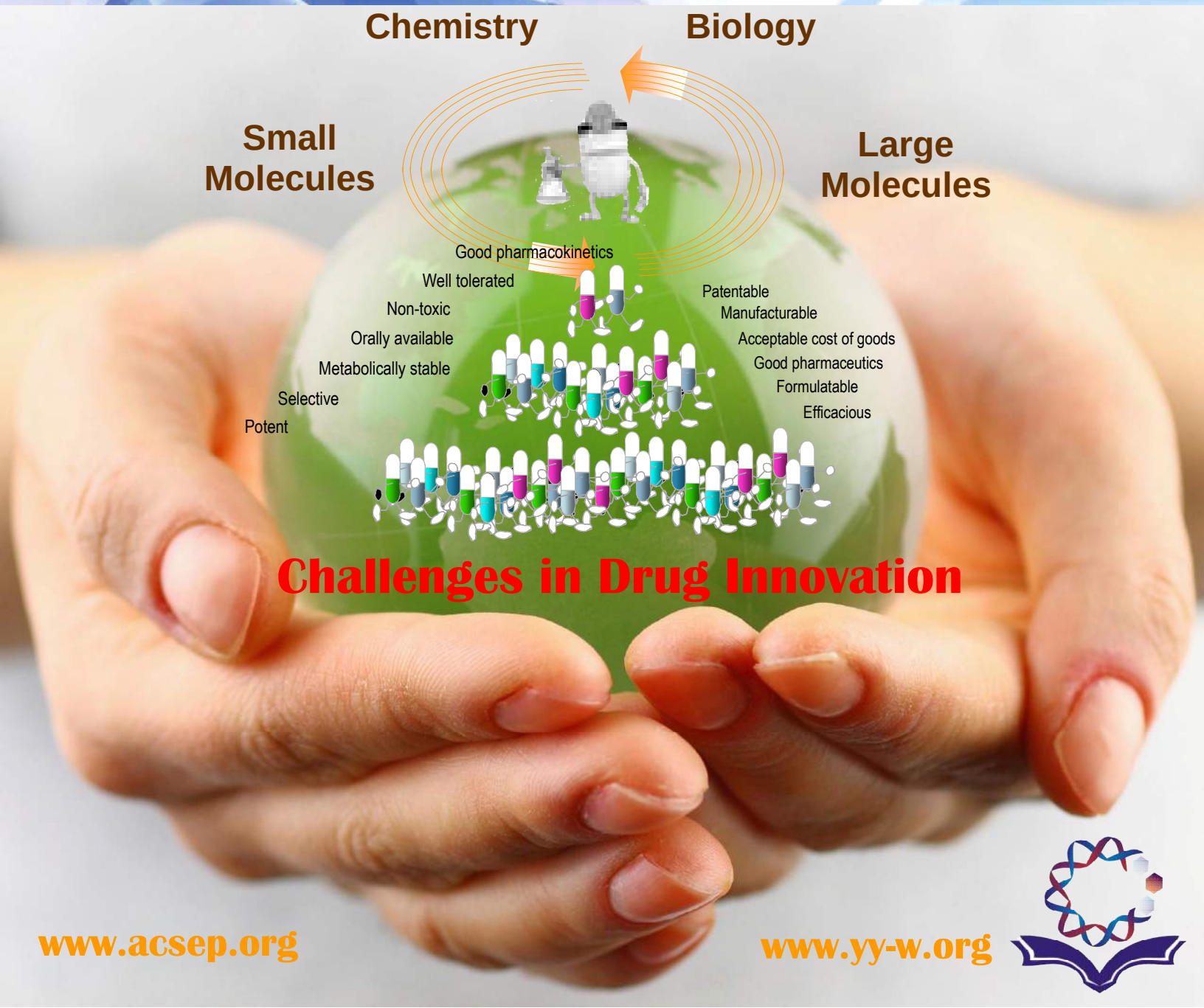
The 2nd Annual Chicago Biotech-Pharma International Symposium

Evolving Trends in Pharmaceutical Innovation and Impact to Emerging Markets

Renaissance Schaumburg Hotel & Convention Center

May 8, 2011



Challenges in Drug Innovation

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About Organizers

Biotech and Pharmaceutical Society of ACSE

The Association of American-Chinese Scientists and Engineers (ACSE, www.acse.org) is one of the largest not-for-profit organizations for Chinese in North America with more than seven thousand members. Biotech and Pharmaceutical Society (BPS) is a professional society of ACSE (www.acsep.org), and is committed to serving the needs of the ACSE members today and in the future in all areas of biotech and pharmaceutical sciences. BPS temps to bring together all Chinese people and groups in North America and beyond with an interest in biotechnology and pharmaceuticals. BPS aims to provide a dynamic platform for the exchange of knowledge among our members, and seeks to offer ongoing education, opportunities for networking, and professional development. BPS encourages the active participation, and is truly driven by the needs of its members.

Yaoyuan (Pharma Open Source)

Yaoyuan (Pharma Open Source, www.yy-w.org) is a web-based initiative with primary objectives of providing a public and Wiki-like information-sharing platform with focus on the following: (1) Latest innovations on drug discovery and development. (2) Information on drug discovery tools from IP, assay and lead optimization technologies, animal models, CMC, to IND filing, (3) A Pharma-Wikipedia, and (4) Resource for pharmaceutical companies both in China and US. Yaoyuan has connections with a good portion of the pharmaceutical companies in China.

CONTENTS

Setting Innovation in Motion

We're driven to improve people's lives. Takeda strives toward better health for patients worldwide through leading innovation in medicine. At Takeda, we make a commitment to make a difference.

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TO ATTENDANTS & COVER STORY

The global economic recovery remains fragile. While emerging markets including China, India and Brazil continue to show strong growth, other parts of the world are still in or at risk of recession and have legitimate concerns about how deep and how long the economic downturn will be. The pharmaceutical industry, in particular, faces even more challenges. Increasing R & D cost, tighter FDA regulations, as well as generic competition, all warrant continuing scientific innovations and a novel, efficient and synergistic business models of drug discovery. The key questions would arise: How are we going to do this? What will the pharmaceutical industry look like in 10 years? The 2nd Annual Chicago Biotech-Pharma International Symposium on May 8 brings together scientific experts, business leaders and professionals in the field and provides an exciting opportunity to discuss these key questions.

The theme of this symposium is "**Evolving Trends in Pharmaceutical Innovation and Impact to Emerging Markets**", emphasizing the latest life science innovations applicable to drug research and development, as well as novel business models for the ever-changing pharmaceutical environment. Prominent speakers from both the US and China , along with information-rich exhibits and job fairs, will fill the agenda.

The scientific program of this symposium consists of four sessions. In the first session, experts from academia will present the latest advances in biological sciences and their applications in drug discovery and development. Topics include bio-innovation in China, biologics-based cancer therapy, and novel treatments for neurological disease. In the second session, executives from major pharmaceutical companies will present cutting-edge sciences and the most advanced technologies that are being pursed to discover novel treatments for human diseases, as well as their in-depth thinking about R & D in the pharmaceutical industry. In the third session, renowned pharma experts from China will provide an overview of drug discovery in their country and describe how the nation's universities act as an incubator for innovation. Case studies from Chinese pharmaceutical companies will also be presented. The final session will highlight the status and possible future directions of CROs in China. The major support from both central and local governments in China to entrepreneurs will be also covered. A partner from Brinks Hofer Gilson &Lione, the largest IP law firm in Chicago, will explain the impacts of intellectual property law in pharmaceutical industry.

In the Lunch Session, two major pharmaceutical CROs in China, Sundia MediTech and Medicilon, will showcase their quality service and collaborative models for drug discovery.

We warmly welcome scientists, students, executives, business and opinion leaders and all other professionals in the pharmaceutical and associated communities to this exciting conference.

Finally, we are very grateful to our sponsors, whose names are listed in a separate sheet. This event could not happen without their generous financial support.

ORGANIZING COMMITTE

of the 2nd Annual Chicago Biotech-Pharma International Symposium

Dr. Gui-Dong Zhu (Chair)
Volwiler Associate Fellow
Abbott Laboratories

Dr. Paul Mar
Founder & CEO
SynChem Co.

Dr. Yingming Zhao
Associate Professor
University of Chicago

Dr. Xuesong Liu
Sr. Scientist III
Abbott Laboratories

Dr. Zhi-Fu Tao
Sr. Scientist III
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Xiangdong Xu
Sr. Scientist II
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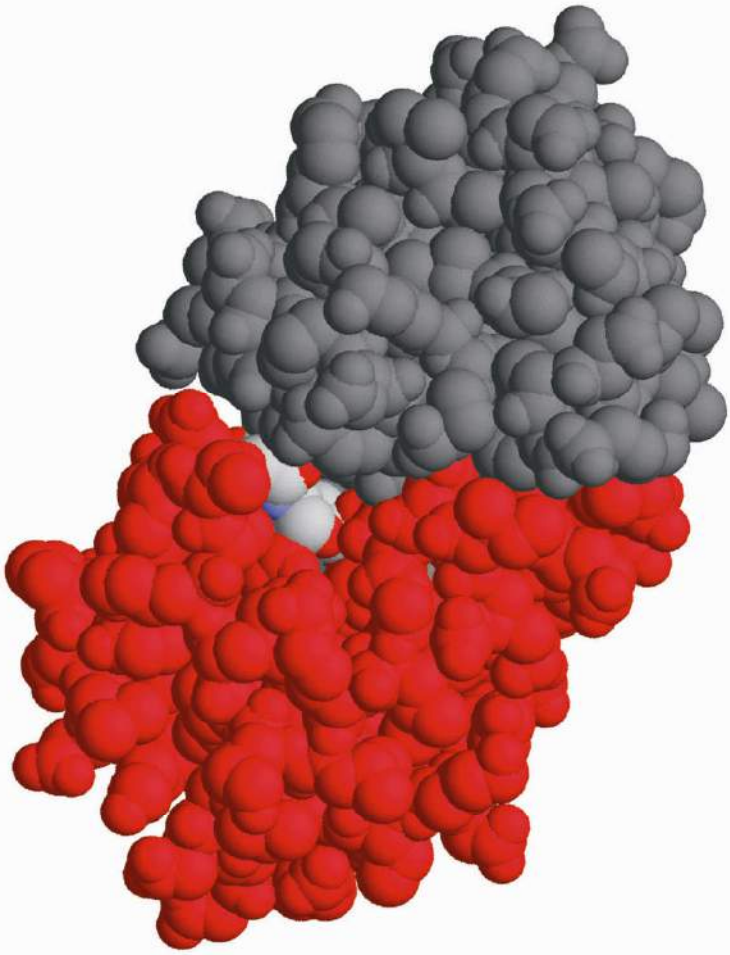
Dr. Haiying Zhang
Sr. Group Leader (former)
Abbott Laboratories

Dr. Lin Zhao
Associate Director
Takeda Global R&D Center

Contact: Gui-Dong Zhu, e-mail: guidongzhu@acsep.org; Tel. (847) 739-6251



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The 2nd Annual Chicago Biotech-Pharma International Symposium

Evolving Trends in Pharmaceutical Innovation and Impact to Emerging Markets

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May 8, 2011

Agenda

8:00 - 8:30 AM Registration

8:30 - 8:40 AM Opening Remark
Dr. Yingming Zhao, Associate Professor, University of Chicago

8:40 - 8:45 AM Introduction to ACSE
Dr. Lubo Zhou, President, The Association of Chinese-American Scientists and Engineers (ACSE)

8:45 - 8:50 AM Greetings from Consulate General of the People's Republic of China in Chicago

8:50 - 10:45 AM Session One
Moderator: Dr. Xuesong Liu, Sr. Scientist III, Abbott Laboratories

8:50 - 9:25 AM Perspective on Bio-innovation in China
Dr. Anning Lin, Professor & Director, Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Science; Professor, Ben May Department for Cancer Research, University of Chicago

9:25 - 10:00 AM The Potential Role of Antibody in Antitumor Treatments
Dr. Yang-Xin Fu, Professor, Department of Pathology, University of Chicago

10:00 - 10:35 AM Small Molecule TrkB Agonist Useful for Treating Neurological Diseases
Dr. Keqiang Ye, Professor of Pathology and Laboratory Medicine, Emory University

10:35 - 10:45 AM Coffee Break

10:45 - 12:30 PM Session Two
Moderator: Dr. Paul Mar, Founder & CEO, SynChem Co.

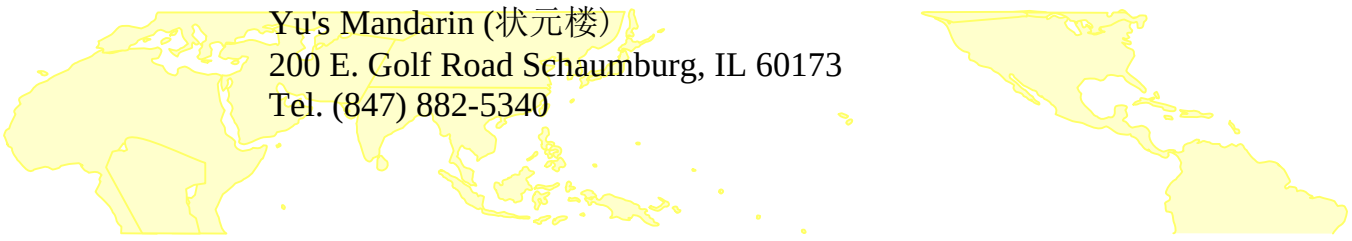
10:45 - 11:20 AM The HCV-Proteas Inhibitor: Telaprevir
Dr. Youssef L. Bennani, Vice President Drug Innovation, Vertex Pharmaceuticals

11:20 - 11:55 AM CNS Drug Discovery in the New World: Can We Innovate Back to the Future?
Dr. Erik Wong, Director of External Alliance, AstraZeneca

11:55 - 12:30 PM Enabling Chemistry Technology - Key role in Future Drug Discovery success
Dr. Stevan Djuric, Senior Director, GPRD, Abbott Laboratories

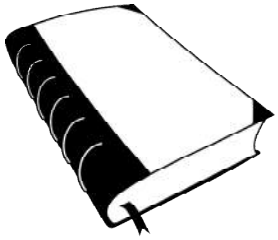
12:30 - 2:15 PM Lunch Session
Moderator: Xiangdong Xu, Sr. Scientist II, Abbott Laboratories

12:50 - 1:20 PM	Sundia: Your Partner for Drug Discovery and Development in China Dr. Charles Huang, VP of Global BD, Sundia MediTech Company Ltd
1:20 - 1:50 PM	Medicilon: Your Partner in Drug Discovery and Development Dr. Bingbing Feng, VP Business Development, Shanghai Medicilon, Inc.
2:15 - 4:00 PM	**Session Three** Moderator: Dr. Zhi-Fu Tao, Sr. Scientist III, Abbott Laboratories
2:15 - 2:50 PM	China Takes on Pharma Innovation Dr. Hualiang Jiang, Professor & Deputy Director, Shanghai Institute of Materia Medica, Chinese Academy of Science; Dean, East China University of Science and Technology, School of Pharmacy
2:50 - 3:25 PM	Beijing University Health Science Center : From Key Innovations to Technology Transfer Dr. Jia Tian, Professor & Director, Beijing University Health Science Center, Technology Transfer Office
3:25 - 4:00 PM	Discovering Me-Better Drugs in China: Magic Formula Dr. Peng Cho Tang, CSO, HEC Pharma Group
4:00 - 4:15 PM	Break
4:15 - 6:00 PM	**Session Four** Moderator: Dr. Haiying Zhang, Associate Research Fellow, Abbott (former)
4:15 - 4:50 PM	Building Synergies in New Drug Discovery: Perspectives on New Scientific and Business Strategies Dr. Xiaochuan Wang, Chairman and CEO, Sundia MediTech Company Ltd
4:50 - 5:25 PM	The Great Opportunity in Jiaxing for Bio-Science Projects – Jiaxing International Bio-Science Park Feng Sheng, Sr. Advisor, Shanghai Pharm Valley Jiaxing International Bio-tech Park; President, StudyManager Inc., China Operation
5:25 - 6:00 PM	What Every Biotech/Pharma Executive Should Know about Intellectual Property Dr. Jeffery Duncan, IP Lawyer & Partner, Brinks Hofer Gilson & Lione
6:00 PM	**Conclusion**
6:30 - 8:30 PM	**Dinner (Invited Guests)** Yu's Mandarin (状元楼) 200 E. Golf Road Schaumburg, IL 60173 Tel. (847) 882-5340



BIOGRAPHICAL SKETCH (in alphabetic order)

Youssef L. BENNANI



Youssef Bennani (*PhD., MBA*) is currently Vice-President of Drug Innovation at Vertex Pharmaceuticals in Cambridge, MA, USA. His responsibility includes leadership of drug discovery chemistry, pharmacokinetics, drug metabolism, computational and analytical chemistry. He obtained his doctoral degree in chemistry under the guidance of Prof. S. Hanessian and furthered his studies with Prof. K. B. Sharpless. He previously worked for Ligand Pharmaceuticals, Abbott Laboratories and Athersys Inc. Over the past ~20 years, he successfully led several research programs in neurology, metabolism, immunology, infection [bacterial, viral and fungal], and oncology, delivering a number of new molecular entities in various stages of pre-clinical and advanced human clinical development. He has been an invited, plenary and keynote speaker in a number of venues both nationally and internationally.

Stevan DJURIC

Dr. Stevan Djuric is responsible for the Medicinal Chemistry Technology and Structural Chemistry groups at Abbott Laboratories. Their current efforts are focused on new initiatives in the areas of high throughput synthesis and purification and the design and construction of novel compound libraries for lead targeting and identification. In addition, he is currently the head of the global Abbott Medicinal Chemistry Leadership Team. During his tenure at Abbott Laboratories, Dr Djuric has been a Project Leader for groups in the Immunoscience, Metabolic Disease, and Antiinfective areas. Several of these programs have advanced compounds into clinical development including Abbott's proprietary rapamycin analog, Zotarolimus, used for the Endeavour stent currently marketed in the United States and Europe. Dr Djuric has over 140 scientific publications, presentations and patents/applications pending. He has also given over 20 invited lectures at universities and national meetings. He is a member of the Editorial Advisory Board for the Journal of Medicinal Chemistry and, in addition, holds an Adjunct Professorship in the Department of Medicinal Chemistry at the University of Kansas.

Jeffery DUNCAN

Jeffery M. Duncan is a shareholder and former chair of the Biotechnology and Pharmaceutical Group at Brinks Hofer Gilson & Lione. Mr. Duncan joined the firm in 1984 upon graduating from The J. Reuben Clark Law School at Brigham Young University. He has been a shareholder since 1990. Mr. Duncan's practice includes counseling and preparing opinions in patent, trade secret and licensing matters; evaluating, negotiating and drafting technology transfer and joint venture agreements; performing intellectual property evaluations, audits and due diligence reviews; litigating patent and trade secrets cases; and preparing and prosecuting patent applications in the U.S. and abroad. His practice has concentrated on the following technologies: pharmaceuticals, biotechnology, diagnostics and chemistry. Since 2005, Mr. Duncan has taught Patent Law as an adjunct professor at The John Marshall Law School. His students at John Marshall have included over 70 officers and examiners from the State Intellectual Property Office of China (SIPO). He has traveled extensively in China, giving lectures on U.S. IP Law and meeting Biotech and Pharmaceutical companies in 15 different cities.

BIOGRAPHICAL SKETCH

Bingbing FENG

Dr. Bingbing Feng is the Vice President of Business Development, Medicilon, responsible for business development in the Central and Eastern United States. Dr. Feng started his career in the pharmaceutical industry in GSK and worked in R&D and manufacturing departments as scientist and group leader. He also served as Vice President of Operation and Business Development, Frontage Laboratories in Shanghai. Dr. Feng graduated from Purdue University with specialty in Analytical Chemistry.

Yang-Xin FU

Dr. Fu graduated from Shanghai Medical University for his medical degree in 1983 and the University of Miami for his PhD in 1990. He completed his resident training in PUMC hospital in 1986. He also passed US medical board in 1993 and clinical residency in Washington University in 1998 and become attending physician and assistant professor in the University of Chicago in 1998. He become few faculty promoting to tenured Professor directly from Assistant Professor in the University of Chicago in 2005. He has published more than 160 papers and currently is an associated editor in the journal of Immunology and China Science (Biology section). Dr. Fu has extensive experience in proposed area. He has worked on tumor immunology since 1987 and LIGHT/LTbR pathway since 1998. His team has published a series reports showing the recruiting and activating role of LIGHT on DC, NK, and T cells for local and distal tumor. They have addressed all aims proposed in previous cycle. His team had a team of two postdoc, one Ph.D student, and a senior technician have worked on various form of anti-neu antibodies and ScFv-LIGHT since 2006. The new approach has revealed that anti-HER2/neu antibody mediated tumor regression depends on not only FcR+ cells but also T cells. It opened new field in antibody-mediated cancer treatment. Currently, a manuscript addressing the role of anti-neu antibody in tumor regression has been well received by Cancer Cell and the revision is under review. There is strong probability that the data obtained here can change the paradigms by which antibody therapy is used, particularly for enhancing long-term immune protection from tumor regrowth, and for combination with immunotherapies. The study is highly significant and translatable, which may potentially change clinical practice of HER2/neu+ tumor in combination of radiation and passive antibody as well as fusion protein with active immunotherapy for improving clinical outcome.

Charles HUANG

Charles Huang joined Sundia in March 2008, a top Chinese CRO that provides fully-integrated drug discovery and development services to its worldwide clients. Charles is currently Vice President of Global Business Development who is responsible for all US and Canadian markets. Prior to Sundia, Charles served as president of Amnova, a pharmaceutical consultant firm in US. He worked for 15 year as medicinal chemist at Neurocrine Bioscience Inc (NBI), Johnson & Johnson and Amylin, including 4-year part-time experience on CRO project management and new market BD for advanced clinic candidate. During his tenure at NBI, Charles made significant contributions to CRF1, CRF-BP, and Insomia projects, all resulting major collaborations with Johnson and Johnson, Eli Lilly and Pfizer. He is co-author for 22 publications, 10 presentations and 12 US patents. Charles graduated with BS in Polymer Chemistry from University of Science and Technology of China (USTC) in 1989, and obtained his MS in organic chemistry at California State University at Northridge. Besides his science and business career in drug discovery, Charles founded a non-profit 501c3 charitable organization in 2004 where he served as President (2004-2008) and Chair of Board (2008-2010).

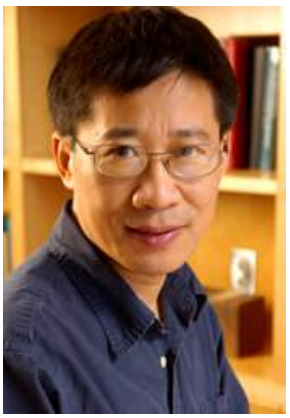
BIOGRAPHICAL SKETCH

Hualiang JIANG

Dr. Hualiang Jiang was born in Wujin County, Jiangsu Province on January 10, 1965. He obtained his Bachelor of Science degree from the Department of Chemistry, Nanjing University in 1987. In September 1989 he entered East-China Normal University, from which he received his Master of Science degree in physical chemistry (quantum chemistry) in 1992. From September 1992 to July 1995, he studied at the Shanghai Institute of Materia Medica (SIMM) at the Chinese Academy of Sciences for his Ph.D. degree in organic chemistry. He is currently a professor at SIMM, where he is also the deputy director of the institute and the director of the Drug Discovery and Design Center . He is the chief-scientist of one 973 project and is a member of the scientific committee of several major research programs in China, such as the 863 Program in Biology and Medical Technology, the National Basic Research Program in Protein Science, and the Major Research Project of the National Natural Science Foundation. He also serves on the Editorial Advisory Boards for several journals such as the Journal of Medicinal Chemistry (Senior Editor) and ChemMedChem. He has been the recipient of numerous awards, including the Natural Sciences Award of China, the 5th Prize of Yong Scientist Awards of China, and the Natural Sciences Award of Shanghai, and has been named one of the Top-10 Outstanding Scientists of Shanghai (2001-2003).

Anning LIN

Professor Anning Lin received his Ph.D. degree at the University of Alabama at Birmingham (UAB) in 1990. Following postdoctoral training with Dr. Michael Karin in the Department of Pharmacology at UCSD from 1991 to 1996, he joined the Department of Pathology at UAB as a tenure-track Assistant Professor. He relocated from UAB to Ben May Department for Cancer Research at the University of Chicago in 1999. He has been a full professor in the department since 2006. Since 2009, he has been the Director of Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Science. Dr. Lin's research focuses on studying mechanisms and regulations of protein kinase-mediated signal transduction in inflammation, apoptosis, and neoplastic transformation. He is one of leading experts in the field of signal transduction and in the biology of NF-kappaB and JNK pathways.



Feng SHENG

Mr. Feng Cheng is the President of China Operation, StudyManager Inc., where his responsibilities are to build StudyManager eClinical Trial system brand name and develop customer base in China. With StudyManager easy-to-use and easy-to-implement solution to customers in China, Feng is able to have more than 10 customers within a year and provide Study Manager Products as the best and affordable solution to CROs and Pharma in China. Prior to StudyManager, Mr. Cheng was a Sr. Director at Vertex Pharmaceuticals Inc., a major BioTech company in Boston, Massachusetts. At Vertex Pharmaceutical Inc., Feng managed staff of 35 that supported 200 end-users in General Administration, Drug Discovery, and Drug Development departments as well as 1,500 end-users at Vertex's three sites. Feng Cheng started his carrier with Warner-Lambert Co. over 20 years ago. His responsibility there was to manage all discovery and development systems. He was successfully developed and implemented GLP or GMP systems. Mr. Cheng currently is a Sr. consultant for Jiaxing Bio-Science International Park and serves as a Board member. He is a Special Advisor to some Chinese Bio-Tech and IT outsourcing companies. Mr. Cheng has broad experience at BioTech and Pharmaceutical industry. He has more than 20 years experience in all aspects of drug discovery and development, including GxP environments, enterprise resource planning, Laboratory Information Management, Electronic Document Management, Clinical Data Management, Clinical Safety, Quality Management, Learning Management, ITIL and systems such as Portals, UNIX, Linux, TCP/IP, DHCP, WINS, DNS, RAID, LAN, WAN. Dr. Cheng received a B.S. in Chemical Engineering, a MS in Computer Science, and a MBA.

BIOGRAPHICAL SKETCH

Peng Cho TANG

Cho is one of the very few medicinal chemists who has discovered and developed clinical candidates first in US and then China and back to US. He is definitely the only one with 11 clinical candidates in total. Cho received his PhD training in organic chemistry here at The University of Chicago with Bill Wulff in just four years. After a postdoctoral training at Columbia University with Gilbert Stork, he has engaged in drug discovery for over 25 years. He is now CSO for Shenzhen Dongguan HEC Pharm responsible for all matters in new drug discovery up to global clinical development. In his first month of taking such role, he has led a New Drug Discovery Innovation team for HEC to apply for funding from Guangdong Department of Science and Technology. His proposal scored the highest points and will receive up to 50millions RMB funding for HEC. In his new venture, he and HEC will bring in new discovery technology with special equal emphasis in medicinal chemistry, discovery biology and pharmacology, including fragment based screening and structural biology, another pioneer move from Cho. Cho is best known as the inventor of SUTENT. Cho is the chief architect of pyrrole indoliones as tyrosine kinase inhibitors that have yielded SUTENT for human GIST/RCC/Pancreatic cancers and Palladia for canine mast cancer. Cho is a true pioneer in moving new drug discovery in China and has since dedicated to help Chinese people and domestic company to develop newer medicines. His first three years of work at Shanghai Hengrui with average only 30 FTEs with 15% of them with PhD degree without support in structural chemistry and biology have yielded six clinical candidates for Hengrui and Hansoh. The most significant milestone for Discovered-in-China clinical candidate is Regaliptin that was Cho's discovery and the first NCE small molecule ever into US clinic for any domestic Chinese pharmaceutical company. Virtually unmatched by anyone in China in 2010, Cho published part of his original work with one J. Med. Chemistry and four Bioorganic Chemistry and Medicinal Chemistry Letters. Cho's true gift is his natural instinct to recognize the needs on how to develop a successful drug discovery team necessary for a successful discovery organization yet suitable within Chinese practices.

Jia TIAN

Dr. Tian is a professor and the director of Technology Transfer Office at the Peking University Health Science Center (PUHSC). Under her leadership, technology transfer at PUHSC has been very successful and has generated significant revenue for the university to support research and education. Dr. Tian was recognized as one of the Nation's Top Intellectual Property Managers in 2010 and is the recipient of numerous awards, including the 13th Beijing Technology Market（BTM）Golden Bridge Award (2010) and the Outstanding Individual in Education and Management Innovation in Beijing (2009). Prior to the Technology Transfer Office, Professor Tian was a deputy director at the Science and Research Division, PUHSC. She was a lecturer at Semmel Weis University of Hungary (2000) and at Salzburg University of Austria (2001). Professor Tian has taught Orthopedic Biomechanics and Sports Injuries for more than 16 years and her research focuses on biomechanics. She is the associate editor-in-chief of *Chinese Journal of Medical Science Research Management*. Dr. Tian received her Ph. D. in biomedical engineering from Sichuan University .

Xiaochuan WANG

Dr. Wang received her Ph.D. degree from the University of Chicago in 1989, specialized in molecular structure design of new drugs. After her Ph.D. training, she worked for 3 biotech companies in USA on R&D research and program management. She has 20 years experience in drug discovery and development for 14 different target, and successfully applied computer aided drug design, medicinal chemistry, compound library design and screening, and ADME analysis. She led teams of medicinal chemists, biologists, and pharmacologist to go through the whole process of drug discovery from 0 to clinical stages. Dr. Wang founded Sundia MediTech Company in Shanghai in 2004, and has led Sundia to grow into a leading Chinese CRO company, especially in new drug discovery CRO services. Sundia was selected by the top VC investors as one of the "Most Valuable Companies for Investment in China" in 2007 and 2008, and was honored in Deloitte High Tech High Growth Companies Top 50 in China, and Top 500 in Asia Pacific. In 2009, Sundia was awarded TOP 100 Fastest Growing Outsourcing Companies in China, Deloitte Technology 500 Fastest Growing Companies in Asia Pacific, Red Herring Top 100 companies in Asia Pacific.

BIOGRAPHICAL SKETCH

Erik WONG

Erik Wong received his PhD from Medical Research Council, National Institute for Medical Research, London, UK. He has spent over 20 years in drug discovery and development, with particular focus on novel agents for psychiatric disorders. He has recruited and led several multi-disciplinary drug discovery teams at Merck Sharp & Dohme Research Laboratory, Roche Bioscience, Pharmacia Pharmaceuticals and Pfizer Inc., leading to late stage clinical development and launches, e.g. MK-801, reboxetine, asenapine, quetiapine. He is the author of over 100 peer-reviewed research publication. From 1998 to 2004, Dr. Wong was an adjunct professor of Psychiatry at Michigan State University. Dr. Wong joined AstraZeneca Pharmaceuticals in 2007. He is currently the Director of External Science for the CNS/Pain Control Research Area, in Wilmington, Delaware, USA. In this role, he is responsible for evaluation and execution of research alliances to identify novel therapeutic approaches for CNS disorders.

Keqiang YE

Dr. Ye received his undergraduate training in Organic Chemistry at Jilin University, China (BS, 1990); Graduate training in Polymer Chemistry at Beijing University, China (MS, 1993); and Graduate training in Biochemistry at Emory University, Atlanta, Georgia, USA (Ph.D. 1998); Postdoctoral training with Dr. Solomon H. Snyder at Johns Hopkins University (1998-2001). At the end of 2001, he joined the faculty of Emory University School of Medicine (Assistant Professor in Department of Pathology and Laboratory Medicine, 2001-2007; Associate professor, 2007-2010; Full Professor, 2010-Present). Dr. Ye is the recipient of numerous professional honors, including the Distinguished Scientist Award from the Sontag Fondation (2003), and he is also one of the semi-finalists for Keck Foundation and American Cancer Scholar (2004). Dr. Ye has made a unique contribution to the anti-cancer drug arsenal in 1998, when he was a graduate student at Emory. He discovered a novel opium alkaloid, noscapine, as an anti-cancer drug. His discovery was broadly reported by numerous major media including ABC News, CNN and Science Magazine in 1998. He has several patents on this drug. Currently, this drug has passed phase II clinical trial. In 2000, when he was a postdoctoral fellow at the Johns Hopkins, Dr. Ye disclosed a long-awaited nuclear GTPase, PIKE, which specifically regulates nuclear PI 3-kinase signaling cascade. This finding provides insight into the molecular mechanism of how nuclear PI 3-kinase is activated in the nucleus. Moreover, he found that PLC-□1 acts as a guanine nucleotide exchange factor (GEF) for PIKE GTPase, resulting in this GTPase initiation and subsequent nuclear PI 3-kinase activation. In 2001, he was nominated as an assistant professor at Emory University. His lab is focused on dissecting neurotrophin-mediated PI3K signaling in neuronal survival. Currently, his lab has identifies numerous novel small molecular agonists for neurotrophin receptors (TrkA and TrkB), insulin receptor (IR) and EGFR inhibitors. These small molecules exhibit potent neurotrophic effect and display great potentials for neurological diseases, diabetes and cancer treatment.

Sundia

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ABSTRACTS (same order as presentations)

Perspective on Bio-innovation in China

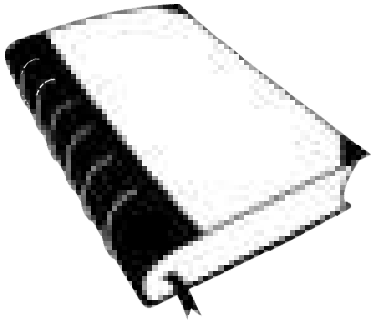
Anning LIN
Shanghai Institute of Biochemistry and Cell Biology,
Chinese Academy of Science
Ben May Department for Cancer Research,
University of Chicago

A brief overview on the current status of pharmaceutical and biotech companies in Shanghai, their ties with the universities and research institutes, as well as the related government policies.

The Potential Role of Antibody in Antitumor Treatments

Yang-Xin FU
Department of Pathology, University of Chicago

Anti-HER2/neu antibody therapy is reported to mediate tumor regression by interrupting oncogenic signals and/or inducing FcR-mediated cytotoxicity. We have now revealed new mechanisms and demonstrate that the mechanisms of tumor regression by this therapy also require the adaptive immune response. Activation of innate immunity and T cells, initiated by antibody treatment, was necessary. Intriguingly, the addition of chemotherapeutic drugs, while capable of enhancing the reduction of tumor burden, could abrogate antibody-initiated immunity leading to decreased resistance to re-challenge or earlier relapse. Increased influx of both innate and adaptive immune cells into the tumor microenvironment by a selected immunotherapy further enhanced subsequent antibody-induced immunity, leading to increased tumor eradication and resistance to re-challenge. In addition to anti-HER2/neu antibody, several other antibodies also utilize similar mechanisms for tumor regression. We have also shown that not only mouse tumor but also human tumor will respond to human antibody in similar way. We will present our new understanding of other conventional treatments with immunotherapy and new combination for more effective cancer treatment. We have now proposed a new model and strategy for antibody-mediated tumor clearance.



Small Molecule TrkB Agonist Useful for Treating Neurological Diseases

Keqiang YE
Department of Pathology and Laboratory Medicine, Emory University, School of Medicine

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, binds to neurotrophin receptor TrkB and triggers activation of the three major signaling pathways involving MAPK, PI3K and PLC-γ1. BDNF plays a critical role in a variety of neurological processes. Moreover, BDNF is of particular therapeutic interest because of its neurotrophic actions on neuronal populations involved in numerous neurological diseases. However, the clinical trials with recombinant BDNF are disappointing. In order to identify small molecules that mimic the neurotrophic activities of BDNF, we developed a cell-based assay and successfully identified 7,8-dihydroxyflavone (7,8-DHF) that acts as a TrkB agonist. 7,8-DHF binds to TrkB receptor and induces TrkB activation in primary neurons and mouse brain. 7,8-DHF selectively activates TrkB but not TrkA or TrkC receptor or other receptor tyrosine kinases. Structure-activity relationship study reveals that the catechol group is critical for eliciting TrkB activation. Addition of 4'-dimethylamino group onto 7,8-DHF strongly escalates the agonistic activity. Oral administration of the parental compound and its synthetic derivatives displays potent therapeutic efficacy in various neurological disease animal models including stroke, depression, Huntington's disease (HD), Parkinson's disease (PD) etc. Chronic treatment with these compounds in mice do not trigger any detectable toxicity, underscoring these compounds are therapeutic efficacious and safe. Hence, our data support that the 7,8-DHF and its synthetic compounds are orally bioavailable TrkB agonists and useful for treating various neurological diseases.

The HCV-Proteas Inhibitor: Telaprevir

Youssef L. BENNANI
Vertex Pharmaceuticals

Teleprevir is a peptidomimetic Heptitis C protease inhibitor, which has successfully completed Phase III clinical trials for the treatment of HepC virus infection. Clinical data from these trials supported the application for its approval with the FDA, EMEA and Health Canada authorities. Its discovery, preclinical profiling and clinical data will be presented.

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CNS Drug Discovery in the New World: Can We Innovate Back to the Future?

Erik Wong
AstraZeneca

Psychiatric disorders are highly complex and polygenic disorders of which the conventional treatment options are not satisfactory. The availability of the next generation of therapeutic agents remains unfulfilled by virtue of failures of research and development in this area. This crisis in failure to translate preclinical efficacy to clinical reality can be traced to a number of factors including: i) inability to pick the right target, ii) inadequency of existing animal models for target validation, iii) the lack of biological basis of disease classification, and iv) lack of biomarkers for patient segmentation. Scientific innovation remains the main avenue to address the above crisis. This talk will focus on state of the art neuroscience approaches to identify novel mechanisms and how to translating them to meaningful targets. We will address new ways to develop animal models to test novel antidepressants and innovative approaches to relate brain circuits to behavioral phenotypes. Last but not least we will discuss the role of precompetitive consortia play in driving translational medicine to address clinical relevant biomarkers and disease understanding.

Enabling Chemistry Technology - Key role in Future Drug Discovery success

Stevan Djuric
GPRD, Abbott Laboratories

The pharmaceutical industry is under significant pressure to discover new drugs of therapeutic benefit quickly. In order to do so Discovery cycle times must become more efficient and cost effective. In this talk, we describe our efforts to incorporate recent advances in enabling chemistry technologies such as flow chemistry, photochemistry and chemical proteomics into our lead discovery workflow. Impact of these activities on target identification and library production initiatives will be presented.

Medicilon: Your Partner in Drug Discovery and Development

Bingbing Feng
Shanghai Medicilon, Inc.

Medicilon was founded in 2004 with the explicit purpose of providing fully integrated pharmaceutical R&D services to the global pharmaceutical community. Its services cover biology, chemistry, preclinical, and integrated drug discovery and development service areas, and are specifically designed to help clients develop their research and discovery programs from the initial idea stage to the IND filing phase. Medicilon has been recognized as one of the top drug discovery contract research organizations (CRO) in China and is managed by a team of scientists with many years of experience in US-based pharmaceutical and biotechnology companies. It has clients from North America, Europe, Asia and Oceania ranging from the Top Ten Pharmaceuticals to virtual biotech companies. Medicilon's preclinical animal facilities in Shanghai have received AAALAC accreditation and has operated in compliant with US FDA GLP standards.

China Takes on Pharma Innovation

Hualiang Jiang
Shanghai Institute of Materia Medica, CAS
East China University of Science and Technology

More and more, both government and industry in China are emphasizing innovation in drug discovery and development. A key component of this effort was the national 'New Drug Creation and Development Programme', launched in 2008 to provide 6.6 billion yuan (US$960 million) to accelerate domestic drug R&D. This initiative supports both academic groups and pharmaceutical companies. The programme outlined three missions: to improve the infrastructure of drug discovery and development by improving standards in good laboratory practice [GLP], good manufacturing practice [GMP], and good clinical practice [GCP]; to discover new molecular entities and new biologics (first-in-class and best-in-class); and to develop prospective technologies for drug R&D. This talk will focus on recent advances of pharma innovation in China.

Beijing University Health Science Center : From Key Innovations to Novel Technologies for Licensing

Dr. Jia Tian
Beijing University Health Science Center,
Technology Transfer Center

Founded in 1912, Peking University Health Science Center (PUHSC) is one of the most prestigious and comprehensive institutions in China for medical education and research. Today, PUHSC, including six academic schools and eight nationally known affiliated hospitals, contributes to medical education, scientific research, and clinical service. PUHSC has been leading China's medical science research for years. It has one state key laboratory, 12 ministerial key laboratories, 19 research institutes, and 38 research centers, with an overall funding of 472.7 million RMB and 662 SCI-cited research articles published in 2010. A number of high quality papers have been published in international top journals including Nature, Cell, New England Journal of Medicine, Lancet, and Angewandte Chemie International Edition. PUHSC has made a series of symbolic achievements in the areas of basic medicine, clinical medicine, public health, preventive medicine, and pharmaceutical science, and has made a big impact world-widely. In the past five years, PUHSC has obtained more

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than 20 scientific awards at national and ministerial levels, including the National Natural Science Award (class two). Besides the scientific and technological achievements, the technology transfer and the intellectual property protection work in PUHSC have also been significantly improved year by year. In 2010, 64 patents were applied, and 43 patents were issued. A total of 456 transfer contracts were signed, which was an increase of 44-fold since 2004. The total funds gaining from these contracts have reached up to 91.10 million RMB, and 51.10 million RMB is already in place. Both numbers have increased 14-fold since 2004, and hit a historic high.

Discovering Me-Better Drugs in China: Magic Formula

Peng Cho Tang
HEC Pharma Group

Drug Discovery in China is NO LONGER a matter of discussion on whether to do it or not but how to do it competitively and aggressively for any domestic company. The successful experience of drug discovery in US and China that have yielded a total of 11 clinical candidates will be shared. How to build a successful drug discovery team for a Chinese Pharma and how to do it again differently will also be the subject of discussion.

Building Synergies in New Drug Discovery: Perspectives on New Scientific and Business Strategies

Xiaochuan Wang
Sundia MediTech Company Ltd

- Innovation and new business models applicable to drug discovery & development.
- Collaborations between academic investigators, CROs and pharmaceutical companies.
- Highlights of new business strategies and models with case studies.

The Great Opportunity in Jiaxing for Bio-Science Projects – Jiaxing International Bio-Science Park

Feng Sheng
Shanghai Pharm Valley Jiaxing International Bio-tech Park
StudyManager Inc., China Operation

Jiaxing International Bio-Science Park is located in Jiaxing City Science and Technology Incubator Center. The park is jointly developed by Shanghai Pharm Valley Corp. and Beautiful Bio-tech Inc. As a leading company in Jiaxing Bio-Science and Pharmaceutical industry, Jiaxing International Bio-tech Park is dedicated to provide services for companies and individuals who are in pharmaceutical research and development, manufacturing as well as related service industries. Jiaxing International Bio-Science Park is invested by Shanghai Pharm Valley Corp. and Beautiful Bio-tech Inc. Currently, the park established partnership with Uppsala Bio, Sweden; University Dublin, Ireland; Kuopio Hi-Tech Park, Finland and other education and scientific research institutions. There are a number of foreign-funded enterprises, such as Study Manager Inc. from U.S. and domestic enterprises like Shanghai Fuhua are registered in the Bio-tech Park. US company Eli Lilly Pharmaceuticals, Shanghai Pharmaceutical Group, and some other well-known enterprises visited the park, and intended to discuss further cooperation. We believe there will be more business partners are attracted to Jiaxing International Bio-Science Park and success with us together in the next five years. Jiaxing International Bio-Science Park will become one of the most influential bio-science parks in Zhejiang Province.

What Every Biotech/Pharma Executive Should Know about Intellectual Property

Jeffery Duncan
Brinks Hofer Gilson & Lione

Based on over 25 years of experience representing Biotech and Pharma companies in the U.S., Europe, Israel and China, Jeffery Duncan will give a presentation entitled “What Every Biotech/Pharma Executive Should Know about Intellectual Property.” He will give a strategic overview, touching on the following topics:

- The Hatch-Waxman system as it relates to Intellectual Property and the USFDA’s approval of new and generic drugs
- Building the patent portfolio for the branded drug (“patent life cycle management” or “evergreening”)
- Patent term extensions and regulatory exclusivities
- Paragraph IV challenges by generic pharma to Orange Book listed patents
- Avoiding infringement of third party and non-Orange Book listed patents

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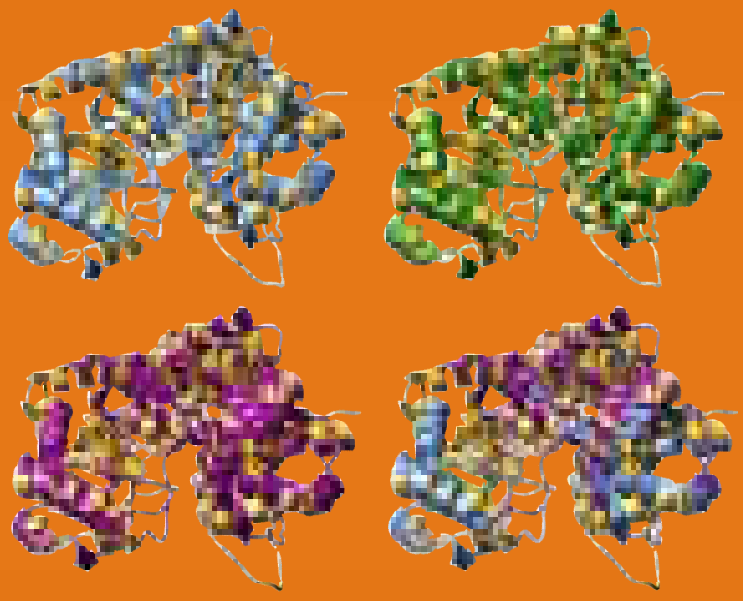

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现代高通量筛选技术在新药研发中的应用

As more and more compounds derived from screening find their way into clinical trials, drug screening has become widely accepted as a critical path in the drug discovery process. Productivity gap and R&D efficiency are still the challenges for all pharmaceutical companies. Pharmaceutical industry continues to face the challenges of developing more new chemical entities and reducing the cost of R&D, the demand for novel technologies and creative approaches for improving the efficiency of screening has intensified. After more than a decade of rapid growth, tremendous progress has been made in assay technologies, laboratory automation, and informatics. These technological developments have not only enabled a drastic increase in throughput and efficiency in drug screening, but have also provided novel solutions in other areas of drug discovery and development.

While automation can magnify efficiency to efficient operations; it can also magnify inefficiency to inefficient operations. Therefore three important parts involved in HTS remain as critically important as they were before, screening the appropriate target in the right format, screening the right compound libraries and adopting the appropriate data analysis. More importantly, the focus has shifted from throughput to quality and reliability. In 2002, 60% of screens are biochemical and 40% are cellular, now, they are 30% biochemical and 70% cellular. The success rates are 85% for kinase, 70% for nuclear receptor, 65% for ion-channel, 40% for non-kinase enzymes, and 35% for cellular targets. Broad functional profiling of molecular libraries against biological pathways has been done for many disease areas. An increasing number of cell-based assays are used in compound screening and high content screening technologies has gained popularity in the industry. After years of intensive research, label-free technologies have finally arrived in the drug screening market place. These technologies provide new ways of interrogating cellular and molecular binding events and enable orthogonal screening approaches to drug targets. A few fundamental assay technologies and applications to drug discovery and development will be discussed in details below.

I. Assay Technologies

Homogeneous fluorescence methods

It is now clear that fluorescence-based techniques are amongst the most important detection approaches used for HTS, given the industry-wide drive to simplify, miniaturize and speed up assays. Fluorescence techniques are well suited to uHTS because they give very high sensitivity, which allows fairly straightforward miniaturization. This is illustrated by the fact that simple fluorescence intensity measurements have been successfully applied in an ultra-miniaturized format. However, HTS assays based upon fluorescence intensity measurements are mainly restricted to fluorogenic enzyme substrates. A more powerful aspect of other, more complex, fluorescence readouts is their ability to yield information on fluorophore environment, which allows predictive design for a wide range of target types. One such technique is fluorescence anisotropy (FP; fluorescence polarization), which yields information on molecular rotation that is related to mass. Anisotropy can be used to measure bimolecular association events within a specific range, as determined by the fluorophore lifetime. Many examples of HTS applications of FP have now been reported, including ligand–receptor binding and enzyme assays. A number of groups have also demonstrated that FP measurements work well in 1536-well plates when using high-sensitivity plate readers. Another important fluorescence readout is time-resolved fluorescence resonance energy transfer (TR-FRET). This is a dual labeling approach that is based upon long-range energy transfer between fluorescent Ln^{3+} complexes and a suitable resonance energy acceptor. This approach has an advantage in that time-gating of the long-lived donor and acceptor signals gives high sensitivity by reducing background. A large number of HTS assays have now been configured using TR-FRET, including the successful miniaturization of the technique to 1536-well plates. Given the large distance for effective energy transfer (~ 90 Å), TR-FRET is highly suited to measurements of protein–protein interactions. Recently, two-alternative approaches with similar capabilities have been developed by Packard/

Biosignal in AlphaScreen and bioluminescence energy transfer. One area of fluorescence measurements that has developed very strongly in terms of fundamental approaches is that of single molecule fluctuation-based measurements. One attraction of these methods for HTS/uHTS is their high information content and intrinsic sensitivity to miniaturization. All are performed using confocal optics in which the observation volume is extremely small (~ 1 fl) and very few molecules are present in the confocal volume optics at any one time, so the output fluorescence signal fluctuates with time as molecules enter and exit. The classical form of confocal fluctuation spectroscopy, known as fluorescence correlation spectroscopy (FCS) has now been demonstrated to be a viable approach to HTS for a wide range of therapeutic targets. FCS can be used to detect binding interactions via changes in translational diffusion rates or, where there is a significant change in brightness during a binding or catalytic reaction, can be configured in a way that is not dependent upon changes in diffusion rates. It is only during the past few years that advances in optics, electronics and computation tools have made FCS a viable proposition for use in routine HTS applications. These same advances have led to a renaissance in the whole area of single molecule fluctuation methods, driven in particular by a number of academic labs and by Evotec Biosystems, who are developing an integrated miniaturized screening system based upon this detection technology. Several new methods for analyzing fluctuation data have now been reported, including methods to determine molecular brightness (fluorescence intensity distribution nalysis; FIDA or related methods). These methods can be used to configure assays in a variety of ways; molecular brightness can change either by environment or energy transfer, or via changes in the stoichiometry of fluorophore molecules present on a single particle. There has been significant progress, using a number of approaches, to extend these methods by simultaneously analyzing data from more than one output channel.

Miniaturized radiometric readouts

While fluorescence assay technologies are growing in importance, the predicted demise of radiometric assays as an important facet of HTS labs has not yet occurred. Current estimates from various surveys of HTS laboratories indicate that radiometric assays presently constitute between 20% and 50% of all screens performed. Although we expect the fraction of radiometric assays to decrease over the coming years, this technology is unlikely to disappear completely. In the early 1990s, several advances in radiometric assay technology were introduced including scintillation proximity assay (SPA) (Amersham Pharmacia Biotech) and FlashPlates™ (NEN Life Science Products, Boston, MA). With these approaches, the target of interest is immobilized onto a solid support (e.g. SPA beads or FlashPlate™ surface) that contains a scintillant. When a radiolabeled molecule binds to the target molecule, the radioisotope is brought in close proximity to the solid support, and energy transfer between the emitted beta particle and the scintillant results in the emission of light. Radioisotope remaining free in solution is too distant from the scintillant and the beta particle dissipates energy into the aqueous environment. Thus, scintillation proximity technologies facilitate a homogeneous approach to radiometric assays. SPA has been used in a wide variety of applications and it is a standard technique in HTS labs. The technology has been applied to kinases, nucleic-acid-processing enzymes, and other enzymes and is widely used for ligand–receptor interactions. FlashPlate™ technology is similar to SPA but the solid surface is a microtiter plate rather than a bead. Recent FlashPlate™ applications include the detection of cAMP levels and ligand–receptor interactions. Of course, radiometric assays have several disadvantages including safety, limited reagent stability, relatively long read-times and little intrinsic information on the isotope environment. However, new technologies are now emerging to address the issue of read-time and assay miniaturization.

Cell-based assay technologies

Advances in technology and instrumentation for cell-based assays have occurred over the past few years. Among these are the emergence of HTS-compatible technology to measure G-protein-coupled receptor (GPCR) and ion channel function, confocal imaging platforms for rapid cellular and sub-cellular imaging, and the continued development of reporter gene technology. The FLIPR™ (Molecular Devices) is a fluorescence imaging plate reader with integrated liquid handling that facilitates the simultaneous fluorescence imaging of 384 samples to measure intracellular calcium mobilization in real time. Historically, these measurements have only been possible on single cuvette fluorimeters and by microscopic imaging. FLIPR™ has been used to identify cognate ligands for orphan GPCRs, to characterize GPCR pharmacology and to screen compound libraries. The instrument is also capable of measuring ion channel function by coupling the activity of a target channel to a voltage-gated calcium channel. An alternative and promising HTS technology for ion channels is based on voltage-sensitive fluorescence resonance energy transfer (VIPR™; Aurora Biosciences, La Jolla, CA). Although kinetic plate readers facilitate cell-based functional screens, they are currently limited to 96/384-well plates and are somewhat labor-intensive. In contrast, cell-based reporter gene screens require fewer cells, are easier to automate and can be performed in 1536-well plates. Recent descriptions of miniaturized reporter gene readouts include luciferase and secreted alkaline phosphate. A novel and sensitive beta-lactamase reporter system has been described that allows the clonal selection of living cells and is amenable to miniaturized HTS. Finally, a Cre recombinase reporter system links signal transduction to DNA recombination and results in a permanent readout of gene expression. Human GPCRs can be screened in yeast to find agonists and antagonists by taking advantage of the pheromone signaling pathway. Although this technology can offer the advantage of a null background for the expression of human receptors, there is only a moderate correlation between ligand activation in yeast and mammalian cells. A yeast-based transcription assay for the human progesterone receptor has recently been performed in 1536-well plates. In addition, receptor assays based on cell darkening can be performed in frog melanophores. Cyclic AMP measurements in cell extracts can be performed with SPA, FlashPlate™, fluorescence polarization

or AlphaScreen™ technologies. A novel fluorescent indicator for cyclic AMP in living cells involves tagging protein kinase A with green fluorescent protein mutants. Recently, laser scanning imaging systems have been developed to measure cellular and sub-cellular quantitation of fluorescence in whole cells. These systems have the capability of bringing low throughput biological studies with high information content into the world of HTS. One of the most advanced systems is the ArrayScan™ (Cellomics, Pittsburgh, PA) which has been used to measure GPCR internalization as well as a range of other applications. Other imaging systems have been used to measure ligand-receptor binding in whole cells. Current instrumentation does not combine sufficient resolution and speed to allow uHTS-level throughput for true sub-cellular imaging. However, a number of approaches are being developed for high speed cellular imaging, which look likely to enable the use of this approach for first-line uHTS in the future.

Label free technologies

Traditionally, fragments had been screened using ligand-based NMR techniques, especially WaterLOGSY (Water ligand optimized gradient spectroscopy) which results in a positive signal upon ligand binding to protein. Typically, a mixture of compounds is tested at once, and the resulting hits are then deconvoluted. With the advent of automated SPR systems (surface plasma resonance**)**, like the Biacore T100 and A100, an orthogonal approach to the screening of fragment libraries was born. Major advantages from SPR-based fragment screening are reduced protein consumption, the elimination of the deconvolution step, and the ability to screen compounds that don't exhibit fast kinetics. Enthalpy arrays are arrays of nanocalorimeters that enable label-free detection of molecular interactions using small sample volumes and short measurement times. Fragments identified in fragment-based screens typically exhibit low binding affinity (0.1 to 1 mM) that is difficult to measure with many established techniques, yet it is beneficial to identify the fragments with a high ligand efficiency ($-\Delta G$/number of heavy atoms) to take through lead optimization. In principle, isothermal titration calorimetry can be used to characterize the thermodynamics of fragment binding to targets, but its use in FBS is severely hampered by the need for large samples (≈0.2-1.5 mL), long measurement times, and high fragment solubility in the injectant. The enthalpy array technology enables measurements with 250 nL drops that only take a few minutes. The technology enables the possibility to determine accurate inhibitor constants for competitive inhibitors from single measurements with a label-free readout.

II. Applications in drug discovery and development

Functional genomics

High throughput screening has evolved from a very specialized tool employed in drug discovery by the pharmaceutical industry into a general research tool which is now found not only in industry, but also at a number of universities. HTS has changed on the scientific as well as the practical level. On the scientific level of this evolution, the advent of siRNA, shRNA and other techniques added to what is now called functional genomics, an interdisciplinary field in which biological questions are addressed by using high throughput techniques and reagents modulating gene function as tools. Chemical genomics is a very similar approach: it relies on specific small molecules and molecular screening as a research tool. Concomitant with this transformation, the novel uses of HTS necessitated novel workflows and allowed for a transformation of drug discovery itself. Prior to the development of functional and chemical genomics, it was an absolute requirement that the protein and its precise disease-modifying function had to be known before a screen for a drug aimed at this target was considered. This has changed to such a degree that screens without a known target are now regularly undertaken, since chemical and functional genomics principles have simplified post screening target discovery.

Fragment-based lead discovery and computational drug design

Fragment-based lead discovery shows great promise as a fast and reliable method to identify small molecule leads with attractive chemical properties. The primary practical challenges in applying fragment-based methods have been finding fragments and linking (or growing) them. The first challenge has recently become much easier. Engineering and software advances have vastly increased the throughput of structural methods such as NMR and X-ray crystallography, and other methods such as surface plasmon resonance, isothermal titration calorimetry, mass-spectrometry, and even high-concentration screening are becoming more useful. Advancing fragments to leads, however, remains a significant hurdle. In silico protein modeling can now allow discovery researchers design new drugs with novel chemistry. Computational tools to help predict which compounds will be safe and have desirable pharmaceutical properties. Public access to protein structure and drug design information has potential to revolutionize the drug discovery industry.

Peptide derived modulators

About 75-80% of all disease relevant proteins are considered to be undruggable, which means that they are not accessible for small molecule or antibody drugs. The "undruggables" comprise such interesting protein classes, like transcription factors, adaptors, scaffold proteins and other mostly non-enzymatic proteins. Pharmaceutical companies now started to focus on the development of drugs acting on such undruggable intracellular target proteins. A new technology platform which uses novel cellular screening systems to identify peptide derived modulators has been developed. These peptide-modulators are cell-permeable and are able to utilize alternative modes of modulation, like allosteric inhibition or inhibition of protein-protein interaction. Intracellular peptide modulators have been identified for important undruggable targets of anti-infective and anti-inflammatory indications. Intracellular peptide drugs are a powerful addition to antibodies and RNAi drug classes and are closing the gap between small molecules and antibodies.

Biomarker assay development

Animal models are commonly used in pre-clinical studies for various areas of disease research, including cardiovascular

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Race for HCV Treatments

Liangjun Lu
陆良军

HCV (Hepatitis C virus) was identified in 1987. It is believed that there are about 170 million HCV patients worldwide; that's 3% of the world's population. Hepatitis C is a contagious, slow-developing, blood-borne disease. Without treatment, about 80% of the HCV patients would develop severe liver problems, including cirrhosis and cancer. Current standard of care of HCV infection involves two drugs: peginterferon alfa and ribavirin, both of which have a number of side effects, and can achieve viral load reduction to an undetectable level in less than 50% of the genotype 1 infected patients. There is an urgent need for a more effective treatment.

Drugs in current SOC (standard of care):

The guideline for HCV regimens uses a combination of peginterferon and ribavirin for 48 weeks. Both interferon and ribavirin do not specifically target HCV. Ribavirin stops the virus that causes hepatitis C from spreading. Interferon prevents viral replication in surrounding cells.

Two forms of peginterferon have been developed: peginterferon alfa-2a (Pegasys: Hoffman La Roche) and peginterferon alfa-2b (Pegintron: Merk/Schering-Plough). These two products are both given subcutaneously and have roughly equivalent efficacy and safety, but have different dosing regimens.

Ribavirin is an oral medication, given twice a day in 200-mg capsules for a total daily dose that is based upon body weight. In certain situations, an 800-mg dose (400 mg twice daily) is recommended.

The side effects of interferon include flu-like symptoms such as headaches, fever, fatigue, loss of appetite, nausea, vomiting, depression and thinning of hair. It may also interfere with the production of white blood cells and platelets by depressing the bone marrow. Ribavirin can cause sudden, severe anemia, and birth defects, so women should avoid pregnancy while taking it and for 6 months following treatment.

Drugs in pipeline:

According to a report by Global Data, the global hepatitis C market was worth $4 billion in 2009 and is projected to grow at a compound annual growth rate of 9.8% to reach $8.5 billion by 2016. A reason for the growth is that the new drugs in the pipeline will make treatment more accessible, tolerable, and effective. Eight of twelve top pharmaceutical companies have active anti-HCV R&D programs. The two front-runners are Merck with boceprevir, and a partnership of Vertex Pharmaceuticals and Johnson & Johnson with telaprevir. Both boceprevir and telaprevir are likely to be finish clinical trial phase III and submit for FDA (Food and Drug Administration) approval during the third quarter of 2011. Telaprevir may have slight edge. Combined with SOC, telaprevir reduced HCV to an undetectable level in 75% of treated patients, whereas boceprevir did so in 68% of patients from clinical trials. But it is too early to predict the winner since they have not been tested head to head; however, it is not in the best interest of the companies.

Combination of multiple drugs to overcome resistance:

Like HIV, HCV can easily adopt drug-resistant mutations, which could wipe off the anti-viral effects of HCV-specifically targeting drugs both *in vitro* and *in vivo*. FDA recommends minimizing the time of a patient's exposure to monotherapy (<3 days) in HCV clinical trials to avoid developing drug-resistance. Similar guidelines were provided from EMEA (European Medicines Agency), which required that patients should not be under monotherapy for more than 5 days. Indeed, the combination of an HCV-specific drug with SOC greatly reduced the failure rate due to drug-resistance in all the clinical trials.

Drugs in the combination therapy usually have different mechanisms of action. Best of all, the regimen should be all oral and interferon free for better accessibility and effectiveness compared to the current SOC. Roche conducted a first-of-a-kind clinical trial (INFORM-I) including two target-specific drugs, RG7128, a nucleoside polymerase inhibitor and ITMN-191, a protease in-

Table 1. Pipeline of Direct-Acting Antivirals Agents (DAA)

Company	Compound	Target	Clinical Trial Phase
Abbott	ABT-333	Polymerase	II
Abbott	ABT-072	Polymerase	II
Abbott/Enanta	ABT-450	Protease	II
Achillion	ACH-1625	Protease	II
Anadys/ Pharmasset	ANA598	Polymerase	II
ArrowTherapeutics	A-832	NS5A	II
Boehringer Ingelheim Pharma	BI 207127	Protease	II
Boehringer Ingelheim Pharma	BI 201335	Protease	III
Bristol_Myers Squibb	BMS-650032	Protease	II
Bristol_Myers Squibb	BMS-791325	Protease	II
Bristol_Myers Squibb	BMS-790052	NS5A	II
Eiger BioPharmaceuticals	Clemizole	NS4B	I
Gilead	GS-9190	Polymerase	II
Gilead	GS-9256	Protease	II
Idenix	IDX320	Protease	I
InterMune/ Roche	RG7227	Protease	II
Medivir/Tibotec	TMC435	Protease	III
Merck	MK-3281	Polymerase	I
Merck	MK-7009 (Vaniprevir)	Protease	II
Merck	SCH900518	Protease	II
Merck	Boceprevir	Protease	III
Pfizer	Filibuvir	Polymerase	II
Pharmasset	PSI-7851	Polymerase	I
Pharmasset	PSI-938	Polymerase	I
Pharmasset	PSI-7977	Polymerase	II
Pharmasset/ Roche	RG7128	Polymerase	II
Phenomix	PHX1766	Protease	I
Vertex	VX-916	Polymerase	I
Vertex	VX-222	Polymerase	II
Vertex	VX-759	Polymerase	II
Vertex	VX-813	Protease	I
Vertex	VX-500	Protease	I
Vertex	Telaprevir	Protease	III

Adapted from: http://www.hcvadvocate.org

ABSTRACT

制药公司正在加紧研发直接抗丙型肝炎病毒的小分子药物，希望成为第一个拥有FDA批准的抗丙肝新药的公司，以抢占每年九十亿美元市场的先机。强生公司和沃泰克（Vertex)联合研制的telaprevir 及默克公司的boceprevir有望在今年获FDA的批准上市。但是，这两种新药仍然必须与目前的标准治疗方法，即皮下注射干扰素加口服ribavirin，一起使用。理想的方案是全口服小分子药物，达到高的治愈率并缩短治疗时间。法马赛特（Pharmaset) 在今年三月份公布的最新临床试验结果显示，在16位接受两种抗聚合酶的小分子药物治疗的病人中，15位体内病毒在14天内降低到不可测的水平。这个振奋人心的消息使公司股票大涨，也使人们在近十年的努力后，看到了彻底治愈丙型肝炎的曙光。

hibitor. Over a 13-day treatment, the twice daily and all oral administered regimen demonstrated significant anti-viral potency in treatment naïve patients as well as in SOC treatment failures. Vertex announced the initiation of a phase II trial of telaprevir/VX-222 (a polymerase inhibitor), including 2 arms with and 2 arms without pegylated interferon/ribavirin in 2010. Other companies currently conduct combination clinical trials are: Abbott (ABT-450+ABT-072 or ABT-333); Boehringer Ingelheim Pharma (BI-201335 + BI-207127); Bristol-Myers Squibb (BMS 790052 + BMS 65032); Gilead (GS-9256 + GS-9190) and Pharmasset (PSI-7977 + PSI-938). All these clinical trials are in phase II. Pharmasset's combination regimen includes two nucleoside analogues and 14 days treatments reduced HCV to undectable level in 15 of 16 patients and none showed viral rebound. These results wowed investors and the company stock price increased more than 100% within three months.

Summary

Pharmaceutical companies are racing for the approval and marketing of the first direct anti-HCV small molecular drug. Merck with boceprevir and Vertex/Johnson & Johnson with telaprevir are the front-runners. However, these agents have to be combined with SOC to achieve a better curing rate and overcome drug-associated resistance. Physicians and patients are excitedly expecting the first interferon-free, all oral regimen which is safer, more accessible and more effective than the current SOC. In this aspect, Vertex and Roche have the edge, but there are some other potential players that are just inches away from them.

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Dr. Lu received his undergraduate training in Medicine at Beijing Medical University (Beijing University), China. He conducted his graduated research in biochemistry with professor Zhiwei Dong, director of Cancer Institute and Hospital, Chinese Academy of Medical Sciences, working on bi-specific monoclonal antibody. He continued his post-graduate studies with Dr. Fink and Dr. Kurup at Wisconsin Medical College (1992-1995) and with Dr. Datta at Northwestern University (1995-1998). Dr. Lu joined the anti-viral program at Abbott Laboratories in 1998 as a senior scientist. He has been a key contributor to the success of Abbott HCV projects, and actively involved in clinical trial supports for both Abbott anti-HIV and anti-HCV drugs.

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disease, osteoporosis, chronic liver disease, and many others prior to translation to human disease research and drug therapies. The development of biomarker panels for disease diagnosis requires ongoing studies and validations of disease biomarkers, including their predictive consistency across different ethnic groups, gender, and other sources of patient population variability. The use of a multiplex panel of proteins to evaluate and set disease parameters is a useful and necessary part of forming diagnostic capabilities of protein markers. Greater understanding of disease characteristics will lead to earlier diagnosis and treatment. With the measurement of target protein biomarkers in pre-clinical rodent studies or human patients, serum protein biomarkers allow continual non-invasive patient monitoring, resulting in a clearer representation of disease status, progression, or regression in a patient's body in a native disease state or response to drug treatments. Multiplex measurement of procollagen type-I and type-III aminoterminal propeptide (PINP, PIIINP) represents a direct measurement of alterations in the metabolism of collagen type I and type III. These markers have been used to assess collagen incorporation into bone or the presence of fibrosis, and have been used in many specific areas of research including osteoporosis and other bone degeneration disorders, liver fibrosis, and muscle anabolism research. The use of multiplex mass spectrometry-based assays to quantitatively measure PINP and PIIINP in a single measurement without antibody enrichment of the target proteins. These multiplexed assays have been optimized for a high-throughput format to handle hundreds of samples simultaneously and result in absolute quantification of the target proteins.

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The Hallmarks of Cancer and Drug Discovery

Xuesong Liu

The revolution of biomedical research in 20th century began with Watson and Crick's discovery of the DNA double helix, and continues to this day. The identification of DNA as genetic information transformed cancer research from descriptive science to the elucidation of molecular mechanism of cancer biology.

Cancer is special because it is not a single disease. In fact, cancer is considered a group of diseases characterized by uncontrolled cell proliferation and metastasis. Since the discovery of the first oncogene, Src, by Michael Bishop and Harold Varmus in 1970s, our knowledge about cancer has exploded due to advances in many frontiers in cancer research.

In order to distill the vast literature on cancer research to provide commonalities or hallmarks shared by all cancer cells, renowned scientists Robert Weinberg, a founding member of Whitehead Institute, and Douglas Hanahan, director of the Swiss Institute for Experimental Cancer Research (ISREC) published their seminal review, "Hallmarks of Cancer", in January 2000 in the journal Cell. The review article has set the paradigm for cancer research for more than a decade and has since become the most cited paper ever published by the journal Cell.

In the March 4th issue of the journal Cell this year, these authors published their long-awaited update- "Hallmarks of Cancer: The Next Generation". This article summarized the progress of the past decade and introduced new hallmarks of cancer.

The original "hallmarks" that characterize cancer includes:
1) Sustaining proliferative signaling: Cancer cells can acquire the capability to sustain proliferation in a number of ways including production of growth factor by themselves, over-expression or amplification of growth factor receptors, and somatic mutations that activate downstream pathways.

2) Evading growth suppressors: Cancer cells can acquire this capacity mainly through deletion or mutation of tumor suppressor genes.

3) Activating invasion and metastasis: It is clear that cancer cells acquire the ability to metastasize as they become more malignant. This process can be achieved through the activation of the epithelial-mesenchymal transition (EMT) and contribution from stromal cells.

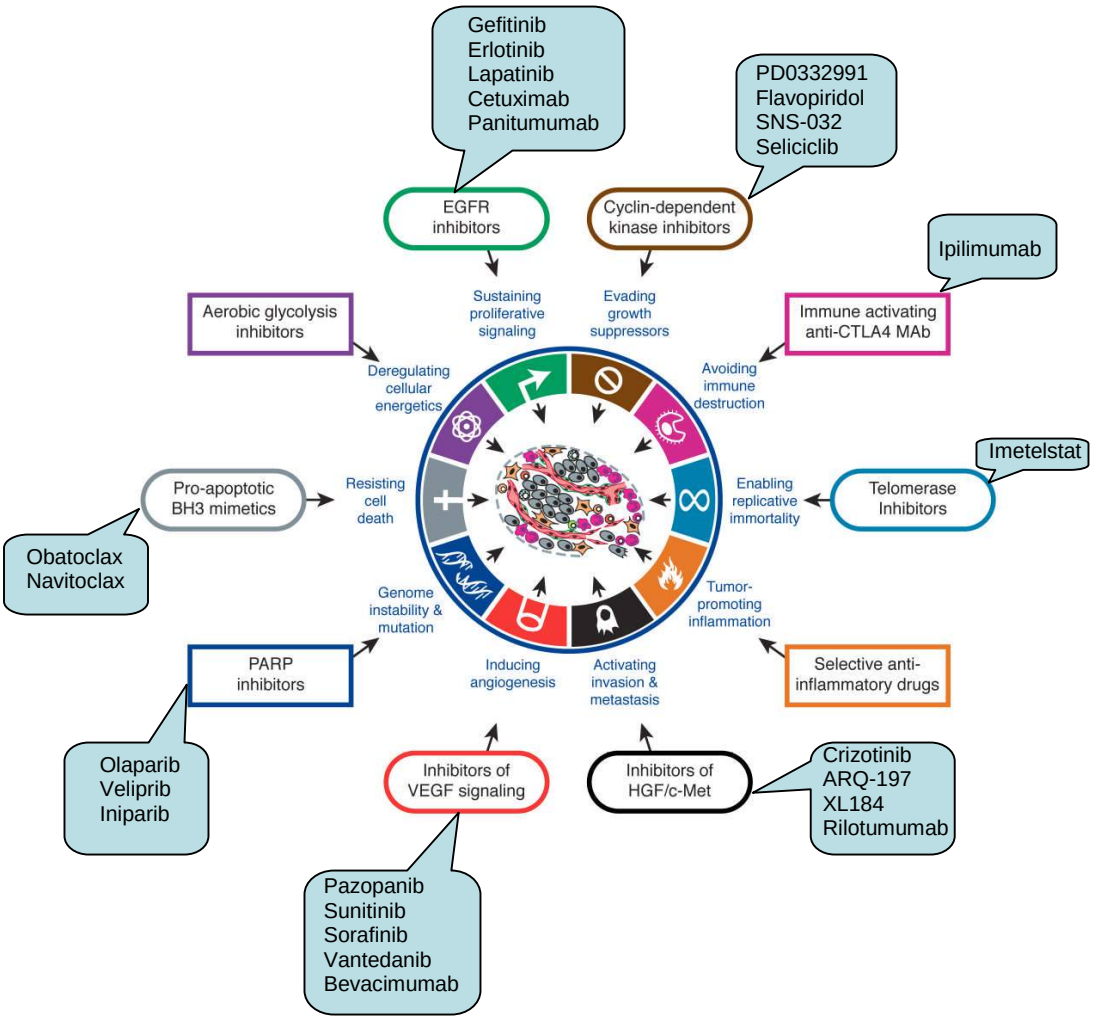
4) Enabling replicative immortality: Cancer cells develop unlimited replicative potential through the over-expression of telomerase that adds tandem hexanucleotide repeats to the ends of telomeric DNA.

5) Inducing angiogenesis: Cancer cells need nutrients and oxygen for their growth and proliferation. Nutrients and oxygen can be obtained via the formation of new blood vessel generated by the process of angiogenesis. Cancer cells have the ability to induce angiogenesis through multiple approaches including oncogene signaling-mediated expression of VEGF and the down-regulation of angiogenesis inhibitors.

6) Resisting cell death: programmed cell death by apoptosis functions as a natural barrier to cancer development. Tumor cells can limit apoptosis in a number of ways such as through the loss of p53 function, over-expression of anti-apoptotic proteins, or down-regulating pro-apoptotic proteins, etc.

In the newly published paper, the authors introduced two new emerging hallmarks of cancer (reprogramming energy metabolism and avoiding immune destruction) and two enabling hallmarks of cancer (genomic instability and tumor promoting inflammation).

7) Reprogramming energy metabolism: Cancer cells mainly employ the glycolytic pathway for energy production even in the presence of oxygen. It is generally believed that the metabolites generated during glycolysis can function as building blocks for cancer cell growth. In addition, the ability to reprogram the energy production via glycolysis gives cancer cells a lot of survival advantages under hypoxia condition.



8) Avoiding immune destruction: The immune system is able to destroy immunogenic tumor cells, which makes it function as a barrier to tumor formation and progression. Cancer cells can acquire the ability to evade immune destruction by disabling components of the immune system that have been dispatched to eliminate them.

9) Genome instability and mutation: tumor formation is a complex process that is driven by a multi-step acquisition of genomic mutations that affect cancer cell proliferation, survival and other hallmarks of cancer. This is achieved through cancer cell's ability to compromise the genome surveillance systems that normally monitor genomic integrity, which eventually leads to mutation and chromosomal instability.

10) Tumor promoting inflammation: tumor-associated inflammation promotes tumor progression in multiple ways such as supplying growth factors, survival factors, pro-angiogenic factors, and matrix-modifying enzymes. The production of reactive oxygen species by inflammatory cells also greatly facilitates the mutability of cancer cells. In general, inflammation of tumors mistaken for wounds by the immune system brings in would-healing cells that encourage proliferation and invasion.

In addition to the above mentioned hallmarks for caner cells, the authors point out that tumors exhibit another dimension of complexity by their ability to recruit a repertoire of normal cells such as endothelial cells, pericytes, immune inflammatory cells, and cancer-associated fibroblasts. These normal cells form the "tumor microenvironment" which contributes to the acquisition of hallmarks of cancer.

Just like the original paper, " Hallmarks of Cancer", published ten years ago, the new paper, "Hallmarks of Cancer, the Next Generation", will most likely become the updated blueprint for cancer research, especially for the discovery and development of anti-cancer drugs. In fact, the rapidly growing targeted therapeutics approved or under clinical development can be categorized according to their effects on one or more hallmark capabilities. Typical examples of targeted therapeutics include inhibitors of EGFR. EGFR plays critical roles in sustaining signaling of cell proliferation for these tumor cells with EGFR amplification and mutation. Current drugs approved as inhibitors of EGFR in the clinic include both small molecule inhibitors (gefitinib, erlotinib and lapatinib) and biologics (cetuximab, panitumumab). Other approved drugs include BCR-ABL inhibitor (imatinib, nilotinib, dasatinib), anti-Her2 mAb (trastuzumab), mTOR inhibitor (temsirolimus, everolimus), and aromatase inhibitor (anastrozole, exemestane, letrozole). Promising compounds under clinical trials include ALK inhibitor (crizotinib) and B-raf inhibitor (PLX4032). VEGF signaling pathway proteins are essential for inducing

angiogenesis. Current drugs approved as inhibitors of VEGF signaling also include small molecule inhibitors (pazopanib, sunitinib, sorafinib and vandetanib) and biologics (bevacimumab). In addition, a plethora of anti-VEGFR compounds are in clinical trials such as tivozanib, axitinib, brivanib,cediranib, linifanib, dovitinib. Recently the approval of anti-CTLA-4 mAb, ipilimumab, for advanced melanoma not only benefit the unmet medical needs for melanoma patients, but also validated the concept that avoiding immune destruction is a hallmark of cancer cells. Besides the above mentioned compounds targeting three hallmarks of cancer, there are currently hundreds of compounds under clinical development for the other seven hallmarks including PARP inhibitors (olaparib, veliparib, iniparib), inhibitors of HGF/c-Met (crizotinib, rilotumumab, ARQ-197, XL184), telomerase inhibitors (imetelstat), cyclin-dependent protein kinase inhibitors (PD0332991, flavopiridol, SNS-032, seliciclib), and pro-apoptotic BH3 mimetics (obatoclax, navitoclax). Compounds that target aerobic glycolysis or function as selective inflammatory inhibitors have not been developed yet. However, there is currently extensive research effort on these fields. For examples, data from recent clinical trials indicate that regular use of aspirin, a non-steroid anti-inflammatory agent, can prevent or possibly reduce the risk of dying from colon cancer. In addition, each of the cancer hallmarks is regulated by redundant signaling pathways, the effect of targeting one hallmark may not be sufficient to eliminate cancer cells. Thus, selective combination of these cancer hallmark-targeting agents will results in more effective therapies for human cancer.

Continued from p. 48（接第48页）

原因之一，从而靶向缺氧设计新型抗癌药，可为攻克肿瘤开辟一条新的途径。

（三）**结语**

抗肿瘤靶向给药系统在近十年来取得了巨大进展，并显示了对肿瘤治疗的巨大潜力。很多包括工艺复杂、载药量小、稳定性差等问题还有待进一步改进。然而，抗肿瘤的靶向治疗已经逐步成为当今抗癌疗法的主流，通过对生物化学、免疫学、细胞及分子生物学、药理学和材料学的进一步探讨，相信在不久的将来，抗癌靶向给药系统一定会开辟一个崭新的时代。

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李晨曦，理学博士，现任南开大学教授，博士生导师。李教授1984年毕业于徐州师范大学化学系，获理学学士学位。1985-1990年在南开大学元素有机化学研究所学习，师从陈茹玉院士，于1987、1990年分别获理学硕士、博士学位，随后去美国哈佛大学化学系做博士后研究。回国后李教授受聘南开大学化学学院，开辟了自己独特的研究领域，通过有机化学途径解决生物化学及分子生物学难题，研究方向包括纳米聚合物药物载体的构建、生物化学靶向性给药体系、生物医用材料、药物缓释材料等。尤其在新型抗癌药物输送载体、生物活性高分子材料的设计合成以及与生物大分子的识别、相互作用机制等方面进行了系统的研究，相关研究成果曾获得国家教委科技进步奖，主持和参加了包括“973”子项目、“863”项目、国家自然科学基金等在内的国家和省部级研究项目16项。其国家重点基础研究发展规划（973）关键课题《材料表面分子识别及其评估方法的研究》深受同行承认，为新型药物载体的设计奠定了基础。李教授在国际知名学术期刊上发表研究论文80余篇，已申请/公开中国专利8项，并多次受邀做学术专题报告。李教授兼任苏州汉德森医药科技有限公司首席技术官，主持多个新药研发项目。

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A brief glance on ADCs development

Zhan Xiao
&
Haiying Zhang

Due to its high selectivity, monolconal antibodies (mAb) against tumor-specific antigens have long been recognized as an effective way to selectively target cancer cells without harming normal cells. However, it has become apparent that most often, naked mAb by itself may not necessarily be very potent and generally speaking only exerts modest cytostatic effects. The emerging antibody drug conjugate (ADC) platform, cytotoxic drugs linked to mAbs though specialized linkers is a smart way to leverage the high target-selectivity of the mAb with the added benefit of potent cell-kill effects of the attached drug payload. Overall, this is the closest we have ever come to realize what Paul Erlich has envisioned over a hundred year ago with the "magic bullet" theory (maximal anti-cancer effect without normal tissue toxicity).

ADC has three components: mAb against a highly selective cancer target, the toxic drug payload and the chemical linker in the middle that links the two together.

Target and mAb

As mentioned earlier, the choice of the target is likely the single most important factor determining the eventual success of the ADC. Since mAbs can only access cell-surface targets, no intracellular proteins can be chosen. To ensure minimal normal tissue toxicity, plasma membrane targets specifically expressed on cancer but not normal tissues are highly coveted. In comparison to the naked mAb platform which requires the target to be critical/essential to the underlying cancer cell's growth or survival, ADC target does not necessarily need to be essential for the tumor viability to be effective. This means the potential target pools for ADC may actually be broader than naked mAbs. In addition, a monoclonal antibody should be able to persist in circulation for long periods of time to allow for prolonged exposure of the ADC to the cancer cells. Monoclonal antibodies that are components of an ADC may be internalized upon binding to their target antigen, which ultimately allows them to deliver the cytotoxic specifically to target tumor cells.

Extreme caution has to be exercised at the target selection level. Failure to observe this cardinal rule could lead to very serious consequence. This is demonstrated by the dramatic toxicity, including fatality, seen in clinical trial of anti-CD44 ADC. CD44 has been shown to be a potential cancer stem cell (CSC) surface marker and enrichment tool for CSC, so it seems to be a desirable target for ADC. However, a persistent question with this target is its fairly wide expression in certain normal tissues. This is likely the underlying reason for the tremendous toxicity.

Usually the conventional way to discover potential ADC targets is to carry out systematic genomic or proteomic studies comparing tumors with normal tissues (with same tissue origin) and pinpoint plasma membrane targets preferentially expressed in tumors. Here proteomic platforms may be more superior since measures such as surface biotinylation could be taken to ensure that the discovered targets are truly localized on cancer cell surface, in contrast, the genomic means cannot simply guarantee that the targets are localized on surface membrane or intracellular membranes.

Regardless of genomic or proteomic means to discover potential ADC targets, every picked target will need to undergo detailed study to confirm it selective tumor expression before undergoing further development. This can be usually done by FACS-based cell-surface profiling in a collection of tumor cell-lines that reflect the in vivo expression pattern of the target, followed by IHC study with primary tumor tissue microarrays.

Having placed a huge emphasis on the lack of normal tissue expression for any ADC targets, the flip side is that this stringent requirement may actually be somewhat relaxed depending on the particular class of targets. For B-cell malignancies, targets such as CD20, CD21, and CD22 have all been used as targets for naked mAbs; some of them have also been explored as ADCs. Rituximab, the anti-CD20 mAb, represents one of the most successful therapeutic mAbs ever developed. However, all these targets are also expressed on normal B-cell compartments so they will also be impacted by the various drugs or drug candidates. Based on vast pre-existing clinical experiences, normal B-cell suppression or even elimination

does not seem to pose a serious safety issue, explaining why rituximab or similar drugs do not confer severe toxicities in vivo. By the same token, this suggests that these B-cell targets may also be viable ADC targets and not carry heightened toxicity risk. But it has to be stressed that this scenario represents the exception but NOT the rule for ADC targets so it is always advisable to be rigorous in target selection.

Just having a cancer-specific target is not enough. The mechanism of action for ADC dictates that the target has to be amenable to either spontaneous or mAb-induced endo-lysosomal trafficking since most of the currently available linkers can only be dissolved in late endosome or lysosome. mAbs that not only possess strong binding affinity to the target but also enable or accelerate the internalization process are highly desirable. To achieve this purpose, high-throughput semi-quantitative internalization assays have been designed to establish the potency of the mAb in this regard.

Cell Surface Target	Target Protein Type	Tissue Distribution
GPNMB	Glycoprotein nonmetastatic melanoma B, trans-membrane glycoprotein NMB, osteoavtivin, type I	Low metastatic melanoma [shedding]
PSMA	Prostate-specific membrane antigen type II inte-gral membrane glycoprotein	Epithelial cells
Cripto	GPI-anchored protein belonging to the EGF-CFC family	Epithelial cells
ED-B	L19 of fibronectin	Stromal cells, vascular cells
TMEFF2	Tomoregulin, trans-membrane protein with EGF-like & two follistatin-like domains 2	Epithelial cells, prostate cells
EphB2	elk-related tyrosine kinase, ephrin receptor B2	Epithelial cells
EphA2	elk-related tyrosine kinase, ephrin receptor A2	Epithelial cells
FAP	Fibroblast activated protein	Stromal cells
av integrin	Integrin	Epithelial cells
Mesothelin	GPI-anchored differentiation antigen	Epithelial cells, mesothelial cells
EGFR	Receptor tyrosine kinase ErbB-1; HER1	Epithelial cells
TAG-72	Tumor-associated glycoprotein-72, CA-72-4	Epithelial cells
GD2	Disialoganglioside GD2	Neuroectodermal cells
CAIX	`eCarbonic anhydrase IX, G250 antigen, CA9	Epithelial cells, endothelial cells, hypoxic cells
5T4	trophoblast growth factor, oncofetal protein	Epithelial cells

Adapted from Teicher BA. Curr Cancer Drug Targets. 2009 Dec;9(8):982-1004

Other functional assays include cell proliferation/viability assays that assess the mAb's ability to confer cell-kill when complexed with a secondary antibody pre-conjugated with certain toxins (saporin, a ribosome poison, is commercially a vailable and the most often used kind). This will circumvent the need to actually construct a direct ADC with the underlying mAb, a laborious endeavor that may seriously decrease the screening throughput.

The table above lists some solid tumor targets currently undergoing development for ADC.

Toxic drug payload

Initial drugs selected for ADC represent traditional cytotoxic drugs that have already been approved as chemotherapies, such as doxorubicin and paclitaxel. However, since ADC can only deliver a very small drug load to the tumor site, ADCs based on these drugs suffered from minimal potency and low clinical activities. It became apparent that much more potent drugs will need to be developed. These include anti-mitotic compounds such as auristatins, maytansines, and DNA-damaging agents such as calicheamicins. Auristatins and maytasines confer cell-kill in a similar mannr like taxol by binding to tubulin and causing mitotic arrest. Monomethylauristatin E, conjugated through a protease-cleavable dipeptide linker (vcMMAE), and monomethylauristatin F, conjugated directly to mAbs through maleimidocaproic acid (mcMMAF) (Seattle Genetics) represent synthetic analogs of naturally occurring auristatins that are more potent. A common trait of these ADC-enabling drugs is that they are too toxic to be dosed as a systemic chemotherapy so ADC is the optimal usage for them.

Compared to MMAE which is more membrane permeable, MMAF is not membrane permeable due to a charged group but displays a higher potency. Application-wise, this difference means that MMAE has the extra potential to confer by-stander (neighboring but non-target expressing cells) killing effect while MMAF does not have the same capacity. The flip side of the coin is that MMAE may confer higher toxicity due to unintended killing of surrounding normal cells.

In contrast to these auristatin analogs, Immunogen, another major player of the ADC field, resorted to develop maytansine analogs, DM1, conjugated through a disulfide or directly through the heterobifunctional succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (SMCC) linker, and DM4, conjugated through a disulfide. Maytansine is a natural product originally isolated from the Ethiopian shrub *Maytenus ovatus*.

A critical parameter for ADC is the exact conjugation method and relative ratio of drugs per mAb molecule (drug loading stoichiometry and consequent conjugation heterogeneity). Any conjugation method should strive to maintain the pharmacokinetic properties of the mAb. For this reason sometimes higher drug loading ratios may not necessarily translate to higher activities since they tend to change the physical-chemical property of the mAb too much. A rule-of-the-thumb finding is that usually 2-4 drugs/mAb loading is optimal for in vivo activity. Currently there are two different conjugation methods: traditional random linking approach through alkylation of reduced interchain disulfides or acylation of lysines, and targeted linking approach through pre-engineered thio-containing residues on the mAb (i.e.: alkylation of genetically engineered cysteines). The conventional method uses a mild reducing method to reduce the interchain disulfides into two cycteines. It has been shown that the random linking approach tends to give more divergent subpopulations of ADC with unequal drug loading ratios while the second method may improve the uniformity of the ADC products.

ADCs in the clinic.

Agent	Clinical status	Target	Indication	Drug class
SGN-35	Phase I	CD30	Hodgkin's disease	Auristatin
CRO11-vc-MMAE	Phase II	GPNMB	Melanoma	Auristatin
Trastuzumab-DM1	Phase II	Her2/neu	Breast cancer	Maytansine
AVE9633	Phase I	CD33	Acute myelogenous leukemia	Maytansine
Gemtuzumab Ozogamicin	Approved	CD33	Acute myelogenous leukemia	Calicheamicin
Inotuzumab Ozogamicin	Phase III	CD22	Non-Hodgkin's lymphoma	Calicheamicin
HuC242-DM4	Phase I	CanAg	Colorectal cancer	Maytansine
HuN901-DM1	Phase I and II	CD57	Small cell lung cancer, multiple myeloma	Maytansine

The table above summarizes the ADCs in different stages of clinical development (From Senter, P. Curr Opin Chem Biol. 2009 Jun;13(3):235-44)

Linkers

There are two types of linkers commonly used in ADC: stable (uncleavable) and cleavable. Theoretically speaking, the design of an ADC linker has to satisfy two criteria: it has to be stable enough that the drug is not released in circulation before reaching the tumor site; however, it has to be labile enough within tumor to allow for dissociation from the carrier mAb.

For the cleavable linkers, there are three main types: linkers that are cleaved under acidic conditions corresponding to environments in late endosome and lysosomes; peptide linkers that are substrate of proteases residing in lysosomes (a major example is VC: valine-citruline that offers a substrate site for lysosomal enzyme cathepsin); and disulfide linkers that will be stable in the more oxidizing conditions of the circulation but cleaved in the more reducing conditions of the intracellular compartments.

For stable linkers, the thioether type is currently the most frequently used. It is stably attached to the mAb until internalization into lysosome and degradation of the mAb. Therefore, for stable-linker ADC to be effective, the ADC has to go through complete degradation before the active payload can be released.

The key difference of the stable linker vs. the cleavable type is obviously the differential requirement of degradation. For stable types, it is a must, whereas for cleavable types, degradation is not essential as long as the ADC can be targeted into the endo-lysosomal route. The functional implication of this crucial difference is that targets amenable to stable linker ADCs would also be amenable to cleavable type, but targets compatible with cleavable linkers may not be appropriate for stable linkers. Hence for targets that only offer moderate internalization rate without undergoing appreciable degradation, cleavable linkers will be essential to confer anti-tumor activity; but for targets undergoing robust lysosomal-based degradation, stable linkers may be more superior.

Besides anti-tumor efficacy, another major concern for ADCs is the potential toxicity. Here the toxicity consists of two distinct parts: target-based and non-target based/systemic toxicity. As mentioned earlier, the way to minimize target-based toxicity is to judiciously choose targets with no or very minimal normal tissue expressions. However, ADC against a target with no normal tissue expression may still confer systemic toxicity due to premature release of the drug in circulation and more often than not, this is the more predominant form of toxicity than the target-based type. Here the choice of linkers plays a critical role: it has been found that cleavable linkers usually are more labile in circulation and thereby elicit more pronounced systemic toxicity; but stable linkers showed less non-specific drug release and thereby caused lower systemic toxicity.

In summary, since the therapeutic window of any ADC is determined by its anti-tumor effect and potential normal tissue toxicity, the best way will be to use a stable linker on a target that undergoes degradation. This way, robust tumor-cell-kill effects will be preserved without incurring substantial systemic toxicity.

ADC drugs in clinical development

A survey of the current ADC research landscape reveals the highly divergent types of targets as well as drug payload and linkers under investigations. ADCs in late stage clinical trials include brentuximab vedotin (SGN-35), an anti-CD30 mAb conjugated to vcMMAE, currently in a pivotal trial for relapsed or refractory Hodgkin lymphoma (HL); and Trastuzumab-DM1, also in late-stage clinical trials, uses the approved anti-Her2 mAb Trastuzumab (Herceptin) directly conjugated to DM1 via SMCC for the treatment of metastatic breast cancer. Both compounds target highly established cancer targets with known overexpression in their respective patient populations; and both compounds achieved dramatic tumor response even in phase 1/2 trials: For brentuximab vedotin, nearly all (93%) of the patients experienced tumor regression during the course of therapy; for Trastuzumab-DM1, a 33% objective response rate in 110 patients was achieved, demonstrating single agent activity in a population heavily pretreated with agents including Trastuzumab. In an era where clinical approval rate for new anti-cancer drugs stands at a

pathetic ~5%, these are eye-popping numbers that really demonstrated the tremendous success that ADC could deliver. For trastuzumab-DM1, the success is even more impressive in light of the fact that the mAb component, Trastuzumab, was initially developed as a naked anti-Her2 mAb without any consideration of use in the ADC setting.

CDX-011 (CRO11-vcMMAE), an anti-glycoprotein NMB mAb conjugated to vcMMAE, currently studied in both melanoma and breast cancer, represents an ADC in earlier stage of clinical development. In similar early stage of clinical development are anti-CD56 IMGN901, a disulfide-linked DM1 ADC for multiple myeloma and solid tumors, the anti-CD19 SAR3419, a disulfide-linked DM4 ADC for NHL, and the anti-CD138 BT-062, a disulfide-linked DM4 ADC for multiple myeloma.

In contrast, a much larger set of ADCs are undergoing pre-clinical stage of development. The targets include some well-known hematological cancer targets such as CD19, CD20, BCMA, and CD79b; and solid tumor targets such as CD133, CEACAM6, TMEFF2, PSCA, MUC16, and p97.

Summary

After some initial struggles, ADC drug development is currently enjoying robust and exciting growth. Eye-popping clinical trial efficacy data from brentuximab vedotin and T-DM1 are finally proving and realizing the long-held belief that ADC are the closest thing to the “magic bullet” cancer therapy. Certainly this impressive recent progress is not lost on all the major pharmaceutical companies since a spate of collaboration deals have been struck between them and the key players in the field (Seattle Genetics and Immunogen). With huge future success already projected by various industry analysts, investment in this area can only be expected to grow at an even more dramatic rate. However, as with all the “hot” therapeutic platforms, ADC also carry some special “baggage” that needs to be carefully triaged before any true success can be realized. But one thing is for sure: we will be hearing more and more of ADC stories for a long time to come.

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摘要

抗体—药物共轭连结技术(ADC)是一种具有治疗癌症潜力的新型技术，也是目前肿瘤治疗研究新方向之一。这种方法有望减少药物对健康细胞的伤害，以减少副作用。具体来说，ADC技术是用特殊的共轭连接，将一种单克隆抗体与杀癌细胞药物结合在一起，并在抗体的结构上修改了特别位点以促进药物连接的稳定缚束，同时又不会影响抗体的整体结构或识别癌细胞的能力。这种新型ADC药物比传统的ADC药物更有效、而且具有更好的耐受性、意味着这种药物对人有更小的副作用。

ADC由三个部分组成：靶向抗体、轭合连接键、细胞毒。

靶向抗体选择对ADC是否成功起了决定性的作用。靶向抗体不仅需要具备对肿瘤细胞有很高的分辩力，而且能通过细胞吞噬过程进入前溶酶体，以便有效地释放细胞毒。肿瘤细胞表面靶标表达的数量、细胞吞噬靶向抗体的速度、以及靶标从细胞膜上脱落等因素都会影响到ADC的活性。CD19、CD20、CD22、 CD30、以及HER2 均为常用的靶向抗体。

轭合连接键大体上分为两类：固定性连接以及可裂解性连接。目前，最常用的固定性连接是硫醚键。该键连接的药物会在抗体被吞噬进入溶酶体后才会分解释放。然而，可裂解性连接却有三种。一类连接键能在酸性环境中被分解的、如在晚期溶酶体和内含体中；肽键能被溶酶体中的蛋白酶分解；最后，双硫键能在细胞内还原的环境中被分解，而在较氧化的循环系统中尚保持稳定的连接、防止药物脱落。选择连接键应以靶标而易。对吞噬率低或连接键不太容易被分解的靶标环境，应选用裂解性连接；反之则用固定性连接为佳。一般来说，裂解性连接的药多少会在循环系统中脱落、以致造成非靶标性的毒性。然而，固定性连接的ADC对肿瘤靶标的选择性较高，因此系统性的毒性会相对得较低，具而起到疗效高毒性小的佳境。另外，从原则上来说，轭合连接需要符合两个标准。一、药物连接的缚束要稳定，不在血液循环中脱落，以确保药物被带到肿瘤靶细胞；二、药物带到靶细胞处需能按要求与抗体分开释放到细胞中、以便发挥疗效。

常用的细胞毒有抗有丝分裂如Auristatins(Seattle Genetics)， Maytansines (Immunogen)和DNA损伤剂。vcMMAE是抗微管蛋白药物，把monomethеylauristatn E 由蛋白酶可裂解的二肽键与抗体相连接、且能渗透细胞膜。mcMMAF 是monomethеylauristatn F由 maleimido-caproic

acid直接与抗体相连。虽然不能渗透过细胞膜，但疗效却高于monomethey lauristatn E。DM1和DM4都是Maytansine的类似物、直接或间接地由二硫键或SMCC与抗体相连接。细胞毒与抗体连接的一个重要参数是细胞毒和抗体的比例、一般来说是2-4比1为佳。

靶向－细胞毒轭合新药初见成效

由抗CD30单克隆抗体（brentuximab）和抗微管蛋白药物（vcMMAE）构成的抗体-药物轭合物brentuximab vedotin引人关注。brentuximab vedotin与表达CD30的肿瘤细胞结合时，可通过内化转运至溶酶体，经剪切释放MMAE至胞浆，后者可作用于微管导致细胞周期停滞、细胞凋亡。该药在霍奇金淋巴瘤（HL）的Ⅱ期临床治疗中疗效显著。总缓解率(ORR)为75%，中位缓解持续时间为29周，完全缓解（CR）率为34%。93%的患者有不同程度的肿瘤缩小，PFS期达25周。患者可耐受治疗，最常见不良反应为外周神经病变、乏力和恶心，半数以上患者停药后外周神经病变消失或改善。

Trastuzumab-DM1是由SMCC直接将单克隆抗体Trastuzumab和DM1连接构成的抗体-药物轭合物。该药在I和II期临床实验中用于治疗转移性乳房癌，疗效显著。在110例病历中，总缓解率达33%。

CDX-011是由CR011-抗糖蛋白NMB单克隆抗体与vcMMAE连接构成的抗体-药物轭合。该药正在进行II期临床试验、主治黑色素瘤和乳房癌。

除此以外，目前有许多ADCs在进行临床前研究、其中用包括许多已知的血液癌和实体瘤的靶标CD19、CD20、CD133、CEACAM6等等。在不久的将来，ADC药会层出不穷地进入临床、最后进入市场，成为肿瘤治疗中的亮点。

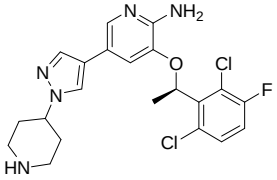
《药源》新闻

www.yy-w.org

ALK酪氨酸激酶抑制剂Crizotinib（克里唑蒂尼）治疗ALK阳性淋巴癌在小组病人中显示惊人疗效

朱贵东

据上个星期美国皮肤协会第52次年会报道，美国辉瑞集团的ALK酪氨酸激酶抑制剂Crizotinib（克里唑蒂尼）在小组ALK阳性淋巴癌病人中显示惊人的疗效。这个小组属于同情性的临床实验只有四个复发后并对细胞毒素显示抗药性的间变性大细胞淋巴瘤（ALCL）病人参加。间变性大细胞淋巴瘤是一种少见且生长迅速的T-细胞淋巴瘤，象其它淋巴瘤一样这种淋巴瘤通常对化疗比较敏感，但一旦复发，目前还没有有效的治疗方法，存活率非常低。该项临床实验是Crizotinib首次用于治疗淋巴癌，实验所有病人在用药几天以后就显示包括发烧及疼痛等症状减轻，两个星期以后这个结果又被正电子成像术（PET）及计算机断层扫描(CT)所确认。目前该项实验中四个病人中的三个达到完全缓解（Complete remission），其中一位已经用药6个月，一个治疗5个月，其他两个开始使用Crizotinib治疗不久。



Crizotinib

附前期《药源》相关文章：

从小分子ALK酪氨酸激酶抑制剂Crizotinib（克里唑蒂尼）的发明看肿瘤新药研发趋势

朱贵东

众所周知，恶性肿瘤是人类健康的主要杀手之一。自从上个世纪七十年代美国尼克松总统倡导对肿瘤宣战以来，人类对肿瘤的认识水平和治疗手段有了瞩目的进展，虽然还不能根治，对部分肿瘤已经做到有效地控制。由于肿瘤的形成机制相当复杂，大部分恶性肿瘤细胞的生长都有多种通路，导致癌细胞有极强的生命力，抑制其一条或部分通路并不能完全消灭癌细胞。反之除通常的病灶转移以外，化疗经常导致癌细胞基因发生突变，致使其产生抗药性。

最近辉瑞集团报道其变性淋巴瘤激酶（ALK）抑制剂Crizotinib对ALK阳性非小细胞肺癌（NSCLC）有显著疗效

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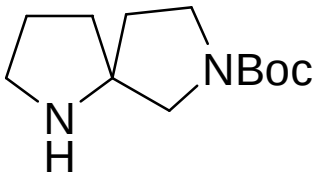

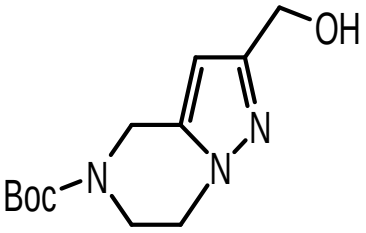

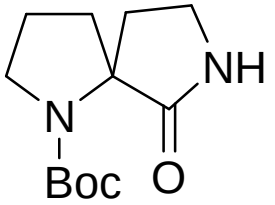

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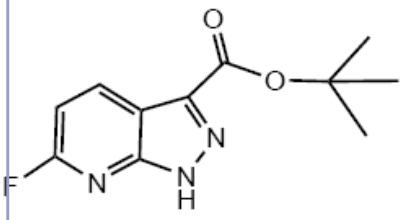

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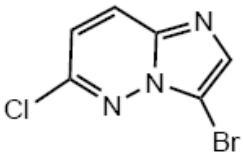

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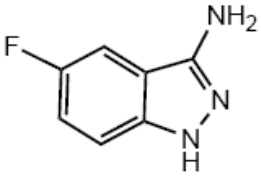

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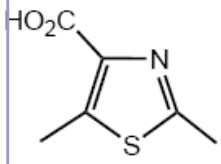

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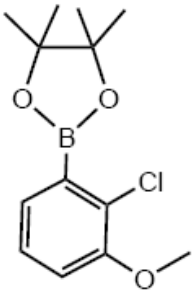

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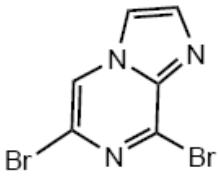

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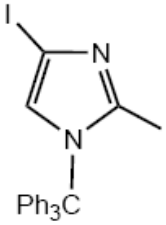

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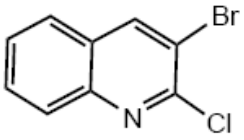

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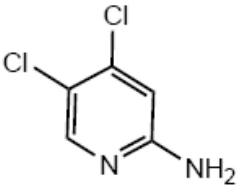

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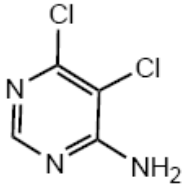

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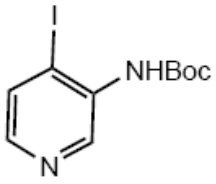

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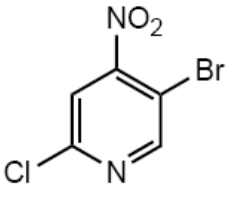

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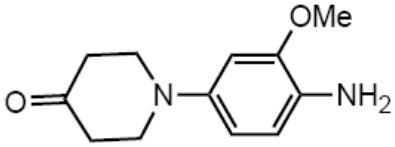

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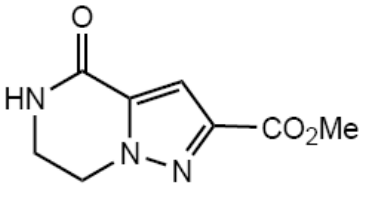

SC-35648

以人工合成糖疫苗与肿瘤细胞表面糖抗原的代谢改造相结合发展新型有效的抗肿瘤疫苗和肿瘤免疫治疗方法

郭忠武

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肿瘤是威胁人类健康的重大疾病。传统的化疗、放疗、手术等治疗方法虽然已在肿瘤治疗方面取得了很大进展，但仍然不能完全令人满意，因此目前仍极需发展有效的肿瘤治疗新方法。由于免疫系统在被激活后可以有效地并选择性地识别和杀灭肿瘤病灶的癌细胞，同时还可以有效地消除血液和淋巴系统中的癌细胞，阻止癌症的转移和扩散，因此，肿瘤的免疫治疗，特别是针对肿瘤相关抗原(tumor-associated antigen, TAA) 的特异性免疫治疗方法，具有专特、有效和低毒等优点，而备受亲睐。

肿瘤相关糖抗原(tumor-associated carbohydrate antigen, TACA)是肿瘤细胞表面的重要TAA。相对于其它TAA来讲，TACA在肿瘤细胞表面的表达更为丰富，同时，它们一般暴露在细胞表面而易于为免疫系统所识别、其结构不容易发生突变而有一定保守性，[1,2]因此，TACA是发展新型抗肿瘤疫苗和发展肿瘤免疫治疗新方法的重要分子靶标，而基于TACA的肿瘤疫苗已成为当前肿瘤治疗学的研究热点之一。

到目前为止，人们已经在各种肿瘤细胞的表面发现了许多不同的TACA，并研究确定了它们的结构。[3,4]例如，GM3是一个末端联有N-乙酰基唾液酸的三糖抗原，STn是一个末端联有N-乙酰基唾液酸的简单二糖抗原，这两种TACA在肿瘤细胞表面以糖脂或糖蛋白的形式存在，在白血病、皮肤癌、乳腺癌、肺癌、前列腺癌等肿瘤细胞有大量表达。针对TACA的肿瘤疫苗研究作为肿瘤治疗的新前沿，近年来取得了不小的进展，例如，有数种疫苗已经进入了临床试验阶段。[5]然而，针对TACA的肿瘤疫苗研发目前仍然存在着许多问题，最主要的是肿瘤病人对TACA 的免疫耐受性问题，这些问题严重阻碍着该领域的进一步发展。

在以糖作为抗原进行疫苗研发的过程中一个极普遍的问题是糖的免疫原性非常差，对于TACA来讲这个问题尤为显著。其实，肿瘤在病人体内的发生与发展说明病人已对肿瘤细胞表面抗原产生了耐受性。为了克服糖抗原免疫原性差这一问题，现在普遍采用的方法是将糖抗原与载体蛋白以共价键方式结合形成具有较强免疫原性的糖蛋白缀合物用作疫苗；其中应用最为广泛和有效的载体蛋白是镇眼帽贝血蓝蛋白(keyhole limpet hemocyanin, KLH)。糖与蛋白缀合的方法虽然在提高糖抗原活性，以及发展抗菌疫苗方面取得了巨大成功，[6]但对于克服TACA的免疫耐受性问题作用相对有限。因此，到目前为止绝大部分TACA仍无法用于发展有效的抗肿瘤疫苗，而研究发现可以克服TACA免疫耐受性问题的新方法和新技术成为研发抗肿瘤疫苗和肿瘤免疫治疗方法的核心问题和难点。

近年来，我们课题组发明了一种免疫治疗肿瘤的新策略，它可以克服TACA的免疫耐受性问题，并用于研发针对TACA的有效抗肿瘤疫苗和肿瘤免疫治疗方法，其基本原理和设计如图1所示。[7]首先，我们通过化学合成的方法制备TACA的非天然衍生物，并将其与蛋白载体KLH偶联制成肿瘤疫苗用以接种免疫肿瘤病人。由于这种肿瘤疫苗含有非天然的抗原结构，它能够很容易地诱导机体产生免疫应答，从而在病人体内建立起很强的和特异性的免疫反应。接下来，我们利用细胞糖代谢工程的技术对肿瘤细胞表面的TACA进行修饰，即供给肿瘤细胞经过化学修饰过的TACA合成单糖前体，肿瘤细胞便可以利用该前体生物合成非天然TACA衍生物，以部分取代细胞原有的TACA。肿瘤细胞的糖代谢工程改造[8,9]是利用了糖生物合成由一系列酶所控制，没有特定模板，而且这些酶可以接受经过一定修饰的前体底物，以及肿瘤细胞高表达某些糖合成酶等特点。最后，已经被激活的免疫系统便可以很容易地并选择性地识别和杀灭经过修饰标记的肿瘤细胞，从而实现肿瘤的免疫治疗。此种免疫治疗方法被称为主动免疫疗法（图1A），因为治疗所需要的免疫反应是用疫苗免疫病人而主动建立的。

与此同时，肿瘤的免疫治疗也可以通过被动免疫的方法来实现，即应用单克隆抗体治疗肿瘤（图1B）。为此，在应用细胞糖代谢工程的技术对肿瘤细胞表面的TACA进行修饰的同时，我们可以用合成疫苗免疫健康个体以获得针对非天然TACA衍生物的特异性单克隆抗体，最后，通过体外方法大量制备的单克隆抗体可用于治疗修饰过的肿瘤。

我们以GM3和sTn为靶标抗原，对此新策略进行了深入研究，并证实其可行性。首先，我们发现由非天然TACA衍生物所形成的疫苗具有很好的免疫原性，可以诱导T细胞介导的免疫反应，这对于肿瘤免

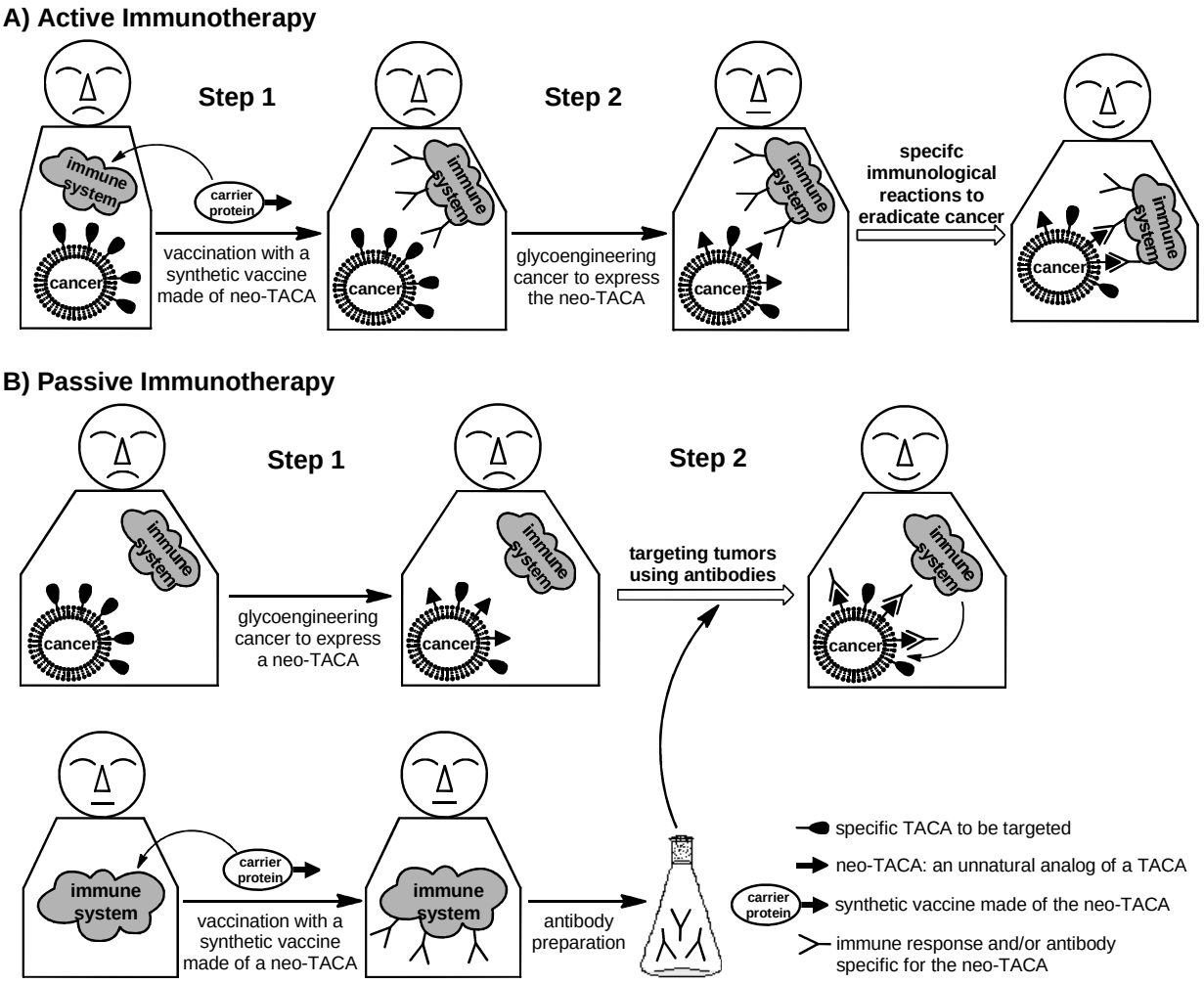

图1. 一种针对TACA的肿瘤免疫治疗的新策略

疫治疗是至关重要的；[10-12]其次，我们已经证实通过糖代谢工程的方法可以对肿瘤细胞比对正常细胞进行更为有效的糖修饰，使肿瘤细胞表达非天然TACA衍生物；[13, 14]再次，我们发现在补体的介导下，合成疫苗所诱导的免疫血清和单克隆抗体可以对糖代谢工程修饰过的肿瘤细胞比对同样处理过的正常细胞或没有修饰过的肿瘤细胞具有高选择性的杀伤作用；[14]最后，初步的动物实验证明新型合成疫苗或相关单克隆抗体与非天然单糖前体结合治疗可以抑制肿瘤的生长和转移。[15]

具体而言，我们合成了一系列含有非天然N-酰基唾液酸的GM3和sTn衍生物，将它们与KLH结合形成疫苗，并在小鼠检验其免疫活性。[10-12]我们发现这些衍生物，特别是N-苯乙酰化的GM3和sTn衍生物，比GM3和sTn自身具有更强的免疫原性，可以诱导产生高滴度的IgG抗体，这说明这些衍生物可以诱导具有高效杀肿瘤活性的T 细胞免疫反应。由此可见，具有非天然N-酰基唾液酸的GM3和sTn衍生物与KLH所形成的缀合物可以发展成为非常有效的肿瘤疫苗。我们还合成了一系列N-乙酰甘露糖胺 (ManNAc)的非天然N-酰基衍生物，研究了它们作为非天然N-酰基唾液酸的前体被细胞利用，并对细胞表面的糖链进行代谢修饰的功能。[13, 14]我们利用抗血清和单克隆抗体并通过酶联检测（ELISA）和流式细胞技术（FCM）等方法分析研究发现，与正常细胞相比，肿瘤细胞，包括黑色素瘤等，可以更有效地摄取和利用这些非天然的N-酰基甘露糖胺衍生物，并在细胞表面表达相应的非天然N-酰基GM3和sTn衍生物。特别是N-苯乙酰甘露糖胺，在微摩尔浓度便可以对肿瘤细胞进行有效的糖代谢工程修饰，使细胞表达N-苯乙酰GM3和sTn。这一发现对于糖代谢工程在体内的实际应用是至关重要的，因为以前的细胞糖工程代谢前体都需要毫摩尔浓度才能对细胞进行有效的修饰，而毫摩尔浓度是很难在体内实现的。同时，我们还研究发现对N-苯乙酰GM3特异的单克隆抗体2H3可以非常有效地杀灭用15-30微摩尔浓度N-苯乙酰甘露糖胺处理过的黑色素瘤细胞，而对于同样处理过的正常细胞却没有任何影响，正常细胞在经过毫摩尔浓度N-苯乙酰甘露糖胺处理后才对抗体2H3诱导的细胞毒性有一点反应；[14]这一结果说明我们可以通过疫苗免疫与细胞糖代谢工程前体治疗相结合对肿瘤实施有效地、选择性地免疫治疗。此外，我们还以白血病为肿瘤模型显示根据我们的新策略所设计的被动免疫治疗可以有效

地抑制肿瘤生长，并完全控制肿瘤的转移和扩散。[15]

总之，我们发展了一种免疫治疗肿瘤的新策略，它可以有效地克服TACA的免疫耐受性问题。我们经过深入研究证实了其可行性，并发现含N-苯乙酰化唾液酸的TACA衍生物可以形成免疫原性非常强的肿瘤疫苗，若以此疫苗免疫肿瘤病人，结合N-苯乙酰甘露糖胺治疗，可以有效地控制肿瘤的生长和扩散，从而形成肿瘤治疗的新方法。该肿瘤免疫治疗的新策略不仅适用于GM3和sTn等抗原，而且也可以应用于其它任何含唾液酸的TACA，因此，它对于肿瘤治疗学研究具有较广泛的影响。

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郭忠武博士长期从事复杂天然产物的全合成、有机合成新方法学、复杂寡糖、糖肽及其它糖缀合物的化学与生物合成、糖生物学、糖药学和糖免疫学等方面的研究，已成为相关领域内国际权威性专家。其研究方向包括细胞表面糖质的生化改造及应用，癌症和细菌糖疫苗及新型生物医学材料的研究，细胞表面糖基磷脂酰肌醇锚定蛋白和糖蛋白的合成、结构和功能研究，及糖靶向的药物新剂型、新方法研究等。研究项目得到美国NIH、NSF、美国癌症学会、美国化学会、中国国家自然科学基金委等机构的资助。除近年已主持完成的多个项目外，目前主持有三个NIH和NSF项目，在研经费270多万美元。至今已在国内、国际主要学术刊物上发表研究论文100多篇，编撰糖疫苗方面专著1本，获得肿瘤和细菌糖疫苗方面的国际专利3项。近年应国内外学术单位和会议邀请做学术报告80余次，曾获得国内外多个科学奖项，包括中国军队科技进步奖(1989和1991年)、德国洪堡基金 (1996年)、美国研究合作组织创新研究奖 (2000年) 、美国化学会糖化学杰出青年学者奖 (2005年) 及日本水谷糖质基金会奖(2008年)等，2009年被第二军医大学评为杰出校友。

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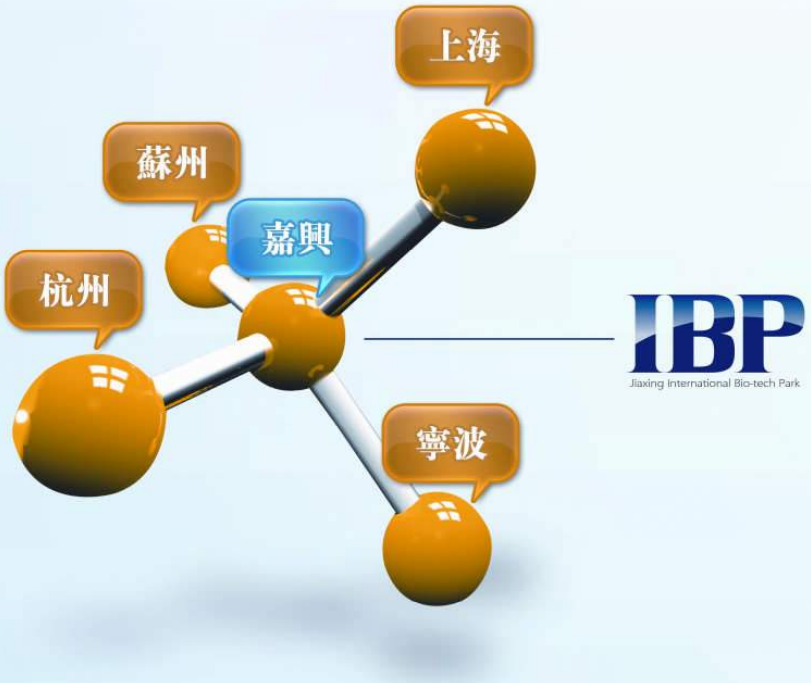

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抗肿瘤靶向药物输送系统的研究进展

李晨曦
南开大学
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YAOYUAN BIOTECH-PHARMA FORUM
Advances in Anti-cancer Targeted Drug Delivery

癌症已经成为当今威胁人类生命的头号疾病。肿瘤的非手术治疗包括放疗和化疗，是以杀死癌细胞为目的。鉴于肿瘤细胞与正常细胞的极其相似性以及更高的生命力，现有非手术疗法需要继续提高对肿瘤细胞的特异性，这就要求抗癌药物具有更高的选择性或靶向传递系统，是目前制药业和科学家一直面临的挑战。随着人类基因组计划的完成，基因组学和蛋白质学研究，增进了人们在分子水平对癌症的认识，相信不久将会有更多的抗癌药物靶点被发现，同时揭开靶向细胞治疗的黄金时代。

肿瘤的靶向治疗是将治疗作用选择性地集中在肿瘤组织、肿瘤细胞或肿瘤基因，从而降低对正常组织的副作用。抗肿瘤靶向给药系统是肿瘤靶向治疗的重要组成部分，把有效抗癌药物专一性或选择性地输送到肿瘤组织，控制特定生理部位的药物剂量，从而降低抗癌药对非靶点部位的副作用和毒性。

抗癌药物靶向给药系统的研究已经有几十年的历史，尽管目前获药物监管部门批准用于临床的数目还很有限，但这些研究已展现出广阔的实用前景和不可估量的潜力，甚至可能使抗癌药的研发发生变革。本文着重介绍现有抗肿瘤靶向给药系统的设计理念和研究进展。

近十几年来靶向给药系统进展斐然。根据抗癌药或其载体透过实体瘤组织或肿瘤细胞的方式，和与肿瘤细胞的作用方式可以把抗肿瘤靶向给药体系分为“生物物理靶向给药系统”和“生物化学免疫靶向给药系统”，当然在很多情况下也可能是以上双重或多重靶向药物输送方式的联合。

（一）生物物理靶向给药系统

生物物理靶向给药系统主要分为两大类：被动靶向和主动靶向。被动靶向给药系统载体包括聚合物络合物、胶束脂质体、以及微米和纳米技术等。而主动靶向是利用特殊的生物过程，如特定酶的性质，抗体—受体等专一性或选择性，从而达到提高靶点的药物浓度。增强的透过及滞留效应和长循环原理是被动靶向给药系统的主要设计理念之一。根据实体瘤丰富的血管及血管的不连续性，水溶性高分子聚合物等载体对实体瘤有倾向性沉积作用，通常称为增强的透过及滞留效应（EPR effect）。而在药物表面连接比如象PEG、聚氧乙烯等亲水性聚合物可降低在循环系统内被单核吞噬细胞系统捕捉的机会，从而延长保留时间。再通过透过及滞留效应，有效地蓄积在实体瘤病灶部位。

由类脂质双分子组成的脂质体(Liposomes) 具有类细胞结构的脂质囊泡。未经修饰的脂质体是另外一种被动靶向药物载体，可以改变被包封药物的体内分布。脂质体是巨噬细胞的天然吞噬对象之一，给药进入循环系统后被作为外界异物捕捉而产生靶向性。未加修饰的脂质体给药系统的靶向性通常是有限的，要达到组织或细胞水平的精确靶向还需连接一种识别因子，从而变成主动靶向给药体系。亚利桑那大学生物医药工程副教授Marek Romanowski和其同事最近发现一种新的脂质体药物输送系统。和其它主动型脂质体靶向制剂一样，亚利桑那课题组首先在脂质体表层连接一种识别分子，通过调整配体分子特异性，通过锁—匙原理，专一地与选择靶细胞表面的互补分子相互作用，使脂质体在靶区汇集。而后再在脂质体表层涂上薄薄的一层金。镀金脂质体制剂更大的优势在于金独特的物理特征，金在近红外光照射下会发热，破坏脂质体表层从而导致迅速地释放抗癌药。

酸碱度或热敏感靶向：依据在肿瘤组织内经常伴随酸中毒或过高热，科学家还通过设计对低pH值或较高温度敏感的材料，从而刺激给药载体在肿瘤组织内释放药物。

磁性靶向给药系统是由药物、磁铁粒子及骨架材料组成。该给药体系可以在外磁场存在下选择性地到达并定位于肿瘤区域。

纳米钻石抗癌药物输送系统：以美国西北大学教授何鼎为首的研究团队将纳米钻石附着在常见抗乳腺癌药物阿霉素（doxorubicin）分子上，这种新型的药物/制剂结合体能消除抗癌药产生抗药性的药物排出泵，从而提高这些抗癌药的疗效。他们将在正常情况下是致死剂量的阿霉素加上纳米钻石注射到小鼠体内，发现散布了纳米钻石的药物有更好的疗效，而且其毒性也比不加纳米钻石时小。此外，散布有纳米钻石的药物比不加纳米钻石时其在小鼠血液中存留的时间延长了10倍。这些结果表明，纳米钻石可使阿霉素在肿瘤中保留的时间要比单一药物更长，并且还能限制健康组织与药物的非必要接触。

在很多情况下，抗肿瘤靶向给药系统是把两种或多种靶向药物输送设计理念结合到一起。比如南开大学陈永胜研究团队把高磁性的四氧化三铁纳米颗粒通过与羧基的共价作用连接到了石墨烯氧化物表面，并由于羧基的定位作用，削弱了四氧化三铁颗粒的团聚，形成了直径约2到4纳米大小的颗粒，该四氧化三铁石墨烯复合物可以在外部磁场作用下发生向肿瘤组织的定向移动。依据很多肿瘤表面含有大量的叶酸受体和叶酸偶联白蛋白纳米粒在肿瘤细胞中的摄取量显著提高这一现象，陈永胜等还把叶酸（也称维生素B9）通过化学修饰连接到以上四氧化三铁石墨烯复合物表面，形成载体第二种对肿瘤细胞的亲和力。由于石墨烯氧化物极高的表面积、SP2共轭效应和分子氢键供受体，该载体可以通过pi-pi堆积和氢键作用负载大量的抗肿瘤药物盐酸阿霉素。随着PH值的改变，阿霉素和载体形成的氢键种类还会发生变化，其中在中性条件下负载量最高，碱性条件下次之，酸性条件下最低。由于肿瘤细胞较正常细胞而言显酸性，该体系对癌细胞药物的释放量预计远高于正常细胞，从而形成第三重靶向效果。

（二）生物化学免疫靶向给药体系

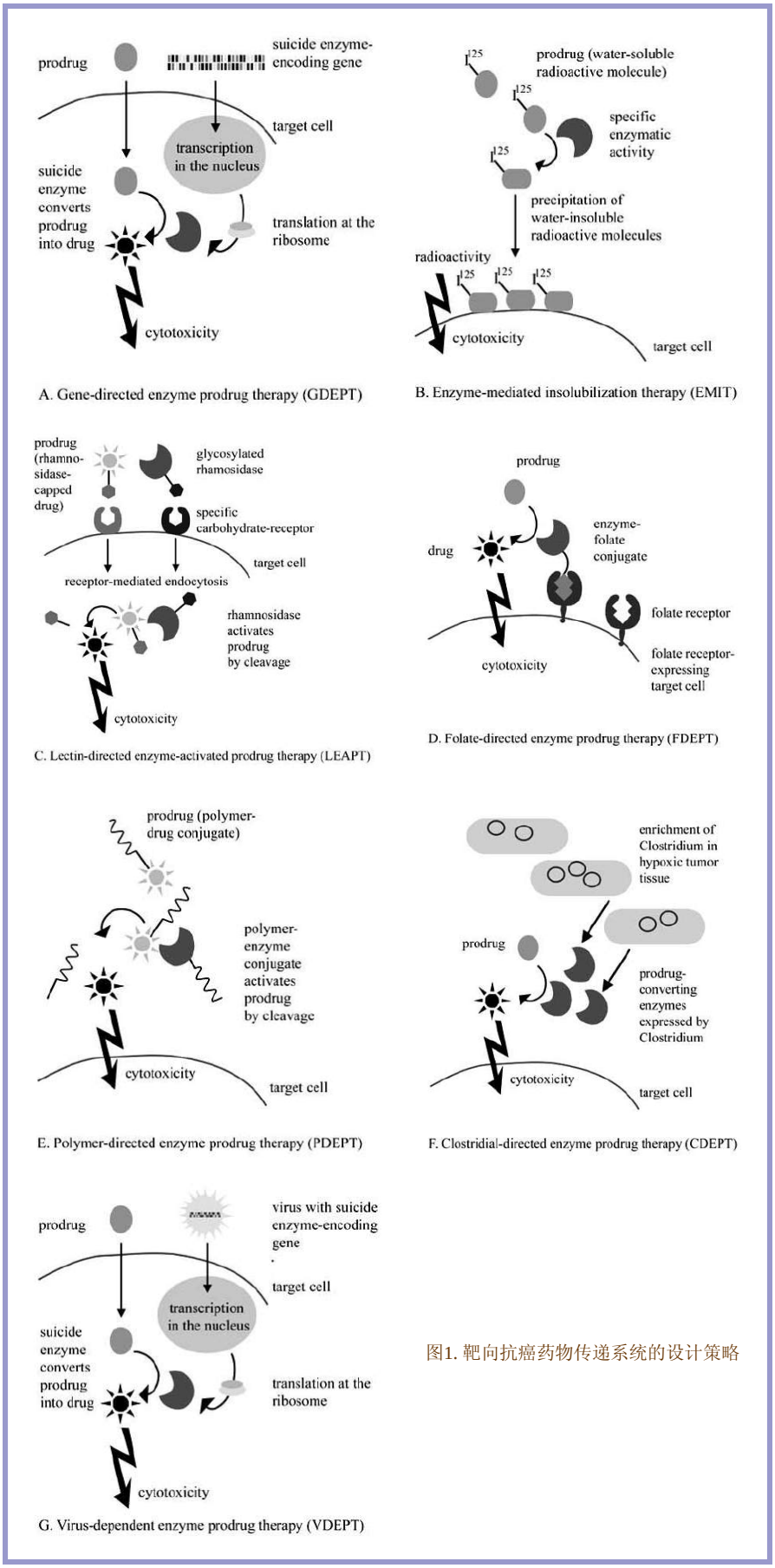

图1. 靶向抗癌药物传递系统的设计策略

Table 1. Immunoconjugates and Folate-Targeted Prodrugs in Clinical Trials

Prodrugs	Description	Target	Status
(A) Immunoconjugates			
IMGN901 (huN901-DM1)	Humanized anti-CD56 conjugated to DM1	CD56+ cells Solid tumors Small-cell lung cancer Gastric Cancer	Phase I
IMGN242 (huC242-DM4)]	Anti-CanAg mAb conjugated to DM4	PSMA expressing prostate cancer	Phase I/II
MLN-2704	Anti-PSMA mAb conjugated to DM1	CD22 expressing cells in B-cell Leukemia	Phase I/II
Inotuzumab-ozogamicin	Anti-CD22 mAb conjugated to calicheamicin	CD33 expressing cells in acute myeloid leukemia	Phase I/II
AVE9633	Anti-CD33 mAb conjugated to DM4	HER2 expressing cells in metastatic breast cancer	Phase I
Trastuzumab-DM1 (T-DM1)	Anti-HER2 mAb conjugated to DM1	CD19 expressing cells in B-cell derived cancers	Phase I/II
SAR3419	Anti-CD19 mAb conjugated to DM4	CD30 expressing cells in hematologic malignancies including Hodgkin Lymphoma	Phase I
SGN-35	Anti-CD30 mAb conjugated to Auristatins		Phase I
(B) Immunotoxins			
Transferrin-CRM107	Transferrin linked to diphtheria derived toxins	Transferrin receptors	Phase II
IL13-PE38QQR	IL13 linked to *Pseudomonas* toxins	IL13 binds to tumors expressing receptors when infused into the brain	Phase III
SS1(dsFV)-PE38	Anti-mesothelin mAb linked to *Pseudomonas* exotoxins	Mesothelin-expressing malignancies	Phase I
(C) Folate-targeted prodrugs			
EC145	Folate-vinblastine hydrazide	Cancer cells expressing folate	Phase I/II
EC17	Folate-hapten	Cancer cells expressing folate	Phase II
EC0225	Folate conjugated to vinca alkaloid mitomycin C	Cancer cells expressing folate	Phase I

生物化学或免疫靶向给药系统是利用肿瘤细胞表面的化学或免疫学特征，设计相应的能和肿瘤细胞表面的特异性抗原或受体有相互作用的前药体系。这些抗肿瘤前药到达标靶以后受包括外源（比如光、化学物质等）或内源（如酶）触发信号的作用而释放药物。常见的生物免疫靶向给药系统包括抗体导向酶前药疗法（ADEPT）、基因导向酶前药疗法（GDEPT）、病毒导向酶前药疗法（VEPT）、凝集素导向酶激活前药疗法（LEAPT）等；图1是该类靶向抗癌药传递系统的设计原理。

1. 抗体、抗原、及受体介导的肿瘤细胞靶向给药体系：

自1975年首次发现单克隆抗体可以与肿瘤细胞的抗原结合治疗肿瘤以来，人们发现许多抗体对大多数肿瘤细胞的特异性抗原都具有识别作用。尤其是重整细胞工程的发展显著降低了工业化生产肿瘤抗体的成本。促进了单克隆抗体以及相关药物的发展。

单克隆抗体最早用于靶向抗癌给药系统，单抗的进一步发展主要集中在抗体的人源化、双特异性抗体、偶联分子的小型化、新的分子靶点和抗癌药物的高效化等几个方面。临床试验表明，鼠源单克隆靶向会引起免疫反应。而通过人源化单克隆抗体，使其不带小鼠序列，可解决免疫反应这一问题。人源化单克隆抗体已被用于临床。美国食品药品监管局（FDA）已经批准惠氏的Mylotarg（gemtuzumab）用于治疗急性髓系白血病。

单克隆抗体—药物偶联物（ADC）是以单克隆抗体为载体，通过一个适合的连接体和常用抗癌药偶联，目前已经显示惊人的商业前景。下表列出以抗体为载体的抗癌药靶向给药体系在临床实验中的进展。

受体介导的分子靶向给药系统：肿瘤细胞表面或肿瘤血管表面通常高度表达一系列受体，并和肿瘤的生长与增殖密切相关。利用受体于其配体结合的特异性、选择性和饱和性，科学家设计以配体为载体的抗癌药靶向

Table 2. Polymer-Conjugates in Clinical Trials

Prodrug	Description	Target	Status
EZN-2208 (PEG-SN38)	PEG linked to7-ethyl-10-hydroxycamptothecin	Passive targeting to solid tumors	Phase I
CT-21006	Polyglutamate linked to camptothecin	Passive targeting	Phase II
Xyotax (CT-2103)	Polyglutamate linked to paclitaxel	Passive targeting	Phase II
Genoxol-PM	Polymeric micelles of PEG-poly(D, L-lactide)	Biodegradable micelles for passive target-ing	Phase II
Inno-206 (DOX-EMCH)	Doxorubicin-EMCH	EMCH is acid-sensitive, binds to albumins, passive targeting	Phase II
ProLindac	HPMA copolymer-diaminocyclohexane platinum	Passive targeting & drug-release in acid milieu	Phase II

给药系统，通过受体的介导作用，增加病灶区域的药物浓度。目前已发现三种高亲和力的叶酸受体（FR—α、FR—β、FR—γ），在多种肿瘤细胞中高度表达。鉴于其配体—叶酸具有分子量小、易得、亲和力高和容易化学修饰等优点，叶酸已经成为一个常用的靶向药物输送手段，用于进一步修饰多种抗癌靶向给药体系。

肿瘤血管相关抗原/受体：肿瘤的血管生成是肿瘤细胞摄取营养的途径，对肿瘤的生长、侵袭和转移都起着关键性的作用。肿瘤血管靶向性治疗是利用肿瘤区域新生血管内皮细胞表面的特异性抗原和/或受体起作用。常见的肿瘤血管标靶包括血管内皮生长因子（VEGF）、生血管素等等。通过把比如对VEGF受体有较高亲和力的多肽、或VEGF本身连接到水溶性高分子载体，从而实现对靶向给药系统的定向投放。

其它常见的受体还包括：

—血管受体：整合素（V3，V5）、核仁素、Endoglin

—血浆蛋白受体：低密度脂蛋白、（LDL）、转铁蛋白

—肽受体：Somtostatin受体、蛙皮素受体、神经肽Y受体、leuteinizing激素释放的受体

—糖受体：去唾液酸糖蛋白受体、半乳糖凝集素、选择素（E,P）、透明质酸质酸受体（CD44、RHAMM、HARLEC）。

2. 高分子靶向酶抗癌药

高分子导向酶抗癌药包含了高分子载体、与载体相连接的活性药物、靶向基因。靶向（或定位）基因的目的是引导大分子药物到达人体中特定的组织及细胞，高分子药物具有控释和靶向两个很突出的优点。

高分子靶向抗癌药按结构可分为三类：⑴ 垂挂型，⑵ 主链型，⑶ 封端型。近十年高分子靶向抗癌药物的研究和应用日益受到广泛的重视，这一研究已带来突破性的靶向治疗方式，已有一些陆续投入临床试验阶段（见表2）。例如，Xyotax (CT-2103)是传统抗癌药紫杉醇与聚谷氨酸聚合物的偶联物。因为聚谷氨酸有极高的水溶性和生物降解性，聚谷氨酸紫杉醇显著提高了紫杉醇在水中的溶解度。除此之外，因为肿瘤血管具有多孔渗透的通路，而连上聚谷氨酸以后体积显著增大，Xyotax在肿瘤血管中通过孔渗透优先被肿瘤血管捕获，在肿瘤中慢慢被肿瘤细胞中的溶酶体酶所代谢，释放出活性的化疗药物紫杉醇，起到靶向输送效果。Cell Therapeutics制药公司已经完成多个Xyotax的人体临床实验，并申报用于临床治疗卵巢癌和非小细胞肺癌。

富集于肿瘤组织的大分子—活性药物偶联物通常被肿瘤细胞中高度表达的特点酶降解，这些酶可裂解特定的化学键，也是靶向输送体系的主要靶点。目前已发现并用于抗癌药物靶向释放的酶有如下几种：① 组织蛋白酶B、D、H和L；② 纤维蛋白溶酶；③ 尿激素/组织型纤溶酶激活物；④ 前列腺特异性抗原；⑤ 基质金属蛋白酶（MMP-2和MM-9）；⑥ β-葡萄糖醛酸酶；⑦ γ-谷氨酰转肽酶；⑧ 羧酸酯酶；⑨ 酸性磷酸酶；⑩ 偶氮还原酶。

正如本卷29页载文所示，肿瘤细胞的任何特征都可以成为分子靶向或靶向药物输送的途径。肿瘤新生血管是肿瘤实体有别于其它组织的靶点，从而发现了VEGF或VEGFR的单克隆抗体或VEGFR酪氨酸激酶抑制剂类靶向抗癌药。而缺氧又是肿瘤新生血管信息传导通路的一个重要因子。作为恶性实体瘤的主要特征之一，缺氧改变了肿瘤细胞的生物学特征，也是传统放化疗失败的主要

continue on page 33 (后接第33页）

HANDE

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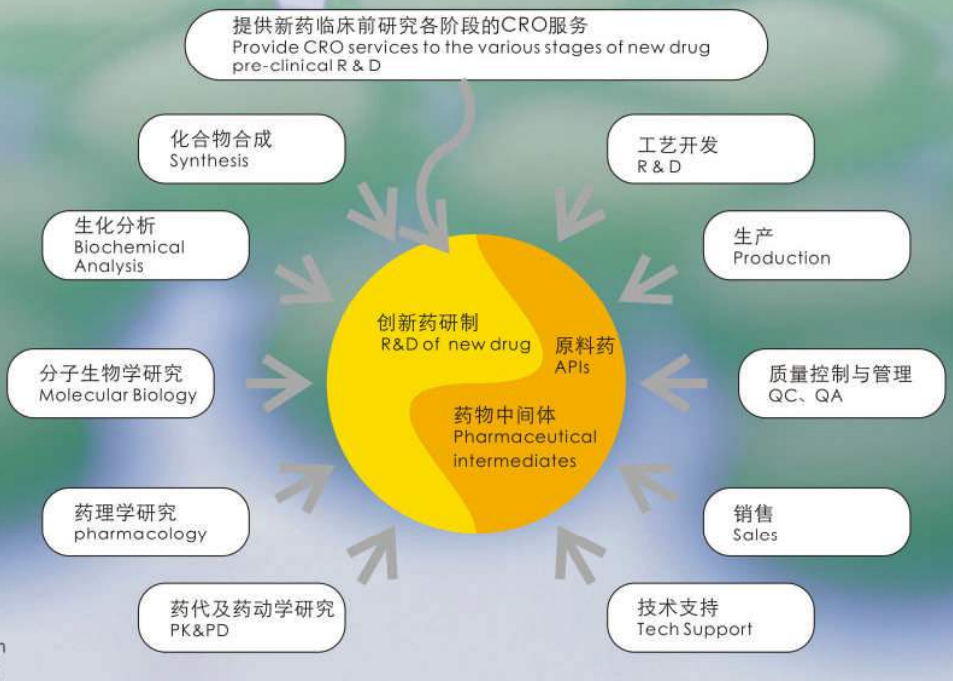
漢德森醫藥科技

汉德森医药科技是以研发抗肿瘤、心血管等创新药物为主体、致力于向社会提供高品质创新药物及其原料药和关键中间体、并持续探索崭新的新药设计理念为发展动力，以帮助无数患者为己任的国家级高新技术企业。

汉德森的研发团队由创新药研发和管理实战经验的优秀的化学合成、药物分析、药理药效等方面专家、以及新药报批、美国FDA注册等专业人才组成，还聘请国际级药物研发专家作为新药研发顾问，指导课题立项、新药筛选、临床前和临床期研究。目前，汉德森基于全新的设计理念、独创的输送途径，结合有效的成药方法和扎实的实验基础，形成了独特的高科技、高回报、低成本的药物研制的新型实体模型，已经研制出拥有自主知识产权的三个系列的高效低毒、具有广阔市场潜力的创新药物，分别处于临床前研究和即将进入临床研究阶段。2010年成为“苏州市分子靶向抗肿瘤药物制备工程技术研究中心”。

汉德森的原料药及中间体生产工艺技术也走在世界前沿，能做到工艺最合理、成本最低、纯度最高，在中试放大和工业化生产、商业化营销各阶段，历经十多年严格推进ISO9001质量体系，始终保证了高品质和高服务。汉德森的技术、产品和服务，不仅得到国内大药企的青睐，更收获了国际医药市场的美誉。

汉德森以“创新，带给您和家人的健康”为己任，持续加大研发投入力度，积极引进国内外有志之士，共同成长，做精做强，逐步形成新药研发、制剂和原料药生产销售为一体的新药研发集团，为中国医药创新发展作出贡献！



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浅谈小分子新药化合物专利申请

朱贵东
&
冯跃忠

YAOYUAN BIOTECH-PHARMA FORUM

Strategies in Patent Application for Small Molecule Biologically Active Compound

众所周知，新药研发是一项高投资、高回报的行业。一类新药从立项到批准投产通常需要长达十年的时间，是一项由分子生物学、药物化学、分析化学、药剂学、动物学、制药工艺学等多种学科相互渗透、相互合作的复杂系统工程。因为常常高达数亿美元的投资、以及极高的淘汰率，导致了新药研发的高风险。而研发集团投入回报的主要保障就是各国政府为鼓励企业研发创新而对知识产权的保护。因药物是一项民生工程，政府既要刺激企业的创新积极性，同时也要把药物价格控制在人民群众可以承受的范围。所以，企业在申请专利时如何利用现有专利法，在合法基础上最大限度的提高并延长知识产权保护范围，保护企业的利益显得尤为重要。

药物专利申请通常被认为可以分成六个方面：（一）覆盖一般通式结构的基本化合物专利，其中含有覆盖面相对较窄且结构相对具体的代表性化合物、常见前药及代谢物等；（二）包括可药用盐、多晶形及溶剂化物的衍生物专利；（三）化合物制备工艺专利；（四）药物组合物（配伍或联合用药）专利；（五）制剂专利；以及（六）适应症用途专利。药物专利有效期在大多数国家自申请日开始二十年（包括美国在1995年6月8号后申请的专利）。考虑到新药研发的长周期，药品批准上市以后对药品的真正有效保护期并不是很长—平均8年左右，要延长专利的有效期并增加知识产权的保护范围无外乎深度和广度两个方面，就是最大限度地利用现有专利法的保护期（专利有效期）和提高专利的保护范围。所以制药集团除了通过技术革新，最大限度地缩短研发周期以外，还经常申请基本化合物专利以外的专利来延长上市药品的保护时间。当然是否得到额外的专利完全取决于自身的创新性或申报主体的不可预见性。详细内容另文讨论，本文主要讨论申请各类专利的契机和覆盖范围。

所有专利申报的时间和专利权利要求的覆盖面都象一把双刃剑，比如提前申请、增加权利要求有益于前移优先权日期，抑制竞争企业的切入，但前者不利于产品上市的有效保护期，后者不利于专利的核准，即使得到国家知识产权局的权利授予，也不能完全避免竞争对手以后对授予权限的诉讼挑战。

当今制药界的竞争日趋激烈，可专利的小分子结构空间也越来越窄。一般来说基本化合物专利应尽早申报，除非专利权人自信该类化合物结构的发明极具偶然性，而这种偶然性短期内相关企业不会碰到。对有开发前景的候选药考虑申请一项或多项诸如可药用盐、晶形、工艺、组合、及适应症等专利，以便延长化合物专利的有效保护期。一般来说，非化合物专利权人也应该申请其它相关专利，不过需要考虑到作为非化合物专利权人即使能得到这类专利授权，具体的专利实施也可能侵犯化合物专利权人的知识产权。因此，二至六项专利的申报时间可以相应推迟。当然潜在的风险包括其它公司抢先申报和新药研发技术日新月异，越来越难以证明权利要求的不可预见性或创新性。

基本化合物专利的权利要求至少要考虑两方面的广度，一个是化合物结构覆盖范围，另一个关于是否包括，或包括多少可药用盐、晶形、工艺、组合、及用途等相关内容。通常认为提高结构的覆盖面有机会增加专利权人的保护范围，但需要相应的数据支持权利要求，否则并一定能提高知识产权局的授权范围，即使得到授权也很难避免将来竞争公司的诉讼挑战。对没有被授权的部分作为已有事实还会阻止将来的专利申请，之所谓损人害己。所以慎重、恰当的选择权利要求非常重要。化合物专利包含的内容或范畴也同等重要，专利覆盖范围越广固然预防其它公司切入的机会，同时也限制了自己将来延长化合物专利寿命的契机。所以在确定权限要求时需充分考虑将来申请比如可药用盐、晶形、工艺、组合、及用途专利的几率，留出将来申报的空间。当然，每个专利的申请都和指定用途紧密相连，在

申报用途权利要求的时候一定要有远见。

以最近联邦巡回上诉法院宣判的关于侵害礼来专利案（案卷号：2010-1105，http://caselaw.findlaw.com/us-federal-circuit/1534488.html）为例，礼来集团早在1983年申报了包括吉西他滨为实施例在内的专利申请，并于1989年被颁发美国专利证书（美国专利号4 808 614，简称614），有效期至2010年5月15日，主要用于抗病毒感染。该专利中第17栏陈述：“申报化合物除了抗病毒用途以外，专利申请书包含的一些化合物，尤其是实施例8（吉西他滨）在通常抗癌筛选中也表现出良好的抗肿瘤活性”，但在该专利的部分继续或继续申请的权利要求部分均没有包括抗肿瘤用途。随后礼来集团又申报了包括吉西他滨在内的同类化合物的新的专利申请，权利要求完全是抗肿瘤用途。该专利于1995年11月7日颁发（美国专利号5 464 826，简称826），有效期至2012年11月7日。在后来和仿制药公司Sun Pharmaceutical的专利诉讼中，密执安地方法院以及联邦巡回上诉法院一致认为礼来826专利属“重复专利”，被认为无效。所以Sun Pharmaceutical不构成对614专利侵权。由此可见，如果礼来最初有意重新申请以此类专利化合物用于抗癌用途的话，不应该在同一化合物专利申请中同时披露部分化合物的抗癌用途。当然，这也有可能提高在以后的时间里其它公司申请这类化合物抗癌用途的可能性。

我国现有约6000家制药公司，其中大部分为中小型企业，效益、结构、技术及管理水平也参差不齐，对知识产权的认识也有待提高。所以中国专利的申请也极具有地区特色。除了要在恰当时机申请恰当范围的专利以外，还要考虑专利法的实施情况。比如说个别企业为追求自己的经济利益，重复建设，恶性竞争，经常利用现有专利法的盲点或实施的难度，未经授权侵犯专利权人的合法权益。而专利诉讼又耗时长久，小公司时常被拖垮。所以，对于相对较难执行的专利项目，比如合成工艺专利等，按照中国专利法，专利权人有义务申报最佳工艺，而技术上又相对容易拷贝，所以很多公司选择不申请专利，而更强调公司内部的保密措施。

除此之外，还要估计到竞争公司也有可能利用现行《专利法》或SFDA的《药品管理办法》，有意识的延长竞争公司的新药研发进度来相对提高自己产品的竞争力。比如说，现行《药品管理办法》第十八条明确指出，“申请人应当对其申请的药物或者使用的处方、工艺、用途等，提供申请人或者他人在中国的专利及其权属状态的说明”，也就是说，竞争公司可以利用专利侵权诉讼要求国家食品药品管理局暂停其它公司相关临床实验或审批的程序。

必须说明，侵犯专利权的行为是指未经专利权人同意或行政许可，以生产经营为目的实施他人专利的行为。按照中国专利法这不包括为科学研究试验而使用有关专利，从技术角度判断专利技术是否可行，或探讨如何改进专利技术。虽然研究行为不构成侵权，但是最终技术成果的实施则可能侵权。专利由国家知识产权局授权，但并不代表被授权人最终的所有权。专利作为一种无形资产，其新颖性、创造性、是否公开充分性的评判常常会出现模糊地带，高级人民法院的最终判决才真正确认最终所有权的归属。

综上所述，新药知识产权的保护不仅重要，也很复杂，以上几点仅仅是笔者个人作为多年新药研发的一些肤浅见解，希望和读者共同探讨，起到抛砖引玉的作用。但无论如何，知识产权的充分保护是一个制药企业生存与发展的命脉，需要企业决策者的充分重视。

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