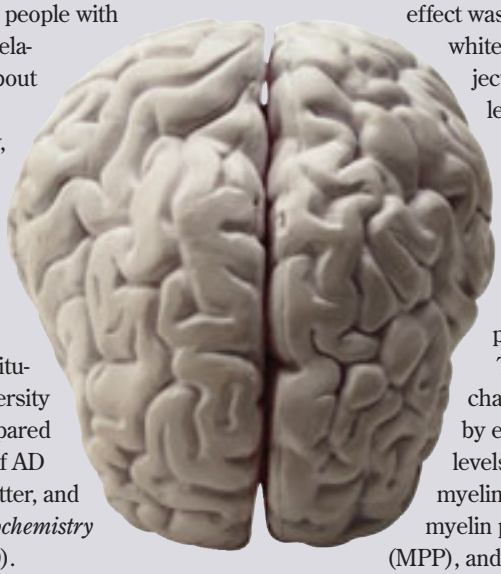
White matter matters

Traditionally, Alzheimer's disease (AD) has been considered a disease of the gray matter—the part of the brain that primarily modulates cognition, the senses, and motor function. Recent evidence, however, has shown that the white matter is altered in people with AD as well, but there is relatively little information about possible changes at the molecular level. Similarly, little is known about the possible effects of AD on myelin development, so critical to neuron function. To address this shortfall, Alex Rorer and colleagues at several institutions, including the University of Texas and Pfizer, compared the biochemical effects of AD on white matter, gray matter, and myelin development (*Biochemistry* **2002,** *41,* 11,080–11,090).



Using a colorimetric assay, the researchers found that AD white matter had 11% less total protein than control white matter, as was the case with AD gray matter versus control gray matter. They then quantified the amyloid-plaque-related Aβ peptide in the samples by using an immunoassay and found that although the total protein levels had decreased, the Aβ levels were more than 4 times higher in AD white matter than in the control.

The researchers also examined the lipid component of AD and control brain samples. Although there was no significant change in cholesterol levels in gray matter tissues compared to control samples, there was a 12% decrease in AD white matter cholesterol compared to the control. The magnitude of this effect was gender-specific; the AD white matter from female subjects showed 12% less cholesterol than samples from their male counterparts. Together with the protein data, these results suggest that the white matter tissues are compromised in people with AD.

The researchers then characterized myelin health by examining the relative levels of three proteins: myelin basic protein (MBP), myelin proteolipid protein (MPP), and 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP). Using Western blots, the researchers found that MBP, MPP, and CNP levels were 16%, 10%, and 17% lower, respectively, in AD tissues than in the controls. These results indicated that nerve health was also damaged in people with AD.

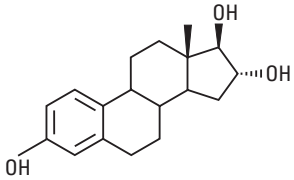
The authors argue that these molecular alterations contribute to AD pathology and that the earlier assumption that AD only affects gray matter is too simplistic.

—RANDALL C. WILLIS

Pregnancy hormone treats MS

Multiple sclerosis is a chronic disabling disease that affects about 1 in 10,000 people, usually between the ages of 20 and 30. It is a progressive neurological disorder with symptoms that include numbness in the limbs, paralysis, and blindness. The disease develops when the immune system becomes overactive and attacks brain cells by stripping the conductive coating. Once the coating is stripped away, neurons have trouble conducting the brain's electrical signals.

Rhonda Voskuhl and colleagues at the David Geffen School of Medicine at UCLA have found in a Phase I clinical trial that the hormone estriol in oral tablet form can decrease the size and number of brain lesions caused by MS and increase protective immune responses in patients with relapsing MS (*Annals Neurol.* **2002,** *52* (4), 421–428). Estriol is a form of the hormone estrogen that is found only in pregnant women. It is made in the placenta and is widely used throughout Europe and Asia to treat symptoms of menopause.



Estriol.

"Finding an easily administered oral treatment is important because patients are less likely to delay treatment if it involves a pill rather than weekly or daily shots," said Voskuhl.

The clinical trial, which was funded by the National Multiple Sclerosis Society, the National Institutes of Health, and the Sherak Family Foundation Fund for Multiple Sclerosis, involved 12 women, 6 with relapsing remitting MS and 6 with secondary progressive MS. The researchers found that of the 10 women who actually completed the trial (2 secondary progressive sufferers dropped out), there was a significant decrease in the number and size of inflammatory brain lesions, an increase in protective immune response, and an improvement in cognitive test scores. When the trial ended and the women were no longer taking the estriol treatment, the lesions increased to pretreatment levels.

"Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting multiple sclerosis," said Voskuhl. "If larger studies confirm the benefits of estriol treatment, further studies for longer periods of time will be needed to determine whether estriol can decrease relapse rates and disabling symptoms."

—FELICIA M. WILLIS

PHOTO: PHOTODISC

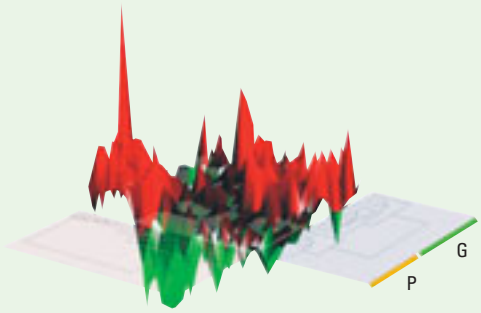
Cancer prognostication

Ovarian cancer is the fifth most common cause of cancer-related death in North America, and because there are few specific early-stage symptoms, the disease is not typically diagnosed until late in its progression.

Pascale Macgregor and colleagues at the University Health Network Microarray Center (Toronto, *www.microarray.ca*) have recently demonstrated the potential for DNA microarrays for early diagnosis and prognosis of ovarian cancer at the Cambridge Healthtech Institute Microarray Data Analysis conference in September in Washington, DC.

The researchers screened 19 serous epithelial ovarian cancer (SEOC) samples from 17 patients and 7 noncancerous ovarian samples on cDNA microarrays carrying 19,200 known genes and expressed sequence tags. Based on the gene expression patterns, the tissue samples were clustered into distinct groups, and the researchers observed a clear down-regulation of 172 genes and upregulation of another 89 genes in the SEOC samples. Among the genes in the former group were activin A receptor type I, which might be involved in cell proliferation, and glutathione *S*-transferase pi, which is involved in detoxification.

The researchers then compared the gene expression profiles of tissues from patients with a good prognosis (i.e., a disease-free interval (DFI) >12 months) and a poor one (i.e., DFI <6 months). Although the overall differences between the two samples were quite small, the researchers were able to identify 46 genes that they believed were outcome classifiers. Among the genes more highly upregulated in poor-prognosis samples were osteopontin, a gene known to be involved in tumorigenesis, and a group of genes involved in cisplatin resistance. Of the SEOC down-regulated genes, higher levels of thrombospondin, a matrix protein that affects tumor growth, were found in the good-prognosis samples.



Good news, bad news. A landscape view of gene clustering that emphasizes two distinct expression patterns for patients with good (G) and poor (P) prognosis for ovarian cancer relapse. (Courtesy of Pascale F. Macgregor, University Health Network, Toronto, ON.)

The researchers are quick to point out that individually, the relative expression levels of these genes are insufficient to predict health or disease prognosis, but when taken together, they provide a valuable tool. They also recognize that this initial study was performed with a relatively small cohort, but they say it provides a worthy proof of concept for predicting the prognosis of ovarian cancer.

—RANDALL C. WILLIS

PHOTO: PHOTODISC

After-sun application?

An experimental skin repair compound might have dual modes of action in reversing the damaging effects of sunlight exposure and, potentially, in preventing the formation of skin cancer, according to recent results from clinical trials conducted by Novogen Limited, a biotechnology company based in Sydney.

In September, one of two concurrent human clinical trials for NV-07α, a synthetic derivative of an isoflavone metabolite, reported that it showed a protective response against ultraviolet (UV)-induced skin DNA damage. The trial tested subjects for levels of metallothioneins (MTs)—proteins synthesized in response to DNA-damaging agents that are believed to provide protection against oxidative-based DNA destruction.

Areas of skin on volunteers that received NV-07α lotion treatment at three increments following UV exposure had significantly higher MT levels than nonirradiated areas, while MT levels in skin treated with placebo lotion did not change.

The other NV-07α trial measured the effects of the compound on immunosuppression, which occurs following sun exposure and, upon chronic exposure, has been associated with the development of skin cancer.

NV-07α was administered to 18 volunteers with a positive tuberculin skin test, which indicates the occurrence of an immune response to TB antigens. Areas of the skin exposed to UV radiation exhibited a significant reduction in this response. However, areas treated with NV-07α immediately following UV exposure and 24 h later displayed considerably less intense immune reduction as compared to those treated with placebo.

A recent report (*www.iarc.fr/pageroot/UNITS/chemoprevention.html*) from a segment of the World Health Organization indicates that there is "inadequate evidence" that sunscreen has a preventive effect against the most severe forms of skin cancer.

"This heightens the need for additional therapeutic intervention to assist in the prevention and repair of UV-induced damage," says Catherine Walker, NV-07α program manager. "Our experimental work thus far strongly suggests that NV-07α will provide this adjunctive therapy."

One very important aspect of these early-stage human trials, according to Walker, is that NV-07α is effective when it is applied after UV exposure.

—DAVID FILMORE

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Viral evolution

Researchers hope that comparative structural and genomic studies of disparate viruses will provide information regarding the evolution of virus behavior as well as point to potential therapeutics. Recently, researchers Roger Burnett and colleagues reported their analysis of the structural characteristics and interactions involved with the bacteriophage PRD1 capsid (*Nat. Struct. Biol.* **2002**, *9*, 756–763). PRD1 is considered the type representative of the *Tectiviridae* phages, viruses that infect many classes of disease-causing, antibiotic-resistant Gram-negative bacteria. Burnett and co-workers used a combination of cryo-electron microscopy and X-ray crystallography as the basis for producing modeled visualizations of the wild-type virus and defined mutants with aberrant or missing capsid proteins to determine structure–function relationships.

Previously, PRD1 had been determined to have a molecular weight of ~70 MDa and a diameter of ~700 Å. The protein capsid surrounds an internal membrane vesicle that in turn coats the 14.9-kb linear dsDNA genome. Structurally, the protein shell is an icosahedral lattice formed of 240 trimers of the major coat protein (P3), with vertices consisting of a complex of the pentameric P31 protein, the trimeric P5 protein, and the bacteria-receptor binding protein (P2). Two other proteins are associated with the capsid, and 10 more are associated with the membrane vesicle.

The key results of the current research were that the N- and C-termini of the P3 coat protein were required for capsid assembly and acted as conformational switches linking the proteins to the membranes and each other.

Although studies of PRD1 have revealed many similarities in virus capsid structure with the human adenovirus—especially in the icosahedral structure—there are significant differences as detailed by this report. The findings are not surprising since a membrane vesicle is found in PRD1, but not in adenovirus.

However, according to the study's authors, there was one hitherto unnoticed similarity that modeling efforts on PRD1 uncovered, further linking it to adenovirus evolutionarily. Specifically, it is the use of "glue proteins at key capsid positions to aid in assembly and stability." They concluded that the capsid structure in PRD1 could be seen as an intermediate between simpler polyomaviruses and the more complex adenoviruses.

—MARK S. LESNEY

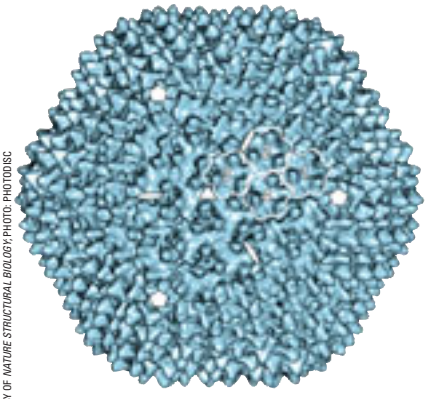


IMAGE COURTESY OF *NATURE STRUCTURAL BIOLOGY*/PHOTO: PHOTODISC

Surface rendering of the wt cryo-EM map, showing icosahedral symmetry axes and the four independent positions in the asymmetric unit.

Spit tobacco trial

An antidepressant used to help smokers quit may also be effective against the spit tobacco habit, according to a pilot study by Mayo Clinic researchers in Rochester, MN.

The few pharmacotherapy trials that have previously been carried out with spit, or smokeless, tobacco users have been for nicotine gums and patches, which have shown little or only very short term effects. The Mayo team conducted the first randomized placebo-controlled study for bupropion (the active ingredient in Zyban, marketed by GlaxoSmithKline for smokers trying to quit) with smokeless tobacco users. They observed abstinence after 12 weeks in 44% of those taking bupropion for that time period, compared to 29% in the placebo group (*Nicotine Tob. Res.* **2002,** *4* (3), 267–274).

Bupropion inhibits neuronal reuptake of norepinephrine and dopamine, which, it is presumed, attenuates the reinforcing behavior of nicotine self-administration. In addition, it may inhibit neuronal nicotinic receptors.

The Mayo team recruited 68 participants for the study; however, 31 discontinued participation during the 12-week medication phase—15 from the control and 16 from the bupropion group—(only 2 due to adverse events, i.e., rash and sleeplessness). In addition to the abstinence data, the study found that the average weight gain—a common problem after quitting tobacco—for those abstinent for 12 weeks was 1.5 lb for the bupropion group, while the placebo group gained an average of 9.7 lb. Furthermore, withdrawal symptoms were reported evenly among the groups for the first few weeks but markedly dropped in the bupropion group after the sixth week and continued to decline.

This data was very promising to the researchers, but 12 weeks after treatment was halted, and 24 weeks overall, the abstinence rate equaled out between the bupropion and control groups at 29%. Weight gain was still greater for the control group abstainers, but the small sample size made the difference not statistically significant.

This study shows early potential for an effective treatment for kicking the spit tobacco habit—one that about 12 million people in the United States have. But, the researchers conclude, to make any definitive assessments, it must be the first among larger clinical trials of longer duration.

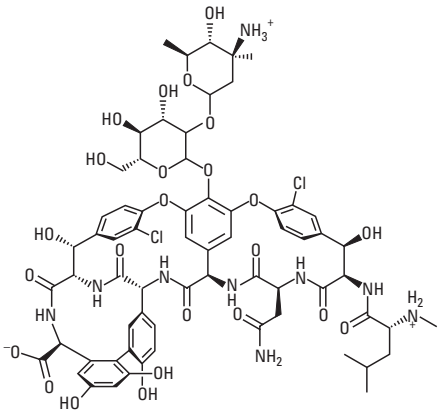
—DAVID FILMORE

Vancomycin dimer: What D, L?

The value of chiral separations has increased in the past decade as significant pharmacological differences have been observed in enantiomers.

An interesting property of certain glycopeptide antibiotics, because of their intricate collection of chiral centers, is their ability to act as enantiomer selectors—a method first introduced in capillary electrophoresis systems in 1994 (*Anal. Chem.* **1994,** *66* (9), 1473–1484). These antibiotics can also act as enhancers of chiral chromatographic separations when used as part of the stationary phase. In solution, however, many of these antibiotics self-aggregate, with some forming micelles or other structures that can interfere with their ability to serve as chiral selectors. But the vancomycin group of antibiotics has the ability to form back-to-back dimers with four hydrogen bonds linking two antiparallel polypeptide backbones, which appears to enhance their utility in chiral separations.

Using the D and L enantiomers of the amino acid derivative dansylvaline as test analytes, Eric Peyrin and colleagues from the Université Joseph Fourier (Grenoble, France) recently investigated the HPLC retention and separation of the racemic mixture using vancomycin as a chiral mobile-phase additive with a silica gel stationary phase (*Anal. Chem.* **2002,** *74* (20), 5205–5211). The researchers constructed a model of the chromatographic behavior of vancomycin that considered the formation of vancomycin dimers both in solution and adsorbed to the silica gel. In this way, they were able to obtain an accurate description of the retention behavior.



Vancomycin forms dimers that enhance chiral separations.

The model indicated that dimerization increased the chiral separation of the test compounds 3.7-fold. This agreed with the finding that enantioselectivity increased with a higher concentration of vancomycin, which is correlated with a rise in dimer formation. Furthermore, an analysis of a vancomycin-immobilized stationary phase showed enhanced enantioselectivity upon addition of the glycopeptide to the mobile phase, mediated by the formation of immobilized dimers.

According to the team, this is the first study of HPLC enantioselectivity dependence on vancomycin group dimers.

—MARK S. LESNEY

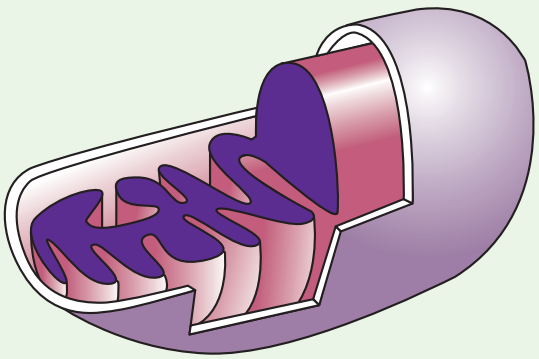
Protecting Parkinson's patients

Coenzyme Q10 (CoQ10), a popular health supplement, has yet to provide conclusive results in its original purpose as an exercise performance enhancer. However, a new study might prove this natural substance to be beneficial in a completely new context. Scientists presenting their work at the American Neurological Association's annual meeting in New York have linked high doses of CoQ10 to slowing the progression of Parkinson's disease.

Parkinson's afflicts up to a million Americans with symptoms such as slowness of movement, tremors when at rest, and muscle rigidity. These symptoms can be traced to the progressive death of nerve cells in an area of the brain called the substantia nigra. What kills the nerve cells is not known, but researchers have found evidence of a mitochondrial breakdown before cell death. Mitochondria produce a variety of molecules critical for proper cell function and depend on CoQ10 to assist in these processes. Previous studies have shown that Parkinson's patients have lower levels of CoQ10, leading to the hypothesis that supplemental CoQ10 could help protect the mitochondria.

To test this hypothesis, Clifford Shultz at the University of California at San Diego and colleagues randomly assigned 80 Parkinson's patients to regimens of CoQ10 at dosages of 300, 600, or 1200 mg/day, or to a placebo group. Patients were evaluated at the beginning of the 16-month double-blind study to appraise their degree of disease, then assessed one month later and every four months afterwards. Researchers tested the patients using the Unified Parkinson's Disease Rating Scale, which assesses mental function, mood, activities of daily living, and motor skills.

By the eighth month, patients taking the highest dose of CoQ10 were scoring significantly better on the scale than patients in other groups. At the completion of the study, those in the high-dose group scored 44% higher on the tests than those in the placebo group. Lower doses of CoQ10 also slowed functional decline relative to the placebo group but were much less effective than the 1200-mg/day dose.



Coenzyme Q10 might protect mitochondria in Parkinson's sufferers.

Shultz cautioned that it would be premature to recommend CoQ10 to all Parkinson's sufferers. However, his group plans to evaluate the results in a second clinical study with hundreds of patients, perhaps testing even higher doses.

—CHRISTEN L. BROWNLEE