[1]: For Services Rendered:

E. Fisher

23/02/16

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The Department of Cell and Systems Biology
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25 Harbord Street, Toronto
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1st May 2016

Dear Prof Sylvester Grant,

As per our original agreement, circa 2009, this letter is to thank you for services rendered to us here in the reconfigurable biomedical engineering group. Suffice to say, your input has been invaluable and your technical insights to the drug have been truly inspired. We continue to work with your younger colleagues in London since your retirement and wish to offer you continued visiting professor status within our group.

Each of us here value your continued input as CFO as we commercialise the drug. Its development, we are sure, could not have been completed, to the sheer degree of its effectiveness without you. From a personal level, please treat this letter as your formal invitation to visit as you will, as I'm sure you are as excited as we are with relation to the recently formalised Glaxo-Smith-Kline interest in the drug. Having said that, I'm sure you'll agree their prospective marketing/brand name, Erebus, (*shadow*), leaves much to be desired.

While I'm sure you have read our recent paper, Clinical Trial Results of a Neuromorphic, Adaptive Treatment for Alzheimer's and Parkinson's Neurological Disorders, Nature Medicine, Jan 2015, we accept that being retired you are likely to have far better things to occupy yourself with, now that your free from the bonds and restrictions of modern academia. In case you haven't read it, I'll give you a brief summary of our progress and the reasons for GSK's interest and ultimate financial backing.

The performance of the drug is unparalleled, but alas it comes at a cost. We had previously discussed that it doesn't correct or reverse neurological degradation, instead it masks the outward symptoms and cognitive decline by increasing the action potentials and firing rate of already present neurons. Mouse trials showed an increase in neurological function in those undamaged cells to the tune of 150

The costs of the drug, as you know, may well be the stumbling block in future commercialisation. That, and the public's detest for anything that could, incorrectly, be perceived as a form of eugenics. While the mouse trials have showed radical improvements in the outward symptoms, the trials failed to show the extent of the life-expectancy reductions, as evidenced by monkey trials. These reductions are typically caused by brain cell death under two conditions, a) removal of the drug or a reduction of dose and b) that continued exposure acts to irreversibly polarise the Potassium distribution of the synapses involved. We are confident that future work can alleviate these factors to some degree, however we suspect a fundamental limit to the effectiveness of any approach to improving these factors.

To reiterate our in-house discussions, for your benefit and indeed the benefit of all of us involved in the drug's development, this drug will come at a significant cost to the human individuals that choose to take it. As such, we will be making the technically-motivated suggestion that GSK a) rename the drug away from the ancient Greek's representation of the personification of darkness, and b) that the drug only be made available to individuals that explicitly and legally exorcise their free-will and chose the drug, with full knowledge of the facts.

While small, the ongoing, unpublished human trials have prompted further interesting developments. At a rate of 25% of the trial's participants, there is a diminishing of the drugs effectiveness depending on the historical cognitive abilities of the patient. While this result is disappointing, it appears that the drug does not have the same life-expectancy shortening effect, despite the same dosages involved. We therefore concluded, subject to further human clinical data, that the drugs action on the neuronal tissues, i.e. increased firing rates and increased potentials, is directly related to the activity of those neurons in the past. While not clinical evidence, the work of one of our junior post-docs has showed that this is indeed the case on test neurons that have been artificially held at their maximum firing rate for 7 days prior to the introduction of the drug.

Suffice to say I'm conflicted. On one hand we have a solution to a significant medical and societal issue, but on the other we have a solution that effectively proceeds upon a eugenics line. Through personal discussion with colleges in our Philosophy and Ethics department, I'm confident that the requirement we will impose of free-will, fully-advised choice, is the only course of action.

As a personal friend, and valued colleague I would ask for your advice and technical insight into the issues from all levels of its development. In the meantime, I do hope that your retirement has been enjoyable. I'm sure this letter will be a refresher from your new lease of life, I can only apologies that its content is rife with rather difficult philosophical issues in our quest for a lower rate of cognitive decline in the over-85 demographic.

Your friend and diligent colleague,

Dr Bertram Richards

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13th August 2016

Dear Dr Bertram Richards,

My retirement is as expected, a relaxing environment, superb weather, but a slight dose of boredom. I relish the thought of visiting, if only to get back to the lab, or at least get back to research. In some ways I envy your progress and current research activities. However, at the same time I see your points, hardly the result we expected when we started this collaboration.

Before we go on, I must break some unhappy news. Now normally, as a typically introvert academic, I'd have declined to disclose these details, but alas being a friend now for over 20 years I feel I must...

Both myself and my wife have been diagnosed with Alzheimer's. It has been caught early in both of us and we are of course on the UK's currently available treatment regime. I'm afraid this is the principal reason for my severely late reply to your letter. The last three and a half months have been difficult from both a personal level and, in all honesty, I have indeed been mulling over the ethical ramifications you alluded to in your May letter. I am actually quite glad the prognosis was not cancer, with your letter there seems to be at least a little more hope for a dignified end.

Now, as I've dispensed with that rather unpleasant detail, I can get to the technical matters we need to discuss. Firstly, congratulations on the results of the trials and indeed the lab work of your post-docs. Congratulations too on being one of a handful of modern scientists that actually consider the ethical issues with respect to their work. We truly do live in a world where our ancestors would have described us as playing God. But thank God your showing some of the forethought I saw in you right from your student days.

Hmm, so tackling the philosophical issue first, if we are even able to. I agree the public may well shun this drug and I very much agree the name must be well thought out. GSK may well progress with commercialisation despite of these issues, and I know my younger colleague, Dr James Masters, has taken on the mantle of being the chief financial officer. For that I am glad. From the delay in my letter and the bouncing emails I've been cc'd on, I can tell that commercialisation is proceeding well. GSK's offer at the start of this month is very worth considering. My gut feeling would be to take it, not just from a rather selfish perspective of wanting it on the market and hence available to me and my wife in a few years, but also to finance the required future work.

From a philosophical perspective, in which I'm hardly the expert, do not underestimate free-will. In my opinion if someone makes the choice to take it, in full possession of the facts, then that is their prerogative. Free-will must be respected, and for my own part, I'd gladly take a shortening of life if I knew that my later years would be free from the frustration and heartache of losing ones marbles! Eugenics does concern me, there truly is no course of action other than complete transparency and putting it forward in a simple, logical manner. The effect, that it is only effective if the neurons had previously been well utilised, is in itself quite logical. We should trust that reason and thought are in the minds of the patient when making their decision to take it. Having said that, I'm very glad to hear it has little negative impacts if the patient doesn't have the correct, how shall we say it, cognitive background.

My suggestion would be to not only inform the patients, but also to restrict when the patient is able to make this choice. As I mentioned, if we are relying on free-will to abate the ethical issues, the patient must be able to exercise that free-will with a sound mind. I would then suggest to GSK that only sub-60 year olds and critically those with no shred of any of the common symptoms are able to make the choice. Clearly a sub-60's demographic to the over 85's demographic is quite a number of years. This works to our advantage as, (as you said they would need to explicitly and legally state their choice), the choice would be in their will for over 20 years. One would hope that that is sufficient time to allow any amendments to be made, despite the costs of modifying one's will.

Now, from a purely technical side, and I'm sure you've already thought of these in during the delays to my return letter, I have some ideas to throw at the polarisation and previous neuronal activity problems. Firstly, I must say, superb paper, I still have access to the university's subscription to the journal. It was quite some read. We must however get more data, and if possible pressurise GSK to allow publication of results. The technical progress is simply too good for its evidence to be locked away in some GSK archive hard drive, never to be read by future experts in our field.

For the previous neuronal activity issue, it seemed your post doc had good results with a relatively short pre-dose stimulation regime. Taking this as a guide, could we investigate the possibility of a) direct brain stimulation as a weekly add-on to the weekly doses of the drug, and b) ensure that public policy and outreach really hits home that everyone should exercise their brain as much as their body. One would also look into the use of chemical stimulants as at least an initial booster to neuronal activity before and during the administering of our drug. Ultimately the issue is one of time to market. Of course this presents an issue for today's 85 year-olds but if time to market is 5 years anyway, that gives 80 year-olds 5 years to improve their cognitive activities themselves. With time one would hope the availability of the drug would prompt people to think more about their future.

The polarisation of neuronal cells does concern me. It is worth asking within the imaging departments to see if the resulting apoptosis is indeed related to polarisation. In the world of electrical impedance spectroscopy of cells, electrical stimulation is AC-coupled or purposely chosen with a 0V DC bias in order to prevent polarisation on internal cell ion distributions. With this in mind, please ask your post-doc to DC-bias his experiment in the reverse spatial direction to the observed cell polarisation. This ultimately would be difficult to achieve from a practical, human-brain clinical perspective but we must start from somewhere, and a simple experiment such as this may illuminate matters somewhat.

We must remember that polarisation is fundamental to the operation of the synapse, so I take it we are talking a level of polarisation where by the receiving dendrites are saturated. Hmm, OK, I see the issue. We know the drugs action to increase action potentials, and of course the higher the voltage across a dielectric the higher the stored ions and hence polarisation on

either side of that junction. Is it worth investigating a) methods to separate the action potential increase from the increase in firing activity and b) sweeping the dosage of the drug using your post-doc's laboratory setup to assess the relationship between increased neuron activation and the eventual degree of polarisation. One would expect that a reduced drug effect, would incur a lower polarisation amplitude, although of course if we restrict this to polarisation amplitude to be less than the saturation level, the half-life of the drug's effect may be very poor.

For now, lets keep in touch. Again my apologies for the delay in my letter, I must visit soon. In the meantime, myself and my wife are in good health, good spirits and the current regime of treatments has its own good track record. Don't be hasty to write me off just yet, I'm only 65, with plenty of time left before I need to consider more problematic intervention. I will be attending the symposia in Boston in September, I do hope to see you there. Its been a long time since we spoke in person. I do miss our, at times lively, interactions.

All the best, and next time not so formal, As per our original agreement..., this letter is to thank you for services rendered. Please, now that I've retired, treat me as your friend first and your old professor second.

All my best, my friend, from my retirement retreat in the sun...

Sylvester (not Prof, bla, bla, bla)

The End...