Bulletin Board

Study sheds further light on the immune response to chronic infections

New findings could help in the design of vaccines and therapeutics against chronic infection.

New research carried out at the Emory Vaccine Center (GA, USA), provides further information on the differing immune response to chronic, compared with acute infections. The research could help in the development of vaccines against acute infections such as HIV and HCV.

The group lead by Erin West (Emory Vaccine Center) used lymphocytic choriomeningitis virus infection as the model for their study. They compared the immune response to chronic and acute infection with the virus. Results showed that in cases of acute infection memory cells were more abundant than naive T cells, and that these memory cells acted quickly to reduce infection. By contrast, in chronic infections, memory cells were lost. The group have suggested three factors that led to this reduction in memory cells: a block in sustaining cell proliferation, an increased reliance on naive T-cell help and regulation by a receptor inhibitor. The receptor inhibitor described by the group is called 2B4, the inhibitor appears to act specifically on memory T cells, it appears on the cells and slows them down. The group suggest that this mechanism is design to prevent over-inflammation in chronic infections. "Perhaps the body says 'I can't take care of this, so I will shut down,' before too much inflammation and damage occurs," notes West. This has consequences for the development of vaccines and therapies against chronic infections. West explained to *Future Microbiology* that "blocking 2B4 or its ligand, CD48, may be a useful therapy for preventing the loss of memory CD8 T cells during chronic infection, and thus, may help in achieving

control of chronic infections. Therefore, understanding the mechanism in which 2B4 regulates memory cells during chronic infections would be useful and is an important avenue of future study."

Vaccines against chronic infection have been notoriously difficult to develop, the fact that memory T cells are lost quickly in chronic infections goes some way to explaining this failing. Since the beginning of the HIV/AIDS epidemic, the development of a vaccine against the virus has been a priority. A collaboration between the WHO and the United Nations named the WHO-UNAIDS HIV Vaccine Initiative, is working to develop such a vaccine. This latest research and particularly the potential for use of a 2B4 blocker could help this search. West concluded in a statement to *Future Microbiology* that "these findings may have implications for vaccine design and therapeutics for chronic infections, such as HIV and HCV, or in other instances where antigen persists."

Source: West EE, Youngblood B, Tan WG *et al.* Tight regulation of memory CD8⁺ T cells limits their effectiveness during sustained high viral load. *Immunity* 35(2), 285–298 (2011).

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Baker's yeast raises hope for a vaccine against aspergillosis

Study shows that baker's yeast is protective against *Aspergillus* in mice.

New research carried out at the California Institute for Medical Research (CA, USA) and Stanford University (CA, USA) suggests that inactivated bakers' yeast is protective against aspergillosis. If verified these results could lead to the production of new vaccines against the often fatal infection.

The group led by David Stevens (Santa Clara Valley Medical Center, CA, USA) vaccinated mice with inactivated *Saccharomyces* (common bakers' yeast) three times at 1 week intervals. The group found that these mice survived infection with the fungus *Aspergillus* even at very high doses. As Stevens notes, "Our results suggest that the protective component of

the yeast is in the cell wall. What's more, the simple preparation we used has been shown by us to also protect against infection due to three other fungi that cause human disease – *Candida*, *Cryptococcus* and *Coccidioides*."

Aspergillus is the fungus responsible for causing aspergillosis, which is a common infection among immunocompromised populations, such as those with AIDS or post-transplant patients. The infection is currently very difficult to treat and is often deadly. Current treatment with antifungals, such as amphotericin B and voriconazole have a high failure rate. Stevens commented, "Research to date, including our study, supports the development of a

yeast vaccine against all pathogenic fungi that infect humans. Such a 'panfungal' vaccine would further reduce mortality in immunocompromised individuals."

The group notes that *Saccharomyces* has already been investigated in human trials and preliminary data suggest that it is safe. The development of a prophylactic panfungal vaccine has the potential to significantly reduce mortality rates in some groups of immunocompromised individuals, particularly solid-organ and stem-cell transplant patients.

Source: Liu M, Capilla J, Johansen ME *et al.* *Saccharomyces* as a vaccine against systemic aspergillosis: 'the friend of man' a friend again? *J. Med. Microbiol.* 60(Pt 10), 1423–1432 (2011).

Studies suggest that commercial serological tests for TB are not accurate or cost effective

Results from two linked studies carried out at the University of Washington School of Public Health (WA, USA) and Johns Hopkins Bloomberg School of Public Health (MD, USA) and sanctioned by the WHO suggest that commercial serological tests for tuberculosis (TB) are inaccurate and not cost-effective. These studies helped inform a recent

WHO policy which recommended that "these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status."

The first study led by Karen Steingart (University of Washington) is a meta-analysis including 67 studies of pulmonary TB and 25 studies of

extra-pulmonary TB. The group found that in all of the studies specificity and sensitivity varied greatly. The group graded the level of evidence for the tests as very low and concluded that "despite expansion of the literature since 2006, commercial serological tests continue to produce inconsistent and imprecise estimates of sensitivity and specificity."

Priority Paper Alerts

Plante K, Wang E, Partidos CD *et al.* Novel chikungunya vaccine candidate with an IRES-based attenuation and host range alteration mechanism. *PLoS Pathog.* 7(7), e1002142 (2011).

Epidemics of Chikungunya virus that cause severe and sometimes chronic arthralgia are re-emerging. Chikungunya virus is a mosquito-borne pathogen and thus previous attempts for control have been based on preventing their contact with people, which have been largely ineffective in most places, leaving vaccines as the best option for prevention. Plante *et al.* developed an experimental recombinant live-attenuated vaccine created by genetically modifying the Chikungunya virus, which protected mice from infection following a single vaccine dose. A live virus vaccine would be relatively economical to produce in large quantities, an essential aspect when treating in countries with limited resources.

Rodríguez D, Daniels AU, Urrusti JL *et al.* Evaluation of a low-cost calorimetric approach for rapid detection of *tuberculosis* and other mycobacteria in culture. *J. Appl. Microbiol.* 111(4), 1016–1024 (2011).

There were 9.27 million new cases of tuberculosis in 2007, yet owing to the lack of an affordable and fast detection method, it has a severe health and economic impact on developing countries. This study by Rodríguez *et al.* demonstrated that less expensive isothermal microcalorimetry instruments, such as TAM Air®, which detect heat production rate, were adequate for mycobacteria detection and agreed with the triphenyl tetrazolium chloride assay.

The second study led by David Dowdy (Johns Hopkins Bloomberg School of Public Health) is a cost-effectiveness study comparing sputum smear microscopy and serological testing for the diagnosis of TB in India. The group found that serological tests resulted in more false-positives and increased costs per patient. The authors conclude: "In India, sputum smear

microscopy remains the most cost-effective diagnostic test available for active TB; efforts to increase access to quality-assured microscopy should take priority."

These studies and the WHO recommendations emphasize the need for increased access to quality microscopy and more widespread introduction of WHO-endorsed tests for TB.

Sources: Steingart KR, Flores LL, Dendukuri N *et al.* Commercial serological tests for the diagnosis of active pulmonary and extrapulmonary tuberculosis: an updated systematic review and meta-analysis. *PLoS Med.* 8(8), e1001062 (2011); Dowdy DW, Steingart KR, Pai M *et al.* Serological testing versus other strategies for diagnosis of active tuberculosis in India: a cost-effectiveness analysis. *PLoS Med.* 8(8), e1001074 (2011).

New study suggests that insecticide resistance is prevalent among mosquitoes in Africa

Results from a longitudinal study into the effects of widespread distribution of insecticide-treated bed nets and artemisinin-based combination therapies in several African countries suggests that increasing rates of resistance to insecticides among malaria-causing parasites might be responsible for reports of increased incidences of malaria in the region.

The study was carried out in Dielmo village, Senegal, and coordinated by the Institut de Recherche pour le Développement, Dakar, Senegal. The group led by Jean-François Trape (Institut de Recherche pour le Développement), monitored and treated malaria attacks in villagers between January 2007 and December 2010. In 2008 the group provided villagers with deltamethrin-treated

nets. The results showed a decrease in malaria attacks after the introduction of nets but the number of attacks increased again 27–30 months after their introduction. The group found that this rebound effect was due to increasing rates of resistance to deltamethrin in *Anopheles gambiae* mosquitoes. The authors note that "the effect of the introduction of [deltamethrin-treated nets] on the survival of *A. gambiae* and *Anopheles arabiensis* in 2008 and 2009 and the change in 2010 when the parity of these vectors returned to pre-intervention levels suggest that pyrethroid resistance could be a major factor in the increase in malaria morbidity in 2010."

These results emphasize the need for strategies to prevent the development of resistance in these mosquitoes, which are

the major transmitter of malaria in Africa. The authors conclude: "These findings are of great concern, since they support the idea that present methods and policies will not sustain – at least in older children and adults – a substantial decrease in malaria morbidity in many parts of Africa where *A. gambiae* is the major vector and acquired clinical immunity is a key epidemiological factor, strategies to address the problem of insecticide resistance and to mitigate its effects must be urgently defined and implemented."

Source: Trape JF, Tall A, Diagne N *et al.* Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. *Lancet Infect. Dis.* doi: 10.1016/S1473-3099(11)70194-3 (2011) (Epub ahead of print).

New research helps explain protective mechanism of live-attenuated influenza vaccine

A recently published study in the journal *Vaccine* has shed some light on the mechanism of action of live-attenuated influenza vaccine (LAIV), commonly named FluMist®, which has previously had a mechanism of action that is uncertain.

Infection with the influenza virus can cause very serious illness. Vaccination is the most efficient method for reducing the spread of influenza infections. Inactivated vaccines induce immunity but only to a single strain of influenza; LAIVs induce T-cell responses against HA and NA influenza surface proteins and have been shown

to offer protection against multiple serotypes of influenza A infection in a mouse/rodent model.

"...FLuMist induces a robust Type 1 memory response including the production of chemokines and cytokines involved in T-cell activation and recruitment."

Study subjects were recruited by the Naval Health Research Center, CA, USA, and they received a dose of commercially

available FluMist. At prespecified times following the administration of the vaccine the subjects' immune response to the vaccine was examined.

In the published study, researchers, led by Laura Haynes from Trudeau Institute, NY, USA, found that immunization with FluMist led to a significant reduction in inflammatory response and in the level of viral titers in mouse lungs following multiple-serotype influenza A infection. In addition, the study's authors described how, in a healthy adult population, FLuMist induces "a robust

Type 1 memory response including the production of chemokines and cytokines involved in T-cell activation and recruitment.” In their article the authors highlight that the results of the study “indicate that LAIV vaccination functions by inducing immune memory which can act to modulate the immune response to subsequent heterosubtypic challenge by influencing both innate and adaptive

responses.” Highlighting the importance of the research into FluMist’s mechanism of action Haynes said, “Influenza infection normally induces a massive inflammatory response in the lungs that leads to significant illness and increases the susceptibility to secondary bacterial infections. The most efficient way to prevent influenza infection is through vaccination. To date, the mechanism of how FluMist induces

protection has been unclear. Our study demonstrates that this vaccine works by inducing a very early nonspecific immune response in the lungs in a mouse model of influenza infection.”

Sources: Lanthier PA, Huston GE, Moquin A *et al.* Live attenuated influenza vaccine (LAIV) impacts innate and adaptive immune responses. *Vaccine* doi: 10.1016/j.vaccine.2011.07.093 (2011) (Epub ahead of print); <http://trudeauinstitute.org>.

About the Bulletin Board

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