

Pfizer Forschungspreis 2011

www.pfizerforschungspreis.ch

Urs Nydegger

Pfizer Research Prize 2011

The 20th Medicine Prize sponsored by the Pfizer Foundation Switzerland (www.pfizerpreis.ch) was imparted in Zurich, early in February 2011. A crowd of ~150 persons, most of them from the science community of our country applauded 10 prize winners coauthoring six prizes to be described in *pipette*, the SULM journal which has reported previously on Pfizer Prize 2009 (Nr. 2, april 2009)

The introductory part of the event defined the basic principles of the Pfizer Prizes: they should be attributed to young researchers with sparkling ideas, they honor published work in peer reviewed impact factor indexed journals and they are held to support further work of the winners on their future career path. The Zurich education minister compared basic research in research to the achievements of Christoph Columbus who set out to discover India yet fell on North America. The minister emphasized the importance of basic school training: biology and mathematics, study of languages and history all should be fed by curiosity in early life. Switzerland is an ideal environment for research with institutions which allow basic research. 'Don't dream your life but live your dreams' and 'the dream of yesterday feeds hope for today and reality of tomorrow' –with these words, the medical manager of Pfizer welcomed the prize winners to unload their scientific baggage. They were introduced by members of the scientific committee and used short video shows to present their work.

A prize was given for research published in European Urology 2010 entitled: **A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder.** The extent by which tumor cells infiltrate local lymph nodes in the pelvic area serves for survival prognosis; removal of local lymph nodes in bladder cancer is standard and 30% of patients can thus be cured. However, pre- & intraoperative estimation of lymph node participation is still imprecise the more so as the pattern of lymph drainage network is ill defined – neither magnetic resonance imaging nor computerized tomography are reliable in detecting micro-metastases, surgeons remove as much lymph nodes as possible. The prize winners have injected radioactive isotopes into the bladder in an attempt to follow the lymphatic drainage flow. For this purpose cystoscopy-guided injection of technetium nanocolloid was done into one of six non-tumor-bearing sites of the bladder. At the winners institution a SPECT/CT set up is installed allowing comparison of functional images of nuclear medicine with the more anatomical modalities like CT. Thus preoperative detection of radioactive lymph nodes with SPECT/CT followed by intraoperative verification with a gamma probe became possible (Figure 1). Backup extended pelvic lymph node dissection for *ex vivo* detection of missed lymph nodes completed the design. The SPECT/CT isotope sensor (similar to a Geiger counter) found lymph nodes to be removed and the workers suggest their SPECT/CT plus intraoperative gamma probe technology to reveal patients' individual template of the bladder's primary lymphatic landing sites. Routine removal so far in use removed only in ~50% of all primary lymphatic landing sites in the ventral portion of the external iliac vessels and obturator fossa; the prize-winning study suggests that extended removal of lymph nodes along the major pelvic vessels will remove ~90%. Assays carried out in the clinical laboratory during this study did not extend beyond usual routine tests.

Another Pfizer prize was awarded to work published in Nature Medicine 2010 entitled: **Development of replication-defective lymphocytic choriomeningitis virus (LCMV) vectors for the induction of potent CD8+ T cell immunity**. The project was devoted to improving vaccination protocols since most of them are based on induction of a powerful adaptive immune response with sizeable titers of vaccine-specific antibodies. The authors set out to harness the immunobiology of this arenavirus for vaccine delivery. By using producer cells constitutively synthesizing the viral glycoprotein, it was possible to replace the gene encoding LCMV GP with vaccine antigens to create replication-defective vaccine vectors. These rLCMV vaccines elicited CTL responses were greater than those elicited by recombinant adenovirus 5 or recombinant vaccinia virus in their magnitude and cytokine profiles, and they exhibited more effective protection in several models. In contrast to recombinant adenovirus 5, rLCMV failed to elicit vector-specific antibody immunity, which facilitated re-administration of the same vector for booster vaccination. The prize winners suggest that rLCMV may show utility as a vaccine platform against infectious diseases and even of cancer. The study is coauthored by Paul-Henri Lambert whose interest in vaccination strategies and risk evaluation is well known and who is a former teacher of this reports author (www.tbvi.eu).

Another prize was awarded for work published under the title of **GM1 structure determines SV40-induced membrane invagination and infection** in Nature Cell Biology 2010. It is good to know that polyoma viruses are tumorviruses which bother immunosuppressed individuals by inducing cancer or other severe diseases. Polyoma viruses use lipid components of cell surfaces as entry sites. Similar to complement systems' C5b-9 punch into cell membranes, polyoma viruses punch holes and deform the cell membrane. Incoming simian virus 40 (SV40) particles enter tight-fitting plasma membrane invaginations after binding to the carbohydrate moiety of GM1 gangliosides in the host cell plasma membrane through pentameric capsid proteins. The viral binding to the cell induces activation of cellular signaling pathways, endocytic internalization and transport of the virus *via* the endoplasmic reticulum to the nucleus. The Pfizer prize winners observed that the association of SV40 with GM1 is sufficient to induce membrane curvatures and deep invaginations with tubule formation not only in the plasma membrane of cells, but also in giant vesicles. Unlike native GM1 molecules with long acyl chains, GM1 molecular species with short hydrocarbon chains failed to support such invagination, and endocytosis and

infection did not occur. To conceptualize the experimental data, the prize winners derived a physical model based on energetic considerations and showed that SV40, other polyoma viruses and some bacterial toxins (Shiga and cholera) use glycosphingolipids and a common pentameric protein scaffold to induce plasma membrane curvature, thus directly promoting their endocytic uptake into cells.

A further prize was given for work published in Nature Methods 2010 entitled: **High-speed in vivo calcium imaging reveals neuronal network activity with near-millisecond precision** focusing on environmental influence on the human brain. Because all processes in our brain proceed, at least in part, at enormous speed, a technique which would allow to closely follow these processes could shed insight into networking of brain cells. Whereas two-photon calcium imaging of neuronal populations enables optical recording of spiking activity in living animals, standard laser scanners currently in use are too slow to accurately determine spike times. The prize is allocated for successful *in vivo* imaging in mouse neocortex with greatly improved temporal resolution using random-access scanning with acousto-optic deflectors. They researchers obtained fluorescence measurements from 34-91 layer 2/3 neurons at a 180-490 Hz sampling rate. With an enormous previously unthought-of speed single action potential-evoked calcium transients with signal-to-noise ratios of 2-5 and determined spike times with near-millisecond precision and 5-15 ms confidence intervals. An automated IT-supported algorithm enabled reconstruction of complex spike trains from fluorescence traces up to 20-30 Hz frequency, uncovering spatiotemporal trial-to-trial variability of sensory responses in barrel cortex and visual cortex. By revealing spike sequences in neuronal populations on a fast time scale, high-speed calcium imaging now facilitate optical studies of information processing in brain microcircuits.

The next prize went to work published in Nature 2010 entitled: **Neural bases for addictive properties of benzodiazepines** pertaining to this group of psychoactive drug whose core chemical structure is the fusion of a benzene ring and a diazepine ring. The first benzodiazepine, chlordiazepoxide (Librium), was discovered accidentally by Leo Sternbach in 1955, and made available in 1960 by Hoffmann–La Roche, which has also marketed diazepam (Valium) since 1963. Drug-dependency with benzodiazepine is a well known side-effect and warrants elucidation of eliciting mechanisms. Benzodiazepines are widely used in clinics and for recreational purposes. Addictive drugs increase the levels of dopamine and also trigger long-lasting synaptic adaptations in the mesolimbic reward system that ultimately may induce the pathological behaviour. The neural basis for the addictive nature of benzodiazepines, remains elusive. The prize winners could demonstrate that benzodiazepines increase firing of dopamine neurons of the ventral tegmental area through the positive modulation of GABA(A) (gamma-aminobutyric acid type A) receptors in nearby interneurons. Such disinhibition, which relies on alpha1-containing GABA(A) receptors expressed in these cells, triggers drug-evoked synaptic plasticity in excitatory afferents onto dopamine neurons and underlies drug reinforcement. Taken together, the winner's data provide evidence that benzodiazepines share defining pharmacological features of addictive drugs through cell-type-specific expression of alpha1-containing GABA(A) receptors in the ventral tegmental area. The data also indicate that subunit-selective benzodiazepines sparing alpha 1 may be devoid of addiction liability.

Another Pfizer prize was awarded to work published in 2009 in *Cancer Cell* entitled:

A lymphotoxin-driven pathway to hepatocellular carcinoma. Hepatocellular carcinoma, also called malignant hepatoma, is a cancer of which one often knows the origin: hepatitis or alcoholic cirrhosis but the liver is also a privileged metastasis-site for colon cancer. The authors were interested in local driving forces which favour hepatoma formation. Thus, hepatitis can be caused by a variety of non-infectious and infectious triggers such as drug or alcohol abuse, toxic fungi but viral infection are the most frequent hepatitis causative reasons in humans. Chronic hepatitis induces hepatic cells to undergo tumorigenesis. Hepatitis B and C viruses (HBV and HCV) cause chronic hepatitis and hepatocellular carcinoma (HCC) by poorly understood mechanisms. The prize winners used liver tissue of patients infected with HBV and HCV and they saw increased concentrations of inflammation-inducing cytokines. In fact, the cytokines lymphotoxin (LT) α and β and their receptor (LT β R) were upregulated in HBV- or HCV-induced hepatitis and HCC. The researchers also used experimental mice, made transgenic, such that these animals produced excessive amounts of lymphotoxins and a strong relationship between hepatitis and liver cancer appeared. Development of hepatocellular carcinoma, composed in part of special tumor cells A6(+) oval cells, depends on lymphocytes. Cells of the clonal cell lines are nontumorigenic, and they express cytokeratin 19, A6 antigen, and integrins, as well as a large panel of hepatocyte and, they can participate in liver regeneration. With such plasticity of cell development, the prize winners demonstrate the existence, in normal adult mouse liver, of a significant pool of clonogenic cells that are (or can become) bipotential and can derail.

In vivo LT β R stimulation implicates hepatocytes as the major LT-responsive liver cells, and LT β R inhibition in LT β R-transgenic mice with hepatitis suppresses hepatocellular carcinoma formation. The Pfizer Prize was awarded here because the authors convincingly propose sustained lymphotoxin signaling as a pathway, hepatitis viruses take to induce hepatocellular carcinoma.