

Genes, nanoparticles, and the problem of persistent chlamydial infection

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Each of the nine species of bacteria currently included in the Order *Chlamydiales* is an obligate intracellular pathogen, requiring passage through a human or other eukaryotic host cell to complete its developmental cycle. Seven of the 9 chlamydial species are economically important pathogens of domestic animals, and two species, *C trachomatis* and *C pneumoniae*, are significant human pathogens. The genomes of these latter two organisms include a large number of coding sequences specifying protein products of unknown function, *ie* having no homologs/paralogs in the various data bases. Our own studies and those of others have demonstrated that the pathogenesis engendered by *C trachomatis* and *C pneumoniae* is almost solely a function of those unknown, uncharacterized gene products. If we are to understand and effectively treat chlamydial infections, it is critical that we understand what those products do and precisely how they affect their host cells. In many systems, manipulation of specific gene products has proved to be useful in defining function. However, no process for genetic manipulation is available currently for chlamydiae. In collaboration with laboratories here at WSU and elsewhere, we are developing a process by which we may be able to manipulate expression of specific genes in both human chlamydial pathogens. That process relies on nanoparticle- and/or dendrimer-based delivery of modulating nucleic acids to chlamydia-infected cells in culture, with controlled release of those modulators to generate a “mutant” phenotype. In this talk, the genetic underpinning of chlamydial pathogenesis will be developed, and experiments undertaken to date to modulate gene expression in these organisms will be presented.

Short Biosketch for Alan P Hudson PhD

Alan P. Hudson, Ph.D. is Professor of Immunology and Microbiology. He came to Wayne State University in 1997. Dr. Hudson received his Ph.D. in molecular biology in 1978 from the City University of New York, and did postdoctoral training with Dr. Giorgio Bernardi at the University of Paris and Dr. Ronald Butow at the University of Texas Health Sciences Center at Dallas.

The primary research interest of Dr. Hudson's laboratory centers on the molecular biology/molecular genetics of the obligate intracellular bacterial pathogen *Chlamydia trachomatis*. This organism is well known to cause the blinding disease trachoma in under-developed parts of the world, and it is the leading sexually-transmitted bacterial infection in the United States. Less well-known is the fact that *C. trachomatis* can cause a serious form of arthritis in some individuals who acquire genital infections with the organism. Over the last decade, Dr. Hudson's laboratory has been instrumental in elucidating not only the molecular details of the synovial pathogenesis process, but also a number of important facets of host-parasite interaction in the joint which end in the arthritis. One facet of particular importance is the observation that under at least some circumstances, *C. trachomatis* can generate persistent, inapparent infections of the synovium, infections which clearly cause the arthritis but which appear to be refractory to antibiotic and other relevant therapies.

An emerging scientific interest of the Hudson laboratory concerns the pathogenic potential of a newly-identified species of Chlamydia, *Chlamydia pneumoniae*. This organism has been shown to cause various infections of the upper respiratory tract, and a good deal of data now indicates that it may also be involved in the pathogenesis process ending in atherosclerosis. The Hudson group has asked whether *C. pneumoniae*, like its sister-species *C. trachomatis*, can cause arthritis, and all initial experimental indications are that it does. Moreover, in an unusual series of studies, the Hudson laboratory has also provided initial molecular and other data suggesting the infection with *C. pneumoniae* may be involved in the neuropathogenesis process ending in late-onset Alzheimer's disease. Studies in these two areas are currently under aggressive pursuit.

A second area of interest in the Hudson laboratory concerns the control of gene expression in mitochondria, and the model system studied in this project is the yeast *Saccharomyces cerevisiae*. The question at issue revolves around the knowledge that components of the mitochondrial electron transport chain are encoded mosaically; that is, some polypeptides required for assembly of the cytochrome b1 complex, the F1/Fo ATPase, and cytochrome oxidase are encoded by genes on the mitochondrial genome, while others are encoded by nuclear genes, synthesized on cytoplasmic ribosomes, and imported into the organelle. Dr. Hudson's laboratory has demonstrated that transcriptional initiation for mitochondrial genes, and for at least some functionally related nuclear genes for mitochondrial products, are governed by a cAMP-dependent trans-activation mechanism. The relevant cis-regulatory element has been identified on mitochondrial DNA, and the trans-activator is currently under study.