BioethicsBytes Extended Commentary

Science and ethics of cybrids – reflections on some recent media coverage

Introduction to this resource

Welcome to this *BioethicsBytes Extended Commentary*. These papers are intended to provide all readers - teachers, learners and members of the public alike – with a more in-depth discussion of issues raised by media presentations of developments in biology and biomedicine. They are supplementary to posts on the *BioethicsBytes* website, and elaborate themes identified in the main commentaries.

In general, they deal with one or more particular bioethical issues raised by featured programmes. They focus on quotes, or exchanges, in the source material that illustrate moral concerns or ethical concepts that have application beyond the context of the episode itself. The extended commentaries draw on a wider range of media and academic texts than can be presented on the main website, and, as such, can provide readers with additional resources on specific topics. This particular commentary looks at the BBC debate programme *The Big Questions* (September 9th 2007) and *The Guardian Science Podcast* (September 10th 2007) both of which included discussion of recent moves to permit the creation of human-animal hybrid embryos. This development is contrasted with another which has been prominent in 2007, namely the reprogramming of differentiated cells to become "induced pluripotent stem" cells.

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Cybrid embryos – a step too far?

The controversial decision of the Human Fertilisation and Embryology Authority to approve the creation of 'animal-human' hybrid embryos, or "cybrids", has generated some interesting debate on the issue. This post takes as its startpoint two recent discussions on cybrids, that are available as multimedia resources. These are The Guardian's Science Weekly Podcast of September 10th and the inaugural episode of the BBC's new ethics programme *The Big Questions*, BBC1, Sunday Sept 9th 2007, 10 am (TRILT code 0008D257 for off-air recording). You may also like to watch a BBC news report following the announcement - go to their News page *'Human-animal' embryo green light* and follow the 'Watch' link on the right-hand side.

On *The Big Questions*, Nicky Campbell put the question "Are hybrid embryos an ethical step too far?" The panelists for this fifteen minute discussion (from 00:25:00 to 00:40:40) were Daily Mail columnist Amanda Platell, Jonathan Bartley, co-Director of Christian think-tank Ekklesia, and Dr Alice Roberts of Bristol University but known increasingly for her work on the 'public understanding of science' (Dr Jeevan Singh Deol from the School of Oriental and African Studies was also on the panel, but was not involved in this debate). Audience participation came primarily from Evan Harris MP, who has been very active in the campaign to overturn the original ban on this technique, Catholic ethicist Prof David Jones, and from two people who might be seen as beneficiaries of any future therapies, identified as Michelle, who suffers from Parkinson's Disease, and Victoria, who's father suffers from Parkinson's.

Nicky Campbell put the question first to Alice Roberts. Dr Roberts started by saying that the terminology being used in this field is unhelpful - 'chimeras' summons up images of Greek mythological animals and embryo sounds like a miniature baby. She pointed out that there is a shortage of human embryos for research and sees this process as preferable to putting women through the trauma of hormone therapy and minor surgery in order to obtain more eggs. "What we are talking about is taking an egg from an animal, removing the nucleus so really all it is then is a bag of fluid" she added.

Campbell turned next to Prof Jones, who countered that scientists call something an embryo because it has the potential, if implanted, to come to term and become a new organism. He made the point that to say experiments were limited to the first 14 days was implicit acknowledgement that something had occurred, "you are talking about 14 days after something has come into existence" he said. He feels that there is not a good case for carrying out this type of animal-human hybrid work and that "we've crossed a big line here". When challenged by Campbell to say whether he was excited by the prospects of finding cures for Alzheimer's, motor neurone disease and Parkinson's, Jones was enthusiastic for research work on those diseases, but not via the cybrid route.

Michelle and Victoria were then brought into the discussion. Michelle was very honest when she commented that her perspective now was very different to the way that she thought prior to her own diagnosis with Parkinson's Disease. "When you watch your nearest and dearest gradually degenerating and you can't alter that course of events and there's no treatment that's going to limit it or cure it, you are on a downward slope, this type of research is very exciting" she said, adding that she didn't expect treatments arising from this research to be available in time for her.

Victoria objected to arguments against the hybrid work on the grounds that it was an offence to the dignity of both humans and animals, arguing that the loss of dignity experienced by sufferers of Parkinson's, Alzheimer's, etc was more tangible.

Amanda Platell echoed some of the concerns expressed previously by Prof Jones. She wishes that a cure could be found to those conditions, but felt instinct says a significant line has been crossed in legitimising cybrid work. Her additional comment that we need as a society to recognise that there is a cycle to life, that people do get sick and that this is something we cannot change was given short thrift by Michelle, whose repost reiterated the emotional cost to individuals, but also introduced the financial cost to the nation of treating people with degenerative diseases.

Amanda stressed that she believes that we should be searching for solutions, but feels deeply uneasy about this type of research. Her cry "aren't there other ways?" was ultimately picked up by fellow panelist Jonathan Bartley. Despite having, or perhaps because he does have, a son with spina bifida, Bartley is cross that other sources of stem cells (he highlighted placenta and bone marrow) are not being adequately pursued. He feels that progress made in those fields offered much more promise than hybrid embryo work which was "speculative" and "may provide false hope".

After a short dialogue with other audience members, Evan Harris came back to the issue of alternative avenues for stem cell research. His apparently magnanimous statement that supporters of embryonic stem cell work do not object to research on adult stem cells but are not afforded the same gesture in return, seems to miss a fundamental point. As a libertarian, Harris has no case for objection to adult stem cell work; opponents to research involving embryos, however, have strong objects based upon their views on the moral status of the embryo and when life begins. Bartley argues (earlier in the programme) that this is actually the position enshrined in the law. "As a society", he comments, "we are saying that it [the embryo] is not just a bag of cells, it's not a baby either, but it's not just a bag of cells - we are reluctant to face up to what we've already decided."

This section of the programme finished with Nicky Campbell bowling a philosophical googly to Prof Jones. If he, as a Catholic, is *de facto* opposed to destruction of an embryo once created, surely he should wish for any human-animal hybrids to be implanted and taken to term - an interesting conundrum.

We will move on to consider the Guardian podcast (rather more briefly) in a moment, but before doing so it is worth reflecting on how this series of exchanges on The Big Issues might be used in teaching. I can see it offering huge potential with an RE class, or Citizenship and/or General Studies as a route into different philosophical approaches. At it's crudest we see the classic clash between deontological viewpoints, as espoused by Jones, Platell and Bartley, versus utilitarian (consequentialist) approaches, as modelled by Harris and Roberts. The two sides are not only disagreeing, they are speaking in different languages, so a consensus is never going to arise. With a class who had previously been exposed to some background in philosophy, I'd like to show the whole 15 minute section and then use it as a discussion for the rest of the lesson (having forewarned them, of course, what to be looking out for whilst viewing the clip).

Blurring species boundaries – does it matter?

So then, moving on to the Guardian Science Weekly podcast. The episode on the 10th September was packed to the gunnels with genetic ethics stories - in addition to the cybrid issue (which we will discuss here), there was also consideration of the suggestion that everyone in the UK should be on the National DNA database (the subject of a different Extended Commentary), of attempts at synthetic lifeforms and the publication of Craig Venter's complete genome (none of which we will be commenting on in this post).

For the discussion on animal-human hybrids (00:10:29 to 00:14:52 in a 32 minute programme), Guardian journalist Alok Jha was joined by fellow Guardian Science writer Ian Sample and University College London philosopher Janet Radcliffe Richards.

Alok Jha has made his own views on cybrid research clear in an earlier blog *Luddites and moralists* on the Guardian's *Comment if Free* site. Janet Radcliffe Richards is also an enthusiast, describing the proposal as "an unequivocally good idea" adding "the question is why people should object to it". Her view was that objections were religious in form and posed the broader question "why should religious objections be taken notice of in... secular government policy".

Joining the discussion, Ian Sample pointed out that there were two main objections (though I don't believe he holds these views himself). Firstly, there is the issue of deliberately creating embryos which are destined to be destroyed. Prof Radcliffe Richards pointed out that this was not an objection to this research *per se*, but to the use of embryos in general and applies equally strongly, probably more so, to research involving *bona fide* human embryos. The second objection raised by Sample is specific to this research, namely that it is blurring the distinction between animals and humans.

At this point, Janet Radcliffe Richards' comment was again insightful. She pointed out that if, post-Darwin, we hold a view that species are evolving then we should not have qualms about blurring the distinction between species because those boundaries are in a state of flux as it is. If, however, we view human life as being special (for whatever reason) then we are going to want to reinforce that boundary as thoroughly as we can. Someone who does see a major ethical problem with the cybrid route to stem cells will therefore seek other means to generate pluripotent cells, be they for research or for therapy.

Alternatives to cybrids – induced pluripotent stem cells

So what other methods of generating such cells might exist? 2006 and 2007 have seen some very significant developments in reprogramming of somatic cells (i.e. 'normal' cells, not reproductive cells) so that they are re-invested with the potential to develop into a range of other cell types. The original breakthrough research in this field was carried out by Takahashi and Yamanaka at Kyoto University in Japan and was the subject of an earlier *Bioethicsbytes* podcast (that same audio file is also, incidentally, a good place to start if you are uncertain about the background biology of stem cells).

In a very clever set of experiments, the Japanese researchers were able to work through a set of 24 genetic factors which they believed were likely to be important in the control of stem cell development. By preparing a series of chemical cocktails each lacking one of the factors, they were able to determine a shortlist of 10 which seemed to be most significant, and ultimately to home in on the most important 4 compounds: Oct4, Sox2, c-Myc and Klf4. Amazingly, when they treated adult cells with just these 4 transcription factors together, the scientists reported that they could turn them into induced pluripotent stem (iPS) cells. These iPS cells shared several important properties with embryonic stem (ES) cells, such as their shape and ability to divide, although some differences in gene expression between the two cell populations were noted.

The discovery of iPS cells and the apparent simplicity of the chemical cocktail was a big surprise and, for a number of reasons, was initially treated with caution. Not only is it generally a good idea to retain healthy skepticism when such groundbreaking work has only been carried out in one laboratory, but the experiments had involved mouse cells not human cells. Coupled with this, at least one of the 4 factors, the protein c-Myc, has long been implicated in the development of cancers. Nevertheless, the observations were sufficiently important that other researchers sought to replicate them.

In July 2007, the original findings were given massive endorsement when three separate labs were able to use the same 4 "Yamanaka factors" to produce cells that were even more ES-like. Yamanaka's own team was one (Okita *et al*, 2007), the others are run by Rudolf Jaenisch (Wernig *et al*, 2007) and by Jaenisch's former PhD student Konrad Hochedlinger (Maherali *et al*, 2007). Not only did the iPS cells produced by all three groups have gene expression patterns more similar to ES cells, but, unlike the earlier iPS cells, these were also able to perform an important characteristic test of pluripotency, namely the ability to generate viable chimaeras when injected into mouse embryos.

Despite being a major step forward, the clinical relevance of these later results was still uncertain since all the research had been performed with animal models and it was not clear that these would be transferable to human cells. By the end of 2007, however, this question too had been resolved. The lead came once more from Yamanaka's group (Takahashi *et al*, 2007) when they were able to use their standard cocktail of 4 transcription factors to convert human skin cells into iPS cells and subsequently into nerve and heart cells. This was rapidly followed by an even more exciting report from the lab of James Thomson, a long-standing leader in the Embryonic Stem cell field. Thomson and his colleagues also reprogrammed human skin cells to become iPS cells using 4 factors, but importantly their experiments worked with a different combination of proteins (Yu *et al*, 2007). Oct4 and Sox2, two of the Yamanaka factors, are retained in the Thomson mix and are absolutely required for reprogramming. Nanog and Lin28, which were not in the original list, enhance the efficiency of the process. It is the lack of requirement of c-Myc in the hands of the Thomson team that is the most significant feature since, as noted above, this protein is known to be involved in cancer development.

Both teams required a large number of skin cells to achieve the production of induced pluripotent stem cells – Yamanaka achieved 10 iPS cell lines from 50,000 facial skin cells; Thomson got 57 colonies from 600,000 foreskin fibroblast cells. Statistically, these are not huge conversion rates, but the ready availability of almost limitless supplies of starting materials, without the ethical issues associated with

embryonic stem cells, means that these inefficiencies are acceptable. These limitations, such that they are, should not detract from the amazing fact that the reprogramming can occur at all.

It is no overstatement to say that the developments on iPS cells in the last two years have turned the stem cell field on its head. In particular, it brings into serious question the need for controversial approaches such as cybrid production. If stem cells for research can be made by the reprogramming of adult cells these are likely to be at least as useful, if not more so, that cybrid cells and without the same ethical quandaries. Similarly, the model of therapeutic cloning based on transfer of a patient's nucleus into an emptied egg cell to achieve individualised stem cells is also superseded by the reprogramming method.

This is not to give the impression that therapies based on the new strategy are going to be imminently available in the clinic. Significant problems remain with the new approach. Although Thomson's work may have shown that the contentious inclusion of c-Myc may not, in fact, be necessary, the key stumbling block remains the fact that the delivery of the factors into cells to achieve reprogramming requires the use of viruses. Integration of viral DNA into the chromosomes of the recipient cell is itself a significant risk factor for the development of tumours. Therefore as well as refining the combination of factors necessary to achieve the reprogramming of cells, researchers are also going to need to develop alternative methods for delivering these agents of change.

The key references on reprogramming to achieve induced pluripotent stem cells are:

Maherali N, Sridharan R, Xie W, Utikal J, Eminli S, Arnold K, Stadtfeld M, Yachechko R, Tchieu J, Jaenisch R, Plath K, and Hochedlinger K (2007) Directly reprogrammed fibroblasts show global epigenetic remodeling *Cell Stem Cell* **1**:55-70

Okita K, Ichisaka T, and Yamanaka S (2007) Generation of germline-competent induced pluripotent stem cells *Nature* **448**:313-317

Takahashi K and Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors *Cell* **126**:663-676

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, and Yamanaka S (2007) Induction of pluripotent stem cells from adult fibroblasts by defined factors *Cell* **131**:861-872

Wernig M, Meissner A, Foreman R, Brambrink T, Ku M, Hochedlinger K, Bernstein BE, and Jaenisch R (2007) In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state *Nature* **448**:318-324

Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukin II, and Thomson JA (2007) Induced pluripotent stem cell lines derived from human somatic cells *Science* **318**:1917-20