Hi Reddit!

In 2010, we watched Sonia's mom die of a rapid, mysterious neurodegenerative disease that baffled her doctors. After her death, we learned that it had been a genetic prion disease, and Sonia was at 50/50 risk. We got genetic testing and learned, in late 2011, that Sonia had inherited the lethal mutation, meaning that unless a treatment or cure is developed, she's very likely to suffer the same fate, probably by about age 50. After learning this information, we abandoned our old careers in law and city planning, and threw ourselves headfirst into re-training as scientists. Four years later, we're both Harvard biology PhD students, and we work side-by-side Stuart Schreiber's lab at the Broad Institute, where we are researching therapeutics for prion disease.

A husband and wife's race to cure her fatal genetic disease, Kathleen Burge, Boston Globe Magazine, February 17, 2016
Insomnia that kills, Aimee Swartz, The Atlantic, February 5, 2015
Computer scientist makes prion advance, Erika Check Hayden, Nature News, October 2, 2014
A prion love story, D.T. Max, The New Yorker, September 27, 2013

We’ll be back at 1 pm EST (10 am PST, 6 pm UTC) to answer your questions, ask us anything!

Update: Hi Reddit, we're going to officially sign off but just wanted to say thank you so much. Four and half years ago, we never would have imagined people taking such an interest in our cause, or our career changes, or this uphill battle we are fighting. It's humbling to have so many people out there pulling for us. Hopefully this story has many chapters to come. Thank you!

From a scientific perspective, I'm wondering what your research approach is. Are you focused on compounds to identify or disrupt, or are you taking a more top down approach and investigating the etiology of formation? It's my understanding that existing prions are both enormously sturdy and somewhat shockingly prevalent, and also that they aren't the only route of protein misfolding, and that many forms of neurodegeneration often arises from 'prion like behavior' in certain proteins (tau, TDP-43, parkin, etc), or in failures of various protein clearance pathways. What do you feel is the most promising course of diagnosis or therapy?

Also, in the topic of microecology, certain prion like proteins seem to be everywhere, and I'm wondering what you can tell us about their role in microbiology?

From a personal perspective, I wanted to applaud the two of you for taking on this task, state that I think in a lot of ways, science is one of the greatest acts of defiance, and I wish you both well in your efforts!

Izawwlgood

Hi, this is Sonia. We are interested in approaches that aim "upstream" in the disease process — at 1) the biogenesis of PrP (the prion protein), 2) native, healthy PrP prior to misfolding or 3) the process of prion propagation and spread. Compared to these areas, we know very little as a field about why
prions are neurotoxic, which makes neurotoxicity a less attractive target for us. In addition, the neurotoxic phase of disease is incredibly rapid and as with any degenerative condition, preventing damage is going to be more feasible than reversing damage. The best proofs of concept in animal models (and prion diseases are modeled really well in animals) suggest that you can achieve the greatest effect in delaying disease by aiming upstream of symptoms.

We believe that prion diseases will be treatable well before we have all of the answers to all of the questions in the field — indeed, we will probably never sort out all of the mysteries! Biology is complicated. The etiology of prion formation is fascinating, and the question of why prion diseases arise in midlife is still unanswered. So far there is no indication that second-site genetic factors or environmental triggers determine age of onset. We aren't going after this question directly — we're focused on interrupting the process of prion formation by reducing the PrP substrate or stabilizing PrP against conversion. We are also interested in pursuing mechanism-agnostic phenotypic screens for inhibitors of prion propagation, if and when the right systems can be developed.

Although there's a lot to be said about prion-like mechanisms in other neurodegenerative diseases, we are very focused on PrP. There is a canon of strong genetic and biochemical evidence supporting PrP as the drug target in prion disease.

First off I just want to say that it is truly inspirational to read that you've both changed careers to try and cure a genetic disease, knowing that it is essentially against a timer. It's a situation that I couldn't imagine being in, and I genuinely wish you all of the luck in the world with your research.

As for my question, I'm afraid it may be a little basic as I'm not a biologist by trade. I've heard how prions are made up of distinctive folded proteins that can cause other proteins to fold in similar ways which causes a variety of diseases and symptoms. A common one we hear about in the UK is Bovine spongiform encephalopathy due to the "mad cow" epidemic in the 80s and 90s. From my reading, mainly of news and science articles, they can also occur randomly in anyone at any time. I was just wondering what the incidence rate is for prions to randomly occur, without being caused by something such as genetic disorders or through the ingestion of meat containing prions, such as with BSE?

OldBoltonian

Eric: First, for clarity, when Sonia and I use the term "prion", we are almost always using the narrow sense - prions composed of PrP, the protein that is the product of the gene PRNP. Some people use the term "prion" more generally to refer to any self-templating protein conformer - everything from Sup35 to amyloid beta. I'll confine my answer to prion diseases in the narrow sense.

We see about 1-2 cases of prion disease per million population per year. It's the countries that work harder at surveilling these diseases that find a figure more closer to 2 per million, so that's probably more accurate, and there is some amount of underdiagnosis in countries with lower figures. This means prion disease accounts for about 1 in every 5,000 deaths, so the average person has a 1 in 5,000 lifetime risk.

Only about 15% of these people have rare genetic variants in PRNP, and these days, <1% can be traced to an infection (e.g. from BSE). The remaining ~85% are sporadic. Sure, other environmental or genetic factors might contribute some of the risk, but overall, sporadic cases appear geographically and temporally random, so it really seems that they just happen. Presumably because even wild-type PrP spontaneously forms prions every now and then.

For references and more detail on these stats, see our paper: https://github.com/ericminikel/prnp_penetrance/blob/master/manuscript.md
Sonia, two questions.

1. How old are you? It was stated in the post that your mother passed away at around 50 and I am sure many are interested in what your approximate timeframe is for this project.

2. How did you initially react to the diagnosis and when did you both decide to become PHD's. Was the decision hard for you both to take the classes?

Edit: Best of luck to the both of you, I am rooting for you!

Azoth1992

Hi, this is Sonia. I turned 32 in March. I should note that while we hope we have ~18 years or so to work to impact my prognosis, the age of onset for genetic prion disease (and my variant in particular) is extremely variable -- so this is just a ballpark. About our initial reaction to the diagnosis: for us, the absolute worst time was learning that my mom's disease was genetic (which we learned from her autopsy, after she passed away) and that I was at 50/50 risk of having inherited her disease mutation. Since prion diseases aren't usually genetic and there was no family history prior to my mom, this came as a shock to us. The limbo of waiting for the genetic test result was the hardest time for us. The 50/50 wreaked havoc with my mind -- it was like I had no place to rest mentally. I just kept turning it over and over. Although of course the result of the test wasn't what we'd hoped for, once we had it in hand we could being to adapt to it, do our grieving and figure out how we were going to cope. It became a fact of life.

As for deciding to do our PhDs, there wasn't a moment where we looked at each other and said, "That's it, we have to go out and cure this thing!" It happened step by step, with the goals changing along the way. Our first goal was to become savvy consumers of scientific information so that we could advocate for ourselves as patients. Then as we learned more, our ambitions grew. I realized when I took my first job in a research lab that this wasn't just a sabbatical from my normal life -- this was a new life. But even from here, deciding to do our PhDs and focus our lives on developing treatments for prion disease was a process. I think first we had to learn enough about the specifics of the prion field to realize that there were things we could do at the bench, in the time we have (or hope we have) that could make a difference.

You are probably aware of it, but there is an extremely interesting report written by the doctors of a person suffering from FFI who attempted to self-medicate and kept a diary of doing so. He ended up beating his life expectancy diagnosis quite significantly.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1781276/

Could certainly be worth looking into if you haven't.

ExxAKTLY

Eric here. That paper was certainly an interesting read. I don't buy any of the therapeutic hypotheses though. Note that the guy was already 10 months post-onset when he started those experimental therapies, which is already 4 months longer than the average survival for someone of his genotype (D178N 129MM), so his exceptionally long survival time may not be attributable to any of the drugs or supplements he took. Also a lot of things he took were oriented around correcting his sleep deficits, whereas insomnia isn't even always a prominent symptom. Sonia's mom presented with rapid onset profound dementia and neither of us would have listed insomnia among her top ten symptoms if you'd asked us at the time. (This is among the reasons we think the old naming scheme of CJD/FFI/GSS is antiquated and we should refer to them all as prion diseases).
What are your thoughts on CRISPR gene editing? From my understanding, it allows you to modify specific sequences, and even single nucleotides, of an entire organism's genome. Do you think it is a viable option for your situation?

Waja_Wabit

Eric here. CRISPR is an awesome tool for engineering cells to study and model the disease in the lab, and we're using it right now. As a therapeutic modality, it has a ways to go, mostly because we don't yet have a way of delivering CRISPR to all 100 billion neurons of the adult human brain.

In cultured cells, CRISPR can achieve maybe 1% homologous recombination (to correct a mutation) and maybe 60% non-homologous end-joining (to knock out a gene). We're more interested in knockout, because it is totally protective, whereas even if you corrected Sonia's mutation, the wild-type protein would be capable of carrying on the disease process if there were prions already in her brain. The trouble is, no one has demonstrated the ability to deliver CRISPR to a high enough percentage of neurons in the brain to make a meaningful therapeutic difference.

There are smart people working on this and I think it is conceivable that major advances in this area could come in our lifetime. It's not what Sonia and I are working on day-to-day though.

For more details, see: http://www.cureffi.org/2014/03/09/how-to-and-how-not-to-knock-out-prnp/

What's the most difficult thing about working as a husband and wife research team?

straydog1980

This is Eric. I just turned to Sonia and asked, "Is anything difficult about it?" I love it actually. Sonia is the bomb. I feel so incredibly lucky to get to spend all day every day with her. It is one of the upsides of all of this happening to us, that we get to spend almost all of our time together.

Your dedication to abandon your careers and dedicate your lives to this is incredible. You both are a shining example of what people can do when you follow through on something you set your mind to. I'm sorry for the loss of your mother.

I apologize if this is crass, but how do you plan on staying objective throughout testing and results if it's your (or your wife's) life on the line? I feel like that would be a very difficult task.

Thank you for this AMA, and best luck and wishes to you both.

tealplum

Sonia: Just answered a similar question below -- basically, when it comes to objectivity, our goal fuels our discipline. I don't think of this as a conflict at all -- we have the most to gain by being true to what the science tells us.

How can I or anyone else help?

MyNameIsNeal

We need patients to participate in research, doctors to collect cerebrospinal fluid so we can look for biomarkers, scientists to train us and mentor us in all sorts of techniques and to share findings and reagents and cells and collaborate with us, pharma companies to take an interest in our disease and our target, regulators to think seriously about how to make it easier for drugs to be approved for rare
fatal conditions, funders (be they philanthropic, government, or industrial) to fund us, and we need people to continue to show us love and support as you have all done so beautifully in this AMA. (THANK YOU - four years ago we never imagined people would take so much interest in our cause).

And a few more general suggestions. Vote. We need more science funding and sound science policy. Blog. The internet is awesome and is how we should be communicating science. I love when I Google something and find an answer because someone else has struggled with the same question and then blogged it once they figured it out. Share. Sharing our personal stories makes us all less alone, more empowered together. Care. When your loved one gets news like the news we got, tell them what our friend Stevie told us - science has answers for you.

-- Eric

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Awesome! -Eric

I'm an undergrad. Last semester, my biology professor went on kind of a tangent about prions, specifically fatal familial insomnia. Her point was basically, they are scary -- that you don't want a prion protein to get in contact with your normal protein. I understand that's how mad cow works. Is it dangerous to work with prions in a lab? Does it pose any actual tangible risk to you, or was my professor exaggerating for effect?

5firtrees

Sonia: Like many things in a lab, prions have to be handled according to established safety protocols if you are going to work with them safely. One of the first biochemical observations about prions is that they are not destroyed by the same techniques that kill bacteria and viruses. Since then, a lot of work has gone into establishing that prions are destroyed by incineration, bleach, strong acids and strong bases. A misconception that we encounter sometimes is that you "can't" decontaminate prions -- this isn't the case, you just have to have the right protocols in place. It's really, really important to take lab biosafety seriously. With that said, the evidence is that researchers and hospital staff who encounter prions in their work have no increased risk of prion disease compared to the baseline population.

Why does the disease wait until about 50 to "turn on"? Are there environmental triggers? Do there seem to be earlier, more subtle manifestations?

ShataraBankhead

Eric here. This is probably THE most common question we get, both from patients and from scientists. And it's a great question. You express the mutant protein your whole life, so why does disease wait 50 years to strike? We have no idea. The same question arises for other mid-life onset diseases too, say for Huntington's or Mendelian forms of Alzheimer's, and across the board, I think the answer is we have no idea. In fact, I don't know I've ever heard a credible experimental plan for how to answer it.
either. It's a tough one.

What are the options you are currently considering to treat or cure the condition?

Do you have a mouse model to study the disease?

haffi112

Sonia: We're lucky to have outstanding mouse models in prion disease. Neurological conditions are in general very hard to model in animals, but we have a unique advantage in that prions can (under specific circumstances) be transmitted. Mice intracerebrally injected with prions develop have a highly predictable disease course which consists of a silent incubation period, followed by full-blown neurological disease that is fatal. Their clinical symptoms and neuropathology resemble human disease.

A challenge with these models is that mouse prions appear to have structural differences from human prions -- prions seem to come in conformationally encoded "strains." There exist small molecules that are highly effective at extending survival of prion-infected mice, that don't seem to have any effect against human prions. However, these models are still useful for many types of studies and for investigating therapeutic strategies that focus on native PrP. There are also mice that have been genetically engineered to express human PrP, that can be infected with human prions, and these provide a closer model of human disease and could be useful for strategies that more directly target prions.

I am a PhD Student in Pharmaceutical Sciences, and I don't want to be the debby downer here, but realistically speaking, what is the best scenario you guys are aiming for? Even if you discover something resembling a cure, testing for approval/getting approval takes upwards of 10 years. Research is a slow thing, sooo in the best case scenario you can have something (let's say) in 5 years and then let's add 15 for development and approval. How would this fit into your time frame?

On a personal note: You guys sound fucking bad ass! With no science training you went and became PhD biology students (at Harvard no less) sooooooooo, if anyone can do it, you guys sure seem to have the drive/ambition to do it! Good luck!!!

Coste10

The real race is to get it into clinical trials. Experimental therapies save lives, even in Phase 1. While compassionate use is one option, we would be keen to enroll Sonia in the actual trial. - Eric

You mention in your bio that you are researching "therapeutics". This might be more of a general medical research question, but what exactly does this mean in terms of a goal for your research? Are you going for a "cure" or simply a treatment that could extend life with the disease? Both? Whichever seems more likely at any given time?

DerbyTho

Sonia: The way we think about our goal is that we're trying to develop a treatment that will extend time to disease onset -- with the ultimate goal of extending it beyond the normal human lifespan. The strategies we're interested in won't result in a one-time fix, but rather a regimen that keeps prions at bay.

Our goal for genetic prion disease is not to extend life with symptomatic disease, but to extend the pre-
symptomatic phase. Once symptoms arise in prion disease, the downhill is amazingly steep (months) and patients quickly reach a stage where all quality of life is gone. Treating sporadic prion disease will be a challenge for this reason, since these patients aren’t identified until they’re symptomatic -- earlier diagnosis will be critical here, and while there have been some promising developments in this area over the past few years (like the RT-QuIC prion detection assay) we still have a long way to go.

You two are an inspiration.

As a statistician I’ve been taught the importance of objectivity in science. Do you worry that the life-and-death stakes of your research will bias any results? How do you stay objective when pursuing research leads and interpreting results when your research is so close to your personal interests?

webbed_feets

Sonia: I couldn’t ask for a stronger incentive than ours to be objective in our science! When your life depends on it, you are less willing than anyone else to entertain marginal results, results that fail to validate, or weak therapeutic hypotheses. One way to think of it is that it’s the other scientists who have a conflict of interest -- if they work for twenty years and don’t find a way to treat the disease, their life will go on!

Abandoned the career in law and city planning and 4 years later, PhD at Harvard. WOOW!

What did you guys major in? Were you always interested in scientific research?

antariksh_vaiqyanik

My undergrad was in Chinese and my Master’s was in City Planning/Transportation. Sonia had a law degree. We definitely had no interest in scientific research before all this. -Eric

Wow, first of all, this is truly inspiring. It almost brought a tear to my eye to read this to think about the implications of the scenario you are both in. The hardest part being that the one you love more than anything in this world is a ticking clock that you are racing against. I’m sure you’re both deeply and fully in love with each other in every way possible - if you weren’t then you probably wouldn’t choose to redesign your lives to tackle this problem together, head on.

My question(s):
What is a typical day for either/both of you? What are the day-to-day activities and how many hours on a daily/weekly basis would you estimate that you are each pouring into the scientific duties that the research of this problem demands? Do you guys still make sufficient time for activities not-related to your research on a recurring basis, or have you both chosen to forego a social life and throw all of yourselves at the problem until you find a solution?

tehrand0mz

So here’s my analogy on the day-to-day struggle. Our quest is like fighting a horse-sized duck guarded by one hundred duck-sized horses.

The duck is huge and terrifying and undefeated. When you set out on this quest you were nobody and you didn’t even know what a duck was, let alone how to fight one. But you didn’t choose the duck, it came after you, and so you have to fight it. And, incredibly, some very smart people have placed bets on you winning against the duck, and have given you the tools and training to fight it.
But to even get close to the duck, you have to struggle through this swarm of tiny horses: applying to school and fellowships and grants, filing protocols and permits and material transfer agreements, reformatting manuscripts, submitting abstracts, practicing talks, booking travel arrangements, sending emails. The most frustrating times are when you spend a whole day mowing down horses and never glimpse the duck.

What makes it worthwhile: on those days when you do glimpse the duck, you see that it is flesh and blood, just molecules like everything else. It is mortal, and the world is cheering you on. Fight the duck!

To the more practical aspects of your question: we do still have a social life. We still cook our own food. We travel a lot but usually together. You have to sharpen the saw.

--Eric

How has all of this affected your relationship? I imagine your work is very stressful, knowing the implications of what you're doing. Thanks for doing this. I wish you all the best.

glenglenglengleng

Sonia: I have gotten to see so many new aspects of Eric through this process, and to be impressed with him in whole new ways. It is impossible to feel sorry for myself for one second when I look at the beautiful human being I am getting to spend my life with.

How optimistic are you?

Misker

Sonia: When we were first wading into the science, we were drawn to the low-hanging fruit -- studies looking at repurposed drugs, supplements, lifestyle changes. We thought we would have to draw optimism from things that could happen fast, or that we could change right away. After 4.5 years coming to understand the field, we have such a different perspective. We've stopped paying attention to things that are being studied for hundreds of different diseases and used in dozens of clinical trials. We've started taking our cues from the specifics of our exact disease: our gene, our protein. I don't think there's an off-the-shelf solution for prion disease, or anything available today that influences disease. But I'm more optimistic than ever, because I think we're aiming right at the heart of our problem, in a rigorous way. It will take time to develop therapeutics that will work, but I feel confident that we're working on approaches that will move the ball forward for patients. The big variable is the timeline, and the honest answer is that we don't know if this will all move on a timeline that's relevant to me. Day to day, I don't think about this much. I tend to operate on the assumption that we have some time, because it's as good an assumption as any and it's the one that allows me to be most productive.

Thank you so much for taking the time to do this AMA. I wish you both the best in your race and if the worst happens please know your work will help others as it's built upon over time.

How was your transition into academia? It's a whole different life and work style than the private sector.

Living off of grad student money is not easy, especially if both of you are scientists. Do you find it difficult having switched from two lucrative careers?

Have you made any breakthroughs with this disease? Or is there anything you feel you are getting close to?
Alantha

Sonia: Academia has been interesting. I'm so grateful that we both turn out to enjoy doing and thinking about science. There's no comparison in terms of how stimulating and fulfilling we find our work in science versus previously, and I love the environment and our colleagues. It's true that the financial side of things is startling. One of the biggest shocks to me when we got into science was the ratio of compensation to years of training among scientists we worked with. We don't require a whole lot, but when I crunch the numbers I do worry about affording child care if we decide to start a family. This is something I passionately wish we were addressing more systemically for all women in science and two-scientist couples.

Very cool that you guys found such strength of will and focus to go after this disease. A few questions,

1) Have you ever been "scooped"? How would/did you feel about it? As academics, we often feel frustration when someone else publishes before us or works on a highly similar project. But you offer a unique perspective, as you predominantly care about the end goal of a "cure."

2) How do you feel about the "10 years, 1 billion dollars" figure that is often cited when discussing bringing new therapeutics past the FDA approval stage? Or are you focusing on retooling already approved therapeutics? Would you be offered the opportunity to participate in a clinical trial?

StarSnuffer

Dude, I would so love to be scooped. We can't do everything, and anyone who can do what we're doing faster and better should absolutely do so.

I am not big on drug repurposing, at least not for our disease. Perhaps it makes more sense for cancer or something - but for prions I think the prior probability of any approved drug working is very low, and so the idea of repurposing tends to just cloud the literature with low-quality hypotheses and false positives.

10 years is to approval, not to a clinical trial (which is when patients can start benefiting) and 1 billion (or 10 billion) dollars is just total R&D divided by drugs approved, i.e. it averages in all the failures, many of which are from low-quality therapeutic hypotheses with no basis in human genetics. - Eric

With time being of the essence, did you follow a normal study path or an accelerated one? Was Harvard accommodating to your situation? I'm also interested how they reacted to your reason for application, and how your class mates (if you studied on campus) felt about this?

Procatstinator

Sonia: We took night classes for about two years while working in research jobs, then applied to PhD programs. Harvard was fantastic, and so were the other programs we interviewed with -- I'm sure our applications were surprising, but we have been so lucky that people have responded incredibly supportively to our personal motivations and focused mission. We definitely didn't take it for granted that we would be so accepted and supported by the scientific community. Maybe there are people out there who aren't into our unconventional path or what we're trying to do -- but I don't tend to meet them.

Hi Sonia and Eric - I work at the MGH and recently read about you in the Boston Globe article by Kathleen Burge and was moved by all the work you are doing. Since I've read that article, you've both crossed my mind a few times and I wonder: Do you ever miss your previous life, or has life become better/the same but different since 2010?
Best of luck in your research!

Lizzitus

I literally never miss it. City planning moves super slow and turns out to be more enjoyable when observed from a distance. Now when something good happens in my city, I can just appreciate it in that moment, without having to think about the 20 years that people spent arduously pushing it through community meetings. Science is way more exciting and way more intellectually stimulating than I ever thought a job could be. - Eric

How difficult was it to leave your positions? I assume you guys were fairly established in your careers, did that make it more difficult to become students? Also, How supportive was your family and friends of such a drastic life/career change?

And also I want to wish you the best of luck on this quest! I can only imagine what you guys are facing, but this will be a tremendous accomplishment because it won't just help you but others who may suffer this rare disease.

tyrandan2

Sonia: It was very humbling to start from the bottom of the totem pole in a new field, after being pretty certain that we had done the schooling we needed to do for our careers. But, paradoxically one thing that helped was realizing early on that biology is by far the most complicated thing I've ever thought about -- and that for this reason, the learning phase necessarily extends for your whole life. This wasn't a cram session to get up to speed but a transition into a whole new way of thinking and a whole new way of relating to uncertainty, in a subject that is always going to be mostly populated by the things we don't know. I should clarify that I don't say this to be pessimistic at all -- what's amazing is that even with such limited and indirect insights into what goes on on the molecular level, we absolutely can and do build tools that influence human health.

I had some amazing mentors early on and this also really helped with the transition. My first post-doc mentor was a wonderful biologist named Marta Biagioli, and she was already quite senior at the time we met, but still took hours and hours to train me on the absolute basics at the bench. On more than one occasion, it brought tears to my eyes.

We experienced a range of reactions from friends and family. Some people asked, "Are you sure you want to be thinking about this all the time?" But I've found that thinking about the science of my disease is really different from thinking about my own mortality every day. From the very beginning, it was a way to interface with this new subject that had come crashing into my life in a way that was energizing, and interesting, and felt like it was on my own terms. We also had friends say things like, "Do you worry that you're just in denial?" But I don't know, aren't we all in denial on some level, as we drift through space on our speck of dust for no reason that we can fathom? Why do any of us do what we do with our limited time on Earth? Overall, we've been incredibly fortunate with the overwhelming support we've received from our loved ones, our friends, our colleagues at the Broad Institute, the prion field, strangers, questioners in this AMA... We had the privilege of seeing the most positive, and most generous side of so many people, and for this I feel very lucky.

Hi Sonia and Eric!

It's great to see that you are both actively searching for a cure. Many patients choose this path, from the Lorenzo's Oil story through advocates in the White House's Precision Medicine Initiative.

My question is how and whether you would want to wade into the FDA treatment approval debate.
Many rare diseases have little likelihood of receiving approved treatments because of a combination of cost, inability to conduct a novel trial design, or lack of natural history data. Have you both looked into how you can pave a path forward for others with the same mutation?

Sonia: Clinical trials will definitely be a major challenge for us as for other rare diseases. One thing about our quest is that we don’t have time to tackle all of the challenges in the drug development pipeline in series; we have to be addressing them in parallel, to the extent that we can. One of our biggest priorities is looking for biomarkers that can predict time to disease in pre-symptomatic individuals, and/or dynamically read out treatment efficacy in advance of symptoms. Establishment of a surrogate endpoint for a prion disease trial would radically scale down the time and cost factors. We also need to build a base of patients interested in participating in research and trials. This is something we’re working on now and hope to make progress on in the next year. None of this will be trivial, but we’re lucky to be coming along in the precision medicine era when many smart people are thinking about strategies/tools for the above.

Hi. First off, I'm inspired by your story. My question is not of a scientific nature and it may be deleted, but I hope it isn't because I'm genuinely curious. How were you able to get into a PhD program so quickly? I assume that, as a lawyer and a city planner, neither of you had a bachelors in biology. Maybe you do, but it seems unlikely. Don’t you need to already have a bachelors in a field before entering a PhD program for that field? Did you have to go back to undergrad?

If Sonia and Eric would rather stick to the science-related questions, maybe somebody else can answer this.

Throw-AwayDixieLand

It did take us a few years. We got the genetic test result in December 2011, started taking night classes in January 2012, got day jobs in science in spring/summer 2012, and applied to grad school in fall 2013 for admission in fall 2014. I think if we had applied right away we probably wouldn't have been deemed credible.

-- Eric

Based on what you have learned so far, what do you see as the most promising way to solve the problem? Would it be to find a way to suppress the production of this protein, or do you think it would be possible to develop a molecule that could neutralize this protein?

millerb

The best proofs of principle are to reduce PrP expression (say, antisense or maybe someday CRISPR if we had a way to deliver it), stabilize PrP in its native fold (probably a small molecule), or antagonize prion formation in some other way (to be discovered through the right phenotypic screens, see proofs-of-concept in IND24, cpd-b, and anle138b). -Eric

Hi thanks for the AMA! I was wondering if you guys were looking into using genetic engineering technology?

Also, my fiance probably has a neuromuscular disorder (his grandad had ALS and his dad is suffering from a horrible side-effect from taking heart meds causing his muscles to degenerate), when you joined/looked for labs to work with did you let them know your intentions, or just convey interest in...
prions?

CarterN10

Sorry to hear about your fiance's disease! To your question - at every step of the way, we have put our story front and center. Without it, nothing about us makes sense. Everyone who's given us a job or admission to school or money or any other opportunity over these past 4.5 years has known about our personal mission. The amazing revelation has been that there seems to be no downside to this. We've met so many people worried about genetic privacy, but being as public as we can possibly be about Sonia's status has only opened doors for us. - Eric

Hello! Thanks for doing this aua on prions. I am so sorry you're in the situation you are in.

Just wondering, will your research possibly help people with CJD? also, I see your mother had it- was there any possibility anyone else in your family has it? I know the famous Italian family can trace it back for generations. Have you had much contact with them?

Thanks so much! Prions are terrifying and captivating and so poorly understood.

antibread

Sonia: We think of prion diseases as a group -- we are less focused on the distinctions between FFI, CJD, GSS etc. than on what they have in common: the same pathogenic protein and disease mechanism. I think that our therapeutic strategies of interest will have relevance across these different prion diseases subtypes. The bigger question in terms of defining a patient cohort, in my mind, will be treating pre-symptomatically versus treating after symptom onset. We certainly hope to be able to do both someday, but they will pose different challenges.

About my family history, there was no sign of neurodegenerative disease in my family tree prior to my mom. We believe that she probably had a de novo mutation. We have had contact with many genetic prion disease families including the one you mention. One of the challenges with such a rare set of diseases will be trial recruitment once we have a therapeutic candidate that we believe in. It's been amazing to connect with these folks and begin building a team.

Some heritable prion diseases affect subsequent generations earlier than the previous generations (ie, if the mother died at 50, the wife in this instance may die at 45, etc.). Have physicians said anything like this?

After researching a little bit it looks like the protein mutated in Fatal Familial Insomnia is affected by a point mutation, rather than repetitive amino acid expansion, which causes the genetic "anticipation" I'm talking about above, so I doubt it will affect Sonia, but still wondering if you've heard anything definitive?

Best of luck, incredibly inspirational story. I will definitely be thinking of you both in the lab today.

thezerosystem

Sonia: There have been some reports of anticipation in genetic prion disease, but as you point out there isn't a plausible mechanism with these classes of mutations. Eric's first paper in biology actually addressed this very question, and showed how ascertainment bias was driving the effect. Available here: http://www.ncbi.nlm.nih.gov/pubmed/25279981
Why do you guys sound so cool? A wife and husband team up and attempt to solve their own disease.
Best wishes towards this cure!

Now then, what do you think of all the publicity you are getting?

VaultTecAnimations

Sonia: I feel so much gratitude to the people who have written about us and filmed us over the years. We’re lucky that the publicity we’ve attracted has been so positive -- true to the stakes and uncertainty of our quest, but also hopeful, which we are. Our only reservation about publicity is a constant struggle to balance our time in the right way, and juggle all of the activities that go into being "us" -- advocacy and outreach, travel and talks, time at the bench, time reading and blogging. There’s no easy answer here and I think all scientists can identify with the feeling that their job is actually ten jobs!

Modern therapeutics take large multidisciplinary teams, decades of time, and tens of millions of dollars before there is even a small chance of having something resembling a cure. What do you think your chances of beating the clock are?

TheJarl84

The main variable is how long is the clock. If Sonia has onset next year, there’s not much we can do by then. If we really do have 20 years, I think we have excellent chances. So many pharmaceutical failures are due to pursuing the wrong therapeutic hypothesis in the first place. We’re lucky to know the molecular basis of our disease and the right target to hit, which gives us a huge advantage. - Eric

(Both) What approach are you taking to cure this mysterious disease?

(Both but mainly Sonia) How are you coping with the knowledge of your "lethal mutation"?

(Both) How difficult was it to break away from your original career and jump into a whole new field?

(Both) On a lighter note, what is your favourite book?

Please forgive me for any spelling/grammatical errors as it is 5 am and I just woke up

The-Lying-Tree

Magician’s Land by Lev Grossman. -Eric

Share your opinions?

1) Sex and reproduction with a fatal genetic disease
2) Assisted suicide with a fatal genetic disease

9gxa05s8fa8sh

1) IVF/PGD 2) https://en.wikipedia.org/wiki/Massachusetts_Death_with_Dignity_Initiative - Eric

Wish you all the best, and to find this cure. I have a couple of questions. Do you have a team with other scientists and doctors helping you? And what about funds? It should be very expensive. In your opinion, can this work be helpful for future researches on neurodegenerative diseases such as
Alzheimer et similia?

glukosio

We have an incredible team here at Broad and some very smart people have been exceedingly generous in mentoring us. It is a huge part of what gives me hope.

Yes, I do think that many concepts that have emerged from the prion field (including prions themselves) have gone on to inform other neurodegenerative diseases, and I hope that this will be true of therapeutics too.

-- Eric