Racing against time for a pandemic influenza vaccine

In preparation for a future H1N1 influenza outbreak, which is estimated to affect one in five people in October, the National Institute of Allergy and Infectious Diseases (part of the US NIH) is sponsoring eight vaccine and treatment evaluation units (VTEUs) across the USA to launch several clinical trials during this summer, testing and validating new potential vaccines.

"Efforts to find an effective vaccine against H1N1 influenza are historic," said Sharon Frey, professor of infectious diseases at Saint Louis University (SLU) School of Medicine (MO, USA), one of the eights VTEUs. "Scientists very quickly identified the flu virus, industry rapidly responded by making vaccine and multiple clinical trials to test vaccine are ramping up. Researchers are pouring a tremendous amount of effort and resources into delivering a safe and effective vaccine to the American public as quickly as possible."

In addition to the VTEU at SLU, the other seven VTEUs are located at Baylor College of Medicine (TX), Emory University (GA), University of Maryland School of Medicine (MD), Children's Hospital Medical Center (OH), Group Health Cooperative (WA), University of Iowa (IA) and Vanderbilt University (TN).

"It's looking more and more like we're going to have a big flu outbreak this fall as soon as the kids get back to school. Influenza is unpredictable, but I believe this pandemic will hit pre-teens, teens and their parents hard, and as many as 60 million Americans could be sick with the flu. It's critical that we find a way to protect people from this disease," said Robert Belshe, director of SLU's Center for Vaccine Development. "The modelers predict the peak will be in October, which means we'll see more H1N1 influenza in September. We'll be in the midst of it before we know it."

The SLU VTEU team led by Frey will evaluate whether an investigational H1N1 influenza vaccine can be given at the same time with the seasonal influenza vaccine (ClinicalTrials.gov ID: NCT00943878). It is likely that both strains of influenza virus will circulate this fall and winter so it is important to be aware of any potential side effects with the coadmission of both vaccines, for example, one vaccine may undermine the effectiveness of the other.

Thousand of healthy volunteers, including adults, children and the elderly, will participate in these clinical trials of the investigational H1N1 vaccine. In other H1N1 influenza trials, VTEU researchers will assess different dosages and dosing regimens of the vaccine to find the best approach with highest protection (ClinicalTrials.gov ID: NCT00943488 and NCT00943631). The seasonal influenza vaccine is also being tested in pregnant women in preparation for future comparison of this well-studied vaccine against the new H1N1 vaccine in this group (ClinicalTrials.gov ID: NCT00905125).

> *"Researchers are pouring a tremendous amount of effort and resources into delivering a safe and effective vaccine to the American public as quickly as possible."*

"Since vaccines work well to protect against the seasonal flu, we believe that an effective vaccine against 2009 H1N1 flu will help to control this pandemic," said Belshe. "But because we are predicting the H1N1 flu will hit sooner than the seasonal flu, which typically strikes between October and March and peaks in February, time is of the essence as we conduct our vaccine research."

Pregnant women and individuals with underlying illnesses of the kidneys, liver, heart and lungs (including asthma) are warned of a higher level of health danger from H1N1 influenza compared with other healthy individuals.

"So far, most of the infections are relatively mild. We're hoping it's going to stay that way, but we don't really know," said Belshe. "With the large number of people who are predicted to become infected, the number of serious health complications, and even deaths, could soar."

Source: Saint Louis University, MO, USA: www.slu.edu

part of future medicine fsg

Anti-IFN-α lupus vaccine demonstrates positive results in mice

Daniel Zagury and colleagues have demonstrated the efficacy of an anti-IFN-α kinoid vaccine, produced by Neovacs (Paris, France), in preventing or delaying lupus development in mice.

Lupus, or systemic lupus erythematosus, is a chronic autoimmune disease that affects millions of people, particularly women and those of Afro–Caribbean descent. The cause remains elusive and the disease mainly affects the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. Treatments are symptomatic and there is no cure as yet.

In this study, Zagury and colleagues used a mouse model of lupus to test the efficacy of the anti-IFN-α kinoid vaccine. IFN-α is a cytokine that has previously been described to play a major role in lupus pathogenesis. The vaccine contains an immunogen derived from IFN-α (IFN-α kinoid) complexed with keyhole limpet hemocyanin, and is designed to trigger a strong IgG antibody response to IFN-α.

Vaccinated animals fell into two groups, good responders and low responders. All but one of the good responders survived, while all low responders died of kidney failure. Anti-IFN-α antibody levels in the survivors were higher, while no cellular (T cell) response was detected, suggesting that antibody response is critical and correlates with the survival rate. No histopathological lesions were detected in half of the surviving mice.

"These experiments are very encouraging. They show that IFN-α kinoid-based immunization may represent an innovative strategy for treating lupus. Indeed, other experimental data due to be published soon suggest that excessive IFN-α, overproduced during human lupus, can be neutralized by the antibodies generated after immunization with an IFN-α kinoid. We hope that clinical trials in man will be initiated rapidly," commented coauthor Zahir Amoura of France's National Reference Centre for Lupus and Antiphospholipid Syndrome at Pitié-Salpêtrière Hospital in Paris.

Sources: Zagury D, Le Buanec H, Mathian A et al.*: IFN-α kinoid vaccine-induced neutralizing antibodies prevent clinical manifestations in a lupus flare murine model.* Proc. Natl Acad. Sci. USA *DOI: 10.1073/pnas.0900615106 (2009) (Epub ahead of print); Neovacs, France: www.neovacs.fr*

Cholinesterase inhibitors may be associated with increased rates of syncope

New research conducted by Sudeep Gill, an Ontario Ministry of Health and Long-term Care Career Scientist at Providence Care St Mary's of the Lake Hospital in Kingston, Ontario, Canada, and a team of scientists have discovered that cholinesterase inhibitors appear to be associated with an increased risk of syncope. It has been known that slower heart rates and fainting episodes are associated with these drugs; however, the extent of these risks had not been entirely clear until now.

Gill and colleagues conducted a large study using province-wide data collected from 1st April, 2002, to 31st March, 2004, to investigate the relationship between cholinesterase inhibitor use and syncope-related outcomes. The team identified 19,803 older adults with dementia who were administered cholinesterase inhibitors and 61,499 controls who were not. Upon analysis, it was found that hospital visits for syncope were more frequent in patients who were administered cholinesterase inhibitors compared with controls (31.5 vs 18.6 events per 1000 person-years). Furthermore, bradycardia was 69% more common among patients receiving cholinesterase inhibitors. In addition, those who were administered dementia drugs had a 49% increased chance of having permanent pacemakers inserted and an 18% increased risk of hip fractures.

> *"Older adults with dementia are vulnerable to adverse drug effects, and future RCTs [randomized controlled trials] evaluating treatments targeted to this population should therefore provide comprehensive documentation of common and serious outcomes such as falls (syncopal or otherwise) and injuries."*

The authors note that the occurrence of bradycardia may cause a person to faint, which in turn could lead to a fall-related injury such as a broken hip.

It is important that any bradycardia associated with the administration of cholinesterase inhibitors is correctly identified to avoid implantation of pacemakers. The insertion of pacemakers is an invasive procedure and can involve serious complications for senior patients. Gill emphasizes that fall-related injuries and insertion of pacemakers are "downstream consequences" of a failure to recognize this drug-related phenomenon.

"This study does not suggest that dementia patients shouldn't take these drugs," explains Gill. "What's critical is that patients, caregivers and physicians be aware of the potential side effects, and weigh these risks carefully against the potential for beneficial effects."

"Older adults with dementia are vulnerable to adverse drug effects, and future RCTs [randomized controlled trials] evaluating treatments targeted to this population should therefore provide comprehensive documentation of common and serious outcomes such as falls (syncopal or otherwise) and injuries," the study authors conclude.

Source: Gill SS, Anderson GM, Fischer HD et al.*: Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study.* Arch. Intern. Med. *169(9), 867–873 (2009).*

Association between intravenous immunoglobulin and lower risk of Alzheimer's disease

Intravenous immunoglobulin (IVIg), used in immunotherapy, involves adding antibodies into the bloodstream, and has been employed to treat various diseases for more than 20 years. Amyloid-β peptide plaque deposition is a consistent feature of Alzheimer's disease and, according to Howard Fillit (Mount Sinai School of Medicine, NY, USA), IVIg "is thought to have an indirect effect on Alzheimer's disease by targeting β-amyloid or plaques in the brain."

In this study, published in *Neurology*, Fillit and colleagues carried out a case-controlled analysis to examine the occurrence of Alzheimer's disease and related disorders (ADRD) in patients treated with IVIg for other diseases compared with untreated patients.

> "*IVIg is thought to have an indirect effect on Alzheimer's disease by targeting β-amyloid or plaques in the brain.*"

The researchers studied records of patients aged 65 years or older, taken from a national database containing 20 million age-qualified patients. A total of 847 patients who had been administered at least one treatment of IVIg over a 4-year period were analyzed, along with 84,700 control patients who were not given IVIg treatment. Other requirements included the fact that all patients should have had at least one medical claim prior to first IVIg treatment to highlight IVIg risk factors and to confirm that the patients did not have ADRD diagnosis before first treatment. As highlighted in the article, all controls were matched '100:1 to cases on age, gender and risk-factors for ADRD.'

> "*The current Alzheimer's drugs on the market treat the symptoms of the disease. Immunization could treat the underlying cause.*"

Kaplan–Meier survival curves and a Cox proportional hazards model were used to estimate relative incidence of ADRD after first IVIg treatment for IVIg-treated patients versus control patients. Results of the Kaplan–Meier analysis demonstrated that treated patients had a lower incidence of ADRD at 2.6% (of the 847 IVIg-treated patients) compared with 4.6% of the 84,700 control patients. The Cox proportional hazard model results indicated the treated patients had a 42% lower risk of ADRD diagnosis, with approximately 4.8% of controls diagnosed with ADRD versus 2.8% of treated patients (at 60 months after first IVIg treatment).

This investigation demonstrates that prior IVIg treatments could possibly protect against Alzheimer's disease. Fillit sates that, "The current Alzheimer's drugs on the market treat the symptoms of the disease. Immunization could treat the underlying cause". According to researchers, a clinical trial is underway to establish whether IVIg could become an effective treatment for Alzheimer's.

Source: Fillit H, Hess G, Hill J, Bonnet P, Toso C: IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders. Neurology *73(3), 180–185 (2009)*

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine. If you have newsworthy information, please contact:

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Recent drug approvals: June to August 2009.

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Cardiology					
Effient™	Prasugrel	For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention	USA	Eli Lilly and Daiichi Sankyo	July 2009
Multaq®	Dronedarone	To reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age > 70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm or left ventricular ejection fraction < 40%), who are in sinus rhythm or who will be cardioverted	USA	Sanofi-Aventis	July 2009
Sorine®	Sotalol HCl	A substitution for oral sotalol in patients who are unable to take sotalol orally Oral sotalol is indicated for maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter and treatment of documented life-threatening ventricular arrhythmias	USA	Academic Pharmaceuticals	July 2009
Tekturna HCT®	Aliskiren and hydrochlorothiazide	A first-line treatment for patients who are unlikely to achieve their blood pressure goals with a single drug	USA	Novartis	July 2009
Tracleer®	Bosentan	Mildly symptomatic WHO Functional Class II pulmonary arterial hypertension	USA	Actelion	August 2009
Tyvaso™	Treprostinil	Pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance	USA	United Therapeutics	July 2009
Ventavis®	Iloprost 20 µg/ml	New York Heart Association Class III and IV pulmonary arterial hypertension	USA	Actelion	August 2009
Tracleer®	Bosentan	Pulmonary arterial hypertension in children	EU	Actelion	July 2009
Rasilez®	Aliskiren	For the treatment of high blood pressure alone or in combination with other high blood pressure medicines	Japan	Novartis Pharma AG	July 2009
Dermatology					
Sculptra® Aesthetic	Injectable poly-L-lactic acid	For the correction of shallow to deep nasolabial fold (smile lines) contour deficiencies and other facial wrinkles	USA	Sanofi-aventis	July 2009
Endocrinology & metabolism					
Onglyza™	Saxagliptin	An adjunct to diet and exercise to improve blood sugar (glycemic) control in adults for the treatment of Type 2 diabetes mellitus	USA	Bristol-Myers-Squibb Company & AstraZeneca	August 2009
Victoza®	Liraglutide	Type 2 diabetes in adults	EU	Novo Nordisk	July 2009
Moapar®	Triptorelin 11.25 mg	Reversible reduction of serum testosterone to the level of castration in adult men suffering from sexual deviations	Switzerland	Debiopharm Group	July 2009

Recent drug approvals: June to August 2009 (cont.).

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Gastroenterology & hepatology					
Prograf®	Tacrolimus	Moderate-to-severe refractory ulcerative colitis	Japan	Astellas	July 2009
Infectious disease					
Isentress®	Raltegravir	For treatment-naive patients, as well as for treatment-experienced adult patients	USA	Merck & Co.	August 2009
Neurology					
Cambia™	Diclofenac potassium 50 mg	For the acute treatment of migraine attacks with or without aura in adults 18 years of age or older	USA	Kowa Pharmaceuticals	June 2009
Codeine sulfate tablets	Codeine sulfate	For the relief of mild-to-moderately severe pain when the use of an opioid analgesic is appropriate	USA	Roxane laboratories	July 2009
Invega® Sustenna™	Paliperidone palmitate	For the acute and maintenance treatment of schizophrenia in adults	USA	Janssen	July 2009
Sumavel™ DosePro™	Sumatriptan injection	Acute migraine, with or without aura, and cluster headache	USA	Zogenix	July 2009
Sumavel™ DosePro™	Sumatriptan injection	The acute treatment of migraine and cluster headache	USA	Zogenix	July 2009
Zipsor™ Liquid Filled Capsules	Diclofenac potassium 25 mg	Relief of mild-to-moderate pain	USA	Xanodyne Pharmaceuticals	June 2009
Remeron®	Mirtazapine 15 mg	Major depressive disorder	Japan	Schering-Plough Corporation	July 2009
Oncology					
Avastin®	Bevacizumab	First-line treatment of patients with advanced breast cancer in combination with docetaxel	USA	Roche	July 2009
Avastin® plus interferon-alfa	Bevacizumab	Metastatic renal cell carcinoma	USA	Genentech	August 2009
Onsolis™	Fentanyl buccal soluble film	For the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain	USA	Biodelivery Sciences International	July 2009
Afinitor®	Everolimus	Advanced renal cell carcinoma	EU	Novartis	August 2009

Recent drug approvals: June to August 2009 (cont.).

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Oncology (cont.)					
Alimta®	Pemetrexed	Maintenance treatment of patients with locally advanced or metastatic nonsquamous, non-small-cell lung cancer whose disease has not progressed following platinum-based chemotherapy	EU	Eli Lilly	July 2009
Instanyl®	Intranasal fentanyl spray	Breakthrough pain in cancer patients who receive chronic opioid treatment for the management of their background pain	EU	Nycomed	July 2009
Iressa®	Gefitinib	For adults with locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK, in all lines of therapy	EU	AstraZeneca	July 2009
Mozobil™	Plerixafor injection	To be used in combination with granulocyte-colony-stimulating factor for patients with lymphoma and multiple myeloma who require an autologous stem cell transplant	EU	Genzyme	August 2009
Rheumatology					
Colcrys™	Colchicine	Gout flares	USA	Mutual Pharmaceutical Company	August 2009
Forteo®	Teriparatide	Glucocorticoid-induced osteoporosis in men and women at an increased risk of fracture	USA	Eli Lilly	July 2009
Aclasta®	Zoledronic acid 5 mg	Osteoporosis in men and post-menopausal women caused by the long-term use of glucocorticoids	EU	Novartis	July 2009
Opthalmology					
Acuvail™	Ketorolac tromethamine ophthalmic solution 0.45%	Pain and inflammation following cataract surgery	USA	Allergan	August 2009
Ozurdex™	Dexamethasone intravitreal implant	Treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion	USA	Allergan	June 2009
Other					
Caldolor™	Ibuprofen injection 400 mg/4 ml and 800 mg/8 ml	Reduction of fever, and the management of mild-to-moderate pain and moderate-to-severe pain as an adjunct to opioid analgesics	USA	Cumberland Pharmaceuticals	June 2009
Colcrys™	Colchicine	Familial Mediterranean fever	USA	Mutual Pharmaceutical Company	August 2009

Recent drug approvals: June to August 2009 (cont.).

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Other (cont.)					
Feraheme™	Ferumoxytol	For the treatment of iron deficiency anemia in adult patients with chronic kidney disease	USA	AMAG Pharmaceuticals	June 2009
Ilaris®	Canakinumab	For the treatment of cryopyrin-associated periodic syndromes	USA	Novartis	June 2009
Lipsovir®	Hydrocortisone and acyclovir	For early treatment of recurrent cold sores to decreases the risk of cold sores, and to shorten the healing time for those cold sores that are not prevented. For adults and children 12 years or older.	USA	Medivir	August 2009
Livalo®	Pitavastatin	Hypercholesterolemia and combined dyslipidemia	USA	Kowa Research Institute & Kowa Pharmaceuticals America	August 2009
Samsca™	Tolvaptan	For the treatment of hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion in adults	EU	Otsuka Pharmaceutical	August 2009
Asmanex® Twisthaler®	Mometasone furoate dry powder inhaler	Bronchial asthma in adults	Japan	Schering-Plough Corporation	July 2009