CROSS TALK

Can a drug for a parasitic disease really treat autism?

BY **GREG BOUSTEAD**

6 AUGUST 2014

In June, **we reported** on findings suggesting that a single dose of a drug called suramin — used for a century to treat African sleeping sickness — improves symptoms of autism in a mouse model. The **mainstream press** also picked up the '100-year-old treatment cures autism' story**.**

The researchers — **Robert Naviaux** and his colleagues at the University of California, San Diego — plan to launch a small clinical trial to test the drug's safety in children with autism later this year. The team is careful to note that reversing deficits in a mouse is far from a cure in people.

Still, some researchers we spoke with for the June article expressed concern about giving suramin to children with autism, even at small doses. They noted that suramin is a powerful drug with serious side effects, including anemia and disruption of the adrenal gland.

Others were skeptical of the proposed mechanism for the drug's effects.

A family of receptors found on the cell surface typically responds to ATP, the body's energy currency, and other signaling molecules known as purines. When mitochondria are disrupted — as Naviaux and his colleagues hypothesize might be the case in people with autism — purines can a ccumulate during infectionand damage cells.

The researchers suggest in the study that suramin alleviates autism-like symptoms in the mice by blocking purine receptors and restoring healthy metabolism.

To dig deeper, we checked in with experts on mitochondrial mechanisms and translational efforts in autism, for our discussion series, **Cross Talk**.

What do you think? Share your reactions and follow-up questions in the comments section below.

David Sulzer

Professor, Neurology, Psychiatry and Pharmacology,Columbia University

Long shot

Professor of Psychiatry, Neurology and Pharmacology, Columbia University
***Thin evidence:* "**While this paper discusses the shortcomings of the model and treatment clearly, it is premature to have confidence that suramin will provide therapy for autism. The various concerns are spelled out clearly and honestly in the study: The model used may not replicate a utism well either in pathogenesis or behavior, and there is little evidence that problems in purine handling or transmission are particularly related to autism.
"Suramin is a relatively large-sized molecule with several actions, and it does not penetrate well into the brain. Most behaviorsassociated with autism are probably driven by abnormalities in regions of the brain into which suramin does not adequately penetrate."
***Mysterious mechanisms*:** "This leaves open the possibility that suramin is working in the rodent model by a different mechanism. Other than asuggestion that an unidentified cellular stress-response pathway is involved, we don't understand why it has effects on the animals' behaviors. Thereare many, many means to interfere with stress responses, such as antioxidants and anti-inflammatories. And while these need to be studied to determine whether they provide therapy, there is little reason to support their use for autism at this time."
***Unlikely involvement*:** "There is an implication in the paper that regulation of mitochondria activity could be involved, but as yet there is no evidence. New studies show that neuronal mitochondria appear to be damaged in the brains of individuals with autism, but so far only in the cortex, which suramin does not appear to reach."
Too quick: "The authors find a behavioral improvement only two days after a single exposure to the drug. It does not seem likely that this can clear out damaged mitochondria, which accumulate for years, and replace them with better organelles so quickly.
"So while this study shows improvements in a few behaviors after the drug in one inflammatory-induced autism model, the mechanism is opaque. It isa long shot at this time that it will provide an effective treatment for autism."

Paul Wang

Senior Vice-President and Head of Medical Research,Autism Speaks

Need to work harder on trials

Senior Vice-President and Head of Medical Research, Autism Speaks

Hedging bets: “Animal models of autism, such as the **maternal immune activation (MIA) model** studied here by Naviaux and his colleagues, are the best tools that researchers have for examining the cellular and molecular pathophysiology of autismand for testing experimental treatments before they can be advanced to human trials.

“But, of course, none of the models can be considered valid until treatment effects in them are proven to be predictive of effects in people. In the case of the MIA mouse, the authors here candidly hedge their bets by calling it a model of bothautism and schizophrenia. Meanwhile, the field of autism research wisely hedges its own bets by studying multiple treatments of the MIA mouse,**including probiotics** as well as antipurinergic therapy.”

Precedent lacking: “Although milestones in the initial stage of testing basic research findings for translational research continue to accumulate — from mGluR5-targeted **rescue of the FMR1 knockout mouse** to suramin reversal of social deficits in the MIA mouse — we appear to be making little headway on the hurdles of clinical trials. From **arbaclofen** to **oxytocin** to ***Trichuris suis* ova**, clinical trial results have been tepid at best. This should not be surprising. We have no successful precedent to guide the design of clinical trials in autism.

“How should we quantitate clinical improvement — or deterioration? How long must treatment be provided before effects are evident? At what age will each treatment be most effective: 6 years? 16 years? 6 months? Which individuals will benefit most from each treatment: those with more severe or more mild symptoms? Those with regression or not? Those with or without comorbidities? Results in Phelan-McDermid syndrome (presented by**Joseph Buxbaum** at the **2014 International Meeting for Autism Research**) represent a rare but preliminary exception to the frustrations of clinical trials.”

Clearing the hurdles: “As basic research continues to generate more candidate treatments for a utism, we need to work harder on clinical trials. Most especially, we need to identify **measures of improvement** that emerge early, potentially within a few weeks of treatment initiation and well before the broad functional improvement that the U.S. Food and Drug Administration is likely to require for drug approval.”

John Jay Gargus

Director, UCI Center for Autism Research and Translation,University of California at Irvine

Mechanism unclear

Director, UCI Center for Autism Research and Translation, University of California, Irvine
Imprecise effects: “I don’t think we can say that suramin is specific for purinergic receptors — it is **not at all specific**. Suraminaffects all G-protein-coupled receptors, a huge family of receptors that includes virtually every kind of signaling molecule that cells use to talk to one another. So as far as a mechanism, I don’t think this work tells us much.”
Trials will tell: “Before anyone jumps the gun on suramin, all one has to do is reflect on any of the many neuropsychologicaldrug trials that have cured mice but ultimately fail in treating people. The only way to gauge the empirical value of suramin will be to conduct a carefully controlled clinical trial.”