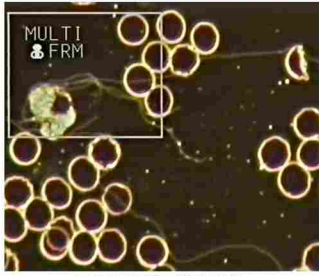


VDR NUCLEAR RECEPTOR IS KEY TO RECOVERY FROM COGNITIVE DYSFUNCTION

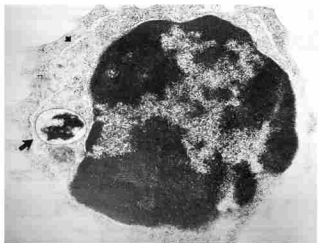
Trevor G Marshall, School of Biological Sciences and Biotechnology, Murdoch University, Western Australia.



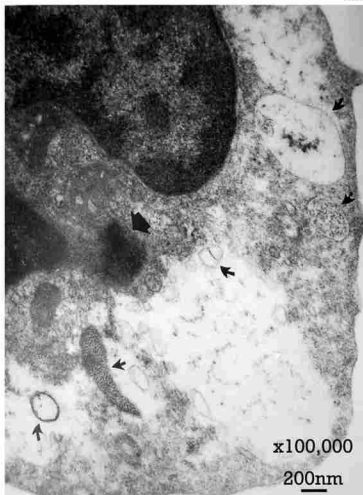
Images courtesy Andrew Wright MD, UK



Bacterial 'Biofilm' Colonies in CFS Patients' Phagocytes



Wirostko TEM Phagocyte study at Columbia, 1988

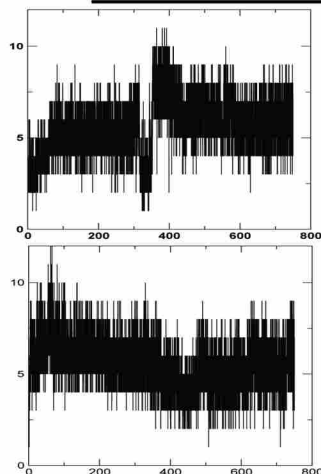


During DMM 2006 we reported that chronic inflammatory disease, including much 'autoimmune' disease, was caused by an intraphagocytic biofilm-like microbiota. Recovery followed activation of the VDR with Olmesartan, and long-term administration of subinhibitory antibiotics. Surprisingly, as the inflammatory disease disappeared from the subjects in that cohort, manifestations of comorbid neurological disease also receded. Memory and cognition returned as the inflammation waned, while suicidal ideation, depression, bipolar disorder, peripheral neuropathies and even obsessive compulsive disorder, receded. Additionally, we found that the neurological symptoms fluctuated with the level of Immunopathology during the healing process, presenting special problems with cohort management. The VDR is at the heart of the innate immune system, responsible for expression of a majority of the body's antimicrobial peptides [1]. Changes in lifestyle and medicine during the 20th century have created an environment favorable to the proliferation of pathogens which evade the immune system by suppressing activation of the VDR [2]. Kandel identified that short term memory involves activation of PKA [3]. We have determined that activation of PKA is regulated by the process of VDR homeostasis in chronic immune disease, pointing towards a putative mechanism whereby immune dysfunction can directly suppress short-term memory. However the above subjects not only reported the return of short term memory, but also of mid-term and long-term memory. The molecular mechanisms linking immune dysfunction and cognitive dysfunction are clearly profound. We propose that studies of linked dysfunction will provide more insight than studies of neurological manifestations alone.

1. Marshall TG: Vitamin D discovery outpaces FDA decision making. *Bioessays*. 2008 Feb;30(2):173-82
2. Marshall TG: Bacterial Capnine Blocks Transcription of Human Antimicrobial Peptides. Abstract presentation, *Metagenomics 2007*, San Diego, July 11-13, 2007. DOI 10.1038/npre.2007.164.1
3. Eric R Kandel: The Molecular Biology of Memory Storage: A Dialog between Genes and Synapses. *Nobel Lecture*, Dec 8, 2000.

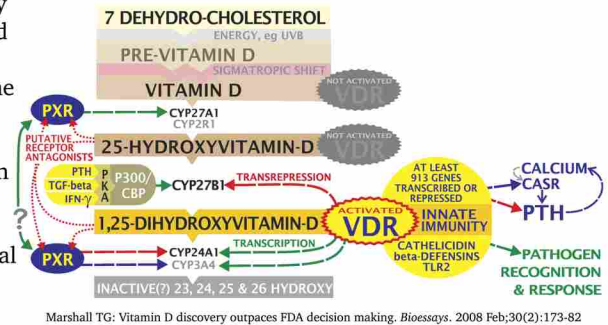
JRA: MLO parasitized vitreous lymphocyte. Uranyl acetate-lead citrate stain (x34,722). Undulating variably staining tubules (small arrow) and a prominent 0.7 um ovoid body (large arrow) are detectable within the cytoplasm. The latter has a well defined outer membrane, abundant periplasm, and a plasma membrane surrounding amorphous electron dense material. The nucleus has an irregular contour with focally indistinct areas.

Sarcoidosis: MLO parasitized vitreous monocyte. Uranyl acetate-lead citrate stain. Innumerable pleomorphic variably staining tubulo-spherical-filamentous bacterial bodies lie within a severely lysed cytoskeleton (small arrows). The upper nuclear pole has a normal appearance, whereas the lower pole is abnormal (large arrow). (Bar = 0.2 micron)

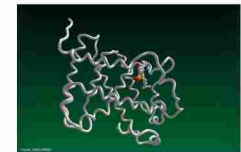


Plots of the instantaneous number of hbonds vs time, compiled during the molecular dynamics simulations, show that the receptor homology differs significantly.

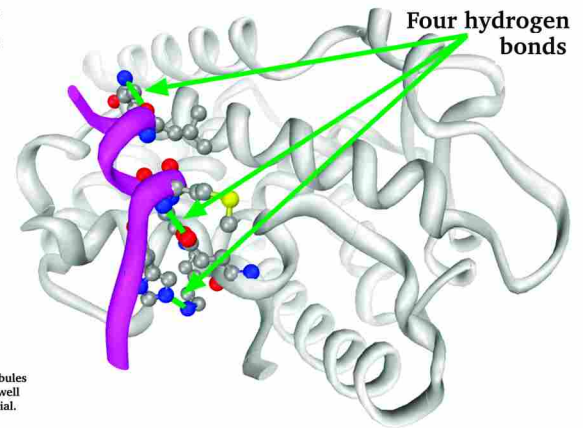
VDR Homeostatic Control (*Homo sapiens*)



Marshall TG: Vitamin D discovery outpaces FDA decision making. *Bioessays*. 2008 Feb;30(2):173-82



Molecular Dynamics Simulation of VDR with Olmesartan Showing Agonism with Human VDR and Antagonism with Murine



Murine VDR cannot emulate human VDR

Analysis of the model of the *Rattus norvegicus* VDR in complex with the DRIP205 co-activator (PDB:1RK3) shows that VDR transcription is only partly due to the AF-2 domain. There are hbonds from GLU416 to DRIP MET629/LEU630, but there are also hbonds from LYS260 to HIS627, and LYS242 to LEU633.

