Hi Reddit,

My name is Michael F. Wells and I am originally from Columbus, OH. Ever since I read the book “The Value of Believing in Yourself: The Story of Louis Pasteur” when I was five-years old, I wanted to be a scientist who studied human disease. I recently completed my PhD at Duke University and am now conducting research at the Broad Institute and Harvard University in Cambridge, MA. My work focuses on creating models of psychiatric disease to unravel the mysteries encasing these complicated and debilitating disorders so that one day we may be able to produce safe and effective treatments. I spent the past 6 years in the laboratory of Dr. Guoping Feng at the Massachusetts Institute of Technology where I was involved in projects focusing on animal models of obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), schizophrenia (SCZ), and attention-deficit/hyperactivity disorder (ADHD). I now work in the laboratory of Dr. Kevin Eggan where I am using human stem cell-derived brain cells to study some of these same diseases.

This past week, my work focusing on a new mouse model of ADHD was published in Nature (http://www.nature.com/nature/journal/vaop/ncurrent/full/nature17427.html). In this study, my amazing team from the Feng lab and the Michael Halassa lab (NYU) removed a gene known as Ptchd1 from the mouse genome (known as the Ptchd1 knockout mouse). We picked this gene because it has been found to be mutated in approximately 1% of patients with ASD and intellectual disability (ID). These mice displayed several abnormal behaviors including cognitive deficits, grip weakness, disrupted sleep, hyperactivity, and attention deficit. Importantly, we found that Ptchd1 is expressed in a part of the brain known as the thalamic reticular nucleus (TRN), which acts as an “information filter” in the brain. The results of our investigation suggest that this filter is allowing too much information to pass through to other brain regions in this mouse. Importantly, we were able to show that these TRN defects were contributing to the hyperactivity and attention-deficit behaviors, both of which are hallmarks of ADHD. Finally, we successfully fixed these ADHD-like behaviors in mice using a drug known as 1-EBIO, which targets an ion channel that we found to be dysfunctional in Ptchd1 knockout mouse TRN cells. It is important to note that 1-EBIO is not meant for use in humans, so much more work needs to be done before we can translate these findings to a safe and effective treatment for humans.

Are mice valid models for human conditions? How do you assess these human-like behaviors in mice? What is the future of disease modeling? I will start answering these questions and more around 1pm (10 am PST, 6 pm UTC) and will stick around until you get tired of listening to me.

Edit: OK I'm starting early because I am the captain now. Let's do this.

Edit #2 (1:47pm): I had some technical issues. They are resolved now so I am back.

Edit #3 (2:44pm): I am staying until you kick me out.

If you have to leave, however, and want to continue the discussion, you can follow me on Twitter@mfwells5

Also, my collaborators and I have set up a Gmail account to answer Ptchd1/TRN questions:TRNquestions@gmail.com

Final Edit (6:50pm): Thanks everyone for your amazing questions. I answered as many as I could before my stem cells started crying for their daily feeding. Feel free to reach out to me if you have any additional questions. It was fun--see ya!
Why not just give the mice some adderall? Why is 1-EBIO different?

petester

Great question. Typically, if you give someone amphetamine and measure their activity levels, you will see that, big surprise, the person moves around a lot more. If you give someone with ADHD the same dosage (in the form of Adderall), it will have the opposite effect and results in decreased hyperactivity. We tested this concept in the mice by giving them a one-time dose of amphetamine at a concentration similar to what you see prescribed for humans. When we did this, the Ptchd1 knockout mice did not respond with decreased hyperactivity. In fact, their performance was identical to the wild-type controls. When we tried 1-EBIO, however, we did see a positive effect that differed from controls. Interestingly, about 30% of people with ADHD do not respond to amphetamine-based treatments, so it is possible that SK channel modulation could help some of these individuals.

Hi Michael thanks for doing this AMA!

Ptchd1...has been found to be mutated in approximately 1% of patients with ASD and intellectual disability (ID)... we were able to show that these TRN defects were contributing to the hyperactivity and attention-deficit behaviors, both of which are hallmarks of ADHD.

Could you explain the relevance to real-world presentations of these diseases? You have taken a protein which is abnormally expressed in a small fraction of individuals presenting very severe neurological dysfunctions, altering it in mice, and then claiming that you are observing symptoms of ADHD-type behaviour and/or is ADHD-type behaviour common in individuals with ASD and ID?

Thanks!

merryman1

This is the best question I have seen so far (sorry everybody) and I was putting it off until I could answer it as clearly as possible. You are 100% correct. Only a very small fraction of people with ASD, ID, and ADHD are missing the PTCHD1 gene. Having said that, 1% is actually a high percentage when it comes to monogenic causes of these disorders. Ignoring that fact for a second, what is important about this type of research is not so much the gene, but the circuit (TRN) we have identified as playing a role in these behaviors. So yes, while there are not millions of people with developmental disabilities living with PTCHD1 deletion, there could be a much larger chunk of the population suffering from dysfunctional TRN circuitry that could be the source of their problems. Our hope is that other labs will start to probe TRN function in other mouse models of psychiatric disease including ASD and ID.

Could you attempt to explain in educed layman's terms how ADHD, autism spectrum and OCD interact with each other? How often are they found comorbid?

Also, have you ever diagnosed an in-law with a chronic mental handicap at a polite dinner?

tigrenus

This is one of the most pressing questions in the field of psychiatric research. There is a surprisingly high comorbidity rate with these disorders. According to a recent study by the CDC, about half of the children observed were co-morbid for ADHD, intellectual disability, and/or epilepsy (Peacock et al 2012, J Dev Behav Pediatr). In addition, one of the hallmark diagnostic criteria for ASD is repetitive or stereotyped behaviors, so you can see how the comorbidity rate between ASD and OCD can be quite...
high (~37% according to Leyfer et al., 2006 J Autism Dev Disord).

In layman’s terms, I think these conditions interact with each other in the sense that they share underlying causes. For example, we recently published a paper describing a mouse model in which we generated two different mutations in the Shank3 gene—one that was found in humans with ASD and another that was found in humans with schizophrenia (Zhou et al, 2016 Neuron). When we tested these mice, we observed both differences and similarities in their circuit and behavioral dysfunction even though it was the exact same gene bearing the mutation. This tells me that the roots of these comorbidities can be found at the gene and circuit level, and this is not even taking into account the almost certain roles played by one’s environment.

Finally, I am not a psychiatrist, so I am not allowed to formally diagnose anyone with a psychiatric disorder (this doesn’t stop me from doing so in my head though). And my girlfriend’s (sorry ladies) uncle is a federal judge, so I would never say anything bad about potential in-laws (Rick if you are listening, please don’t send me to jail. I’ve seen “Making a Murderer” so I know what you can do to me).

Thanks for doing this great work.

I’m curious: what could be done to help you and your colleagues accelerate your research(besides money)? What problems do you have? What are the ideal tools that you could imagine(given no constraints) would look like?

furyfairy

Besides money? Hmmmm….probably money. I am very fortunate to have worked in relatively wealthy labs, meaning money has rarely been an issue when designing experiments. That being said, most labs do not have this luxury and the funding is increasingly becoming concentrated in the top 1% of the labs (excuse me, but it is time for me to channel my inner Bernie). While this wealth gap is benefiting me at this moment, it will soon be to my disadvantage when I try to start my own lab and fall to the bottom of the totem pole (assuming I am even able to get a job running my own lab, which is becoming more and more difficult in the current funding environment). This is killing young scientists and forcing many to leave academia. So, more money in the field would hopefully trickle down (channeling my inner Reagan) to more (new) labs, which would mean more fresh minds driving the field.

To answer your other question, I imagine the most important tools to solving some of these problems are the ones that we have not even thought of yet. That being said, optogenetics and CRISPR have clearly established themselves as critical for advancing neuroscience. I personally am awaiting progress in the field of targeted genetic engineering of non-human primates (NHPs). If we are able to create disease-relevant mutations in NHPs in a relatively inexpensive and high-throughput manner, I think you would start seeing a much higher percentage of animal studies resulting in treatments for humans.

What’s your view on Vitamin and Mineral supplementation, such as Magnesium Threonate, Amino Acids and Vitamin D3 to alleviate the symptoms of certain psychiatric conditions?

There are a lot of companies pushing their supplements in this way these days, with Magnesium Threonate in particular argued to cross the blood brain barrier while other supplements like Magnesium Citrate cannot.

Anecdotally there are a lot of people online making bold claims such as Magnesium, Amino Acids, and Vitamin D3 “cured” their symptoms of anxiety, ADHD etc..
Is this junk science peddled by the supplement industry, or does it have any validity?

Thank you for taking the time to speak with us!

EX_NO_CONTACT

Sounds like bullshit to me. Trust me, if there was a supplement that was a cure-all to these psychiatric diseases, we would all know about it and my job would be done. There are definitely things like magnesium and calcium that play critical roles in the brain, but simply taking one of these pills is not going to correct whatever is going wrong in this highly complex system.

What do you think humans will accomplish with brain implants over the next 25 years? I know it's an insanely difficult problem, building a brain-chip interface, but how difficult is it?

Also, how does neuroplasticity figure in with disorders like ADHD and ASD? Why can't the brain compensate for the disordered behavior in certain special cases?

afndale

Though this is outside my area of expertise, I can say that I share your excitement for the progress we are making in brain-machine interfaces (BMIs). When I was an undergrad at Notre Dame around 2007-2008, I came across a New York Times article describing the work of Miguel Nicolelis at Duke University who is a pioneer in this field. The article focused on his experiments involving monkeys controlling the walking behavior of a robot through a BMI. I was so fascinated by his work that I applied to Duke University’s neurobiology PhD program and eventually accepted their offer. Once I got there, I realized I was way too dumb to work in Miguel’s lab (my engineering and coding skills are that of a 4-year-old Golden Retriever). Instead, I joined Guoping Feng’s lab. That being said, I think you will first see BMIs tackling “simpler” behaviors like movement. This may be wishful thinking, but I do believe we will be able to treat some types of paralysis using BMIs in the next 25 years.

To answer your other question, neuroplasticity definitely plays a role in ADHD and ASD. In fact, I would argue that this is partially why you see cases of the same genetic mutation resulting in a wide array of different behavioral symptoms. Why can’t the brain compensate for the mutation? Well I think that depends on the gene with the mutation. There is redundancy in the human genome, so in some cases, the loss of one gene is corrected by another non-mutated gene that is already present in the system. For example, once again using gene knockout technology we found that the Shank3 gene is critical for the presence of ASD-like behaviors in mice (Peca et al., 2011 Nature). Mice express Shank1, Shank2, and Shank3 in their brains, but importantly, only Shank3 is expressed in the brain region known as the striatum. Therefore, even though Shank1 and Shank2 may be able to compensate for the loss of Shank3 in a brain cell, there is no Shank1 or Shank2 in the striatal brain cells to replace the lost Shank3. Given that Shank3 is a building block for the synapse, which connects one brain cell to another, you can see how the lack of this gene may create problems that neuroplasticity in the system may not be able to overcome. (note: Since our publication in 2011, others have found that Shank2 is also a candidate gene for ASD).

There’s been a lot of press surrounding language like “hacking” the brain. I worry that this kind of language is misleading to the public and promising more than we can currently deliver. Do you believe that we actually have enough understanding of these complex systems to say this sort of thing?

jrclimer

Yes and no. I think it depends entirely on how you define the word "hack." I use this buzzword in reference to manipulation. Can we use tools like optogenetics to control the movements and emotions
of mice? Yes, very much so. Can we remove or overexpress a gene to alter the behavior of these mice? Yes, very much so. When we do these things, are taking over their free will? I am not a philosopher, but I would still lean towards saying yes to this question (and I hope to see a discussion on this latter issue somewhere in this thread).

Now are we are to do these same things at the same level of a human being? Nope. Are we still able manipulate, and therefore, "hack" the human brain in some ways? Yes. Deep-brain stimulation and pharmaceutical drugs are just two examples that come to mind. And this is just the beginning. We are only going to find more ways to use these tools to treat these disorders.

Here at /r/science we just changed our rules to require that titles include the model when relevant. We felt it was important to distinguish between human and animal studies.

But just how valid are mice as models for human health issues? How are they alike and in what important ways are they different with respect to this kind of research?

firedrops

I think it was a very smart decision by the mods to mandate the model system in post titles. It is true--mice are not humans. Though there are genetic and circuit similarities, there are many, many differences between these two species. Just look at communication deficits, which is one of the hallmark diagnostic criteria for autism. Mice do not speak like humans do. They do produce ultrasonic vocalizations, but this is nowhere near the complexity of human language. The differences in behavioral and circuit complexity are most definitely contributing to the ~90% of drugs that work in mice but fail at the human clinical trial stage.

So if this is true, why bother studying them? Despite the differences, mice do resemble humans in many ways. If you look at the protein coding regions of our genomes, mice and humans are 85% identical. We share many of the same cell types throughout the brain that are connected to each other in similar ways. Behaviorally, you can see hyperactivity, depression, repetitive behaviors can be observed quite easily in mice. More complex behaviors like social interaction and cognition are a bit trickier, though entirely feasible, to observe in my opinion. So, to directly answer your question, mouse studies give us clues that we are currently unable to ascertain any other way. I hope that we continue to make progress in generating human stem cell-derived tissues and computational models of brain networks so that we can start to reduce our dependence on animal models.

Hi Michael. This may not be the time or the place but I would like to try to get through. I was diagnosed as a child with 'ADD' before 'ADHD' was a thing. I was given Ritalin for 15 years roughly. By the time I was 21 i was prescribed roughly 40mg of time release at 2 times per day. And roughly 25mg of regular ol' 5mg yellows for studying before bed. I am an adult now. I stopped taking Ritalin after related heart failure in 2002. After the episode I ended up with a psychosis that was diagnosed differently by every doctor I saw (8ish) and they continued to throw drugs at it.

Since that time I have acquired 3 graduate degrees, owned and operated a successful global business, become a university professor, coached a national sports team and even spent some time doing stand up comedy when I took a year off of the hard stuff. I am an adult now. I stopped taking Ritalin after related heart failure in 2002. After the episode I ended up with a psychosis that was diagnosed differently by every doctor I saw (8ish) and they continued to throw drugs at it.

Although this is anecdotal, there are 1000's of people who have been diagnosed by whomever with whatever types of ADD who become very successful entrepreneurs and or research colleagues. I am sure some of your colleagues have been diagnosed with some AD(H)D (or have been exposed to Ritalin since you are at Harvard and we all know how Ritalin can be used at Harvard).
I would rationally never want to shut off the ADD or the overactive imagination despite any challenges it creates considering the things it has allowed me to achieve. I believe I was drugged as a child because of behavior that wasn't "normal", I was diagnosed with psychosis because I lost touch with reality after a near death experience and if I had listened to one doctor who told me "i would never be normal again" i would be far from who I am today.

How will your research avoid creating similar circumstances for gifted individuals? Do you ever think of the creative genius associated with AD(H)D and the effects associated with 'shutting it down'? Have you ever looked to determine what advantages the AD(H)D mice have over the 'normal' mice?

TLDR; I was misdiagnosed with different types of psychosis after an episode when my heart failed during exams after 15 years of heavy Ritalin use prescribed for ADD. After lots of treatment attempts the best thing I ever did was stop taking drugs they gave me, stop listening to psychiatrists and try to maximize the potential of my unique brain. Since that point I believe my ADD has allowed me to think in a very special way and accomplish really incredible things. I feel like shutting it down would be the equivalent of taking away a super power.

Does anyone in the scientific community feel this way? Is anyone who has ADD involved in this research?
Is there any research on maximizing the potential of people with special brains? or do you think the research will continue to try to simply normalize them?

There are a handful of questions semi related [ sorry it's the ADD :) ] if you can't answer them all i understand, please just try to answer some. Thanks

concept2creation

I am in no way trying to reduce the variability in humans by making everyone the same. We need this variability. We need these differences. We need people like you who think differently.

Having said all of this, every person lies on a spectrum of these disorders. If you feel happy and have no desire to change yourself, then great--let's keep it that way. There are many people, however, suffering from these diseases who want to improve their lives. They can't function, they can't form lasting relationships, and most importantly, they are not happy. I want to help these people. I hope this answers your question and I'm sorry it took so long for me to get to it.

Edit: a typo

Fascinating work, it must be quite challenging to figure out what behaviors are due to the gene alteration and which ones are just dopey mouse behavior. How long did it take to recognize the effects? Did you have to spend weeks doing what amounts to mouse Olympics? What led you to test the behaviors that you found to be different?

nate

Weeks? Try years. This project was started in January 2011 and did not wrap up until January 2016. A solid chunk of that time was spent breeding mice so that I would have a colony large enough to make comparisons between the Ptchd1 knockout mice and their unaltered wild-type littermates/siblings. I would start the mouse Olympics at about 6 weeks of age, which roughly translates to late adolescence in humans. From what I could see, the abnormal behaviors were apparent at this age and did not change much relative to the wild-type littermates as the mice grew older. In the end, the behavioral characterization took about 2 years.

There is actually a pretty cool story behind why we chose these behaviors. Most of them were chosen because they are included in the standard panel of behaviors that should be tested in every mouse
model. Some of them, however, were conducted as a result of my conversations with a parent in Australia named Mick. Mick’s son Joshua is missing the PTCHD1 gene. To find others out there affected by PTCHD1 deletion, Mick launched a website (which is no longer active) called ptchd1.com. I spoke with Mick through email and Skype over the past few years. During these talks, he told me about some of his son’s grip issues and his frequent, sometimes violent, temper tantrums. To try to model this in the mouse, we ran tests for grip strength and aggression and found abnormalities in both. In addition, a paper was published after we had finished most of the behavioral tests that described 22 PTCHD1 deletion patients and their symptoms (Chaudhry et al. 2015 Clin Genet). If you read the acknowledgment section of our paper, you will see that we thank Mick and Josh for their help (in fact I probably would have quit the project in its infancy if I didn’t meet Mick and Josh).

Hi, you guys are doing awesome work.

Can you name some things that still baffles you when doing experiments?

Azymphia

In general, I am baffled by how long everything takes. Research is a slow, arduous process.

Though this is not your question, the one thing that amazes me when I am conducting behavior experiments is how similar our behaviors are to that of mice. Yes, there are many differences and humans are much more complex. Having said that, it is remarkable how both species are driven by the same factors like hunger, fear, and reward. We are truly basic creatures (Cue "The More You Know" banner).

Interesting research and thanks for sharing! I know this is about your research, but I suspect I've understood all about your research that I will likely comprehend. What do you hope to do with your science career? What are your ultimate goals in your career (e.g., do you hope to cure a disease or just bring better understanding to disease)? What can the non-science community do to help further the development of science such as the project you are working on?

lawdogslawclerk

I hope to one day run my own lab so I can continue to do research on a wide array of psychiatric diseases. Will I live to “cure” any of these diseases? Probably not. I do hope to play an important part in the development of some treatments, though I think we are still a long way away from anything that resembles what we call a cure.

The non-scientific community plays a huge role in these projects. The NIH budget has remained relatively stagnant for over 15 years. Why? Because there is little to no political pressure to increase the amount of federal money that goes to research and development. If Sen. Sherrod Brown (my fav senator) announced that he wanted to cut defense funding by 25%, he would be dragged out of office by my fellow Ohioans. If he made the same statement about NIH research funding, it wouldn't even make the front page of the Columbus Dispatch (are you guys liking all of these local references?). We need the non-scientific community to be more engaged in the process so that our leaders feel the need to funnel more money to R&D. Scientists need to do their part as well by effectively communicating to the general public why our work is important and how it can affect their lives and those of their children.

I have been reading the book Infectious Madness and last night I got to a bit about the different strains of mice bred for different traits. That was rather mind boggling. Then it goes on to say how the tests
are structured and interpreted and it is all very eye opening.

Anyway, what do you think about the current speculation that mental disorders are the results of an infection? This seems like quite a paradigm shift to me although the book recounts many instances where this line of inquiry has been raised in the past.

There has been a lot of finger pointing as far as toxoplasma gondii, my very favorite parasite. When I first read about it in 1983 in a book that recounted the behavior changes it caused in mice a lightbulb went off in my head - if rats, why not humans? Why would we not be susceptible to behavior changes? My answer to myself was, damn, we wouldn't be exempt.

shillyshally

THANK YOU FOR BRINGING THIS UP. I do believe that maternal infection during early trimesters is playing an important role in psychiatric diseases. There is already some evidence suggesting a link between schizophrenia and maternal exposure to influenza. I do hope to devote a portion of my future studies using brain organoids (aka mini-brains in a dish) to study the effects of infection on development. That being said, if I were to bet money, I think in the end we will see that genetics/epigenetics are the #1 factor underlying these diseases.

Hi Dr. Wells,

I've been studying the Ptchd1 receptor and Hedgehog signaling a little bit. I'm surprised to hear that a ptchd1 KO mouse would be able to develop and survive at all! Is this a conditional KO?

You mention that ptchd1 is mutated in some autistic patients, but that your mouse model is a KO rather than a mutant knock-in. Wouldn't it make more sense to use a mutated receptor in case the mutant has some residual function, or even just to make your model as similar to the actual disease as possible?

Finally, and you touch on this in your introduction, but how valid are animal models for autism considering that many of the more profound effects of autism are applicable pretty much exclusively to humans? I've read about Purkinje cell ablated mice showing some of the same behaviors as autistic humans - social withdrawal, repetitive behavior etc - but how useful are such models in reality?

Jinglebellsjingleatw

We need to talk.

Hi Dr. Wells!

Thanks for doing an AMA - I'm sure you agree that more transparency and outreach in science can only be a good thing.

I have two brief questions:

1) You mentioned that you are working with stem cell-derived brain cells in the Eggan Lab, but the work you describe about mouse behavior and neurology sounds like it has been done in vivo. Do you implant engineered stem cell-derived neurons into the mice to achieve relevant models?

2) You also talked about how the thalamic reticular nucleus acts as an information filter in the brain. Is there a general consensus or hypothesis as to the mechanism governing this filtration?

NietzscheanSlip

First of all, the paper I described in the introduction was from my time as a graduate student in Guoping...
Feng’s lab. All of this work was done in vivo and did not involve stem cells. I joined the Eggan lab in October where I have switched my focus from mice to human stem-derived neurons as models of these conditions. Though I am not currently working on stem cell implants, I do have long-term (i.e. have not gotten past the shower thoughts stage) plans to bridge these two technologies. I would love to hear (i.e. steal) everyone's ideas on how to do this.

To answer your second question, the TRN is a much more complex structure than previously believed, and I am glad to see that it is getting the attention (wink, wink) it deserves. The TRN is purely inhibitory and it acts on the thalamic relay nuclei that then project to the cortex, which in turn blah blah blah blah. Without getting too technical (and if you want a more technical answer, I can direct you to some great review articles), the TRN inhibits information coming from the thalamus en route to the “higher-order” processing centers in the cortex. What information is coming through the thalamus? Pretty much everything coming from your environment. Sights, sounds, touch, you name it all get shuttled to the various nuclei in the thalamus. Before this input can get to regions like the prefrontal cortex, it must first pass through the TRN gates. We believe that people with ADHD have “weaker” TRN gates due to decreased inhibition. As a result, the “leaky thalamus” is able to send more information to the cortex, thereby allowing distracting information to get through and potentially overload the system.

My collaborator Mike Halassa at NYU is the king of the TRN. You should all visit his website and then flock to join his growing lab (http://halassalab.org/).

I'm at home so can't view the article right now, how extensive in the gene in the brain? In other words, is it relatively specific to the TRN or is it also found in other cognitive areas. If it is found in these areas, wouldn't a DREADD or opto approach then be optimal?

Also, what was the attention task? Was it a signalled-reward probability sustained attention task so you could look at motivation as well or did you just ignore that?

**Asshole_Economist**

The gene is expressed in many parts of the brain in adulthood, but mainly in the TRN early in life (of mice). Interestingly, outside of the TRN, which is composed of inhibitory neurons, Ptchd1 is expressed predominately in excitatory cells. I have no idea what this means--just thought it was cool. We have not used DREADDs or optogenetics to tease apart the circuit defects underlying some of these behaviors, though I would shocked if that is not done in the next year or so.

The attention task involves training food-deprived mice (don't worry, we feed them, just not as much as other mice) to respond to a light cue that is displayed to either the left or right of the mouse. We use their motivation to drink a milk reward to get them to correctly respond to the light cue. After weeks of training, we then introduce distracting cues. These distractors had no effect on wild-type mice, but completely messed up the performance of the knockout mice.

Do any of your animal models incorporate mitochondrial function/dysfunction? Have you encountered theories of mitochondrial dysfunction in pathology of psychiatrically diseased mice?

**meatball4u**

I have not worked with these models so I do not know much about them. For those of you wondering, the mitochondria is the powerhouse of the cell, so it comes as no surprise that defects in this organelle can lead to many problems.
Do you think 1-EBIO or something similar had potential to be used as a human treatment down the line? If so, how do you get that ball rolling? Do you just hope that a drug company reads your paper and is interested in pursuing this idea?

I'm wondering how often promising treatments in mice or other model animals never get translated to humans simply because of a broken research pipeline, since it's not the same researchers.

slowlyslipping

1-EBIO is definitely not the answer, but I do think we have a chance at correcting some of these behaviors if we can generate a more specific SK2 modulator. In a sense, yes, I do have to wait and hope a pharma company reads the paper and starts getting to work on developing such a drug. Before a company starts throwing money at this target, however, I would expect that other researchers would first need to validate and build upon our findings. Unfortunately, no single academic lab can afford to finance the experiments and clinical trials necessary to get a drug to market.

(Pssst Don't tell anyone but I have heard rumors that SK modulators are already the focus of some disease-related projects at a handful of major pharma companies.)

Peaches, Dr. Wells. (From now on I'm thinking of you as a Flash villain.)

How selective is 1-EBIO as a K channel blocker, and how did it affect the cell populations in the TRN in mice without the knockout?

Zeraphil

1-EBIO hits multiple K channels throughout the brain, not just SK2 channels in the TRN. We didn't measure the effects of the drug on other cell types, but I am sure it is doing something outside of our target. This drug was used as part of a proof-of-principle experiment, meaning we just wanted to know if enhancing SK2 current would have benefits. We and others need to repeat these experiments with drugs that are more specific to SK2.

Can you please share with us details about the treatment of your lab mice? How do you respond to ethical critiques of animal testing?

EyreiSawElba

There are both state and federal laws governing the treatment of lab mice. The mice have to live in properly ventilated cages with access to food and water. Their cages need to be cleaned when dirty. Only so many mice can be placed in one cage to counteract overcrowding and fighting. We strictly follow these rules and if we are caught breaking them, we could lose the ability to work with animals.

On a more personal note, I consider myself to be an animal lover. I have had pets my entire life, including a mouse that I illegally kept in my dorm room 8 years ago in college (RIP Charlie). I do not like hurting mice. I do not like having to sacrifice them for an experiment. None of us do. Have you seen a 10 day old mouse pup?? They are adorable! But I believe that these things need to be done for me to help people.

I have spoken with families that are struggling trying to raise a child with developmental disabilities. When I hear the mother of a child with a SHANK3 deletion tell me that her son has almost 200 drop seizures per day as a result of his deletion, I find it a bit easier to work with mice. It might sound like a cop-out, but this is just how I feel. Thank you for this question--it is a very important topic that we need to continue to discuss.
Do you believe humanity is following the trend of the Calhoun Rat Experiment and also the blue print for the demise of human civilization?

WidmerBeer

Short-term: no. Long-term: probably. That is why (I'm not joking) making advancements in space travel is so important.

If you could only point out 1 precursor to watch out for in any of the diseases you have worked with, what would it be and why?

SneakyHomunculu5

I really can't think of one unifying precursor other than a family history of mental illness. I think in the future as we identify more genetic mutations linked to these diseases and genome sequencing becomes more widely available, individuals will have a better idea of their risk to these disorders.

Hey Dr. Wells, thank you for sharing your knowledge with us! I have one question due to some fellow students of mine use brain stimulating drugs like Modafinil or Ritalin during exam periods. What do you think about these, their effects in short run and also in the long run? Do you think they might harm some people? Concluding to that, how do you see your results, that in the future there will be some bio engineering that people improve their brain to outperform others?

thegrey_m

I'm not a medical doctor, but abusing prescription drugs for exams sounds like a bad idea. My guess is that this probably does have negative side effects, especially when taken during a time when you brain is still developing (and yes, your brain is still developing even in your late teens/early 20s).

To answer your second question, I think we are far from the Gataca scenario where we are bioengineering people. Not only is the science not there, but I think societal pressures will rightfully stop this from happening.

Thank you so much for this AMA, Dr Wells.

Do you think in the future we’ll be able to use genetic therapies safely and with efficacy, and possibly cure some of these diseases? Through your studies, do you think we’ll be able to someday map the brain genetically so we can have more targets for therapies (such as nanotherapies) and would they be reliable maybe?

(plus: in all this controversy about the link between vaccines and autism, what is your opinion?)

Thanks in advance!

flickerish

I do think we will create effective genetic therapies for these diseases, though I think it will take some time before these are deemed safe. We really do not know yet all that could happen when we introduce genetic material to the human brain. We may “fix” the problem while creating 1000 new ones.

And yes I do think we will continue to map the brain genetically. Whole genome sequencing is getting
cheaper and cheaper, which will allow more labs to conduct these types of experiments. In addition, the work being done at the Allen Brain Institute has served and will continue to serve as the foundation for many of the types of experiments that need to be done to achieve this goal.

(Andrew Wakefield is a sociopath and should be in jail.)

What source would you recommend to a psychiatric beginner that would simply describe a model of brain/mind?

shivan21

Hmmmm great question. I do not read a lot of science-related books (I am more a lover of dystopian fiction) so I may not be the best source. Having said that, if you want to understand genetics as a whole read "The Selfish Gene" by Richard Dawkins. If you want to understand everything about the brain, read "The Synaptic Organization of the Brain" by Gordon Shepherd. If you want to understand me, read my favorite book "A Staggering Work of Heartbreaking Genius" by Dave Eggars.

This might not be up your alley however, what are your thoughts on DARPA's foray into peripheral nerve stimulation to facilitate learning?


snowleopard83

I had not heard of this. I will read more about it. Looks promising. Thanks for the head's up.

Ever think that testing on mice is not only cruel but also hardly constructive when considering how advanced human brains are compared to mice?

Raidann

I would whole-heartedly disagree with the claim that the work is not constructive. Yes the human brain is more complex than that of a mouse but that does not mean we have not benefited tremendously from mouse research. I would also disagree with the claim that the work is cruel (see below).

If a similar mutation and an effective treatment are found for humans, how would the condition be diagnosed?

Would a DNA test show it? Would it be expressed in everyone with the genetic marker, or is there some epigenetic factor necessary for triggering the condition?

covington

Currently, diagnosis for a majority of these disorders is based on symptoms or behaviors, not the underlying cause. As a result, you typically do not see someone being diagnosed after a genetic test before the presence of behavioral abnormalities. Hopefully the application of genome sequencing will help identify people who might be at risk for certain psychiatric disorders based on their genetic and epigenetic profile. If we can identify this population, we may be more likely to intervene prior to disease onset.
I will try to hit the questions I haven't already addressed elsewhere.

It takes a very, very long time between the first publication and FDA approval of a drug. The last time I checked, it takes a pharma company on average 18 years of research and development to get a drug on the market. Part of this is a good thing. We want to make sure our regulatory agencies are not giving people drugs that have not been fully vetted. This slow-down occurs at the tail end of the project. We would of course love to speed up the steps earlier in the process. For this I think we simply need better models. I have heard from several people working in pharma that they have trouble replicating some of the behaviors observed in some of the published animal models. This could be due to sloppy techniques, improper reporting of the data/statistics, and, I am sure in some cases, to data fabrication. To do my part in bucking this trend, we conducted these experiments in multiple Ptdch1 knockout lines from multiple genetic backgrounds. We also included in our recent publication all of the raw statistics for every behavior test (which partially answers questions #3).

For question #2, we chose this gene because of the previous work done by other labs linking the deletion of this gene to autism and intellectual disability. We had no idea that we would see the TRN defects leading to some of the abnormal behaviors. Sometimes you just get lucky and observe something that the universe has been hiding from us.

What are your thoughts on the evolution of the market economy of the southern colonies?

Besides that, I actually never got a chance to ask you personally during our bromantic trip to NY this weekend (yeah that's right reddit we're actually shameless BFFs in real life -- good guy good guy) what're your thoughts on the CRISPR battle happening right now?

okaysteve13

GREAT QUESTION STEEEEEEEVE. I work for the Broad, so I think I am too biased to answer this question fairly. Having said that, I think the two entities should battle it out either through interpretive dance or a rap battle of some kind.

Hello Dr. Wells, thank you so much for doing this AMA!

As a current undergrad student who is adding a major in neuroscience, where do you see the largest potential for growth in the field? We have seen such an influx of studies focused on psychiatric diseases like you have done research on, but do you believe there are any other fields within neuroscience that may launch to the front of the field in the near future?

Also, what other focuses within neuroscience are you interested in and would like to do research on if you are given the opportunity?

Samthegard

The hottest topics right now are CRISPR, optogenetics, and induced pluripotent stem cells. I advise that you learn at least one of these techniques as a graduate student. In fact, treat graduate school as 5-6 years of learning different techniques that will make you an attractive post-doc candidate. Do not worry about trying to create or be an early-adopter of the next best thing as a grad student. You will do this as a post-doc.

TL;DR. This field is moving so fast that the techniques that will drive your upcoming scientific career do
not even exist yet.

Hi thanks for doing this AMA!

My question is in regards to the consequences of removing these genes long term. If you theoretically were able to identify and remove a certain gene that was attributed to autism from an adults' genome, will that person be completely 'cured' mentally & physically? or would it have to happen earlier on in a humans development?

I guess I'm wondering if this type of treatment would be effective in grown adults

dillistone

These individuals are actually missing fully functional copies of these genes, so we would actually be replacing the gene, not removing it. We have recently shown that we can replace the Shank3 gene in a mouse model of autism that is missing this gene. When we do so, we can correct some of the hallmark behaviors of autism. Others have done similar studies in other animal models, so there is hope.

What does an ASD model look like for mice when we are still learning so much about the disorder in humans? Is mouse-Autism defined behaviorally as it is with humans?

StudentII

Great point. We are still learning about autism in humans. This is why you see the diagnostic criteria in the DSMs continuing to make adjustments and evolve on the issue with each volume. We mainly assess autism-like behaviors in mice by testing their social interaction skills and their repetitive behaviors, both of which are hallmark behaviors in humans with autism (some groups analyze ultrasonic vocalizations in mice as a proxy for language, but I have yet to try these experiments).

Though the tests are rather simple and do not fully represent the complexity of human behaviors, we still are able to gain insight from these behavioral assays.

Very interesting study! Thank you for doing this AMA?

Do you find expression of Ptchd1 evenly distributed throughout the TRN? Do you think portions of TRN dedicated to given sensory modalities is more or less affected than others? Is Ptchd1 expression maintained through the lifespan?

Also, I really like the term "leaky thalamus". Thanks for that. :)

LadySovereign

Ptchd1 is evenly distributed throughout the TRN. I would estimate 80-90% of the TRN cells show this expression by early adolescence. The latest I looked for Ptchd1 expression was 6 weeks of age, though this looked similar to the 8 week old mouse data from the Allen Brain Institute.

You can thank Mike Halassa for the leaky thalamus term. I thought it was quite brilliant when he said it.

Thanks for your work! You cited "The Value of Believing in Yourself" as an inspiration, but are there other people around you affected by ADHD or schizophrenia that inspired you to tack down this particular line of research? (My sister has schizophrenia, but I never felt the urge to go into neuroscience.)
katarh

I have a long history of disease in my family, ranging from schizophrenia to bipolar disorder to alcoholism. I somehow hit the genetic lottery and avoided all of these conditions. This didn't necessarily motivate me to study these diseases, but it did get me interested in neuroscience as a whole. Once I became a bit more familiar with the field, I chose to study disease because it had the most interesting unanswered questions.

What's the biggest goal in psychiatry right now?

ForScale

I think everyone in the field has a different answer for that question. Personally, I hope to live to see the day when we have a thorough understanding of all of the causes of each of these disorders (and trust me, there will several if not hundreds of causes for each of these disorders). This would be a big step forward in developing effective treatments that benefit a large portion of the affected population.

Is it possible to regenerate brain cells today? If it is, how? If it isn't, when do you expect for the availability of this technology?

YamnuanEmpire

We are able to generate human brain cells in a dish using stem cell technology. Experiments injecting the mouse version of these neurons into mice has only recently begun, so there is still some time before we start doing this in humans. Having said that, I do believe this is an exciting avenue for future treatments of neurodegenerative diseases such as Parkinson's and Alzheimer's disease.

Hi Dr. Wells, I'm about to graduate with my biology degree and I've found many projects at the Broad Institute very fascinating. I've applied to several research tech positions there. I know this might not be the kind of question you want, but do you have any advice to a college grad looking for work there?

kcall123

Send me an email (mfwells@broadinstitute.org). The Eggan lab will be looking for techs that we will hire through the Broad in the next few months.

Thanks for taking some time to answer these questions, my brother has autism and I'm looking forward to a cure soon :P Regardless, I was wondering if you had any information about how it's formed in a human brain? And also what is holding us back from curing it?

50shadesofrayy

There are many theories concerning what is causing autism in humans. I am biased towards the synaptic theory, which states that defects in the synapse (i.e. the part of the brain cell that connects it to other brain cells), are the root of the problems. However, we simply do not know enough about the brain to make attempts at "curing" this disorder. The last thing we want to do is give someone a treatment that actually worsens the condition in an irreversible manner. So, lack of understanding is the main impediment to a cure. This will only be overcome with time.
How do you know ADHD is a disorder and not just a different type of person who might have problems learning but might excel at other things in life if we in western society didn't have only one model for raising children of the masses (schools). How come it's mostly just a western problem like depression. Why not put your mind to something more critical like Alzheimer's. Why don't all scientists work on one problem till they fix it then move on to the next instead of farting around with thousands of projects.

alexbyasse

To answer the first part of your question, ADHD is very much a real disorder that afflicts millions of people. It has nothing to do with schooling. This is a biological problem.

And I choose to fart around with different projects because you never know what is going to work. I start several projects with the hopes that at least one of them pans out to answering some questions.

You may think that Alzheimer's is more critical than ADHD, but I think someone with severe ADHD may disagree.

Is there a correlation between psychiatric diseases and infections?

liketosee

Yes absolutely. Flu during pregnancy can greatly increase the risk of bipolar disorder and schizophrenia. This is an important aspect of psychiatric disease that I personally hope to study in the next 5-10 years. Great question.

Can mice experience depersonalization or derealization?

NoLongerInPurgatory

I don't know. We have no way of really testing this as far as I know. If you have any ideas on how to observe this in a mouse, I would love to hear them.

Do you use the CRISPR-Cas9 technique?

MorsLess

I do now in my stem cell work but didn't in the Ptchd1 mouse project. The Feng lab has started using this technique more frequently.

What are the known factors that lead to mutation of the Ptchd1 gene?

hipretension

Most of the deletions are de novo, meaning neither the mother or father have the deletion. Instead, the deletion was introduced at the gamete stage (female egg). Some of the mutations have been inherited from the mother (note: Ptchd1 is on the X chromosome, so a vast majority of the deletion patients are males who receive the mutated gene from the mother).

We don't really know what exactly causes these de novo mutations. Obviously, environmental factors can lead to spontaneous mutation. At the same time, some studies have suggested that increasing paternal age can increase the probability of autism-relevant de novo mutations. In other words, dudes
out there should try to have kids while they are young.

Congrats on your work.

First of all, can you explain how does something like OCD have an effect on animals since their brain is much simpler and don't see as much as we do, do they just have to do something repeatedly beside looking for food?

Also, how do you translate your work to human since human brain and mind are much more complicated than mouse? With that plus DNA, chemicals difference, how much could your work assist human with these illness?

kariers

The Feng lab published a paper in 2007 describing the Sapap3 knockout mouse model of OCD (Welch et al, 2007 Nature). These mice displayed increased grooming behaviors which resulted in skin lesions. They would essentially pull the hair out of their skin, which is seen in humans with trichotillomania. We tied this behavior to defects in the striatum, which is a structure in the brain responsible for habit and reward. So while there are differences between mice and humans, we can still see rather rudimentary forms of these disorders in mice.

It is difficult to translate what we see in mice to humans. I addressed this issue a bit more thoroughly in another thread. If you still have questions, feel free to ask away.

To what degree can mental illnesses we usually think of as distinctly human (depression, schizophrenia, multiple-personality, etc.) appear in animals? How would a human recognize such illnesses?

SergeantDarwin

I think the personality disorders definitely fit into the realm of human-only. You see things like depression and OCD in all kinds of species. You can see this in mice and even more easily observe this in dogs (don't worry, I did not do any experiments on dogs, I have just been around them my entire life). We are special beings, but not that special.

How big part of the "diseases" are a result of prenatal, youth or adult environment of the subject, and which role do the epigenetic factors play in the study? Does changing the living conditions, diet and social connections help in beneficial way compared to only giving a chemical compound?

Animals do have personalities, so how does one see the difference in genetics compared to learned behavior? How much of that is an actual measureable disease and what part can be explained with different personality traits?

micefy

We know that early infections and exposure to toxins (e.g. lead) can manifest in these diseases or at least in behavioral symptoms that are used as diagnostic criteria for these diseases. We also know that an enriched environment and education plans can help alleviate some of the symptoms of these disorders if applied early enough in development. A healthy diet and routine exercise are also known to help with bipolar disorder in some cases. For some lucky individuals, these interventions are enough to help them manage these disease without drugs. For many people, however, these things help but are not enough. This is where chemical compounds come into play. Though they are far from perfect and
there are serious concerns I have concerning some of the business practices employed by some of these drug companies, I think we as a field will continue to improve these treatments to minimize side effects and enhance on target effects. It will take some time though.

And yes animals have personalities (this is most obvious to me in cats and dogs) but I would argue that it is very difficult to observe the personality of a mouse. Genetics do play an important role in human personality though I am not well-versed enough in the literature to give an expert opinion on this matter.

Fellow Columbus native here.

I was wondering what your thoughts are on the role of neuroscience in the development of new artificial intelligence technologies, and vice versa, as these are increasingly becoming the center of mainstream scientific discussion. Do you think it is possible that an artificial model of the brain and nervous system could effectively be used to study something such as psychiatric disease? Maybe more effectively than mice? Thank you.

bloodyhotelroom

It is possible, though I think that in order to create a perfect artificial model of the brain, we would first have to more completely understand the brain, which would require investigations in mice. I do think that as we make progress in computational models, we will be able to better understand some of the emergent properties of the system that goes beyond individual cells acting in a bubble. I think the main impediment to the application of this technology would be modeling human behavior. Though there are some fundamentals in human behavior, it is such a complex system that I think it would be difficult for us to replace the mouse with a computer any time soon. I am hopeful though.

Are you finding that psychiatric disorders are/are not chemical imbalances? Do you believe the current swath of medications for people with psychiatric diseases are more focused on treating the symptoms and not the fixing the deficits in brain function? Will we ever see a "cure" for psychiatric problems, or will medication always be the sole medical treatment (therapy/life style excluded)

Thats_an_alrightname

Chemicals like dopamine and serotonin are definitely playing a role in psychiatric diseases. These chemicals are very important for many, many brain functions which is why they tend to have wide-ranging side effects. Most of the first generation drugs target these chemicals. Given the progress we have made in the past 20 years or so, I think we will start to see more drugs that have more specific targets. This should reduce the side effects while amplifying the on-target effects.

For the foreseeable future, I see medication as continuing to be the main tool for medical treatment. I am optimistic about the prospects of gene therapy, which I view as playing a critical role in the personalized medicine revolution.

In fact, the Feng lab recently published a paper in which they "turned on" the Shank3 gene in mice lacking this gene (Mei et al, 2016 Nature). Mice lacking Shank3 display ASD-like behaviors, including social interaction deficits and repetitive behaviors. By turning on Shank3 in early adulthood in mice that had spent their entire lives lacking Shank3, they were able to fix both of these behaviors. This suggests that future treatments aimed at replacing the Shank3 gene in ASD patients can restore normal behaviors.
Recently I have begun to see animal studies (and a few human studies) suggesting that microbes in your gut may have a large influence on the way the brain behaves.

Is this line of thinking something you feel has merit? Would you ever be interested in looking into the effects that microbes could have on psychiatric disease in mice?

For reference

Frankyg170

I have colleagues who are wrapping up experiments describing the role of diet on behavior via gut microbes. Though I have no plans on doing these experiments, I do think this work is merited and needs to be investigated further. There are so many things we do not understand about the brain in both the "normal" and "diseased" state. We should not be ignoring any possible explanations for how and why the brain deviates during development to produce these disorders.

Are you seeing more profound cases of anxiety disorders due to the demands of modern living?

Seabhac1

I am not sure if and how much the numbers have increased, but I would guess that the answer is yes. Our brains have evolved over an immense amount of time to the pressures of our environment. Over a relatively short period of time, our environment has drastically changed. Even though the system can adapt to changes, there is no way we can adapt to everything. Take attention as an example. Thirty years ago, I could have gone to lab and not have to struggle with the constant urge to go on Reddit for 4 hours rather than write that preliminary grant proposal that was due yesterday. We have more and more distractors which are making straining our attentional circuits. I can imagine that with the added demands of modern living could be straining the circuits involved in anxiety to similar levels.

Hi Dr. Wells and thanks for being here.

I have two quick questions (lots of long ones too but I'll look those up). First, you have the knockout but in my 30 seconds of internetting i saw that there are 8 isoforms (shapes that can allow alternate functions) of Ptchd1. Have you done more selective mutations to isolate which of those functions is most detrimental? Does the prevalence and function of those isoforms change with maturity?

I suppose this makes three questions but those two were related. Thanks to your work (and some other people's too) there are a few examples of genes involved in cognitive dysfunctions. Have those functions been included in any predictive models (fancy math that gives you clues of where to look and what's important)?

Thanks again for being here and go Tarheels.

CompMolNeuro

We knocked out exon 2 in one mouse and exon 1 in another. Ptchd1 is a 12-pass transmembrane domain. By targeting exon 2, we generated a early stop mutation that gets rid of most of the transmembrane domains. So, if the protein is produced, it is unable to carry out its proper function. We can not confirm this, or completely exclude the possibility that the protein fragment has a dominant-negative effect, until an antibody is produced that can target Ptchd1 (we tried 22 different antibodies and they were all terrible).

I am not sure about the predictive models. As far as I know, I have not seen a good computational model of cognitive dysfunction, though I do hope to see something like this in the future.
Congratulations on getting a publication in nature! My question is simple, why did you use mice and not rats? I know that their CNS have more in common with humans than mice.

NBPS

Great question. It is a simple answer—it is easier to genetically engineer mice compared to rats. Rats are easier to train and show more robust behaviors, so I would have preferred to work with them. I think advancements in CRISPR technology will improve this shortcoming but for now, mice are the standard species for these types of manipulations.

If we were to throw ethics out the window and begin testing using human brains, what advancements could be expect to achieve in the next 5-10 years?

The-Princess

If we were to completely ignore ethics, I think you would see several groups try to use optogenetics to learn about the circuits underlying different behaviors in humans. This would require introducing the protein necessary for these experiments (i.e. channelrhodopsin) into humans, which would most likely have detrimental effects if we used the technology we have at our disposal at this moment. We would then have to implant blue lasers into these brains, which is by definition an invasive brain surgery. I could also imagine people using CRISPR gene editing of embryos to manipulate the genome in humans, much like what we do in mice.

But to be clear, any biological advancements we make would surely be negated by the giant leap backward we would take as a moral society.

Years ago I took Mefloquine as an anti malarial for an overseas's trip. Since then I have suffered from a panic disorder. I have tried to read as many studies as I can and a lot of it is over my head. What I'd like to know is, can an anti malarial such as Mefloquine cause damage to an individual in a way that they end up with a permanent anxiety disorder. I ask because I have a hard time understanding if a disorder like panic attacks is a mental disorder or one that is physical in such as the brain can be damaged and the damage can be viewed.

I'll provide a link as an example of some of the studies I try to understand as an example of what I am trying to explain. Thanks for your time.

1: Idiosyncratic quinoline central nervous system toxicity
2: Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry

TheShallowCurtain

I really wish I could help more in answering your question. There are some examples of medications and drugs (such as LSD) triggering psychosis and other disorders, though I do not know how this particular medication could lead to your symptoms.

Will this work continue? I'd be interested if anything could be learned about bipolar disorder?
I do not have any current plans to do this work but there are ongoing experiments using mouse models of both depression and mania (though I am not sure how many genetic models there are that show both poles of this disease). Many of the next generation anti-depressants use these animal models as a foundation.

FYI a good example of a mouse model of mania can be found here: http://www.ncbi.nlm.nih.gov/pubmed/24153177.

Hi Dr. Wells, I am a grad student who also works on the genetics of psychiatric disease. I am familiar with Dr. Feng's work on Shank3, and went to the Broad Conference on psychiatric genetics in 2013.

My question is how do you suggest we begin to model psychiatric disease in light of its polygenic nature? Presently, we focus on individual risk genes and how they specifically affect an organism in terms of behavior and molecular mechanisms. However, in reality, it is the interaction of multiple genes and the environment that confers risk and leads to these disorders. As we progress in this field, do you think we can eventually model these disorders polygenic nature in mice?

NeuroscienceNerd

Yes this is an important point. We mainly focus on single gene models of disease. We are coming to appreciate more and more the role of multiple genetic factors. I think CRISPR gene editing technology will help with this problem. Using older methods, it would take considerably more time to create a genetically-engineered mouse. CRISPR has cut some of this time due to its high efficiency. I anticipate more "double hit" or "triple hit" animal models in the future that target multiple genes at the same time. It won't be easy and the breeding costs allow to generate a triple knockout mouse will be prohibitive for most labs. Nevertheless, this is something I see happening sooner than later.

I was curious if any related research has gone into Borderline Personality Disorder?

Youreagoomba

Not that I know of. Personality disorders are ridiculously difficult to study in mice since they don't really have personalities, per se (note: if there are any mouse owners out there, please don't get mad at me for saying that they do not have personalities).

Hi! Can you discuss your strategies for data management/data organization with big genetics-based projects like yours? I know this is becoming increasingly difficult in labs, and I'm curious what kind of process you rely on. Especially as it relates to data sharing and metadata requirements.

clandestino

There actually wasn't a crazy amount of data for this project. Yes, there were GBs of videos recording mouse behaviors, but nothing that couldn't fit on a 1 TB external hard drive. Data management is more an issue with the whole genome and whole exome sequencing data that goes on at the Broad Institute. I am not currently participating in those studies, so I have little to share on that matter.

Thanks for giving us the chance to ask these questions!

I now work in the laboratory of Dr. Kevin Eggan where I am using human stem cell derived brain cells to study some of these same diseases.
How does one go about studying neurological function of brain stem cells? Are the individual parts of the brain actually grown (seems unlikely) or are the stem cells grown into nuclei and studied on a smaller scale?

**JackDenninger**

We use a technique that starts with a human stem cell that we then convert to a human brain cell. We can then study these cells from both patients and healthy controls to identify differences in molecular pathways and firing properties.

Hi Dr Wells, and thank you for your outstanding work. I just wanted to share, if it will help in your efforts at all, the results of Dr Hyman Schipper at the Lady Davis Institute in Montreal, who has developed an exceptional mouse model for schizophrenia and other disorders. The model has been used to promote his work, which was published in the Journal of Neurochemistry.

**dancohen-av**

Thanks for the head's up. I will be sure to read this paper.

Michael, congratulations on your work and accomplishments. I hope you learned everything you could have at Charles River Technical Institute.

A few things:

1- What are the barriers to seeing how this works in humans?

2- What do you make of the findings that point to some severe cases ADD/ADHD being misdiagnosed as Fetal Alcohol Syndrome Disorder?

3- Go Cards?

**Heresyourchippy**

1- We need to validate the cellular defects in human stem cell-induced neurons. Unfortunately, there is no protocol to generate TRN-like cells from stem cells. Once this happens, we will have a better idea concerning whether or not SK2 enhancement can correct the TRN firing defects.

2- I was not aware of this. I will read up on this later.

3- St. Charles, hail. (For the uninitiated, this is a reference to the high school I attended in Columbus, OH)

Do you think you could grow a mouse brain with neural interfaces that can be communicated with via computer? Given the tools such as stem cells, 3d printers, and a proper ion-electrode interface (molecules capable of converting bytes into impulses and vice versa)

I would like to grow a brain someday not human, but I think the technology is almost there...

**throwawaymoparizer**

This was once considered science fiction. I think we are starting to warm to the idea that this could be a reality. Cebbral organoids (aka mini-brains) have only been around a few years and are progressing at an excitingly fast pace. Could we stick an electrode in a brain organoid and connect it to a
computer? Sure, why not? Will this tell us anything about how the brain develops? Well only time can tell on that one. We still don't fully understand the power of these tissues.

Dr Wells, what's your favorite bar in Cambridge?! On a serious note, how do you balance the desire to leave academia for a more lucrative career in industry? Is it enough for you that your gene may be a target for a drug one day? Or do you want to be a part of the drug development process? Thanks for your work.

geneticswag

1. Russell House in Harvard Square
2. I am still not certain which route I want to take. Yes, pharma is more lucrative but does not have the job stability of a tenured professor. I would like to be more involved in the drug development pipeline, which is why I am considering industry. At the same, I would not have complete autonomy to study whatever I want if I would were to make the leap into industry. I plan on making this decision in the next two years, though I am leaning towards academia.

Given what you know about the inner workings of the brain, what's your position on “free will”?

thowedendaliver

Great question. I was saving this for the end because I was having trouble coming up with an insightful answer. Here is my attempt at sounding smart:

At the most basic level, we are slaves to dopamine. We do anything and everything to spike dopamine levels in our brains, whether that be eating five slices of $0.99 NYC pizza in one day (which I did this past weekend) or trying to solve diseases affecting the brain (which I tried to do over the past 5 years). Different things motivate different people, but it all comes down to that sweet, sweet dopamine reward. Most animals seek out this dopamine signal for immediate gratification. Humans have evolved to a level of complexity that has allowed us to delay this gratification for the hopes of a larger reward (dopamine spike). So while believe we have free will in the sense that I do not believe there is some sentient being controlling our every movement, I do believe we are fooling ourselves if we think we are not being manipulated by our basic desire for pleasure.

I'm a graduate research student who works with a Cre-Lox knockout model of Brain Derived Neurotrophic Factor in skeletal muscle of mice. What type of mouse model engineering does your research generally use for knockouts or other manipulations? (Crisper, Cre-Lox, etc).

RyBry

We have historically used the Cre-lox system to control the gene of interest and the flp-frt system to control our gene for selection (usually, NEO). The Feng lab is getting away from this system with some of the newer mice being generated using CRIPSR.

Hi Dr! I am really passionate and interested in Neuroscience and I wish I could pursue a career in your field. However I worry about the pay as I heard that its quite low for the time actually invested. Can you please tell me what I should expect income wise?

sephiroth_vg

We don't do it for the money. We do it for the power, fame, and women.
Seriously, though, you don't make much as a grad student or post-doc, but if you are successful enough to run your own lab, the pay and benefits are quite comfortable. There is a lot you can do with a PhD. I have several friends making plenty of money working in industry or biotech or consulting.

i guess my question after sticking around to read all your answers is why did you not acknowledge my question even though it was voted into the top 50th percentile? it appears you have skipped it? do you need proof of my claims?

concept2creation

I just answered. Sorry for the delay.