ABSTRACTS

Abstracts for Invited Lectures:

IL1.

PROTEOMIC STUDY REVEALS PLASMA PROTEIN CHANGES IN CONGENITAL HEART DISEASES AND POTENTIAL CLINICAL SIGNIFICANCE

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Objectives: Congenital heart disease (CHD) is the most common birth defect in newborns. Plasma proteins may often serve as indicators of disease and is a rich source for biomarker discovery but little has been studied in CHD, The present proteomic study examined the hypothesis that plasma proteins may be altered and related to the pathological changes of CHD. Such alternations might be useful in development of biomarkers in the diagnosis and treatment of CHD.
Methods: Differential protein analysis was performed in the plasma of patients with tetralogy of Fallot (TOF), isolated ventricular septal defect (VSD) and normal controls by using two-dimensional electrophoresis (2-DE) and mass spectrometry. Candidate proteins that might be related to disease processes were further confirmed by enzyme-linked immunosorbent assays (ELISA) in the new samples (n=40).
Results: Eighteen differentially expressed protein sports and 10 corresponding proteins or polypeptides were identified by 2-DE and mass spectrometry. Among those, two down-regulated proteins (gelsolin, ficolin-3) has significant clinical relevance. Gelsolin is related to rapid platelet activation and shape changes and ficolin-3 is a recognition molecule in the lectin-pathway of the complement system and plays an important role in innate immunity. These two proteins were further analyzed as candidate proteins for validation and measured by ELISA. The plasma gelsolin (76.3±4.42 vs. 131.80±23.46 μg/ml in control, P=0.025, n=40 in each group) and ficolin-3 (4.93±0.36 vs. 10.58±1.58 μg/ml in control, P=0.001, n=40 in each group) levels in TOF patients were significantly lower than those in normal controls. The ficolin-3 plasma level was also lower in the patients with isolated VSD (5.55±0.34 vs. 10.58±1.58 μg/ml in control, μg/ml, P=0.003, n=40 in each group).
Conclusion: In the present study we have for the first time, by using proteomic methods, demonstrated the plasma protein changes in CHD patients. Our study may reveal the possible reasons for the prolonged bleeding time in TOF patients and the susceptibility to pulmonary infections in patients with CHDs.

IL2.

GENOME-WIDE ASSOCIATION STUDY IN HEART DISEASES: PRINCIPLE AND APPLICATION

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Objective: In the past decade, the sequencing of the human genome provided a route map to catalogue and interpret genetic variation among individuals. The scale of diversity is vast, ranging from microscopically visible variation at the level of individual chromosomes to variation at the deoxyribonucleic acid (DNA) sequence level with nucleotide substitutions, insertions and deletions, including >10 million SNPs (dbSNP, http:www.ncbi.nlm.nih/gov/projects/SNP/). Submicroscopic structural variation, notably copy number variation (CNV), is increasingly recognized and plays a critical role in cardiovascular diseases. We studied patients with tetralogy of Fallot and coronary artery disease with regard to reveal SNPs and CNVs.
Methods: We performed genome-wide CNVs analysis on TOF patients and normal age-matched children using the Affymetrix SNP 6.0 Array (Affy6.0 array). Taqman assay was then performed in TOF patients or age-matched control for validation of the CNVs identified by Affy6.0 array. The further validation was performed by using Tagman qPCR assay. Two to three Taqman probes were designed to detect each of the CNV regions in TOF patients and normal controls. The CNV loci from Taqman assay, which were consistent with the GWAS results, were considered to be the successfully identified CNVs. In coronary artery disease, we studied those with myocardial infarction and arrhythmia.
Results: In 60 tetralogy of Fallot (TOF) patients and 60 age-matched and 870 other controls, we have found more that 20 rate CNVs that containing encoding genes and more that 50 possible SNPs in TOF patients. The validation study has been further performed to identify these CNVs. In coronary artery disease, we studied 100 patients and control with myocardial infarction and arrhythmia. The studies have also identified both CNVs and SNPs.
Conclusions: Our studies have demonstrated that GWAS followed by validation studies may successfully identify disease-causing genes in congenital and coronary artery diseases. In particular, identifying rare CNVs may reveal these disease-causing genes in congenital heart diseases.

ABSTRACTS

Abstracts for Invited Lectures:

IL3.

ARE ALL ARBs CREATED EQUAL FOR BP LOWERING?

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Drugs that inhibit the renin-angiotensin system (RAAS) are the cornerstone of therapy for cardiovascular (CV) and kidney disease risk reduction because they protect against worsening outcomes in the respective target organs. However, there are eight ARBs and they differ in their BP lowering ability and other pharmacodynamics effects. They are all well tolerated however, with the lowest overall adverse effect profile of any of the antihypertensive medications. Recent results from the ONTARGET study have confirmed that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) confer similar cardioprotection, with little to no benefit of the combination in CV disease. For renoprotection, it remains unclear whether one class is superior to another, and dual RAAS blockade does not offer more advantages over single agent blockade. Losartan and Irbesartan are the two ARBs with indications for renal protection and telmisartan the only one FDA approved for use when the patient is ACE intolerant. Azilsartan has the greatest effect on BP lower of any of the ARBs and the only one combined with chlorthalidone, the evidence based diuretic. Given that the FDA has indicated that BP lowering is associated with CV risk reduction using an agent that will insure maximal initial efficacy for BP reduction is warranted.

IL4.

THE SLOWER, THE BETTER

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It has been a long journey since, in the late seventies, the discovery of I_f current in sino-atrial node till ivabradine opens the path to an innovative treatment for patients with Angina 20 years later. Resting heart rate is considered today as a major cardiovascular risk factor for CAD and Heart Failure. The SHIfT study demonstrated the beneficial effect of ivabradine on outcomes in heart failure patients leading to new treatment guidelines in Europe.

IL5.

DEVELOPMENT OF STEM CELL PRODUCT – "CELLGRAM"

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The clinical application of the stem cell technology began with the first bone marrow transplantation in 1956. This success led to the quantitative and qualitative growth of stem cell therapy through bone marrow transplantation. In the 1990's, the marrow stromal stem cell, one of the stem cells in the bone marrow, began to be utilized in various ways. Of course, the study of the properties of this stem cell has begun a long time ago. In Korea, the first attempt was made in 1999 to overcome the mismatch of histocompatibility by using the mesenchymal stem cell cultured from the donor's bone marrow for bone marrow transplantation. In Korea, however, as the government announced the definition of the cell therapy product in 2002, the regulation set by the Korea Food and Drug Administration (KFDA) began, and since then, all cell therapy products have needed to be licensed by the government. Most of the leading researchers of the development of stem cell therapeutics were doctors of that time. They established their own companies as a means to go against the government regulation, and 'Pharmicell' was one of them. Our company was established in 2002, and we prepared clinical trials that were compatible with this regulation. Developers and government officials needed to have a process for solving many difficult problems rationally. Stem cell therapy products consist of live cells. Established methods for manufacturing and quality control which have been suggested by the government are not proper for stem cell products. For example, the potency test is very important. It must include reproducible quantitative methods that can represent the effect of the drugs. In 2005 after 4 years of preparation, the application from Pharmicell for the clinical trial was submitted in regard to the heart disease. The KFDA conducted preclinical study prior to the clinical trial which means that the KFDA was willing to apply the fast track to medical products with these characteristics. The preclinical study clarified the procedure and objective of the clinical trial to minimize errors of the clinical trial, thus recognizing the results of clinical trials that were conducted in this way. It is similar to the special protocol assessment (SPA) program of FDA in the USA. As the IND phase III study had already been permitted for the ischemic stroke, phase I for AMI was exempted, and phase II and III were permitted at the same time. The clinical trial began in 2006. The mesenchymal stem cell cultured from the autologous bone marrow was infused once intracoronarily. The follow-up period is 6 months, and the primary end point was the improvement of left ventricular ejection fraction, and the measurement method was the radioisotope test, SPECT. At that time, MRI could not be used as it was yet to be developed. A randomized, open labeled study was conducted. Six months later no cardiac death or major toxicity related to medication was found, and the SPECT test confirmed that the left ventricular ejection fraction increased by 5.9% as compared to the pretreatment status. Patients who succeeded in reperfusion within 6 hours after the AMI occurred accounted for 60% of all patients. These patients' left ventricular ejection fraction increased by 8.3%, and the difference was statistically very significant. These results indicated the possibility that, even though the stem cell product was injected into the heart 4 weeks after the myocardial injury, the injured myocardium could be recovered. In other words, the function of the myocardium around the necrosis that is not completely disappeared can be improved after the injection of our stem cell product. This finding supports the theory that the anti-inflammatory effects, stem cell homing in tissues, angiogenesis and fibrolysis act together rather than the stem cell product replacing tissues. The long-term follow-up is now underway, five years after the start of the clinical trial. Soon, we will be able to clarify the long-term effects or side-effects. At the moment, our company (Pharmicell Co., Ltd.) is conducting clinical trials for ischemic stroke (IND III) and spinal cord injury (IND II/III). By 2014, we will be able to release the results of the clinical trials.

ABSTRACTS

Abstracts for Invited Lectures:

IL6.

MECHANISMS OF SOMATIC CELL REPROGRAMMING

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The generation of induced pluripotent stem cells (iPSCs) by defined exogenous transcription factors represents a model system to understand the epigenetic basis of mammalian cell fate determination and has remarkable implications for regenerative medicine and disease modeling_ENREF_8. At present, reprogramming is viewed as an inefficient multistep procedure in which a series of exogenous (the extracellular millieu) and endogenous (the somatic cell genetic program) barriers must be overcome to trigger the transition from intermediate states to pluripotency_ENREF_13_ENREF_13. Improved understanding of the molecular basis of these barriers and how they are suppressed is relevant because it may facilitate higher fidelity of the conversion through experimental manipulation. My talk will focus on the work our lab has done in recent years to understand the mechanisms of mouse iPSC generation.