Scientists from Switzerland win Young Investigator Awards at the European Society of Cardiology's Annual Meeting

Munich, 24–29 August 2012

The European Society of Cardiology accommodated around 27,279 participants from more than 40 countries, with most delegates from Germany (2,049), France (1,126), Italy (1,051), Japan (975) and the USA (971). From Switzerland, 685 physicians and scientists attended the meeting.

The European Society of Cardiology has launched several initiatives to motivate young cardiologists and scientists to be active in cardiovascular medicine. The Young Investigator Awards are among those initiatives. Switzerland can be proud that three scientists working in our country won a Young Investigator Award:

Dr Francesco Paneni (fig. 1), a cardiologist from University of Rome Sapienza, is currently working in the Cardiovascular Research at the Institute of Physiology, University of Zurich, under the supervision of Professor Francesco Cosentino.

Dr Paneni won the Young Investigator Award in Basic Science presenting a work entitled "Vascular hyperglycaemic memory is driven by $p66^{Shc}$ via epigenetic changes and posttranslational modifications: pathophysiological insights for the progression of vascular complications despite intensive glycemic control". His work demonstrated that both in diabetic mice and human endothelial cells glucose normalisation did not revert upregulation of $p66^{Shc}$ protein, a mitochondrial adaptor critically involved in ROS generation. Persistent $p66^{Shc}$ overexpression was explained by reduced promoter methylation as well as increased histone 3 acetylation by gene control non-derepressible 5 (GCN5). Moreover, $p66^{Shc}$-dependent ROS generation was responsible for upregulation of PKCβII and PKCβII-dependent eNOS inhibitory phosphorylation at Thr-495, thus feeding a detrimental vicious cycle despite restoration of normoglycaemia. Persistent oxidative stress also accounted for sustained vascular apoptosis via PARP and caspase 3 activation. Endothelial-specific knockdown of $p66^{Shc}$ blunted persistent endothelial dysfunction and oxidative stress in the vasculature of diabetic mice, suggesting that $p66^{Shc}$ protein drives ROS-induced hyperglycemic memory. This study provides molecular insights for the understanding why vascular complications progress despite an intensive glycemic control in patients with diabetes.

Dr Erik W. Holy (fig. 2), PhD, University of Zurich, won the Young Investigator Award in Thrombosis Research with his work on "Targeting vascular PI3K/p110α expression: a new concept in drug eluting stent design?"

Despite reduced restenosis rates, impaired healing and stent thrombosis remain safety concerns associated with the use of drug eluting stents (DES) in the treatment of coronary artery disease. Tissue factor is the major trigger of blood coagulation and arterial thrombosis. Hence, it does not only promote cardiovascular events such as myocardial infarction and ischaemic stroke, but is also crucially involved the development of stent thrombosis. Recent studies demonstrated that drugs used on DES such as rapamycin or paclitaxel not only inhibit reendothelialisation, but also induce tissue factor and enhance arterial thrombus formation. The phosphoinositide 3-kinase (PI3K) pathway controls crucial cellular processes thereby representing an emerging drug target. In vascular cells, the PI3K isoform p110α is predominantly expressed. Currently, its role in arterial thrombus formation has not been investigated yet. Moreover, its effect on activation of vascular smooth muscle cells and endothelial cells, and on reendothelialisation in particular, remains unknown. In his study, Erik Holy demonstrated that inhibition of PI3K/p110α impaired arterial thrombus formation in vivo. This effect was mediated by a decrease in TF and plasminogen activator inhibitor-type 1 expression in vascular cells. Furthermore, PI3K/p110α inhibition selectively impaired proliferation and migration of vascular smooth muscle cells, while sparing endothelial cells completely. In contrast to rapamycin or paclitaxel, inhibition of PI3K/p110α did not induce endothelial senescence nor did it inhibit eNOS expression or endothelium-dependent vascular relaxation.

Figure 1
Francesco Panemi, MD, Zurich/Rome, wins Young Investigator Award (YIA) Basic Science at the ESC in Munich this year for his work on p66shc in diabetic vasculopathy and metabolic memory. YIA in Basic Science (left to right): winner Francesco Paneni, Konrad Hoetzenecker, Piyushkumar Kapopara and Akio Monji.

Figure 2
Erik Walter Holy, MD, PhD, Zurich/Baden, wins Young Investigator Award (YIA) Thrombosis at the ESC in Munch 2012. YIA in Thrombosis (left to right): Jonas Bjerring Olesen, Beytullah Cakal, winner Erik Walter Holy and Katharina Hess.

Figure 3
Susanna Sluka, Zurich, wins Best Abstract Award on Vascular Biology (second left) pictured with Rob Krams, Claudia Monaco and Christian Weber (left to right) for her abstract "Tissue factor disulfide mutation causes a bleeding phenotype with gender specific organ pathology and lethality".

Results generated by this study may identify PI3K/p110α as a new promising therapeutic target in cardiovascular medicine, in particular in the context of DES design.

Dr Holy studied medicine at the University of Vienna and successfully obtained his MD/PhD Programme at the University of Zurich in 2011 and is currently training in internal medicine at the Kantonsspital Baden. He performs his work in cardiovascular research in the Department of Cardiology and the Institute of Physiology at the University Hospital and the University of Zurich, Switzerland.

Susanna Sluka (fig. 3), PhD student, wins Best Abstract Award on vascular biology for her work on "Tissue factor disulfide mutation causes a bleeding phenotype with gender specific organ pathology and lethality".

Susanna Sluka is currently a PhD student at the Institute of Physiology, Cardiovascular Research, a Division belonging to the Department of Cardiology of the University Hospital. Under the leadership of Prof. Felix C. Tanner, she worked on tissue factor and mutations of this important protein involved in bleeding and coagulation. Best abstract awarded at the European Society of Cardiology is part of her PhD thesis at the University of Zurich.

Tissue factor (TF), the key initiator of coagulation, is expressed in sub-endothelial tissue, particularly in heart, lung and brain. The extracellular allosteric disulfide bond Cys186–Cys209 of human TF shows high evolutionary conservation. In vitro experiments suggest that TF pro-coagulant activity depends on the intact Cys186–Cys209 disulfide bond. To investigate the role of this allosteric disulfide bond in vivo, we generated a C213G mutant TF mouse by replacing Cys213 of the corresponding disulfide Cys190-Cys213 in murine TF.

Homozygous C213G TF mice presented with a bleeding phenotype, affecting predominantly heart, lung, and brain. This resulted in a gender specific lethality with reduced survival especially in homozygous males. Pro-coagulant activity of C213G TF was reduced by about 100-fold. Homozygous female mice exhibited bleeding in lung less frequently, while bleeding in heart and brain occurred equally frequent in males and females. At the molecular level, gene regulation patterns of C213G TF hearts and brains showed high homology between males and females, whereas patterns of gene regulation were very different in lungs of females compared to males.

These studies indicate that the allosteric Cys190-Cys213 disulfide bond is of crucial importance for in vivo activity of murine TF. C213G TF mice suffer from a bleeding phenotype affecting heart, lung, and brain. Male mice further suffer from decreased survival and discriminate from females by a higher abundance of lung bleeding paralleled by a different pattern of pulmonary gene regulation. These findings suggest lung bleeding as the major reason for reduced survival in mice lacking the Cys190-Cys213 disulfide bond.