Podcast Interview: Fred H. Gage

Fred (Rusty) Gage was elected to the National Academy of Sciences in 2003 for his work in systems neuroscience. At the Salk Institute, his research concentrates on the adult central nervous system and the plasticity and adaptability to environmental stimulation that remains throughout the life of all mammals.

Interviewer: Hello, this is Kaspar Mossman. Today we’re speaking with Fred Gage, a Professor in the Laboratory of Genetics at the Salk Institute in La Jolla, California. In this program, Dr. Gage talks about his connection with the legendary Phineas and explains how in the future stem cells may be used to treat Parkinson’s disease.

Are you really called Rusty?

Dr. Gage: I am really called Rusty, by, by friends but I also have been called that for many, many years. I was called Rusty by my family, because I’m Fred Harrison Gage the third, came up with a nickname and I had sort of rusty hair, I suspect, when I was very young.

Interviewer: And another thing that I just have to ask, are you in fact a descendent of Phineas Gage?

Dr. Gage: So, my grandfather was an amateur genealogist, collected all this data, and he, I was tracking down one of my relatives in New Hampshire, whose name was Phineas Gage. I have letters from him to the Harvard Museum of Anatomy where the tamping iron and the mask is of Phineas Gage. So we have some documentation in his genealogy. Now, I don’t have any genetic analysis of that!

Interviewer: What kind of diseases might we be able to treat with stem cell therapy?

Dr. Gage: I’d like to start off by just distinguishing between two different types of uses of stem cells. In one is the idea of transplanting, restoring cells to areas of the brain where damage or cell loss has occurred. But the other, most strikingly, is that human embryonic stem cells can be grown in culture and they can be induced to become neurons. And one can then either over-express a mutation in those cells and monitor how they differentiate, or take skin biopsies from patients and dedifferentiate their cells into embryonic cells and then differentiate them into neurons of the type that die or are damaged as a function of the disease. In so doing, one is really studying the development, the time course, of this disease in culture in ways that you really can’t do this by looking at a patient who’s diagnosed with a disease, really the disease that they have is already there. And I must say that I’m as, I’m more optimistic, actually, of developing therapies in a very generalizable way using these human embryonic stem cells as biological assays for human disease as I am transplantation.

Interviewer: How would you carry out an operation to inject or transplant cells into the brain or spinal cord?
Dr. Gage: Now I need to make another distinction, if we’re into the transplantation strategy. So there are embryonic stem cells. People are attracted to this because these cells can give rise to all cells of the body, therefore they have the potential for giving rise to all cells of the brain, which means that they could potentially be used in substitution for different diseases of the central nervous system. But there are other neural stem cells from fetal tissue, so from aborted fetuses or from even cadavers, where one can harvest, not embryonic stem cells but adult or post-natal or pre-natal neural stem cells. But if we just focus on the embryonic stem cells for a second, it’s unlikely that transplanting the embryonic stem cells directly into the brain is going to be a viable option because they can give rise to every tissue and they may give rise to hair and stomach and other kinds of cells in the brain.

Let’s take one disease in particular: Parkinson’s disease. Very selective neurons in an area of the brain, called the substantia nigra, that makes dopamine and sends it, these neurons in the substantia nigra, send their processes up to an area that is involved in the initiation of motor behavior, called the basal ganglia. Now, these dopamine neurons in the substantia nigra, they die progressively with the disease, and this was thought of initially as a really pretty good target for transplantation because perhaps just transplanting more of these cells that could give rise to dopamine cells might be a useful strategy. But there’s two sides to this. One is how mature do the ES cells have to be upon transplantation so they know or can respond to the brain and fully differentiate into these functional dopamine neurons? And on the other side, where do you put the cells? Do you put them into the substantia nigra or do you put them into the target area where the substantia nigra releases its dopamine? And as a result of a lot of work that’s been done before, using human fetal, aborted fetal tissue, and really a lot of experimental animal work, transplanting cells into the substantia nigra is not as effective because these cells, in the context of the adult damaged brain in particular, these cells don’t grow up their processes into the basal ganglia where they can, can release dopamine in the appropriate place. So people have instead implanted the, what we call dopamine precursors or dopamine, immature dopamine cells, into the basal ganglia itself, where the evidence is pretty good that they survive and can release dopamine and have some impact on the diseased basal ganglia.

So how would this be done with regards to embryonic stem cells? Well, these studies are underway in animals and are certainly being thought about for humans with the idea we would take embryonic stem cells and the idea would be to take those immature cells and differentiate them up to a state where they are already committed to become dopamine neurons but haven’t fully differentiated, so they don’t have all their complex processes, and transplant them at a time where they’re already committed but not fully differentiated and then implant them into the basal ganglia, which is the target area where the dopamine is released. And the idea is that this would be a source of cells to replace or reduce the need for L-dopa, which is currently the therapy for Parkinson’s patients. So that’s just one example. Now, in a more refined way, we’d be using the re-programming strategy where you would take a patient and take their own skin and reverse them into embryonic stem cells and then make them into the same dopamine precursor cell and transplant. In that case you’ve really obviated the need for immunosuppression, because it’s the same patient’s own skin. The problem there that we don’t know a lot about is if that patient has Parkinson’s disease, or other neurological disease, how do you know that those cells that you’re transplanting won’t also carry in with them the disease? And that’s just a, frankly an unknown currently.
**Interviewer:** Dr. Gage is Professor and Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases at the Salk Institute.