Breathe easy? Exhaled molecules may reveal those who have been infected with influenza

Research suggests that examining the compounds in exhaled breath may help to avoid unnecessary flu vaccinations.

A new study published in the *Journal of Breath Research* has indicated that a simple, noninvasive breath test might be used to distinguish individuals who have recently been infected with influenza. This approach could provide a novel avenue towards combating vaccine shortages during a future pandemic.

Following the recent discovery that more than half of the people vaccinated in Glasgow during the 2009 H1N1 'swine flu' pandemic may already have been infected with the circulating virus, it is apparent that a significant proportion of individuals may have been vaccinated unnecessarily.

These findings emphasize the potential value of obtaining a fast, noninvasive test to determine individuals who have been infected with influenza. Indeed, not only would such a tool help to prioritize people who would benefit most from immunization, but it could significantly reduce the risk of vaccine shortages during a future pandemic.

In response to this demand, researchers from the Cleveland Clinic (OH, USA) and Syft Technologies (Christchurch, New Zealand) set out to examine whether an immune response to influenza infection could be detected in exhaled breath – an approach that is currently adopted to monitor asthma, measure alcohol intoxification and test for the rejection of transplant organs.

The senior author of the study, Raed Dweik (Cleveland Clinic, OH, USA), commented to *Therapy* on the rationale behind this approach: "Since it is difficult to study the natural infection if you want to obtain a measurement before and after the infection (by the time individuals present, they have already had the infection), we decided to study the breath changes before and after live-attenuated vaccination, which is the next best thing where we at least know when the infection started."

The study included 11 healthy participants, of which nine were given the H1N1 2009 monovalent live intranasal vaccine (a virus that mimics the natural infection of the pandemic flu strain). A breath test was then used to measure the levels of a panel of exhaled biomolecules on each of the seven days following vaccination.

Notably, this approach revealed a significant increase in the level of exhaled nitric oxide on the third day after exposure to the H1N1 virus. This molecule has previously been linked with influenza infection, and is suggested to play a role in the immune-mediated clearance of the virus.

> "*While this study is preliminary, it has provided a proof-of-concept that a noninvasive breath test can detect changes in the breath after a live vaccine...*"

Although no significant differences in exhaled nitric oxide were observed on any other day of the study period, the peak on day three coincides with the height of symptom severity following H1N1 infection, therefore corroborating a potential link between this exhaled marker and the immune response to the virus.

Among the remaining molecules examined, a significant change was only observed in one other compound – isoprene. This factor is a major component of exhaled breath, and is thought to be an indicator of oxidative stress in the airways. Once again, a significant increase in isoprene levels was only evident on the third day following H1N1 vaccination.

Despite encompassing a relatively small study group, these findings provide a strong validation of the potential utility of exhaled markers in distinguishing individuals who have been infected with influenza.

"While this study is preliminary, it has provided a proof-of-concept that a noninvasive breath test can detect changes in the breath

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after a live vaccine," said Dweik. "If confirmed and fully developed, the hope is that a breath test will be able to tell in real-time whether somebody is infected with the flu or not (and even what type of flu). This has potential implications for detecting other infections as well."

Sources: Press release from the Institute of Physics: www.iop.org/news/11/july/page_51483.html; Mashir A, Paschke KM, van Duin D et al. *Effect of the influenza A (H1N1) live attenuated intranasal vaccine on nitric oxide (FENO) and other volatiles in exhaled breath.* J. Breath Res. *5(3), 037107 (2011).*

Initiation of in-patient clinical trials with a novel oral therapy for multiple sclerosis

Advancell and Neurotec Pharma have recently announced the initiation of Phase IIa in-patient clinical trials with NT-KO-003, the first neuroprotective drug for multiple sclerosis without immunosuppressive effects.

A total of 105 patients from 11 hospitals in Spain and three hospitals in Germany are to be included in the trial, named NeuroAdvan. Research will be led by Pablo Villoslada (Director of Neuroimmunology at IDIBAPS, Hospital Clinic de Barcelona, Spain) in collaboration with Alex Rovira (MRI Analysis and Research Center in Neuroimaging and Multiple Sclerosis, Hospital Vall d'Hebron, Spain).

Recent figures from the WHO suggest multiple sclerosis affects approximately 2.5 million individuals worldwide. Current treatment plans for the disease rely heavily on immunomodulators, which have significant side effects, require parenteral administration and are limited in their effectiveness.

NT-KO-003, which has been codeveloped by both companies, has an entirely new mechanism of action than previously seen in multiple sclerosis treatments. It is also the first orally administered treatment to potentially slow disease progression and limit neurological damage. Data collected from animal models during preclinical trials demonstrated the drug has an anti-inflammatory and neuroprotective effect thus the treatment is potentially able to be used in combination therapies without increasing toxicity and can be administered to a wide spectrum of patients.

Villoslada (IDIBAPS, Hospital Clinic de Barcelona) commented on the treatment's potential, "NT-KO-003 holds great promise because of its safety and ease-of-use … also because it's mechanism of action is new and complementary to existing treatments." NT-KO-003 is not limited to use in multiple sclerosis. Owing to its neuroprotective mechanism of action, Advancell and Neurotec are exploring the possibility of utilizing the treatment in other neuromuscular diseases, such as amyotrophic lateral sclerosis.

With the initiation of this clinical trial, Neurotec Pharma will be hoping for clinical proof-of-concept for NT-KO-003, which is their first molecule to reach the Phase II trial stage. It is hoped that the treatment could be a large step to changing the direction of multiple sclerosis treatment. Results from the NeuroAdvan study are predicted for late 2012.

Source: www.neurotec-pharma.com

Transcatheter heart valve receives positive opinion from the US FDA

Edwards Lifesciences Corp. has announced that the US FDA advisory panel have recently voted to recommend approval for their recent transcatheter device, the Sapien® valve.

The Circulatory System Devices Panel of the Medical Devices Advisory Committee met in July, to vote on the safety, efficacy and risk:benefit ratio of the transcatheter device, based on the data provided. All three votes resulted in majorities in favor of recommending approval, although there were concerns expressed in the safety category.

Support for Edwards' marketing application comes from the Placement of aortic transcatheter valves (PARTNER) trial, recently published in the *New England Journal of Medicine*. Results from the trials were promising, with the authors of one publication concluding, "In patients with severe aortic stenosis who were not suitable candidates for surgery, transcatheter aortic valve implantation (TAVI), as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause, or repeat hospitalization and cardiac symptoms."

Cardiologist, Ajay Kirtane (Columbia University, NY, USA), believes that "the completion of the … PARTNER trial … represents a landmark achievement in the treatment of patients with calcific aortic stenosis. The favorable results from both randomized cohorts (in surgically inoperable patients and patients at the highest risk for aortic valve surgery) demonstrate that catheter-based valve replacement is a compelling option for some of the sickest patients with aortic stenosis".

However, the trials also raised concerns regarding adverse events with the valve, in particular the risk of stroke and neurological effects were seen to be higher in the transcatheter group compared with surgical valve repair group.

Given this positive opinion, the FDA is expected to approve the Sapien valve in due course. Post-marketing studies are likely to be undertaken to monitor longer-term outcomes with the device.

Sources: Edwards Lifesciences press release: www.edwards.com/newsroom/Pages/NR20110720.aspx; *Smith CR, Leon MB, Mack MJ* et al. *Transcatheter versus surgical aortic-valve replacement in high-risk patients.* N. Eng. J. Med. *364(23), 2187–2198 (2011); Leon MB, Smith CR, Mack MJ* et al. *Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery.* N. Eng. J. Med. *363(17), 1597–1607 (2010).*

Promising preliminary short-term pharmacokinetic and glucodynamic effectiveness demonstrated by a novel inhaled insulin formulation

An inhaled insulin formulation, developed by Generex Biotechnology Corporation, has demonstrated promising short-term pharmacokinetic and glucodynamic effectiveness, and 1-year safety according to preliminary results released recently by the company.

Oral-lyn™ (Generex Biotechnology Corporation) has been developed as a simple, fast, effective and pain-free alternative to subcutaneous injections. The manufacturers have previously discussed early clinical data with the US FDA, and received written feedback regarding their concerns. The company's investors hope this will mean the pivotal trial design will satisfy some of the regulators queries, increasing chances of approval.

Preliminary data recently released was from the Prevoral trials, which enrolled 31 patients exhibiting prediabetic impaired glucose tolerance. The mean BMI of participants was 33. In the trial, the inhaled formulation was administered 30 min before a standard glucose tolerance test. After drinking 75 g of glucose, glucose and insulin levels were measured at baseline, and 30, 60, 90, 120 and 180 min after drinking. Glucodynamic results showed that a mean reduction in glucose levels of 15.8% was achieved. Plasma insulin was also significantly increased at 30 min but not at 2 or 3 h, compared with injectable insulin. Longer-term results showed statistically significant improvement in hemoglobin A1c levels as compared with diet and exercise alone at 6 months.

The second trial presented was the 084 clinical trial conducted in 463 Type 1 diabetic patients. Head-to-head comparisons of hemoglobin A1c concentrations over 12 months were carried out between oral and injectable insulin. Patients treated with inhaled insulin did not lose metabolic control over the 12-month trial period or over the 6-month extension period and demonstrated similar safety to injectable insulin.

Physicians will look forward to publication of these and further Phase III results. Publication of the full program is expected in 2013 following which Generex is expected to file the formulation for approval with the FDA.

Source: Generex press release: http://investor.generex.com/releasedetail.cfm?ReleaseID=590202

ISENTRESS (raltegravir) demonstrates efficacy in combination therapy during 5-year extended Phase II study in previously untreated patients with HIV-1

Merck has recently presented results from their 240-week extended Phase II clinical study, investigating the efficacy of its integrase inhibitor ISENTRESS (raltegravir) in combination therapy, at the 6th International AIDS Society Conference on HIV pathogenesis, Treatment and Prevention in Rome, Italy. The therapy containing ISENTRESS showed efficacy in improving CD4 counts in treatment-naive adult patients. Efficacy was also seen when suppressing HIV-1 viral load to undetectable levels (less than 50 copies/ml) and was comparable to that of efavirenz combination therapies, thus meeting both primary end points of the study.

In this double-blind, randomized Phase II study, 198 previously untreated patients with HIV-1 were given 400 mg ISENTRESS orally twice daily (n = 160) or 600 mg efavirenz orally once daily (n = 38).

Both drugs were given in combination with tenofovir/lamivudine. This began at week 48 where prior to this patients receiving the ISENTRESS were randomized into four dose regimens (100, 200, 400 and 600 mg).

ISENTRESS is an integrase inhibitor and is currently the only fully approved drug of this type for HIV-1 treatment. Inhibition of the enzyme Integrase prevents the insertion of HIV-1 DNA into human DNA, resulting in the inability of the virus to produce new virions. Other treatments currently approved for HIV-1 treatment focus on prevention of reverse transcription by blocking reverse transcriptase and blocking formation of infectious virions by targeting viral proteases.

The study's secondary end point was also met when data on ISENTRESS in combination therapy showed fewer reported drug-related adverse effects when compared with efavirenz. Also included in the presentation was data detailing a modest impact on low-density lipoprotein cholesterol and triglycerides. Eduardo Gotuzzo (Professor of medicine, infectious diseases and tropical medicine, Universidad Peruana Cayetano Heredia, Lima, Peru), who presented the Phase II data in Rome, commented on the importance of these findings, "Because physicians consider many factors when selecting antiretroviral therapy for adult HIV-1 patients new to treatment, the results seen in this Phase II study with ISENTRESS in combination therapy showing a modest impact on low-density lipoprotein and triglycerides provide important insights."

These Phase II results allow Merck to begin to directly compare their intergrase inhibitor's performance against efavirenz in combination therapies. The study provides positive efficacy data and meets both its primary and secondary end points, solidifying ISENTRESS as an effective HIV-1 treatment and potentially as a highly effective treatment for previously untreated patients with HIV-1 when used in a combination therapy.

Source: www.merck.com/newsroom/news-release-archive/prescription-medicine-news/2011_0718.html

About the News and Views

The News and Views highlights some of the most important events and research. If you have newsworthy information, please contact: Laura McGuinness, Editor, *Therapy*

Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK; Tel.: +44 (0)20 8371 6090;
Fax: +44 (0)20 8343 2313; l.mcguinness@futuremedicine.com