BRAIN SCIENCE PODCAST

with Ginger Campbell, MD

Episode #61

Interview with Dr. Allan Jones

Chief Scientific Officer of the Allen Institute for Brain Science

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INTRODUCTION

"On any given day we have approximately a thousand researchers from, really around the globe, come and access the data that we've created, as well as the tools."

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This is Episode 61 of the *Brain Science Podcast*, and I'm your host, Dr. Ginger Campbell. Today's episode is an interview with Allan Jones, the Chief Scientific Officer at the Allen Institute for Brain Science in Seattle, Washington.

If you are new to the *Brain Science Podcast* I want to welcome you, and also explain briefly how the podcast is organized. I call it 'the podcast for everyone who has a brain' because my goal is to create a show that can be enjoyed by

everyone, not just scientists. This means that the show has a very diverse audience, which is why I try to vary the content from month to month.

Last month's episode about play is an excellent episode for new listeners. This month's episode will be of particular interest to young people who are contemplating a career in science, and to those of you that are interested in how science is actually done.

As always, detailed show notes and an episode transcript will be available at brainsciencepodcast.com. And you can write to me at docartemis@gmail.com.

I will be back after the interview with a few brief announcements, and I will announce this month's book winner.

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INTERVIEW

Dr. Campbell: My guest today on the *Brain Science Podcast* is Allan Jones, the Chief Scientific Officer for the Allen Institute for Brain Science in Seattle, Washington. Allan, it's great to have you on the show today.

Dr. Jones: Thank you.

Dr. Campbell: The focus of our interview is going to be the Allen Institute for Brain Science, but I was hoping you would start out by telling us a little bit about yourself and how you came to work at the Institute.

Dr. Jones: OK. I will go back to my research career, which started back working as an undergraduate at Duke University. I was actually a very eager student who wanted to work in a lab desperately, and I ended up working in the lab that worked on *Chlamydomonas*, which is a little unicellular green algae.

The project that I got started with working in that lab was what was called a biolistic transformation. They were just developing some new technology in which they would shoot a gun onto cells—basically on the little tiny particles that were coated with DNA—and they would transform those cells. And specifically they wanted to transform, or make a transgenic *Chlamydomonas* green algae—so transforming the chloroplasts.

That was a lot of fun. I worked there. I did some *E. coli* work, and then ultimately ended up going to graduate school in Washington University in St. Louis. There I worked on *C. elegans* (I think you recently had someone on your program who works on *C. elegans*)[1] and I did developmental biology there. So, again, working on these model systems.

C. elegans is a little tiny 1 mm long nematode worm, and it's a great model system for doing genetics and understanding problems in developmental biology. I did my PhD thesis on developmental biology in *C. elegans*, and then moved to The University of Pennsylvania, and worked on a plant model system which is called *Arabidopsis thaliana*. It's a little tiny mustard plant, and it's also a model system for studying plant biology.

I was doing developmental biology there, and then I did a little change of course and ended up working for a biotech company in the Philadelphia area in the suburbs. That gave me, I think, a unique opportunity to go work on something very different in a much more applied way. And I really fell in love at that point with a sort of biotech approach: a sort of very driven—good resources applied to problems—but always driven in a very focused way.

I ended up after that out in Seattle working for a company called Rosetta Inpharmatics. This was a technology development company that was developing

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[1] Episode 59 was an interview with Guy Caldwell, PhD from the University of Alabama. Dr. Caldwell studies the dopamine neurons in *C. Elegans* with the hope of curing Parkinsons's Disease.

microarray technology. And so, the technology that we were developing was an adaptation of an ink jet head. Rather than spitting out the colors that you normally do in an ink jet printer, it actually spit out the letters of DNA (A, C, G, and T) and you would be able to synthesize onto a glass surface various DNA molecules and use those to read out the levels of genes that are turned on—RNA molecules that are turned on—in the cell.

Rosetta happened to be acquired by Merck Pharmaceuticals. I guess that was around 2001 or 2002. And so, I got an opportunity to actually work for a big pharmaceutical company. And that was very interesting and very eye-opening to see all the challenges of how these large companies try to get something that's therapeutically valuable from an idea into something that you can actually put into humans and have work in humans.

From there I got a lot of experience doing more of the business side, the management of projects. So, I moved much more away from the bench and into the management of projects. And in 2003 I ended up being able to take that information and apply it towards a new project that was just getting going, which was the Allen Brain Atlas.

So, that sort of takes us up to my time at the Allen Institute. And I was hired originally as a research alliance manager. I eventually became the project director of that project, and then subsequently was moved into a role which is titled Chief Scientific Officer.

Dr. Campbell: So, you probably saw yourself as being a bench scientist when you started your career. You probably never anticipated being where you are now.

Dr. Jones: I think that's pretty safe to say. At least when I started my career I was thinking that an academic track was what I wanted to take. But I ultimately

found out that I seem to have a good skill set for doing more of the business side, and also really enjoyed it.

Dr. Campbell: Well, I'm glad to know that you really enjoy it, because that's important. I'd hate to think that you've gotten away from what you really wanted to do.

One of the things I do on my podcast in talking to various different scientists is I give them a chance to let listeners know what their line of work is like. I have students that listen, and it's good for them to get an exposure to different kinds of science careers. We'll come back a little bit to that near the end if we have time, I hope.

Dr. Jones: OK, great.

Dr. Campbell: There was a request from a listener that I do something on the Allen Institute for Brain Science, so that's why I contacted them. All I knew before researching was I had this vague knowledge that the Allen Institute for Brain Research had been started by Paul Allen. But I didn't really know anything about it. So, let's just start from there and let you tell us the story of how the Institute got started.

Dr. Jones: I actually wasn't involved in the very early planning stages, but I can tell you the story as I know it. Most people probably know of Paul Allen. He was one of the co-founders of Microsoft. He left Microsoft in 1983—so actually quite a long time ago—and has been pursuing lots of different interests since then.

People may know Paul from his sports interest. He is the owner of the Seattle Seahawks and the Portland Trailblazers. He is part owner of the Seattle Sounders, a new soccer team here.

He's also interested in Jimi Hendrix, and rock and roll memorabilia, and also science fiction memorabilia. So, right here in Seattle there is an Experience Music Project, as well as a science fiction museum. He has gotten into restoring vintage World War II aircraft, and so there's a place called Flying Heritage which is set up here in Seattle. He's had this wide variety of interests.

And when he gets interested in an area, he typically convenes a group of experts. Now, how he got interested in brain science, I'm not entirely sure. It's a question for Paul. But I think around 2001 he convened a group of scientists, broadly challenging them with what could be done in the field of neuroscience that would be of great impact, that might change the field in some meaningful way.

And he likes to approach the problems in that way—throw that out to the experts and have them suggest different interesting ideas. If you'll recall, the genome projects were sort of declared finished in the early 2000's. So, you've got this stage in history where for the first time we have the genome sequence of the human and of the mouse.

So, the project that was thrown out there was, OK, if we know the what—we know the genome now; we know the letters of our genetic code—let's talk about the where. Where are these genes actually turned on to create something as complicated as the nervous system or the brain?

So, in 2002 a group was convened to actually figure out how to do this. Early in 2003 official hiring began for a project to actually execute on a project. It was decided that we were going to start with the mouse. There were a number of reasons for doing it in the mouse first. The mouse brain is a lot smaller than the human brain.

The goal was always to do the human brain. But we started out with a mouse. The goal was to create a project that would systematically investigate where all of

the approximately 20,000 genes in the mouse genome are turned on in the adult mouse brain. And so, we systematically set about doing that with getting operations set up in Seattle in early 2003.

Dr. Campbell: And I guess one of the things we want to say up front is that all this information that's being generated is being made freely available. Right?

Dr. Jones: Yes. One of the really exciting things about this place—and again, coming from academic research, and a number of our staff who also come from various different environments—it's that great public-facing mission that we have.

So, not only do we get to bring to bear a lot of great resources towards a very interesting scientific problem, but we get to really make a concerted effort to make sure that the data is free and available to anyone throughout the world who wants to use it. And we create a lot of effort in terms of making sure that those tools are user-friendly and that the data is of the highest quality.

Dr. Campbell: Just to summarize where we're coming from, the goal is to be able to tell at any point in the brain—both of the mouse, and then eventually the human—what genes are turned on.

Dr. Jones: Yes. So, most listeners to your show are probably very familiar with this concept that the place in the brain is linked to function. So, you're doing functional imaging studies where a specific part of the brain is turned on.

The brain is really all about those functional divisions, and it's very important to understand how those functional divisions relate to the underlying biochemistry of those places. The underlying biochemistry of those places is driven by the genes that are turned on in them. I'll leave it at that, and if you have more follow-up questions we can go from there.

Dr. Campbell: Then, for example, this would mean that if we knew what genes were active in a particular place, then it might give us clues such as clues about genetic components of brain diseases?

Dr. Jones: Right. So, specifically, let's take something like the striatum, for example, which degenerates in Parkinson's disease. One of the first things that people did was to look for genes in the mouse brain that were turned on in that particular part of the brain. They were specifically looking for genes that might be amenable to biochemical manipulation through pharmaceutics.

So, there are things that are called G protein-coupled receptors. They're a kind of protein that sticks out on the outside of a cell, and when they receive a signal they turn on a signaling cascade within a cell and change the activity of that cell in some way.

Dr. Campbell: I'm sorry, was that G protein-coupled receptors?

Dr. Jones: That's correct. We call them GPCRs, and there are a number of drugs that are already out there in the market that target G protein-coupled receptors. And so, pharmaceutical companies, for example, really look for these kinds of molecules and say are they turned on in some interesting part of the brain that we'd like to try to modify the activity? That's just an example of the kinds of things that people would want to go into this data set and start looking for—things that might give them a handle on manipulating it, or might give them a really unique way of reporting.

For example, in the mouse you can go make a transgenic animal, and if you know a gene that its expression is restricted to just a particular subset of cells that you're interested in—you're interested in understanding a feeding circuit, and there are some cells in the hypothalamus that you know are involved—you might go through our Atlas and try to find something that is very specifically turned on

in only those cells, or in a subset of those cells, and then make a transgenic animal that drives some reporter of activity. Perhaps it's a fluorescent reporter or perhaps it creates a toxin receptor that allows you to selectively eliminate those cells from the circuit and see the effect. So, it's a very powerful tool for being able to do follow-up studies in the mouse.

Dr. Campbell: Would you mind defining what a transgenic mouse is?

Dr. Jones: Sure. The technology has existed for many, many years. I think Nobel Prizes have been awarded for this technology of being able to get an exogenous gene—some sort of gene that you have cloned outside of an animal—and actually put it back in and integrate it within the chromosome of an animal. In this case it's in the mouse, and the mouse is the most mature technology.

So, by making a transgenic mouse what you've done is you've put something in there that maybe allows you to turn on a foreign gene, a protein, a fluorescent tag, that will enable you to further your research goals, whatever they might be. The nice thing about a transgenic animal is, once you've created that animal through breeding you can distribute more of those animals out to other researchers.

Dr. Campbell: So, it doesn't necessarily mean that the component you've added into the DNA is not a mouse gene. It could be something in the mouse that you've manipulated, or it could be something from another species?

Dr. Jones: Correct.

Dr. Campbell: OK.

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podcast. If you aren't already a member you can get a free download by going to audiblepodcast.com/brainscience, or by clicking on the ad at brainsciencepodcast.com.

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Dr. Campbell: I want to talk about why the mouse. But before we do that, could you just explain how you're doing your project of how you figure out which genes are turned on?

Dr. Jones: That's a great question; and it's worth walking through a little bit of the technology. There's a process that was invented probably about 25 years ago. It's called in situ hybridization. And genes themselves are encoded by DNA and they live on our chromosomes. When a gene is turned on it needs to put forward a message that it's turned on, and it does that by a process called transcription.

Transcription is when a gene gets turned on and it gets transcribed from being this double-stranded DNA nucleic acid in the cell into a single-stranded molecule which becomes the message. That single-stranded molecule is called RNA or mRNA, and that's the thing that we read out when we're looking at gene expression, or when a gene is turned on.

That RNA molecule is a single-stranded molecule, and there's this nice property of nucleic acids where, once they find a complementary sync to them, they zip up and form a helix. Most people are familiar with the DNA helix, I think. When you have an RNA molecule it doesn't have a helix partner. But we can actually create synthetically a helix partner for that RNA molecule for any gene that we want to detect. We create it synthetically, and when we create it synthetically we actually incorporate a little chemical tag into it.

Then we can take brain tissue—and this is human brain tissue, or mouse brain tissue, or mouse spinal cord tissue—and we cut it very thinly, and we put it on a

microscope slide. When we slice this tissue very thinly it allows us to then perform this in situ hybridization process where we take that synthetically tagged RNA molecule and we hybridize it, or put it in liquid and let it find its counterparts within that tissue within the cell.

After we've done that and it has found its partner and it has made a helix in that tissue, then we build up the signal from that chemical tag that we incorporated into it. That chemical tag provides a little handle, and we build up the signal where we ultimately end up with a dark purple precipitate—or in some cases we can use a fluorescent tag—to basically tag where that gene is turned on in a particular cell.

Dr. Campbell: The more tag you see, then that means the more active that particular gene is?

Dr. Jones: Correct. And so, then what we've done is we've serialized that entire process so we can do that over and over and over again in a very sort of high throughput way, and that allows us then to very systematically go through and do a gene-by-gene investigation.

We started out first by doing the adult mouse brain. We've done projects using the mouse spinal cord, the developing mouse brain, and more excitingly, recently there has been a lot of work on the human brain—on postmortem tissue from the human brain. First we've been doing parts of the human neocortex , and we're gearing up to do the whole human brain.

Dr. Campbell: That's really exciting. I mean that's going to be an incredible database for researchers.

Let's go back now, if you don't mind, and talk a little bit about the mouse brain and why you started with the mouse.

Dr. Jones: There are a number of reasons to start with the mouse. First, the complexity of the system. It's a lot more simple system to deal with. It's a much smaller brain. The technology needed to be worked out to do that.

The other thing is that with the human we're not able to use the same technology at that level and scale to do everything. The human brain is just simply too big. But we can do it in the mouse. We can look at all the brain structures, and be very comprehensive, and look at all the genes at a very fine level in the mouse.

In the human we're going to be tissue-limited, but we're also limited by the sheer size of it. In the human there are approximately 20,000 genes, just like in the mouse. But we're probably going to be able to look at between 100 and 500 of those genes within any given structure, as opposed to the mouse, where we could do all of the genes. So, part of the reason was the scale.

Part of the reason is that the mouse, again, is a great model system. Let me explain a little bit why it's a great model system. Of all the brain structures that the mouse brain has, it has all the same structures, by and large, that the human has. So, it has a hypothalamus that does all the basic functions that the human hypothalamus does. It has a hippocampus that does all of the basic functions that the human hippocampus does.

So, there are a number of similarities sort of at the brain structural level that are important. And then at the gene level there is also what we call homology, or similarity between mouse genes and human genes. There's a term called ortholog, which molecular biologists and evolutionary biologists use, which means something that is likely to be the same sort of functional counterpart between humans and mice, for example.

And so, in a given ortholog between a mouse and a human there is roughly a 97-99% identity at the amino acid level—meaning that they make very similar

kinds of proteins. What this allows people to do is to use the mouse model system to learn a lot, and then apply that to their study of humans.

Dr. Campbell: So, the Mouse Brain Atlas has been finished for a couple of years?

Dr. Jones: Yes, we completed that project in September of 2006.

Dr. Campbell: So, that in and of itself is a very, very valuable tool to researchers.

Dr. Jones: On any given day we have approximately a thousand researchers from, really around the globe, come and access the data that we've created, as well as the tools. We don't require people to even register to use the data, but from reading the URLs we can understand where people are coming from. So, that's basically every academic institution that you could possibly name.

This is worldwide usage. There has been so much demand for the data that we've had to create a mirror site in Europe, and I think another one is on its way in Asia. And a mirror site is just simply a place where all of the data has been cloned. Every major pharmaceutical company uses our data. Biotech companies use our data. So, it's really been, I think, a very powerful resource for people.

Dr. Campbell: Can you talk a little bit about the surprises that came out of creating the Mouse Brain Atlas?

Dr. Jones: There were a couple of things that surprised most people. There were estimates that maybe on the very high side, 65% of all genes were turned on somewhere in the brain. Our study suggested that that number was more like 80%. So, 80% of all the genes that are on our genomes are turned on somewhere in the adult mouse brain. And we expect a similar number to hold true for the human.

And that means a couple of things. One, our genomes are supporting a lot in a very complex organ, and it just, I think, points out the importance of reuse of different genes for different functions. So, there's a lot of redundancy of use, or a lot of genes that are turned on in multiple different areas.

And that was another thing that I think was kind of surprising to most people in general, was the notion that on a very specific structure you might find something that was highly specific to that structure only. And what we find is that the genes that tend to be specific to one structure tend to be also specific to multiple structures.

What I mean by that is that they might be restricted to a very specific subpopulation in the hypothalamus, but they also might be turned on in a specific layer of the cortex or in another part of the hippocampus as well. So, there were very few cases we could find in which a gene was just turned on in one small subpopulation of cells.

Dr. Campbell: That has important implications for designing things like drugs that are aimed at genes, doesn't it.

Dr. Jones: Absolutely. My take on all of that was a renewed interest in what people are calling polypharmy—this idea that you might need to actually attack problems with more than one molecule to get specificity.

Dr. Campbell: Can you give us an example of how the Mouse Brain Atlas is currently being used?

Dr. Jones: What we typically do is track people who have cited our publication to know how people are using it. So, we've got great examples of just about every kind of brain biology that you can imagine that are citing our papers. These are people studying fragile X mental retardation, these are people that are studying hearing loss, these are people that are studying obesity, these are people that are

studying learning and memory, these are people that are studying schizophrenia or autism.

And each of them is doing it in some slightly different way. Usually what people are doing is they have been doing a particular study and there's a gene that they're already interested in for some other reason. And they want to come see where that gene is turned on in the mouse brain. It gives them some clues. For example, as you just mentioned, if you're understanding that perhaps you want to develop a drug around this, you'd like to see all the regions in which a gene is turned on.

Another thing that people are often doing is, as we've mentioned before, people know a lot about brain function as it relates to a very specific part of the brain. For example, if you're interested in learning and memory, you're going to be very interested in specific parts of the brain in the hippocampus. And our resource allows people to come in and look for genes that can potentially be targeted to those particular regions.

So, we have people who are mining through the data, finding those few genes that really give a very specific expression pattern, or are turned on in a very specific subset of cells. And then they might go build a research program around manipulation of those cells in some way, or understanding better the circuitry that's involved in the process that they're looking at.

Dr. Campbell: What about when people use knockout mice? Would you talk a little bit about how that would work?

Dr. Jones: When you mention knockout mice, just to explain a little bit about that technology. It's similar to making a transgenic animal, but what you're trying to do there is eliminate that gene from the genome, and then you want to see what the effect is. And so, this can certainly be a nice driver of people

selecting genes that they want to knock down the activity to confirm some hypothesis that they might have about the function of that gene.

Dr. Campbell: Yes, I can see that if you actually knew everywhere it was supposed to be active, then that would make a big difference in designing your experiments. I mean before, when they were doing knockout mice, sometimes they didn't always get exactly what they expected, because they didn't know that the genes had such a wide area of activity as you now appreciate.

Dr. Jones: Right. And again, this is the beauty of having such a resource, where you've gone in and looked at pretty much every gene. You can very quickly come in and just look at this resource and say, 'Aha, here's an area where I wasn't expecting this gene to be turned on.'

And there have been, sort of anecdotally, a number of genes where there are things that have been quite well-studied by people, but only studied for a very specific part of the brain. And no one has done something comprehensive where you've gone in, like we've done, and found new areas of the brain where these genes are turned on.

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Dr. Campbell: Obviously one of the reasons you did this in mice first was so that you could perfect the techniques involved. You said that the in situ hybridization was a technique that already existed. What kind of new techniques did you have to develop in order to get this project going and to succeed?

Dr. Jones: One of the nice parts about this project was that the technologies, by and large, existed. And so, we weren't limited by trying to develop any new technologies. So, our challenge wasn't really so much about technology development as it was about technology integration and scaling.

And so, the challenge in doing something like this project, there have only been a few times within biology where people have taken very large-scale projects—and the Human Genome Project would be one of those examples—where you really needed to take a sort of an industrial approach to doing something on a very large scale. And this was one of those cases where we had to do that.

So, for the sheer volume of stuff that we were processing through, we needed to create these sort of under-the-hood systems—things like a lab information management system—things that allowed us to track the huge volume of stuff we were running through the production floor. Just taking everything to scale requires a whole series of standardization of processes, of making sure that you've got all your positive controls working, your negative controls are giving you what you expect, and really taking all of that into massive scale, collecting all of that data.

When we were in full swing in the project, because we actually capture our end result in electronic form, we were taking about a terabyte of image data every day. And so, you have to have the systems that can handle that, support it, map that back in, and ultimately be able to serve that out into the web.

A terabyte is 1000 gigabytes of data. A gigabyte is 1000 megabytes. So, these are very large data sets that we generate. And especially when we started this project in 2003, that was a lot of data. We've generated to date now about a petabyte of data, which is now 1000 terabytes of data.

Dr. Campbell: So, besides data management, you're talking about techniques that are highly repetitive. Is most of this automated?

Dr. Jones: We have a lot of automation, but there's also a lot of lab technician work that supports what we do. We've got a great team here that does arguably the most painstaking part of this, which is doing the thin sectioning of tissue.

That is still done by hand, very carefully by very skilled technicians. And the manipulation, moving of slides, there's still a lot of manual work.

But there is also a huge amount that has been automated. The in situ hybridization process itself has probably about 40 different steps to it, and that has all been automated. The act of actually cover-slipping a slide—which if anybody ever had to do that in a high school biology course, it's a very tedious task, and you often get bubbles and other things—there's a piece of equipment that actually has automated all of that so it lays down a cover slip that's perfect every time.

We've also automated—and others have provided commercial solutions for automating—the scanning of the microscope slide at high resolution. Our largest bottleneck early on in the project was the ability to capture electronically the image data for all of this data that we were generating.

Dr. Campbell: What's the biggest challenge in going from the mouse brain to the human brain?

Dr. Jones: I would say that every aspect poses its own unique challenge in scaling to the human brain. Right out of the gate it's just getting human brain tissue. Obviously human brain tissue is coming to us postmortem, and the postmortem tissue—especially from what we're gunning for, which is normal human brain tissue from people that are between the ages of 20 and 60—those are typically coming from accidental death of some sort. So, there's a lot of logistics that have to happen to make sure that you can get high-quality human brains.

The longer that a brain is sitting there after death and before we're actually able to obtain the tissue and freeze it down, you have issues where the tissue is starting to degrade, and the RNAs that we would like to measure—which are

telling us at what level a gene is turned on—are starting to degrade. So, there are important things that relate to that.

And then there's the whole issue of scale. The human brain is about 2000 times as large as the mouse brain. All of our equipment and other things were set up to be handling microscope slides that are of standard format, which is a 1 inch x 3 inch microscope slide. The human brain, if you take a whole coronal slab, needs to fit on a 6 inch x 8 inch microscope slide. And so, a lot of the automation things that we had for the mouse brain needed to be scaled up accordingly.

Dr. Campbell: So, that was a whole project, obviously.

Dr. Jones: We have an engineering team here that goes in and starts doing measurements and design. And we ultimately ended up with a lot of custom pieces of equipment and other designed pieces.

Dr. Campbell: I want to go back to the question of the brains, because I read—I guess it was in a *Wired* article—that the Human Brain Atlas is going to be based on about fifteen unique human brains vs. thousands of almost identical mice brains that were used in your Mouse Atlas.

Dr. Jones: That's correct.

Dr. Campbell: Do you think that there are going to be problems with the fact that everybody's brain is different. How are you controlling for variability from brain to brain?

Dr. Jones: The answer is that you don't. One of the challenges in working with humans is that you're going to get what you're going to get. We do a lot of screening up front before we take the tissue, to assure that we have a brain that is by all accounts normal. We've had many discussions here at board meetings and other things about what constitutes a normal human brain.

One could argue that there is no normal human brain. But you want something where there's no history of psychiatric disease. You certainly don't want a history of drug abuse or a history of alcoholism. So, there are a number of things that we're screening for up front that we want to avoid.

But even with all of that, when you take a small number of individuals—and especially in the study of humans—you're going to get what you're going to get. And so, in terms of a statistical sampling it's certainly not all that satisfying to do such a small n. When we deliver our first version of our product next year it will probably only have an n of 4.

But, what an important n of 4! It's really the first time that anyone will have looked at this level of where all the genes are turned on in the human brain. There's a history of human brain atlases that are driven by a single brain. For example, a common coordinate framework like Talairach, those are single brains. They're not population averages.

There are better techniques that people have used in the functional imaging world. And people in the imaging world use population-averaged atlases. And we certainly plan on being able to take magnetic resonance imaging of the postmortem brains that we're using for this project, so that we can map into those coordinate frameworks.

So, that will actually give us, I think, a good handle for people who are doing those imaging experiments to be able to map in and get additional information. But there will be a certain amount of error associated with those measurements because each brain is so unique.

Dr. Campbell: Obviously the map that you're going to create is going to use statistical techniques and represent some kind of statistical average of the unique

brains. Will the data that belongs to each unique brain be preserved—be able to be traced back?

Dr. Jones: Yes. And, again, with such a low n, any statistical map that we do, or an average that we do is by nature going to be fairly compromised, so we want to provide the individual brain information for each of those as well.

Now, what gives me a little bit of comfort for doing such a low n is we have done a fairly nice study looking at just the human neocortex—and all this data is already out on the website—where we've looked at the human visual cortex, as well as the temporal cortex. And we've looked at the expression of about 1000 genes.

When we've done that study we can actually see that, by and large, when you have a gene that's turned on in a specific pattern there's really not a whole lot of variation across human populations. It's probably less than 5%. And so, we've looked at these across multiple individuals.

So, we actually feel that, by and large, even though there is likely to be variation in gene expression that's driven by population differences, that's likely to be a small proportion as opposed to the larger commonality between us. And sort of how you want to look at the problem, humans are a lot more similar amongst each other than they are dissimilar. Although we like to, I think, sociologically view us as being very different and unique.

Dr. Campbell: That makes sense. I'm going to talk about a few other subjects before we close, but is there anything else you want to say just about the basic project before I ask you a few closing questions?

Dr. Jones: Just to reemphasize that what we're heading for now is all the adult human brain. We anticipate being able to put our first product out, looking at gene expression in the entire human brain, by summer of next year. Probably June or July of next year is when we'll do a data release. And we're just

incredibly excited about being able to make this resource available. We think it's going to have a huge impact on both human health and the study of human brain disease.

[music]

I want to take a moment to thank those of you who are supporting the *Brain Science Podcast* with your donations. If you are interested in learning how you can help support my work, go to brainsciencepodcast.com and click on the tab at the top of the page labeled Donations and Subscriptions.

[music]

Dr. Campbell: I wanted to talk a little bit about the scientists that work at the Allen Institute for Brain Science. How many do you have, and what kinds of scientists do you have?

Dr. Jones: That's a great question. You heard a little bit about my background. I'm actually not a neuroscientist by training. I don't come from a brain science background at all.

We have about 120 people working at the Institute. About 20 of them are in the sort of general and administrative roles. We have general counsel, and the business and finance folks. So, about 100 of those are specific people working on the projects that we do here.

Of those 100, 30 of them are PhD level scientists of some sort. Those people have PhDs in disciplines such as math and physics, as well as traditional neurosciences, like neuroanatomy. And then we have people with PhDs in other biological sciences—like myself—in genetics and developmental biology. So, we have a whole range of different scientific disciplines here.

In addition we have a full staff of people that are in information technology. For example, software developers and server administrators—people whose full-time job it is to create an infrastructure around supporting this massive data collection, and then serving up a very robust website so that people can actually use the data in a meaningful way.

Dr. Campbell: The last thing I want to talk about is the implications for how science is done. I mean this is, from most points of view, a different way of doing science compared to what we have traditionally done. Not only in the scale, but in the approach of collecting a huge amount of data rather than testing a specific hypothesis.

Dr. Jones: Right.

Dr. Campbell: Do you have any thoughts on that?

Dr. Jones: Sure. It's something we discuss quite often. And I think there is plenty of room for projects and efforts like the Allen Institute is doing. But there is always a balance, because the thousand people a day that use our database are scientists who are doing hypothesis-driven science. So, it's very important that that work continue. It's who we create these resources for.

So, I think there's always a nice blend of the kinds of things. If you can find the right projects which become these enabling platforms and allow people to really use and mine them, I think it's a good model.

I think where often this gets a little bit confused is when there are efforts that are put forward that are larger-scale, but behind it it's really not so much of an effort to create a public resource as it is to sort of indirectly pursue specific hypotheses. So, I think as long as the motivations are always pure—in terms of our main mission in doing something large-scale is to create this broader public resource that helps everyone—I'm very encouraging of these sorts of efforts.

It's hard to fit in culturally to a traditional academic environment, however. So, we're quite unique in that we're structured and run much more like a biotech company. We're milestone-driven in terms of creating these products and delivering the data. And that doesn't necessarily mesh well with the traditional academic culture where people need to pursue specific hypotheses and publish papers for their career goals.

Dr. Campbell: What kind of implications does that have for the scientists that work at the Allen Institute for Brain Research? Are they people who will probably stay in biotech? Would they be able to go back into academia if they wanted to? Do you see that as being a problem?

Dr. Jones: We've had examples, I think, of both. This is an interesting blend somewhere between academia and something like biotech or industry. And the people that come here, we always try to let people know, you come in eyes wide open about what it is that we are and what it is that we are not.

And what we're not is someplace where someone can come in and pursue individual ideas and develop a research program around it. We're just not that thing. And if you're not in for that, if you're much more in for the team environment, then come here. But if you're really about ultimately having your own lab, this probably isn't a good place for you.

The people, by and large, that we have here get and understand that implicitly, and I think are enthusiastic about being able to work on something that's a lot bigger than they could ever entertain doing themselves in a small lab, for example.

Dr. Campbell: There's one other thing that sort of came to my mind when I was reading about this. I remember there was a magazine article last year —I can't remember where I read it—talking about now data is king, or something like

that. As if you could get to new theories just from the data, without any kind of theoretical framework. And I'm wondering about the temptation that this might bring to mistake—and I may be making a jump here, so just tell me if you think it's not clear—but mistaking correlation for causation.

Dr. Jones: Yes. Well, it's always about taking resources such as these and using them for what they are—which is largely a hypothesis generator. Because nothing here was designed as a good experiment, but rather as a broad base of information by which hopefully people can leapfrog their way into some new understanding—but that they always have to test that.

So, I guess I lean a little more towards what you're saying, which is there aren't that many cases in which you can just use the data as is and say, 'This is the conclusion,' but rather use the data as it is and say, 'I think this is the conclusion; let me go test it.'

Dr. Campbell: That makes sense. The resource that you're creating for designing experiments based on your data is just endless, then.

Dr. Jones: Right. And that's the wonderful part about it—it's sort of done in this very open way. You never know who's going to use it in some unique way that you never in your wildest dreams thought of.

Dr. Campbell: What do you see yourself doing when the Human Brain Atlas is completed?

Dr. Jones: Well, it's interesting; periodically, every couple of years, we talk about what should the Institute be doing next. And right now we're kind of in that process as well, saying what shall we do after we do this Human Brain Atlas.

There is a myriad of different possibilities. And so, the fun part now is being able to convene the experts again, convene our Institute advisors, and talk about what

might be on the horizon. What is a new direction for the Institute in which we can create yet another scientific resource that can be widely used and have broad impact?

Dr. Campbell: But you did say that you weren't going to be able to test every gene for the first version of the Atlas. So, one job would be constantly improving the Atlas by adding more genes?

Dr. Jones: Absolutely. There's certainly an almost inexhaustible repeating of multiple measurements, etc., that could be done. There might be other opportunities in other spaces, however, that might have ultimately more impact. And so, I think that's where we convene our advisors and we talk about whether more of the same is a good direction, or is some other new direction better in terms of the overall impact that the Institute could have?

Dr. Campbell: Well, Allan, I really appreciate you taking the time to talk with me today. I hadn't really thought about this very much, so I'm glad that one of my listeners was interested enough to push me to learn more.

Dr. Jones: Well, I thank you again for your time. I appreciate being able to talk about our project.

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First I want to thank Dr. Jones for taking the time to talk with me. I have no doubt that we are going to be hearing about a lot of important discoveries, and even treatments that use the databases that the Allen Institute is developing. The Mouse Brain Atlas alone is a tremendous resource for researchers, because the mouse is such an important part of brain research. It was also interesting to hear about his career path and reflect on the new kinds of science careers that are evolving.

Before I close I want to remind you to check out my other podcast, *Books and Ideas*. The next episode will be out on the last Friday in September. It is an interview with Tom Clark from the Center for Naturalism. And in October I will be posting an edited version of the live podcast that I recorded last week at Dragon*Con in Atlanta, Georgia. You can find *Books and Ideas* in iTunes and at booksandideas.com.

Next month's *Brain Science Podcast* will be an interview with Dr. Warren Brown, co-author of *Did My Neurons Make Me Do It?*. Episode 53 of the *Brain Science Podcast*—which was a discussion of *Did My Neurons Make Me Do It?*—generated quite a bit of discussion on the Forum, so I know you won't want to miss it.

Now for this month's book winner: The winner is Ernest S. Croot, from the School of Mathematics at Georgia Tech. He will be receiving a copy of *Memory and the Computational Brain: Why Cognitive Science Will Transform Neuroscience*, by C. R. Gallistel and Adam Philip King.

There are two ways you can get your name entered into the monthly drawing. If you make a donation of at least $25 you are automatically entered. Or, if you can't afford to donate, just send me an email with the words 'Podcast Book Giveaway' in the subject line.

Last month someone sent me a blank email. If you're going to send me an email, I would actually like to get some feedback. My email address is docartemis@gmail.com.

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Thanks again for listening. I look forward to talking with you again next month.

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Transcribed by Lori Wolfson
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