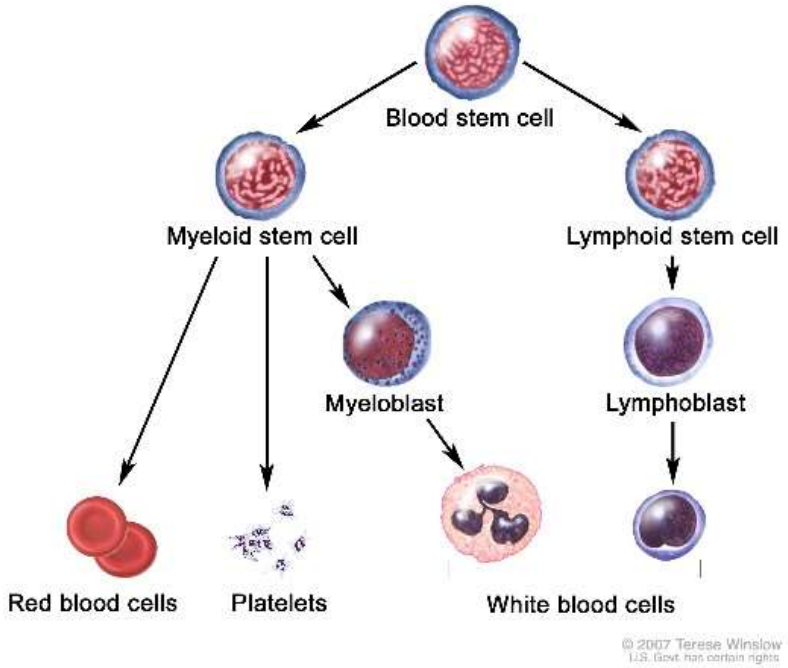

Figure 2 – Representation of Hematopoietic stem cell line (also called blood stem cell). It divides into the myeloid line and the lymphoid line. The myeloid line can produce red blood cells, platelets, and some white blood cells, whereas the lymphoid line can exclusively produce white blood cells.

Hematopoietic stem cells have resulted really helpful in the medical area for patients whose bone marrow or immune system has been diseased or damaged and therefore their HSCs don't form properly the red and white blood cells and platelets. This transplanting technique has had an uprising fame in the past half century thanks to discoveries on how to bypass histo-incompatibility. Still, bone marrow transplant is mainly settled by the patient themselves or close relatives (with matching bone marrow characteristics). This procedure is used mainly for cancers that affect the production of blood cells, such as myeloma and leukaemia, and some autoimmune hereditary diseases, such as Fanconi anaemia, in which the bone marrow doesn't develop its function. However, HSC transplant entails considerable risk, especially to the recipient. HSCs are found in very low frequency, therefore it is often the case that their extraction methods cause side effects. This includes allergic reactions, alveolar haemorrhage, and a dip in the levels of haemoglobin and platelets in the body, which don't restore to normal levels until a month after.

In the case of cancers, radiation and chemotherapy that targets bone marrow destroys the stem cells in it, suppressing the immune system in a way that will not be restored by itself. That is where HSC transplants come into place, where the cells make up for the loss and bring blood cell levels in the body to a more normal state. Recipients suffer the risk of getting an infection, due to the weak immune system that cancer treatment has caused, or even get a hostile reaction where instead of curing, the HSCs attack the already damaged cells.

In other diseases, the patient usually has a disorder in the bone marrow stem cells and therefore do not self-renew and differentiate properly, needing the donors' to compensate.

2.3.2 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are mainly located in the bone marrow, just like HSCs, although recent studies have proved that these (or very similar to these) cells have been found in adipose tissue, muscle tissue, umbilical cord tissue, amniotic fluid, corneal stroma (inside the eye) and baby teeth. Morphologically speaking, MSCs are characterized by a long and thin structure, presenting a prominent nucleus and some cell organelles.

Inside the bone marrow, MSCs make up for around 0,01% to 0,001% of all cells and can specialize into bone cells (osteocyte), cartilage (chondrocyte), muscle cells (myocyte) and fat cells (adipocyte). Elsewhere, studies have shown that MSCs can differentiate into other cell lineages, such as nerve cells or heart muscle cells, although it appears that it might be result of the stem cells having fused with other specialized cells.

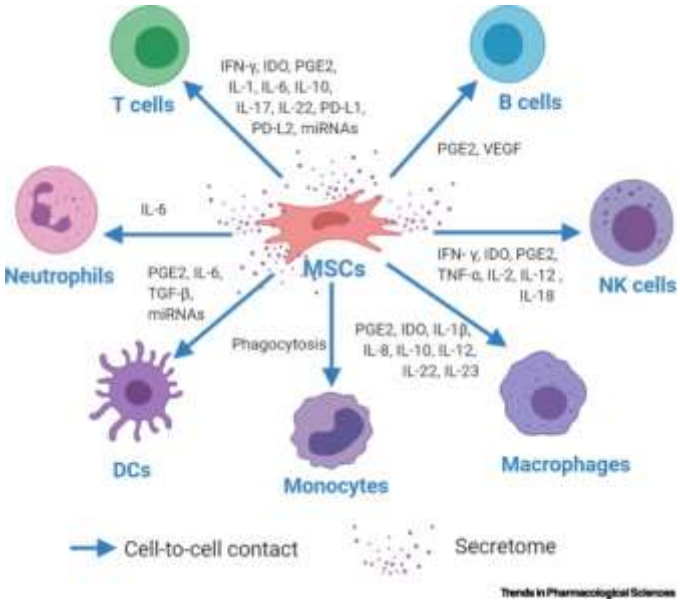

Figure 3 – Representation of mesenchymal stem cell line. The cell can develop into Neutrophils, T cells, B cells, NK cells, Macrophages, Monocytes, and/or DCs

Therapeutically speaking, mesenchymal stem cells offer great potential, owing to the fact that they have shown to avoid a negative response by the recipient's immune system, they have a wide cell lineage spectrum to specialize into and they have a rapid proliferation capacity. These cells are a great tool to reconstruct bones and cartilage (due to degenerative changes), for aesthetic medicine, in the case of some cardiovascular diseases and general cell transplantation.

Although we possess great knowledge about their *in vitro* attitude, *in vivo* characteristics are not yet all the way determined, which is why there are many clinical trials circulating to develop functional and reliable treatments for the near future.

2.3.3 Neural stem cells

Neurons are born in some locations of the brain that are rich in their precursor cells, which are neural stem cells (NSCs). These stem cells are in charge of providing the central nervous system (CNS) with the neurons needed to replace those that are damaged. The nervous tissue is extremely complex and incomprehensible, which makes it so unique among the other tissues of the body. Ultimately, the CNS is responsible for the vital functions of the human body to be carried out and gives us the intellectual capacity that distinct us from other animals.

In embryogenesis, the ectoderm gives rise to the nervous system as a whole and therefore develops into neurons, astrocytes, and oligodendrocytes. These are responsible for transporting information in the form of electrical signals from the brain to the rest of the body and vice versa.

Therapeutically speaking, these stem cells are impossible to extract from the adult neural tissue without scarring neighbouring cell to cell interactions, therefore are only examined in animal models. However, cell cultures of induced pluripotent stem cells differentiated into a neuron-like state are very useful in drug screening and understanding interactions within the CNS. Recent breakthroughs have also been able to use these cultures for regenerative medicine in the case of spinal cord injury.

2.3.4 Epithelial stem cells

The epithelial tissues in the adult human body are characterized by their varying structure and function, though they are unified by the fact that they all undergo continual lifelong cell turnover. This is ultimately done by epithelial stem cells, which maintain the tissue homeostasis [10]by self-renewing and differentiating if the need arises.

Epithelia are sheets of tightly packed interacting cells that constitute the surface (epidermis), line body cavities, and hollow organs, to provide a variety of functions such as protection, secretion, absorption, excretion, and more. Through the lifespan of the human body, the epithelial tissue needs to replace damaged or dead cells (due to physical trauma, disease or deterioration), therefore needs presence of epithelial stem cells.

Clinically speaking, epithelial stem cells are starting to be used in the treatment for extensive wounds that cannot be repaired by themselves, such is the case of third-degree burns.

[10] State of balance between the internal body systemsl.

2.4 Induced pluripotent stem cells (iPSC).

Induced pluripotent stem cells are artificially obtained by the genetic reprogramming of somatic cells, reverting them into an undifferentiated and pluripotent state very similar to an ESC. These are very beneficial since they do not raise any ethical questions due to their harmlessness to the mammalian embryo (case of the ESCs). Furthermore, iPSCs are already being used and show great promise in the drug testing and human physiology industry, since they can rapidly proliferate *in vitro* and resemble a patient's specific tissue.

The breakthrough of induced pluripotent stem cells was first pioneered by Shinya Yamanaka's lab in 2006, and it has catapulted forward the field of stem-cell biology. Making them requires retrovirus that insert four types of genes (Oct4, Sox2, Nanog and Lin28), the same way as they would infect a cell, into various somatic cells (usually epidermal or blood cells) *in vitro* extracted from medical biopsies. These genes will form proteins that will enter the nucleus and act on its DNA to convert the cell into an embryonic-like stem cell.

This newly formed iPSC has the capability to proliferate forming a tissue of choice with a very precisely matching morphology to the cell donor's, which is an important factor in research of disease modelling, drug screening, and many other therapeutic purposes. Nowadays, iPSCs are being used all throughout the clinical world in a concept called organoids, which will be explained later on in much greater depth.

2.5 Identification, isolation, and preservation

Now we have seen that there are many types and sorts of stem cells throughout our body, but how do scientist find and store these inconspicuous little organisms?

In the case of human embryonic stem cells (hESCs), it is a fairly easy job, scientists have to fertilize an egg *in vitro* to then wait for it to develop into the Blastocyst stage. Having located the ICM, which is the target, a simple extraction of around 100-400 ESCs is done. Now they just have to make sure no abnormalities are present and preserve the sample so it doesn't lose its properties. This is done by placing it in a vitrification solution and

then plunging it into liquid nitrogen through a straw. These straws are now stored and will be used further on for medical purposes.

Induced pluripotent stem cells need no identifying, since they are somatic cells (which are all over our body) that need genetical reprogramming. What has troubled scientists over the last decade is the difficulty of maintenance of iPSC, due to the instability of their undifferentiated state and sensitivity to mechanical stress. The conservation process is a long and complex series of stages in which temperatures are changed, solubilizers are added and state-of-the-art machines are used.

Adult stem cells, however, are a whole different case. Spotting such cells can be a long and tiring affair, since there are no morphological criteria to do contrast them with neighbouring cells. This is partly due to the lack of appropriate experimental techniques and their latent behaviour. Once they are extracted, they go right through to the transplantation process.

2.6 Stem cell involvement in cancer

The widely infamous disease cancer is believed to be greatly related with stem cells. Cancer is characterized by the uncontrolled growth of abnormal cells in the body, and some say that these cells may be stem cells in some or even most cases of cancer. This means that within the tumour, stem cells that have a genetic malformation are continuously supplying the malignant mass with cancerous cells.

Stem cells, on the contrary to regular somatic cells, have a much larger lifespan, increasing the chances of genetic mutations. Only a few mutations can make the stem cells lose control over their self-renewal and differentiation, which is why studies are trying to assess their impact on tumorigenesis. The cancerous stem cells can metastasize if they break loose from the tumour and get in the blood stream, meaning that they will infect other parts of the body with this malignant proliferation and therefore further damage the patient's health.

On the same note, cancer can also be result of a deteriorated stem cell niche. The niche concept in stem cells refers to the microenvironment within the adult tissue that

regulates cell fate. It plays an essential role in avoiding uncontrolled proliferation and maintain tissue homeostasis by providing proliferation-inhibiting and proliferation-promoting signals.

If these hypotheses are true, it might explain why the many treatments available fail to reduce the malignant mass to its roots, therefore giving it a chance to relapse. New therapies however, are targeting specific cancer stem cells for a much more effective result and to avoid recurrence.

3. Organoids

The field of human biology research has had an historical reliance on the use of animal models[11]. However, their capability is limited and does not extend to the mimicking in precise detail of the human physiology, therefore have very little purpose in the study of most chronic diseases. But with the advent of human organoids, it is now possible to inspect in remarkable detail common medical disorders in our society, such as dementia and cancer.

Human organoids are three-dimensional cell cultures derived from stem cells that resemble the architecture and physiology of human organs. These organoids arise from pluripotent stem cells (PSCs) stationed in an in vitro configuration and differentiated into the cell lineage of choice by using genetical engineering, or in some cases from ASCs (mainly from cell types found in the epithelium), presenting a much simpler and easy to use structure. This new model system offers great promise in the study of embryogenesis thanks to its ability to self-organize into a 3D structure. It allows scientist to learn about cell-to-cell interactions with much better accuracy and asses how external factors, such as drugs and chemicals, affect its composition, thereupon providing valuable information to the pharmaceutical industry.

[11] System in which living organisms are used to carry out research.

3.1 Background

For a long time, the use of animal models and classical two-dimensional cell lines has improved our knowledge in many scientific areas. They have successfully helped us understand intercellular signalling pathways[12], cell culture reaction to drugs, and have guided many of the drugs that treat common diseases to be available in our global health system. Their use has reached a universal and crucial agreement that has helped in the historical exponential progression of biomedical research.

The common principles that are shared between mammals and humans have led for many experiments to be physiologically compatible with mice, which have been the main component in research of diseases' pathology[13]. *Mus musculus* is the most frequent species within the rodents and is the most used one in laboratories. These mice are very effective in that they are relatively simple and easy to manipulate and allow for the use of Patient-Derived Xenograft [14](PDX) models, which are immunocompromised mice with surgically established patient-derived tumour tissue. This essentially provides extensive background and characterization of the specific cancerous disease. Other animal models such as *Caenorhabditis elegans*, *Drosophila melanogaster* or *Danio rerio* have also been used, which are usually robust, fast-growing species that can be propagated rapidly and at low cost. While animal models have a long tradition of use in research, the information obtained does not completely reflect the one of human physiology. Organoids however, emerged in the early 2010s, can be seen as "*a novel experimental model that bridges the gap between animal models and human beings*" (Kim, et al. 2020), since the technology can theoretically generate any tissue of our body.

[12] Series of chemical reactions in which a group of molecules in a cell work together to control a cell function.
[13] Study of the causes and effects of diseases.
[14] Tissues or organs transplanted between tissues.

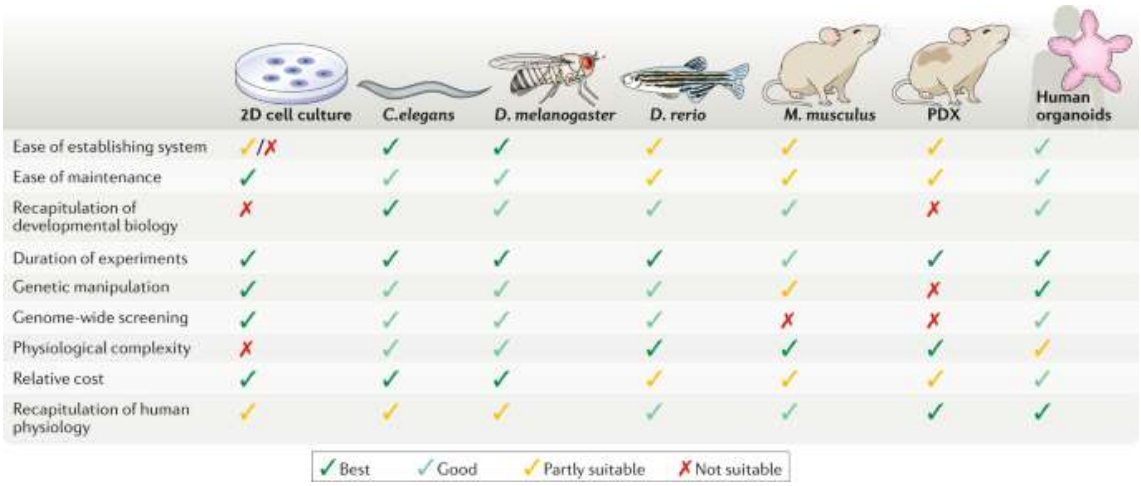

Figure 4 – Table showing all of the primary experimental models and their application classified as: best (dark green), good (light green), partly suitable (yellow) and not suitable (red).

3.2 Concept

Organoids are cell cultures that have self-structured into a 3D complex that resembles with much greater precision the organs and tissues of an individual than any other experimental animal model. The self-renewing and differentiation properties of the stem cells mimic in vivo organ development, allowing more complex tissue structures and multiple cell types to be modelled simultaneously. As well as to generate diseased models and study the comparison of behaviour between the different cell populations.

Their exponential increase of demand has been closely associated with the rise of the number of patients suffering from chronic and/or degenerative diseases. Since the harvest of cadaveric donor tissue [15]is very limited and highly complex logistically speaking, the need of an unlimited source of cell cultures has been focused on the *in vitro* proliferation of pluripotent stem cells.

As mentioned before, organoids can be classified in two branches, iPSC-derived and ASC-derived. This is of course excluding ESC-derived, which played a very important role in the uprising of stem cell knowledge, but are not necessary anymore since iPSC can provide an unlimited supply of them, therefore bypassing the ethical controversy. It is expected that, in the near future, the variety and complexity of organoid models will have increased, and therefore will provide a series of powerful and efficient platforms

[15] From brain dead people.

for studying human development, physiology and pathology. All of which goes closely associated with advances in technology.

3.2.1 iPSC-derived organoids

iPSC-derived organoids were first introduced after concluding the technical limitations that ESC-derived organoids presented, as well as their strong ethical concerns. This new technology consists in reverting an ordinary fibroblast [16]into an undifferentiated and pluripotent state, achieved by the forced expression of a specific set of transcriptional factors[17] and the use of CRISPR-Cas9 technology[18]. These can then be differentiated into a cell line of any of the three germ layers, each one with a specific protocol that requires: cell culture media[19], supplements, bioactive small molecules, and growth factors. The use of fibroblasts in research has owed to their ease of extraction and cost-effectiveness in tissue biopsy.

As our knowledge of human development is yet very limited, the use of mice development to parallel both worlds has helped a lot in determining which media and supplements must be used to obtain the appropriate progenitor cells to generate the human-like cell culture.

Differentiated Cell Type	Media and Supplements	Characterization Antibodies
Neural Stem Cell	DMEM/F12, Glutamine, Neurobasal Media, N2, B27, SB431542, CHIR99021, Compound E, Human LIF, Noggin, bFGF, EGF Order Complete Media	Nestin, PAX6, OTX2, SOX2

Figure 5 - Example of cell fate protocol (neural stem cell). Media and supplements required and characterization of the antibodies.

There are still technical limitations that have hindered the extended use of iPSC-derived organoids in the medical division. For example, they do not represent the typical microenvironment that are usually present at tissues, therefore lack in the number of

[16] Cell from the connective tissue.
[17] Proteins involved in the regulation of gene transcription (DNA to RNA).
[18] Clustered Regularity Interspaced Short Palindromic Repeats with the use of Cas9 proteins.
[19] Combination of compounds and nutrients designed to support cellular growth.

variables taken into consideration in the *in vitro* configuration. Immuno-suppressive microenvironments[20] in the case of some cancers would be an example of a big alternating factor that cannot be mimicked *in vitro*.

The genetically unstable nature of the CRISPR reprogramming is algo a big factor, as well as its low efficiency. Also, it is nearly impossible to provide the *in vitro* sample all the biochemical cues that drive cell differentiation and 3D tissue assembly at precisely the right time, place, and concentration. Therefore, it is nearly impossible to obtain error-free iPSC-derived cell cultures.

Fortunately, the *in vivo* biological nature of cells to follow a semi-autonomous differentiation trajectory allows to generate an unlimited supply of human stem cells, with the potential of biobanking [21]the samples if their need were to arise in the future.

3.2.2 ASC-derived organoids

ASC-derived organoids, on the contrary to PSC-derived, are not genetically engineered into a non-original differential state, meaning that they only present the self-renewal characteristic. This technology requires the isolation of the tissue-specific stem cell population, in a complex process involving protein markers and close professional examination (due to their practically identical physiology to surrounding cells). These can then be embedded into an extracellular matrix[22], where they will be differentiated in the presence of niche factors and cultivated to generate a three-dimensional tissue culture.

[20] Environments in which the immune system attacks its surrounding.
[21] The storing of biological samples in a cryogenic state.
[22] Large network of proteins and other molecules that give support to cells and tissues in the body.

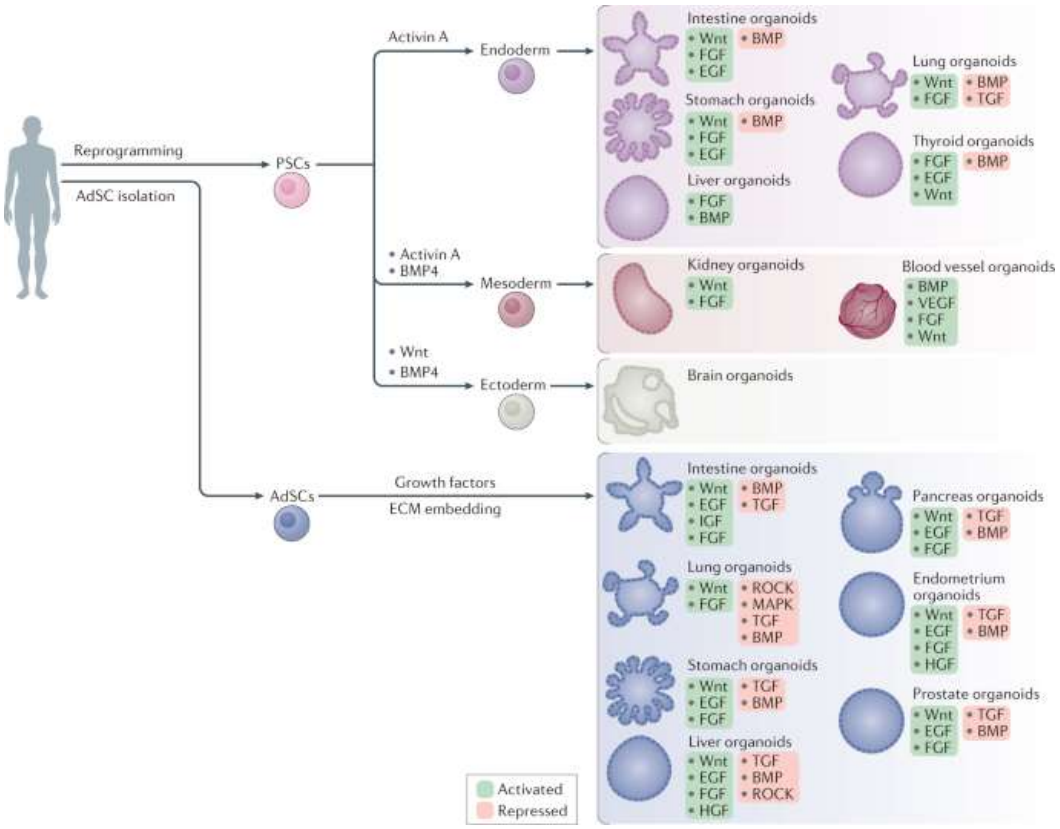

Figure 6 - Organoid production from PSC-derived and ASC-derived. PSC-derived initially have to be reverted into a cell of one of the three germ layers, to then be specialized into their final tissue. ASC-derived uses the extracellular matrix, and the growth factors involved, for a more straight-line differentiation, without the need of cellular reversion. Signaling components (proteins) are crucial for the guided differentiation, and are shown activated in green, and inhibited in red. Signaling pathways include: bone morphogenic protein (BMP), epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), RHO-associated protein kinase (ROCK), transforming growth factor (TGF) and vascular endothelial growth factor. (Kim et al., 2020)

3.3 Opportunities and challenges

The development of functional and stable pluripotent-derived organoids is still in its infancy, with many advances and opportunities right around the corner. The models used currently are very specific and lack many features and characteristics that would make a sustainable tissue with the ability to design disease, participate in drug trial, and be used to supplant conventional human donor-patient transplant. Nonetheless, although this technology is largely funded on its enormous potential and not on its

current applications, it is thought by experts that organoids could revolutionise disease research in a profound manner.

Bridging the gap between animal models and humans is largely the main opportunity that the cell culture presents, allowing a series of studies to replace their animal model-based research methods, therefore achieving much more in-depth and precise results. Furthermore, this would also cease the harmful handling of the thousands and possibly millions of animals used to this day for research purposes. Their suffering due to repulsive conditions and the manipulation of their genes to achieve some sort of disorder would be rendered unnecessary, while organoids can be directly obtained from a simple harmless tissue biopsy from a healthy or unhealthy person. In addition, the length of time required to establish a fully functional organoid is faster than in the case of establishing a fully functional animal model, taking only a couple of weeks and with ability of handling a large number of organoid lines simultaneously.

Organoids also contribute to basic research regarding human biology and its processes (development, homeostasis, cell-cell interactions, external stimuli, etc.). This allows a much more transparent understanding of our development parallel to the rodents used priorly. Moreover, the patient-derived samples can also be used for biobanking, where it is stored as a resource for future use. For instance, if the person in question were to need a tissue transplant in the future, they would have a perfectly usable sample which matches identically their immune system, therefore also creating a solution to the issue of an unbalanced supply-demand of organ donors around the world.

As mentioned before, organoids serve as a system for disease modelling: to understand the mechanisms of infectious diseases and how they spread throughout the cells, how inheritable genetic disorders damage certain body regions and limit one's psychomotor [23]skills, and finally the study of cancer, which is still in its battle for finding a sustainable cure after so many decades.

Finally, the three-dimensional cell culture is used for precision medicine, where they can be used to predict response to drugs and perform drug-screening analyses.

[23] Relating to the action which unifies body, mind, and emotions.

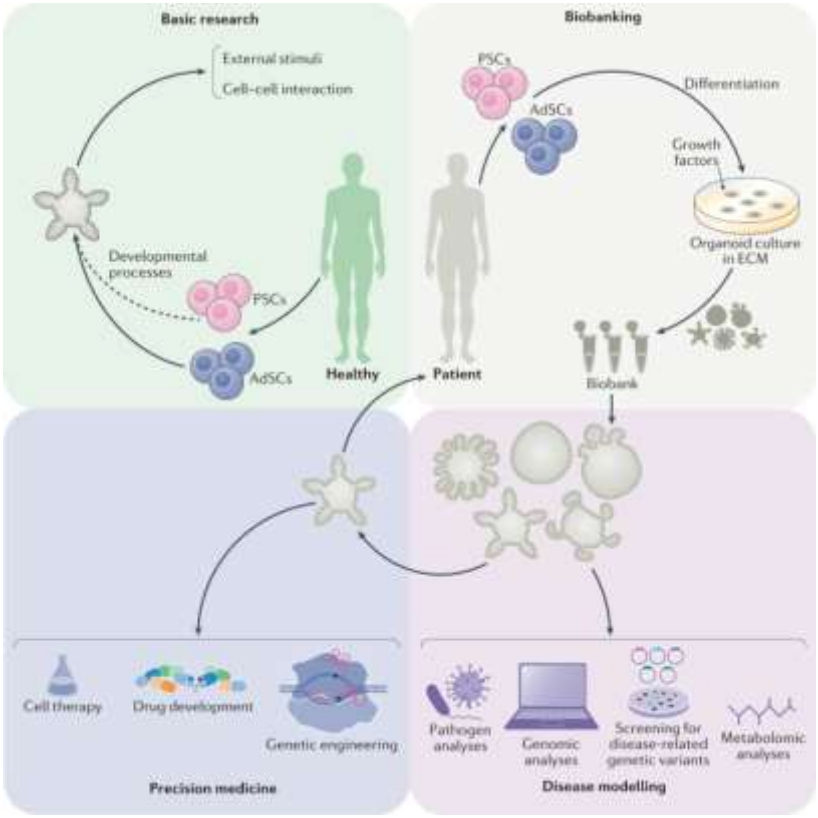

Figure 7 – Diagram of organoid use in different research areas. Healthy person can be used for basic research. Unhealthy patient can be use for disease modelling and precision medicine.

Organoid complexity has to be acknowledged as an additional component to *in vitro* tissue formation, considering the complexity should be appropriate to each study and be thoroughly reasoned. For instance, cancer models from simple cell tissues are sufficient to perform clinical trials and response analyses. However, if the study reviews immuno-oncology therapies or any sort of metabolic pathways, the level of complexity should be at its highest. Unfortunately, the lack of standardized protocols and guidelines for any given lab study regarding organoid and/or derivatives have pushed individual research centers to determine the most appropriate system for themselves.

4. Conclusions

Organoids hold great promise in the research area for the following years, owing to the advantages listed above. Despite the many challenges that these cell cultures present, the rapid development of new technologies assures us a revolution in the chronic disease treatment department, as well as in the study of human biology; development, homeostasis and life sustainability. Starting off as simple two-dimensional mouse-derived model systems, organoids are now capable of self-organization, self-renewal, and the differentiation into any tissue of choice, including the formation of the incredibly complex organ that is the brain. Furthermore, these advances also allow the cryopreservation for biobanking purposes, a powerful yet infant tool that could potentially end with the world-wide organ transplantation insufficiency problem, as well as bypass the immunological incompatibility between individuals. Finally, it would end the use of animals for experimental purposes, concluding an era of dreadful research methods and bioethical dilemmas, all for the sake of the human species.

Medicine as we know it nowadays has had a drastic progression, which has been shown to be correlated with advances in techniques and tools. In this review we have tried to enlighten the common reader how medicine might develop, talking from a purely biological standpoint. Organoids and other stem cell derivatives promise a completely new way of looking at disease treatment, as well as new methods to learn more about basic human biology. Looking at the progression this technology has had over the last decade, the statistics show great potential to establish it as a primary source for medical purposes, facing some of the big problems we as society encounter.

After speaking to a medical specialist with many years of accumulating knowledge, we have gained insight into what could be a very real case scenario of how medicine might develop over the decades. Robots are of course the elephant in the room, having nowadays some incredible tools that are slowly replacing the hand of the doctor. The Da Vinci robot for example, is a machine capable of performing surgical operations with a millimetric accuracy, recording some astonishing results in terms of surgical success. Furthermore, medicine will be more focused on prevention and early treatment, rather than curing. With advances in artificial intelligence, algorithms will be able to tell if a person is suffering, or is going to suffer from, a disease, therefore being able to act much

quicker and stop or reverse the process. Genetic and immuno-therapy is also an aspect of medicine which has been under constant development, with the ultimate goal of remedy genetical disorders such as cancer and diabetes.

On the whole, medicine promises some unprecedented results that will increase the global lifespan and overall wellbeing of many people, reaching as well developing nations with limited access to healthcare.

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6. Annex

5.1 Empirical work

Structured interview with Dra. Maya García

Dra. Maya García is a specialized doctor with a formation in vascular medicine and phlebology. She graduated in 1990 at the University of Montpellier as medical and surgical specialist. Her many years of experience, working for different entities and finally working in her own clinic, has given her an insight into medicine like few people get in their lifetime. For that purpose, we thought it would be appropriate to ask some questions. Even though her field of application does not relate to stem cell cultures and relatives, her work contributes to newer approaches towards patient wellbeing, which in the end is the goal of modern medicine.

WHAT'S THE FUTURE OF MEDICINE?

(translated to Spanish for comfortability of the speaker)

- Determinar los parámetros de la entrevista; confidencialidad y consentimiento.

Antes de empezar esta entrevista, me gustaría establecer unos acordes en base a la confidencialidad y el consentimiento.

¿Acepta ser entrevistado/a por Xander Bedaux con la finalidad de ser utilizado para el *treball de recerca* que se pide a los alumnos de bachillerato de los institutos catalanes?

Si, acepto.

¿Acepta que su nombre sea presentado en el anexo junto a esta entrevista?

Si, acepto.

- Descripción del *treball de recerca* dirigido por Xander Bedaux, breve explicación para entender el motivo de la entrevista.

El trabajo trata de mostrar las últimas aplicaciones de la formación de culturas de células madre tridimensionalmente para así ser utilizados en aspectos biológicos y médicos. En las últimas décadas esta tecnología ha ido desvelando su potencial, marcando un nuevo camino hacia la medicina personalizada. Esto ha sido sobre todo gracias al descubrimiento de la reversión celular, que consiste en volver una célula

somática (células neuronales, epiteliales, del tejido conjuntivo…) a su estado original, que viene a ser un estado sin especialización. Gracias a esto ya no se necesitan embriones para "cosechar" células madre pluripotentes (que se pueden especializar en cualquier tipo de célula somática) y así evitar cualquier controversia ética.

- Explicación de la necesidad del punto de vista del/a entrevistado/a para realizar la conclusión cualitativa del trabajo.

Le he preguntado por hacer una entrevista para así conocer un poco el punto de vista de algunos especialistas del ámbito de la medicina. Con esto podré formular una conclusión cualitativa en base al trabajo de investigación.

Preguntas:

1- En tu punto de vista, ¿Cómo crees que se desarrollará la medicina en las próximas décadas?

Pienso que la medicina en las próximas décadas evolucionará cada vez más hacia la prevención de las enfermedades y en su tratamiento precoz. Los avances en el diagnóstico precoz de las enfermedades están muy adelantados, pero la inteligencia artificial y sus aplicaciones a la medicina permiten y permitirán avances reales en los métodos diagnósticos y en los tratamientos. El futuro está cada vez más cerca, en unos años serán robots los que operaran , y ya existen algunas cirugías hechas por robots, pero esto es solo el principio, también he visto el uso de realidad virtual para la sedación de los pacientes , es maravilloso…. A nivel de tratamientos , la ciencia está avanzando mucho , hemos visto con el COVID como la ciencia y los investigadores han ido muy rápido en el descubrimiento de diagnósticos , despistajes, tratamientos y vacunas . En cuanto a la terapia genética e inmunológica esto permitirá una medicina personalizada permitiendo optimizar los tratamientos en los pacientes.

2- En tus años de experiencia como experta en medicina vascular y flebología, ¿consideras que el desarrollo de las nuevas tecnologías ha mejorado significativamente las técnicas medicinales para el bienestar del paciente?

En mis 25 años de graduada, he visto mejorar las técnicas diagnósticas en ecografía vascular , la precisión es cada vez mayor , permitiendo diagnósticos cada vez más precoces. La semana pasada en un congreso en Francia vi un brazo robot que practicaba las ecografías para prevenir así el cansancio del brazo y del hombro del médico …. En cuanto a los tratamientos quirúrgicos estos también han evolucionado en ser cada vez más mínimamente agresivos. Cada vez se hace más medicina preventiva tratando directamente los factores de riesgo del paciente , y los pacientes son diagnosticados en estadios más precoces .

3- Seguro que al largo de tus estudios y tu carrera profesional has oído el término bioética a menudo, que relaciona todos los aspectos morales con la biología y medicina. ¿Consideras que la medicina se debería guiar más con la bioética y los factores morales o más con la racionalidad política, social y económica?

La ética médica y la bioética son conceptos distintos, la ética médica es el juramento de Hipócrates que todos recitamos el día que nos graduamos y que no deberíamos de olvidar , el concepto de bioética es la ética relacionada con el desarrollo social y científico y que abarca muchos campos en el planeta , en nuestras vidas y en nuestro bienestar como seres humanos y pienso que los políticos deberían de tomar en cuenta estos nuevos factores en sus decisiones económicas , pero lamentablemente no es así .

4- Cómo le he explicado al principio de esta entrevista, este trabajo trata sobre las células madre y sus aplicaciones médicas, incluyendo la reciente y prometedora tecnología de los organoides. ¿Has oído hablar de esta tecnología recientemente a través de conversaciones con compañeros o compañeras de trabajo o simplemente por curiosidad personal?

He oído hablar de las células madre en pacientes diabéticos con problemas vasculares , pero tendré que investigar más….

5- La terapia personalizada, que se especializa en desarrollar un tratamiento personal y específico para cada paciente en enfermedades crónicas como el cáncer y la diabetes, ha sido un factor prometedor y con un potencial inmenso en la medicina en la última década. ¿Cómo ves a esta tecnología para suplantar los tratamientos actuales para enfermedades crónicas? Unos tratamientos que en casos tienen unos efectos secundarios muy severos.
Para algunas de estas enfermedades mediadas por genes, el futuro será el tratamiento directamente dirigido a estas mutaciones genéticas para corregirlas , por ejemplo con la diabetes, evitando así las complicaciones tan graves de esta patología.

6- Finalmente, me gustaría saber tu punto de vista en torno al uso de culturas de células para estudiar: el efecto de algunos medicamentos, para estudiar la fisiología y morfología del desarrollo embrionario e incluso para estudiar la patología de algunas enfermedades crónicas.

Conozco solamente el uso de los cultivos de células madre para el tratamiento de leucemias y linfomas , y patologías de la córnea, será parte de la medicina del futuro, pero el uso de células madre embrionarias , aunque prometedor, plantea problemas éticos que habrá que definir .