KING'S College LONDON
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Contested cultures: views from the beta cell lab on controversial science and ES cell therapies for diabetes

E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

Goldsmiths UNIVERSITY OF LONDON

Introduction

This poster draws on our social research on the problems and prospects of stem cell biology in the field of diabetes, liver disease and neuroscience (Williams *et al*, 2003; Wainwright, 2005; Kitzinger & Williams, 2005; Wainwright et al, 2006a, 2006b, 2006c).

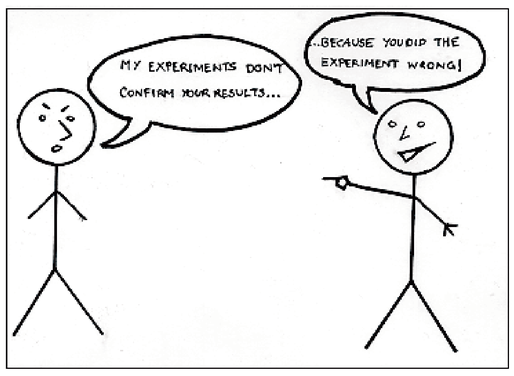


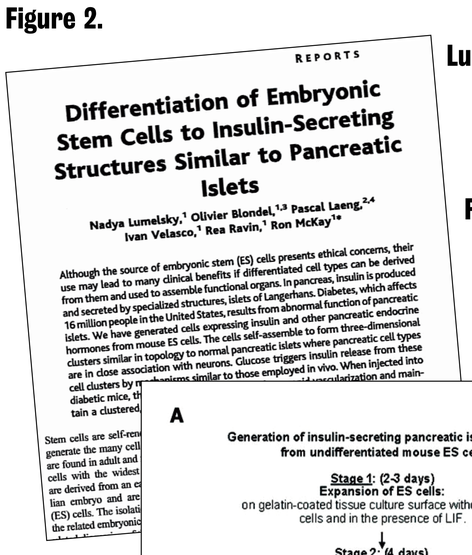
Figure 1. Contested science: the experimenters' regress (Collins)

- Recent advances in the transplantation of human islets into patients with Type-1 diabetes have stimulated research on making beta cells.
- We report on how seven biomedical scientists from one UK lab, who work on turning ES cells into insulin producing beta/islet cells, view the scientific literature and their research in this field.
- We highlight the impact of two seminal papers, published in the prestigious journal *Science*.
- We draw on Harry Collins' notions of the experimenters' regress and the core set, *i.e.*, if findings from an experiment are not replicated in another lab, the original group may argue this is because their procedures were not followed **(Figure 1)**. The meaning of the experiment is contested and this regress can only be broken through negotiations within a core set of researchers who are expert in generating and resolving scientific controversies within their field.

A revolution in beta cell biology?

Lumelsky *et al* (2001) showed that cell types of the endocrine pancreas could be generated from ES cells in vitro **(Figures 2 & 3)**.

Figure 2.


REPORTS

Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets

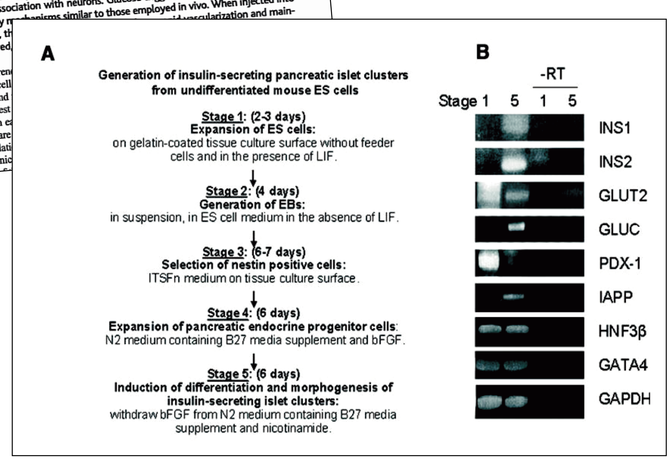
Nadya Lumelsky,[1] Olivier Blondel,[1,3] Pascal Laeng,[2,4] Ivan Velasco,[1] Rea Ravin,[1] Ron McKay[1]*

Although the source of embryonic stem (ES) cells presents ethical concerns, their use may lead to many clinical benefits if differentiated cell types can be derived from them and used to assemble functional organs. In pancreas, insulin is produced and secreted by specialized structures, islets of Langerhans. Diabetes, which affects 16 million people in the United States, results from abnormal function of pancreatic islets. We have generated cells expressing insulin and other pancreatic endocrine hormones from mouse ES cells. The cells self-assemble to form three-dimensional clusters similar in topology to normal pancreatic islets where pancreatic cell types are in close association with neurons. Glucose triggers insulin release from these cell clusters by [illegible] diabetic mice, th[illegible] tain a clustered

Stem cells are self-ren[illegible] generate the many cell[illegible] are found in adult and [illegible] cells with the widest [illegible] are derived from an e[illegible] lian embryo and are[illegible] (ES) cells. The isolati[illegible] the related embryonic

Lumelsky et al, 2001

Figure 3. Lumelsky protocol, A; RT-PCR of pancreatic gene expression, B



However,

> The Lumelsky paper... was a little bit of a misguided paper because it wasn't well reproduced, but it was probably good in terms of impetus, it got a lot of people doing this. (Scientist 4)

Subsequently, the Melton lab (Rajagopal *et al*, 2003) demonstrated that rather than the cells producing insulin **(Figure 4)**, insulin was absorbed from the culture medium and then secreted by cells **(Figure 5)**.

> We know that the initial Lumelsky paper that sparked this all off was based on an error. The cells weren't making insulin, they were taking it out [of the culture medium]. We knew that before that was published, because we couldn't find any significant gene expression... So it was clear there was something wrong with the protocol... Melton had the brains to publish it in Science. That knocked off the first paper [Lumelsky et al, 2001] and undermined a whole series of papers in press... The results tend to be: 'We have reproduced this. A small number of cells differentiate to an insulin genotype'. But it's not clear what the phenotype of the cells is, in our opinion. We think that the cells are doing it themselves rather than responding to any external stimulus. (Scientist 3)

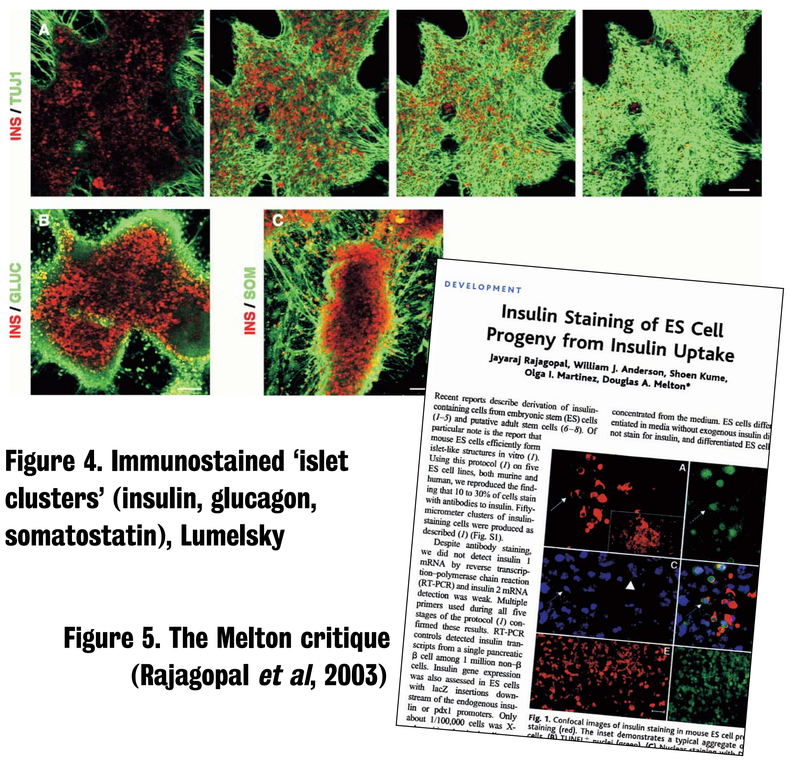


Figure 4. Immunostained 'islet clusters' (insulin, glucagon, somatostatin), Lumelsky

Figure 5. The Melton critique (Rajagopal *et al*, 2003)

Turning stem cells into beta cells?

The oral culture of the lab contests published results on making beta cells from ES cells.

> I don't want to be a Cassandra and say it's never going to happen... The science of stem cells is very difficult... We know very little, and that's why we are having trouble directing them. (Scientist 1)

This lack of knowledge consists of several problems: cell culture, *in vitro* developmental biology, and understanding experimental processes etc. For example, the lack of appropriate biological markers to track the transformation of hES cells into beta cells:

> You need to understand the whole process of how you get from the non beta cell to a beta cell. What steps are involved in that process of differentiation? The first important thing to have is some kind of marker for different stages of differentiation. These are known in the mouse, but there is virtually nothing known about the way that cells differentiate in humans. (Scientist 5)

Conclusion

Stem cell research is 'science-in-the-making' rather than established 'ready-made-science', hence turning ES cells into beta cells is contested. Is this a field of science that scientists should invest their time, resources, and staff in? **(Figure 6)** The difficulties of laboratory science illustrate the salience of the core set and the experimenters' regress for social research on the cultures of science.

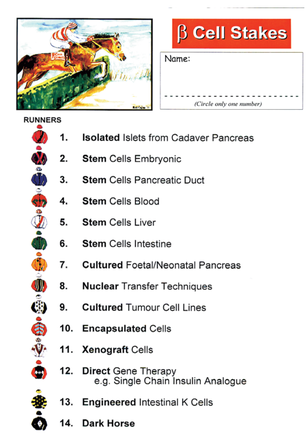


Figure 6. Making beta cells for 'a world without insulin': backing scientific winners?

Acknowledgements

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