Coordinator: Welcome and thank you for standing by. All participants will be able to listen only. Today's conference is being recorded. If you have any objections, please disconnect at this time. I would now like to turn the conference over to Ms. Dana Brimmer. You may begin.

Dana Brimmer: Thank you. Good afternoon everyone. My name is Dana Brimmer and I’m a visiting scientist and contractor working with the ME/CFS program at the Centers for Disease Control and Prevention. On behalf of the program, I'm pleased to welcome you to today's ME/CFS Stakeholder Engagement and Communication conference call, known as SEC. Our primary purpose here is to share information with a large number of people with interest in ME/CFS as part of our regular outreach and communications series.

Before we get started today, I want to briefly review how the SEC calls work. Notification of calls will be sent by email and information is also posted on the CDC ME/CFS Web site. There is no need to register or RSVP for the call. Simply dial the 800 number and use the participant code provided in the email or found on the CDC Web site. Due to the large number of call participants, we are unable to have call lines available in speak mode. Therefore, we will take questions via email using the ME/CFS SEC call email system. Please note that this email address cannot respond to inquiries. Please note that due to time constraints, CDC and the guest speaker may not be able to answer all questions. But the CDC ME/CFS program looks forward to reading all of the emails received.

Our guest presentation today is “Metabolic Features of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome,” by Dr. Robert Naviaux. First, we will hear from Dr. Elizabeth Unger, who will provide updates about CDC's ME/CFS program. After both Dr. Unger and Dr. Naviaux speak, we will answer questions that were submitted via email. I will first read the questions out loud and then our speakers will answer each one.
I will now read a disclaimer. These calls are open to the public. Please exercise discretion on sensitive content and material. The confidentiality during these calls or items submitted via email cannot be guaranteed. Today's call will be recorded by CDC and a transcript will be available at a later date on the CDC ME/CFS Web site. The views of non-CDC presenters expressed during this conference call are their own and do not necessarily represent the views of the U.S. Department of Health and Human Services or the Centers for Disease Control and Prevention. I'd like to now ask Dr. Elizabeth Unger, Chief of the Chronic Viral Diseases branch at CDC to start the call. Welcome, Dr. Unger.

Elizabeth Unger: Thank you very much Dana and greetings to everyone. You probably noticed that we changed the name of our calls from PCOCA to SEC. And we made this change to avoid confusion with COCA calls, which is another group call that was sponsored by CDC. We didn't change the format. So we still view this as our ninth call in our series. So welcome back to those of you who have participated before and greetings to our new callers.

Quickly, for those who are new to this forum, we implemented these calls to have a channel for regular communications with the ME/CFS community about CDC’s activities and also to allow experts to share their information on their work related to ME/CFS clinical management or research. Our program receives suggestions about topics of interest, identifies the topic and invites speakers based on their expertise and availability.

After accepting the invitation, the speakers independently prepare their talk. The speakers therefore represent their own views and not any official position of CDC. They've all graciously volunteered their time and we are so appreciative of their participation. We always look forward to hearing what they have to share with us and today is certainly no exception. Please feel free to use the SEC mailbox to suggest topics for further presentations. And that address is just mecfssec@cdc.gov.

So I’d now like to give you an update on some of CDC's activities starting with our educational initiatives. Education and dissemination of information about ME/CFS was identified as a critical need by the Institute of Medicine, that's the IOM, report on ME/CFS. To assist in this, we began a process for broad stakeholder input into the materials to be developed, specifically focusing on how the IOM recommendation should be communicated. In September, we held a face-to-face meeting of ME/CFS patients, advocates, clinicians with ME/CFS expertise, healthcare professional organizations, medical educators, researchers, foundations and other government agencies.
The goal of the roundtable meeting was to provide an opportunity for individuals to share their thoughts on how the IOM reports could best be communicated through materials and content on CDC's Web site. We had a very successful meeting and thank all of those who took the time to travel and participate. The summary report from the roundtable meeting is now available on the CDC Web site. We found that the direct communication between stakeholders that happened at the roundtable meeting helped everyone explain their differing point of views. Involving medical professional groups makes it more likely that they will share information with their members. We are using all of these recommendations to update CDC's ME/CFS Web pages. Additional educational needs, such as toolkits, continuing medical education courses, and treatment guidelines are the next steps and we are in the process of developing a timeline for these activities.

All of the CDC the web pages are undergoing a format change. In addition, CDC communicators are emphasizing the importance of what is called “plain language” for web pages that are designed for the general public. Therefore, we divided the process of getting new content for the web prepared and approved into stages. At this point, the information for the general public will be ready when the ME/CFS Web site is shifted to the new look in midsummer. The new format should be easier for people to use. The first version will have temporary placeholders for content that is still being developed. We are actively working on the next stage, which are the sections for the healthcare providers.

We published a summary of the 2016 Public Health Grand Rounds as an article in *Morbidity and Mortality Weekly Reports*, also known as MMWR. MMWR is a widely distributed CDC publication and is often called the voice of CDC. The report included an option for receiving continuing medical education credit. As a result, the public health grand round information has been made available to a larger and more diverse audience.

Even though the presentation from the grand rounds is no longer eligible for continuing medical education credit, it is still available for viewing and has been viewed nearly 8,000 times. We also published our first teaching module through the American Association of Medical Colleges’ MedEd Portal. This module and the additional modules that are in preparation or under review are directed to educating medical students and allied health students on ME/CFS.

May 12, 2017 marked the 25th ME/CFS and Fibromyalgia International Awareness Day. CDC hosted an ME/CFS Awareness Day posting on the CDC Features home page and included a link to
the NIH Director's blog on ME/CFS. In addition, for the first time, our program posted a message on the CDC Public Health Matters blog and used Twitter to help spread the word about this hidden health crisis. On that day, so many of us involved with CDC’s ME/CFS program wore blue to lend our support to the ME/CFS community that we had a group photo taken so that we could highlight this initiative throughout the division through our division newsletter.

So now shifting to updates on our multi-site clinical assessment of ME/CFS study and we call this MCAM. This continues to be a major focus of our group. And, as a quick review, this study was designed to use a standardized approach for collecting information on patients in the clinical practices of clinicians with ME/CFS expertise. We are greatly indebted to these seven clinicians and their staff and even more so to their patients who have been so willing to participate. The synopsis of the MCAM study can be found in the CDC web page under the resources section.

We are now in the sixth year of this study. When we first planned the study, we weren't certain that it would work and as we planned and we weren't sure we could enroll and collect complete data on enough patients. However, it has been very successful. We started with a clinical epidemiologic study of adults with ME/CFS and healthy controls and expanded to include pediatric, homebound and recent-onset patients. As we worked with the different sites and principal investigators, we added more protocols to help us look at ME/CFS.

In addition to collecting questionnaire information, we expanded to collect blood and saliva samples and data from cognition and exercise testing. We are also asking each clinic to use a standardized method for evaluating dizziness when standing as part of the physical examination. This test, which is called the naphthalene test, may help healthcare providers more clearly see and document the problems their patients with ME/CFS experience.

The first scientific article from this study was published in the American Journal of Epidemiology, and it was selected as the editor's choice for the issue in which it appeared, on April 15, 2017. This means that it was made available as a free publication. The paper provides details about how the study was designed and implemented, and this will give other researchers information they need to understand the outcomes and adapt methods for their own studies.

For the adult longitudinal study protocol, we've completed about 90% of the baseline data collections, 50% of the first follow-up and 40% of the second follow-up. We've completed about
60% of the cognitive testing and about 55% of the exercise testing protocols. The natural killer cell function study is now underway. And I want you to know that I was invited to share information on the MCAM study at the Biomedical Research into ME Colloquium 7 that's being held in London on May 31, 2017.

In December 2016, we held the sixth meeting of the seven participating clinicians and study coordinators on CDC's campus. We reviewed the progress to date and discussed topic areas for future research in ME/CFS. To address the immediate gaps in the MCAM study, CDC has just announced two contract solicitations. One is to ask for more clinics to provide data from children or adolescents with ME/CFS. And the other is to ask more clinics to provide data from patients with other illnesses as comparison groups. These additional data will increase the sample size and power to examine the similarities and differences between ME/CFS and ill comparison groups and provide much-needed data on pediatric ME/CFS.

We also continue to be involved in other partnerships. In January 2017, Georgia advocates Timbre Lindsey and Ryan Prior and University of Alabama researcher Jarred Younger provided an educational session on ME/CFS for the Georgia General Assembly's health and human services committee. Representative Sharon Cooper, the committee chair, invited CDC to send representatives to this session to be available to answer committee questions on ME/CFS. Two people from our program and two people from our division attended this session and provided fact sheets on ME/CFS to the committee. The committee members were very engaged and clearly learned a lot from the session that was organized by Georgia's advocates.

CDC has been actively collaborating with other agencies across the Department of Health and Human Services to ensure each agency's activities provide the greatest of benefit to the American public. One of our collaborative projects is co-organizing the common data elements project on ME/CFS with the National Institutes of Health. This will enable information to be consistently captured and organized across ME/CFS studies. We will also participate in the FDA qualification process facilitating collaborative efforts to select measures for fatigue in ME/CFS. At this point, I would like to turn the call back to Dana so that she can introduce our speaker. Thank you very much.

Dana Brimmer: Thank you, Dr. Unger. I'd now like to introduce our guest speaker. Dr. Robert Naviaux received his M.D. and Ph.D. from Indiana University and completed a post-doctoral fellowship at the Salk Institute in La Jolla, California. He is a professor of genetics in the Departments of Medicine,
Pediatrics and Pathology at the University of California, San Diego School of Medicine and co-founder and co-director of the Mitochondrial and Metabolic Disease Center. His work focuses on the mitochondrial mechanisms of disease and he is applying this research to ME/CFS as well as other illnesses. Welcome.

Robert Naviaux: Thank you very much Dana and thank you very much Dr. Unger. Today's talk will cover a number of points that will be new to people and some I hope will be familiar. But to help everybody, we've made available a PDF copy of the 22 slides that I'll be going over. And I hope you'll be able to follow along with the slides. It will make understanding a lot easier.

On the first slide, we have the title and an acknowledgement to the children with mitochondrial disease that started off my career in medicine and specifically the Christini Fund that has funded much of our research. And the second slide we have an outline of the topics we're going to cover. And the first topic is just going to be what is the cell danger response. I'll introduce the concept of metabolic reflexes and the healing cycle. I'll talk about purinergic sensory processing receptors that are needed for detection of cell danger and safety.

I'll talk about the metabolic lessons we've learned from studying the antiviral response. And then review some of the findings in our PNAS paper from last August on the metabolomic or metabolic features of ME/CFS. And I'll finish with a discussion of the metabolic features of the exit from dauer, so dauer being a persistent low energy state that allows survival in the face of danger but also is responsive to environmental changes that allow recovery. And we're using this as guidance and clues for possible future treatments.

On the third slide, there - I start with John Dryden's quote from 1681 that "self defense is nature's oldest law." So every cell living -- now living on the planet -- is descended from ancestors whose genes were selected for their ability to manage every threat that those cells and those organisms encountered before they could reproduce. Those threats came in many forms from viruses to bacteria to predators to harsh winters and famine, chemical exposures. But our genome bears in it the tools necessary to manage that our ancestors used to manage every one of those threats until at least their first child.

And so we're interested in mitochondria because they represent metabolic canaries in the coal mine. Their activity, their enzymatic metabolic activity is so fast that they are the first to sense danger or
toxicity just in the way that canaries are used to sense low oxygen or toxins in a mine. So mitochondrial are regulators of cell oxygen not only because they consume it but also when they don't consume it, it means that oxygen levels begin to rise in the cell causing oxidative stress. Regulators of cell defense and innate immunity, mitochondrial coordinate cellular defense and they act as a cellular power plant. In addition, they regulate over 500 different reactions in metabolism. So when cells encounter danger, mitochondria alter their function and they produce universal alarm signals that we've characterized as a cell danger response.

In the fourth slide, I answer the question what is the cell danger response. And on the left there's a picture of a cell with a pink halo around it that represents a chemical halo of metabolites that are produced by the cell. And then I also have illustrated a virus that we consider an archetypal stress of viral infection. You'll also note the capillaries bringing oxygen to the cell and waste products away from the cell.

The cell danger response is a coordinated multisystem metabolic reflex that is caused by an electron’s field. So what does that mean? When a physician taps your knee and your foot kicks out, you know, it's automatic that your big toe and your little toe also reflexively move according to the stimulus. It turns out that the cell danger response is a parsimonious collection of up to 30 different biochemical pathways that all are coordinately regulated, some up and some down, in response to different kinds of cellular stress. And that can be biological stress in the forms of viral or bacterial or protozoa infections. It could be water stress. It can be heat stress, oxygen stress, many different things.

When the cell is infected by a virus, the virus will utilize -- try to usurp electrons that are needed for the assembly of its own macromolecule. The virus needs to make its own RNA or DNA or its own phospholipids for a cell membrane. And so it will try to use those, the resources in the cell and ultimately carbon/carbon bonds require electrons. And when electrons don't make their way to mitochondria, then mitochondria decrease the amount of oxygen they consume. And when that happens, then the dissolved oxygen concentration in the cell begins to rise because mitochondria are like a sink at the bottom of a bowl that normally allows oxygen to be converted to water and energy. But when that sink, that drain becomes restricted, then the water starts rising in the bowl and this is the oxygen rising in the cell.

When that happens, it shifts the cell from polymer to monomer synthesis. So you go from large molecules of phospholipids and single lipids to inflammatory fatty acids to smaller molecules like
acetate and formate. And the mitochondria will fission. They'll go from the so-called spaghetti configuration to the meatball configuration, which is associated with a decrease in their ability to make energy.

Lipid rafts, single lipids in the membrane, will start to aggregate and the membranes themselves stiffen. They'll be — in bullet point number three (slide 4), there's a release of antiviral, antimicrobial chemicals like reactive oxygen, heat shock proteins, AMPs or antimicrobial peptides, aldehydes and polyamines. In bullet point four (slide 4), I've illustrated this switch from fused mitochondrial configuration in a large interconnected reticulum that's well arborized and highly efficient to a less-efficient fission mitochondria that also is associated with an increase in the unfolded protein response, because when the mitochondrial membrane potential begins to decrease, fewer proteins are imported and that reduce - it produces a proteostatic load in the cell phytoplasm.

In bullet point number five (slide 4) is a change in the DNA and histone methylation. Methylation is also coordinated with this and chromatin structure is. You'll have DNA that becomes demethylated and that will result in the mobilization of endogenous retroviruses, L1 retro transposable elements and a number of other mobile elements. In bullet point number seven (slide 4) is actually a warning to other cells that this cell has been either infected or exposed to stress and so I've listed one of those signals as a purinergic halo. Cells will actually release ATP and other molecules traceable to mitochondria under conditions of stress. And ultimately that on a systemic level affects how the brain operates and will result in a change in behavior that will persist until the healing process is completed. Okay.

On the fifth slide, I have the title Starting with the CDR is Universal with Every Single Stress. In order to start the healing response, the very first thing that cells do is they begin to release extracellular nucleotides in response to this intracellular stress. I’ve illustrated the nucleus on the bottom yellow is communicating with mitochondria and mitochondria are communicating metabolically back to the nucleus, what I call the short path retrograde signal. And then mitochondrial ATP, UTP and other nucleotides are released through gated channels in the membrane. I've illustrated one type called a pannexin P2X7 channel.

And that ATP then can actually go - bind to extracellular receptors and signal back to the nucleus, and the nucleus will then change its program to adopt the cellular defense metabolism. You know, that information is also communicated through that pericellular unstirred water layer and then diffused out to neighboring cells to also allow them to respond to the danger. I've illustrated more
of the channels that through which ATP can escape and when ATP -- these channels open up under cell stress and they close when the cell is under baseline conditions.

Under baseline conditions, the energy that mitochondria make in the form of ATP is well conserved inside and can be used for normal activities. But under stress, that ATP is released to the outside where it can participate in sounding the alarm. But that results in a dissipative loss of extracellular ATP. So I went searching for a drug that might be able to block that e-flux much like in a water balloon if you have little pinholes in the water balloon, little fountains of water will be released and the pressure inside the balloon will fall.

And that's similar to what is happening metabolically in cells as they lose ATP. The inside ATP production has to increase or the overall utilization of ATP has to diminish. I've illustrated red balls that will block the different e-flux channels and I've called that anti-purinergic therapy and we'll return to that because there are classes of drugs. We use one called Suramin that can affect this change.

In the sixth slide, we have how do cells smell safety and danger in the world. And it turns out that every cell is imbued with the capacity to monitor its environment through receptors that are interestingly like olfactory receptors, so smell receptors that we use. It turns out that these are G protein coupled receptors. They have seven transmembrane domains. They hail back to the largest super family of all genes that we find even in the ocean that are bacteria rhodopsins, molecules that change, well send signals in response to light. And we have four of those different receptors in our retinas.

Under the OR column in this diagram, we have 388 olfactory receptors. We have two pheromone receptors, these V1R receptors. And then we have taste receptors that respond to bitterness and to sweet or umami. These are all related to each other through evolution and in this A section I talk about the receptors that are responsive to cytokines, chemokines, ATP and UTP, short chain fatty acids, lysophosphatidic acids, nicotine and then neurotransmitters like nicotine or pain transmitting molecules like (betakenen).

On the seventh slide, I just emphasize that all of our work started with mitochondria and we were interested in how mitochondria played a role in healing and ultimately how healing will return us back to baseline health and fitness. And we found that when the pathway to healing is blocked by
that red line that it produced self-sustaining chronic disease syndromes and ultimately 50% of the world's population lives with one chronic -- at least one chronic disease.

And in children in the U.S., 30% of children are living with chronic disease and up to 15% have asthma, 12% ADHD, 2% with autism. So this led us to a rather bold question and answer what causes chronic disease and the hypothesis is maybe it's as simple as a failure to complete the healing cycle. That if we can't heal, then we're unable to recover from whatever the trigger was that pushed us away from normal health.

On slide number eight, we have the healing cycle and its regulation. And, we have health as a green ball on the left. And a variety of different dangers and stress, injury, infection, trauma, toxins, etcetera can push that toward the injured state, this red square. And it turns out in our studies of the metabolism of healing, we've been able to identify three separate stages of the cell danger response. These are stages of healing that have to be progressed past through in sequence.

And you can be blocked in each one of these different stages. And if you are, then you have a chronic disease. And interestingly, one of the ways to relieve the block is something called anti-purinergic therapy to actually block that extracellular ATP signaling. And we're working a lot on that right now.

So what causes fatigue in ME/CFS? Slide number nine talks about two main factors. One is the dissipative loss of ATP through channels in the cell membrane that I illustrated. And two is a reallocation of cellular resources, a way for mitochondrial energy production and oxidative phosphorylation towards cellular defense. And so it's not that the mitochondria are defective in any way. They're just under new orders from the nucleus. And so they have a kind of regulated mitochondrial dysfunction.

If you're expecting them to act the way that they do under health conditions, they will not do that. However, it's not because they're dysfunctional or mutant in any way. It is because they are operating in cooperation with the cell nucleus in order to come up with a strategy that maximizes the chance for the cell to survive. And so that leads to this quote that I've made in the past that says it takes more energy to relax than to react. So anxiety, restlessness, irritability, fear of change, OCD behaviors, sensory and chemical hypersensitivities and meltdowns these are - even seizures are all hallmarks of a low energy state.
And this has actually a thermodynamic basis that has to do with the ability of mitochondria to provide the energy for the cell to lower its membrane potential. When a membrane potential goes from let's say minus 50 millivolts to minus 60 millivolts, it is actually a cell that is capable of resilience and respond to extra - in response to extracellular stimuli. But as it goes from minus 50 millivolts to minus 40 millivolts, then the cell becomes closer to the threshold for excitation and irritability and actually neuronal hyperactivity and sensory hyper sensitivities can result.

Okay. Now onto metabolomics in slide number ten. We view taking a sample of blood as sampling from a river or ocean ecosystem where the water contains or the blood contains all of the resources that all the cells need to survive and their waste products. And so it's a microcosm. And that one drop of blood we process and put through a $.5 million blue box called a lipid chromatography tandem mass spectrometer, LCMSMS, in order to study the chemical basis of health and disease.

On slide number 11 - by the way if anyone gets off of the slides where if what I'm calling out does not correspond to the slides you see in front of you I hope that the moderators, Dr. Unger and Dr. Brimmer, will chime in and let me know. Okay. So in slide number 11, we have two different plots of multivariate statistical analysis of our metabolomic result. Each ball represents a patient in whom we've measured metabolites. And using a specific set of metabolites we're able to separate controls and chronic fatigue syndrome in males and in females. It's actually interesting that the response of males and females to stress is similar but not identical and there are unique features as well as shared features.

So what are the pathway abnormalities in slide number 12, you know, defining the metabolic reflex, so the cell danger response. So in our paper in PNAS in August of last year we found that single lipids and phospholipids and sterols and cholesterol were pathways that were abnormal, purines and fine and cysteine, (prokinate), Kreb cycle, full 8B12 on a square base. All of those are ones that we found. Now interestingly in a paper that was just published last week in Cell by (Leadol) where they looked at adults in response to the Zostavax live attenuated vaccine for shingles, they found that the Kreb cycle, purines, single lipids, sterols and cholesterol, (mevainine), propionate, you know, and (ospholipids), porphyrin and (aminocycolic) lipid sugars were all dis-regulated.

In fact in the little window over on the right hand side that lists the statistical significance of each one of those. So purine metabolism you'll see is number two and the most significant. The TCA cycle is what specialists actually call the Kreb cycle. So but 12 out of the 14 of these that they found
that were disregulated after immunization were things that we identified also in chronic fatigue syndrome. The interesting thing is sometimes they're in the opposite direction. It's a key concept that we can talk about more later but it is wrong to think that the individual increases in metabolites are the cause of the disorder. The metabolites just tell us about the flow of resources through the cell and body and how that is changed under conditions of health and disease.

On slide 13, I talk about the metabolic pathway abnormalities in males and females with ME/CFS. In the first study, we identified nearly 20 pathways and half of those were shared between males and females. But a quarter were more developed more abnormal in males and another quarter were more abnormal in females.

When we did a receiver operator curve, a characteristic curve analysis, a way that scientists decide or measure the accuracy of diagnostic classifiers, we found that using metabolomics we could identify males, male controls and males with chronic fatigue syndrome with a 94% accuracy and females with a 96% accuracy. I'm quick to point out that we are conducting a national validation study on a completely independent population of adults with chronic fatigue syndrome that is funded with the help of the Open Medicine Foundation in order to validate the metabolic signatures that we found in the first study.

So what about slide number 15 is the hypo metabolic persistence and survival states in nature? Are there conditions in nature that we can study that where nature has already come to different solutions to manage highly stressful environments. One of these that's seen in bacteria is called persister cells, so both Lyme disease the (beryllia) as well as tuberculosis mycobacterium will adopt these - this low metabolic state in cells that because of the low metabolism they do not take up antibiotics well and as a consequence are not killed by those antibiotics.

And so when you use antibiotics, the persister cells persist. In that middle yellow oval you'll see two red bacteria. And when the antibiotics are taken off for a period of time, those will reactivate and allow possible re-growth. There's also something called embryonic diapause which is a state that over 100 mammalian species use that allows for fertilization of an egg that will then progress to the zygote and blastocyst stage and then just settle on top of the surface of the uterus and hang out there for months without consuming energy in just this persistent state until extra external stimuli are received that say that the environment is - it's all good to go. You can start - the embryo can start developing. And so pandas and polar bears and kangaroos will do this among many others.
The hibernation that you're all familiar with I've just shown a little ground squirrel in the hand of a person who's in hibernation. Torpor is something you may not be familiar with. It's something - it's a hypometabolic state that a number of animals will undergo when they are - the food availability and the environment for the times they need it is not available. The metabolic rates of hummingbirds, for example, are very high, and at night they don't feed but they still have this - they would have a high metabolic rate but they're able to actually lower their oxygen consumption and metabolic rate when food is not available and then that's called torpor. And they'll reawaken and reactivate in the morning.

Estivation is a phenomenon that desert animals will use where they will - when the environment's too hot, they'll have a different kind of hibernation that allows them to survive the heat and dryness by decreasing their metabolic rates. Tun is a state that little, a little multi-cellular organization called a tardigrade can adopt. In its tun state it is actually resistant to large amounts of ionizing radiation to dryness and then can reactivate when the conditions improve.

Dauer is something that many animals will use in order to extend their life span under conditions of harshness and we've studied this in a little called caenorhabditis elegans. Caloric restriction and longevity research is another area that lowers our metabolic rates and on the right you'll see what we really try to do is divert the normal sequence of aging so that we can maintain that upright posture in in row A. But currently the longest lived individuals in society almost always end up in a wheelchair before they die and we're trying to see if we can alter that fate. So here's on slide number 18 I'm looking at C. elegans and the lifecycle which normally takes three days. They have menopause in six days. The normal lifespan is about 14 days.

Dana Brimmer: Oh excuse me, Bob, it's actually slide 16 on ours.

Robert Naviaux: Oh thank you very much. Okay so slide 16. Thank you very much. So in slide 16, the red circle circles this dauer stage which is an alternative developmental stage where the animals instead of dying in two weeks will live for four months but it's a clearly altered kind of metabolism. You see that down on the bottom they've accumulated lipid droplets the way that a bear puts on fat for the winter to survive the winter and they've also decreased the total amount of muscle mass needed to survive. So they get thinner. In the shifts they literally will stop eating so that leads to caloric restriction. But mitochondrial (oxfas) declines, oxygen consumption declines. Lipid droplets accumulate. Glycolysis can actually increase and then there's some interesting other metabolic pathways that will also change.
So what do we do? We look at the changes associated with the exit from dauer. So we're not studying the triggers that lead to chronic fatigue syndrome. We're wanting to see if we can learn from these little animals on how to recover chronic fatigue syndrome. Okay?

So in slide 18 in the choreographed metabolic features of the dauer - of dauer exit, I have again a plot of animals. In the lower left pink, there's animals, the metabolic features in dauer that goes up. And then as we start to recover the animals, you know, in two hours they go into the green circle. In ten hours they go into the purple circle and in 20 hours they go into that aquamarine circle and will - that's the recovery stage and they'll be able to restart their lifecycles then. Okay?

And we measure metabolomics, each of these different stages we can identify things like NAD plus that increase at 20 hours, NAD Ph that start to increase at ten hours and also at 20, glycerol at 10 and 20 and citrulline that really, you know, starts picking put at ten hours early. And then there's hundreds of other molecules that we're also studying.

Okay so what's the treatment strategy? This is a generalized strategy. It's basically the first thing is if you can identify the trigger for the cell danger response and it's still present, you have to treat that. Okay? The other is to refill the metabolic tank. This is really an effort of trying to convert this winter, deep winter metabolism that this hypometabolic that, you know, restricts your activities to spring and summer metabolism. And so some of that we use metabolomics to guide individual responses.

I should point or emphasize this is an important point is that in all of the abnormalities that we measure in each individual, only 25% of the abnormalities are diagnostic for ME/CFS and 75% are unique to the individual are kind representative of the path they took to get to chronic fatigue syndrome in addition to what part of the healing process they happen to be stuck in.

And so that's using metabolomics to guide that is something we think will be important. And then anti-purinergic therapy with low dose suramin is something that we were planning to use to an attempt to reprogram metabolism to progress through the healing cycle. …
So on slide 21, this is just to emphasize the fact that seasonality is a part of life on earth and that any organism that was unable to manage the different metabolic needs of low calorie availability during winter new calorie availability during spring and summer on the right and then back to fall metabolism is an organism that was, that it cannot maintain health throughout the year. Okay so that ends my slides.

Slide 22 is just a mention of our research support. And again it's showing you that this little girl that lived to be only two years of age has actually made it possible for us to do all of the science we've done over the last 20 years. And thank you very much. So that ends my slides and then I can go onto answering some of the questions that we've received if you'd like to do that. So let me know Dana what you'd like.

Dana Brimmer: Oh great. Thank you Dr. Naviaux. That was very interesting. We don't have time for all of the questions but why don't I start by asking the questions so everyone can hear and then we'll have you answer them. So let's start. One question we received was can you tell us more on how the metabolomic profile of ME/CFS compares to the metabolomic profile of other illness and are these other illnesses with the cell - do they have a similar pattern? And to what degree could a sedentary lifestyle explain the abnormalities?

Robert Naviaux: Sure. So let me start out first with the sedentary lifestyle question. So we've been - so I'll just say straight out that does not explain what we see. There's a much richer chemical message in the metabolomics than we see that is not seen in healthy individuals who whose activity is reduced. But let me also say that we've conducted now clinical metabolomic studies and nine different chronic complex diseases and healthy aging over the last two years and these have included two independent studies in autism, major depressive disorder, post traumatic disorder, traumatic brain injury, ME/CFS, Gulf War illness and an autoimmune disease caused primary sclerosing cholangitis and then also the study of exercise and healthy aging in both young and old subjects.

And the ME/CFS signature in comparison to the others is starting - when we do a Venn diagram of the metabolic pathways involved in these, it's starting to create something that looks almost like a daisy where the individual petals of the flower are the individual diseases. And at the center there's a circle that where there's some shared pathways and that's - those are pathways that relate to the cell danger response.
So I can say, for example, one example that we'll publish later this year is - it shows that Gulf War illness instead of having low single lipids has elevated single lipids and so how the pathways are used is influenced by the actual ultimate disease. And so there's a lot more to be done but we're excited about how far we've gone so far.

Dana Brimmer: Another question we received is based on your discovery of a hypometabolic state in some ME/CFS, is it possible to gather a clear and concise dos and don'ts fact sheet for these patients to help them self-manage with regards to exertion, exercise, nutrition, medication and other key factors?

Robert Naviaux: The shorter answer is no because the individual differences make it very difficult to come up with a generic solution. The other fact is that the sequence of the interventions, the therapies are - is important. So you can't just give a blanket recommendation that's good for everybody. As I mentioned earlier, 75% of the metabolic abnormalities that we've - that each patient has are individualized. And therefore, you know, we hope that eventually metabolomics will become a clinically available tool that will help guide physicians. It's - it'll probably be another two years before that becomes ready for prime time. Right now we're really just developing the technology. But I hope that that will be available.

In the meantime the thing that is common to everybody is this pathological persistence of this modified form of the cell danger response which we will attempt to - well we will test to see if suramin might be able to bring that into abatement and allow people to return toward regular progress toward healing. So short answer no but important to recognize individual differences. And the signaling function of ME/CFS we'll be testing a treatment for later this year.

Dana Brimmer: Okay. Thank you. And related to that question is a question that says in capital letters is there anything that you can recommend we do while we wait for treatment options?

Robert Naviaux: Well I wish I had a better answer for this but I think perhaps the most important advice that I can give for a patient with ME/CFS is to find a good doctor who will listen, who will listen to your symptoms and your past responses to other therapies you've tried that won't try to categorize you as just one of thousands but as an individual with your own individual symptoms, some of which are more severe than others. And when you have a doctor that is work - that will work with you sometimes this requires a - also a kind of a multidisciplinary approach that will involve a physician, a nutritionist, and many other healthcare professionals in order to meet the needs of the individual.
And so I think my hope is that our research will lead to a baseline a way to start therapy, this effort to move from winter metabolism back to spring and summer, but right now it really requires getting to a physician who you can trust who is listening to you that won't try to make you a square peg in a round hole.

Dana Brimmer: And I think we have time for one more question for Dr. Naviaux and then one for Dr. Unger. So Dr. Naviaux the first - or, I’m sorry, the last question for you is I have a question regarding his publication, Metabolic Features of Chronic Fatigue Syndrome and the correction that was issued on this article. I don't fully understand the implications of this correction. Was the data invalidated?

Robert Naviaux: Yes this is an important question. So none of the data was invalidated. None of it was even affected. All the correction does is allow allowed Dr. Ron Davis who was responsible for he was an editor and he sent out the paper to external reviewers. He wanted to note in the correction that his son, who has a severe form of ME/CFS, was not part of the study and although he had consulted with me about metabolomics after the study was done and he had worked previously with Dr. Gordon, one of the co-authors, Dr. Davis had no involvement in the study and no involvement in the interpretation of the results. So the correction was just a clarification that Dr. Davis did not have a scientific conflict of interest in evaluating the paper.

Dana Brimmer: Well thank you for that explanation. Dr. Unger we have one question for you before we close our call today. The question for Dr. Unger, you indicated during the February 2016 P-COCA call that Dr. (Chia) had provided the CDC with 30 tissue samples for testing. What is the status of the CDC's tissue sample testing? What studies of infections in general in ME/CFS is the CDC conducting or planning to conduct?

Elizabeth Unger: Dr. (Chia) sent 30 specimens and they were received and tested by the picornavirus laboratory in the Division of Viral Diseases in 2015. This group are the experts on enteroviruses at CDC and they consulted with Dr. Chia about the nature of the specimens that he sent and used to publish independent pan-enterovirus molecular methods that they routinely employee for enterovirus detection and identification. Their results were negative. They returned the residual material to Dr. Chia and remain in communication with him and other investigators interested in persistent enteroviral infections and autoimmunity.
At the moment, we have no studies underway and the CDC ME/CFS in the Chronic Viral Diseases Branch is not currently testing samples from the multi-site study for infectious agents. But this viral repository is available for future hypothesis directed research including those related to infectious diseases. And if the material has been collected appropriately, it could also be used for a validation of some of the metabolomics findings that Dr. Naviaux and others in the field have found. So that is the main goal of our bio repository.

Dana Brimmer: Okay. Thank you Dr. Unger. This brings us to a close for our call today and we want to say many thanks to our speaker Dr. Robert Naviaux for taking the time to be with us and for a very, very interesting presentation and also thank you to the participants on the call for your time and interest. To submit questions and ideas for future topics and speakers, please direct all correspondence to mecfssec@cdc.gov. And more information about the CDC ME/CFS program is available on this CDC Web site which is www.cdc.gov/cfs. And both of these links will also be available at the bottom of the communications email you received for the call. Thank you again for your participation and we look forward to having you join our next call.

Robert Naviaux: Thank you very much.

Coordinator: This concludes today's call. Thank you for your participation. You may disconnect at this time.

Dana Brimmer: Thank you.

END

Related Presentation: The Metabolic Features of Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS) [PDF – 2.47MB]

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