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A1 Translational medicine in China: improving public health

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China’s national 12th Five-Year Plan (2011-2015) stated that, by 2015, China should increase the average life expectancy by one year (estimated to reach 74.5 years old) relative to that of 2010. Additionally, China’s new around of health reform was initiated in 2009. Translational medicine, which is moving basic discoveries in the laboratories into human studies to promote new preventions, diagnostics, treatments and cures, is the engine to the health care reform and the proposed life expectancy increase. The potential of translational medicine in China has never been greater.

Starting in 2005, translational research centers began to spontaneously appear in China. Since 2009, more and more centers have been emerged. Currently, translational centers are founded most independently by local cities, universities and hospitals. There’s a lack of policy support and guidance, funding support, resource standardization and sharing. We are still in the exploratory stage. To find better diagnostics and treatments, China’s translational medicine focuses more on innovations and how to push laboratory discoveries to clinical practice. Guided by the concept of “cure a disease before its onset”, China’s translational medicine also puts more effort on public health. As part of translational medicine initiative, China already supported many translational medicine projects during the 11th and 12th Five-Year plans through National High-Tech R&D Program of China (863 Program), 973 project and National Nature Science Foundation. As a developing country with 1.3 billion people, China faces many challenges to promote translational medicine and health care reform.

♦ How to combine translational medicine with basic research, clinical medicine and public health?
♦ How does translational medicine better serve China health care reform?
♦ How to further develop traditional Chinese medicine (TCM) through translational medicine?
♦ How to evaluate translational centers and translational medicine programs?

To build a modern health service system and better serve the society, China should list digital health as a priority to develop. Additionally, I would like to suggest that more emphasis should be placed on the establishment of translational medicine-related policies, laws and regulations, resource standardization and sharing. Looking forward, translational medicine is a revolutionary opportunity for China.

A2 New infrastructure to support clinical translational research at the US National Institutes of Health: role of the NIH Clinical Center

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The development of new drugs and devices is expensive with long timelines and high rate of failure. The director of NIH is concerned with these issues and has made reengineering the translational sciences a top priority [1]. One outcome of the planning has been the creation of a new NIH National Center for Advancing Translational Sciences (NCATS) [2]. NCATS has three major goals: reengineering translational sciences, creating a network of clinical and translational science awardees (CTSAs) at 60 academic institutions in the US and supporting research on rare diseases and therapeutics. Recent novel approaches to technology development under NCATS leadership include designing new “organ chips” and use of induced pluripotent stem cells (iPS cells) to screen for drug toxicity. Another project is the 1000 genomes project which estimated that human genomes typically contain about 100 genuine loss of function variants with about 20 genes completely inactivated but without obvious disease consequence. In some cases the loss of function variants are associated but with protection from disease thereby providing new targets for drug discovery [3]. Another effort to reengineer drug discovery is a drug repurposing project that has resulted in partnerships with 8 pharmaceutical companies who recently announced 58 compounds available for repurposing studies [4]. The Office of Rare Diseases Research has moved into NCATS and is working to establish partnerships throughout the world for the study of rare diseases. The Office of Rare Diseases Research continues to work on the development of novel treatment strategies. The NIH Clinical Center, the largest hospital in the world totally dedicated to clinical research, will work closely with NCATS. A new vision for the NIH Clinical Center will be “to open its doors” to outside investigators through new partnerships between extramural scientists and investigators in the NIH intramural program. These partnerships will include access to the special technical resources at the Clinical Center, access to the clinical research training programs including the NIH curriculum for clinical research training, courses designed to demystify medicine for PhDs, as well as a sabbatical in clinical research.

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management. In addition, the Clinical Center will make available new tools it has developed for protocol management and information technology (see http://www.cc.nih.gov/ for review of the Clinical Center programs). The many approaches NIH is implementing to improve translational research will be monitored closely for success.

References

A3
Developing innovative targeted therapies for China
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Background: MedImmune is the biologics business unit of AstraZeneca with a mission of helping patients with significant unmet medical need by developing innovative medicines. MedImmune has a rich pipeline across five therapeutic areas including oncology, respiratory, inflammatory and autoimmunity, infectious diseases, neurosciences, cardiovascular and gastrointestinal diseases. To realize our vision of personalized healthcare—treating the right patient with the right drug at the right dose, we are applying cutting edge tools such as next-gen sequencing, circulating tumor cells and advanced PK/PD modelling across the pipeline.

Materials and methods: Fundamental to our goal of developing personalized healthcare is gaining deep understanding of diseases across different populations and specifically in Asians. To this end, we have formed partnerships with Chinese academic institutions, government agencies and industry partners, and have a history of working with scientists/physicians in China to develop medications that target the Asian/Chinese patient population. For example, the AstraZeneca product IRESSA (gefitinib), is already frontline therapy in China for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with an activating mutation in the EGFR gene.

Results: Most recently we set up an exciting collaboration with the Shanghai Chest and Renji Hospitals to develop a rich annotated database of lung cancer and hepatocellular cancer patient samples to aid in identifying novel drug targets and developing therapeutic strategies to aid patients. This presentation will provide examples in our pipeline that give us reasons to believe in such approaches, e.g. a type I interferon gene signature for an anti-IFN-alpha or anti-IFNAR monoclonal antibody in patients with systemic lupus erythematosus.

Conclusions: MedImmune is committed to helping Chinese patients with significant unmet medical need and we believe collaborations with leading Chinese PIs and innovation are key to our mission.

A4
Rationale for key elements of Sino-American collaboration in clinical research
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When new scientific discoveries are properly evaluated within the translational research continuum and definitive evidence is generated regarding the balance of benefits and risks associated with therapeutic interventions, dramatic health improvements are seen both for individuals and populations. Until recently, however, technological limitations dictated that definitive evidence could be generated for only a fraction of interventions under development, because clinical investigation was limited by geography and access to expertise. Today, less than 15% of major medical decisions are informed by high-quality evidence [1]. Furthermore, increasing knowledge about the roles played by genetics and practice environments demonstrates that we must develop multinational studies to generate evidence relevant to particular biological and cultural contexts [2]. It is now time to begin to plan for a global learning health system.

Modern informatics and information technology have enabled the sharing of research data without regard to geographic boundaries. These new capabilities expand the concept of human biomedical research from an activity conducted in a limited number of specialized centers to a global activity accessible to all patient populations and qualified practitioners [3]. With appropriate informatics support, shared protocols, and facilitative cultural elements, common diseases can be studied on a larger scale and clinical trials in rare diseases will be able to accrue adequate sample sizes, enabling valid inferences to be drawn. In essence, the limits on knowledge generation will henceforth be determined by two key factors: (1) the number of qualified individuals in the clinical and translational research workforce and (2) the degree to which regulatory and funding sources encourage broad-scale collaboration.

Examples of therapeutic areas where progress could be accelerated include diabetes (which affects global populations in large numbers), congenital heart disease (which affects 1% of all global populations) and Pompe disease (a rare disease with a new effective therapy). In each case, collaborative studies between China and the United States—two of the world’s largest funders of biomedical research—could provide the example to stimulate similar activity on a global scale.

We propose that five key programs specific to clinical and translational research [4] (Table 1) will need to train and educate a vast workforce over the coming decade in order to capitalize on these technological advances.

Table 1 (abstract A4) Key programs for clinical & translational research

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<th>Clinical research training</th>
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<td>Epidemiology and global health</td>
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References

A5
Clinical and translational medicine in Europe – horizon 2020 and beyond
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Background: Health providers and thereby academy and industry is challenged by gradually increasing demands from not at least an ageing population, including increases in cancer, cardiovascular and neurological diseases, diabetes, and complex disease patterns with multimorbidity. At the same time, economical restraints will not allow the society to increase resources spent on health care.
Methods: The effects of the ageing population, changes in lifestyle (overweight, obesity, poor dietary habits, lack of physical activity) needs to be dealt with. Demands from patients are to improve quality of care and adding life to years instead of just adding to your life. To provide European citizens with lifelong health and wellbeing, visions for horizon 2020 (and beyond) has been performed (Copenhagen Research Forum). The global evolution in biomedicine will provide access to new technologies that will require implementation. At the same time, as health care is a factor for investment including industry, education and training is also a possibility to create innovation and work in research and improved health.

Results: Preventive measures will future on have large impact on the health care situation and both clinical and translational research, including e.g. lifestyle, food intake, environmental factors. The willingness from the society to spend more money on health care will be limited. The ageing population will face advanced home care using remote health monitoring, smart phones with medical apps etc, rendering communication with health care providers. Bioinformatics, advanced diagnostics, novel combinations of therapies and improved knowledge on the individual biological phenotypes (genomics, proteomics, metabolomic profiles) will drive diagnosis and treatment towards personalized medicine. The previously long established “one-size fits all” concept will be replaced by individualized and tailored management, i.e. a true paradigm shift. Biobanks will be of substantial help, providing e.g. novel biomarkers for diagnosis and therapy. Novel technologies bridging the fields of medicine and technology/ chemistry will provide us with e.g. nanomedicine, both for imaging and treatment, as well as artificial, bioartificial and tissue engineered organs.

Conclusions: The economical restraints future on will force us to translational and clinical research towards personalized medicine (diagnostics and treatment) and thereby steering efficient therapy e.g. with companion diagnostics and increasing cost effectiveness in health care. This paradigm shift will demand academia and industry to provide completely novel tools and thereby possibilities for innovation and potential commercialization within life science in close collaboration between health care, academia, and industry, focusing on the patient’s need.

A6
Advanced cardiovascular imaging: from patients to populations
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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in both men and women in developed nations. Gender and population differences in the prevalence, presentation and prognosis of CVD, as well as in the role of traditional risk factors in determining its risk have been increasingly recognized. Thus, multi-ethnic studies are necessary to fully understand the basis for optimal prevention and management of CVD. Cardiovascular imaging is a well-validated form of non-invasive diagnostic and prognostic testing. Coronary artery calcium (CAC), carotid intima-media thickness (IMT), and elevated left ventricular (LV) mass and geometry as assessed by cardiac magnetic resonance (CMR) offer highly specific phenotype data on the extend of CVD. Due to their high sensitivity, these modalities are being increased used to characterize CVD risk in clinically asymptomatic individuals. Noninvasive imaging of the heart and blood vessels has the potential to replace invasive angiography for the evaluation of ischemic and nonischemic cardiomyopathy. Computed Tomography (CT) angiography allows coronary vessels to be accurately assessed for stenosis. Magnetic resonance imaging (MRI) at 1.5 Tesla and 3 Tesla offers superior evaluation of myocardial structure, function and perfusion, as well as atherosclerotic plaque and tissue composition. In summary, new imaging techniques for the heart and blood vessels offer the potential for advanced tools for patient diagnosis. The application of advanced cardiac CT and MRI to study numbers of patients is underway in epidemiologic studies to help understand risk factors and genetic relationships [1,2].

References

A7
The somatic genetic architecture of human cancer: heterogeneity and the challenges for translational medicine
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Advances in sequencing technology have led to an unprecedented opportunity to characterize the genomes of human cancers. Our work has been focused on characterizing intra- and intertumoral heterogeneity in several tumor types. Work on breast cancer has revealed substantial complexity of operative cancer genes, with marked diversity between cancers revealed by exome sequencing. Further work in both renal and breast cancer has begun to define the architecture of intratumoral heterogeneity – revealing evidence for substantial branched and, in some cases, convergent evolution within the same tumors. These data and others, particularly as they relate to the challenges of translation and genomics-base medicine will be discussed.

A8
Targeting androgen receptor as a new potential therapeutic approach to battle tobacco carcinogens-induced non-small cell lung cancer
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Background: Lung cancer is the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancers. The incidence and prognosis in NSCLC demonstrates gender difference [1,2]; therefore, sex steroids and/or their receptors may play important roles during lung tumorigenesis and cancer progression. In our previous investigation, cell proliferation, migration, invasion, and tumor formation were inhibited by shRNA interference of androgen receptor (AR) in non-small cell lung cancer (NSCLC) cells lines. The expressions of cyclin D1 also decreased to less than 50% after AR knockdown. However, the roles of androgen receptor in treatment of NSCLC are still controversial.

Materials and methods: To validate therapeutic effects of targeting androgen receptor on NSCLC, initially we administered 8 doses of tobacco carcinogens, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK) and benzo[a]pyrene (BaP), to induce lung tumorigenesis in female A/JB6.129-lox-lox-Tg(Mx1-cre)1Cgn mice when they were 5 weeks old. In the next step, targeted AR gene disruption was induced with 6 doses of polyinosinic: polyricydlic acid (poly:C) intraperitoneal injection in Mx1-cre+ mice when they were 26 weeks old. We also performed 6 doses of normal saline injection to NNK+BaP-treated female A/JB6.129-lox-lox-Tg(Mx1-cre)1Cgn mice in the same time point for the control group. Finally, all mice were sacrificed in 31 weeks old and total lung nodules and tumor larger than 1 mm in diameter were calculated under dissection microscope.

Results: In immunohistochemical studies, AR expression in lung was deficient in Mx1-cre+ mice after poly:C treatment. Pulmonary expression of cyclin D1 was also suppressed in poly:C treated Mx1-cre+ mice. The number of total nodules in bilateral lungs from poly:C treated Mx1-cre+ mice (n = 8) was 7.375 ± 5.476 (mean ± SE). In comparison, the total number of lung nodules from normal saline treated Mx1-cre+ mice (n = 8) was 14.375 ± 7.269 (p = 0.0456, 95% CIs on the mean = 9.235 to 19.515). The number of large nodules (>1 mm in diameter) in bilateral lungs was 1.375 ± 1.188 in poly:C treated Mx1-cre+ mice and 6.25 ± 4.464 in normal saline treated Mx1-cre+ control mice (p = 0.00492, 95% CIs on the mean = 3.093 to 9.407). Deficient AR expression through inducible disruption of Ar
gene could reduce lung tumor multiplicity and further inhibit tumor progression (decrease tumor volume) in tobacco carcinogens-induced lung carcinogenesis model. 

Conclusions: Our data indicate that androgen receptor warrants consideration as a novel therapeutic target for NSCLC in a clinical lung cancer treatment trial.

References:  

A9 Molecular genetic study in hepatocellular carcinoma: microRNA deregulation in multistep hepatocarcinogenesis  
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Deregulation of microRNAs (miRNAs) plays an important role in human carcinogenesis. However, miRNA deregulation in the pre-malignant lesions and expression changes during multistep hepatocarcinogenesis remain elusive. We investigated the expression changes of seven cancer-related miRNAs during the early stages of HBV-related hepatocarcinogenesis, including dysplastic nodules (DN), small hepatocellular carcinomas (HCCs), and their corresponding non-tumorous livers. We found that down-regulation of miR-145 and miR-199b and up-regulation of miR-224 were frequently observed in pre-malignant DN and these changes persisted throughout HCC development. Restoration of miR-145 in both HepG2 and Hep3B HCC cells significantly inhibited cell proliferation and reduced cell migration and cell invasion. Furthermore, these inhibitory functions of miR-145 could be substantially reduced by anti-miR-145 inhibitor. Our results showed that miRNA deregulation was an early event and accumulated throughout the various steps of HBV-associated hepatocarcinogenesis. On the other hand, we investigated the mechanisms of HCC metastasis and identified an antimetastatic miRNA, miR-139, that is down-regulated in human HCC samples. Down-regulation of miR-139 in HCC was associated with poor prognosis of patients and features of metastatic tumors, including venous invasion, microsatellite formation, absence of tumor encapsulation, and reduced differentiation. miR-145 expression was reduced in metastatic HCC tumors as compared with primary tumors. Overexpression of miR-139 in HCC cells significantly reduced cell migration and invasion in vitro and the incidence and severity of lung metastasis from orthotopic liver tumors in mice. miR-139 interacted with the 3' untranslated region of Rho-kinase 2 (ROCK2) and reduced its expression in HCC cells. Levels of miR-139 correlated inversely with ROCK2 protein in human HCC samples. Expanding insight into the keys of miRNA dysregulation involved in HCC metastasis will yield important clues to our understanding of the complicated mechanisms underlying HCC progression and may enhance the development of new therapeutic regimens in treating advanced HCCs.

Presence of tumor thrombi in the portal veins (venous metastases) is a clinicopathological feature of metastatic HCCs. By analyzing the miRNA expression profiles of non-tumorous livers, primary HCCs, and venous metastases in the same livers from 20 HCC patients with low density microarray (LDA), we identified the precise alterations of miRNA expression from non-tumorous livers to primary HCCs and venous metastases globally. Non-tumorous livers were distinctly segregated from primary HCCs and venous metastases, whereas no discernible difference in the expression pattern could be found between primary HCCs and venous metastases. However, a marked global reduction of miRNA expression levels was detected in venous metastases, as compared with primary HCCs. These data suggest that miRNA deregulation may be an early event in liver carcinogenesis and the later global miRNA down-regulation aggravates the pre-existing miRNA deregulation to further promote HCC metastasis. Our study has enriched the current understanding of the deregulation of miRNAs in HCC progression and highlighted the sequential and distinctive alterations of miRNA expression in primary HCC and venous metastases formation.

A10 Prevention for colorectal cancer: from basic research to clinical study  
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Background: Colorectal cancer (CRC) is the third most common cancer in world. Both incidence and mortality of CRC in China are increasing. Pooled individual data indicated that the recurrent rate of colorectal adenoma (CRA) underwent the polyphey is high.  
Methods: Papers in major gastroenterology journals published were retrieved from MEDLINE. The data from my group and other medical centers were also analyzed.  
Results: Folic acid (FA) and butyrate suppress the cell proliferation in CRC cell lines and in mouse. The tumor incidence in DMM group and DMM + butyrate group were 90% and 30%, respectively. And the subgroup of providing FA without precancerous lesions was more effective than that with precancerous lesions. The data from RCT, Cohort and case-control study showed that many studies report that aspirin decrease the incidence and mortality of CRC in average-risk persons, aspirin and Celecoxib prevent the initial and recurrence of advanced CRA. However, NSAID are ulcerogenic to the stomach and duodenum and lead to a threefold to 10fold increase in ulcer complications, hospitalisation, and death from ulcer disease. Followed along with the increasing the dose of cox2 inhibitors, although prevention effect increased, while the serious cardiovascular events was increased. Many studies indicated that a dose-response inverse association between dietary folate intake and risk of colon cancer. However, the result from clinical trial published in JAMA 2007 showed that FA at 1mg/d does not reduce CRA recurrent risk, and was associated with higher risks of having 3 or more adenomas and of non CRC. In fact, the FA prevention effect is associated with FA concentration at baseline. For patients who’s FA concentration lower than 7.5ng/mL, FA decrease the recurrence rate of CRA, but not patient who’s FA high than 7.5 ng/ml. A report published in Am J Clin Nutr indicated that folate intake and risk of CRC and CRA: modification by time. The association between fiber and colorectal neoplasia has been intensively investigated. However, in some studies this topic remains controversial. Many studies showed that calcium and vitamin D reduce risk of CRC. We also found that calcium prevent the recurrence of sporadic CRA.  
Conclusions: The primary prevention for CRC contains the primary and secondary prevention for CRA. Primary prevention also is to reduce the incidence of CRA.

A11 Translational research to practice for gastric cancer: molecular classification and outcome prediction based on genomic and proteomic profiling  
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Background: We have generated genomic and proteomic profiling to approach cellular and molecular mechanism and to discover diagnostic and predictive biomarkers of gastric and colorectal cancer. Based on these gene expression profiles, we explored the characteristics of molecular changes and its potential for clinical significances.
Materials and methods: As our present data and systemic analyses for gene expression pattern, pathway distribution, gene function category, biosignature and clinical significance shown, we have been able to document the entire gene expression profiles for intestinal- and diffuse-type gastric cancer (GC) and normal appearing tissues (NATs) matched tumors. A group of specific or typical genes were identified as having dramatic changes in tumors and NATs compared with the verified normal samples. Among these genes, at least three gene sets were analyzed using pathway analysis tools and integrated with biological assay data to construct a network for GC carcinogenesis.

Results: Our data show that these genes are involved in several well-studied signaling pathways associated with development and progression of GC. Our results indicated that alterations of MMP11, MT2A, p42.3, CyR61 and GKN1 at mRNA and protein level were consistently detected in GC cell lines and primary tumors compared with matched normal tissues. Importantly, serum MMP11 levels were also significantly elevated in GC patients compared with those of the control subjects, and the positive expression was well correlated with metastasis and recurrence in GC patients. As its pilot study, we have generated primary data of its genomic alterations, in combination and comparison with the gene expression profiles. Dramatic correlations have been observed between the gene expression profiles and DNA Copy Number Variations (CNVs), with statistically significant differences between tumors of Stages I-II and III-IV GC. We have also defined a group of specific gene or mRNA alterations, which could be associated with metastasis and recurrence in GC patient.

Conclusions: Taking together, we have been the first to provide a systematic analysis for comprehensive gene expression profile integrated with microRNA, genomic or proteomic analysis for gastric cancer. Additionally, we have defined a group of genes associated with development and prognosis in gastric cancer.

A12
PHC: the future of oncology drug development
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Journal of Translational Medicine 2012, 10(Suppl 2):A12

Background: Major investments in basic science have created an opportunity for significant progress in clinical medicine. Moleculary targeted therapies aim to interfere with molecular mechanisms, selectively involved in carcinogenesis and tumor growth in order to optimize the efficacy and minimize the side effects of anticancer treatment. Moving from concept to clinical use requires basic, translational, and regulatory science. Today, about 10% of labels for FDA-approved drugs contain pharmacogenomic information — a substantial increase since the 1990s but hardly the limit of the possibilities for this aspect of personalized medicine.

Materials and methods: There has been an explosion in the number of promising markers but significant gap exists in independent analysis of the validity of the tests used to identify them in biologic specimens. The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies.

Results: In this presentation, case examples of how MedImmune/AstraZeneca incorporate personalized medicine/molecular diagnostic into clinical development to ensure targeted therapeutics successfully reach the right patient population will be discussed. These examples will illustrate how close cooperation among basic science, translational, clinical and regulatory departments together with partnerships with diagnostic companies are needed to reduce the dream of personalized healthcare into practice.

Conclusions: By identifying the right patient population at the outset of the clinical development process we hope to improve the probability of success of oncology clinical trials, which is an urgent requirement across the industry, but especially for cancer patients with significant unmet need.

Acknowledgements: Koustubh Ranade, Jiaqi Huang, and Brandon Higgs contribute to the abstract and work discussed in the presentation.

A13
Translational medicine research on early detection and early diagnosis of colorectal cancer in China
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Journal of Translational Medicine 2012, 10(Suppl 2):A13

Background: Colorectal cancer (CRC) is the most common cancer in China. The incidence of CRC is increasing rapidly. The early detection and early diagnosis is the effective way to decreasing the mortality and increasing the survival rate.

Materials and methods: From 2007, a CRC screening program was begun in three cities (Hangzhou, Haerbing, and Shanghai city, aimed at finding more early CRC cases and premalignant lesions such as adenoma. The two steps screening model was applied. As the primary screening, the Simultaneous iFOBT (immunochemical Fecal Occult Blood Testing) and high risk factors questionnaire investigation (HRFQ) will be employed for selection the high risk population from target population. Then the high risk population will be further selected by colonoscopy.

Results: The compliance of the two steps screening model was only 34.88% (1650/4730) in city target. The overall positive rate in the first screening stage was 13.5% (4,730 of 35,037). In the second stage, the positive rate of total colorectal neoplasm was 27.27% (450/1650) in the total study population. The detected rates of cancer, adenoma, non-adenomatous polyps, and advanced neoplasm were 13%.

Conclusions: The combining iFOBT and HRFQ as primary screening methods is an efficient CRC screening strategy in economically and medically underserved population. But the novel early CRC markers were still needed to improve the compliance of the screening program.

A14
Understanding hepatotoxicity – from patients to mice to computer
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Drug Induced Liver Injury (DILI) remains the major adverse drug event that leads to termination of clinical development programs and regulatory actions including failure to approve for marketing, restricted indications, and withdrawal from the marketplace. The type of DILI that is most problematic is “idiosyncratic” meaning that only a very small fraction of treated patients are susceptible to the DILI. Current preclinical models, even “humanized” ones, do not reliably identify molecules that have this liability and, conversely predict liabilities in molecule that are in fact quite safe for the liver. For example, current preclinical testing does not detect the DILI potential of xymelagatran, a drug withdrawn from worldwide markets due to idiosyncratic hepatotoxicity but would predict a high liver risk for acetaminophen (paracetamol) even when taken as directed. Reliable preclinical testing will probably not be developed until there is greater understanding of the mechanisms underlying DILI. Reasoning that the best models to study DILI are the people who have actually experienced it, we are capitalizing on the resources of the US Drug-Induced Liver Injury Network (DILIN-supported by the National Institutes of Health) that is collecting genomic DNA and other biospecimens from patients who have experienced DILI. In addition to genetic studies, we are partnering with Cellular Dynamics International to reprogram induced pluripotent stem cells from DILIN subjects in whom we have collected exomic DNA sequence with the goal of producing patient-specific liver cultures, and ultimately, humanized mice. We are also partnering with the Shanghai Centers for Disease Control to prospectively collect a variety of biospecimens, including whole blood for transcriptome analysis, from patients treated for active tuberculosis as part of a larger biomarker
Discovery initiative. We are using panels of inbred mice to mimic patient population genetic diversity and to identify genes and pathways that may underlie DILI susceptibility in patients. Finally, we have established the DILIsim Initiative which is a public-private partnership that is building a computer model to synthesize the rapidly accumulating data with the goal of predicting DILI liability in drug candidates. DILIsim involves 10 pharmaceutical companies and the Food and Drug Administration.

A15
Circulating microRNA, secreted microRNA and exogenous plant microRNA
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Dysregulated expression of microRNAs (miRNAs) in various tissues has been associated with a variety of diseases, including cancers. Here we demonstrate that miRNAs are present in the serum and plasma of humans and other animals such as mice, rats, bovine fetuses, calves and horses. The levels of miRNAs in serum are stable, reproducible, and consistent among individuals of the same species. Employing Solexa, we sequenced all serum miRNAs of healthy Chinese subjects and found over 100 and 91 serum miRNAs in male and female subjects, respectively. We also identified specific expression patterns of serum miRNAs for lung cancer, colorectal cancer and diabetes, providing evidence that serum miRNAs contain fingerprints for various diseases. Through these analyses, we conclude that serum miRNAs can serve as potential biomarkers for the detection of various cancers and other diseases.

Here, we also report that secreted miRNAs can serve as novel signaling molecules mediating intercellular communication. In human blood cells and cultured THP-1 cells, miR-150 was selectively packaged into microvesicles (MVs) and actively secreted. THP-1-derived MVs rapidly entered and delivered miR-150 into human microvascular endothelial cells (HMEC-1), and elevated exogenous miR-150 delivered from MVs effectively reduced c-Myc expression and enhanced cell migration. In vivo studies confirmed that intravenous injection of THP-1 MVs significantly increased the level of miR-150 in mouse blood vessels. MVs isolated from the plasma of patients with atherosclerosis contained higher levels of miR-150, and they more effectively promoted HMEC-1 cell migration than MVs from healthy donors. These results demonstrate that cells actively secrete miRNAs and deliver them to specific recipient cells where the exogenous miRNAs can regulate target gene expression and recipient cell function.

A16
Susceptible genes of type 2 diabetes and their disease predictive power in Chinese population
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Type 2 diabetes mellitus is influenced by the environmental factors and genetic factors. Due to the heterogeneity in environmental factors as well as genetic background, the susceptibility of type 2 diabetes mellitus in different ethnic populations is totally different, with low susceptibility in Caucasians, while modest susceptibility in Chinese Hans. The recent success of genetics have identified 50 susceptible genes of type 2 diabetes in the Caucasians by biology candidate study, linkage study as well as genome-wide association study, among which some loci such as KCNJ11, TCF7L2, TCF2 genes have been replicated successfully in our Chinese Hans populations with the odds ratio (OR) ranging from 1.41-1.31. Besides, by replicating the susceptible genes specific for the East Asian, 6 loci showed significance in our Chinese samples, with KCNQ1 showing the strongest association with type 2 diabetes. Furthermore, we have been searching for new susceptibility genes in Han Chinese. We also performed a positional cloning study and found that one of the nominal associations was located in the gene NOS1AP. We also used GWAS to identify susceptible genes of the Chinese and identified eight novel hits by collaboration with East Asian groups. However, although nearly 50 susceptible genes for type 2 diabetes were identified so far, the prediction effects were still limited. Thus the utility of both genetic and environmental factors will be worthy to explore in the disease prediction.

A17
Metabolic profiling of human colorectal cancer: a top-down approach to translational cancer research
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Tumor cells exhibit distinct metabolic phenotypes that are essential for them to sustain higher proliferative rates and resist some cell death signals, altering the flux along key metabolic pathways, such as glycolysis and gluconeogenesis. When used as a translational research tool, metabolomics enables the discrimination of distinct metabolic profiles and metabolite markers noninvasively in vivo that correlate to pathological stages and different responses to treatment modalities. Cancer metabolomics research aims at evaluating and predicting pathophysiological changes of cancer patients by investigating metabolic signatures in body fluids or tissues, which are influenced by genetics, epigenetics, environmental exposures, diet, and behavior. A particular advantage of metabolomics is that it represents a top-down tactic in that all of the molecules detected are interrogated, providing a global picture of dynamic metabolic changes involving key markers and pathways that were not already associated with carcinogenesis.

We describe here our studies with mass spectrometry based metabolomic profiling of serum, urine and tissue samples from colorectal cancer (CRC) patients. The metabolic profile of CRC involves several significantly altered pathways, including increased glycolysis and an impaired TCA cycle, gluconeogenesis, down-regulated urea cycle, dysregulated tryptophan, nucleotides, carnitine, and choline metabolism, and an significantly altered gut microbial-host co-metabolism. Our experimental results highlight the potential for the metabolic approach to have a multitude of uses in oncology, including the early detection and diagnosis of cancer and as both a predictive and pharmacodynamic marker of therapeutic effect.

A18
Systems pharmacology and drug repositioning—an integrated approach to metabolic diseases
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The discovery of new therapeutics is highly risky endeavor. Current estimates show the average timeline from early discovery to market is greater than twelve years at a cost of over $1 billion per each new NCE. The lack of translation from pre-clinic to clinic has been identified as a major bottleneck. This has led to the question of how we can improve the probability of success in drug discovery and development. One approach is to use a systems pharmacology approach to provide a comprehensive phenotype approach to disease and potential therapeutics vs. the reductionist approach which was a dominant approach the last 20 years. This comprehensive phenotypic approach or, systems pharmacology, can also be applied to phenol typing marketed and failed therapeutics as well as the new therapeutics progressing from candidate selection to Phase II. Statistics show that from 2007-09, 30-40% of drugs or biologics that were approved or launched for the first time in the US were either drugs repositioned for new indications, reformulations or new combinations of existing drugs. The identification of new indications for failed or approved therapeutics has been referred to as drug repurposing or drug repositioning. Historically, this repositioning has come from serendipitous discoveries in late stage clinical
trials or post-approval. Examples include Viagra, Thalidomide, and Gleevac. Using an integrated approach through the application of systems biology technologies for in vitro and in vivo pharmacology studies provides the opportunity to move drug repositioning to earlier stages in drug development and apply a more deterministic vs. serendipitous approach to identify new indications from late stage lead discovery to Phase II studies. This talk focuses on strategies, tactics, and techniques employed to develop a systems pharmacology approach to identify and validate new indications. Examples will be provided demonstrating success at the lead, candidate, and failed assets as well as potential new indications for marketed therapeutics.

A19
Pharmacogenomics in type 2 diabetes management: towards personalized medicine
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There is inter-individual variability in the responses to anti-diabetic treatments, partly due to genetic factors involved in drug absorption, distribution, metabolism and target. The identification of genetic markers related to drug reaction can help physicians with the decisions of drug selection, dose titration, treatment duration, and avoidance of adverse drug reactions. We focused on the effects of susceptibility genes for T2D on anti-diabetic drugs' efficacy. With respect to repaglinide, genetic variants at multiple loci such as CYP2C8, SLCO1B1, KCNJ11, TCF7L2 and SLC30A8 affect either its pharmacokinetics or pharmacodynamics. We also made some efforts on pharmacogenetic studies of repaglinide efficacy. We recruited a total of 104 Chinese patients with type 2 diabetes and with no history of prior antidiabetic medications, to whom subsequent repaglinide monotherapy with a 48-week follow-up was applied. Based on studies on this cohort, genetic variations at KCNJ11, ABCG8, NOS1AP and KCNQ1 were found to be associated with repaglinide efficacy. Moreover, we also focused on investigations into possible genetic factors for rosiglitazone efficacy, and have already suggested effects of ABCA1 and SLC30A8 variants on the response to rosiglitazone treatment. In spite of all these advances in the field of pharmacogenetics of type 2 diabetes, the pace of clinical application of these findings is rather slow. Consequently, more researches especially randomized clinical trials into the practical utility should be conducted.

A20
Hypoxia in obesity - from bench to bedside
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It is generally accepted that hypoxia is related to sleep apnea in obesity. This concept has been changed since the report of hypoxia response in adipose tissue of obese mice by our group in 2007 [1]. The observation has been confirmed by many laboratories in multiple obesity model systems including mouse and human [2-8]. The adipose tissue hypoxia has been a new concept to explain the adipose tissue dysfunction in obesity [9,10]. It provides a unified answer to all of the pathological changes in the adipose tissue under obesity, such as chronic inflammation, ER stress, leptin expression, adiponectin reduction, adipocyte death, elevated lipolysis and adipocyte insulin resistance [9,10]. Studies suggest that capillary dysfunction occurs during expansion of adipose tissue [11,12], and leads to reduction in adipose blood supply [13], which is responsible for the tissue hypoxia. In this aspect, the adipose tissue dysfunction is a result of local vascular failure in obesity [13]. In addition, the hypoxia-induced inflammation response has beneficial effects in the body. For example, inflammatory response stimulates adipose tissue remodeling [11,14] and promotes energy expenditure to fight against obesity [15,16]. These new insights into the adipose tissue biology suggest that the hypoxia response may be a feedback mechanism in the protection of body against obesity.

In translation of this view into clinical setting, it is believed that sleep apnea is also a protection mechanism in the body to maintain energy homeostasis in obesity. It uses the hypoxia response to trigger the onset of multiple protection mechanisms in the body.

References

A21
Translational research in type 2 diabetes
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The risk factors for type 2 diabetes, and the association between diabetes and cancer are two hot topics in translational endocrinology that have caused researchers’ high attention. Bisphenol A (BPA) is one of the world’s highest production volume chemical in use. People widespread and continuously expose to BPA, and whether BPA associates with human health needs further research. The association between diabetes and cancer has been realized as a very important issue in the field of diabetes and diabetes care. However, how diabetes is linked with cancer and whether the duration of diabetes, as well as the degree of glycemic controls modify the risk of cancer are not well defined.

We recruited 3423 participants aged 40 years or older from Songnan Community, Baoshan District, Shanghai, and all the participants were underwent a 75-gram oral glucose tolerance test and blood and urine samples were collected. Risk evaluation of cancers in Chinese diabetic Individuals: a longitudinal (REACTION) study is an effort to evaluate thoroughly the risk of site specific cancers in Chinese diabetic individuals. In 2011, a study population of 250,000 people was identified from 25 communities across China, aims to research the interaction between type 2 diabetes and cancer, as phase I of a prospective study.

Our study showed that the detection rate of urinary BPA was 87.7%, with a median value of 0.81 ng/mL. Higher levels of urinary BPA associated with a higher prevalence of type 2 diabetes (OR:1.37, 95%CI: 1.08-1.74), generalised obesity (OR: 1.50, 95%CI: 1.15-1.97), abdominal obesity (OR:1.28, 95%CI: 1.03-1.60), insulin resistance(OR: 1.37, 95%CI: 1.06-1.77), and low-grade albuminuria (OR: 1.23, 95%CI: 1.13-1.34). Urinary BPA was positively associated with free triiodothyronine (FT3) (men: β = 0.011, P = 0.003; women: β = 0.013, P < 0.001) and negatively associated with thyroid-stimulating hormone (TSH) (men: β = -0.065, P = 0.002; women: β = -0.11, P < 0.001), and higher urinary BPA was associated with high thyroid function (OR: 1.68, 95% CI: 1.24-2.27). Results from the REACTION study indicated that type 2 diabetes associated with higher prevalence of all types of cancer and digestive system malignant tumors. BPA might be a risk factor for endocrine diseases, and people should eliminate BPA exposure in daily life. The REACTION study will provide clinical evidence for the interaction between diabetes and cancers.

A22 A grand challenge about multiple metabolic control: health care delivery from tertiary level hospital to primary care health center
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Because of the economic growth and changes in lifestyle, diabetes has become a major public health problem in China. A national study from 2007 to 2008 showed that the age-standardized prevalences of diabetes and prediabetes were 9.7% (10.6% among men and 8.8% among women) and 15.5% (16.1% among men and 14.9% among women), respectively, accounting for 92.4 million adults with diabetes and 148.2 million adults with prediabetes. Data from Shanghai urban communities surveys indicated that the 3-year cumulative incidence rates of diabetes and pre-diabetes were nearly 5% and 11%, respectively. In diabetic patients, the prevalence of diabetic retinopathy was 16.9%. One of five known diabetic (KDM) patients and one of ten newly diagnosed diabetic patients had diabetic retinopathy. Even in the prediabetic group, the prevalence was over 5%. Among diabetes and prediabetes, the prevalence of albuminuria was 25.7% and 12.7%, respectively. The prevalence of peripheral vascular disease in diabetic patients was nearly 15%, much higher than that in prediabetes. Type 2 diabetes and its complications are imposing heavy economic burdens on individuals, families, health systems and countries including China. Since 2003, with the support of Department of Disease Control of Chinese Ministry of Health, Chinese Diabetes Society of the Chinese Medical Association published the Guideline for Diabetes Prevention and Treatment in Chinese. The guideline has been revised twice according to the evidence-based clinical trials. So far, multiple metabolic disorders control of diabetic patients is a global problem. Recently, we developed a Hospital-Community Diabetes Integrated Management to increase “three rates”, which were control rate, screening rate of chronic complication and awareness rate of diabetes knowledge in Shanghai communities. We established collaboration between urban hospitals (Tertiary hospitals) and community health services. The hospital and community health services center have their own responsibilities. Tertiary hospital was in charge of training, establishing management guideline and providing referral platform. The community health services center was in charge of organizing management team and medical record, implementing the management according to the guideline and starting dual referral. Up till now nearly 9,000 high risk individuals completed diabetes screening in 3 communities. And more than 5,000 and medical records were managed by the community health services. The “three rates” improved significantly as consequence.

A23 Development of targeted biologics for systemic lupus erythematosus
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Many of these advances are based on the rigorous definition of the antimitochondrial response, the serologic signature of PBC. First, it is well established that AMA are directed against members of the 2-oxoacid dehydrogenase complexes (2-OADC), among which the major epitopes are within the lipoylated domains of the E2 subunit of the pyruvate dehydrogenase complexes, a key mitochondrial enzyme needed for energy production.
dehydrogenase complex (PDC-E2). Second, autoreactive CD4+ and CD8+ T cells can be detected in PBC peripheral blood, regardless of the AMA status, and the infiltration of autoreactive T cells in the liver and periductal spaces is one of the most prominent immune features. Autoreactive T cells of both subtypes recognize PDC-E2 sequences overlapping with the AMA epitopes. An increase in cytotoxic T cell precursors in the blood in the early stages of the disease compared to the advanced ones and a 10-fold increase of specific liver CD8+ T cells compared to peripheral blood have been demonstrated. Third, additional data on the immunobiology components of PBC autoimmunity has been recently obtained in CD4+CD25+ regulatory T cells which appear to be functionally reduced in PBC. PBC bile duct cells manifest unique features during apoptosis while co-culture experiments do not support a direct role for these cells in determining their immune –mediated injury. Apoptotic cells are phagocytosed by BECs and consequently are an exogenous source of autoantigens in cholangiocytes, possibly through anti-CD61. As a result, the impact of putative changes in apoptosis and autophagy specific to BEC remains to be fully determined in PBC. Fifth, the innate immune compartment has been recently investigated in PBC with promising results. PBC monocytes manifest an increased response to pathogen associated stimuli, as indicated by higher levels of pro-inflammatory cytokines. Further, the hyper-IgM associated with PBC is secondary to an aberrant innate immune response, potentially induced by stimulation of toll like receptor 9 by bacterial CpG-R.

The female preponderance may hold an important key to PBC etiology. X-linked genes determine gender-related characteristics at different levels while also regulating the immune function, particularly to maintain tolerance. Major X chromosome defects such as those leading to Turner’s syndrome or premature ovarian failure are commonly characterized by autoimmune comorbidities (particularly thyroid disease) and, less frequently, cholestasis. Our group first determined a significantly higher frequency of monosomy of the X chromosome in peripheral leukocytes (particularly those of the adaptive immune response, i.e. T and B cells) in women PBC compared to age-matched control women. Monosomy frequency correlated with age in all three groups, as expected but monosomic cells were not microchimeric cells. We further demonstrated that the X loss in PBC affected was not random but affected more frequently one parentally-inherited chromosome. Several key animal models of autoimmune cholangitis have now been described. First, a genomic variant of the non obese diabetic (NOD) mouse (NOD.C3©H) has been observed to manifest autoimmune cholangitis with AMA and ANA positivities in 50%–60% and 80%–90%, respectively. Liver histology demonstrated portal lymphocyte infiltration with chronic nonsuppurative cholangitis and PBC-like granulomas. Second, a dominant negative form of trasforming growth factor (TGF)b receptor II (dnTGFbRII) mouse develops serum AMA in 100% of mice. The TGF receptor II regulates lymphocyte activation and the appearance of PBC in this model suggests that a specific condition of T cells with impaired TGFb signaling in the presence or absence of B cells is involved. Third, the knockout of interleukin 2 receptor a leads to a murine phenotype with 100% serum AMA positivity, 80% serum ANA positivity, and portal lymphocyte infiltration and vanishing bile ducts. This model is of particular interest based on the report of autoimmune cholangitis in a pediatric case of IL2Rdeficiency. Fourth, Ae2a,b also develop autoimmune phenomenon and a PBC-like disease. Finally, immunization of mice with chemical xenobiotics has also been shown to lead to a PBC-like disease. These data and observations will be put in the context of the key mechanisms, including the role of TLRs in modulating these responses.

Autoimmune hepatitis (A1H) is a chronic inflammation of the liver caused by an abnormal autoimmune reaction against hepatocytes. The pathogenesis of A1H involves a loss of tolerance to hepatic self antigens in a susceptible host. The diagnosis is based on histological abnormalities, and characteristic clinical and biochemical findings, which include abnormal levels of serum globulins, and the presence of one or more characteristic autoantibodies such as ANA, SMA, and anti-SLA. Interface hepatitis with abundant plasma cells in the infiltrate is characteristic histologically of both subtypes. Although the prevalence data are scare, A1H has emerging as major course of non-viral chronic hepatitis in China. More and more liver centers launch liver biopsy and serum autoantibody detection regularly. Alertness and awareness of hepatologists and histologic physicians on histologic features of A1H contributes to more and more AIH patients diagnosed in our clinics who were considered as cryptogenic chronic hepatitis previously. The simplified criteria have high sensitivity and specificity for diagnosis of AIH in Chinese patients. The revised original criteria have the complementary role to avoid the false negative diagnosis in atypical AIH patients. Immunosuppressive treatment can attenuate hepatic inflammation, revert fibrosis, and eventually improve the patient’s prognosis and life quality. Corticosteroids, either alone or in combination with azathioprine, are the standard treatment of choice for AIH. Most Chinese patients with A1H show a good response to immunosuppressive treatment, although patients with late-stage or severe disease are less likely to achieve remission. Liver transplantation is the last choice for AIH patients with decompensated end-stage disease. Transfer of regulatory immune cells such as regulatory T cells may become a potential therapy in the near future.

A26

From common origin of life to seeking common path of diseases – a new paradigm of translation

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More than 13 billion years ago, the universe emerged and continued expending after the Big Bang. 4.6 billion Years ago, our earth was formed in solar system with no oxygen and no any signs of life. 3.8 billion years ago, primitive elements of life of RNA and DNA were accidentally formed within rocky vent in deep water of Atlantic Ocean. From single cell to multiple cell life, and to multi-organ species, it took billions years. The ocean turned blue, the land got green and oxygen fills our air. The life started move on to the land. The lives were evolving for adapting with the surrounding environment and the forms of life were diversified. However, inside each basic block of life, the cell, our common ancestor inscribed the deep common marks. From genome to protein, to signal transduction, to organelles, to cell membrane, we all life on earth are in a big family. This is the basis for our human who benefit from using our sister species to do medical experiments. The fates of life are also in common. Through the journey of birth, growth, aging and death, we all reach the same destiny. Cells are subject to the fates of senescence, mutation, apoptosis, and necrosis. The clock of life is ticking down in according with the shortening of telomeres. Once our tissue is injured, regardless of either from inside of autoimmune response or metabolic disorder, or from outside micro-organism invasion or traumatic damage, our repairing potential is intrigued, which induces the common reactions include inflammatory cells infiltration, extracellular matrix formation. Once the damage is repaired, the inflammatory cells commit programed death, the apoptosis, and healing is achieved. If the injure continues and inflammation persists, the fibrosis and scaring process dominate, and then, the organ lost function and slides to end stage.

Understanding the nature of common origin of life and exploring common path of disease would help us to see a big picture about life science, and lead us generate big ideas to deal with disease. With integration of multi-discipline collaborations, the common targets for treatment of diseases are being identified and right strategies can be developed. Efficiently developing new drugs and wisely applying old ones, rationally combining biologic with small molecule, focusing on both physical and mental would speed successes in translation and achieve the healthy lives in human being, and even dial the life clock back.
**A27**
The role of imaging informatics in clinical translational research: perspectives and challenges from a US academic institution

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Nearly all in clinical medicine specialties, medical images and other multimedia related data are generated and need to be distributed to points of decision. Recently, the electronic patient record (ePR) with image distribution system is gradually taking over as the method for distribution of multi-media content to the clinical environment. New challenges are accompanying its spread into other clinical fields. Particularly important are the modeling and analysis workflow of the affected clinical disciplines as well as interface and integration issues with the image-connected electronic patient record. Although the awareness of these issues is increasing rapidly, equally important is the recognition in the professional community that more rigorous scientific methods are needed to handle the clinical system development and deployment. Furthermore, medical imaging informatics is not only based on many existing concepts, theories, terminology, and methodology derived from health informatics, but also deals with different types of data including multi-dimensional medical images, graphics, waveforms, graphics and text which are focused on the cellular, tissue, and organ systems. Accordingly, medical imaging informatics requires new concepts and new tool sets to handle these types of data. This presentation aims to first introduce the basic concepts of Medical Imaging Informatics infrastructure in both research and clinical environments including PACS, RIS, HIS, ePR, standards, databases, and system integration. This will be followed with discussions of new frontier areas of research in medical imaging informatics with some examples of clinical applications in Surgery, Neurology, Oncology, and Neuro-Rehabilitation.

**A28**
Brain imaging biomarkers for the Alzheimer’s Prevention Initiative

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Alzheimer’s disease (AD), the most common disabling impairment in older adults, takes an unacceptable toll on patients and families. With the growing number of people living to older ages, it is projected to affect more than 100 million people around the world by 2050. While there is an urgent need, it takes too many cognitively normal (CN) individuals and too many years to evaluate presymptomatic AD treatments using traditional clinical endpoints.

We and our colleagues have been using imaging techniques to detect the brain changes associated with the predisposition to AD in CN individuals with 2, 1 and 0 copies of the apolipoprotein E (APOE) ε4 allele, the major late-onset AD susceptibility gene, and in CN presenilin 1 (PSEN1) mutation carriers and non-carriers from the world’s largest autosomal dominant early-onset AD kindred in Antoquia, Colombia; we developed several image-analysis techniques and a composite cognitive measure with improved power; and we estimated the sample sizes needed when using these endpoints.

We recently proposed the Alzheimer’s Prevention Initiative (API) to help in the effort to launch an era in AD prevention research. The API will include preclinical AD treatment/biomarker development trials in individuals at increased genetic risk for early-onset and late-onset AD, an extremely large Colombian early-onset AD Prevention Registry; and an extremely large North American Alzheimer’s Prevention Registry to support several preclinical AD trials. The API’s first trial will test the anti-amyloid immunization therapy crenezumab in CN PSEN1 mutation carriers using the best established brain imaging and cerebrospinal fluid measurements and our composite cognitive measure as the primary clinical endpoint. It is intended to test an anti-amyloid agent in the preclinical treatment of AD, help determine the extent to which a treatment’s biomarker effects predict a clinical outcome, provide a better test of the amyloid hypothesis, and provide raw data and biological samples to the research community. With support from the U.S. National Institutes of Health, philanthropic funds from the Banner Alzheimer’s Institute, and Genentech, it is also intended to help provide a new paradigm for research collaboration in clinical trial.

In this presentation, we will briefly introduce the crucial role of fluorodeoxyglucose positron emission tomography (PET), amyloid PET, structural and functional MRI in the preclinical detection, tracking, and treatment of AD. We will present the novel image processing methods we have developed to help in this endeavor, as well as their implementation in the APIs preclinical treatment/biomarker development programs.

**A29**
Magnetic resonance imaging for translational and basic life sciences

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Background: With advances in engineering and computing, an extraordinary body of imaging technologies and applications has developed over the last 35 years. One of the most important applications of such technologies is the study of anatomy, physiology, pathology and functions in humans and animal models of human development and diseases. Among the various in vivo and non-invasive imaging modalities available or under development today, magnetic resonance imaging (MRI) is the most powerful and versatile technology platform. Its unparalleled in vivo and quantitative capabilities offer a broad range of applications covering from noninvasive morphologic measurements, tissue microstructural characterization, hemodynamic and vascular characterization, metabolite measurements, sub-system physiologies, brain functions to monitoring of cell migrational dynamics. This presentation will illustrate these technological developments with some of the ongoing rodent brain MRI projects in our laboratory, highlighting the capacity of MRI as a platform technology to visualize the central nervous system (CNS) in vivo from molecules to systems levels. They include diffusion characterization of neural tissue microstructure; functional study of molecular pathways by spectroscopy; functional study of brain development and injury; monitoring of endogenous neural stem cell activities; and novel contrast agents for brain imaging.

**A30**
20 years translation of ultrasonic elastography: technology innovation and clinical applications

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Stiffness change of tissue is often seen with the progression of pathology. In the past two decades, ultrasonic elastography has emerged as a powerful complementary technique to B-mode ultrasonic imaging, in which strain of target tissues can be imaged and their stiffness can be
assessed. The physical principle of elastography is, when deformation is generated in the tissue by an external or internal mechanical stimulus, coherent acoustic echoes can be tracked by a pulse-echo system, then induced strain inside the tissue can be estimated and the relative mapping of strain can be imaged. In addition, the viscoelastic properties of the tissue can be assessed if the mechanical wave velocity propagating in the tissue was measured. Now this technique has been developed to be more flexible and accurate. The qualitative results presented by quasi-static elastogram have changed to numerical quantification of viscoelastic modulus achieved by other innovative methods, such as sonoe lastography, transient elastography, acoustic radiation force elastography imaging (ARFI), shear-wave dispersion ultrasound strain imaging (SDUI) and supersonic shear imaging (SSI). Aiming for different tissue or organs, these methods can achieve viscoelasticity assessments on various target objects with sizes from tens of millimeters to several microns. Short or trains of mechanical or acoustic radiation force impacts have been used to generate displacements with different patterns. The induced deformation in the tissue has also been tracked by different algorithms based on both cross-correlation and texture matching approaches. Some of these techniques have been studied by our group, and the combination of ultrasonic elastography and particle imaging velocimetry (PIV) using microbubble contrast agents has been also explored. Ultrasonic elastography has been verified on many normal/abnormal tissues and now widely used in clinical practice, such as on breast disease (fibroadenomas, cysts and cancers), liver fibrosis and cirrhosis, dermatology (melanomas and scars), cardiovascular disease (cardiac muscle disease and arteriosclerosis), musculoskeletal studies, minimally invasive surgery and hyperthermia therapy (temperature monitoring and lesion detection in HIFU). During these 20 years, ultrasonic elastography has been developed to be a powerful adjunctive technique to traditional medical imaging methods and expected to become an excellent tool for clinical diagnosis and treatment.

A31 Positron emission tomography imaging of amyloid-beta plaque deposition: a decade of translation
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Positron emission tomography (PET) radiotracers developments over the past decade have enabled in vivo measurement of amyloid-beta (Aβ) plaque deposition, a key neuropathological hallmark of Alzheimer’s disease (AD). This presentation will provide an overview of the translational research path for one of the most widely used PET Aβ imaging agents, [11C]PiB, early preclinical ex vivo characterization revealed the capacity of [11C]PiB to bind to fibrillar Aβ plaques [1]. Real-time in vivo multiphoton microscopy demonstrated that [11C]PiB labeled individual Aβ plaques in transgenic mouse models of AD [2]. Human proof-of-concept studies then showed nearly 2-fold greater uptake of [11C]PiB in AD patients relative to controls in areas of brain known to contain amyloid in AD (frontal cortex, p<0.0001), while retention was equivalent for both groups in areas known to be relatively unaffected by amyloid deposition (subcortical white matter, pons, cerebellum; p>0.2) [3]. These semi-quantitative studies were followed by fully quantitative arterial-based kinetic modeling PET studies that supported the validity of simplified (non-artificial) [11C]PiB PET retention outcomes that exhibited good test-retest reliability (5-10%) needed for improved study feasibility for clinical application on cross-sectional and longitudinal bases [4] and for large collaborative multi-site studies, such as the Alzheimer’s disease neuroimaging initiative (ADNI). Early translational findings include cross-sectional evidence of amyloid deposition (i.e., [11C]PiB retention) in 20-30% of cognitively normal elderly controls, variable retention in subjects with mild cognitive impairment (MCI) that ranged from negligible to AD-like levels and additional findings in those at risk for the development of AD [5, for review]. Emerging longitudinal results indicate small significant increases in [11C]PiB retention in AD and MCI groups, and in controls who had high baseline retention [6]. Efforts are ongoing to establish relationships between in vivo imaging measures and post-mortem measures of Aβ deposition in those scanned with [11C]PiB PET imaging before death. Anti-amyloid therapies have shown promise based on [11C]PiB PET imaging results in early treatment trials. Lastly, the development of [18F] labeled Aβ imaging agents (several-fold longer radioactive half-life than 11C) has allowed greater distribution and translational capability, with one such agent recently being approved by the U.S. Food and Drug Administration for use in the rejection of AD diagnosis in patients under evaluation for AD. A decade of translation has further clarified the need for sensitive early detection of AD pathophysiology in order to identify those who might benefit most from future therapeutic intervention.

References

A32 Building Biomedical Imaging and Informatics e-Science platform for translational medical research
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Background: As there are urgent demands to bring medical imaging research and clinical service together more closely to solve the problems related to disease discovery, medical research, diagnosis and education, a new imaging and informatics infrastructure and paradigm need to be developed to promote multiple disciplines of medical researchers, clinical physicians and biomedical engineers working together in a secure, efficient, and transparent cooperative environment [1]. In this presentation, we outline our preliminary work of building Biomedical Imaging and Informatics (BMII) “e-Science” platform to support collaborative research among multi-disciplines to enable translational research in multiple affiliated hospitals and academic institutions of Shanghai Jiaotong University (SJTU), and Chinese Academy of Sciences (CAS).

Materials and methods: SJTU has 12 large affiliated hospitals located in multiple districts of Shanghai city with a lot of medical and biomedical imaging modalities (e.g., Clinical CT/MI, Micro-PET/CT) being decentralized used in these hospitals and research centers. Also, there is a powerful Shanghai Sychronous Radiation Facility (SSRF) developed by CAS to support large scale of biomedical imaging researches from molecular level to organ parts [2]. So, we designed and developed the e-Science platform to promote the multi-disciplines working together cross these hospitals and academic institutions, and adopted the Service-Oriented Architecture and grid-based concept to build it. In order to enable efficient collaborating, we designed the work and data flows with Principal Investigator (PI)-oriented information model, and developed a documents/data sharing mechanism based on IHE XDS/XDS-I profiles and the access control standard of XACML in this platform.

Results: We implemented the BMII e-Science platform across Shanghai Ruijin Hospital, two campuses of SJTU, SRS and Shanghai Institute of
Technical Physics, CAS. The data communications of the e-Science platform from site to site are fast enough as they are going through the China Education Network in Shanghai with backbone of a few of Gb/sec. There were two kinds of collaborations in the e-Science platform, one is to perform real-time interactively or synchronously biomedical imaging experiment among onsite users and remote users, and the other is to share the image data or documents among collaborators.

Conclusions: The developed BMII e-Science platform can promote multiple disciplines of medical researchers, clinical physicians and biomedical engineers working together in a secured, efficient, and transparent cooperative networking environment. Now, the research, clinical physicians and students can use this e-Science platform to perform biomedical imaging experiments and to do collaborative researching cross multiple hospitals and academic institutions.

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References

A33
Thinking about translational medicine and traditional Chinese medicine
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Translational medicine is a new concept developed in the past two decades. At present, translational medicine has become popular in China and has been introduced into Traditional Chinese Medicine (TCM). In my opinion, putting translational medicine into TCM should consider the characteristics, problems and needs of TCM.

Traditional medicine in TCM is different from western medicine: TCM has a unique theoretical system and mainly reflects the characteristics of the experience-based medicine. The development model of TCM is “from clinical practice to theory and then clinical practice”. Experience accumulated from thousands of years’ practice is a great treasure house. A lot of effective herbal medicines and therapeutic methods have been widely used in clinical practice. Because of these, the orientation, contents and mission of translational medical research in TCM and western medicine are different. The strategy of translational medical research in TCM should be “standing on the earth and then achieving the sky”: use modern technologies and methods to solve practical problems in clinical diagnosis, treatment and drug development of TCM; and then establish related standards to leading the development of TCM; finally TCM can be used at a higher level, a wider range in health services.

Enhance clinical translational research, standardize the treatment protocol and then improve the clinical services level of TCM: TCM clinical practice is based on the theory of overall concept and ‘Bianzheng lunzhi’. TCM is a typical individualized medicine which is an advanced developing direction of modern medical science. However, more flexibility than standardization, poor repeatability and lack of high quality evidence are the key issues hinder the clinical service level of TCM. Therefore, the critical task of translational medicine in TCM is to translate the achievements of medical research into clinical practice, to establish a series of clinical diagnosis and treatment technical standards, guidelines and/or pathway which are scientific, generalizable and acceptable by both TCM and western medicine practitioners. The evaluation and validation of the safety and efficacy of Chinese herbal medicine, prescriptions and treatment techniques are key points. Translating the individual experience to the group law can promote the clinical service capability and level of TCM. In addition, the clinical evidence from translational research provides a robust basis and direction for basic research.

Do translational medical research around key nodes of Chinese medicine R&D, and promote the modernization development of TCM:
From active ingredient screening to structural modification, from cell evaluation to clinical trial, target-oriented drug R&D has faced great challenges: low success rate, high cost and high risk. Chinese medicine R&D is not necessary to and should not copy the model of western medicine. Creating new drugs from classic and commonly used prescription, especially the secondary development of marketed Chinese Patent Medicine, is an important content of translational medical research of TCM. Unclear clinical indication, obsolete manufacturing process, unclear material basis and action mechanism, low-level quality control and poor intellectual property protection are the problems more or less existed in the Chinese medical preparations. Using modern technology to solve these problems can achieve the seamless transformation of research results. There are several typical successful examples of translational medical research in TCM. For example, the successful development of artemisinin, the mechanism discovery of arsenic for treating leukemia and Compound Danshen Dripping Pills completed phase II clinical trials in the USA.

Strengthen the multi-disciplinary cooperation; cultivate translational medicine research team of TCM in practice: Translational medicine is a new medical concept, but no proprietary research methods. Translational medical research of TCM not only needs the knowledge of TCM but also multi-disciplinary technologies and methods, such as biology, chemistry, information science, pharmacology, statistics, epidemiology, economics, etc. Paying more attention to the exchange and integration of multi-disciplinary will improve the efficiency of translational research and generate more achievements. To promote the collaboration of universities, institutes and pharmaceutical companies and establish postdoctoral research sites or postgraduate courses for company workers which not only can transform the research results to solve the practical problems but also can cultivate a number of outstanding researchers who are familiar with both company requirement and research methods. Introducing the concept of translational medicine into TCM, it will take some time from understanding to practice. Translational medical researches should focus on the “need” in practice.

A34
Utilizing traditional Chinese for the discovery of efficacious new drugs
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Western medicines, while being developed using a plethora of powerful research technologies, still often fail in the clinic due to efficacy problems as well as exhibiting side-effects. Part of this problem can be attributed to the development of protein-targeted drug discovery methods, which do not consider the whole organism during the discovery stages, but only a very (possibly over-) simplified model system. Hence, results cannot be translated easily into the clinic, which gives rise to the problems mentioned above.

In this work, we hence propose to utilize the knowledge compiled by traditional medicines (such as Traditional Chinese over large time spans, which consider the phenotypic effect (the effect in man) of treatments from the onset. Recent developments in analytical chemistry enable us to determine the bioactive principles in compound mixtures and in silico (computational) protein target prediction tools allow for the speedy determination of target proteins, shortening the time needed for subsequent optimization of formulations. We will focus on diseases where treatments in the West are lacking, such as cardiovascular diseases; cancer; liver fibrosis and liver cirrhosis; as well as diabetic retinopathy, and determine active principle and mode of action of traditional medicines which have shown promise against those diseases.

The particular case studies to be examined initially are Danshen Dripping Pills, Danshen pectoris and cardiovascular diseases; Ginseng and Ginsenosides (cancer and inflammation); Fu Zheng Hua Yu (liver fibrosis and cirrhosis) and Qiden Mingmu (diabetic retinopathy).

The aim is, at the end of this project, to have bioactive compounds (or mixtures of compounds) at hand which can be further developed into efficacious treatments, with an increased likelihood of success in the clinic.
A35

Traditional Chinese medicine for irritable bowel syndrome: from classic formula to modern medicine development
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Background: Irritable bowel syndrome (IBS) is a very common functional gastrointestinal disease. Epidemiological studies showed that 14% of males and 27% of females in the US (white) have symptoms of IBS. In Hong Kong, one survey reported a similar prevalence of this condition among Chinese (3.6% in males and 3.8% in females with Rome II criteria). Because the mechanism of IBS is not well understood, the IBS sufferers are not satisfactory about the symptoms management; and the new chemical drug development targeting IBS is facing big challenges. In traditional Chinese medicine, there is no term of IBS, although many classic literature record coving the pathophysiological concepts and therapeutic approaches bout “painful diarrhea”.

Results: Our research group have developed a new Chinese medicine formula, called JCM1602, based on “Important Formula for Painful Diarea” and our clinical therapeutic experience. The aim of our study is to develop a modern new drug based on the Chinese medicine theories and modern pharmaceutical approaches. For this purpose, firstly, we evaluated the efficacy and safety of JCM1602 in a randomized double blinded, double dummy, control study. Eight four patients were assigned to JCM1602 plus placebo holopon arm, holopon plus placebo JCM1602 arm and double placebo arm; and all patients went through 8 weeks treatment and 8 weeks follow-up. The primary outcome is the general improvement of symptoms. Results showed that IBS patients with JCM1602 have significant symptom relief during the treatment period and the follow up period, comparing with that of the holopon group and placebo group. Based on the clinical study results, a new Chinese medicine drug development process was adapted from the pharmacognosy, pharmacology, efficacy, safety aspects. Further, two animal models, including neonatal maternal separat model, two animal models, including neonatal maternal separation-induced visceral hyperalgesia model, 2,4,6-trinitrobenzene sulfonic acid-induced post inflammatory IBS model, have been applied for the efficacy confirmation and mechanism discovery.

Conclusion: The results support the efficacy of JCM1602 in patients, and found that the analgesic effect and anti-diarrhea effect is accomplished through serotonin pathway. Furthermore, the active fraction of JCM1602 was identified. This active fraction is the base for the new drug development for IBS.

A36

Modern research of TCM etiology and pathogenesis theory and translational medicine
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To develop the basic theory based on clinical practice, and further to guide clinical for improving the therapeutic effect is one of the important characteristics of TCM thinking way. In a sense, the development and innovation of TCM basic theory is equivalently a process of translational medicine. The typical examples are “defense, qi, nutrient and blood pattern identification” and “triple energizer pattern identification”. The knowledge and technology using in modern integration of TCM thinking way, to solve the clinical problems, to improve the therapeutic efficacy of the disease and the patient’s quality of life. The methods of TCM are to establish a series of systematic research from the clinical (efficacy) – experiment – drug efficacy mechanism, and constantly to find and solve new problems, thereby to promote the development of medicine.

TCM etiology and pathogenesis theory is based on the visceral manifestation, meridian and collateral, essence, Qi, blood, fluid and humor, etc. Judging by clinical observation, it is eventually verified whether the treatment effect can be overall restored. Against pathological features of modern diseases, TCM has given full play to the advantage of macro overall thinking, cognized and found TCM basic etiology and pathogenesis of the disease or the critical key affecting disease development and prognosis. To develop TCM effective therapies and formulas, further to develop TCM etiology and pathogenesis theory for understanding deeply western diseases, is essentially a kinds of the crossover and recreation process between TCM and western medicine. The etiology and pathogenesis theory belongs to the “principles” scope within TCM “principles, methods, formulas and medicinal”. It must be verified repeatedly which combines closely with the therapeutic effects. Then it could form the etiology and pathogenesis theory which guides widely the diagnosis and treatment of clinical disease. That also is a key issue of TCM possessing “translational medicine” features.

In order to adapt to the development of modern society, and promote the theory innovation, TCM etiology and pathogenesis theory must adhere to the own theory and thinking principles, connect closely with the development of modern science, explore more convincing scientific evidence, and be constantly revised and improved in practice. Thereby it will fully show the practical significance in improving the clinical efficacy. At the same time, it is also an important way that finds a new prescription or a new use of mature prescription on treatment modern complex, refractory-disease.

We have once analyzed the patients with post-hepatitis B cirrhosis under the guidance of traditional Chinese medicine thinking, which conjecture the disease reasons based on ZHENH and verify them according to clinical efficacy. Through clinical practice and large samples epidemiological survey combined with analytical processing technology, we found that “Qi Deficiency and Blood Stasis” is the basic DISEASE pathogenesis of liver cirrhosis, “Liver and Kidney Yin Deficiency” and “Dampness-Heat Smoldering” are the major ZHENH pathogenesis of liver cirrhosis. Targeted to liver cirrhosis disease and ZHENH pathogenesis, we have adopted 4 classical prescriptions with different effects, such as “boosting qi”, “tonifying yin”, “eliminating stasis” and “clearing heat and draining dampness”, to carry out the experiments in 4 different classic animal models of liver cirrhosis. We found that Huangqi decoction could have good therapeutic effect within three models of liver cirrhosis. The results provided the experimental basis for establishing the liver cirrhosis TCM pathogenesis theory of “deficiency and detriment generating the accumulation”. Furthermore, using liver histology assessment as the primary efficacy endpoint, we found that Huangqi decoction could improve liver histopathological status of cirrhosis, compared with Fuzheng Huayu decoction, which can reinforce the healthy qi and resolve stasis. Consequently, we confirmed that “boosting qi and engendering essence, tonifying and replenishing to improve the deficiency and the detriment” are the fundamental principle on treating liver cirrhosis. According to the active mechanism of tonifying and replenishing medicinal, combined with TCM essential and qi mutual transformation theory, we analyzed the pathobiological basis of liver cirrhosis TCM pathogenesis theory of “deficiency and detriment generating the accumulation”. The major characteristics of tonifying and replenishing medicinal on treating liver cirrhosis could include inhibiting the activation of hepatic stellate cell and liver epithelial-mesenchymal transition, inhibiting hepatocyte apoptosis, protecting liver sinusoidal endothelial cells and hepatic parenchymal cells. The outcomes communicated the concepts of TCM pathogenesis and modern pathobiology, and systematically demonstrated the connotation of liver cirrhosis TCM pathogenesis theory of “deficiency and detriment generating the accumulation” and treating disease from the root.

A37

Evidence-based quality criteria in research, development and application of Chinese medicines
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TCM mainly consists of crude drugs, slices for decoction, extracts and Chinese patent medicine preparations. Crude drugs are the raw and starting materials of preparation of slices, extracted intermediates and the finished products.
The crude drugs being collected or cultivated from nature has many factors affecting its quality. Different species/varieties, different produce areas, different harvest times, different processing methods and different storage conditions can all cause an enormous diversity on the quality.

It has been evidenced that the multi-originated herbs showed diverse in chemical profiles and consequently un-equivalent in pharmacological potency. This situation may be well recognized by pharmacognosists, however are often neglect or ignored by pharmacologists and TCM doctors in the biological activity screening, in non-clinical investigation research, and in clinical trials, which undoubtedly led to unrepeatability of the results and even wrong conclusive direction.

As examples, four species of Rheum are recorded for Rhubarb in Chinese Pharmacopoeia but only one or two species possess diarrhoea effects. As for Curcumae Radix, only the root of Curcuma longa L showed potent choleric activity among the fure species of Curcuma recorded in Chinese Pharmacopoeia.

In view of this consideration, the importance of a pre-experiment assessment of the starting material and the standardized and advanced methodologies for the authentication and quality evaluation of TCM herbs/products will be addressed in this presentation.

A38
Current status and considerations on biosimilar in China
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Since the WHO “Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)” was published in April 2010[1], twenty two Countries and regions including EU and FDA have established their guidelines or guidance drafts on evaluation of biosimilar.

In terms of the technical features, WHO guidelines are consistent with that of EU[2-4], head-to-head comparison exercise between SBP and reference biotherapeutic product (RBP) are required. In the prerequisite of quality similarity, the unnecessary or repeated non-clinical and/or clinical data might be reduced. Furthermore, extrapolation to other indications of the RBP may be possible. As for the FDA draft, requirements of interchangeability and substitution of SBP with RBP were introduced [5,6]. Guidelines of other developing countries generally used the WHO guidelines and the FDA guidance draft as blueprints to set up the technical requirements. These regulations and guidelines have far-reaching significance for each country’s biotechnology industry development and the availability and affordability of public medicine use.

Up to now, there are not yet specified regulations for SBPs in China. Based on “The Provisions for Drug Registration (SFDA Order 28)” [7], Part I “Biological Products for Therapeutic Use” of the appendix 3 includes fifteen categories, three of them (7, 10 and 15) are related to SBPs. With respect to the technical requirements, there are no essential differences between China and WHO guidelines. However, our current regulations pay more attention to the requirements for the new drug approval. Consequently, some candidate SBPs products which might be suitable for abbreviated licensure pathway still need to experience the complete non-clinical and clinical studies. In addition, extrapolating to other indications is not allowed in our current regulations.

Among the research projects of the “Twelfth Five-Year Plan” significant new drugs creation special, me too biotherapeutics are still the major part of the projects of biotechnology medicines. Therefore, accelerating the process of establishing our SBPs guidelines has great benefit for achieving the goal of ensuring the availability and affordability of public medicine and improving the development of our country’s biotechnology industry. Recently, our department has initiated the process of surveying the need to draft a specified SBP guideline. As some suggestions, due to very hard to obtain and very high costing of RBP would surely increase the difficulties of developing and evaluation of SBPs, how to define the requirement of RBP should be elaborately considered during the process of establishing our guidelines. Besides, special attention should be focused on how to perform the comparability exercise with RBP in the non-clinical and/or clinical study during the development of SBPs of therapeutic monoclonal antibodies. We believe that a SBPs guideline which considering both the actual situation of development of biomedicine in China and the general WHO framework would be established in the near future.

References
1. GUIDELINES ON EVALUATION OF SIMILAR BIOThERAPEUTIC PRODUCTS (SBPs). [http://www.who.int/biological_areas/biological_therapeutics/BIOThERAPEUTICS_FOR_WEB_22APRIL2010.pdf].

A39
A strategic thinking of the scientific system of drug regulatory in China – advancing drug standards of China
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Drug is special goods to prevent diseases or used for rehabilitation and health care, and therefore is essential for human society development. Drug safety directly related to people’s health and life safety, and also tightly associated with the government management and public safety. Our national pharmaceutical and health care policy has paid equal attentions on Traditional Chinese Medicine and western chemical drugs, and implemented the significant new drugs creation strategy. Plenty of strategies, approaches and technologies have been applied in the drug research field, and have promoted the fast development of biomedical industry.

Now we are on the way to be a big country of pharmacy, which supplies favorable conditions and available development spaces of constructing the novel drug regulatory system. According to the overall serious problems of China biomedical industry, such as small scale, low concentration; excess capacity, weak innovation and competition on market, and homogenization under low-end technology and quality, etc. Additionally, the development of society is facing urbanization, industrialization and aging problems, new requirements of the safety, efficient and availableness of drug have been raised. Therefore, Constructing the new system of national drug regulatory, improve the level of drug quality control and ensure the drug safety in society are essential products as the progress of times and society development, and also are important questions that to pay more attentions during drug regulatory process. We need to deeply understand them with the basis of practice and innovate drug concept and measures, to ensure the drug safety and efficient is controllable. After all, we need to persist on thinking systematically, enhance the top design, emphasize on the entire process regulatory, to construct a new system of drug regulatory which is suitable to domestic conditions.

A40
US regulatory approaches to chemistry, manufacturing, and controls for botanical drug products
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Many botanical products are used widely in the United States. Depending on its labeling and intended use, a botanical product can be a food, a dietary supplement, and/or a drug. If a botanical product is intended for use in diagnosing, mitigating, treating, or curing disease, it is a drug under the Food, Drug, and Cosmetic Act and is subject to applicable drug regulations. The CDER Guidance on Botanical Drug Products defines the term “Botanical” as a finished, labeled product that contains drug substance from plant origins, which may include plants or plant parts, algae, macroscopic fungi, and combinations thereof. The term does not include highly purified substances or chemically modified substances derived from botanical sources. This presentation provides an overview of the Chemistry, Manufacturing, and Controls (CMC) information recommended to support the clinical studies of a botanical drug product under an investigational new drug application (IND) in the United States.

Vegetable (sinectachins) ointment was the first botanical drug product approved by the FDA since publication of the Botanical Guidance (2004). While the Guidance gave a general pathway for IND submissions, it was silent on the requirements for NDA approval. A “CDER Botanical Guidance rewrite Working Group” has been established and the work is in progress to consolidate the FDA’s current scientific and regulatory thinking in the future Botanical Guidance.

References

A41
Translational toxicology and exposomics for food safety risk management
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Background: China embraces the use of risk analysis in the development of risk-based approaches for the management of public health hazards in food safety. Risk analysis is made up of three components and Figure 1 illustrates the relationship between the three components of risk analysis [1]. Estimating the magnitude and distribution of benefits and costs of particular risk management options may require addressing a myriad of concerns, e.g., changes in the availability or nutritional quality of foods; impacts on consumer confidence in the safety of the food supply or in the food regulatory system [2]. This is a brief introduction on risk management options for dealing with the new outcome from risk assessment approaches in China.

Materials and methods: Traditionally, risk assessment is based on deterministic endpoints, i.e., use of the no observed (adverse) effect level (NO(A)EL) and the mean or high level of exposure. In the 21st century, exposure science has increasingly embraced deterministic models to predict levels of diverse exposures based on categorical data and on measured levels of pollutants in biological fluids and tissues. Increasingly, more probabilistic and distributional methods are included, to characterize the hazard(s) as well as the exposure(s). Investigations of total personal exposure initially employed external measurements of chemicals that can enter the body, which provide the more probabilistic and distributional methods. These approaches allow for more description of variability in the population as well as uncertainty in the risk estimates. Moreover, additional risk assessment outcomes are being reported, such as the margin of exposure (MOE), which gives a relative indication of the level of health concern with actually quantifying the risk [3-5].

Results: The manner in which health reference guide values (HBGVs) such as the acceptable, tolerance, and reference dose (RfD) are estimated usually generates deterministic values in that they imply a demarcation between what is a “safe” level of exposure (i.e., exposures below the value) versus a “non-safe” level (i.e., exposures above the value). In many instances over the years, these deterministic values have been used as a common “bright line” approach to managing risk. Decision makers and competent authorities use these reference values to set standards and regulations for what are appropriate exposures. If uncertainty and variability be kept in mind, probabilistic modeling (e.g., with distributions around the values) provides risk managers more detailed dose response modeling with greater transparency of the uncertainty surrounding many of these values. To aid the decision, the risk assessment should provide information on the nature and magnitude of uncertainties in both the toxicological and exposure data that make up the inputs to the distributions being modeled.

For risk managers, the distribution around the reference value and its probabilities and uncertainties makes decision making more complicated, particularly about who specifically or what portion of a population to protect. Considerations need to be made regarding whether the most
sensitive individual(s) needs to be protected or the bulk of the general population (e.g., to decide on a goal that at least 95% of any population should not exceed the acceptable/tolerance intake (in some cases this could be a long term goal)). For some contaminants, it may be useful to establish more than one reference value (e.g., a RfD for the general population and an acute RfD for pregnant women). The two examples will be summarized for risk-benefit analysis for universal iodized salt (figures 2) [6] and maximum limit development of inorganic arsenic in rice (table 1 and figures 3).

Conclusions: One can imagine a future in which individuals’ exposomes are contrasted between diseased and healthy populations for molecular epidemiology. In either case, the goal would be to discover causes of ill health and to generate hypotheses regarding identification and elimination or reduction of harmful exposures. These expansions of risk assessment tools and information provided require additional risk management approaches, included in the platform to translational toxicology and exposomics.

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References
The role of corporate-academic research partnerships in bringing
novel therapeutics and diagnostics to the market
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Healthcare industry participants – whether biotech, diagnostic, medical
device or classical pharmaceuticals – depend in large part on successfully
collaborating with academic institutions as a source of innovation and
clinically-relevant new products. Historically this has most often been in
the form of pure licensing arrangements, whereby new inventions and
discoveries are licensed by the manufacturer for their internal further
development and eventual marketing, and royalty payments accrue to
the institution. In this model, the ‘discovery’ is the providence of the
academic researcher, and the risk and cost of development is borne by
the manufacturer.
Increasingly, however, collaborative partnerships are forming between
industry and academia that encompass a broader scope, longer duration,
and involve greater risk sharing. A major driver of these collaborative
activities is the increasing recognition that translational medicine –
linking discovery with clinical application – is a means for both the
industrial and academic partner to reduce their respective risks, quickly
demonstrate new product safety and efficacy and more rapidly bring new
treatment and diagnostic modalities to market.
Prime examples of this new paradigm are now being created in the areas
of cell therapy and personalized medicine, particularly companion
diagnostics. In this talk, we will discuss these examples, the new model
that is developing, and how both academic institutions and industry can
form successful partnerships.
A43
Approaches in rare diseases and pediatrics across international boundaries
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Rare diseases are designated as affecting less than 200,000 individuals (US) and of the approximately 7000 designated rare diseases, the majority of these occur in pediatric patients, and across international boundaries. An example is pediatric ARDS (Acute Respiratory Distress Syndrome) which is not diagnosed until a previously healthy child presents in the PICU with severe symptoms and in which more children die each year than from cystic fibrosis and leukemia, combined. The Nathaniel Adamczyk Foundation (NAP) is focused on identifying risk factors and opportunities for prevention of this devastating disease. Both the diagnosis and patient management are challenged by having to deal with a syndrome in a critical care situation in a heterogeneous patient population.

NAP has undertaken the development of an (inter)national tissue and data repository to support both clinical research and enhanced clinical decision support on patient management. Creation of an analytical platform to integrate, access and analyze temporal clinical data ranging from the PICU to also incorporate neo-natal ICU and pregnancy history is underway with a prototype already in testing. Analytical methods are being evaluated in collaboration with Dr. Mike Quasney (Medical College of Wisconsin) and the Virtual Pediatric ICU and PALISI (Pediatric Acute Lung Injury and Sepsis Investigators). This effort is exploring expanded international partnerships in both Europe and China to increase the accessible data for analysis and to further participate in the development of better diagnostic standards. We will present the initial state of both the analytics and platform development to encourage extension of this international effort to interested clinicians and clinical researchers. We believe that this unique approach, which focuses first on addressing the critical need to improve patient management through disease stratification, will not only benefit pARDS but be extensible to many other pediatric rare disorders.

A44
Translational medicine from observation to hypothesis to interpretation
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A cancer immune signature implicating good prognosis and responsiveness to immunotherapy was described that is observed also in other aspects of immune-mediated, tissue-specific destruction (TSD). Its determinism remains, however, elusive. On one side it appears that the genetic background of the host’s bears significantly on immune responsiveness, on the other it appears that tumor can behave differently within the same genetic background (as in the case of mixed responses). This apparent paradox can only be explained by a multi-factorial model of cancer immune responsiveness. It should be emphasized that host and cancer genetics are largely overlapping since cancer cells carry the majority of the immune responsive genotype. In this model, a favorable genetic background of the host is necessary but not sufficient for tumor rejection as the possession of a shotgun is necessary to shoot a duck but at the same time a skill in shooting is required. A good example is provided by the analysis of patients with IRF-5 polymorphism; the “immune resistant phenotype” appears to almost exclusively preclude cancer rejection during adoptive therapy with tumor infiltrating lymphocytes; however, “the immune responsive phenotype” can be segregated into two categories; one enriched in patients responding to therapy and the other of non-responding. Although, other host’s genetic factors could be responsible for this sub-classification, it is also possible that, given a favorable genetic background, the genetics of the tumor may become the determining factor.

We recognize that this classification of factors that may influence immune responsiveness may be too rigid. In reality, immune responsiveness may depend upon a continuum determined by the interaction of a multitude of factors that for simplicity can be separated into broad categories depending upon the host’s genetic background, somatic mutations, and external factors such as intensity and effectiveness of treatment, general condition of the patient and a multitude of other hidden co-factors. In the presentation at the NY Academy of Sciences we will present our strategy to dissect the question of cancer immune responsiveness by study dynamically the behavior of human cancers under natural conditions on in response to therapy.

A45
Suboptimal health: a potential preventive instrument for non-communicable disease control and management
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Suboptimal health status (SHS) is characterized by ambiguous health complaints, general weakness, and lack of vitality, and it has become a new public health challenge in China [1,2]. SHS is believed to be a subclinical, reversible stage of chronic disease. As studies of intervention and prognosis for SHS are expected to become increasingly important, a reliable and valid instrument for its assessment is essential. A questionnaire for measuring SHS in urban Chinese was developed based on focus group discussions and a literature review [1]. Questionnaire validity and reliability were evaluated in a small pilot study and then in a cross-sectional study of 3000 individuals [2]. The analyses included tests for reliability and internal consistency, exploratory and confirmatory factor analysis, and tests for discriminative ability and convergent validity. The final questionnaire incorporated 25 items on SHS (SHSQ-25), and encompassed 5 subscales: fatigue, cardiovascular system, digestive tract, immune system, and mental status [1,2]. The SHSQ-25 has proved to be a reliable and valid instrument for measuring suboptimal health status in urban Chinese [2]. The progress of a combined genomics and glycomics study for screening biomarkers and exploring SHS as a preventive tool for non-communicable disease control and management will be presented [3].

References

A46
The challenge of studying complex diseases undergoing complex treatments: the metastatic cancer model
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The challenge of studying complex diseases undergoing complex treatments: the metastatic cancer model
A cancer immune signature implicating good prognosis and responsiveness to immunotherapy was described that is observed also in other aspects of immune-mediated, tissue-specific destruction (TSD) [1,2]. Its determinism remains, however, elusive. On one side it appears that the genetic background of the host's bears significantly on immune responsiveness, on the other it appears that tumor can behave differently within the same genetic background (as in the case of mixed responses). This apparent paradox can only be explained by a multi-factorial model of cancer immune responsiveness [3]. It should be emphasized that host and cancer genetics are largely overlapping since cancer cells carry the majority of the host's genetics. Thus, inherited genetic factors may affect the biology of cancer cells besides that of normal cells. It could be postulated that some patients carry a genetic background that make them resistant to immunotherapy by effecting either the biology of the immune response, the biology of the cancer cells or both. On the other hand, "an immune-responsive genotype" may still be limited by the genetics of the tumors: in other words, although the patient may be predisposed to cancer rejection the tumor lacks additional properties necessary for its recognition by the immune response [4]. In this model, a favorable genetic background of the host is necessary but not sufficient for tumor rejection as the possession of a shotgun is necessary to shoot a duck but at the same time a skill in shooting is required. A good example is provided by the analysis of patients with IRF-5 polymorphism [5]: the "immune resistant phenotype" appears to almost exclusively preclude cancer rejection during adoptive therapy with tumor infiltrating lymphocytes; however, "the immune responsive phenotype" can be segregated into two categories: one enriched in patients responding to therapy and the other of non-responding [6,7]. Although, other host's genetic factors could be responsible for this sub-classification, it is also possible that, given a favorable genetic background, the genetics of the tumor may become the determining factor [8].

We recognize that this classification of factors that may influence immune responsiveness may be too rigid. In reality, immune responsiveness may depend upon a continuum determined by the interaction of a multitude of factors that for simplicity can be separated into broad categories depending upon the host's genetic background, somatic mutations, and external factors such as intensity and effectiveness of treatment, general condition of the patient and a multitude of other hidden co-factors. In the presentation at the NY Academy of Sciences we will present our strategy to dissect the question of cancer immune responsiveness by study dynamically the behavior of human cancers under natural conditions on in response to therapy.

References

A47

Cell phone based telemedicine - brief introduction
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The application of Personalized Medicine strategies of matching specific disease genotypes and phenotypes with specific pharmaceutical drug treatment has shown tremendous efficacy in several important diseases. The most successful example is the targeting mutations of the epithelial growth factor receptor by small molecule antagonists of the tyrosine kinase in non small cell lung cancer. The expansion of this treatment paradigm into other diseases has led to new thinking considering the diagnosis and treatment of disease, including "Precision Medicine", which seeks to provide a molecular taxonomy of disease that can be used for guiding targeted therapy in individual patients. Today we have only a cursory understanding of the patterns of actual uptake of drugs or their active metabolites at such targeted sites in the body. In the past such studies required extrinsic labeling of the parent drug (ie radioactivity in PET) that potentially changed the chemical and biological properties of the drug. New technologies such as MALDI-MSI mass spectrometry have revolutionized the label-less tracking of drugs within targeted disease tissue sites [1]. A spectral image of drug distribution in biopsy tissue compartments is created by monitoring the signal intensity of signature ion mass fingerprints unique to each compound and its metabolites at contiguous sampling windows separated by < thirty microns. In a Proof of Principle study, we have applied MALDI-MSI to track the uptake and distribution of an inhaled muscarinic receptor antagonist [2], ipratropium in the bronchial airways of COPD patients shortly after administration. Direct measurement of the unlabeled drug in bronchial biopsies showed that the ipratropium (parent drug ion mass, m/z 332.332, daughter ion masses m/z 166.2, and m/z 290.2) was transported and localized to areas of airway smooth muscle that expressed the targeted acetylcholine receptor M3, as shown by immunohistochemistry performed following mass spectrometry analysis. This result is the first reported co-localization of the unlabeled drug and its targeted receptor in man. In addition to the drug position and intensity signatures it is possible to simultaneously map the patterns of thousands of ion masses representing peptides, proteins, phospholipids, and metabolites that characterize healthy and
diseased states. Further, the effect of drug on the relative abundances and histological positions of these ion signatures may also provide important indices of response to therapy. Together, these catalogs will likely become an important part of the molecular taxonomy of disease being developed with Precision Medicine frameworks using genomic, genetic and proteomic approaches defining the micro-environment of disease.

References


A49

A Quaternary Equation for Interdisciplinary Medical Research (IMR)

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A popular model for developmental therapeutics is one in which drugs are developed by biotechnology and pharmacy. Candidate molecules are then handed off to academia and Clinical Research Organizations (CRO’s) for clinical testing. We have embarked on a different approach whereby 1. Potential targets are identified in a candidate pathway, 2. Gene expression/genomics are interrogated in normal and diseased human tissues for their relevance, 3. Highly specific chemical reagents against putative targets are developed to determine their importance, 4. Model compounds are tested in pre-clinical cell and mouse models. 5. Collaborations are established with biotechnology/pharma for drug development. We have taken this approach with the goal of stimulating drug development in an as yet relatively unexplored important survival pathway, the Unfolded Protein Response. Interest in this complex pathway, expressed in all eukaryotic organisms, has recently surfaced, and particularly in cancer and neurodegenerative diseases. Our team includes faculty with expertise in high throughput drug screening, kinase chemistry, cell biology, and clinical research. Specific compounds have been identified, further modified and tested against all 3 branches of the UPR: Ire1, PERK and ATF6 using chemical and cell system analysis of microRNA expression of RNA extracted from fresh frozen and formalin-fixed paraffin-embedded samples. RNA 2007, 13(1):1668-1674.

References


A50

Biobanking and microRNA – small but with great dividend

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Biobanking represents a critical resource for personalized translational medicine discovery. It is a great challenge to establish a high quality and comprehensive tissue biobank for cancer research. Many hospitals and clinical centers have large archival existing formalin fixed paraffin embedded (FFPE) tissue depository in the pathology department along with rich history of clinical diagnosis and long term follow up information. This is an existing gold mine for biomarker discovery. Our laboratory has first systematically demonstrated that unlike coding mRNA, a class of non-coding RNA, microRNA (miRNA), is rather stable in FFPE specimens [1]. This discovery established the foundation of miRNA based biomarker discovery using archival FFPE specimens. The superior stability of miRNAs in archival FFPE, and serum samples provides ideal candidates for biomarker discovery using current tissue bank. Mounting evidence showed that post-transcriptional and translational controls mediated by various regulatory molecules, such as RNA binding proteins and miRNAs, are critically important in cancer. Research involved in the translational regulation of suspected genes in cancer has become a new frontier in recent years. Our laboratory was first discovered that a number of miRNAs were regulated by tumor suppressor p53 in colon cancer [2]. Such regulatory mechanism was important in regulating cell proliferation, cycle control and cell death [3]. To investigate the impact of miRNA in chemoresistance to fluoropyrimidines and anthotoplates, we discovered that miR-215 suppresses the expression of both thymidilate synthase and dihydrolefotate reductase [4]. In addition, the expression of miR-215 was directly regulated by p53. The expression of miR-215 was significantly associated with colorectal cancer patient survival [5]. miR-140 modulates chemosensitivity by suppressing HDAC4 expression, and the levels of miR-140 and miR-215 were elevated in colon cancer stem cells [6]. Our recent studies have shown that miR-194 was directly involved in epithelial-to-mesenchymal (EMT) transition, a critical event for tumor progression and metastasis. The expression of BMI-1 protein was suppressed by miR-194 directly at the 3’-UTR region of BMI-1 mRNA [7]. Given the significant role of miRNAs in many aspects of tumor development such as proliferation, cell cycle control, invasion, EMT and maintained tumor stem cell phenotype, we remain hopeful that miRNA based therapeutics, diagnosis and prognosis may emerge in the near future to benefit patients.

References


A51

Biobanks and cancer genome projects in China

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Cancer is the first cause of death in China. Approximately 1.6 million people died of cancer and more than 2.2 millions of new cases were diagnosed each year. In order to reveal the puzzle of genomic alterations and biology of human cancers, the new-generation sequencing technology has been set up and started to carry out large-scale cancer genome study in China. The Chinese Cancer Genome Consortium (CCGC) was organized in August 2008.
to launch and coordinate a number of research projects as a publicly-funded network with over 30 university hospitals and research institutions to share a common goal and platform. The CCGC has done a serial of activities including organization of clinical research teams and working groups, the selection of cancer types and define of research strategies, the technical and bioethical issues for biospecimen collecting and quality control, which shall be collected using a Standard Operating Procedure (SOP) provided by the CCGC Project Secretary Office following International Cancer Genome Consortium (ICGC). We have proposed the missions and working plan for coming 5 years. The CCGC has announced approximately 15 types of common cancers in China to be initiated, including gastric, hepatocellular, esophageal, nasopharyngeal, colorectal, bladder, lung, thyroid, breast, renal, ovary, pancreatic cancer, leukemia and glioblastoma. Furthermore, we will focus to optimize the biospecimen collection network and running system for pathological and molecular quality control to support CCGC projects to be healthy growth.

A52

**Bringing the basic biomedical researches and clinical practices with biomedical informatics**

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The emergence of genome-wise high-throughput technologies have led to the creation of the interdisciplinary field between biotechnology and information technology, where bioinformatics came out. With the application of these technologies in medical research, the concept of “translational medicine” has attracted more and more attentions and concerns. How can we translate the results of basic biomedical research into clinical practices? How should we promote basic research to meet the demands of modern medicine? These questions are the core issues in translational medicine. To solve these problems, information technology is the key. The integration and interaction between biotechnology, medicine and information technology leads to the formation of Biomedical Informatics.

The challenges of building modern medical information systems are to reduce the redundancy of the data and functions, to seek the Inter-connection and Inter-communication technology for different data structures and system architectures in the complex business environment, and to build an efficient and flexible content management system. To meet these challenges, we need to build a high-quality information system integrating clinical data and basic biomedical research data, which is the core of translational medicine and the key to obtain the transformation “from the laboratory bench to hospital bed”. This information system should include three parts: de-identified clinical data repository (de-id CDR), “omics” databases including analysis platforms and tissue banks (diseases and normal controls) adhering to the requirements of research design.

The health information technologies related to clinical data acquisition, storage, management, and applications are essential for the 21st century medical and health services. The automatic or semi-automatic form filling for research by importing and integrating data from different information systems, e.g. PACS, HIS, EMR and LIS, can significantly improve the data accuracy and work efficiency. However, in current medical information systems, a large number of important clinical data exist only in free text documents and reports. To extract these data, medical natural language processing technology has become a hot and challenging field in biomedical informatics research. The automatic processing of medical text in English has been studied for many years, and many tools have been developed. But in China, research on automatic processing of Chinese medical documents has rarely been reported. Considering the sheer size of the population in China, Chinese medical language processing technology may be an important subject in translational medicine research in China. Translational medicine research depends on a large cohort of human tissue samples. Tissue bank is the core of clinical research information platform. The efficiency of procedures about disease prediction, personalized treatment, and assessment studies will be judged on the protein or gene level using human tissue, blood and body fluids. The research results of these biological macromolecules in human tissues will directly determine their values in clinical practices and commercial prospects. The establishment of high-quality and high-level information systems is one of the foundations of translational medicine.

A53

**Boosting health care reform and servicing people health - project description of national digital health key technology and application of regional model**

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“Eleventh Five-Year Plan” National Science and Technology Support Key Project--National Digital Health Key Technology and Application of Regional Model*: By constructing uniform standard Electronic Health Records (EHR), Electronic Medical Records (EMR), Interactive Health Care Information Platform, Two-way Referral of the communities and hospitals, telemedicine, distance education and health consultation system; By sharing digitization of health care resource, digitization of medical services, digitization of urban and rural community health services, digitization of public health services and protection regional model to effectively upgrade the disease prevention and control, capabilities of public health emergency responses, to improve service availability, to promote the reform and development of medical and health system, so as to achieve breakthroughs in information silos, integrate health care resource, optimize service processes, improve the medical treatment efficiency, reduce medical costs, make better relations with doctor-patient, protect people’s health, achieve the goal of “Everyone has basic medical and health services”. The implementation of National Digital Health project get a high opinion from leaders at all levels and domestic and foreign experts, its research get a tremendous impact on construction of health information, play a technical supporting role of boosting health care reform and servicing people health, and make important significance to promote the development of Chinese public health care.

A54

**Health informatics standardization and RHIS construction patterns**

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This report mainly introduces the importance of health informatics standardization and the current international and Chinese research status, analyzes the developing trend and prospects of health informatics standardization, discusses the RHIS (regional health information system) of two kinds of construction Patterns. On this basis, this report points out the difficulties of health informatics standardization implementation and application, and some corresponding resolving measures and advice.

A55

**Exploration on intelligent control of the hospital infection - the intelligent reminding and administration of hand hygiene based on the technologies of internet of things**

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The administration and control of the hospital infection is one of the most important parts in the quality management of modern hospital and medical
security. The hand hygiene is a major subject in the administration and control of the hospital infection. As evidences show, the hands of the medical staff carry a lot of germs and up to 30 percent of the hospital infection result from the situation that the medical staff does not wash their hands according to the desired standard. Normative hand hygiene can make the hospital infection rate reduced by 50 percent. There are several factors that affect the compliance of the hand hygiene of the medical staff. How to improve the poor compliance is a very challenging problem in the administration and control of the hospital infection. The developments of intelligent reminding and administration of hand hygiene system (IRAHHS) is a good way to radically solve the problem.

Based on the Radio Frequency Identification technology and intelligent analysis system, the IRAHHS has many reading and writing devices with perception in major infection control areas, danger areas such as around infected articles and the bedside of the patients, and hand disinfect or washing areas. When the medical staff with intelligent electronic tags touches the sources of the pollution in these areas, the electronic tags communicate with the devices and record and remind the staff of the status of their hand hygiene and ask them to do required hand hygiene behaviors. The information will be recorded and sent to the backstage simultaneously. The IRAHHS is connected to the central information system of the hospital and provides the manager with the ability to search, access, analyze the data and judge. The IRAHHS achieves the functions of intelligent perception, reminding and tracking with the help of technologies of Internet of Things. It is a novel attempt in the administration of hand hygiene and also a new idea in the administration and control of the hospital infection in China.

A56
Continuously improve the medical care quality and hospital management level through medical information system construction
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Background: The construction of medical information is important to improve the hospital medical care capability, the management decision-making level of health and the hospital operational efficiency. The construction of medical information system of the first Affiliated Hospital of Zhejiang University was begun in 1980s. Nowadays the comprehensive hospital information services and management platform have been established, centering on electronic medical records and electronic pathway. The establishment and use of these information systems played an important role in improving the degree of patient satisfaction, enhancing hospital efficiency and healthcare quality, protecting the safety of healthcare, and reducing healthcare costs.
Materials and methods: Through the construction of clinical data repository (CDR) centering on electronic medical records, the integrated medical information system has been established in our hospital. At present, CDR has integrated the clinical diagnosis and treatment system, such as the electronic medical records system of inpatient and outpatient, nurse information system(NIS), laboratory information system (LIS), radiology information system (RIS), picture archiving and communication (PACS), ultrasonic information system (UIS), pathology information system (PIS), anesthesia management system, the remote medical network service platform, and the hospital outpatient and emergency registration system, outpatient appointment service system for disease diagnosis and treatment, physical equipment management system, cost management system, financial analysis system and the construction of hospital portal website.
Results: The outpatient appointment rate of experts was more than 79%. The utilization ratio of hospital electronic medical records was almost 100%. The good quality medical record rate was over 98%. And overall efficiency of writing medical record was improved by 52.54%. The defect-free medical record rate was over 90%. The average hospital day was reduced by 7.8%. The 94 types of the clinical pathways were developed and applied in 24 departments. The remote medical network service platform was established with 90 hospitals.
Conclusions: The establishment and application of hospital information systems improve hospital services and management standards, and ultimately improve the quality of medical services, reduce the medical errors, ensure the medical safety, and reduce healthcare costs.

A57
The application and practice of the electronic clinical pathway
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Background: Since the Ministry of Health of the People’s Republic of China carried out the clinical pathway in 2009, one hundred and ten pilot hospitals in China have implemented more than 330 sorts of clinical pathways, with some hospitals adopting the hard copy version. With the increasing number of diseases in clinical pathway and the increasing number of cases in clinical practice, as well as the developing informatization reform in hospital, the rationalization of electronic management of the clinical pathway is urgently needed.
Methods: With the partition of original time division axis by key diagnosis and treatment nodes, the First Affiliated Hospital of Zhejiang University, College of Medicine has developed the electronic edition of clinical pathways through the integration of the electronic medical records, hospital information system, picture archiving and communication system, laboratory information management system and so on, which were based on the key nodes and gradually put this into clinical practice since March, 2010.
Result: Ninety five sorts of clinical pathways were developed, with 76 applied into practice. A total of 6,782 cases were managed in the clinical pathway, of which 5,913 successfully completed, with a completion rate of 67.25% and a mutational rate of 29.50%. During the recent three years, with the implementation of clinical path management, the average time length of hospital stay and preoperative hospital stay were decreased, as well as the disease mortality, hospital infection rates, the postoperative complication rates. The average cost by disease and the average daily cost remained flat or turned to be even lower.
Conclusion: The application of the electronic clinical pathway can effectively improve the efficiency and quality of health care services, and appropriately control the growth of medical cost. Nevertheless, the understanding and compliance of the clinical path application by the medical staffs is to be enhanced further. Meanwhile, the key to the implementation of the clinical pathway is to provide the clinical path management software, which is consistent with the hospital information system and can effectively reduce the workload of medical staffs.

A58
Evaluation of cardiac function at different time points after myocardial infarction of rats
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Backgrounds: Myocardial infarction (MI) model of rats is commonly used in cardiovascular research. However, the noninvasive functional evaluation parameters of this model are lack. Echocardiography is an important tool for assessment of cardiac function in clinic. This study is to explore whether changes of the cardiac function after MI of rats could be detected by echocardiography accurately.
Methods: MI were induced in rats by ligating the left anterior descending coronary artery. Cardiac function and pathological changes were measured by Dimension echocardiography and transmission electron microscope (TEM) at 24h, 1w, 2w and 4w after MI, respectively.
Results: Compared with sham group, cardiac function did not change in 24h group after ligation, but the interventricular septum thickness at end-systole and interventricular septum thickness at end-diastole in groups of 1, 2, 4 weeks after operation were significantly decreased (P < 0.05); the left ventricular internal dimension at end-systole in groups of 1, 4 weeks after MI and left ventricular internal dimension at end-diastole in 4w group were dramatically increased (P < 0.05); the ejection fraction and left ventricular fraction shortening in groups of 1, 2, 4 weeks after MI declined significantly (P < 0.05); in addition, the mitral valve E peak in 2w group was greatly reduced (P < 0.05). These data suggested that both left ventricular systolic and diastolic function were affected 1 week after MI, with changes of cardiac structure. Moreover, TEM illustration showed that nuclear pyknosis, myocardial disruption, mitochondrial swelling were present in all MI groups and severe reconstruction and fibrosis were observed especially in 4W-MI group.

Conclusion: Although cardiac structure was damaged 1 day after MI, its function was unchanged due to compensatory effect of normal tissues. With time goes on, the infarcted cardiac tissue was severely deformed and cardiac function was decreased accordingly. Echocardiography could detect the changes of cardiac function accurately after MI, which will provide important experimental evidences for the clinical diagnosis, treatments and prognostic assements of MI patients.

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A60
The role of AMPKα2 in cardiomyocytes anoxia/reoxygenation injury mediated by CI
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Background: During anoxia/reoxygenation (A/R) injury, intracellular chloride ion concentration ([Cl-]) homeostasis may play a role in maintaining the normal physiological function of cardiomyocytes. The cells protection was induced by CI-free when they were subjected to A/R injury, and we have found involvement of AMP-activated protein kinase-α2(AMPK-α2) in A/R injury. In the current study we investigated the mechanism of CI-free induced protection against A/R injury in H9c2 cells.

Methods: AMPKα2 shRNA recombinant plasmid was constructed by using pSuer.Retro vector. The H9c2 cells were randomly divided into five groups: (1) Control group; (2) A/R group; (3) removal of extracellular CI- A/R group (CI-free A/R group); (4) pSuper+ CI-free A/R group; (5) pS-AMPKα2 CI-free A/R group. The AMPKα2 protein expression was detected by western blotting. The activity of LDH was determined by auto-biochemistry analyzer. Cells viability was analyzed by MTT, MDA, SOD and GSH-Px activity in H9c2 were detected by kits. The level of intracellular ROS, the percentage of apoptosis and the mitochondria membrane potential were measured by flow cytometry.

Results: AMPKα2 shRNA recombinant plasmid was constructed successfully. A/R injury obviously decreased H9c2 cell viability, activity of SOD and GSH-Px. CI-free A/R group has been shown to produce a protective effect against A/R injury by increasing antioxidant enzyme. Once knocking down the level of AMPKα2, the protective effect against A/R injury mediated by CI-substitution apparently disappeared. Its cell viability, activities of SOD and GSH-Px, the mitochondria membrane potential were decreased while LDH activity and the level of ROS and apoptosis were remarkably increased in H9c2 cells compared with CI-free A/R group (p<0.01). There was no significant difference between CI-free A/R group and pSuper+ CI-free A/R group.

Conclusion: AMPKα2 participated in the protective effect against A/R injury produced by administration with CI-free, and sh-AMPKα2 could abolish the protective effect. The mechanism underlying CI-free against A/R injury is mainly that of low [Cl-], attenuate oxidative stress by AMPKα2.

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A61
Combination therapy of atorvastatin and probucol on ischemic stroke in clinic
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Background: Atorvastatin combined with probucol was considered in theory to be effects in treating ischemic stroke and preventing recurrent. However, the clinic data about it were very few, so we observed the effects of atorvastatin and probucol in combination in the patients with ischemic stroke.

Methods: 90 inpatients of emerging ischemic stroke were randomly selected in this study. All patients in research group,diagnosed by CT and MRI inspection, which comply with the diagnostic criteria of cerebral infarction amended by the fourth national conference. All of them signed informed consent document. And this study had unambiguous exclusion criteria. The patients were divided into 3 groups, atorvastin + probucol group(n = 30), atorvastin group(n = 30), control group(n = 30), observing for 6 months. Difference of every clinical index of these three groups was insignificant on admission. The blood lipids (including total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol
(LDL-C) and high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), pregnancy associated plasma protein (PAPP-A) level, intima-media thickness (IMT) and area of carotid intima of atherosclerotic plaque were tested before and after treatment respectively. The neurological deficit scores on the admission day and one month after admission were assessed, and the relationship between hs-CRP and the U.S. National Institutes of Health Stroke Scale (NIHSS) score and activities of daily living scale Barthel Index (BI) was analyzed.

Results: A significant drop of blood lipids (P < 0.01), IMT(P < 0.01), area of Carotid intima of atherosclerotic plaque(P < 0.01), PAPP-A(P < 0.01) and hs-CRP(P < 0.01) were observed in atorvastatin+ probucol group. All parameters were improved significantly comparing with atorvastatin alone. Neurological deficit scores of these two groups had significantly different after treatment (P < 0.01). Combination therapy had better efficacy. The correlation analysis showed that seriousness of ischemic stroke on admission day and 1 month of treatment was associated with the hs-CRP levels significantly.

Conclusion: Short-term use of atorvastatin combining with probucol could have a significant effect on ischemic stroke in clinic.

A62 Effect of Notch signal pathway on H9c2 cardiomyocytes apoptosis induced by hypoxia/reoxygenation via ROCK2
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Background: It is very important to explore the new strategies of prevention and treatment of ischemic heart disease (IHD) in molecular level. Notch signaling pathways are very expedient in terms of the protection and recovery of myocardial when the heart muscle is impaired. It is also known that ROCKs are closely related to the apoptosis of cardiomyocytes. We infer that there are interactions between Notch signaling pathways and ROCKs on cell apoptosis in H9c2 cardiomyocytes model of H/R.

Objective: 1. To investigate the effects of Notch signaling pathway on hypoxia/ reoxygenation (H/R) induced apoptosis of H9c2 cardiomyocytes in rat. 2. To explore the interaction between ROCK2 and NICD on H/R and then to reveal the mechanisms of Notch signaling pathway involved in the modulation of apoptosis and recovery of H9c2 cardiomyocytes model of H/R.

Methods: 1. The total length of cDNA fragment encoded with NICD was obtained from H9c2 cardiomyocytes from rat by reverse transcription polymerase chain reaction (RT-PCR), then the cDNA fragment was inserted into pcMv-Tag2B vector. The recombinant plasmid was confirmed by restriction endonuclease (EcoRI and SalI) digestion and DNA sequencing. H9c2 cardiomyocytes were transfected by pcMv-Tag2B-NICD and the expression of NICD was detected by Western blot. 2. The cultured H9c2 cardiomyocytes were randomly divided into six groups: Control group; H/R group; NICD group; NICD+H/R group; DAPT group; DAPT+H/R group. Apoptosis of each group was analyzed by flow cytometry (FCM), and Western blot was applied to assess the expression of ROCK2 and NICD proteins.

Results: 1. The recombinant plasmid pcMv-Tag2B-NICD was successfully constructed. After transfection into H9c2 cardiomyocytes, Western blot analysis showed that NICD was highly expressed in H9c2 cardiomyocytes. 2. The overexpression of NICD resulted in a rise of protein expression of NICD, and reduces the protein expression of ROCK2 and apoptosis of H9c2 cardiomyocytes; on the contrary, the supression of NICD leads to a reduction of protein expression of NICD; and increases the protein expression of ROCK2 and apoptosis of H9c2 cardiomyocytes.

Conclusion: 1. The recombinant plasmid pcMv-Tag2B-NICD was successfully constructed. 2. After hypoxia/reoxygenation, the protein expression of NICD was significantly increased, and the protein expression of ROCK2 was decreased, compared to control group. 3. Notch signaling pathway reduced the H/R-induced apoptosis of rat H9c2 cardiomyocytes by suppression of ROCK2 from the rat.

A63 Discovery and pharmacological study of a novel diuretic Baoxue Yang1, Wei Li, Hong Zhou, Tianluo Le
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Diuretics are widely used to raise renal salt and water clearance in a variety of conditions, such as oedema, as well as in non-edematous states such as hypertension, which can reduce morbidity and mortality of cardiovascular and cerebrovascular diseases, especially the frequency of stroke and congestive heart failure. However, long-term use of conventional diuretics has several adverse effects including electrolyte disorders, hyperuricemia, hyperlipidemia, and glucose tolerance decrease. Electrolyte abnormalities can induce cardiac arrhythmias and sudden death. Therefore, discovering a new diuretic that does not cause electrolyte disturbance becomes a hot issue. Phenotype analysis of knockout mice lacking urea transporter UT-B or various UT-A isoforms has provided evidence for the involvement of UTs in the urinary concentrating mechanism. Functional deletion of UT-B or UT-A isoforms markedly caused polyuria and urea selective low urine concentrating ability. However, deletion of UT-B or UT-A did not affect GFR and clearance rate of the principal solutes (Na+, K+, Cl-) in urine except for urea. Therefore, we suggested a hypothesis that UT inhibitors might be novel diuretics to excrete water without disturbing electrolyte metabolism. Present study discovered a potent small-molecular urea transporter inhibitor, UT-A4, using an erythrocyte osmotic lysis assay. Stopped flow light scattering experiment, a classical assay for measuring water and urea permeability, confirmed that UT-A4 reversibly inhibited UT-B activity. The experiments also showed that UT-A4 targeted the intracellular part of UT-B protein and had the same inhibition activity on influx and efflux of urea across membrane. UTinh-A4 has inhibition activity on human, rabbit, rat and mouse UT-B. We used rats as an in vivo test model for determining the diuretic activity of UT-A4. Interestingly, UT-A4 caused dose-dependent polyuria, low urine osmolality and urea concentration in rats. 18-h water deprivation raised urine concentrating ability in rats with or without UT-A4 treatment. However, urine osmolality and urea concentration remained significantly less in UT-A4 treated rats than that in control rats, except of unchanged non-urea solutes. Osmolality and urea concentration was significantly decreased in inner medullary tissue of UTinh-A4 treated rats, but not in HCTZ treated rats. All these results suggest that UTinh-A4 caused urea selective diuresis. The excretion of osmoles, urea and non-urea solutes had no significant difference between control and UTinh-A4 treated rats. However, HCTZ treated rats had significant higher excretion of osmoles and non-urea solutes than control and UTinh-A4 treated rats, which made lower blood Na+, K+ and Cl-. These results indicate that UT-A4 is a selective UT inhibitor and has urea selective diuretic activity without disturbing excretion of electrolytes. It might have potential value on drug discovery as a new diuretic without electrolyte imbalance and metabolic disorder. It might also be used as a tool drug to study the physiological roles of UTs in big animal models.

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A64 Metformin improves IKCa-mediated endothelial dilative dysfunction of arteriole in diabetic rats Li-Mei Zhao, Yong Yang, Yan Wang, Xi-Ling Deng*
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Background: Activation of intermediate conductance Ca2+-activated K+ channel (IKCa) in endothelial cells has been shown to contribute to vasodilation, especially in small vessels. The aim of this study is to observe the effect of metformin on endothelial dilative dysfunction in
diabetic rats and investigate whether the alteration of IKCa is involved in the underlying mechanism.

Methods: Diabetic rat model was induced by a single intraperitoneal injection of 30 mg/kg STZ after high fat and glucose diet for 8 weeks. Animals whose blood glucose > 11.1 mmol/L were included in diabetic and metformin group. Age-matched animals fed with standard chow and injected with citric acid buffer were served as control. Four weeks after STZ injection, rats in three groups were fed with normal diet for additional 8 weeks. After that, fasting blood was drawn and third-order mesenteric arterioles were separated. Hemoglobin A1c (HbA1c) was measured with an automatic analyzer. The changes of Ach- and NS309 (opener of IKCa) stimulated vasodilatation mediated by IKCa in mesenteric arterioles of each group and mesentry arterioles of normal rats incubated with 200 μg/mL AGE-BSA (200 μg/mL BSA as control) for 3 hours were measured by multi-myograph system. The effect of metformin on AGE-BSA (200 μg/mL) and H2O2 (100 μmol/L) induced changes of IKCa mRNA and protein expression in cultured human umbilical vein endothelial cells (HUVECs) were detected by RT-PCR and Western blot. The level of malondialdehyde (MDA) and the activity of Cu-Zn superoxide dismutase (Cu-Zn SOD) in cellular supernatant were determined by colorimetric method.

Results: Increased HbA1c level and reduced endothelium-dependent dilative response mediated by IKCa in mesenteric arterioles were observed in diabetic rats, and metformin treatment (300 mg/kg/day by gavage) restored the adverse condition. The vasodilatation mediated by IKCa was also impaired in 200 μg/mL AGE-BSA-incubated mesentry arterioles. AGE-BSA at 200 μg/mL concentration and H2O2 (100 μmol/L) significantly decreased the mRNA and protein expression of IKCa. AGE-BSA also increased the production of MDA and inhibited Cu-Zn SOD activity in HUVECs. Metformin of 10 μmol/L and 100 μmol/L reversed those effects.

Conclusion: Metformin significantly improves endothelium dilative dysfunction mediated by IKCa in diabetic rats, which is likely related to the inversion of AGEs-induced oxidation and downregulation of IKCa expression in endothelial cells.

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A65
Increased cardiac contractility by decreased HAX-1 expression
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Background: The HS-1 associated protein X-1 (HAX-1) is a ubiquitously expressed protein that protects cardiomyocytes from programmed cell death. HAX-1 is mainly located in cardiac mitochondria and sarcoplasmic reticulum. Recently, it has been recognized that HAX-1 serves as a binding partner of phospholamban, which plays a fundamental role in controlling basal contractility and constitutes a key downstream effector of the β-adrenergic signaling cascade. However, the functional significance of HAX-1 in the heart remains unclear. Our previous studies have shown that overexpression of HAX-1 in vitro or in vivo by adenoviruses and transgenesis reduced cardiac myocyte contractility and calcium transients under basal condition without significant alterations of isoproterenol response. Conversely, in vitro downregulation of HAX-1 enhanced calcium kinetics and mechanics under basal conditions.

Methods and results: To further investigate the role of the endogenous HAX-1 in the cardiac contractile function, HAX-1 heterozygous deficient mice with 36% of HAX-1 expression in the heart were characterized, since the homozygous mice are lethal at 5-12 weeks afterbirth. Interestingly, in vivo echocardiography showed that decreased HAX-1 expression was associated with significantly enhanced cardiac performance, including fractional shortening and ejection fraction, when compared to age-matched wild types. Ex-vivo Langendorff perfusion suggested markedly increased rates of contraction and relaxation, compared to wild types (Figure 1).

Furthermore, at the cardiomyocyte levels, we also found similar cardiac phenotype with elevated fractional shortening, rates of contraction and relaxation as well as calcium kinetics under basal conditions. The functional improvement in the heterozygous HAX-1 deficient mouse hearts does not play a role in the expressions of major SR calcium handling proteins, including: SERCA2a, calsequestrin and phospholamban. However, the affinity of SERCA2a for calcium was significantly increased without alteration of maximal velocity of this calcium pump. The enhanced cardiac contractility is not related to any significant cardiac remodeling and histology changes at the age of 10-12 weeks.

Conclusion: These results indicate that decreased HAX-1 expression in the heart is associated with increased cardiac contractility and calcium handling, suggesting that HAX-1 may be a novel regulator in cardiac contractile performance.

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A66
Protective effects of berberine on doxorubicin-induced nephrotoxicity in mice
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Figure 1(abSTRACT A65) WT: Wild type, HAX-1 KO HE: HAX-1 knockout heterozygous. A: EF% (percentage of ejection fraction) and FS% (percentage of fractional shortening) by echocardiography. B: Rates of contraction (+dp/dt) and relaxation (-dp/dt) by Langendorff perfusion. *: P<0.05, compared with WT.
Background and purpose: Doxorubicin, a very potent and often used anti-cancer drug, is largely limited due to the dose-related toxic effects. The present study investigated whether berberine, a natural product alkaloid, could reduce the renal injury induced by doxorubicin.

Experimental approach: Mice of either gender were randomly divided into four groups: the control group, doxorubicin group, berberine group, and berberine + doxorubicin group. In the tests, body weight, general condition and mortality of the mice were observed, and serum blood urea nitrogen (BUN) and serum albumin (Alb) levels were determined to evaluate renal function. Furthermore, the renal was excised for determination of the weight changes, as well as histopathological analysis in the tissues.

Key results: Mortality rate and significant decline in body weight, general condition and mortality of the mice were observed, and serum blood urea nitrogen (BUN) and serum albumin (Alb) levels were observed in doxorubicin-treated mice. These changes were significantly prevented by pretreatment with berberine. Histopathological studies showed that doxorubicin caused structural injuries, such as glomerular, tubular epithelial alterations and interstitial edema in the renal. These histopathological changes were largely attenuated by berberine pretreatment.

Conclusions: These findings indicate that berberine could play an important role in ameliorating the doxorubicin-induced toxicity.

A67 The effects of mitochondrial Ca\(^{2+}\) transport on intracellular Ca\(^{2+}\) waves in cardiomyocytes
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Background: Recent studies have implicated that mitochondria play important roles in intracellular Ca\(^{2+}\) homeostasis of cardiac myocytes. The major pathways for mitochondrial Ca\(^{2+}\) transport include mitochondrial Ca\(^{2+}\) uniporter and Na\(^+\)/Ca\(^{2+}\) exchanger, as well as mitochondrial permeability transition pore (mPTP) under certain pathophysiological conditions. However, it is still unclear if mitochondrial Ca\(^{2+}\) flux can affect the generation of Ca\(^{2+}\) waves and triggered activities in cardiomyocytes.

Methods and results: Cytosolic Ca\(^{2+}\) (Ca\(^{2+}\)\(_{cyt}\)) was imaged in fluo-4-AM loaded ventricular myocytes isolated from mice. Spontaneous SR Ca\(^{2+}\) release and Ca\(^{2+}\) waves (CaWs) were induced in the presence of high external Ca\(^{2+}\) (Ca\(^{2+}\)\(_{ext}\), 4 mM). The protonophore carbonyl cyanide p - (trifluoromethoxy) phenylhydrazone (FCCP) reversibly raised basal Ca\(^{2+}\) levels in the presence, as well as absence of Ca\(^{2+}\)\(_{ext}\), suggesting Ca\(^{2+}\) release from intracellular stores. Mitochondrial membrane potential (\(\Delta\Psi_m\)) was monitored by TMRM fluorescence. FCCP at 0.01- 0.1 µM, which partially depolarized \(\Delta\Psi_m\), increased the frequency and amplitude of CaWs in a dose-dependent manner. Simultaneous recording of cell membrane potentials showed the augmentation of delayed after depolarization amplitudes and frequencies, and induction of triggered action potentials. On the contrary, FCCP at higher concentrations (>0.5 µM), which completely dissipated \(\Delta\Psi_m\), eliminated CaWs while the basal Ca\(^{2+}\) remained high. The cease of CaWs was most likely due to the reduction of SR Ca\(^{2+}\) content as evaluated by rapid exposure to10 mM caffeine. Blocking sarcolemmal Na\(^+\)-Ca\(^{2+}\) exchanger by substituting Na\(^+\) with Li\(^+\) in the perfusant further elevated basal Ca\(^{2+}\) and restored CaWs. The effect of FCCP on CaWs was mimicked by antymycin A (an electron transport chain inhibitor disrupting \(\Delta\Psi_m\)) or Ru360 (a mitochondrial Ca\(^{2+}\) uniporter inhibitor), but not by oligomycin (an ATP synthase inhibitor) or iodoacetic acid (a glycolytic inhibitor), excluding the contribution of intracellular ATP levels. The effects of FCCP on CaWs were counteracted by the mitochondrial permeability transition pore blocker cyclosporine A, or the mitochondrial Ca\(^{2+}\) uniporter activator kaempferol.

Conclusions: Mitochondrial Ca\(^{2+}\) release and uptake control plasma Ca\(^{2+}\) levels and plays an important role in regulation of intracellular CaWs and arrhythmogenesis.