This response was submitted to an expert consultation held by the Nuffield Council on Bioethics on *Novel neurotechnologies: intervening in the brain* in February 2012. The views expressed are solely those of the respondent(s) and not those of the Council.

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1. Please briefly describe the neurotechnology or neurotechnologies you are working with and the nature of your research. Please also describe whether you do basic/translational/clinical research.

We are researching factors that act in or on neural stem cells (NSCs) and their derivatives in the embryonic and adult NSC niches. In theory, such factors (or their agonists and anatagonists) could be used to aid regeneration and repair after trauma or disease in the CNS. They could be used to stimulate proliferation of the NSCs or progenitor cell types, and/or to direct differentiation (and survival) as appropriate (into specific neurons and/or glia). They could be used to manipulate either endogenous cell populations or cells after transplantation. We have evidence that at least one of these factors is important for regeneration of the niche.

Our research is mostly basic, where we are uncovering novel factors and their mechanisms of action. However, we do work in collaboration with others on a more translational project, where we are exploring the use of these factors to treat stroke, either directly or in combination with (more or less sophisticated) artificial NSC niches that we are trying to make in vitro and then introduce into stroke-damaged brains.

2. What, if any, are currently the main clinical applications of this technology?

There have been many pre-clinical and several clinical trials where NSCs have been introduced into patients with the aim of treating disorders such as Parkinson's disease and trauma such as stroke. For example, there is clinical trial going on at present in Scotland using pure populations of NSC grafted into the brain as a potential treatment for stroke. This is currently a safety trial, following experiments in animals (mostly rats) where functional benefit was obtained. However, from the animal studies it is not clear how it works as few of the introduced cells survive and give neurons. Our experiments are aimed at finding ways to improve on this work and to promote more substantial and longer-term repair. However, I stress that we are still many years away from any clinical applications.

3. What clinical applications of the technology do you envisage *in the future*? (Please try to specify a timeframe for these developments)

The technology could in theory be used to treat a wide range of conditions where the CNS is damaged by disease or trauma.
I cannot give any sensible timeframe. We are still at a very basic level in our research.

4. What are, or were, the main barriers to overcome in translating your research into the clinical application(s)?

One significant issue to be addressed is whether rodents are a sufficiently good model to test methods relevant to humans when dealing with the CNS, or if larger animals (sheep, pig, etc) or non-human primates will be beneficial or even essential.

5. How could the technology you work with help address unmet needs of neurologists and psychiatrists?

I am not sure it could, but we will probably need their input if we ever get to a clinical trial.

6. What do the technologies currently cost, and will it be possible to include them as part of regular service in the NHS? If not, what are the likely markets or funders?

No idea !
Introduction of chemicals or proteins into the CNS can be a challenge, but far less than introducing cells. The latter would almost certainly involve surgery and as such be at least as costly as any personalized treatment of this type. However, costs of performing the treatments need to be balanced against the costs to patients and the economy in general of not performing them. If the treatment allows patients to care for themselves and especially if they can resume productive working lives, then of course they will be cheaper than alternatives in the long run and should be adopted by the NHS.

7. Are there currently any non-medical applications of this technology? How far have these been researched and developed and commercialised? Are devices you work with available on the internet/direct-to-consumer?

Not yet.

8. What non-medical applications of the technology do you envisage *in the future*? (Please try to specify a timeframe for these developments)

In particular, the in vitro artificial stem cell niches could be used to screen for beneficial drugs and against toxicity, etc.

9. Are there any unexpected or unintended effects of the technology, and if so, how frequent and serious are they? (Where applicable, please include clinical and non-medical applications)

Too early to even guess.

10. Is there anything in your area of research and development that you find particularly problematic? Where do you feel you need more guidance? What is there in the way of guidance for these problems already?

It is a very ambitious project. The biggest problem is finding money to support the research, especially as it involves several labs in the UK and in the USA.

## Questions if you work with patients

11. In your experience, what do patients and/or users expect from the technology?

12. What risks are patients and/or users willing to take, and why?

13. How well-informed are patients and/or users about the technology, and how helpful is the notion of informed consent in your experience? What happens if patients lack the capacity to consent?

14. After an intervention: are expectations of patients and/or users regularly met?

## Broader questions about the field of novel neurotechnologies

15. If you consider the whole field of novel neurotechnology development, what advances do you believe are possible over the next ten years? What aspects (e.g. material technologies, theories of underlying mechanisms and pathways, treatment targets) of today's novel neurotechnologies will be with us in ten years' time?

The fields of stem cell biology, tissue engineering and regeneration are advancing very rapidly. They all offer huge potential, especially when combined together. However, much of what we learn is how ignorant we are !
I am therefore very loathe to speculate on advances (although we will definitely make these and learn a lot more), especially about treatments and when these will become available. It can take 5 years just to get a paper published in a good journal – in most cases it is going to take far more than 10 to get anything into people.

16. Looking at the whole field, what are the main challenges/barriers in the innovation trajectory from idea to bedside/ market for novel neurotechnologies, and how could these be tackled?

Good animal models.
Animals containing human material (genes or cells) can more closely mimic the human situation.

17. Recently concerns have been raised about the regulatory regime for medical devices both in the US and in Europe. What are your views on the current regulatory regime for novel neurotechnologies in your region, and in what ways, if at all, do you think it needs to be improved?

Regulation is very important, notably to retain public trust in science and clinical practice. But there is a lot of needless bureaucracy, which adds time and expense to any project. The level of bureaucracy is often far in excess of the risks, especially when the needs of patients is taken into consideration. This tends to push trials to countries that may have less red tape, but also with lower ethical standards. Simplifying the regulatory requirements does not necessarily mean a lowering of standards.

18. Could there be a need for more regulation of novel neurotechnologies *in the future*; and if so, what should this permit, prevent, and inspire?

I am sure there will be, but it has to be done in proportionate manner. Regulatory systems where experts (in science, law, ethics) decide provide a much better process than having prescriptive laws.

19. Advances in neurotechnologies raise a lot of interest and many hopes. Do you believe that there is 'hype' surrounding these technologies? If so, how can we distinguish between the 'hype' and the reality? And who is responsible for creating the hope and for managing the hype?

Yes, there is hype – but there is also hope. The former is inevitable given the highly competitive nature of science funding and publication (which are linked), and the pressures put on scientists and clinicians (by their employers, grant givers, etc) to be seen to be doing high impact work. It is too easy to blame journalists, and of course there are occasions when it is their fault, but more often it will have been something the scientist/clinician has said that will prompt this. For example, the frequent and obvious, but rather stupid question about "how long will it take to get to the clinic ?" (as asked above) will almost invariably lead to hype. But it is the very nature of scientists to be optimistic. Better understanding of the scientific process and of the pitfalls of translational work, by the public and by (non-specialist) journalists would help.

20. What do you think are the main social and ethical concerns raised by novel neurotechnologies and their applications?

There are many, depending on the type of intervention, and the route by which they are developed.
For example:
The use of inappropriate animal models.
The use of appropriate animal models when these are non-human primates.
If it is a drug, and therefore simple to take, then what are the effects on "normal" people and can this lead to abuse.
If the technologies are invasive and involve cells or genes or devices (or combinations of these), then (a)

they are likely to be expensive and this leads to questions of social justice (do only the rich benefit ?), and (b) can they be extended to alter personality, etc, and in what way ? (Frontal lobotomy was once commonly practiced as it was thought to be beneficial to patients).
If the technologies can lead to enhancement, will employers – or even societal demands – put undue pressure on individuals to use them ?

There are also issues surrounding clinical trials and consent. For example:
In clinical trials, what are the appropriate controls when invasive brain surgery is involved ?
For toxicity studies in trials, drugs are often tested on healthy volunteers. But is this OK when a drug is expected to enhance neurogenesis or brain function ?
If brain function is adversely affected by the disease or trauma to be treated, how does this affect the patients ability to give consent ?

21. Who do you think should be the target audience for a report on the ethics of novel neurotechnologies that intervene in the brain? If the Working Party developed direct recommendations to any particular groups or institutions, who should they be in your view? What would you like the Working Party to recommend?

Target audience: Policy makers, but also the public.
Recommendations should be aimed at those who can do something about them ! This includes scientists (perhaps via the relevant academies), clinicians (via the Colleges), and politicians.
The recommendations should include:
(i) More/better public engagement.
(ii) A robust, but well-informed and flexible regulatory process.