Feature extraction methods including Principal Component Analysis (PCA), Independent Component Analysis (ICA) and Discrete Wavelet Transform (DWT), are used to extract the most relevant features from the detailed Radar Target Signatures of the tumours, which are then classified with a number of different classification techniques: Linear Discriminant Analysis (LDA), Quadratic Discriminant Analysis (QDA) and Support Vector Machines (SVM). In addition to these techniques, a number of different multi-stage classification architectures are considered. The feature extraction and classification algorithms are evaluated for both homogeneous and heterogeneous breast tissue models, for a range of different tumour sizes and shapes.

Also, the first experimental results using a pre-clinical UWB prototype imaging system for tumour classification based on the shape of tumours. A database of benign and malignant tumour phantoms was created using dielectrically–representative tissue-mimicking material. Classification of benign and malignant tumour models of the experimental data was completed with Linear Discriminant Analysis, Quadratic Discriminant Analysis and Support Vector Machines classifiers.

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Preventive handling of drug nephrotoxicity with antioxidant cotherapies: Preclinical studies and clinical perspectives

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Abstract

Worldwide, nephrotoxicity poses a considerable health and economic burden. Nearly 25% of the top 100, most used drugs in intensive care units are potentially nephrotoxic. Moreover, nephrotoxicity causes 10-20% of the acute renal failure cases (ARF). ARF is a very serious condition with high incidence and mortality rate, which is estimated at approximately 50% of the cases despite dialysis application, especially within critically ill patients. Mortality increases to 80% when ARF courses with multi-organ damage. The clinical handling of renal injury and ARF is difficult and expensive because, other than dialysis, there are no available treatments. For this reason the search for strategies to prevent nephrotoxicity constitute an active area of investigation. In addition to drug targeting and medical chemistry for new and safer molecules, a line of interest is the identification of renoprotective adjuvants for co-administration along with potentially nephrotoxic drugs.

At the preclinical level, many chemically unrelated antioxidants have been shown to protect the kidneys from cisplatin nephrotoxicity, especially in experimental animal models. They include curcumin, N-acetylcysteine, naringenin, selenium, vitamin C, vitamin E and other dietary components that scavenge free radicals formed by exposure to cisplatin. Although promising, antioxidants have not yet demonstrated a clear benefit in the clinical research conducted so far, which requires further investigation. In this line, a pre-clinical selection of candidates to be assayed at the clinical level must be pursued in order to (i) improve the efficacy of the preclinical-to-clinical transition; and (ii) to reduce early failure rate in clinical assays through the drug discovery process.

One of the main problems identified in the translation of antioxidants to the clinical practice is their very low bioavailability derived from a very low absorption upon oral administration. Our research line has been focused on the effect of the natural antioxidants resveratrol and quercetin, and the antidiabetic metformin, at preventing drug nephroxicity. Our studies clearly show their renoprotective effect at the preclinical level. We are testing these molecules in the clinical setting and developing new nanoformulations which will enhance their solubility and, hence, their bioavailability to prospectively achieve clinical utility.

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Restoring the function of the glutamate-nitric oxide –cGMP pathway by treatments acting on different brain targets restores cognitive function in rats with minimal hepatic encephalopathy

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Abstract

Chronic liver disease (e.g. cirrhosis) affects brain function. There is a high incidence of mild cognitive impairment and psychomotor slowing in patients with cirrhosis. This condition, known as minimal hepatic encephalopathy (MHE) affects more than 2 million people in the European Union and has serious health, social and economic consequences. There are no effective treatments for MHE.

Rat models of MHE reproduce cognitive and motor alterations seen in patients, showing reduced performance in different types of cognitive tests, including learning a conditional discrimination task in a Y maze. We have shown that reduced ability to learn the Y maze task is due to reduced function of the glutamate-nitric oxide (NO)-cGMP pathway in cerebellum, assessed in vivo by microdialysis. This results in reduced formation of cGMP in response to activation of NMDA receptors and impairment of learning ability. We have found that both hyperammonemia and neuroinflammation contribute to impair this pathway. The effect is mediated by enhanced tonic activation of NMDA and GABAA receptors and of MAP-kinase p38. Based on this mechanistic studies, we have designed and tested new therapeutic strategies acting on specific targets in the brain, which have successfully restored the function of the glutamate-NO-cGMP pathway in vivo and learning ability in rats with MHE. This can be achieved by therapeutic treatments using:

a) phosphodiesterase 5 inhibitors (sildenafil, zaprinast), that increase cGMP levels by reducing its degradation
b) extracellular cGMP
c) antagonists of type A GABA receptors (bicuculline)
d) neurosteroids that modulate GABAergic tone (pregnenolone sulfate)
e) inhibitors of cyclooxygenase (ibuprofen) which reduce neuroinflammation
f) inhibitors of MAP- kinase p38 (SB239063), that reduce microglial activation and neuroinflammation
g) Translation of some of these treatments to clinical practice would improve cognitive function, quality of life and life span of patients with cirrhosis and MHE and reduce health systems costs.

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Modeling and simulation the conduit connecting translational medicine with portfolio management

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Abstract

Translational medicine science and the volume of information generated in this field have grown exponentially in the last decade and continue to grow faster every day. This has generated a huge amount of data. The application of

Modeling and Simulation (M&S) in drug development has also grown in the last two decades, but mostly has been limited to analysis of single studies or to analysis of pooled data from several studies. Such application traditionally has been used either to support a new drug application or to make Go/No Go decisions about a given development program. However, rarely M&S has been integrated as a tool in portfolio management based on a quantitative evaluation of all the data in hand (e.g., translational medicine data). In other words, many organizations utilize M&S still as a tool aiding study data analysis or at best a tool to guide a given development program, but not use M&S in portfolio management systematically (the large dashed box shown in the Fig. 1). Therefore, M&S scientists are mostly labeled purely as technical experts rather than strategic leaders who could provide an evidence based portfolio management. This presentation provides short examples of traditional application of M&S at study and program levels, but also presents examples of application of M&S in portfolio management based on Translational Medicine information.

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DNA-methylation and autoantibodies based cancer diagnosis from body fluids

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Abstract

Special focus and aim of our research activities at AIT, the Austrian Institute of Technology, is to define reliable biomarkers suitable for early and non-invasive disease diagnosis from body fluids such as serum/plasma and saliva. Along a selection of research projects, which are described in more detail underneath, we will present and introduce the broad portfolio of high throughput technologies we successfully apply for diagnostic biomarker discovery and validation. As a first show case of successful non-invasive disease biomarker discovery we will present a study where we investigated and compared the genome wide methylation levels of lung cancer patients, patients suffering from lung fibrosis, patients with COPD (chronic obstructive pulmonary disease), and DNA samples derived from healthy lungs. Along this study we could identify specific methylation patterns for each of these lung diseases. After quantitative PCR validation of 240 disease specific methylation markers in the discovery sample set, the 90 top markers were picked and applied for serum testing (n=204). When we applied gradient boosting classification for differential diagnosis of tested lung diseases and healthy controls an AUC value of 0.95 was reached here to separate cancer from all other non-cancer samples whereas in differential diagnosis of healthy-, COPD and fibrosis patients AUC values of 0.71 and 0.49 were obtained for fibrosis, respectively COPD. Thus in case of COPD the presented method may be used to monitor cancer risk within COPD patients. Our second show case comprises a study where we screened cancer patients' sera for tumor-specific antibody profiles using an in-house developed 16k protein-microarray. This methodology, which will be described in detail, enabled us to define different tumor-associated antigen (TAA) classifier panels for the big 4 cancer entities (breast, colon, prostate and lung cancer) which all showed very promising classification successes in distinction of patients versus controls. We will further present preliminary data obtained when comparing serum and saliva auto-antibody profiles of breast-cancer patients and healthy controls.

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Mass spectrometry-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

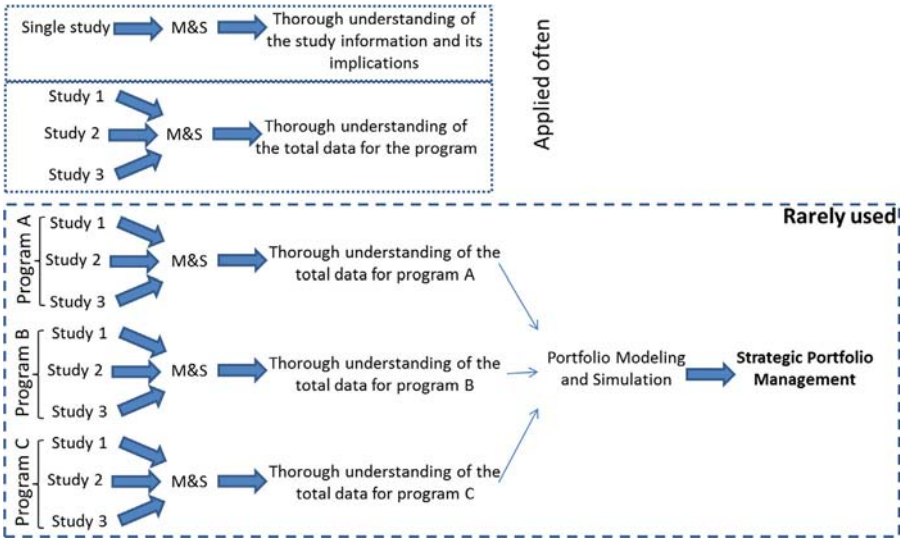

Fig. 1