"Visus" the valve diseases. Transcatheter technologies take advantages from the open heart technique using catheter based instruments for elderly and high risk patients. Transcatheter mitral valve commisurotomy was the first surgical therapy converted to transcatheter one in the 1980. Today with a new art of transcatheter technology, with more clinical efficacy and safety is this "The Procedure of Choice" with a faster recovery and less peri-operative pain. But although it seems the TAVI procedure is more effective at elderly high risk or non-operable patients. The German TAVR registry shows that at low risk population, the observed mortality & morbidity is higher than that population by the EUROSCORE. The key and the crucial point at the introduction of a new clinical technology is the optimal "TRANSLATION" to the daily human practice. The new interventional technology has to be supported – after previous excellent results of animal and all clinical phase studies - by "Clinical Evidence**!!!**". In this technology imaging is the crucial factor in the selection with and in the screening process, to guide patients to the right size and art of device selection, as well as in playing a fundamental role during procedures to guide the implant safely and effectively. In the future the best imagination with a real touch will be probably holographic by an almost "REAL " 3D or 4D anatomical peri-operative representation.

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PTEN as a therapeutic target in motor neuron diseases (ALS/SMA)

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Abstract

The tumor suppressor protein Phosphatase and Tensin Homolog deleted on Chromosome 10 (PTEN) is a member of the protein tyrosine phosphatase family that can negatively regulate the serine/threonine kinase Akt to exert its tumour suppressor function. In addition to its normal functions such as neuronal migration and neuronal size control, PTEN protein is involved in pathological processes surrounding neuronal injury such as those associated with brain ischemia, neurological and mental disorders. It has been shown that modulation of the PTEN/mTOR pathway promotes axon regeneration in the adult CNS. We have previously shown that down-regulating the expression of PTEN protects against ischaemic neuronal death in vitro and in vivo (Ning et al. 2014). Recently, we showed that PTEN knockdown via siRNA increases motor neuron survival in Amyotrophic lateral sclerosis (ALS) (Kirby et al. 2011) in vitro and spinal muscular atrophy (SMA) in vivo (Ning et al. 2010, Little et al., unpublished). Our preliminary data show that the PTEN inhibitor, bpV, promotes cell survival in NSC34 G93A motor neuronal cell line. We have also showed that PTEN silencing increases cell survival in iPS-derived motor neurons from human fibroblasts (D-J Yang et al., 2014). Taken together, PTEN inhibition results in neuroprotective effects on motor neuron survival in vitro and in vivo. The outcome of our studies provide evidence that PTEN is potential therapeutic target for neuroprotection in ALS or SMA patients and other neurodegenerative disorders.

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Poster Presentations

SRM-based quantification of malignant biliary stenosis biomarkers in human bile

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Abstract

The differential diagnosis of biliary stenosis is a critical problem for gastroenterologists. An early identification of malignant lesions would enable the rapid resort to surgical resection which currently represents the only potentially curative option. Unfortunately, the diagnostic value of all available methods (e.g. imaging technics, standard serum biomarkers) is limited by relatively poor accuracy and negative predictive value. Recently, our group and others highlighted new potential cancer biomarkers in bile by using comparative proteomic analysis. Nevertheless, to date, only a few candidates have been verified for their diagnostic performances in discriminating between malignant and non-malignant stenoses. In addition, no data have yet been collected on the simultaneous measurement of these proteins with the intent of evaluating the diagnostic interest of a panel of biomarkers. To overcome the limitation of classical verification tools and give a new impetus to the translation of bile biomarkers into clinical diagnostics, mass spectrometry-based quantification could represent a rapid and cost-effective opportunity thanks to its capacity for multiplexed, high-throughput analysis, combined with its analytical specificity and reliable quantification. Here we developed the first Selected Reaction Monitoring (SRM) assay for the multiplexed measurement of cancer biomarkers in human bile. For this purpose, 8 potential biomarker candidates previously highlighted by proteomic analysis were selected. Equal volumes of bile collected from patients presenting with malignant and non-malignant biliary stenosis were stacked on the top of a SDS-PAGE gel. Proteins were then digested in-gel with trypsin and proteotypic peptides of each candidate biomarker were quantified by nanoLC-SRM on a 5500-QTrap mass spectrometer (ABSciex) using heavy synthetic peptides as standards (PEPotecTM, Thermofisher). SRM data were finally analysed using Skyline software and manual validation. The developed assay proved to be valuable and reliable to quantify all the selected candidates. Moreover, the results confirmed the simultaneous overexpression of some of the proteins in bile samples from malignant stenoses. Overall, our data demonstrate the ability of SRM to quantify cancer biomarkers in human bile and emphasize the interest of using multiplexed SRM assays to assess the diagnostic potential of a panel of bile biomarkers in differentiating biliary stenoses. Work supported by the PRIME-XS consortium.

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Hemopexin, a potential biomarker for the diagnosis of chronic predisposition to acute kidney injury

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Abstract

In the last years, the new concept of predisposition to acquire acute kidney injury (AKI) is emerging. This concept was observed in our group when experimental animals exposed to an absolutely subnephrotoxic acute treatment with certain drugs (e.g. gentamicin and cisplatin) developed AKI when they were treated with a second insult with another drug, while control animals exposed to the same second drug experimented no toxicity. On these grounds, we decide to study if chronic exposure to nephrotoxicants might induce this predisposition to AKI and investigate how to detect this condition by the search of predisposition biomarkers. To this end, rats (Sprague-Dawley) were treated with a subtoxic dosage of the experimental nephrotoxin uranyl nitrate (UN) in the drinking water for 22 weeks, or plain water (as control). After 21 weeks both groups were treated with subtoxic regime of getamicin during 7 days. Renal function was monitored by means of serum creatinine, serum urea, proteinuria, N-acetyl-beta-D-glucosaminidase and lactate dehydrogenase excretion measurement. After and before

gentamicin treatment a subset of rats were sacrificed and their kidneys used for histology. With the purpose of identifying biomarker of predisposition, proteomic studies were performed before gentamicin administration at week 21. Chronic administration of UN in drinking water during 21 weeks did not modify renal function or renal tissue integrity. However, when rats exposed to UN during 21 weeks where challenged with low doses of gentamicin, they developed an overt renal failure as shown by an increase in creatinine, urea and by histological alterations. These alterations were not observed in the control group. Using a proteomic analysis, hemopexin was detected which was validated by Western blot. Urinary excretion of hemopexin was statically higher in the exposed group than in the control group. Our results suggest that chronic exposure to UN, at doses that apparently does not produce damage, predisposes to AKI when animals were subjected to a second insult at subtoxic doses. Hemopexin protein might be potentially used as marker of chronic predisposition to ARF. This new diagnostic tool might help to reduce AKI incidence and severity, and also the associated sanitary and socioeconomic costs.

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Listening to shiny body: In vivo photoacoustic tomography

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Abstract

High-resolution volumetric optical imaging modalities, such as confocal microscopy, two-photon microscopy, and optical coherence tomography, have become increasing important in biomedical imaging fields. However, due to strong light scattering, the penetration depths of these imaging modalities are limited to the optical transport mean free path (~1 mm) in biological tissues. Photoacoustic imaging, an emerging hybrid modality that can provide strong endogenous and exogenous optical absorption contrasts with high ultrasonic spatial resolution, has overcome the fundamental depth limitation while keeping the spatial resolution. The image resolution, as well as the maximum imaging depth, is scalable with ultrasonic frequency within the reach of diffuse photons. In biological tissues the imaging depth can be up to a few centimeters deep. In this presentation, the following topics of photoacoustic imaging will be discussed: (1) multi-scale photoacoustic imaging systems, (2) morphological, functional, and molecular photoacoustic imaging, (3) potential clinical applications, and (4) contrast agents for photoacoustic imaging.

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Melanoxoin reduces tumor growth in xenograft animial model and inhibits cell migration in human lung cancer cell lines.

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Abstract

Natural products remain the best sources of drugs and drug leads. Various anticancer drugs are derived from the natural products. In our previous studies, we found that methanol extract of Pterocarpus santalinus exhibited potent cytotoxicity and anti-inflammatory activities. Among the series of compounds isolated from Pterocarpus santalinus, melanoxoin demonstrated the highest cytotoxic effects with a IC50 of 1.98 Î¼g/ml in human non-small cell lung cancer H1299 cells. The results showed that melanoxoin regulated the transcription of several cell cycle regulators in H1299 cells. Melanoxoin induced tubulin depolymerization, suggesting that melanoxoin causes G2/M arrest thus increasing apoptosis in tumor cell. The results of neutral comet assay showed that treatment with melanoxoin induced significant DNA damage in H1299 cells, while the in vivo efficacy of melanoxoin was revealed by the mice xenograft models. Clinical data showed that an increase (61%) of MET expression was observed in non-small cell lung cancer samples compared with adjacent normal tissues. HGF/c-Met signaling is involved in the cancer progression, metastasis and gefitnib resistance. In particular, we also found that melanoxoin can inhibit HGF-induced cell migration using the wound healing and transwell migration assay. Altogether, our results indicated that melanoxoin displays an outstanding inhibitory activity toward tumor growth and metastasis. Thus, it exerted great potential to be developed into novel anti-cancer agent.

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Regulation of renal fibrosis by the transforming growth factor beta-1 receptor Alk1

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Abstract

Tubulointerstitial fibrosis –a common end-stage feature of chronic kidney disease- is characterized by the presence of renal myofibroblasts and excessive accumulation of extracellular matrix proteins (ECM) in the renal tubular interstitium. The cytokine transforming growth factor beta 1 (TGF-β1) promotes myofibroblast activation and ECM proteins expression through intracellular Smads activation, having an important role in renal fibrosis. We have recently reported that the heterozygous disruption of the TGF-β1 receptor activin receptor-like kinase 1 (ALK1) leads to an increase in TGF-β induced renal fibrosis after ureteral obstruction. Thus, we analyzed the effect of ALK1 heterozygosity in TGF-β1 induced signaling and its consequent fibrotic response in mouse embryonic fibroblasts (MEFs). We have analyzed Smad signaling pathaways in ALK1 heterozygous MEFs (ALK1+/-) and their respective controls (ALK1+/+) in basal conditions and after TGF-β1 treatment by Western blot and immunofluorescence. Moreover, we have analyzed collagen I, fibronectin and connective tissue growth factor (CTGF) expression in basal conditions, after TGF-β1 stimulation and after ALK5 inhibition –with SB431542- and Smad3 inhibition –with SIS3-. TGF-β1 stimulation induced Smad2 and Smad3 phosphorylation and Smad2/3 translocation into the nucleus in ALK1+/+ and ALK1+/- MEFs, being this increase higher in ALK1+/- MEFs. Basal Smad2 and Smad3 phosphorylation was higher in ALK1 heterozygous fibroblasts. TGF-β1 stimulation did not induce Smad1 phosphorylation in ALK1+/- MEFs and a very small Smad1 phosphorylation in ALK1+/- MEFs. ALK1 heterozygous MEFs expressed more collagen I, fibronectin and CTGF than their respective controls in basal conditions. Stimulation with TGF-β1 lead to an increase in collagen I, fibronectin and CTGF, being the increase in fibronectin and CTGF higher in ALK1+/- MEFs. Inhibition of ALK5 and Smad3 reversed the ALK1+/- phenotype. Summarizing, ALK1 heterozygous disruption leads to an impairment of TGF-β1 signaling and increased TGF-β1-induced fibrotic response in mouse embryonic fibroblasts.

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