Nominate a living woman biologist for a Nobel prize and justify your choice

Now is a great time for women in science, and we see that clearly in biology. Many female biologists have made incredible breakthroughs that have revolutionized modern science in recent times. They come from across the world and range from the conservation works for chimpanzees by Professor Jane Goodall, to the development of harnessing the potential power of the protein CAS9 and CRISPR technology by Jennifer Doudna, not to mention many others - all of whom are worthy of a Nobel prize. However, for the purpose of this essay I have chosen to 'nominate' professor Magdalena Zernicka-Goetz for her seminal work on embryonic stem cells and embryonic development.

She is perhaps best-known today for her work on fate decisions in preimplantation embryos (whether it is induced due its position or polarity), cytoplasmic movements in zygotes to predict developmental success, in vitro development of the implantation stage and the building of synthetic embryos from stem cells. For the purpose of this essay I am going to be focusing on three of her major breakthroughs, the impacts they have had in the science community, and what they could mean for future development.

Her first major breakthrough came in 2016 with the outlining of a new technique that allows embryos to grow in a lab for up to 13 days, rather than the previous restriction of just 7. This opened a whole new perspective into the world of post-implantation embryology. Prior to this development, the science had been very limited since the 7-day in vitro stage was before the point at which the embryo would normally implant into the womb, and so no embryo had been studied to see what happened after this point. The technique, which mimics the environment found in the womb, involves creating a scenario in the lab which allows embryo cells to organize themselves to form the foundations for future growth. They could then develop past the 'blastocyst' stage which was previously restricted. Many famous scientists tried and failed at what Zernicka-Goetz managed. She was told by her college that it would be impossible and a 'waste of her time'[1], yet through persistence and originality, it was achieved after 7 years. Until the discovery of this new technique, the truth behind post-implantation embryology was still a mystery; Zernicka-Goetz had opened a door to a 'new' science which she has continued to build on in recent years.

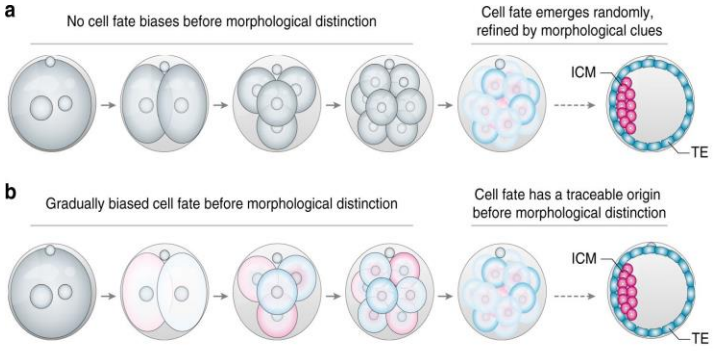
In March 2017, Professor Zernicka-Goetz's lab published a paper on how they had 'built' an embryo whose architecture and development very closely resembled those of one which had been naturally conceived. They achieved this through combining genetically- modified embryonic stem cells (ESCs) and trophoblast stem cells (TSCs) - which will form the body and the placenta respectively – as well as a 3D scaffold which is known as an extracellular matrix.

[1] Quote from an interview the Professor gave in 2017

The structure managed to assemble itself like a normal embryo with an extraordinary level of communication between the two types of stem cell. At this discovery, there was a media frenzy over the profound results for the study conducted – however, Zernicka-Goetz had more to come.

The biggest issue with the embryonic structure built by Zernikca-Goetz's lab was that it didn't contain the final type of stem cell – primitive endoderm stem cells (PESC's) - which form the yolk sac, contain essential nutrients, and ensure that the organs and tissues of the fetus develop properly (evidently an extremely important part of development). Without these cells, the embryo wouldn't be able to undergo gastrulation. Gastrulation is debatably the most significant part of an embryo's development; It is the defining moment when the single layer of cells transforms to three – an inner layer (endoderm), a middle layer (mesoderm) and an outer layer (endoderm). This separation leads to the determination of which cells will transform into what structure, wither tissue or organ. Replacing the jelly structure, they used in earlier experiments with the PESCs seemed like the next logical step to undertake – and they achieved this with great success. For the first time, scientists were able to see cells undergo gastrulation and have reached the closest point they can get to without needing a mother to implant into or an artificial placenta. They have a striking resemblance to real embryos by mimicking almost exactly the timing, architecture and patterns of a real embryo's gene activity.

Her second major achievement is coming up with new models that regularly challenge accepted conceptions, but perhaps the most ground-breaking of these was their "Early Heterogeneity Model".

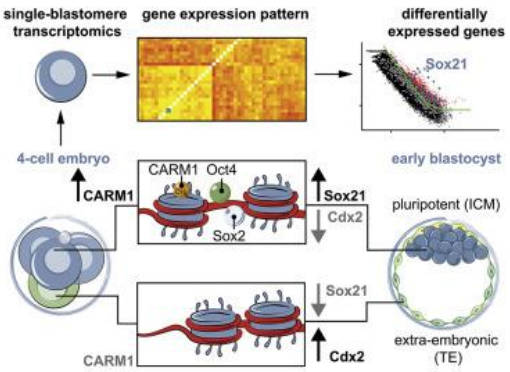


The original and accepted model for cell fate was that it was decided purely on the random positioning of the cell within the embryo (see diagram A to the left) - the position drove the outcome of how the cell would specialize. However, this was challenged 14 years ago with a new model that suggested something a lot more structured. It suggested that the cells begin to differ at the 4-cell stage and then because of these changes, their behavior and then in turn positioning is affected (see diagram B above). This set up cell fate in a much less flexible manner. This model had one problem at the time- the technology wasn't developed enough to prove it and so it was subject to a very hostile reception. 5 years ago, this changed.

The model was picked up again with new technology that could target it in a molecular way, which would in turn lead to a stronger case with further evidence for it. The scientists used

time-lapse to track cells and in doing so, found that some cells are more biased to develop into the fetus over any extra embryonic structures, and equally some the other way around as well. To show that there was a bias from the 4-cell stage, Zernikca-Goetz and her team set up an experiment. This comprised of building two artificial mouse embryos – one of cells they thought to be bias to give rise to a fetus and one which was made of cells believed to be biased towards forming extra-embryonic structure. The results showed that the fetus biased cells worked well, and the pregnancy was a success; however, the placenta/yolk sac biased cells quickly failed. The team quickly noticed this must mean a difference at a gene transcription level and so the next logical step would be to find out what these genes are. To their surprise, most of the highly differential gene expression had one common factor- they were all targeted by the two most important pluripotency transcription factors called Sox2 and Oct4. The example that they used to show this was a gene called Sox21. This gene is also found to be prominent for differentiation in colon cancer.

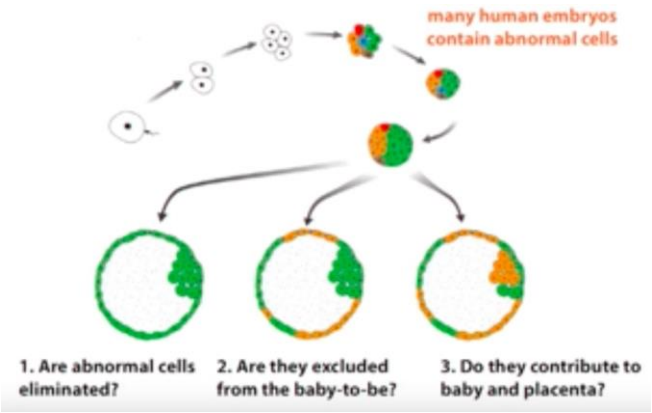
The next task was to show that Sox 21 was actually responsible, and to do this, the scientists varied the level of Sox21 gene expression into parts of the embryo to see whether if it would differentialize preferentially to the linage that would make a placenta, and this was found to be true and proved to be because Sox21 actually represses another major differentiation gene – Cdx2. After many more tests upon the gene, it was also found that Sox21 gene expression is caused by an enzyme known as carm1 (which also drives other pluripotency genes for cell fate). The results of the experiment showed that where the Sox21 gene was at a high, the fetus biased cells formed, however where the gene was at a low, cells biased to form extraembryonic structures appeared. The team were amazed at how such small differences in the level of the enzyme carm1 would be amplified and end up driving the entire complexity of life.



The final breakthrough that Zernicka-Goetz has had –and which I believe to be the most important - was her model for abnormal cells in an embryo and what happens to them during pregnancy. By being able to understand the limitations behind cell plasticity, Zernicka-Goetz suspected we would then be able to understand the limitations behind the self-recovery mechanism is used so successfully.

Zernicka-Goetz discovered that there wasn't a model to address abnormal cells if they are in the context of normal cells (work together side by side) and so took it upon herself to investigate. At the time, it was widely accepted that majority of human embryos show some cells at the early stage of preimplantation to have some abnormalities, but the question was, where do they go after? Three hypotheses were formed (see right), and they were that the

abnormal cells would be eliminated from the entire embryo, the abnormal cells would be excluded from the fetus and made up the extraembryonic structure instead, or the abnormal cells would contribute equally to both placenta and baby.



The scientists tested the hypotheses in mice as they have the closest embryonic structure to that of a human; however, they don't have abnormalities like human embryos do. This meant that an extra step had to be taken to induce these abnormalities and they achieved this by using a drug called reversine. Reversine inhibits the surveillance mechanism by disallowing the spindle assembly checkpoint to function and so chromosome mis-segregation begins to appear. Once setting up the abnormal cells correctly, the team had to combine both normal and abnormal cells together at the 8-cell stage and followed the development of the structure through the rest of the preimplantation stages. The results of this astounded everyone as they witnessed the abnormal cells undergoing programmed cell death (or apoptosis) and eliminating themselves.

Furthermore, the normal cells surrounding the abnormal cells were shown to "clean up" the debris left behind by engulfing and then destroying them. This process started at the time of implantation and continued throughout the duration of the study. Another discovery that was made showed that although the abnormal cells in the fetus get destroyed, the placenta abnormalities and just left alone. As they do not contribute to the baby, the body sees no need to get rid of these cells as they are non-threatening.

The final question that the lab wanted to answer was what the proportion of normal cells to abnormal cells was needed for the mouse embryo to survive through the pregnancy. They ran tests at different levels and discovered to their amazement that the embryo could survive all the way unless the entire population of cells was abnormal. Even with 75% of cells being abnormal, there was still a 40% chance of survival which showed the scientists just how durable and adaptable these embryos really were.

In conclusion, the work Professor Magdalena Zernicka-Goetz has dedicated her life to has provided groundbreaking understanding of cells which will radically enhance the way modern medicine works, especially in IVF treatment - but with positive application beyond this field. It has allowed researchers to better understand how ESCs, TSCs and PESCs communicate through the altering of conditions and pathways within one cell type to explore how it affects the others. Scientists can apply this knowledge gained from the study of mouse embryos to the equivalent human SC types and hense can deduce what happens within our own early embryonic system. The period in pregnancy that she has provided so much for is key for scientists to investigate due to the high levels off miscarriages that occur (70% of total failed

pregnancies are within this time frame), yet so little is known. By being able to understand how this process works, we will hopefully also be able to like it to why the process also sometimes fails. Zernicka-Goetz's work on cell plasticity and heterogeneity will allow for more precise screening for genetic disorders and will contribute to a greater success rate for IVF. Ultimately, she deserves the Nobel Prize because she has had the bravery, creativity and tenacity to challenge accepted thoughts – such as the early heterogeneity model – and effectively produce a paradigm shift in our understanding of how all mammalian embryonic cells work. She has changed the outlook of modern human reproductive science more significantly than anyone else today.

WORD COUNT: 1997

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