

Trends, Challenges and Opportunities in Biopharmaceutical Industry

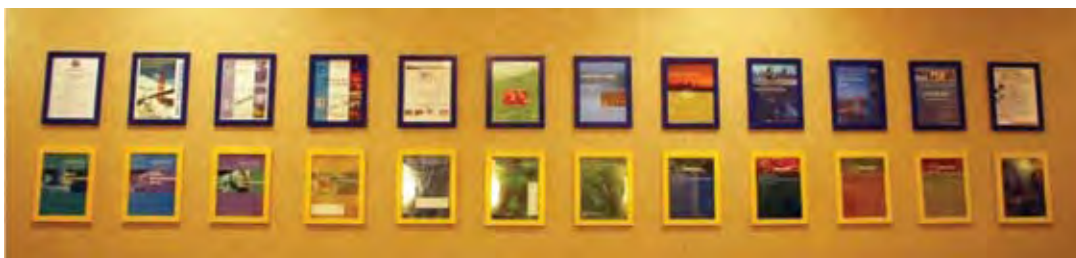
- Report on the 2008 CABS Annual Conference

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The 2008 Annual Conference of Chinese American Biopharmaceutical Society (CABS) was successfully held on June 21st at the Crowne Plaza Hotel in Foster City, California. This conference was of particular significance in CABS' history, as it marked the 10th anniversary of this organization. The theme of the conference is on the Trends, Challenges, Successes and Opportunities in the Biopharmaceutical Business. As it has been done successfully in the previous years, the annual conference provided a forum for scientists, educators, investors and business leaders involved in the broad fields of life sciences to learn about new trends, exchange ideas, foster collaborations, and extend networking. The excellent conference program attracted well over 300 attendees from local biotech companies, research institutions, investment and law firms, as well as a large number of delegates from China.



The meeting participants were first welcomed by the conference chairperson and incoming CABS President **Dr. Leping Li**. In addition to welcoming all the meeting participants, he thanked all the speakers, volunteers and sponsors for making the CABS organization strong and the meeting successful. In delivering the opening remark, current President Dr. Naibo Yang provided a brief recap of the state of the **CABS** organization and the major achievements in the year of 2007-2008. The past year was filled with a large number of highly successful and well attended events, including the educational workshops and expert forums on drug R&D, organized by the Science & Technology committee. The workshops on how to establish a company and business plan competition series, organized by the Business Development subcommittee, were well attended and appreciated by our members. He also pointed out that **CABS** has grown to become one of the most influential professional organizations in biomedical and biopharmaceutical fields in the greater northern California region.



Display of 10 year's Annual Conference brochures and issues of TBI during CABS 2008 Annual Conference



The meeting quickly tuned to the main theme. The morning plenary session featured three well-known figures in the biotechnology and biomedical fields. The first speaker was Dr. Bill Rutter, who was an accomplished professor at UCSF and Co-Founder and Executive Chairman of Chiron, and currently is Chairman and CEO of Synergenics. In **Dr. Rutter's** brief introductory talk, he stressed that changes are necessary in biotech and pharmaceutical research, especially fundamental changes in thinking. The old model of treating symptoms of diseases has passed its prime time and he outlined three key new directions for biotech R&D: preventive medicine, decisive treatment and diagnosis.

One of the keynote speeches was delivered by **Dr. Regis B. Kelly**, Director of the California Institute of Quantitative Biosciences (QB3). Dr. Kelly is a distinguished neuroscientist and served as Executive Vice Chancellor at UCSF before taking current responsibility. QB3 is a partnership between the State of California, private industry, venture capital firms, and the University of California campuses at Berkeley, San Francisco, and Santa Cruz. QB3 is one of four California Institutes for Science and Innovation established in 2000 to ensure the future of the California economy by promoting research and innovation. QB3 aims at “moving innovation from academia over the ‘valley of death’”, according to Dr. Kelly. It brings academic and clinical researchers (184 faculty affiliates), venture capital firms and the biotech industry under one roof. It makes sure that innovations from the academic labs will be turned into products helping the mankind without long delays, with funding from VC. Dr. Kelly likened QB3 to the innovation garage, with comparison to the famed start of HP. Currently many startups are being fostered in QB3 facilities in an open atmosphere. The QB3 Mission Bay facility has also attracted many mature companies such as Merck, Novartis and Pfizer to set up biotech research subsidiaries next to it. Most recently, the concept of QB3 has been adopted by Chinese City of Taizhou, Jiangsu Province, which has just completed a brand new facility modeled after and with guidance from QB3. Taizhou is located on the north shore of Yangtze River, a stone's throw away from both Shanghai and Nanjing, two major academic research hubs in China. The Taizhou City government has invested millions of dollars in QB3, and QB3 (Dr. Kelly) will advise the new venture in Taizhou.

Dr. Jim Wells, Professor of Pharmaceutical Sciences at UCSF, discussed targeting protein-protein interactions which have been regarded as “high hanging fruits” of the drug industry. Protein-protein interactions are difficult to disrupt by small molecule compounds because they have flat interfaces, tight complexes, no natural small molecule ligands and limited success by HTS. However, because many cellular functions are mediated by protein-protein interaction, success in interfering with these interactions can potentially correct many disease processes. Professor Wells reasoned that targeting protein-protein interactions is perhaps more feasible than previously realized because some of the interactions are actually quite local (hot spots), adaptive and flexible as shown by recent structural work. Indeed, there have been several successful stories, such as the Bcl-2 compound using a fragment-based approach by Abbott Laboratories, and the HDM2 compound using an HTS-based



approach by Roche, and the tethering approach that Professor Wells took at Sunesis to target IL-2 binding to its receptor. From all these examples, potent compounds were obtained and some of them have been advanced to clinical studies. Professor Wells gave an optimistic view of the future by predicting that more of these “high hanging fruits” will be reached by scientists.

There is no doubt that RNA interference has been a hot area of pursue by researcher and drug hunters in recently years. A presentation on the challenge and promise of RNAi as a therapeutic modality was given by **Dr. Alan Sachs**, Vice President of RNA Therapeutics at Merck Research Laboratories and Site Head of the Sirna Therapeutics. He summarized the research field of the small interfering RNA (siRNA). Dr. Sachs listed the challenges faced by siRNA as human therapeutics, such as poor stability, limited tissue uptake, innate immune response, and off-target gene silencing. He then outlined how those challenges are overcome by chemical modifications of oligonucleotides. For example, replacing the “2-hydroxyl” on the ribose sugar with methoxyl or fluoro group greatly improves the in vivo properties of siRNA. Gene expression array is used to select candidates with high specificity. In addition, Sirna is among very few research organizations which have successfully developed siRNA primate models, which are crucial in selecting siRNA therapeutic candidates for clinical trials in human. The most advanced siRNA clinical candidates are already in phase II trials.



Dr. Sachs' talk was followed by a presentation on gene therapy and antisense therapy from **Professor Mark A. Kay** of Stanford University. Dr. Kay is the Director of the Program in Human Gene Therapy at Stanford and a world renowned expert in the field. Many challenges facing siRNA also first confronted and are still confronting the development of gene and antisense therapies. In Dr. Kay's group, recombinant adeno-associated viruses (AAV1 and AAV2) are developed as vectors to deliver genes. AAVs are found in human and non-human primates and are not associated with human tumors or other acute pathology. These features make AAVs ideal as vectors for delivering genes and over 40 clinical trials have been approved for AAVs. Finally, Dr. Kay stressed that no animal models, even non-rodent large animal models, can predict the outcomes of human clinical trials in gene therapies.

Professor Didier Stainier of UCSF presented his work on embryonic development of endoderm-derived tissues in zebra fish as a model organism. Using forward genetic screens, his lab discovered a number of genes involved in the development of endoderm-derived organs, such as liver and pancreas. A particular interest of the lab is the study of the development of β cells in pancreatic islet. Because β cells are the cells that secrete insulin, understanding their development may help derivation of these cells from embryonic stem cells in cell replacement therapy for diabetes. Professor Stainier described a study in zebra fish where he discovered that the Hedgehog signaling pathway is critical for the early development of the β cells in a non-autonomous manner. Such result is very helpful in guiding stem cell researchers to generate fully functional β cells for cell therapy. Professor Stainier finally revealed a novel approach to specifically ablate certain cell types in zebra fish. This genetic approach uses nitroreductase and a



pro-drug which selectively destroy β cells in the pancreas. This assay can then be used to screen for compounds that restore the cells as potential drugs in regenerative medicine for diabetes.

Stem cell research and its application to human therapeutics in an industry setting were exemplified by a presentation by **Dr. Tim Hoey**, Vice President of Cancer Biology at Oncomed Pharmaceuticals. The cancer stem cell theory views cancer from a developmental biology perspective. It hypothesizes that many cancers are maintained by the self-renewal and differentiation of a few stem cells, and these cells are why current chemotherapy cannot eradicate cancers. Oncomed scientists isolate putative cancer stem cells from primary tumors, then directly xenograft them in mice. These primary tumor models preserve the cancer stem cells and are more reflective of human tumors than traditional cell line-based xenografts. They elect to target a few pathways known to be important for stem cell self-renewal and differentiation, such as the Wnt pathway and the Notch pathway. One of their drug candidates, antibody OMP-90R210, is approaching Phase 1 clinical trials.



Dr. Mark Gallop, Co-Founder and Senior Vice President of Research of XenoPort, presented the successful story of XenoPort, a company that was built to harness the power of nutrient transporters for optimizing drug absorption and disposition. There are 47 recognized SLC (solute carrier) families responsible for the absorption of a wide variety of nutrients, such as amino acids, peptides, sugars, nucleosides, and vitamins. Prodrugs can be designed as substrates for these transporters to enhance the in vivo properties of the parent drugs, including permeability, solubility, absorption, half-life, first-pass metabolism, CNS penetration, and tissue targeting. Dr. Gallop illustrated the advantages of transported prodrugs with the example of XP13512, a prodrug for gabapentin. Gabapentin has achieved blockbuster status but suffers suboptimal PK (high inter-patient variability, short half-life, not amenable for sustained release, ceiling concentration in blood), and thus suboptimal efficacy in certain indications. XenoPort designed XP13512, a substrate of MCT (monocarboxylate transporter) as a prodrug. The prodrug is well absorbed in the GI track and rapidly converted back to the parent drug, which achieves plasma exposure several times higher than that of gabapentin. Also very importantly, XP13512 was successfully formulated for sustained release to achieve once daily oral administration. Due to the superior properties compared to its parent, XP13512 was partnered on very attractive financial terms with GSK. Finally, the company has developed strategies for the compound to avoid competition with cheap generic gabapentin by focusing on diseases where gabapentin was found limited efficacy (thus not approved for the indications), such as restless leg syndrome, migraine prophylaxis, and diabetic neuropathy. XP13512

has shown significant efficacy in restless leg syndrome in phase 2 clinical trials and currently is in phase 3 development.

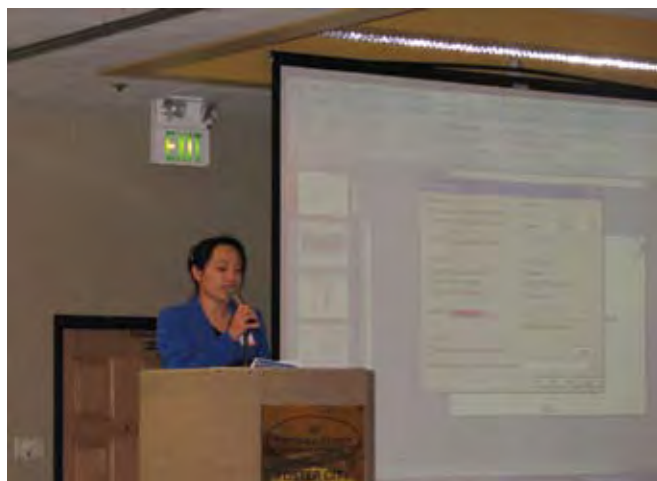
With the day progressing, the focus of the discussion gradually moved toward the business



aspects of the spectrum. The partnership and collaboration between academia, biotech companies and traditional pharmaceutical companies were the hot topics of discussion.

Mr. William Keller, Consultant to Zhangjiang High-Tech Park, Shanghai, provided an overview of the Zhangjiang High-Tech Park. Mr. Keller is among the few people who had the vision and faith in Zhangjiang more than ten years ago, and has been awarded Honorary Citizen of Shanghai by the municipal government. He was the General Manager of Roche China Ltd. and Shanghai Roche Pharmaceutical Ltd. from 1994 to 2002, and started his own consultant business in Shanghai in early 2003. Zhangjiang High-Tech Park was founded in 1992 and has now become the prime location for innovation and high tech in China, having drawn thousands of local and overseas talents and entrepreneurs to the park. Zhangjiang Pharma Valley is an integrated life science value chain with focuses on biotechnology, modernized Chinese medicine, chemical drugs, medical devices and diagnostics, and specialty chemicals. It has over 29 major plants, over 14 R&D centers established by multi-international companies, over 32 contract research organizations, and over 226 medium to small size biotech companies. Its incubator facilities have housed many young and innovative companies and attracted great interest of local and global venture capital funds. In the past 18 months, around 250 million US dollars was invested in Zhangjiang for life science, and the investment is accelerating.

Dr. Jing-Shan Hu, Director of Licensing & External Research of Merck, delivered a talk entitled “Partnership: a model for success.” In her current capacity, Dr. Hu is responsible for identifying and developing new product and technology opportunities in Mainland China, Hong Kong, and Taiwan for Merck. Dr. Hu highlighted the difficulties and challenges in the development of clinical drug products in today’s business environment, including pressure to increase probability of success, pressure to decrease time and cost, competition from both large and small companies, loss or expiration of intellectual property protection, increased regulatory scrutiny, and pricing pressure. Faced with these challenges, it has become more and more difficult to develop a clinical drug product. For example, in 2007, there were only 19 new drugs and vaccine that were approved in the United States, the lowest number since 1983. Dr. Hu indicated that innovation remains the key to long term success, and that companies should not only encourage innovation internally, but also look externally for resources and complementary strength. Biotech and small pharmaceutical companies, academia, and research institutes are very strong in discovery and innovation. Big pharmaceutical companies, on the other hand, are very strong in commercialization and product development. A win-win situation will be created by combining these two complementary strengths. For example, collaboration and partnership have been increasingly important to Merck’s long term business and research strategy. Approximately 250 significant transactions occurred over the past five years. Intellectual property has been critical for the different types of collaborations, including acquisition, product licensing, technology licensing, and partnership.



Following Dr. Hu’s talk on business partnership and collaborations, **Mr. Tom Duley**, of counsel from Morgan Lewis & Bockius LLP, provided an overview on legal issues in business agreements, including service agreement, licensing agreement, and collaboration and joint ventures. Collaboration and joint ventures is usually the most complex legally and operationally, and involves negotiations on various aspects such



as the scope of the collaboration, intellectual property rights, sharing of costs and profits, and other factors. **Mr. Duley** emphasized that, in addition to patent rights, technology know-how is another kind of intellectual property that needs to be considered and negotiated during the drafting of the business agreement. Freedom to operate is another important issue to keep in mind, as parties need to understand whether third party intellectual property is needed for the operation of the business and whether licensing of the third party intellectual property is possible and necessary. **Dr. Duley** also emphasized that alliance management is important for a successful collaboration. As for cross-border collaborations, which involve unique cultural, financial, and legal issues, **Mr. Duley** advised that effective communication and reliance on financial

and legal expert is critical for a successful collaboration.

Following a relaxing and entertaining dinner banquet and performance show, the evening session of the annual conference devoted to discussions on the future of Chinese biotech and pharmaceutical business.

Dr. Marietta Wu, Vice President of the Great China Group at Burrill & Company, was the first speaker at the evening session. Burrill & Company is one of the largest and most successful life science venture capital companies. In her current capacity at Burrill & Company, Dr. Wu focuses on venture capital investing in China related life sciences opportunities and manages the fund raising effort for the Burrill China fund. Dr. Wu has identified several aspects of the Chinese life science industry that make it a potential center of gravity for the life science industry. These include rapidly growing local market, efficient drug development resources, increasing support from the government by funding major life sciences clusters across China, and significant improvement on the enforcement of industry and regulatory standards and intellectual property laws. The unparalleled business opportunities in China are particularly appealing because IPO and mergers and acquisitions are all possible exits for Chinese life sciences companies. Dr. Wu indicated that the investment opportunities in China have gone beyond sales, marketing and services and shifted towards drug development, particularly in the areas of infectious disease, cardiovascular disease, diabetes, and oncology. Dr. Wu predicted that, by 2020, China will become the second largest pharmaceutical market globally and be a major source of funding and innovation.



In her talk titled “The Historic Opportunity,” **Dr. Xiaochuan Wang**, Chairman and CEO of Sundia Meditech Company Ltd., used Sundia as an example to show how the CRO industry in China has evolved in recent years to meet the huge market demand. Sundia was founded in 2004 and has now become a leading pharmaceutical and biotech R&D outsourcing company. Recently merged with United Pharmatech and allied with HD Biosciences, Sundia offers broad and integrated services of custom organic synthesis, medicinal chemistry, process chemistry, API manufacturing, bioassay, and PK studies both in vitro and in vivo. Sundia has successfully established collaborations with over 50 client companies in North America, Europe, and Japan. The company has 300 employees, and was named one of the top 50 companies for investment in China in 2007.

The annual conference was concluded with an insightful and stimulating panel discussion moderated by **Dr. Marietta Wu**. Other panelists include **Dr. Xiaochuan Wang**, **Dr. Jing-Shan Hu**, and **Mr. Tom Duley**, **Ms. Shuang Zhang** (CEO of Suzhou Research Co.) and **Dr. Cheng Liu** (CEO of Eureka Therapeutics) also participated in the panel discussion. Each panelist provided their unique perspective on conducting business in China. **Dr. Jing-Shan Hu** discussed the challenges in identifying potentially valuable technologies for licensing from among the many different technologies and business opportunities presented. **Dr. Liu** discussed the necessity of reconciling the cultural and ideological differences between US and China in managing his cross border company. **Ms. Zhang and Dr. Wang** discussed the exciting and challenging opportunities in the booming CRO industry in China.

The 2008 CABS annual conference concluded with great success and highly positive feedbacks from the attendees, and once again raised the bar for future CABS conferences.

