The Suramin Autism Treatment-1 (SAT1) Trial

Questions and Answers with Dr. Naviaux

June 14, 2017

Q1: What is the main point of your paper?

A1: The first thing you need to know about our paper is that it is not about suramin. Our research is aimed at finding a unifying cause for autism and an explanation for why it, and nearly 20 other chronic diseases have been increasing over the past 30 years. Our research is leading us to the conclusion that autism is caused by a *treatable metabolic syndrome* in many children. The exact percentage is currently unknown. Metabolism is the language the brain, gut, and immune system use to communicate. These three systems are linked. You can't change one without changing the other. Each of these systems works differently in autism, but more specifically, the communication between these systems is changed in autism. Such changes occur both during and after the pregnancy. Suramin can only improve metabolic functions after a child is treated. While antipurinergic therapy (APT) with suramin may not immediately change brain structures that are already present, APT may improve the function of many brain circuits. And in children and teens whose brain is still developing, the course or trajectory of brain development might also be changed by treatment. The science of neuroplasticity and how it can be activated during child development is still in its infancy.

The metabolic syndrome that underlies the dysfunction is caused by the abnormal persistence of the cell danger response (CDR). Aspects of the CDR are also known to scientists as the "integrated stress response". Both genes and environment contribute to the CDR, so even genetic causes of autism lower the threshold for CDR activation and produce the metabolic syndrome. Ultimately, if the symptoms of autism are caused by a metabolic syndrome, the hopeful message is that the symptoms can be treated, even though we can't change the genes.

Q2. What can you say about the study for neuroscientists and families who have never heard of the cell danger response or purinergic signaling?

A2: The main conclusions from the study do not require any background knowledge. Although the study was small and preliminary, the main conclusions were three: 1) For many children, the symptoms of autism are not permanent and can be improved dramatically with the right treatment, 2) A treatable metabolic syndrome contributes to the core symptoms of autism, and 3) A single treatment with low-dose suramin was safe and produced significant improvements in the core symptoms and metabolism associated with ASD.

Q3: Why was your study so small?

A3: This work is new and this type of clinical trial is expensive. We did not have enough funding to do a larger study. And even with the funding we were able to raise, we had to go $0.5 million in debt to complete the SAT-1 trial. Fortunately, the goals of establishing basic safety, tolerability, and activity of suramin in autism were accomplished with just 10 subjects. Based on these initial promising results, we will now attempt to find funding for a larger trial.

Q4: What are the caveats?

A4: After summarizing the design and results of the study, we are left with the conclusion that either the results are wrong because of the small size of the study, or they are an important advance. We won't know which until the results can be replicated in larger studies. Even so, I am optimistic that we are on the right path. My hope is that other investigators will soon join in. Together we can all move faster to gather the data to support or disprove the CDR hypothesis and test the safety and efficacy of antipurinergic therapy (APT) in autism.

Q5. What is the cell danger response (CDR)?

A5: The CDR is a natural and universal cellular response to any injury or stress. Its purpose is to help protect the cell and to jump-start the healing process. But sometimes the CDR gets stuck. This prevents completion of the natural healing cycle and can permanently alter the way the cell responds to the world. When this happens, cells behave as if they are still injured or in imminent danger, even though the original cause of the injury or threat has passed. On a molecular level, the defended set points for cellular homeostasis are altered. This creates a pathological metabolic memory—an abnormal cellular response—that leads to chronic disease. When this happens during early child development, it causes autism and many other chronic childhood disorders. When it happens later in life, a persistent CDR can lead to immune exhaustion and it can lower the resistance to chronic infections. When it swings in the other direction, the immune system takes on a hair trigger and it leads to inflammatory and autoimmune disorders. In both cases, it increases the prevalence of chronic disease. The UCSD media relations team created a nice whiteboard animation on Youtube that illustrates the way we think suramin works. You can see it at: https://www.youtube.com/watch?v=zIdUufy8Lks

Q6: How is purinergic signaling connected to the CDR?

A6: In a second discovery from the lab, we found that extracellular nucleotide signaling called "purinergic signaling" maintains the CDR. This led us to the possibility of a unified approach to the treatment of autism. Antipurinergic drugs can treat the abnormal metabolic syndrome that causes autism by sending a cellular "all's clear" or "safety signal" like the one that is announced when a fire is extinguished telling you it is safe to return to school. Suramin is just the oldest antipurinergic drug available, and the only one that inhibits the particular purinergic receptors that cause autism. Many more antipurinergic drugs are in development. Suramin is just the first of a whole new class of medicines, like the first statin for high cholesterol, or the first beta blocker for high blood pressure.

Q7: How does suramin work?

A7a—The Pharmacology: Suramin has several actions. One of its best-studied actions is as an inhibitor of purinergic signaling. Inside the cell, nucleotides like ATP and UTP are energy carriers and important molecules in normal metabolism. Stressed cells release ATP and other molecules made by mitochondria into the extracellular space through channels in the cell membrane. Extracellular ATP (eATP) is an ancient danger signal. It is called a "damage associated molecular pattern" or DAMP. When too much eATP is released, it binds to purinergic receptors it activates the cell danger response (CDR). Suramin inhibits the binding of eATP and eADP to these receptors and sends the cellular equivalent of the "all's clear" or safety signal. In this capacity, suramin and other antipurinergic drugs, are a kind of molecular armistice therapy (MAT), signaling the cellular war is over, the danger has passed, and cells can return to "peacetime" jobs like normal neurodevelopment, growth, and healing. See the animation of suramin action at: https://www.youtube.com/watch?v=zIdUufy8Lks.

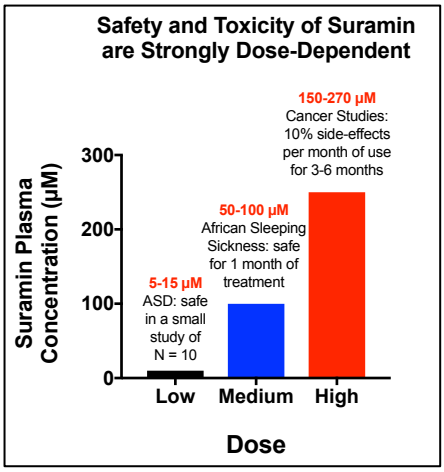
A7b—The Clinical Effects: Suramin works by removing negative signals that block or slow natural child development. It is more like removing the brakes then pressing the accelerator. Accelerated catch-up development occurs in the first few weeks when the brakes are removed because the child is ready to develop, but was otherwise blocked by their illness. This reminds me of giving a child who has an inborn error of metabolism in a vitamin or nutrient that they can't make, or taking away a toxin—the children begin to blossom. Children with severe oral motor dyspraxia in the SAT-1 study started humming and singing nonsense tunes around the house in the first few days after suramin. Like a baby learning to talk for the first time, they began making new sounds with their mouth, lips, and tongue that they had never made before. We had four non-verbal children in the study, two 6 year olds and the two 14 year olds. The 6 and 14 year old who received suramin said their first sentence of their lives about 1 week after the single suramin infusion. This did not happen in any of the children given placebo.

Q8: How many purinergic receptors are there?

A8: There are 19 different purinergic receptors. Geoff Burnstock discovered purinergic signaling in 1972, and has been characterizing the nucleotide and nucleoside ligands, their receptors, and their biology ever since.

Q9: What about the side effects of suramin?

A9: We did not find any serious side effects or safety concerns in this first study of a single, low-dose of suramin. The children did develop a self-limited rash, but that was asymptomatic and disappeared without treatment in 2-4 days. It is important to note that the low-dose that we used in the study produced blood levels of 5-15 µM and has never been tested for any disease in the nearly 100 years that suramin has been used in medicine. All previous uses of suramin have been at medium doses for sleeping sickness that produced blood levels of 50-100 µM for 1-3 months, or high doses for cancer chemotherapy that produced blood levels of 150-270 µM for 3-6 months.



It is important to remember that our study was small and only 5 boys received suramin. We were unable to detect rare side effects that might affect fewer than 20% (1 in 5) patients. Suramin caused a self-limited, asymptomatic rash, but this disappeared without treatment in 2-4 days. Larger clinical trials will be needed to detect uncommon side effects. For example, a

study in which at least 100 children received suramin would be necessary to detect a side effect that occurred in just 1 out of 100 (1%) of children.

Q10: Tell us more about the rash. Didn't this invalidate the whole study?

A10: First, it is important to remember that children can have both a red patch on their skin for a few days, AND show dramatic catch-up development language, social interaction, and many other areas that unfolds over weeks after a treatment. Many of the reports we received were from therapists and school teachers who never saw a rash and were unaware that the child was in a clinical trial of a new treatment. However, because those reports were individualized responses, they were considered "anecdotes" and not mentioned in the scientific report. You can download the parent statements at: http://naviauxlab.ucsd.edu/science-item/autism-research/.

A rash presents challenges for the technical blinding of the study, but it does not invalidate the biological and behavioral results. Next, it is important to remember that the primary outcome measure was ADOS scores. ADOS is a test that is designed to be administered by an objective examiner, so it does not depend on parental impressions. Medical exams and behavioral testing were conducted at two different locations. Only the medical team saw the rash, and the parents were told not to discuss it with the behavioral testing team, to minimize the chances of bias.

We were also lucky that none of the children had a rash that was visible during any of the examinations. At the 2-day time point a few children still had a patch here and there, but it was hidden by clothing. None of the ADOS scores were changed at 2 days despite the medical team and one of two ADOS examiners knowing about the rash from phone interviews. Because the rash was asymptomatic, it came and disappeared in 2-4 days. The parents were still focused on autism-related symptoms like language and social interactions. Each parent in the placebo group was still hoping their child got drug. 6-weeks after the infusions, the ADOS testing was repeated. None of the children who received placebo showed improvements, while there were significant improvements in all the core symptoms of autism in the suramin-treated group.

Q11: Why didn't you see a placebo effect?

A11: First, because the primary outcome was ADOS score measured by the observations of an objective examiner, the primary outcomes did not depend on parental impressions. Second, for the parent-based questionnaires, we asked parents to list a behavior as changed only if it was changed for at least 1 week. This eliminated a lot of the natural ups and downs that children with ASD will experience with regard to meltdowns and irritability. Third, there was a large qualitative difference in the kinds of things the parents observed in the children who received suramin and placebo. We removed all the individual responses from the scientific report of the clinical trial results because reviewers consider these "anecdotes" and lower their opinion of the paper when individual responses are included. However, all 10 parents provided written statements describing their observations during the study. The parents were never told whether their child received suramin or placebo, so these comments are still blinded. As mentioned above, you can download these by clicking the "parent statements" button on our website at: http://naviauxlab.ucsd.edu/science-item/autism-research/

Q12: What about the risk of infections? If suramin blocks the CDR, won't children have trouble clearing common infections or responding to toxin exposures?

A12: In theory, this could be a risk of suramin. However, we looked at this carefully in the trial. The infusions were done from October through February, so winter colds were a known risk. We found that two children in the placebo group got colds. Two children in the suramin group also had colds. The severity was the same in both groups. The duration of congestion and symptoms was 7-10 days, and also about the same in both groups. We did not find an increased risk of infection in the SAT-1 study. However in theory, any broad-spectrum antipurinergic drug (APD) might inhibit the CDR, so this will be a potential risk to monitor in future studies.

Q13: What problems can you imagine that might derail future suramin trials in autism?

A13: If the improvements that occurred with suramin treatment stopped after a few months, even when effective blood levels were maintained, then the trials would fail. Also, if we encountered a safety issue that was unacceptable after a few months of treatment, then the trials might fail.

Even if suramin itself is not the best antipurinergic drug for autism, our studies have helped blaze the trail for the development of new antipurinergic drugs that might be even better. Before our work, no one knew that purinergic signaling abnormalities were a part of autism. Now we do, and new drugs can be developed rationally and systematically.

Q14: Will suramin need to be given for life?

A14: I don't think so, but we don't have the science to answer this question yet. More studies will be necessary to see if improved development can become self-sustaining without the need for regular suramin treatment.

Q15: What about the effect that suramin might have on common therapies?

A15: We found that during the time the children were on suramin, their benefit from all their usual therapies and enrichment programs increased dramatically. Once suramin removed the roadblocks to development, the benefit from speech therapy, occupational therapy, ABA, and even from playing games with other children during recess at school skyrocketed. Suramin was synergistic with their other therapies.

Q16: What is the rate-limiting factor to progress right now? Where are the bottlenecks?

A16: The rate-limiting factor is money. Lack of funding has slowed our research progress on the CDR and purinergic signaling in autism for the past 9 years. We can't do the next studies without new funding. We have plans for 5 additional studies over the next 5 years to collect all the data the FDA will need to decide about the approval of suramin for autism. With adequate funding, culminating in a multicenter, phase III, registrational trial, these studies can be completed without further delays. Usually, the multimillion dollar cost of new drug development is covered by the Big Pharma that will benefit from FDA approval. Unfortunately, since suramin is 100-years old, the usual patent laws don't apply and the next clinical trials will require grass roots support from families and foundations, and other approaches to raise the needed funding. See our website at naviauxlab.ucsd.edu for information about helping to support these studies.

Q17: Do you think that suramin could help the genetic causes of autism too? Why?

A17: Yes. Each of the genes that increase the risk of autism is connected to the cell danger response (CDR). For example, the Fragile X gene naturally prevents the translation of a large number of proinflammatory proteins. When the Fragile X gene is mutant, then those proinflammatory proteins like TNFα and IL1β are made, which activates the CDR. The causal gene in Angelman syndrome is thought to be the ubiquitin protein ligase E3A (UBE3A). When this gene is not expressed, worn-out proteins in the cell are not removed properly. This triggers the unfolded protein response, which activates the CDR. The causal gene in Smith-Magenis syndrome is thought to be the retinoic acid activated gene 1 (RAI), which is needed for a normal antiviral response. Failure to express RAI prevents normal handling of infections and results in a persistently activated CDR. We don't think that suramin will treat the physical features and non-autism symptoms of these genetic disorders. However, we think that suramin will be effective in improving the core symptoms of autism in these genetic disorders, and produce improvements in language, social behavior, and decrease repetitive and restricted behaviors.

Q18: What about teens and adults with ASD who don't want to be treated but rather want to be accepted and appreciated for their unique talents, abilities, and differences?

A18: ASD is a label we use to talk about a group of children and adults with a recognizable pattern of neurodevelopmental differences. In the extreme, some non-verbal children with ASD will grow up to be non-verbal adults who cannot speak for themselves and may not ever be able to care for their own daily needs or hold down jobs. In the other extreme, the special gifts of some children with ASD will lead them to become activists as teens and adults whose voice is highly sought out by local and national agencies to express the needs of others and to help guide progress. We had a gifted teen with ASD as part of the team on the SAT1 study. He is a graphic artist and helped us to design the storyboards that allowed each parent and their child to visually review and prepare for the steps of the study, with special attention to sensory issues that were important for children with ASD. Another gifted teen associated with the SAT1 study wrote a poem about his experiences. This can be found at: http://naviauxlab.ucsd.edu/science-item/autism-research/.

The core symptoms of autism are the same in all children with ASD by diagnostic definition. Therefore, the core symptoms are not the things that make children and adults with ASD unique. When people talk about the special gifts of children and adults with ASD they are typically referring to the different way some teens and adults with ASD see and understand the world. Amazing abilities can occur, like the ability to solve a math problem in a way no one ever thought of before. Or the ability to write a beautiful poem or paint a masterpiece, or compose and conduct a symphony, or solve an engineering or computer problem that has stumped the best "neurotypical" brains in the world.

I have no desire to create new treatments to remove these special abilities. Nor do I want to create new treatments for anyone who does not need or want treatment. The right to self-determination and the right to healthcare choice are fundamental freedoms. However, unless research continues, new treatments for ASD will not be discovered, and the complementary freedom to choose an effective treatment when it is desired will be lost. We can respect both rights; the right to choose no treatment for some, and the right to choose new treatments for others. Both are possible, and both must be actively chosen to protect freedoms for all.

There is another point that needs to be made. In 2017, after nearly 75 years of trying, there are no effective pharmacologic treatments for the core symptoms of autism. I believe this is

because a *unifying theory* for the cause of autism does not exist. People's experiences with ASD treatments to date have taught them that the treatment is often worse than the disorder. None of the treatments currently available actually get at the root problem in autism. If the root problem is ultimately proven to be the CDR and abnormalities in purinergic signaling, then the core symptoms like social anxiety, fear of changes in routine, and difficulties with verbal communication might be improved without suppressing the gifts that make children and adults with ASD exceptional.

This new generation of treatments has a chance to precisely target the symptoms that hold people back with ASD, while not touching the gifts that allow them to excel.

Q19: Why is treating autism so important?

A19: Autism spectrum disorder often affects children who have shown early gifts, and might otherwise grow up to become some of the best and brightest of their generation. Even if this is only true for a fraction of children, it means that some children now living with disabling forms of ASD, whose parents fear they might never be able to live independently, could have a chance for independence and live happy, self-reliant lives. And because many children with ASD are significantly impacted by their symptoms, these children, once freed from their most disabling symptoms, might be just the ones the world needs to solve the greatest problems facing our planet in the next century.