



Presentation of Inge Lindseth
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 "Treatment of Chronic Fatigue Syndrome
 as an Immunological Disorder"



AUTOIMMUNITY 2012 conference website: www.kenes.com/autoimmunity2012

Treatment of Chronic Fatigue Syndrome as an immunological disorder, using a novel immunostimulatory therapy

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 Transcript of <http://www.youtube.com/watch?v=2IMdAV6SIMU> video.



The next speaker is Inge Lindseth from ... Oslo Norway, ... he is going to speak on treating Chronic Fatigue Syndrome as an immunological disorder.

Transcript

00:00:08

I am a clinical nutritionist working at a multidisciplinary clinic in Oslo. Over the last decade my clinic and several other clinics around the world have treated various chronic diseases with a novel immunostimulatory therapy, also known as the Marshall Protocol.

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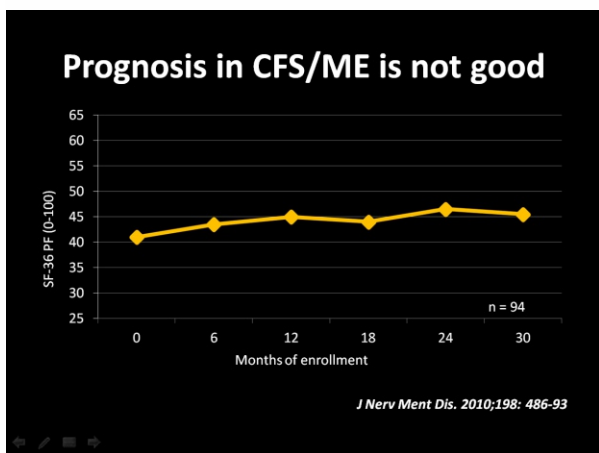
Results of this therapy have been presented at various Autoimmunity Congresses the last few years, the last time in Singapore by Doctor Goetze-Pelka, where she pointed at the inflammatory nature of psychiatric diseases and pointing to the possible etiological role of persistent, chronic infection.

While CFS, which I am going to talk about today, is not regarded as psychiatric disease, the cognitive dysfunction can be severe, adding further weight to the close connection between the body and the brain in chronic disease. Thus, our approach, whether the symptoms stem mostly from the brain or the rest of the body, is to treat the disease on a whole body level.

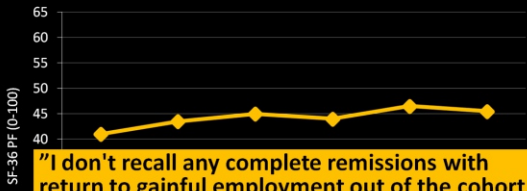
In my talk I am going to talk about the basis for our treatment approach and tell you about you the results we are seeing in our CFS patients.

00:01:26

Before we get to that, I just want to point out the poor prognosis CFS patients generally have. In the cohort represented here, at the start of the observation period, the subjects had a physical function at about 40 on the SF-36 Physical Function scale. This is a level of functioning which implies only being able to take care of little more than one's most basic needs, and not being able to work, for instance.



Prognosis in CFS/ME is not good



"I don't recall any complete remissions with return to gainful employment out of the cohort we followed."

Don Ciccone (Lead author of study. Personal message)

J Nerv Ment Dis. 2010;198: 486-93

00:02:03

So, over 30 months, you see there is little improvement, although there are individual differences in the trajectories, and as the author says, he doesn't recall any complete remissions in this cohort and nobody returned to work.

So, new solutions in terms of treatment are clearly needed in this disease.

Infectious associations in CFS/ME

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We use an immunostimulatory therapy in this disease.

Why would we want to do that?

Well, there are several lines of evidence pointing at infection being the cause of CFS.

Epidemics of CFS/ME

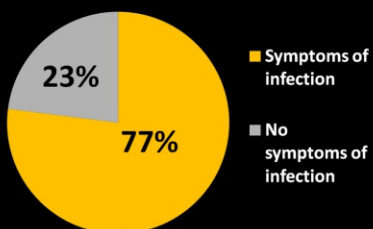


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One line of evidence comes from the fact that there have been several epidemic type outbreaks of CFS, and when a disease spreads in an epidemic manner, one of the usual prime suspects are infections.

As you see in the Norwegian Giardia-induced Bergen outbreak (2004), an actual infectious trigger has been identified as the cause.

Evidence of infection at onset of CFS/ME



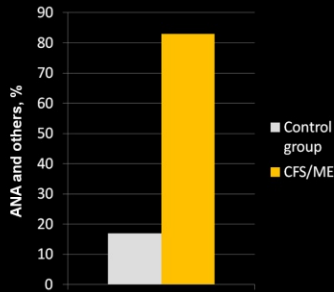
n = 873

in vivo 24: 185-188 (2010)

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Another line of evidence comes from the fact that most CFS patients experience flu-like symptoms at the start of their disease, as exemplified here in this large Norwegian cohort.

Autoantibodies in CFS/ME



Arthritis Rheum 1997 Feb;40(2):295-305

00:03:12

And although the findings are mixed, autoantibodies have also been found in CFS to be increased compared to control group in this study.

IgA and IgM against LPS in CFS



* IgA/IgM not detectable in controls

J Affect Disord. 2007 Apr;99(1-3):237-40

00:03:25

Also, findings of increased levels of IgM and IgA against common enterobacteria have also been found. I would like to also add that the level of symptoms that the patients have is correlated to the amount of IgA and IgM in these patients.

So, you have all these infectious associations and many more that I have not mentioned here today, but when it comes to finding one single living microbe—one single species of microbe—in this disease, the results are scarce and mixed.

This could mean that infection is merely a trigger of the disease, but not what causes it to continue. Or, as we believe, there might be other reasons for not finding the microbes and identifying infection as being the cause.

Persistent infection?



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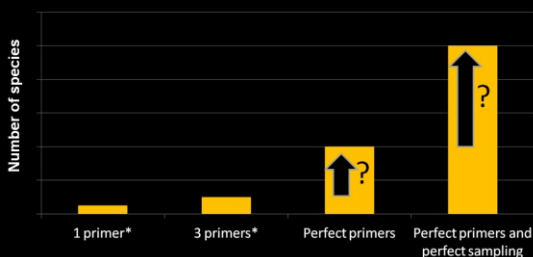
So let us look into what we believe is in this black box.

One reason for this still being a black box problem, I believe, lies in microbial detection methods. One of the more sensitive methods in routine use is PCR.

Now, would PCR detect everything?

No single microbe has consistently been associated with CFS/ME

PCR misses an unknown (large) part of microbial diversity



* ISME J. 2009 Dec;3(12):1365-73.

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The data in this graph, on the two bars to the left here, shows that when one uses a single primer to detect microbes in a given sample it misses half of what three primers can detect.

It then follows that when there is such a large difference between 1, 2, and 3 primers, the use of 4, 5, or more primers would also lead to a pretty large differences in the amount of microbes recoverable. That is to say, that using even 3 primers would miss a lot of the complexity. And that is what can be detected if the primers—if the sampling mix—are perfect, but as we know, sampling methods are not perfect. Bacteria may be hiding within cells and within biofilms.

PCR misses an unknown (large) part of microbial diversity



* ISME J. 2009 Dec;3(12):1365-73.

For more on the limitations of PCR and other microbial detection methods, do have a look at our chapter in the book, *Metagenomics of the Human Body*.



00:05:35

Another reason for not making the possible connection between persistent infection in CFS might be that one is looking for one microbe as the cause of the disease. Now, just looking for one microbe and limiting oneself to just looking for one microbe does not make sense in the era of the metagenome.

We are asking the question: Can CFS be caused by a diverse microbiota, where the individual pathogens play a secondary role?

Our treatment approach



Vitamin D Receptor, with olmesartan in the LBP

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So, although the possible pathological microbiota in CFS has not been well characterized, our treatment approach has the premise that what is in the black box is a **diverse** microbiota.

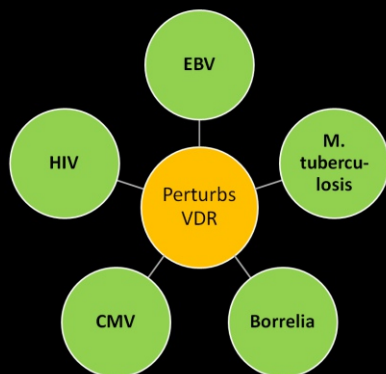
We try to target the microbiota not by attacking it directly, but by enhancing the function of this receptor, the VDR. And amazingly, as Trevor said, this approach works! The reason it works, we believe, is that the VDR is a very key factor in innate immunity, mainly as an inducer of AMP production, anti-microbial peptide production.

While enhancement of these functions in itself could be a logical way to increase resistance to infection there are other signs that this might be particularly important.

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One major reason for that is that several microbes are known to be associated with a reduced function of the VDR.

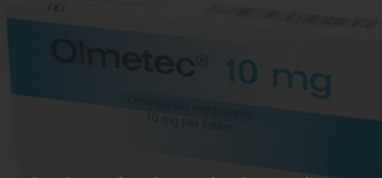
Rather than the microbes just having different kinds of shields against the immune system's attacks, a logical and smart alternative way not to succumb to the host's immune system would be to reduce the amount of missiles directed at them. That is to say, to disable the missile launching system, i.e., the VDR.



PMIDs: 20593215, 12890386, 19461888, 18566437, 9814454

Olmesartan is...

... a putative **VDR agonist**



VDR activation stimulates the innate immune system, which is of particular importance to the defence against intracellular bacteria



00:07:23

What we have done is to retarget a medication that has been on the market for some time. That medication is olmesartan. We use it at increased dosages and in a more frequent administration, something which is key to proper activation of the VDR and to getting the clinical results that we see.

00:07:48

So basically, what this medication is doing, is to out-compete the microbial ligands for the Vitamin D binding pocket. We try to use this medication to get the patients to the finish line, that is, to get their health back.

00:08:10

Here I report the results of 64 consecutive patients—Canadian and Norwegian patients. The Canadian patients treated by a physician named Greg Blaney, which presented at the Autoimmunity Congresses before, and myself, treating the Norwegian patients.

And I would like to stress that all of patients we are currently treating are included in this cohort, whether they have been on treatment for zero years or six years.

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Asking the patients to rate their health on a scale from 0 to 10, and defining improved as a decrease in symptoms by more than 20 percentage points, these are the results after 0-6 years. In a disease with such an overall poor prognosis as we saw earlier, I find these results very promising, indeed.

Only 2 of the 64 were in some level of gainful employment at the start of therapy. After 0-6 years of therapy 22 were working, most of them working full time. I would like to point out that this is substantially different from the average in the cohort I mentioned to you earlier, with zero patients returning to work in about the same average time frame and an average improvement in that cohort which was far below the 20 percentage points most of this cohort has reached.

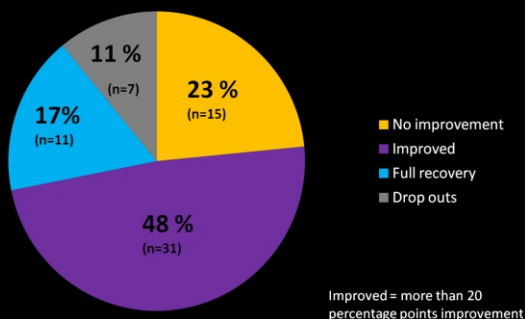
Experiences using a novel immunostimulatory therapy in CFS/ME

Results from a cohort of 64 consecutive patients, many of which are still undergoing treatment

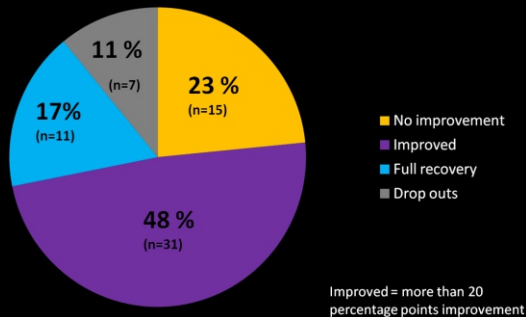
(0 to 6 years treatment duration)



Overall symptom improvement



Overall symptom improvement



11 of our patients are in the category of full recovery, which is defined as being back in full time work and essentially not having any symptoms. Since many of the patients have been on the therapy for a short time, we expect these results to improve over time in this cohort.

The dropouts are mostly early dropouts and the reason for dropping out is mainly that they found the symptom increase after starting therapy too hard to handle.

No easy fix:

Immunopathology (a.k.a. Jarisch-Herxheimer):

Symptoms that arise due to microbial death and immune activation

00:10:00

So this therapy gives an increase in symptoms before they get better. Why is that so?

Well, as Trevor alluded to earlier, with the killing of microbes comes collateral damage, also known as immunopathology [IP]. And IP are symptoms that arise due to microbial death and the activation of the immune system.

Immunopathology as a result of treatment is already well known in different diseases

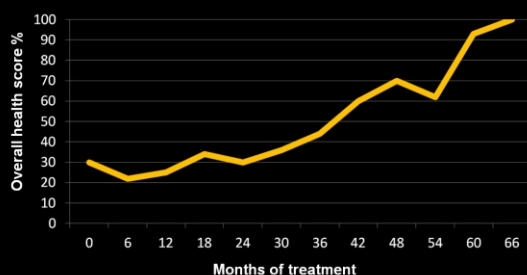
- HIV
- Lyme disease
- Tuberculosis
- Pneumonia
- Syphilis

00:10:25

That treatments yield increased symptoms as a part of recovery of infectious diseases is not a new phenomenon. Compared to treatments for these diseases with conventional medicines, we were rather surprised to see how profoundly many of our patients were affected by immunopathology, with symptoms in many of our patients increasing severely for quite some time before getting better.

These reactions do not indicate a real worsening of the disease process, but rather the opposite, the body is finally dealing with the pathogens in an efficient way. So, we see increased symptoms as a good sign, it means that the treatment works. In fact, the severity of the reactions can be seen as a measure of just how powerful this treatment is.

Typical symptom trajectory on "frequent olmesartan treatment"

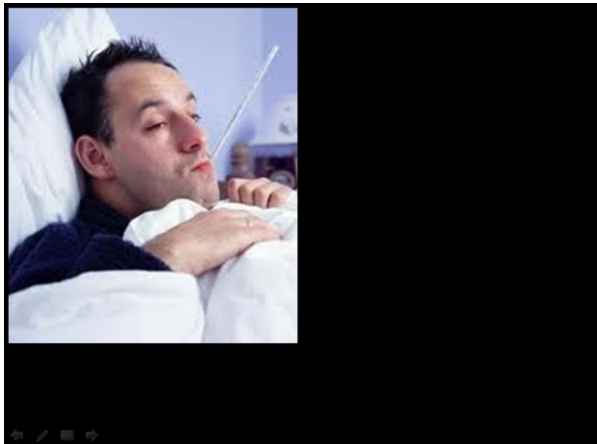


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And the effects we see can hardly be ascribed to side effects of the medication, in part because as the treatment continues these symptoms tend to disappear although they [patients] are still on the same dose of the medication.

So the immunopathology can go on for quite some time, and can be seen as a reflection of the apparent large amount of microbes the immune system has to kill.

One is looking at a treatment length of at least two-three years before recovery is achieved.



00:11:41

So, could the results we are seeing just be due to the fact that we have a long enough observation time?

It does not seem to be this way, and there are not many data on this, but in a study that I referred to here, the author of this study, Jason, had followed CFS patients for 10 years and he concludes: "The current study found that over time in a community-based sample, unbiased by help-seeking behavior, the CFS group remained rather ill with a variety of different conditions over time."

And I might add, at the two extremes of the long term health of these patients: Out of 32 patients 4 had died, and at the other extreme, one is classified as being remitted.

So the point is, that under standard care, CFS is indeed as chronic a disease as other well known chronic diseases, and, treatment options, whether palliative or disease-resolving, are very few, indeed.

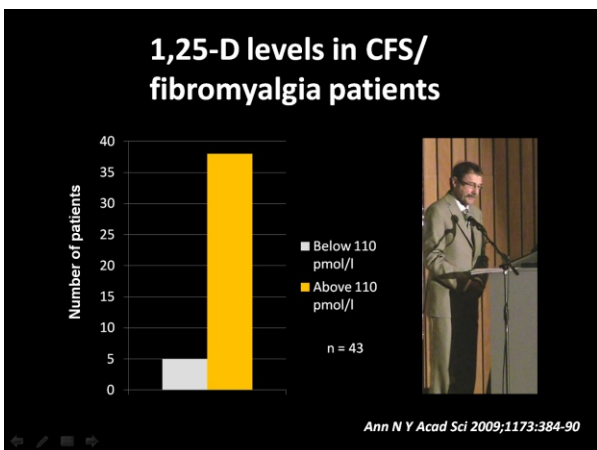


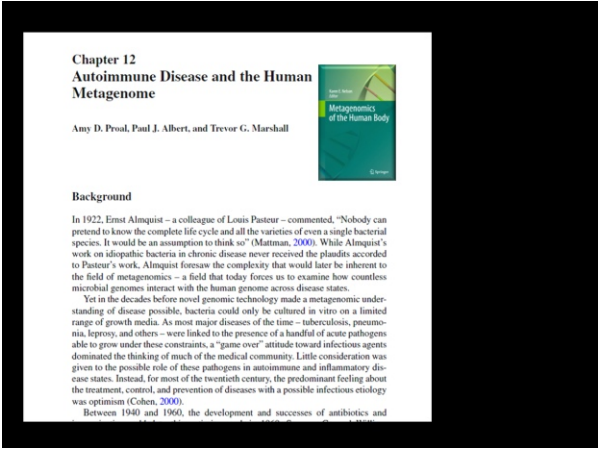
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If you are a physician, and you would like to find out if your patients have a disturbed, non-functional VDR, what marker could you look for?

I find it useful to use vitamin 1,25-D, which is not the usual marker/metabolite of vitamin D that a doctor measures.

And as you can see here, in the study by Greg Blaney published in 2009, the 1,25 vitamin D level is indeed increased in these patients and as they progress on therapy—starting using olmesartan—you will see that this level drops, indicating that it is, indeed, a VDR agonist.





00:13:32

For more on our hypothesis do take a look at our published papers, and our book and do test our hypothesis.



00:13:41

What is needed for the future is more clinical trials to better characterize the clinical effects and to better characterize the actual mechanisms involved.

I hope some of you have found inspiration to instigate such trials. Thank you.

