Creating international and interdisciplinary collaboration for health

It has been a gruelling winter from every perspective: AONM has done its best to keep the information flowing with regular webinars on a variety of topics relevant to both chronic disease and the acute crisis we have been faced with. Sadly, the potential for chronicity has become evident as a sequel to COVID-19. Long-Covid clinics are emerging across the country. With the huge research being pursued into this new virus and the funds being released for its management, hopes are high that other diseases so long neglected will find some relief in the wake of Long-COVID therapy – whether M.E., chronic Lyme Disease, or the many unexplained syndromes patients have often suffered from for years if not decades. This newsletter covers a number of related aspects, as well as looking forward to the online as well as in-person events ahead. As always, we welcome your feedback: please contact us on info@aonm.org.

CONTENTS

1. Revisiting AONM's recent exciting webinars

The "Cranial Connection" series: All three speakers gave an excellent, rounded perspective on a multi-disciplinary approach to helping chronic pain patients.

A) Professor Francis Smith:

The first talk in the "Cranial Connection" webinar series was by Professor Francis W. Smith M.D, FFRRCSI, FRCR, FRSC(Ed), FRCP(Ed), FFSEM. In his presentation entitled "The Craniocervical

Junction, Hypermobility, and Upright MRI" he discussed the use of upright, weight-bearing MRI for the investigation of the spinal column. He explained the value of imaging the spine in the upright position. It shows the spine under the natural load of gravity, and enables images to be made with the spine both flexed and extended. Professor Smith stressed the importance of imaging the entire cervical spine from skull base down to the thoracic region. Common practice is to leave out the vital junction between the head and spine – the cranio-cervical junction: "An MRI exam of the cervical spine traditionally only includes the lower part of C2 down to T1. They forget C1."

B) Dr. Iain Smith

The second talk in this series was given by Dr. Iain Smith DC, CC, BCAO, on "Hypermobility/CCI/AAI/ Craniocervical Junction Misalignment...? The Importance of diagnosis and staging in managing Craniocervical Syndromes". Dr. Iain Smith explained that misalignment of the Atlas bone has been shown to negatively affect the hydrodynamics of the central nervous system by applying direct tension to the brain stem and the delicate neurovascular structures that support it. He described the specific upper cervical chiropractic techniques that can bring about cranio-cervical correction. Gently reducing the various mechanical strains of the skull can improve cranial compliance and ultimately facilitate the flow of these vital fluids. Dr. I. Smith also gave a follow-up talk in which he presented three case studies and answered listeners' questions.

C) Dr. Peter J. Bishop

The final talk in the series was by Dr. Peter J. Bishop BDS, LDSRCS: "Fixing the Bite: Diagnosing and treating dental occlusal disorders". Dr. Bishop highlighted the links between atlas-orthogonal/ cranio-cervical instability and occlusal dysfunctions, and described a patient's pathway from referral to diagnosis and treatment of these disorders.

The "Long-COVID" series: This series is intended to show the links and overlaps between the chronic form of the novel Coronavirus COVID-19 and conditions we are already more familiar with, such as chronic Lyme Disease and autoimmune encephalopathies.

A) Dr. Robert C. Bransfield

The first talk in our Long-COVID series was given by Dr. R C. Bransfield MD DLFAPA, Clinical Associate Professor of Psychiatry Rutgers RWJ Medical School. Dr. Bransfield, an honoured member of AONM's Advisory Panel, spoke about chronic Lyme Disease and chronic COVID-19. He explained how to identify chronic symptoms in patients with Lyme/tick-borne disease, patients with COVID-19, and patients with both Lyme/tick-borne disease and COVID-19. Dr. Bransfield examined the complex, interactive infections that CV-19 appears to trigger in some cases, and particularly its neuropsychiatric symptoms.

B) Dr. Craig Shimasaki

Our most recent webinar was a tour de force by Dr. Craig Shimasaki, who spoke about "*Long-COVID, A Post-Infectious Autoimmune Syndrome: Understanding Commonalities and Biological Clues from Other Post-Infectious Autoimmune Syndromes"*. It covered the typical SARS-CoV-2 infectious cycle, then examining the differences between Long-COVID and a "typical" COVID infection. Dr. Shimasaki then looked at possible biological mechanisms that target the brain and heart. He then connected these to infection-triggered autoimmune encephalopathy and other infection-triggered autoimmune disorders that target the brain and heart characteristic of "PANS" and "PANDAS" (for further information on these conditions, please see https://aonm.org/cunningham-panel-panspandas/). This was a stunning talk that contained very new information that Dr. Shimasaki had not presented anywhere else worldwide. Please go to https://aonm.org/view-past-webinars/ for the recording and other past webinars.

The third talk in our Long-COVID series will be "Therapies for Long-COVID" by Dr. Sarah Myhill on Thursday April 29th at 7.00 pm. To register go to https://us02web.zoom.us/webinar/register/WN_Q6QRjrAeQBaM_yzRHtYJtQ

2. What are syncytia, and should we be worried about them?

A March 2021 press release entitled "*Measure What Fuses – Tissue Damage through Cell Fusion in COVID-19 and the Role of the Spike Protein*" states "The Coronavirus SARS-CoV-2 enters human cells by membrane fusion after contact of its spike protein with the ACE2 receptor. New studies provide proof for a second role of the protein in COVID-19: fusion of body cells. Smallest amounts of spike protein present in cell culture suffice to allow infected and non-infected cells to fuse and die."(i)

This press release heralds the publication on 19 March 2021 of an article in iScience entitled "*Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without*".(ii) This article highlights the fusogenic activity of the S protein of the SARS-CoV-2 virus: it is not just a passive anchor – it is biologically active, and can stick cells together.

The study found that the SARS-CoV-2 S protein is capable of three distinct membrane fusion processes: i) S-mediated cell fusion, ii) "fusion-from-within", and iii) "fusion-from-without". The first, S-mediated cell fusion, is particle-cell fusion, the process that mediates fusion between viral and cellular membranes during the entry of viral particles into the cell. The second, fusion-from-within (FFWI), is the ability of the S protein to mediate "fusion of infected cells with uninfected cells."(iii) This enables the virus to spread: the multinucleated giant cells are called "syncytia". The third membrane fusion process, fusion-from-without (FFWO), is the process by which particles of enveloped viruses can instigate the fusion of target cells even if no viral replication is taking place.

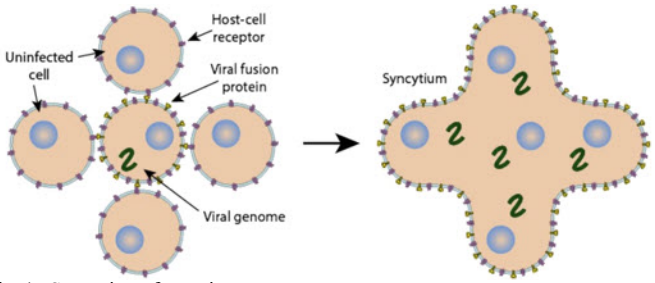


Fig 1. Syncytium formation, https://viralzone.expasy.org/5957?Outline+all_by_species

The potential these syncytia have to cause cellular disruption is evident: these multinucleated giant cells can block vessels and capillaries, leading to thromboses/microemboli and tissue destruction. Sequelae of this kind have indeed been found in COVID-19 patients.(iv) (v) This means SARS-CoV-2, the infection, has this capability even before it has noticeably become the disease COVID-19. What, in that case, is the appropriate dividing line? The sequelae that can occur will of course depend on which tissues the spike protein has adhered to – most naturally the respiratory system, in its wild form.

Can other viruses instigate these syncytia, too? They most definitely can: the phenomenon is well-known for example in many of the (DNA) herpes viruses. With the human simplex virus (HSV),(vi) these syncytia have been detected in the skin. There are also studies on their development in certain types of Epstein-Barr virus(vii) and Varicella Zoster virus (viii). Large syncytia have been found after infection with Cytomegalovirus ("megalo" meaning large – perhaps a clue), and with HHV-6, too: "These findings suggest that FFWO, which HHV-6A induced in a variety of cell lines, may play an important role in the pathogenesis of HHV-6A, not only in lymphocytes but also in various tissues".(ix)

This would appear to be a characteristic shared particularly by the neurotropic α-herpesviruses. "Syncytia (large, multinucleated cells) are clinically indicative of α herpesvirus infections, and peripheral neuropathies are clinical hallmarks."(x)
What about the RNA viruses? "Large enveloped RNA viruses Paramyxoviruses enter by fusion at the cell surface and can cause syncytia."(xi) The respiratory *syncytial* virus of course, too. It has been found that these syncytia can even cross the blood brain barrier: in experiments with mice, *Ferren et al* found hyperfusogenic proteins in encephalitis caused by the measles virus, often manifesting years later.(xii) Certain retroviruses also have this property, HIV being the most well-known: "Syncytia or multinucleated giant-cell formation is one of the major cytopathic effects induced by human immunodeficiency virus (HIV) infection".(xiii)

Should therapists be focusing more on the possibility of syncytia-driven damage when patients are suffering from viruses? Microemboli if they are blocking a blood vessel would only be one aspect. Multinucleated giant cells may be mistaken for a granulomatous disease – if they occur in the breast, for example, they may be picked up as suspicious when they are not. When they die (as the study mentioned at the outset found they do if they have been induced by spike protein), they have to be expelled via apoptosis or necrosis – necrosis causing inflammation and an additional load on the blood

stream, where hypercoagulation is a risk due to the accumulation of white blood cells (see here for further information: **https://www.youtube.com/watch?v=tzhEtmhtEDo**). Hypercoagulation always equates with a degree of hypoxia – is this a natural concomitant of viral infection (of certain kinds), and should therapists be trying to address this head on, or focus on eradicating the virus? Or both?

It seems there is renewed interest in this topic now that it has been discovered how major this feature is in SARS-CoV-2. MDPI's renowned journal "Viruses" is preparing a special edition on "Virus-induced Syncytia" to appear later this year. We will report on that edition when it comes out.

In the meantime, the foregoing suggests that even the "latent" value (identified in Arminlabs Elispots, for example for EBV and CMV) may indicate that the potential for syncytia formation is there, even if the viruses are not actively replicating.

(i) https://www.pei.de/EN/newsroom/press-releases/year/2021/03-tissue-damage-through-cell-fusion-covid-19-role-spike-protein.html
(ii) https://www.sciencedirect.com/science/article/pii/S2589004221001383?via%3Dihub
(iii) https://www.embopress.org/doi/full/10.15252/embj.2020106267
(iv) https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.120.317447
(v) https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.051828
(vi) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869023
(vii) https://pubmed.ncbi.nlm.nih.gov/6273915/
(viii) https://jvi.asm.org/content/78/6/2884
(ix) https://jvi.asm.org/content/76/13/6750
(x) https://www.futuremedicine.com/doi/abs/10.2217/fvl.14.100
(xi) https://clinicalgate.com/large-enveloped-rna-viruses/
(xii) https://pubmed.ncbi.nlm.nih.gov/31684034/
(xiii) https://pubmed.ncbi.nlm.nih.gov/1347963/

3. The magnanimity of innate immunity

We have two key arms of immunity: the first line of defence is innate or cellular immunity, and the second is humoral or acquired immunity – B cells: antibodies.

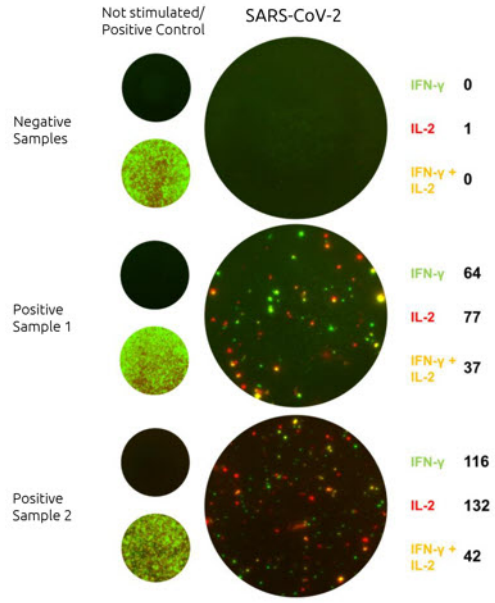
We have specific cells as part of that first line of defence, our innate immunity, called CD8+ cytotoxic T cells (natural killer cells, killer lymphocytes) that can eliminate virus-infected cells, control viral infections and provide immunological memory enabling long-lasting protection.(i) After activation they release the highly toxic contents (perforins, granzymes) of their cytotoxic granules and induce apotosis (cell death) of the virally infected cells. Very recent studies have described T cell responses of these killer lymphocytes to viral peptide megapools in donors that had recovered from COVID-19 as well as in individuals not exposed to SARS-CoV-2.(ii) The presence of these cells in non-exposed individual is indicative of potential T cell cross-reactivity. Very recent studies have reported pre-existing SARS-CoV2-directed T cell responses in groups of unexposed individual as well as those who are seronegative for SARS-CoV-2, suggesting cross-reactivity between human common cold coronaviruses and SARS-CoV-2.(iii) The study published in Nature Immunology in January 2021 by Nelde et al demonstrated post-infectious T cell immunity in 100% of individuals convalescing from COVID-19 and revealed pre-existing T cell responses in 81% of unexposed individuals.(iv)

What happens to this innate immunity when exogenous approaches are layered onto it? How sensible to perhaps first use screening to find which individuals already have this natural CD8+ immunity described above, which would suggest (depending on other factors like age and underlying conditions) less of a need for antibody-generating interventions? Another logical next step might be to test one's T cells to see the extent to which one perhaps already has immunity to the virus? A study by Nature just out shows that not only do people infected with SARS-CoV-2 develop lasting immunity, but so too can their close contacts. "Overall, this study demonstrates the versatility and potential of memory T cells from COVID-19 patients and close contacts, which may be important for host protection."(v) See the November AONM newsletter for further information (https://aonm.org/wp-content/uploads/2020/11/AONM-Newsletter-November-2020.pdf).

(i) Nelde A. et al. (2020). SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition, Nature Immunology.
(ii) Grifoni, A. et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell 181, 1489–1501 (2020); Braun, J. et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19 Nature https://doi.org/10.1038/s41586-020-2598-9 (2020); Le Bert, N. et al. SARS-CoV-2-specifc T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584, 457–462 (2020).
(iii) Reference i, Op. cit.
(iv) Reference i, Op. cit.
(v) https://www.nature.com/articles/s41467-021-22036-z

4. Testing for Cellular Immune Responses and Possible Immunity

Arminlabs has a test of T cell immunity using cellular/innate immunity, rather than serology (the antibody arm), called the "CoV-iSpot". It tests for active infection, memory cells from past infection, and a mixture of both, using Elispot (enzyme-linked immunosorbent spot) technology.

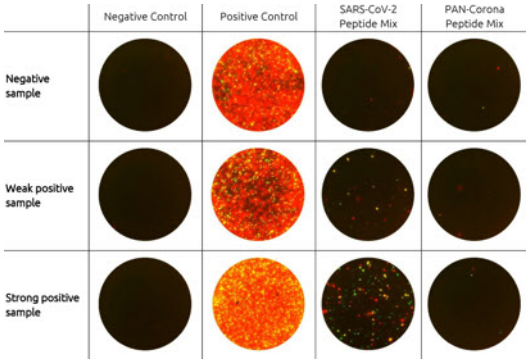


In this test for active infection, a specific antigen mix is added to the patient's blood (PMBCs, peripheral blood mononuclear cells). This mix consists of a pool of defined small peptides from the SARS-CoV-2 S, E, M and N genes, including the receptor binding domain (RBD). The S peptides are the most immunodominant in this mix. The cytokines expressed due to this antigenic activation are captured by antibodies on the coating of the membrane on the the well plate, and if they react to Interferon gamma (IFNγ), the green fluorescebcnt channel identifies them, and their quantity. The memory T-cells for past infection are identified by cytokine reaction with Interleukin 2 (IL2), and this channel fluoresces red. The patient may have a mix of both if he/she is in convalescence, beginning to overcome the infection.

This test is so valuable because it shows both current infection and T-cell immunity from past infection.

It also provides a differential marker: it shows whether the patient has a Corona infection of a different kind (not SARS-CoV-2), as some common cold viruses are also Coronaviruses. This is identified via a so-called "PAN Corona" peptide mix containing peptides from Betacoronaviruses.

This test underwent intensive validation, evidencing a perfect correlation of the positive and negative (control) cohorts in the study when T cells were stimulated with their antigen panels. The specificity of the SARS-CoV-2 S pool for IFNγ was 98.7%, 92.7% for the memory response with IL2, and for the double-positive response it was 96.7%.

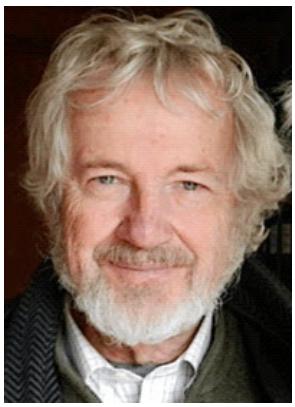


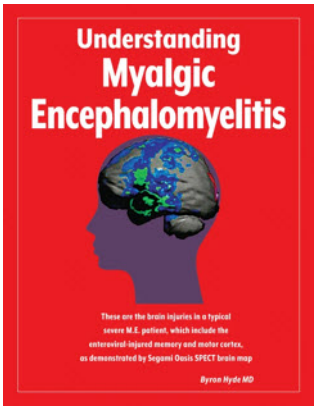
A recent article (03/2021) by Zuo et al(i) backs up the huge importance of T-cell testing: "We analyzed the magnitude and phenotype of the SARS-CoV-2-specific T cell response in 100 donors at 6 months following infection. T cell responses were present by ELISPOT and/or intracellular cytokine staining analysis in all donors". This T-cell immunity was present for at least 6 months, which is longer than has been found for IgG antibodies in some cases. The November 2020 AONM newsletter also contained many similar references from scientific journals (https://aonm.org/newsletters/). If IL2 in the form of "Pan Corona" is present – i.e., this memory T cell has been detected to Corona viruses in general – then this may still confer immunity, as described in Nelde et al.(ii)

In some cases, these T cells have been there for a long time. From a recent BBC report: "When researchers tested blood samples taken years before the pandemic started, they found T cells which were specifically tailored to detect proteins on the surface of COVID-19."(iii) And the same study, underlining the value of testing for PAN-Coronavirus immunity, too: "Importantly, we detected SARS- CoV2-reactive CD4+ T cells in 40%–60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating "common cold" coronaviruses and SARS-CoV-2."(iv) This shows that immunomonitoring is not just serology: T-cell studies using the other arm of the immune system are perhaps even more valuable.

i. Zuo, J., Dowell, A.C., Pearce, H. et al. Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection. Nat Immunol (2021)
ii. Nelde A. et al. (2020). SARS-CoV-2-derived peptides define heterologous and COVID-19-induced T cell recognition, Nature Immunology
iii. https://www.bbc.com/future/article/20200716-the-people-with-hidden-protection-from-covid-19
iv. https://www.sciencedirect.com/science/article/abs/pii/S0092867420306103?via%3Dihub

5. New book: Understanding Myalgic Encephalomyelitis





Dr. Byron Hyde, a doctor who has dedicated his practice to M.E. since 1984, and who gave two resounding talks on M.E. at the AONM annual conference in May 2019, has brought out a new book: "Understanding Myalgic Encephalomyelitis", It is a magnificent work based upon his 37 years of caring for M.E. patients and investigating epidemics around the world, and explains this thesis that M.E. (according to his very tight definition, which excludes CFS) is frequently a Polio enterovirus mutation – a post-encephalitic disease that causes major brain dysfunction. He discusses how to analyse these encephalitic injuries using HMPAO Segami Oasis SPECT software. This is a seminal work that follows on from Dr. Hyde's recent "The Return of Polio to the USA". Please refer to his past talks on this subject to AONM at this link: https://aonm.org/2019-improving-patients-lives/
Please see here for an "Introduction for Physicians and Patients to Modern SPECT Technology": https://forums.phoenixrising.me/threads/the-nightingale-march-april-newsletter-dr-byron-hyde.83414/

6. Upcoming events

AONM

AONM Long-COVID Webinar Series
29th April 2021
"Therapies for Long-COVID" by Dr. Sarah Myhill on Thursday April 29th at 7.00 pm. To register go to https://us02web.zoom.us/webinar/register/WN_Q6QRjrAeQBaM_yzRHtYJtQ

Klinghardt Institute

Autonomic Response Testing Level 2 online
20th April 2021
A.R.T.2 Intermediate Online Programme

Autonomic Response Testing Level 1 online
6th July 2021 A.R.T.1 Beginners Online Programme
See www.klinghardtinstitute.com for further details and to register

Biolab Medical Unit

Mitochondria Day
17th September 2021
Holiday Inn
Carburton Street
London
https://www.eventbrite.co.uk/e/mitochondria-day-tickets-61684068710

British Society for Ecological Medicine

BSEM Training Day 8
Spotlight on Cardiology
Friday 23rd April 2021
Hallam Conference, London.
Click to download programme

BSEM Scientific Conference

Mould Related Pathology: Infections, Allergies & Mycotoxins
Friday 18th June 2021
Cavendish Conference Centre, London.Click for full details

General Naturopathic Council

Please watch out for an upcoming webinar by Dr. Eric Yarnell on low-grade postate cancer, the latest in a series of webinars available to members of the GNC.
https://gncouncil.co.uk/

For more detailed information about AONM please see our website
www.aonm.org

+44(0)3331 210 305 info@aonm.org