

# Breakthroughs in the Cause and Treatment of Autism and Chronic Fatigue Syndrome



From the Naviaux Lab, University of California, San Diego

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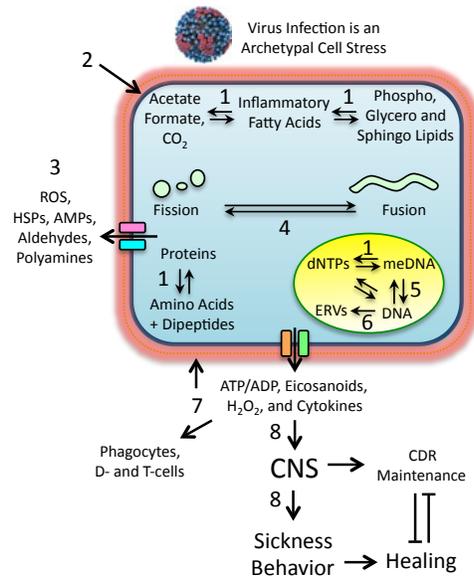
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**Figure 1. Mitochondria** were the lighthouses that have guided the way to new discoveries in autism and chronic fatigue syndrome research.



**Figure 2. Children with Mitochondrial Disease** provided the first clues that revolutionized how our lab thinks about autism spectrum disorder (ASD), and many other complex disorders.



**Figure 3. The Cell Danger Response.** All cells mount a coordinated defense when threatened. This causes disease if it persists after the threat is gone.



**Figure 4.** Many children with ASD are trapped behind the glass shield made by the cell danger response (CDR) Any effective treatment must help to remove this shield.

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## Background

All the breakthroughs that have come from our lab in understanding complex disorders like autism spectrum disorder (ASD), myalgic encephalomyelitis/chronic fatigue syndrome, (ME/CFS), Gulf War Illness (GWI), post-traumatic stress disorder (PTSD), and post-treatment Lyme disease syndrome (PTLDS) (see: <http://naviauxlab.ucsd.edu/>) have come from our early work in genetic forms of mitochondrial disease. These are called primary mitochondrial diseases. All these studies have been supported since 1999 by the UCSD Christini Fund (<http://www.christini.org/>). It was clear to us since 1995 that the major setbacks in mitochondrial diseases like Leigh and Alpers syndromes were associated not with the start of a metabolic stress like an infection, but were most common and most severe later, during the healing phase that came after the initial stress or injury. In pivotal collaborative studies conducted from 2003-2008 with the brilliant inventor and laser physicist, Dr. Paul Gourley at Sandia National Laboratories in Albuquerque, NM (Figure 5), we studied the biophysics of the cellular and mitochondrial response to stress. That work showed that any kind of stress—environmental, genetic, or a combination of both—led to profound changes in mitochondrial structure and function. We next began a series of



**Figure 5. Paul L. Gourley, PhD.** Sandia National Labs, Albuquerque, NM



**Figure 6. Ellen Heber-Katz, PhD.,** Philadelphia, PA

breakthrough studies in collaboration with the renowned immunologist and trailblazer in regenerative medicine, Dr. Ellen Heber-Katz, then at the Wistar Institute in Philadelphia (Figure 6). In experiments from 2005-2009, we drilled down into the molecular mechanisms of healing in the super-healer MRL mouse. These “mighty mouse” studies led to the discovery that healing from any injury requires both a mitochondrial *reserve capacity* and the ability to shift from one kind of mitochondrial function to another under times of stress or injury. These properties were abundant in the MRL mouse, and in other animals during fetal development, but are missing in children with inherited forms of mitochondrial disease, and are gradually lost with aging. These studies

on the role of mitochondria in stress and healing set the stage for all our next studies in complex disorders like ASD and ME/CFS.

## The Autism-Mitochondria Connection

In 2008, Dan Wright, the chairman of the board of the United Mitochondrial Disease Foundation (UMDF), called Dr. Naviaux up on the phone. He said, “Autism is an epidemic. This is a national tragedy. I think you might be able to help. I’d like to send you to a meeting at NIH so you can start thinking about autism.” Within one month, Dr. Naviaux had the germ of an idea. Within 6 months he conceived the “purinergic theory of autism”. In 2010, Dr. Naviaux organized the first special session at the annual meeting of the United Mitochondrial

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Disease Foundation (UMDF) on mitochondria and autism. In April of 2011, Dr. Naviaux was awarded one of just three international “Trailblazer” awards by Autism Speaks to test this idea. In March 2013, Dr. Naviaux and his team of trailblazers at the University of California, San Diego (UCSD) School of Medicine published their exciting results in *PLOS One*<sup>1</sup>. Several other studies have now been published that have confirmed the importance of mitochondria and ATP-related purinergic signaling in ASD<sup>2-4</sup>. You can see a video about mitochondria, the cell danger response<sup>5</sup> and suramin at this link: <https://www.youtube.com/watch?v=zIdUufy8Lks>

## The SAT1 Study

The SAT1 (suramin autism treatment 1) trial tested the safety and efficacy of a single dose of intravenous suramin in a small study of 10 children, ages 5-14 years. Half the children received suramin and half received placebo. The results were remarkable. In 6-weeks after one IV dose of suramin, all the core symptoms of ASD were improved. Several children spoke in sentences for the first time. All of the children who received suramin experienced a kind of catch-up development, and one child advanced through 3 years of school work in 3 weeks. The response to all their normal therapies, eg, ABA, OT, PT, and school work, etc., was magnified. The children who received placebo did not experience any of these changes. But the effects of suramin were not permanent. After about 8 weeks, as the medicine washed away, the children gradually returned to their pretreatment baselines. New studies will test if continued treatment will result in continued benefits. You can read more about the trial and read the parents’ observations at: <http://naviauxlab.ucsd.edu/science-item/autism-research/>.

## Newborn Screening for Autism

Nearly 2% of the 4 million children born in the US each year will be diagnosed with ASD by the time they reach 4 years old. New research in the Naviaux Lab is aimed at trying to identify metabolic markers (biomarkers) of risk that can be measured before the first symptoms appear. We are trying to see if we can use a new kind of newborn screening to identify and prevent ASD. This would be similar to what was done for a genetic disease called PKU (phenylketonuria). Without treatment, PKU causes brain damage and permanent disability. As adults, people with PKU require lifelong care if they were not identified and treated in childhood. But children with the DNA mutations that cause PKU can be identified at birth. When they are treated with diet and supplements before symptoms appear, children with PKU grow up without any brain damage and can lead completely independent lives. Last year, in Phase 1 of the newborn screening study, we found that the 62 tests that are routinely performed on dried blood spots collected at birth are not enough to predict the future risk of autism. We are now entering Phase 2 of this study: <http://>



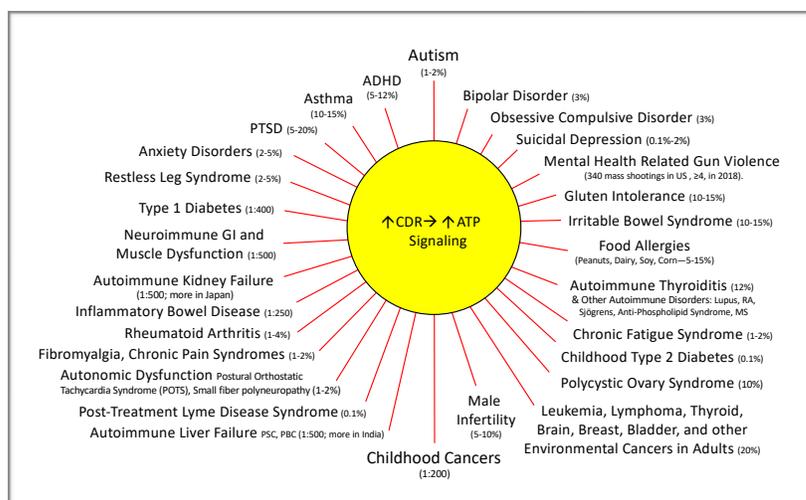
[naviauxlab.ucsd.edu/study/](http://naviauxlab.ucsd.edu/study/). In Phase 2, we will test dried blood spots for over 1000 natural and manmade chemicals in children from 400 families. If you have a child age 3-10 years with ASD or is typically developing, you may qualify for participating in this study. We are actively recruiting for this study. Qualifying families will receive a \$40 Amazon eGift card for their participation. We believe that if children at risk for ASD can be identified before the first symptoms, that perhaps as much as 50% of all ASD might be prevented.

## Exposomics and Metabolomics

Dr. Naviaux has been tracking over 30 chronic diseases that have increased 2-100 times since the 1980s. Some of these are illustrated in Figure 7. In the case of ASD, the prevalence has risen from 1 in 5000 (20 in 100,000) in the 1970s to 1 in 59 (1700 in 100,000); an 84-times increase) in 2014<sup>6</sup>. It has been calculated that 60% of the apparent increase can be explained by changes in the diagnostic criteria for ASD over the past 40 years<sup>7</sup>. However, even with this conservative correction, the adjusted prevalence of ASD of 1 in 59 children today represents an absolute increase of 34 times ( $84 \times 0.4 = 34$ ) from the 1970s. A similar calculation and correction for ME/CFS shows that there has been a 62-fold increase since 1985.

Our DNA cannot change this fast. Therefore, the rise in the prevalence of chronic illness in the past 30-40 years is not caused by DNA, but by a change in the environment and the interaction of our DNA with the environment—ecogenetic factors.

Over 7,000 chemicals are used in the United States at amounts of 25,000 to over 1 million pounds per year. These include pesticides, plasticizers, lubricants, flame retardants, teflons, food additives, preservatives, dyes, sunscreens, veterinary antibiotics and antifungal medication, and many others. Fewer than 5% of these have ever been tested for developmental toxicity. These chemicals have entered the human food chain, water, and air. In 2005, study conducted by the Environmental Working Group found that the umbilical cord blood of newborn babies in the United States already contained an average of 287 pesticides,



**Figure 7. Chronic Health Disorders that have increased 2-100 times since the 1980s.** Forty percent of children born in the US today and 60 percent of adults under 65 live with at least one chronic illness.

**Abbreviations:** CDR, cell danger response; ATP, adenosine triphosphate; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder.

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pollutants and other environmental chemicals<sup>8</sup>. Using a combination of LC and GC mass spectrometry, the Naviaux Lab has developed new methods in “exposomics” that allow us to measure the chemicals in blood that can cause chronic illness, and the chemicals that can lower our resistance to chronic illness.

## Plans for 2020

### *The SAT2 Trial*

Suramin is now being made by a new company that will be sponsoring the next clinical trial in autism spectrum disorder. The new trial will be called the suramin autism treatment 2 (SAT2) trial. The SAT2 trial will test the effect of suramin in about 50 children with ASD at two or more medical centers. We are on track to launch the SAT2 in the summer or fall of 2020. If the SAT2 is successful, it will open up the possibility of using antipurinergic drugs like suramin in several other disorders. Dr. Naviaux wants to conduct clinical trials in ME/CFS and primary forms of mitochondrial disease like NARP. If these are successful, nearly 20 other disorders may also benefit. If ATP-related cell signaling is found to be a fundamental cause of blocks in the healing cycle<sup>9</sup>, then many investigators and drug companies will launch programs of drug discovery to find new medicines that work like suramin, but may be even better. For example, Dr. Naviaux believes that there are many natural products with antipurinergic properties yet to be discovered in the rain forests and coral reefs of the world.

### *ME/CFS—Triggers and Networks that Connect the Metabolome and Exposome*

An unanswered question in the biology of ME/CFS is, “Why do patients who are able to recover still have a life-long risk of recurrence?”. Dr. Naviaux believes that life experiences and exposures to environmental chemicals and biotoxins come together with genes to create a “perfect storm” that causes ME/CFS. Even after recovery, this perfect storm leaves a mark—a *metabolic and epigenetic memory* that changes how the network of chemicals in the blood is regulated and how it responds to future exposures. In 2020, we will launch a new study to examine the network connections between the metabolome and exposome. Using advanced machine learning and network dynamic analysis, this new study will help pave the way for the future suramin ME/CFS treatment trial. Other exciting studies include a new collaboration with the brilliant virologist, Dr. Bhupesh Prusty at the University of Würzburg, Germany. Using a new, cell-based assay system, we are hot on the trail of both the identity and the biological control of the activity in ME/CFS blood that causes fatigue. This “**fatigue factor**” looks like it could be the same thing that coordinates the mitochondrial and metabolic features of the cell danger response (CDR) and inflammation<sup>5</sup>, changes impedance in the nanoneedle<sup>10</sup>, inhibits recovery from illness by blocking the healing cycle<sup>9</sup>, induces a dauer-like state<sup>11</sup>, and triggers collagen remodeling over time that can cause acquired forms of Ehlers Danlos-like syndromes. If successful, these studies will help fill in missing details in how suramin, copaxone, and elamipretide (SS31) might work to treat ME/CFS.

## Lyme Disease

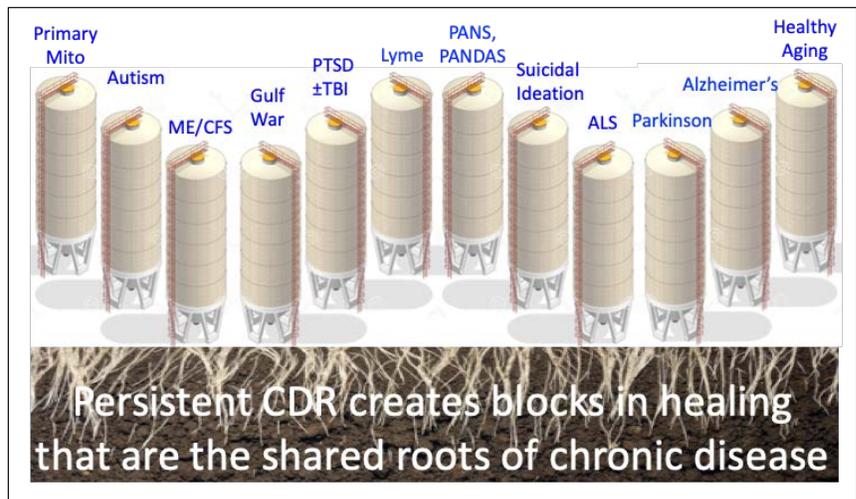
Lyme disease and post-treatment Lyme disease syndrome (PTLDS) have also increased dramatically in the past 30 years. Much of this increase may result from warming temperatures and more year-round exposure to ticks. However, an unknown fraction of the 400,000 new cases of Lyme disease in the US each year may result from decreased resistance to the bacterium (*Borrelia burgdorferi*) that causes Lyme. The innate immune response that controls this resistance is strongly regulated by mitochondrial health and the exposome. In an exciting new study funded in part by the Steven & Alexandra Cohen Foundation, the Naviaux Lab will test nearly 400 blood samples in an effort to identify markers of risk and recovery from Lyme. These studies are being conducted in collaboration with the Bay Area Lyme Foundation, and investigators at Johns Hopkins and Columbia University.

## Back to the Future—The 2020 UMDF Symposium

Dr. Naviaux and Dr. Richard Haas are the co-chairs of the annual meeting of the UMDF, Mitochondrial Medicine Society (MMS), and the Mitochondrial Research Society (MRS) that will be held in Phoenix, AZ, on June 24-27, 2020. This meeting will include special sessions on progress in gene therapy, the biology of aging, stem cells, clinical trials of new treatments, and the first special session devoted to mitochondria and autism since 2010. An exciting addition for this meeting will be a special session devoted to “Mitochondria in Space” in which scientists from NASA will report on the biological challenges to long-term space flight posed by changes in mitochondrial function that occur in microgravity. You can learn more about the conference at: <https://www.umd.org/symposium/scientific-clinician-program/>

## Tying it All Together

Work in the Naviaux Lab over the past 8 years has characterized the metabolic signatures of 10 chronic complex disorders. Several of these are illustrated in Figure 8. For the past 70 years, the best scientists in the world have labored to create deep silos of knowledge for each medical illness. The past goal has been to find the *differences* that distinguish each silo of disease. However, research in our lab has led us to the conclusion that it is not the differences, but



**Figure 8. Silos of Chronic Disease.** New research has revealed that it is not the *differences*, but rather the *similarities* that are shared by all chronic illnesses that are most important for treatment. The Naviaux Lab is pioneering a new generation of treatments that are designed to promote healing. If successful, a handful of treatments may be all that is required to treat dozens to hundreds of chronic illnesses.

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rather the *similarities* that are shared by all chronic illness that are more important for treatment. Our research is showing that the shared roots of chronic illness are blocks in the healing process itself that are caused by abnormal persistence of the cell danger response<sup>9,12</sup> (Figure 8). This seminal insight is driving new experiments to identify the molecular basis of healing and recovery. If successful, this paradigm shift in medical science will usher in a new book of medicine—a book that teaches us how to prevent the chronic diseases that have increased so quickly over the past 30 years, and how to cure a large number of them with a new generation of treatments designed to remove blocks in healing and to promote resilience. You can read more about this at our website: <http://naviauxlab.ucsd.edu/science-item/healing-and-recovery/>

## Helping to Support Future Research

The rate of progress in the Naviaux Lab is currently limited by the small size of our lab. Starting in January 2020, Dr. Naviaux will have a team of 5 full-time researchers, 4 part-time scientists and staff, and 3 mass spectrometers to analyze hundreds of samples each year. The annual budget for this research is \$900,000. Our goal is to add two additional full-time scientists and a research nurse practitioner over the next two years. To do this we will need to raise \$1.2 million a year for the next 2 years. For more information about how you can help see: <http://naviauxlab.ucsd.edu/support/>. One year of support for a research scientist in Dr. Naviaux's lab costs \$125,000. This includes all the costs for salary, benefits, and research supplies for one PhD, or MD/PhD scientist. Gifts of \$500,000 to \$1.5 million can help significantly by establishing a program of research with support for 3 or more years. In addition, we are incredibly grateful for gifts of all sizes. Small gifts, collectively, make a huge difference and provide vital support for the lab.

## Thank You

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## References

1. Naviaux RK, Zolkipli Z, Wang L, Nakayama T, Naviaux JC, Le TP et al. Antipurinergic Therapy Corrects the Autism-Like Features in the Poly(IC) Mouse Model. *PloS One* 2013; 8(3): e57380.
2. Naviaux, J.C., Wang, L., Li, K., Bright, A.T., Alaynick, W.A., Williams, K.R., Powell, S.B., and Naviaux, R.K. (2015). Antipurinergic therapy corrects the autism-like features in the Fragile X (Fmr1 knockout) mouse model. *Molecular Autism* 6, 1.
3. Gevi, F., Zolla, L., Gabriele, S. & Persico, A.M. Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism. *Molecular Autism* 7, 47 (2016).
4. Horvath, G., Otrokocsi, L., Beko, K., Baranyi, M., Kittel, A., Fritz-Ruenes, P.A., and Sperlagh, B. (2019). P2X7 Receptors Drive Poly(I:C) Induced Autism-like Behavior in Mice. *The Journal of Neuroscience* 39, 2542-2561.
5. Naviaux, R.K. (2014). Metabolic features of the cell danger response. *Mitochondrion* 16, 7-17.
6. Baio, J., and Investigators, D.D.M.N.S.Y.P. (2018). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *MMWR CDC Surveill Summ* 67, 1-28.
7. Hansen, S.N., Schendel, D.E., and Parner, E.T. (2015). Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. *JAMA Pediatrics* 169, 56-62.
8. Houlihan, J., Kropp, T., Wiles, R., Gray, S., and Campbell, C. (2005). Body Burden—The Pollution in Newborns a Benchmark Investigation of Industrial Chemicals, Pollutants, and Pesticides in Umbilical Cord Blood. Environmental Working Group, Washington, DC.
9. Naviaux, R.K. (2019). Metabolic features and regulation of the healing cycle-A new model for chronic disease pathogenesis and treatment. *Mitochondrion* 46, 278-297.
10. Esfandyarpour, R., Kashi, A., Nemat-Gorgani, M., Wilhelmy, J., and Davis, R.W. (2019). A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *PNAS (USA)* 116, 10250-10257.
11. Naviaux, R.K., Naviaux, J.C., Li, K., et al. (2016). Metabolic features of chronic fatigue syndrome. *PNAS (USA)* 113, E5472-5480.
12. Naviaux, R.K. (2019). Incomplete Healing as a Cause of Aging: The Role of Mitochondria and the Cell Danger Response. *Biology (Basel)* 8.