to detect breast cancer using dynamic area telethermometry, in combination with sophisticated algorithms to analyze the data. The system also makes use of highly sensitive infrared camera technology originally developed by NASA's Jet Propulsion Laboratory for the military's Strategic Defense Initiative.

'We have developed some algorithms that were very effective in the dynamic domain,' Anbar said. Preliminary test results were very promising, he claimed, 'but because we only studied a relatively small number of patients, these results are insufficient to warrant clinical use of the methodology' [3].

More data needed

To convince others that its technology has merit, Anbar says, any company involved in developing thermal imaging equipment designed to detect breast cancer must run hundreds or thousands of tests on both normal and abnormal patients. 'They would have to look at patients for quite a while, and those patients would then have to go to excision surgery,' he explained, 'and then the findings of surgery would have to be compared to their findings.'

Both OmniCorder and ONR (in collaboration with hospitals located throughout the USA) are in the process of conducting such clinical trials. But it will take several years before they collect enough data to determine whether the testing methods they use have sufficiently high sensitivity and specificity to recommend the use of thermal imaging for the diagnosis of breast cancer.

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Inhalant induces tolerance against stroke

Stephani Sutherland, freelance writer

Scientists at the US National Institutes of Neurological Disorders and Stroke (NINDS; http://www.ninds.nih.gov) have used an idea that dates back to the early 20th century to devise a preventive strategy against stroke. If the treatment is as successful in humans as it was in rats, people could inhale a nasal spray to cut their risk of neurological catastrophe. The study showed that genetically stroke-prone rats that were given the vaccine were far less likely to have either an infarct or a hemorrhage, and the resulting damage was far less severe [1].

Stroke claims an estimated four and a half million lives each year worldwide, with millions more people affected by physical and cognitive disabilities. It is among the most difficult neurological conditions to treat, in part because the symptoms can be hard to recognize. Even the most advanced treatments for stroke are useless unless delivered within only a couple of hours of the brain attack. Despite a recent boon of insights from research into the molecular events underlying stroke, the results of clinical trials of new drugs have been disappointing [2]. Stroke prevention – rather than damage control – would improve the outlook dramatically [3].

A log jam in the brain

Unlike a conventional vaccine, the strategy in the rat trial induces tolerance [4]. Originally described in 1911, tolerance prepares the immune system to suppress a reaction, rather than to mount an attack, and the antigen is an endogenous – or 'self' – protein instead of an invader. NINDS senior investigator John Hallenbeck and his colleagues chose the adhesion protein E-selectin (ES), expressed by vessel endothelial cells, as their antigen. Regulatory T-cells normally flow through blood vessels, but during activation – mediated by inflammatory cytokines – ES is upregulated in the vessel wall, causing T-cells to slow down, to begin rolling along the wall, and eventually to become tethered to the protein platform. Other molecules aggregate at the site, causing a log-jam in the vessel that can lead to thrombosis.

Hallenbeck speculates that the cyclic pattern of activating and subsiding could be intensified in the stroke-prone rats, so that the system gets into a positive-feedback situation – to a point of no return – that leads to stroke. By making the immune system tolerant to ES, the team hoped to shut down the cycle at its foundation.

'One advantage of tolerance is 'bystander suppression,' explained Howard Weiner, a neurologist at Harvard Medical School and Brigham and Women's Hospital (http://www.brighamandwomens.org/) who was not part of the study team. When you initially present an antigen – in this case ES – the immune system is trained to recognize that protein specifically, but the suppression is not exclusive; it occurs wherever that protein is expressed. Now imagine that other proteins act at that same site. Those bystanders are suppressed along with the initial antigen. The molecular co-localization lends non-specificity to the mechanism of tolerance. This feature lends insight to the molecular events:

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Hallenbeck and Weiner agree that the suppression is mediated by anti-inflammatory cytokines released by regulatory T cells – primarily transforming growth factor (TGF)-β and interleukin (IL)-10 – rather than by an antibody to ES. (Antibody to ES was not detected in the rats given the tolerizing treatment.)

The scientists took advantage of evolution by delivering the antigen in a nasal spray. Cells lining the gut and respiratory tracts are continuously being presented with proteins of various types and origins. 'If every time a protein appeared that wasn't 'self' we broke out every weapon in the arsenal to mount an attack against it, we'd be tearing ourselves apart,' Hallenbeck pointed out. Oral tolerance, in which antigens are ingested, works the same way.

Dosage is critical

Proper dosage is a key to developing tolerance. A single, large dose of the antigen wipes out the antigen-reactive T cells, which is the population of cells that mediates immune suppression. By contrast, a single administration of a low dose of the antigen was not enough to tolerize the animals: rats given a single dose of ES had 12-fold more infarcts than those given continuing booster shots. 'This is not like pharmacology, where dose effects are linear, and at some point you reach toxicity,' said Hallenbeck.

Other diseases are poised to reap the benefits of tolerance as well. 'It's a very broadly applicable concept,' Weiner observed. Studies are under way in animal models of atherosclerosis, Alzheimer's disease and various autoimmune diseases [5]. But Hallenbeck says that stroke is among those with greatest potential for success, because the targeted inflammation is at the molecular level, rather than in a hot, swollen arthritic joint, for example.

Weiner is optimistic about plans for the stroke vaccine to go to Phase I clinical trials, but notes that success in humans is never certain after an animal study. There have been mixed results in clinical trials attempting a similar strategy against other ailments, notably multiple sclerosis and rheumatoid arthritis. Although tolerance has yet to be shown as a miracle cure (or prevention), the failures seem to lie in the details, says Weiner. The good news is that mucosal delivery of tolerance-inducing antigens in humans 'was safe and didn't have side effects, so it's attractive in that regard.'

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News in brief

Viral targets and mechanisms

Adenovirus: a molecular Houdini

New light has been shed on the mechanism by which a virion exits its host tissue into the wider environment, allowing it to spread further. Researchers at the University of Iowa (http://www.uiowa.edu/) have revealed the molecular details of how adenovirus makes its way through the protective layers of epithelial cells lining the airway [1].

Adenovirus, which causes flu-like symptoms, infects epithelial cells lining the respiratory tract. These cells are held together by adhesion molecules, including one known as CAR (cozsackie and adenovirsu receptor). The researchers found that a protein called Fiber on the surface of adenovirus can bind to CAR and disrupt its adhesive properties, thus opening a gap in the endothelial lining. Fiber alone, without the rest of the virus, is enough to cause a breakdown of cell adhesion. In addition, blocking Fiber prevents the virus from escaping into the airway.

To improve its chances of escape, the replicating virus makes excess Fiber and defective viral particles that possess Fiber but are not infectious. Thus, when an infected cell dies and spills its contents, nearby CAR molecules are overwhelmed by a variety of viral protein forms. The virus also uses Fiber as part of its mechanism to gain entry into host cells. Robert Walters, the lead author of the study, explained the potential applications of these findings: 'In most viral infections, people shed the virus before they are noticeably sick. So being able to understand how the shedding occurs might allow us to prevent spread of infection among people in close quarters, such as in schools or military barracks.' The authors speculate that this mechanism could be used widely by other viruses and even bacteria.

1 Walters, R. *et al.* (2002) Adenovirus Fiber disrupts CAR-mediated intercellular adhesion allowing virus escape. *Cell* 110, 789–799

Viruses driven to extinction

Treating a common virus with a mutation-inducing cancer drug causes the virus to mutate so much that it can no longer reproduce and is driven to extinction. This intriguing find could lead to new methods to treat and eliminate viral infections.

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