Clin. Invest. (2014) 4(3), 205–208

CLINICAL INVESTIGATION

News

Highlights from the latest news and research in Clinical Investigation

CHILD-INNOVAC project demonstrates effective nasal vaccine against pertussis in Phase I trial

Researchers from the CHILD-INNOVAC European research program, a project coordinated by Inserm (Paris, France), has developed a new vaccine that could be effective against pertussis. Results from a Phase I trial have been published in *PLoS ONE*, and demonstrate the efficacy and safety of the intranasally administered vaccine in human subjects. The CHILD-INNOVAC project brings together ten European partners, which including both laboratories and private companies from seven countries. The project received a budget of €5 million, awarded by the European Commission under FP7.

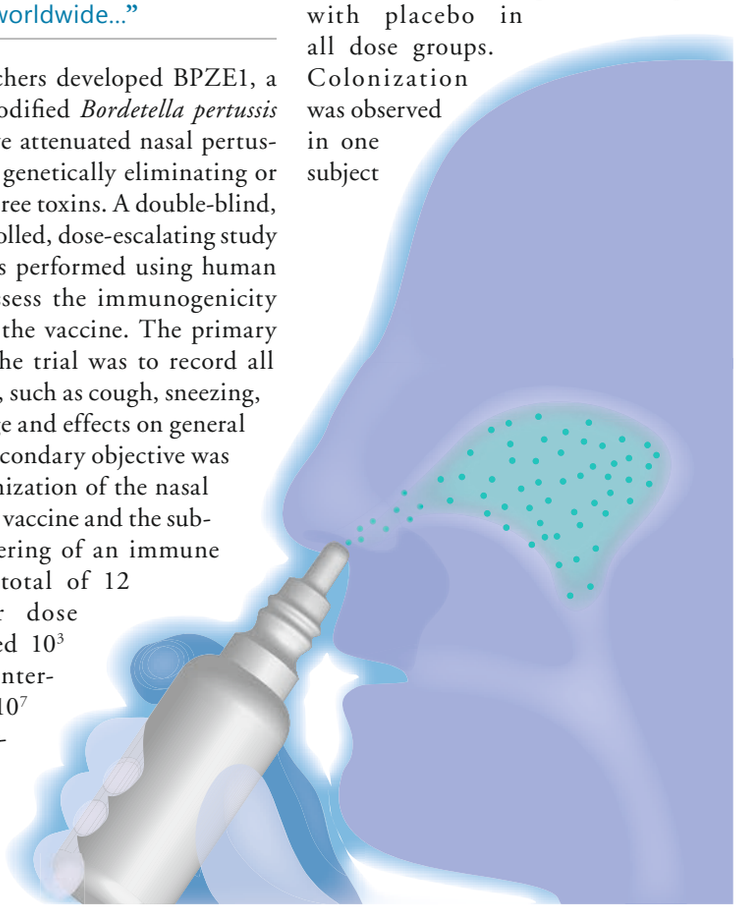
Pertussis is a highly contagious bacterial disease, affecting several tens of millions of individuals worldwide, as well as being responsible for the deaths of approximately 300,000 children annually. The morbidity and mortality of the disease are increasing; a notably resurgence is also taking place in many developed countries, including the USA, Australia and the UK.

The CHILD-INNOVAC project is specifically focused on combating *Bordetella pertussis* and respiratory syncytial virus, two of the major respiratory pathogens. The vaccines currently available are ineffective for infants who contract these infections, who are typically in the age range of 0–6 months. In addition, the project aims to provide proof-of-concept that these types of vaccines can be translated to other respiratory infections. This was the first trial of a live attenuated vaccine specifically designed for the respiratory tract. The trial took place in Sweden, which was identified as having the most 'naive' population with respect to vaccination against pertussis; vaccination was discontinued in the country due to reasons of inefficacy.

> "Pertussis is a highly contagious bacterial disease, affecting several tens of millions of individuals worldwide..."

The researchers developed BPZE1, a genetically modified *Bordetella pertussis* strain, as a live attenuated nasal pertussis vaccine by genetically eliminating or detoxifying three toxins. A double-blind, placebo-controlled, dose-escalating study of BPZE1 was performed using human subjects to assess the immunogenicity and safety of the vaccine. The primary objective of the trial was to record all adverse events, such as cough, sneezing, nasal discharge and effects on general health. The secondary objective was to assess colonization of the nasal mucosa by the vaccine and the subsequent triggering of an immune response. A total of 12 subjects per dose group received 10^3 (low), 10^5 (intermediate) or 10^7 (high) colony-forming units as droplets, with half of the dose administered to each nostril. In addition, 12 controls received a diluent. The local and systemic safety and immune response were assessed over a period of 6 months, and nasopharyngeal colonization with BPZE1 determined by repeated cultures over the course of a 4-week period following vaccination.

It was found that the vaccine induced no adverse events in patients compared with placebo in all dose groups. Colonization was observed in one subject



ISSN 2041-6792
10.4155/CLI.14.10

at low dose, one at medium dose and five in the high-dose group. Of particular note, immune responses against pertussis antigens were seen in all dose groups. Camille Locht, head of the research consortium and Director of the Centre for Infection and Immunity of Lille explained the significance of the results: "It is of special interest that a single nasal administration was able to induce an immune response that was maintained for at least 6 months, that is, for the duration of the study."

One of the successes of this project has been the achievement of developing a vaccine for which the immunogenicity and safety could be assessed in humans in just 2.5 years, compared with the usual 5–7 years for most projects of this type. Locht explained that this reduced timescale was due to "the skills and motivation of the consortium, which brought together experts in their respective areas of specialization from seven European countries. It was possible to relay the data in a flexible and efficient manner at the different stages of the project." Following on from these results, BPZE1 can now undergo further clinical development; specifically, the researchers will administer higher volumes of the vaccine with the aim of increasing the level of colonization of the nasal mucosa. A key goal will be to improve the stability of the vaccine and move it towards industrial development. The investigators believe that the original method of administration could make the vaccine available to a greater number of people at a reduced cost.

– Written by Jonathan Wilkinson
Illustrated by Benjamin Pearce

Sources: Inserm press release: http://presse-inserm.fr/en/a-good-outcome-for-the-child-innovac-project-successful-test-in-humans-of-a-nasal-vaccine-against-pertussis/10572; Thorstensson R, Trollfors B, Al-Tawil A *et al.* A Phase I clinical study of a live attenuated bordetella pertussis vaccine – BPZE1; A single centre, double-blind, placebo-controlled, dose-escalating study of BPZE1 given intranasally to healthy adult male volunteers. *PLoS ONE* doi:10.1371/journal.pone.0083449 (2014) (Epub ahead of print).

Researchers identify drug with the potential to reduce the spread of breast cancer by more than 80%

Up to 12,000 breast cancer patients a year develop metastasis, involving the progressive spread of cancer to vital organs, often several years after initial diagnosis of a breast lump. Now, researchers at Cardiff University, UK, are developing a novel compound known to reverse this spread of malignant breast cancer cells.

The work has involved a recent series of studies, whereby the researchers have identified a previously unknown critical role for a potential cancer causing gene, *Bcl3*, in metastatic breast cancer. "We showed that suppressing this gene reduced the spread of cancer by more than 80%," explained Richard Clarkson from Cardiff University's European Cancer Stem Cell Research Institute, "Our next goal was to then find a way to suppress *Bcl3* pharmacologically."

Clarkson collaborated with Andrea Brancale and Andrew Westwell from Cardiff's School of Pharmacy and Pharmaceutical Sciences to develop small chemical inhibitors of the *Bcl3* gene. Using computer-aided modeling of how the *Bcl3* gene functions inside the cell, the group were able to identify a pocket on the surface of *Bcl3*, essential for its function. Using state-of-the-art computer software, the team then screened a virtual compound library for chemicals that could fit inside this pocket, identifying a drug candidate that potentially inhibits *Bcl3*.

This compound has now been trialed on mice with metastatic disease, with the resulting effect that the drug completely inhibited the development of the mice's metastatic tumors. "There is therefore a clear unmet clinical need to identify new drugs to reverse or at least to slow down disease progression," Clarkson enthused.

The research has now received financial backing from Tiziana Pharmaceuticals (UK), in order to progress the compound to clinical trials, with the aim of developing a therapeutic agent capable of blocking metastatic disease in breast cancer and a variety of tumor types.

– Written by Ruth Williamson

Source: Experimental breast cancer drug: www.cardiff.ac.uk/news/articles/experimental-breast-cancer-drug-12349.html?utm_source=cu-home&utm_medium=slide&utm_campaign=news

Personalized brain tumor vaccine may benefit patients with recurrent glioblastoma multiforme

A new study, published recently in the journal *Neuro-Oncology*, reveals that an experimental personalized vaccine that is made from the patient's own resected tumor tissue may improve survival rates for patients with glioblastoma multiforme (GBM).

GBM is the most common primary brain malignancy, however, prognosis is still poor. Even with standard treatment, the median survival from diagnosis remains at approximately 15 months. Orin Bloch, assistant professor of neurology at Northwestern University Feinberg School of Medicine (IL, USA) and lead author of the study, explained why the research is important: "We are talking about fast-growing tumors that invade normal brain tissue and are very difficult to treat. These tumors occur in up to 23,000 Americans annually, and are typically treated with surgical resection of the tumor followed by chemotherapy and radiation treatment."

It is thought, therefore, that immunotherapy could potentially hold the key for GBM treatment as it may produce a more sustained and less toxic effect than

conventional therapy. There are currently vaccines available for cancer treatment, however, as yet, none have been approved for use against GBM. In this open-label, single-arm, Phase II study, the researchers enrolled 41 adults with recurrent GBM tumors between 2007 and 2011, and developed a vaccine, called HSPPC-96, which was specific to each patient by using their own resected tumor tissue. On average, each individual received six doses of the HSPPC-96 vaccine.

At 6 months follow up, 90.2% of patients were alive (95% CI: 75.9–96.8) and 29.3% were alive at 12 months (95% CI: 16.6–45.7). The median overall survival was 42.6 weeks (95% CI: 34.7–50.5) and there were no treatment-related deaths.

> "Someday, thanks to studies like this one, we'll we'll get to the top of the mountain and convert this particular cancer into a chronic disease..."

Further study is needed to determine the efficacy of the HSPPC-96 for the treatment of recurrent GBM because GBM almost always returns after treatment. As Bloch explained, "The grim prognosis is exactly why new research is important. GBMs have been around for a long time, and still outcomes are poor. With studies such as this one, I believe we can change that." Andrew Parsa, corresponding author of the study, chair of the department of neurological surgery at Feinberg School of Medicine, added: "When it comes to brain tumor research, I picture our Northwestern Medicine team climbing a mountain and with every new discovery that shows the potential to prolong survival, we are establishing a new base camp. Someday, thanks to studies like this one, we'll get to the top of the mountain and convert this particular cancer into a chronic disease – something that patients can live with, controlled by medication."

– Written by Natasha Leeson

Sources: Northwestern University Feinberg School of Medicine press release: www.feinberg.northwestern.edu/research/news/2013/brain-tumor-vaccine.html; Bloch O, Crane CA, Fuks Y *et al.* Heat-shock protein peptide complex-96 vaccination for recurrent glioblastoma: a Phase II, single-arm trial. *Neuro Oncol.* 16(2), 274–279 (2014).

Update provided on ongoing Phase III METIV-HCC trial

ArQule, Inc. (MA, USA) has recently provided an update on the ongoing Phase III METIV-HCC trial, announcing that the Data Monitoring Committee of the METIV-HCC has approved the continuation of the liver cancer trial following safety and pharmacokinetic analyses.

> "In clinical trials to date, treatment with tivantinib has been generally well tolerated and shown clinical activity..."

The METIV-HCC trial, conducted by Daiichi Sankyo Company, Ltd (Tokyo, Japan) and ArQule, Inc., is a randomized, double-blind study of tivantinib as a single agent therapy in previously treated patients with MET diagnostic-high, inoperable hepatocellular carcinoma. The primary end point is overall survival in the intent-to-treat population, and the secondary end point is progression-free survival in the same population.

Tivantinib is an orally administered selective inhibitor of MET, a receptor tyrosine kinase that present in low to normal levels in healthy individuals and supports natural cellular function. However, in certain cancer cells, MET is inappropriately and continuously activated and becomes involved in numerous aspects of malignancy, including cancer cell growth, survival, angiogenesis, invasion and metastasis. There is also evidence that MET signaling pathways are involved in the acquired resistance to EGF receptor inhibitors.

In clinical trials to date, treatment with tivantinib has been generally well tolerated and shown clinical activity in the tumors studied but is not yet approved for any indication in any country.

A dose reduction from 240 to 120 mg tablets b.i.d. was implemented in September 2013, following the observation of a higher incidence of neutropenia in the initial phase of the METIV-HCC trial than was observed in the Phase II trial in the same patient population where a 240 mg b.i.d. capsule dose was administered. Certain enhanced patient monitoring procedures had been temporarily instituted to confirm the safety profile of the lower dose.

– Written by Emma Sinclair

Sources: Press release: http://investors.arqule.com/releasedetail.cfm?ReleaseID=819847 Clinical Trial information: www.clinicaltrials.gov/ct2/show/NCT01755767?term=METIV-HCC&rank=1

Researchers synthesize potent antibacterials with more backbone

Acyldepsipeptides (ADEPs) are a class of molecules that can destroy bacteria by binding and dysregulating ClpP peptidase activity. Recently, scientists from Brown University (Providence, RI, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA) have demonstrated that the biological potency of ADEPs can be significantly increased by providing the ADEPs with more backbone, subsequently making them more rigid.

The study, published in the *Journal of the American Chemical Society*, demonstrated that in the ADEP–ClpP crystal structure, the ADEP conformation is "fortified by transannular hydrogen bonding and can be further stabilized by judicious replacement of constituent amino acids within the peptidolactone core structure with more conformationally constrained counterparts."

The research group generated a number of new ADEP molecules through altering

the amino acids to increase the molecule's rigidity. They then investigated the strength of hydrogen bonds within the molecule by placing the ADEP into a deuterium-rich solution. If the modified ADEPs exchanged deuterium atoms with hydrogen atoms more slowly, it would suggest stronger hydrogen bonds and a more rigid molecule. In this study, the modified ADEPs exchanged deuterium as much as 380-times slower than natural ADEP, indicating increased rigidity.

The group then determined that, *in vitro*, the more rigid ADEP analogs were capable of binding and activating ClpP at lower concentrations. This indicated that the modified ADEPs bound ClpP approximately seven-times better than normal ADEP. Furthermore, it is claimed that the compounds in this study "have up to 1200-fold enhanced antibacterial activity when compared to those with the peptidolactone core structure common to two ADEP natural products."

This investigation supports the ideas that rational modulation of conformational dynamics could have a positive impact on the bioactivities of natural products. Senior author of the published work, Jason Sello, stated "The work is significant because we have outlined and validated a strategy for enhancing the potency of this promising class of antibacterial drug leads." He continued, "The molecules that we have synthesized are among the most potent antibacterial agents ever reported in the literature." An investigation into the compounds' usefulness in mice is now in progress.

– Written by Hannah Branch

Sources: Carney DW, Schmitz KR, Truong JV, Sauer RT, Sello JK. Restriction of the conformational dynamics of the cyclic acyldepsipeptide antibiotics improves their antibacterial activity. *J. Am. Chem. Soc.* doi: 10.1021/ja410385c (2014) (Epub ahead of print); Brown University press release: http://news.brown.edu/pressreleases/2014/01/adeps

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:

Alice O'Hare
Commissioning Editor, *Clinical Investigation*
Future Science Group
Unitec House
2 Albert Place
London, N3 1QB, UK
Tel.: +44 (0)20 8371 6090
a.ohare@future-science.com