一、前言

2006年是我国“十一五”规划的启动之年，也是中科院知识创新工程三期的开局之年，在这重要的战略机遇期，生物大分子国家重点实验室紧紧抓住这个的时机，面向国家战略需求和瞄准世界科技前沿，抒己所长力争在国家的基础科研中发挥骨干和引领作用。在上级领导的大力关怀和扶持下，在生物物理研究所领导的大力支持及全体同仁的共同努力下，生物大分子国家重点实验室取得了斐然的成绩。

2006年，科技部对生命领域的国家重点实验室进行评估，生物大分子国家重点实验室是唯一免评而直接获得优秀国家重点实验室称号，这主要得益于实验室十几年来连续3次被评为优秀国家重点实验室的业绩。在此，我们要由衷地感谢邹承鲁院士、梁栋材院士、杨福愉院士等老一辈科学家为生物大分子国家重点实验室所作出的杰出贡献。

2006年，生物大分子国家重点实验室新增主持省部级以上科研课题共计55项，其中国家重大科学研究计划课题：8项；国家“973”计划课题：7项；国家“863”计划重大、重点、专题课题：9项。 国家自然基金委重点项目：4项（包括优秀重点实验室项目1项）；国家自然基金委海外青年学者合作研究项目：1项，国家自然基金委面上项目：18项；国家自然基金委国际合作项目：2项。中国科学院知识创新方向性项目：6项。2006年在研项目经费到位共计：2800万元左右。

2006年，生物大分子国家重点实验室发表在国外著名学术期刊上的学术论文共计：73篇，其中IF影响因子大于4.0的有：36篇；IF影响因子大于10.0的有：3篇。饶子和课题组连续在《Journal of Virology》上发表了SARS冠状病毒nsp10和nsp15(MHV)的晶体结构及其功能的研究成果。Nsp10的晶体结构解析，为蛋白质结构家族增添了一个新的折叠类型，展现了每个单体含有两个锌指结构的球形十二聚体的晶体结构；而MHV的nsp15为具有活性的六聚体结构，是第一个尿嘧啶特异性的内切核酸酶的三维结构，揭示出蛋白质结构家族的一个崭新的折叠类型，为抗冠状病毒感染提供了新的结构信息；徐涛课题组在《Cell》子刊—《Cell Metabolism》发表了Munc13-1蛋白对胰岛素储存囊泡成熟的调控机制研究成果。关于胰岛素的两相分泌产生的机制一直是人们关注的焦点，该工作以Munc13-1基因敲除小鼠和二酰基甘油（DAG）结合位点突变小鼠为模型，在细胞和器官水平证明了Munc13-1为慢相胰岛素分泌所必需，同时发现慢相的产生涉及细胞第二信使DAG的激活；陈润生课题组在《Genome Research 》杂志上发表了线虫新的小非编码RNA的发现和其转录组的组织研究成果。非编码RNA及其基因的研究是当前的国际热点领域，但对完整非编码转录组的研究迄今还没有。陈润生研究组以线虫为对象在发现了100个全新的非编码基因的基础上又确定了两个非编码基因家族、三个归属于非编码基因的启动子序列，研究结果显示非编码基因与编码基因一样各自有一套独立的转录调控系统；范祖森课题组发现LIGHT活化的NK细胞激发肿瘤特异性CD8+T细胞来清除已建立的肿瘤，该研究成果发表在《Blood》杂志上了。

NK 细胞能够识别肿瘤细胞和分泌细胞因子参与抗肿瘤作用，但NK细胞如何被活化和激发适应性免疫反应尚不清楚。范祖森课题组与傅阳心课题组进行了合作研究，首次发现TNF超家族成员LIGHT是NK细胞活化的重要配体。NK细胞表面表达HVEM受体并与其配体LIGHT结合介导NK细胞活化，体外及动物实验研究表明激活的NK细胞可以通过分泌IFN-γ 直接活化肿瘤特异性CTL细胞介导有效的肿瘤排斥，表明LIGHT是介导肿瘤免疫治疗的有效效应分子，IFN-γ是沟通先天免疫与适应性免疫的桥梁。从而证明固有免疫在肿瘤发生早期能激发肿瘤特应性免疫应答来清除已建立的肿瘤，上述研究将为肿瘤的免疫治疗提供新策略。

2006年，生物大分子国家重点实验室在注重基础科研工作的同时，也注重面向国家需求为生命科学相关行业的发展提供科学支撑。我室有2项专利获得国家知识产权局的授权，其中阎锡蕴课题组发明专利《高效广谱抑制肿瘤生长和转移的新型抗体》在《全国杰出专利预展项目》展览上展出，相关发明专利被评为“全国杰出专利工程技术评审预展项目”。两项发明专利技术转让。

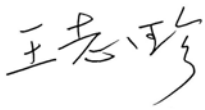
2006年，生物大分子国家重点实验室成功地主办了北京国际纳米生物技术和结构生物学研讨会。大会邀请到Prof. Alexander Rich、Prof. Alexander Varshavsky、Prof. Alan Fersht、Prof. Wolfram Saenger、Prof. Alexander Spirin、Prof. Joel Janin并作了本领域发展前沿的学术报告使我们受益匪浅，参会人数达230多人。另外在“2006诺贝尔奖获得者北京论坛”期间，通过“与青年学生面对面”、“生命科学圆桌会议”等活动，诺贝尔奖获得者与我们的年轻学者进行了面对面的交流与沟通，这种方式同样促进了我们科技能力和科研水平的提高。由国际结构基因组学联合会主办，我室和中国科学院生物物理研究所、清华大学、中国生物物理学会和中国晶体学会联合承办的第四届国际结构基因组学大会于2006年10月22-26日在北京友谊宾馆隆重召开，大会由生物大分子国家重点实验室主任饶子和院士担任大会主席，本次大会吸引了来自中国、法国、美国、日本、德国、意大利、韩国、新西兰、澳大利亚、新加坡、以色列和中国台北等21个国家和地区的520多名专家、学者，其中与会外国专家、学者近300名。大会的成功召开，进一步促进了结构基因组学的国际交流与沟通，为我国结构基因组学的研究与发展起来积极推动作用，同时体现了我国结构生物学对国际结构基因组学的贡献。

人才建设始终是生物大分子国家重点实验室发展的根本，2006年我们引进“百人计划”人才2名，引进研究员2名。目前实验室现由36名研究员组成（其中院士7名；中国科学院“百人计划”入选者19名；国家杰出青年基金获得者6名；“长江学者奖励计划”特聘教授2名），已经发展成为在国内、外具有重要学术影响的高水平的研究群体。研究生历来是我们的后备生力军，也是流动队伍中不可或缺的重要部分，实验室目前在读研究生290名，其中121名博士生，169名研究生。获得博士学位23名,14名博士后。博士毕业生柳振峰的学位论文获得2006年全国优秀博士学位论文；博士生朱永群等4人分别获得中国科学院院长优秀奖、刘永龄优秀奖、地奥奖学金。

2006年，是令我们振奋的一年，我们实现了晋升国家实验室的发展目标－“蛋白质科学国家实验室”。在科技部启动国家实验室建设工作通气会上，由中国科学院牵头、以生物物理研究所为依托单位的蛋白质科学国家实验室成为批准建设的十个国家实验室之一，这无疑是对我们辛勤工作的肯定。我们有决心在依托单位生物物理所的领导下，进一步凝练科学目标，面向国家重大战略需求和科学前沿，发挥优势和特色，开展一系列战略性基础研究、重大竞争前高技术研究和重要社会公益性研究，为国家经济建设、社会发展和国家安全做出重要贡献，为推动企业技术创新和行业技术进步发挥重要支撑和引领作用。

2006年，生物大分子国家重点实验室第一届室主任，中国生物化学的奠基人邹承鲁院士永远的离开了我们。邹承鲁先生为我国率先实现胰岛素的人工合成做出了重要贡献，创立了“邹氏公式”和“邹氏作图法”，建立了酶活性不可逆抑制动力学的理论体系，提出了酶活性部位柔性的学说。先生一生治学严谨，正直敢言，对工作兢兢业业，他的离去无疑是给我们带来了巨大的损失，而他勤奋工作，永不自满的精神也是留给我们后人宝贵的财富。他将激励我们不懈努力而取得更大的成绩。

生物大分子国家重点实验室主任： 

生物大分子国家重点实验室学术委员会主任： 

I. Introduction

2006 was the first year of China's 11th 'five-year plan', and also marked the beginning of the third stage of the Chinese Academy of Sciences (CAS) "Knowledge Innovation Project". The National Laboratory of Biomacromolecules (NLB) aims to play a crucial and leading national role in fundamental research during this strategic period, guided by national priorities and working at the frontiers of international science and technology. Under strong and supportive leadership of the Directors of the CAS Institute of Biophysics, and through the strenuous efforts of all the staff, the NLB has produced significant achievements.

In 2006, the Chinese Ministry of Science and Technology evaluated all the State Key Laboratories in the life science field. The NLB was the only such laboratory to be classed as excellent with exemption from evaluation. This was on the basis that the Laboratory had been classed consistently as excellent in each of the previous evaluations over the past decade or more. In regard to this, we wish to gratefully acknowledge senior scientists such as the CAS Members Chen-lu Tsou, Dongcai Liang and Fuyu Yang, whose contributions have made the NLB what it is today.

In 2006, the NLB obtained a total of 55 new research grants, including 24 funded by the Chinese Ministry of Science and Technology (MOST) and 31 funded by the National Natural Science Foundation of China (NSFC). The total value of research grant income received during 2006 was equivalent to 3.6 million US dollars.

During 2006, members of NLB published a total of 70 papers in international journals, of which 35 papers had an SCI impact factor (IF) greater than 4.0; and 3 papers had an IF greater than 10.0. Prof. Zihe Rao's research group solved the crystal structures of two coronavirus nonstructural proteins, SARS-CoV nsp10 and MHV-CoV nsp15, which were published back-to-back in the *Journal of Virology*. The crystal structure of SARS-CoV nsp10 shows a novel protein structural fold with two novel zinc finger motifs and twelve nsp10 monomers, which form a unique dodecamer with proposed biological function. MHV nsp15 was found to form an active hexamer and it is the first crystal structure of a uracil-specific endonuclease at atomic resolution, indicating a new member of a protein structural fold family, which provides a new target for anti-coronavirus drug design. The group of Tao Xu revealed the regulating mechanism of Munc13-1 on the insulin granule priming process, which was published in *Cell Metabolism*. A key question in this field concerns how and why glucose stimulates pancreatic beta cells to secrete insulin in fast and slow phases. Based on the data obtained from the Munc13-1 knockout and DAG binding site mutant knockin mice, Tao et al proved that Munc13-1 is necessary for the slow secretion phase, and signaling of DAG second messenger is also associated with the slow phase. The group of Prof. Runsheng Chen published a study on new ncRNA genes and their transcriptomic characteristics in the nematode *C. elegans* (*Genome Research* 16: 20-29, 2006). Although studies on non-coding RNA have been topical for years, research on their transcriptome has never been reported. In this work, Chen's group characterized 100 new ncRNA genes, including two novel classes, and discovered three promoters specific to ncRNA genes. The research results also show that ncRNA genes

are transcribed by a transcriptional system different to that of protein genes. Zusen Fan's Lab published a recent study in *Blood*. NK cells play an important role in antitumors by recognizing tumor cells and secreting cytokines. It is unclear how NK cells evoke adaptive immunity to eradicate tumors. TNF superfamily member LIGHT is a critical ligand for the activation of NK cells. HVEM is expressed on NK cells and its engagement with LIGHT mediates NK cell activation. The expression of LIGHT inside tumors leads to rapid rejection in a NK-dependent manner. IFN-γ-deficient NK cells fail to effectively activate CD8+ T cells, demonstrating that IFN-γ plays an important role in NK-mediated activation of CTLs. Fan et al.'s findings establish a direct role for LIGHT in NK activation/expansion and a critical helper role of activated NK cells in priming CD8+ T cells and breaking T cell tolerance at the tumor site.

In addition to emphasis on fundamental research, the NLB also supports the development and application of research results in the life science industries, according to national demand. In 2006, two patents were authorized by the State Intellectual Property Office. One, entitled "Novel antibodies targeting neovasculature and inhibiting angiogenesis", is the work of Xiyun Yan's group. It was included in the Exhibition of Outstanding National Patents, and passed the final selection as an "Outstanding National Patent in Engineering and Technology".

In 2006, the NLB successfully hosted the "China International Nanotechnology Conference", at which Profs. Alexander Rich, Alexander Varshavsky, Alan Fersht, Wolfram Saenger, Alexander Spirin and Joel Janin gave presentations representing the cutting-edge of their respective fields. Over 230 people attended the conference. In addition, during the "Nobel Laureates Beijing Forum 2006", a number of activities were held such as 'Meeting with students of CAS' and 'Panel Discussion on Life Sciences', giving our young researchers an inspirational opportunity to communicate with Nobel laureates face-to-face. "The 4th International Conference on Structural Genomics" of the International Structural Genomic Organization (ISGO) was held from 22-26 October 2006 in the Beijing Friendship Hotel, organised by this Laboratory, the Institute of Biophysics CAS, Tsinghua University, the Biophysical Society of China and the Chinese Crystallography Society. The chairman of the conference was CAS Member Zihe Rao, Director of NLB. Almost 520 experts and researchers attended the conference, from 21 countries and regions, including France, America, Japan, Germany, Italy, Korea, New Zealand, Australia, Singapore, Israel, Taiwan and Hong Kong, as well as mainland China. About 300 of the experts came from overseas. The success of the conference contributed to international communication, and established a basis on which to further develop structural genomics research in China and to promote the actualization of China's research program into liver proteins.

Development of a talented research team is always a major priority at the NLB. This year we recruited 4 new researchers, 2 of whom are funded under the "hundred talents" program of CAS. NLB currently has 35 principal investigators, including 7 Members of CAS, 19 scientists funded by the CAS "hundreds talents" program, 6 NSFC "Outstanding Young Investigator" awardees, and 2 holders of Professorial Chairs under the "Yangtze River Scholar Award Program". Thus, NLB possesses a research team with significant academic influence both nationally and abroad. Graduate students are an important resource and contribute significantly

to the research output of the Laboratory. There are currently 290 graduate students, including 121 PhD students. Twenty-three students were awarded PhD degrees in 2006, and there are currently 14 researchers undergoing post-doctoral training. The PhD thesis of Zhenfeng Liu was selected as a "2006 National Outstanding Doctoral Thesis". Four current PhD students were awarded national prizes.

2006 was an exciting year in that we achieved formal recognition as a 'National Laboratory', having previously had the status of 'State Key Laboratory'. We have been designated as "The National Laboratory of Protein Science", remaining under the auspices of the CAS Institute of Biophysics. We are one of 10 National Laboratories established by MOST. This is affirmation of our hard work to date, and sets a challenge for the future, to advance the frontiers of science and to contribute to the health, security and economic standing of the nation.

In 2006 we completed the re-appointment process of our Laboratory Director and Academic Committee Chair. Prof. Tao Xu was selected as the new Director and CAS Member Prof. Chih-chen Wang was selected as the Chair of the Academic Committee.

The CAS Member Prof. Chen-lu Tsou was the first Director of the NLB and one of the founders of biochemistry research in China. Sadly, Prof. Tsou passed away in November 2006. Prof. Tsou played an important role in the chemical synthesis of insulin, established 'Tsou's equation' and 'Tsou's plot', derived a theoretical system for 'enzyme activity irreversible inhibition kinetics', and was first to put forward the 'flexible active site of enzyme hypothesis'. Throughout his life, his rigorous scholarship, outspoken integrity and conscientious attitude were an example to us all. His absence is a great loss. However, his spirit of diligence and lack of self-complacency is a lasting legacy to us, which will encourage us to work untiringly and will spur us on to greater achievements.

National Laboratory of Biomacromelecules Director: 

Academic Council Chairman: 

二、组织机构

（一）名誉主任

邹承鲁院士

梁栋材院士

杨福愉院士

（二） 主任、副主任

主任 饶子和院士

副主任 徐　涛研究员

龚为民研究员

（三） 学术委员会

主 任 王志珍院士

委 员 **(以字母拼音为序)**

常文瑞院士	中国科学院生物物理研究所
高光侠研究员	中国科学院生物物理研究所
郭爱克院士	中国科学院生物物理研究所
贺福初院士	军事医学科学院
李伯良研究员	上海生命科学研究院
李家洋院士	中国科学院遗传与发育研究所
林其谁院士	上海生命科学研究院
强伯勤院士	中国医学科学院基础研究所
饶子和院士	中国科学院生物物理研究所
施蕴渝院士	中国科技大学生命科学院
王志新院士	清华大学
徐　涛研究员	中国科学院生物物理研究所
阎锡蕴研究员	中国科学院生物物理研究所
叶朝辉院士	中国科学院武汉物理与数学研究所
于　军研究员	中国科学院北京基因组研究所
张先恩研究员	科技部基础司

学术秘书

阎锡蕴研究员	中国科学院生物物理研究所

II. Organization

1. Honorary Directors **Chen-lu Tsou, Member of CAS (deceased)**

Dongcai Liang, Member of CAS

Fuyu Yang, Member of CAS

2. Director and Vice Directors

Director **Zihe Rao, Member of CAS**

Vice Directors **Tao Xu, Professor**

Weimin Gong, Professor

3. Academic Council

Chairman **Chih-chen Wang, Member of CAS**

Members:

Wenrui Chang	Member of CAS	Institute of Biophysics CAS
Guangxia Gao	Professor	Institute of Microbiology CAS
Aike Guo	Member of CAS	Institute of Biophysics CAS
Fuchu He	Member of CAS	Academy of Military Medical Science
Boliang Li	Professor	Shanghai Institute for Biological Sciences CAS
Jiayang Li	Member of CAS	Institute of Genetics and Developmental Biology CAS
Qishui Lin	Member of CAS	Shanghai Institutes for Biological Sciences CAS
Boqin Qiang	Member of CAS	Institute of Basic Medical Research CAMS
Zihe Rao	Member of CAS	Institute of Biophysics CAS
Yunyu Shi	Member of CAS	University of Science and Technology of China
Zhixin Wang	Member of CAS	Tsinghua University
Tao Xu	Professor	Institute of Biophysics CAS
Xiyun Yan	Professor	Institute of Biophysics CAS
Zhaohui Ye	Member of CAS	Wuhan Institute of Physics and Mathematics CAS
Jun Yu	Professor	Institute of Genomics CAS
Xianen Zhang	Professor	Ministry of Science and Technology

Academic Secretary:

Xiyun Yan	Professor	Institute of Biophysics CAS

（四） 国际科学委员会

1．主席

Robert Huber (诺贝尔奖获得者) Max Plank Institute for Biochemistry (Germany)

2．副主席

Erwin Neher (诺贝尔奖获得者) Max Plank Institute for Biophysical Chemistry (Germany)

3．委员会成员

Giuseppina Barsacchi	Laboratori di Biologia Celluare e dello Sviluppo	(Italy)
Guy Dodson	University of York	(UK)
Khalid Iqbal	NYS Institute for Basic Research	(USA)
Neil Isaacs	University of Glasgow	(UK)
Jack Johnson	The Scripps Research Institute	(USA)
David Stuart	University of Oxford	(UK)
Joel Sussman	The Weizmann Institute of Science	(Israel)
Michael G. Rossmann	Purdue University	(USA)
Bi-Cheng Wang	University of Georgia	(USA)
Brian Matthews	University of Oregon	(USA)
Louise N. Johnson	University of Oxford	(UK)
Johannes Frederik Gerardus Vliegenthart	Bijvoet Center for Biomolecular Research	(Netherlands)

（五）实验室固定成员：(以字母拼音为序)

毕利军	常文瑞	陈　畅	陈润生	邓红雨
范祖森	高光侠	龚为民	杭海英	姬广聚
蒋太交	江　涛	焦仁杰	靳　刚	柯　莎
梁栋材	梁　伟	刘志杰	刘迎芳	马　跃
秦志海	饶子和	孙　飞	唐　宏	唐　捷
王大成	王金凤	王盛典	王志新	王志珍
徐　涛	阎锡蕴	杨福愉	杨福全	殷勤伟
张旭家	邹承鲁			

4. International Scientific Committee

（1）Chairman:

Robert Huber (Nobel Prize Laureate)	Max Plank Institute for Biochemistry	(Germany)

（2）Vice Chairman:

Erwin Neher (Nobel Prize Laureate)	Max Plank Institute for Biophysical Chemistry	(Germany)

（3）Members:

Giuseppina Barsacchi	Laboratori di Biologia Celluare e dello Sviluppo	(Italy)
Guy Dodson	University of York	(UK)
Khalid Iqbal	NYS Institute for Basic Research	(USA)
Neil Isaacs	University of Glasgow	(UK)
Jack Johnson	The Scripps Research Institute	(USA)
David Stuart	University of Oxford	(UK)
Joel Sussman	The Weizmann Institute of Science	(Israel)
Michael G. Rossmann	Purdue University	(USA)
Bi-Cheng Wang	University of Georgia	(USA)
Brian Matthews	University of Oregon	(USA)
Louise N. Johnson	University of Oxford	(UK)
Johannes Frederik Gerardus Vliegenthart	Bijvoet Center for Biomolecular Research	(Netherlands)

5. Research Faculty

Lijun Bi	Wenrui Chang	Chang Chen	Runsheng Chen	Hongyu Deng
Zusen Fan	GuangxiaGao	Weimin Gong	Haiying Hang	Guangju Ji
Taijiao Jiang	Tao Jiang	Renjie Jiao	Gang Jin	Sarah Perrett
Dongcai Liang	Wei Liang	Yingfang Liu	Zhijie Liu	Yue Ma
Zhihai Qin	Zihe Rao	Fei Sun	Hong Tang	Jie Tang
Dacheng Wang	Jinfeng Wang	Shengdian Wang	Zhixin Wang	Chih-chen Wang
Tao Xu	Xiyun Yan	Fuyu Yang	Fuquan Yang	Qinwei Yin
Xujia Zhang	Chen-lu Tsou (deceased)			

三、管理

（一）实验室管理

实验室依据“国家重点实验室建设与管理暂行办法”对实验室进行全面管理。本室实行实验室主任负责制、学术委员会评审制；实验室采用以研究方向为导向，以研究组为基本科研单元的运行模式，每年 2-3 月间召开上年度学术年会。

实验室主任就年度运行管理、经费使用提出可行方案，并向学术委员会汇报上年度的实验室工作总结。

（二）学术委员会

学术委员会结合本室学术年会每年召开全体会议一次，评议实验室的工作，内容包括确定实验室研究方向、制定及修改课题指南、审批课题申请、检查课题进展情况、监督经费使用、评审科研成果及审议学术活动计划等。

（三）研究方向

1. 蛋白质三维结构与功能研究
2. 蛋白质功能与折叠原理研究
3. 生物膜和膜蛋白功能结构研究
4. 计算与系统生物学
5. 感染与免疫的分子基础
6. 蛋白质药物与多肽药物

（四） 课题管理

实验室成员每年应按时向实验室秘书提交以下材料:

1) 当年发表的具有“生物大分子国家重点实验室”署名的全部著作目录（包括专著、论文，国际及全国性学术会议论文等），并提交版面清楚平整的论文单印本一式一份及论文电子版;
2) 当年获得国际、国家或省部级科技奖励的证书复印件一份;
3) 年度工作报告（中、英文各一份）的电子文档。报告格式按实验室秘书提供的文档模版填写。

III. Management

1. Management of the NLB

The NLB is managed strictly according to the "Temporary Regulations of Establishment and Management of National Key Laboratories". The Director is responsible for running the NLB, and the Academic Committee is responsible for evaluation. The NLB is organized according to research areas, with research groups as the basic unit. An academic conference is organized every year in February or March. The director of the NLB presents a summary of the previous year and a proposal for running and expenditure for the current year.

2. Academic Committee

The Annual Meeting convened by the Academic Council provides a forum to discuss and appraise the research of the Laboratory. At this meeting, ongoing research projects are assessed, new research proposals are considered for approval, the accounts are inspected, the research achievements of the Laboratory are examined and the priorities and direction for future research are set.

3. Research Areas

1. Three-dimensional Structure and Function of Biomacromolecules
2. Protein Function and Folding
3. Membrane Biology and Membrane Protein Function and Structure
4. Computational and Systems Biology
5. Molecular Mechanisms of Infection and Imunity
6. Protein & Peptide Drugs

4. Management of Projects

Members of the NLB submit the following materials to the secretary of the NLB:

1) All publications (a reprint and an electronic version) that have the NLB as the corresponding address, including papers, book chapters, and presentations at national and international conferences

2) Photocopy of national and international awards received in the past 12 months

3) Progress report (Chinese and English versions)

四、工作进展

（一）蛋白质三维结构与功能研究

1. 嗜热菌和人源结构基因组的结构分析

梁栋材组

（1）利用单波长反常散射方法解析了人源 Dnlc2a 的 1.9 Å 的三维结构

Dnlc2a 是 RLC7 家族的一个成员。它作为动力蛋白的轻链，通过与中轻链 IC74 的 C 末端相互作用，参与了动力蛋白的组装。此外，Dnlc2a 作为 TGF 信号系统中受体 II 的结合蛋白，在参与动力蛋白调节以及癌症发展方面有重要作用。根据晶体结构分析了其可能的蛋白质结合位点，发现 Dnlc2a 是以二聚体形式存在，二体之间通过 20 个氢键及疏水相互作用紧密连接在一起。与其它蛋白质结合的可能位点主要存在于二体的一面，包括 α 螺旋 α1/α1 及它们之间两个单体的由 10 个 β 折叠片拼接而成的 β 折叠片层。这一表面形成一个弯曲的正电通道，可以通过盐桥与其它蛋白质相互作用。其中，由残基 79－82，88，90 等围成一个带正电性空洞，可能是参与于其它蛋白质尤其是 IC74 相互作用的关键位点。文章已发表（Biochemical and Biophysical Research Communications）。

（2）完成了来自嗜热菌 T.tengcongensis 中二种重要功能酶的三维结构研究

①利用单波长反常散射(SAD)方法解析了 T4 蛋白的 2.15 Å 的三维结构。T4 属于具有类 β-内酰氨酶结构域的金属水解酶家族，该蛋白折叠形式为 α β/β α 形式， β-内酰氨酶折叠结构域的金属结合位点在水解共价键的过程中起作用。文章正在整理中;

②同时完成甘油磷酸二脂酶 GDPD 的 2.0 Å 的三维结构。结构分析表明：其结构核心是由 α8/β8 的桶状折叠构成，Glu 44, Asp 46 和 Glu 119 组成了一个金属结合位点。结构与功能分析工作正在进行中。文章正在整理中。

IV. Research Progress Report

1. Three-dimensional Structure and Function of Biomacromolecules

(1) Crystal structural analysis of the structural genomes of thermophilic eubacteria and humans

Dongcai Liang Group

1) We have solved the 1.9 Å crystal structure of Dnlc2A using single anomalous diffraction (SAD) method. Dnlc2A is not only the human light chain of the motor protein dynein, but also a novel TGF-β-signaling component, which is altered at high frequency in epithelial ovarian cancer. Therefore it has important roles as a mediator of dynein and in the development of cancer, due to its ability to bind to the DIC, and regulate TGF-β-dependent transcriptional events. The proteins form a homodimer in solution and interact mainly through the helix α_2, strand β_3, and the loop following this strand in each protein to generate a 10-stranded β-sheet core. The surface of the β-sheet core is mainly positively charged and is predicted, using the software PPI-Pred, to be the site that interacts with other partners. At the same time two holes in the core are formed by the residues 79-82, 88 and 90 of each molecule. The residue 89 of each molecule, which is crucial for the DIC binding function of Dnlc2A, is located in the holes. Based on these observations, we propose that the homodimer is the structural and functional unit maintained by hydrogen bonding interactions and hydrophobic packing, and the patch of the surface of β-sheet core should be the main interaction area with other partners by salt bridge. The two holes should be the key sites to interact with IC74. This work has been published in *Biochemical and Biophysical Research Communications*.

2) Solution of the crystal structures of two enzymes of important function from *T. tengcongensis*

(i) We have solved the 2.15 Å crystal structure of T4 using single anomalous diffraction (SAD) method. T4 belongs to a metal hydrolase family, which posses a β-inneracylammoniase domain. The T4 molecule exhibits a αβ/βα fold. Its metal binding site plays an important role in the process of covalent bond hydrolysis. The manuscript is in preparation.

(ii) We have solved the 2.0 Å crystal structure of GDPD using the MR method. Results show: the GDPD molecule exhibits a TIM-barrel fold and displays a central eight-stranded parallel β-sheet barrel, which is surrounded by eight α-helices (α8/β8). Glu 44, Asp 46 and Glu 119 compose a metal binding site. Analysis of structure and function is in progress.

2. 重要病毒蛋白质三维结构研究

饶子和组

（1）SARS 病毒蛋白质及相关蛋白的结构和功能研究

我研究组对 BJ01 毒株中 SARS 基因组的全部结构蛋白和非结构蛋白进行了克隆表达，展开了对 SARS 冠状病毒蛋白质组学的研究。在之前工作的基础上又解析了 SARS 冠状病毒 NSP10 和 NSP15(MHV)以及 SARS 病毒和 MHV 的 S 蛋白融合核心蛋白及其复合物的晶体结构。利用 SARS 冠状病毒主要蛋白酶（3CLpro）及其复合物的三维结构设计了一系列针对四种冠状病毒都有效的抑制剂。

（2）禽流感病毒重要功能蛋白的结构研究

禽流感病毒重要蛋白质的结构生物学研究及药物设计工作。分别在原核、昆虫杆状病毒以及酵母等表达系统构建了十个禽流感重要蛋白质的表达载体。对可溶性表达的 NP、NS1、NS2 和 M1、M2 结构域进行晶体生长条件摸索和优化。目前我们正在进行基于 NA 抗原的 NA 单克隆抗体制备鉴定工作；同时也进行了针对 NA 和 HA 相关结构模拟和药物设计方面的工作。

（3）乙型肝炎结构蛋白及其相关蛋白的结构和功能研究

通过解析乙型肝炎病毒（hepatitis B virus, HBV）主要结构蛋白 S 蛋白、P 蛋白和 X 蛋白的三维结构，研究各蛋白分子和相关复合物的功能，为针对乙型肝炎的药物设计和治疗方法提供结构生物学基础。目前已经完成了 HBV 聚合酶和 X 蛋白（含 domain）的表达，正在进行共表达和蛋白质的纯化工作；得到了酵母系统和哺乳动物细胞表达的 HBV S 蛋白质，目前已获得微晶，进一步优化中；此外目前已有多个与 HBV 相互作用的蛋白质获得表达。

（4）诺罗病毒结构和功能研究

诺罗病毒是引起人类传染性胃肠炎的主要的非细菌病原体。病毒衣壳蛋白中的 P 结构域直接参与这个过程。我们得到了 2.0 Å 的重组 P 蛋白与 A 型和 B 型合成三糖复合物的晶体，并进行了结构解析，从而准确定位了 HBGA 末端糖抗原与病毒衣壳的识别位点，并且阐明其识别机理。

(2) Study of three-dimensional structures of important virus proteins

Zihe Rao Group

1) Structural and functional studies of SARS virus proteins and other related proteins

We have cloned all the structural and non-structural proteins of the SARS genome in BJ01 strain and have been studying on SARS coronavirus proteomics. Based on former work we resolved NSP10, NSP15 (MHV) and analyzed the crystal structure of SARS and mouse hepatitis virus (MHV) spike (S) protein fusion core. Moreover, we designed a series of inhibitors that are effective against four kinds of coronavirus based on the SARS Mpro structure we determined previously.

2) Study on structures of primary Avian flu virus proteins

Our research group has been studying on the structural biology and drug design of primary proteins of the Avian flu virus. We have constructed cloning vectors for bird flu virus proteins within prokaryotic, baculovirus and yeast systems. So far NP, NS1 and M2 full-length proteins or domains were obtained as soluble proteins and we are trying to purify the rest of them. The preparation and identification work for NA monoclonal antibody by NA antigen we obtained before is in progress. At the same time we have focused on drug design and structural simulation related to NA and HA.

3) Structural and functional studies on structural proteins of HBV and related proteins

Our aim in this project is to determine the three-dimensional structures of structural proteins, S protein, P protein and X protein, of hepatitis B virus (HBV) and to study the functions of proteins and their related complexes. Based on these we are trying to clarify the mechanism of the behavior of HBV on host cells, and to provide a biological basis for drug design and clinical treatment. The expression of HBV polymerase and X protein (containing domain) has been completed, and their co-expression and purification is underway. We successfully expressed the HBV S protein in yeast and mammalian cell systems. Micro-crystals have been obtained for the purified HBV S protein. In addition, we studied on the proteins which interact with HBV and many of them were properly expressed.

4) Study on structure and function of Noroviruses

Noroviruses are one of the major causes of nonbacterial gastroenteritis epidemics in humans. The P domain of the norovirus capsids is directly involved in this recognition. A recombinant P protein of norovirus VA387, a GII-4 strain, was co-crystallized with synthetic types A- or B-trisaccharides. Based on complex crystal structures at 2.0 Å resolution, we determined the precise location and receptor binding mode of HBGA carbohydrates on the viral capsids and demonstrated the recognition mechanism.

3、光合膜蛋白的结构与功能

常文瑞组

以高等植物光合作用系统中的 PS-II 为研究对象,使用蛋白质晶体学,生物化学和分子生物学的研究方法和手段,对组或 PS-II 的不同层次的蛋白色素复合体开展结构与功能研究,旨在从原子水平的三维结构的基础上,探讨光能吸收、传递及能量转换的机制。

高等植物的 PS-II 由二十多种蛋白色素复合物组成,可分为捕光色素复合物、反应中心复合物和放氧复合物等不同层次,不同功能的复合体。本课题在已首先突破菠菜主要捕光复合物 LHC-II 的晶体结构的基础上,又已完成黄瓜主要捕光复合物的晶体结构分折, 2.66A 分辩率的电子密度图清晰表明 LHC-II 中两个 Lutein 分子具有不同的构象, 分析结果认为由 Lut620 与 Chla611/612 叶绿素对组成的有利于能量传递的特征结构是 LHC-II 分子可能的激发能淬灭位点,并认为结晶过程中分子间作用力引起的构象变化是形成这一淬灭位点的主要原因.研究结果已总结成论文(待发表)。PS-II 中其它组分,包括次要捕光复合物、PS 核心复合物等的样品制备纯化和结晶的探索工作已启动,进展正常。

4、一些重要蛋白质及其复合物的三维结构与功能研究

王大成组

主要进展情况如下:（一）完成 4 个新蛋白质的结构解析：(1) 甜味蛋白 Mab II，是一种甜味蛋白的全新结构类型，通过实验确定了其主要活性位置和与甜味受体相互作用的特征。(2) 氨基酸结合蛋白（复合物）Glu/Asp BP，是细胞中氨基酸传输系统的重要组成部分，结构在原子分辨率（1.15Å）解析。(3) 肉碱代谢重要酶 CaiE，结果显示该分子具有十分少见的左手　螺旋结构，并给以确切的功能指认。(4) 人氯离子通道 CLIC4 结构，首次观察到三聚结构。另有 3 种蛋白质的结构解析正在进行中。（二）启动 Cul3 介导的泛素连接酶复合物的结构与功能研究：已建立 Cul3 和 BTB 蛋白 SPOP 重组可溶表达体系，开始构建 Cul3-SPOP 稳定复合物。（三）抗肿瘤蛋白 AAL 的作用通路及其靶蛋白研究：AAL 为从我国药用植物中发现的一种抗肿瘤蛋白。已完成 AAL 的高分辨率晶体结构解析，同时构建了 10 个功能相关突变体，深入研究了结构-功能关系；建立了进行作用通路研究的基本条件。（四）蛋白质 NCg1110 与 DNA 复合物的研究。NCg11110 是微生物芳香基团降解途径的转录调控蛋白，已获得其可供 X-ray 衍射分析的结晶，确认其辨识的基因，开始鉴定其专一结合的 DNA 片段，为 NCg11110-DNA 复合物构建建立条件。

(3) The structure and function of membrane proteins involved in photosynthesis

Wenrui Chang Group

The studies on photo-system II from green plants use the methods of protein crystallography, biochemistry and molecular biology. The purpose of this project is to investigate the mechanism of energy harvesting, transmission and transformation based on the three dimensional data at atomic level.

PS-II from higher plants consists of more than twenty protein complexes including the light harvesting complex, the reaction center complex and OEC. After the crystal structure of LHC-II from spinach was determined in our lab, the cucumber LHC-II structure was also determined recently. The electron density map of LHC-II at 2.66 Å shows that two Lutein molecules in LHC-II have different conformations, and the hetero-trimer formed by the Lut 620 and Chla612/611 pair has a special structural conformation, which facilitates energy transfer, and may be one of the possible quenching sites in the LHC-II molecule. Based on the structural analysis, we proposed that the extrusion between molecules in a certain direction caused by the crystallization process is the main cause of the formation of the above hetero-trimer. The studies on the preparation, purification and crystallization of other photosynthetic membrane proteins are in progress.

(4) Study of three-dimensional structure and function of some significant proteins and their complexes

Dacheng Wang Group

(1) Crystal structure determinations of four proteins, including: (a) sweet protein Mab II, which reveals a novel structural type for sweet proteins; (b) novel periplasmic amino acid binding protein Clu/AspBP (complex) at atomic resolution 1.15 Å; (c) an enzyme CaiE significant for carnitine metabolism, which reveals a unique left-handed -helix fold; (d) soluble intracellular ion channel CLIC4, in which a trimer structure was observed for the first time.

(2) The Cul3-BTB protein complex mediated by ubiquitin ligase Cul3 – the crystal structure and potential function in tumorgenesis. The soluble expression system for the recombinant proteins has been established and the stable complex is being constructed.

(3) Anti-tumor protein AAL and its target protein – elucidate the 3D structure of AAL and try to find the pathway of its functional performance. The crystal structure of AAL has now been determined at 2.0 Å resolution and about 10 mutants have been constructed for structure-function relationship investigation. A series of experiments to investigate how AAL could interact with cells are in progress.

(4) NCg11110-DNA complexes: NCgl1110 is a transcriptional regulator for the degradation process of some aromatic groups in microbes, which can bind to the corresponding DNA of the gene. Crystals of NCgl1110 have been obtained and the DNA sequences specific to binding are being identified in order to form the complex.

5、人二磷酸甘油酸变位酶的研究

龚为民组

二磷酸甘油酸变位酶是红细胞中特有的酶，它催化一系列分子间的磷酸基团转移反应，其主要功能是催化血红蛋白的别构效应因子——2，3-二磷酸甘油酸的合成反应。本研究中我们直接观察到了酶活性中心与底物在磷酸转移过程中的时实运动过程。我们解析了磷酸基团转移过程中不同阶段的一系列高分辨率的二磷酸甘油酸变位酶与 2，3-二磷酸甘油酸共结晶的晶体结构。这些结构不仅清楚地阐明了二磷酸甘油酸变位酶这类酶家族的底物结合方式，而且以一种“慢电影”的方式描述了关键的组氨酸被磷酸化的完整过程，同时我们还观察到二磷酸甘油酸变位酶的构造随着反应的进行不断地发生着变化。这些结果为“直线”的磷酸转移机制提供了直接证据，同时也确定了一些关键氨基酸在磷酸转移过程中的作用。

6、吡哆醛激酶以及雄性激素受体的晶体结构研究

江涛组

（1）吡哆醛激酶属于核糖激酶超家族成员，它催化维生素 B6 ATP 依赖的磷酸化反应，使之转变为磷酸吡哆醛。 我们利用大肠杆菌表达人吡哆醛激酶，并解析了其 2.8 Å 的晶体结构。与天然羊脑吡哆醛激酶的晶体结构比较后发现，一段在活性位点处起关键作用的 12 个残基肽段在羊脑吡哆醛激酶中呈现“loop”状态，而在人吡哆醛激酶中呈现 ß-折叠/loop/ß-折叠“flap”的构象。此外，人吡哆醛激酶拥有更加疏水的 ATP 结合口袋。该晶体结构的解析将有助于人们对人吡哆醛激酶生化性质的深入了解并开展以结构为基础的相关药物设计。

（2）雄性激素受体（AR）是胆固醇类细胞核受体超家族中的一个重要成员，在基因水平上调节雄性激素睾丸激素和二氢睾酮的受体活性。 LGD2226 是一种合成的非甾醇类的新型具有组织选择性的 AR 配体，在动物模型的试验中已经证实，它能够阻止骨骼的流失，促进骨骼的新生，促进肌肉的生成，同时降低了在前列腺中的副作用。我们解析了 LGD2226－AR LBD 复合物的晶体结构，分辨率达到了 2.1 埃，并且比较了它与 R1881－AR LBD 复合物的结构，进一步的揭示了它们结构的细微差别，我们认为这些细节上的差别与非甾醇类 AR 配体的组织选择性密切相关，这将有助于拓展雄性激素治疗的研究与应用。

(5) Seeing the process of histidine phosphorylation in human bisphosphoglycerate mutase

Weimin Gong Group

Bisphosphoglycerate mutase is an erythrocyte-specific enzyme catalyzing a series of intermolecular phosphoryl group transfer reactions. Its main function is to synthesize 2,3-bisphosphoglycerate, the allosteric effector of hemoglobin. We directly observed real-time motion of the enzyme active site and the substrate during phosphoryl transfer. A series of high resolution crystal structures of human bisphosphoglycerate mutase co-crystallized with 2,3-bisphosphoglycerate, representing different time points in the phosphoryl transfer reaction were solved. These structures not only clarify the argument concerning the substrate binding mode for this enzyme family, but also depict the entire process of the key histidine phosphorylation as a "slow movie". It was observed that the enzyme conformation continuously changes during the different states of the reaction. These results provide direct evidence for an "in line" phosphoryl transfer mechanism and the roles of some key residues in the phosphoryl transfer process were identified.

(6) Crystal structural study of pyridoxal kinase and androgen receptor

Tao Jiang Group

1) Pyridoxal kinase, a member of the ribokinase superfamily, catalyzes the ATP-dependent phosphorylation reaction of vitamin B6 and is an essential enzyme in the formation of pyridoxal-5'-phosphate, a key cofactor for over 100 enzymes. We solved the 2.8 Å crystal structure of human pyridoxal kinase (HPLK) expressed in Escherichia coli. Structure comparison reveals that the key 12-residue peptide over the active site in HPLK is a ß-strand/loop/ß-strand flap, while the corresponding peptide in the sheep brain enzyme adopts a loop conformation. Moreover, HPLK possesses a more hydrophobic ATP-binding pocket. This structure will facilitate further biochemical studies and structure-based design of drugs related to pyridoxal kinase.

2) The androgen receptor (AR) is a ligand-inducible steroid hormone receptor that mediates androgen action, determining male sexual phenotypes and promoting spermatogenesis. LGD2226 is a synthetic nonsteroidal ligand and a novel selective AR modulator. The crystal structure of the complex of LGD2226 with the androgen receptor ligand-binding domain (AR LBD) at 2.1 Å was solved and compared with the structure of the AR LBD–R1881 complex. It is hoped that this will aid in further explaining the selectivity of LGD2226 observed in *in vitro* and *in vivo* assays and in developing more selective and effective therapeutic agents.

7、酵母 DCN-1 和人复制起始复合物中 ORC6 的结构与功能研究

刘迎芳组

(1)DCN-1 参与蛋白质泛素化类蛋白 Nedd8 修饰过程的分子机制

DCN-1 是一个新发现的起促进蛋白质泛素化蛋白 Nedd8 修饰过程的分子,在酵母及线虫中,DCN-1 的缺失造成 Ubiquitin E3 ligase 组分 CULLIN（Cdc53）蛋白 Nedd8 修饰水平的下降，但是 DCN-1 在 Nedd8 修饰过程中的作用机制尚不清楚。我们解析了酵母 DCN-1 全蛋白的三维结构，发现该蛋白是一种砖型结构，结构中可见的区域为全 helix 结构，表面正负电荷分别分布在蛋白两侧，并且与一种 Ubiquitin E3 ligase 蛋白 CBL 有相似的 EF-hand 结构域，另一个结构域也与 CBL 有类似的折叠方式。根据这一结构特性，我们推测这一蛋白可能是 Nedd8 修饰过程中的 E3 ligase，进而推测该蛋白与另一已知的 Nedd8 修饰过程中的 E3 ligase Rbx-1 相互作用。我们体外实验证明了两者的相互作用。根据以上结果，我们构建了 DCN-1 参与蛋白修饰的分子模型。

(2)人复制起始复合物 ORC 的修饰亚基的结构与功能研究

ORC（Origin Recognition Complex）是真核生物染色体复制起始蛋白复合体，在 DNA 复制过程中结合于复制起始位点，进一步招募其它复制所需蛋白，从而启动 DNA 复制过程。这一复合体由 6 个亚基组成，分别为 Orc1-6，Orc1-5 为含 AAA 型 ATPase 类结构域的蛋白，而 Orc6 与其它 5 种蛋白都不同，是复合体的调节亚基。尽管这一复合体十分重要，但一直没有获得它的结构。我们首先从 Orc6 入手，开展解析这一蛋白结构工作。我们获得了该蛋白一个结构域约 100 氨基酸的结构。结果表明，该蛋白极有可能是招募其它 DNA 复制酶的分子，并且参与与 DNA 的相互作用。进一步研究在进行中。

8、人源多功能转录共激活因子 p100 结构与功能研究

刘志杰组

IL-4 信号传导通道是人体免疫反应的重要通道之一。实验表明 IL-4 信号传导通道与许多疾病如过敏，哮喘，癌症等密切相关。多功能转录共激活因子 p100 蛋白是此通道中的一个非常重要多种功能蛋白。p100 蛋白发现至今已有近十年历史。到目前为止，发现的 p100 蛋白涵盖的功能有：p100 蛋白是 EBNA2 的转录调控激活因子; p100 蛋白与转录因子 cMyb 和丝氨酸/苏氨酸激酶 pim1 结合并增强活性；p100 蛋白与病毒 mRNA 合成密切相关的 nsp1 特异性结合；p100 蛋白是 RNA 介导的沉默复合物(RISC)的重要亚基之一，并能够与富含 U · I 和 I · Upair 的 dsRNA 相互作用；p100 蛋白作为共激活因子促进 STAT5 和 STAT6 介导的转录活性调控，并形成多种蛋白质复合物，包括 RNApolII-p100-STAT6; p100-STAT5；STAT6-p100-RHA 等。目前为止尚无有关 p100 的全面的结构和功能研究的报道。

我们表达和纯化了人源 p100 蛋白 Tudor 结构域，并获得了晶体，解析了其精细三维结构，为进一步研究 p100 和蛋白质复合物的结构和功能提供了有利证据。目前进一步的结构和功能分析正在进行中。

(7) Structural and Functional Studies of Yeast DNC-1 and Human ORC6

Yingfang Liu Group

1) Structural and functional studies of yeast DCN-1

DCN-1 has been shown to promote Cullin neddylation in vivo, and it binds directly to Nedd8 and associates with Cdc53p. DCN-1's ability to mediate various protein-protein interactions is believed to be important for its neddylation function, for which the structural basis remains to be understood. We determined the crystal structure of yeast DCN-1 to 1.9 Å resolution. The structure shows that the region encompassing residues 66-269 adopts a cuboid-like overall fold, consisting of an EF-hand motif and two closely connected 3-helix coiled-coil motifs. The EF-hand motif structure is highly similar to that of the c-Cbl ubiquitin E3 ligase. Our *in vitro* binding results show that DCN-1 binds directly to Rbx-1p, which plays an important role in protein neddylation. Our results suggest that the protein functions as a neddylation E3 ligase, and could possibly interact with its partners during neddylation processes in a unique way.

2) Structural and functional studies of human ORC6

ORC (Origin Recognition Complex) is a conserved protein complex in eukaryotic organisms and functions in DNA replication initiation. It consists of six subunits, that is, ORC1-6. ORC1-5 are proteins with AAA-type ATPase domains, while ORC6, the smallest subunit in the complex, is different. ORC has been studied for over a decade since it was identified in 1992, but its molecular mechanism remains unclear to date, especially the structural and functional relationship of ORC6. We plan to study the functional and structural relationship of the ORC complex as well as its subunits. We determined the first structure of one domain of human ORC6. The structure suggests that ORC6 may bind to DNA on its own, and may function to recruit other replication factors to the DNA replication origin and to initiate the DNA replication processes.

(8) Structural and functional study of human transcriptional coactivator p100

Zhijie Liu Group

Cytokines regulate the growth and differentiation of nematopoietic cells through action of certain tyrosine kinases (JAKs) and STAT transcription pathways. Deregulation of the JAS/STAT pathway has been implicated in several human diseases, particularly cancer, allergy and polycystic kidney disease. IL-4 is a pleiotropic cytokine, and the biological response to IL-4 stimulation is cell type-dependent. P100 (a 100 kDa protein) was found to bind ST6TAD and acts as a bridge for the recruitment of RNA polymerase II and histone acetyl transferase activity to STAT6. P100 has been reported to interact with c-Myb and Pim-1 serin/threonine kinase through sequences located in SN-like domains. The P100 protein was found to bind nonspecifically with viral mRNA, but its function is not yet clear as many new functions are being discovered and reported in rapid succession. The three-dimensional structure of the P100 protein is currently unknown. The P100 C-terminal domain (residues: 651-872) was expressed, purified and crystallized. The 3D structure has been determined to a resolution of 2.0 Å. Further structural and functional analysis is in progress.

9、线粒体呼吸链复合物结构与功能研究

孙飞组

本课题组利用电子显微镜和 X 射线晶体的方法开展膜蛋白、病毒以及生物超分子复合体的结构研究。研究方向为现代结构生物学，包括 X 射线结构生物学、冷冻电镜结构生物学和冷冻电镜断层成像的细胞结构学三个大的方面。

研究进展包括: 已经成功纯化了含 13 个亚基的大肠杆菌 NDH－1 膜蛋白复合物，并获得了类晶物; 获得了细菌脂蛋白合成通路上两个重要膜蛋白的晶体; 与王志珍院士研究组合作，解析了内质网蛋白质质量控制系统中第一个人源全长 ERp44 蛋白的三维晶体结构，目前正在进行总结和文章写作; 利用电镜和 X 射线晶体学开展利用二型分子伴侣 α 和 β 的结构研究，成功利用负染方法完成了 α 分子外形的三维重构，观察到了同一种复合体内的两种分子构像，此外还获得了 α 分子和 β 分子的晶体，进一步的冷冻电镜工作和晶体学工作正在开展中。

(9) Mitochondrial respiratory Complex II structural electron transfer mechanism

Fei Sun Group

We will focus on the structure of membrane proteins, viruses and biological super molecular complexes via the combination of electron microscopy and X-ray crystallography, including X-ray structural biology, cryo-electron microscopy structural biology and cryo-electron tomography cell biology.

We have already successfully purified the *E. coli* NDH-1 membrane complex containing 13 subunits and obtained some semi-crystals. We also obtained the crystals of two important membrane proteins related to the bacterial lipoprotein synthesis pathway. In addition, in collaboration from Prof. C.C. Wang, we solved the first crystal structure of human ERp44 related to the protein quality control system in the endoplasmic reticulum. Finally, we successfully reconstructed the 3D structure of archaeal type II chaperon using negative staining, revealing two different conformations in one complex, and we also obtained crystals of chaperon and chaperon . Further work on cryoEM and X-ray crystallography is now underway.

（二）蛋白质功能与折叠原理研究

1. 蛋白质二硫键异构酶四个结构域的环形排布及其协同作用

王志珍组

用小角 X 射线散射(SAXS)技术测定了人蛋白质二硫键异构酶（PDI）在溶液中的结构。这是首次报道的人源 PDI 全长分子在溶液中的低分辨率结构。重构模型表明 PDI 是一个短的椭圆柱体形状的分子，计算分子质量为 69 kDa，分子大小为 105 × 65 × 40 Å。四个具有硫氧还蛋白折叠 ((Trx)-fold) 模式的结构域按 a-b-b’-a’ 顺序以环形的方式排列。原子力显微镜成像结果也表明 PDI 分子在溶液中大概是一个扁平的椭圆柱体。基于分子筛测定的表观分子质量为 116KDa 的 PDI 组分长期被认为是一个同源二体，但是超离心分析的结果表明它实际上是单体。PDI C 端的 441-491 序列可能是造成 PDI 分子筛行为异常的原因。PDI 的环形排布模型诠释了 PDI 在行使异构酶和分子伴侣活力时四个结构域的相互协同作用。

2. 分子伴侣 Hsp70 通过与不同中间体相互作用抑制 α-synuclein 形成纤维

王志珍组

α-Synuclein (AS) 是帕金森氏症患者大脑神经元中淀粉样沉淀所形成的包含体－路易氏体的主要成分。我们鉴定到热休克蛋白 Hsp70 至少通过阻止 AS 纤维前体的形成、结合 AS 纤维前体阻止 AS “核”形成、结合 AS“核” 抑制 AS 纤维延伸三种作用来抑制 AS 形成纤维；并且抑制 AS 纤维前体所诱导的脂质体通透性的增加。 Hsp70 的底物结合结构域本身已足以抑制 AS 形成纤维，而与 AS 纤维前体结合只需要底物结合亚结构域，但结合 AS“核”则同时需要 C-末端盖状亚结构域和底物结合亚结构域。分子伴侣抑制 AS 形成纤维的研究结果为阐明 AS 形成纤维的机制提供了分子基础，同时也为分子伴侣在许多神经退行性疾病中阻止有关蛋白形成毒性物质的机制提供了分子基础。

3. 大肠杆菌 DsbC 的折叠行为 ——单体折叠中间体的鉴定

王志珍组

通过构建单体和二体突变体，分析盐酸胍诱导的同源二聚体 DsbC 的去折叠和重折叠的平衡态和动力学的过程。我们监测到 DsbC 在折叠中的单体中间体。说明 DsbC 的二体结构和非活性中心二硫键对其结构的稳定和功能的发挥起到重要作用。

2. Protein function and folding

(1) Annular arrangement and collaborative actions of four domains of protein-disulfide isomerase: a small angle X-ray scattering study in solution

Chih-chen Wang Group

Using small angle x-ray scattering (SAXS), we for the first time reported the low-resolution structure of intact protein disulfide isomerase (PDI) in solution. The restored model revealed that PDI is a short and roughly elliptical cylinder with a molecular mass of 69 kDa and dimensions of 105 × 65 × 40 Å, and the four thioredoxin-fold domains in the order *a-b-b'-a'* are arranged in an annular fashion. Atomic force microscope imaging also supported the finding that PDI appears as an approximately flat elliptical cylinder. A PDI species with apparent molecular mass of 116 kDa measured by using size-exclusion chromatography, previously assumed to be a dimer, was determined to exist mainly as a monomer by using analytical ultracentrifugation. The C-terminal fragment 441–491 contributed to the anomalous molecular mass determination of PDI by size-exclusion chromatography. The annular model of PDI accounted for the cooperative properties of the four domains in both the isomerase and chaperone functions of PDI.

(2) Heat Shock Protein 70 inhibits α-Synuclein fibril formation via interactions with diverse intermediates

Chih-chen Wang Group

α-Synuclein (AS) is the main component of Lewy bodies in midbrain dopamine neurons pathologically characteristic of Parkinson's disease. We show that heat shock protein (Hsp) 70 inhibits AS fibril formation via preventing the formation of prefibrillar AS (PreAS), binding with PreAS to impede nuclei formation, and binding with nuclei to retard fibril elongation. Also, Hsp70 suppresses the PreAS-induced permeabilization of vesicular membrane through interactions with PreAS. The substrate-binding domain alone is sufficient for Hsp70 to inhibit AS fibril formation. The binding of Hsp70 with PreAS only requires the substrate-binding subdomain, while the binding with AS nuclei requires the C-terminal lid subdomain as well. The results may form the molecular basis for elucidating the mechanism of AS fibril formation and the crucial roles of chaperones in protecting proteins from toxic conversion in many conformational diseases.

(3) Folding of *Escherichia coli* DsbC: characterization of a monomeric folding intermediate

Chih-chen Wang Group

We have studied the guanidine hydrochloride (GdnHCl)-induced unfolding and refolding of DsbC using mutagenesis, intrinsic fluorescence, circular dichroism spectra, size-exclusion chromatography and sedimentation velocity analysis. Folding of DsbC follows a three-state transition model with a monomeric folding intermediate formed in 0-2.0 M GdnHCl. The folding of DsbC in the presence of DTT indicates an important role of the non-active-site disulfide bond in stabilizing the conformation of the molecule. Dimerization ensures performance of chaperone and isomerase functions of DsbC.

4、蛋白质错误折叠与疾病

柯莎组

（1）Ure2 prion 化的分子机制：N 端和 C 端结构域分别在 prion 化中的作用

酵母 prion 蛋白 Ure2 在体内和体外都能形成淀粉样结构，其 N 端的 prion 结构域（PrD）和 C 端部分区域被发现在体内能影响 Ure2 的 prion 化。为了揭示 Ure2 prion 化的机制，我们已经研究了一系列 PrD 缺失的 Ure2 突变体的性质，发现 PrD 在纤维化的成核过程中有重要作用，C 端区域决定 Ure2 的折叠性质。我们也进行 Ure2 折叠的动力学和热力学分析，发现 Ure2 至少存在三个折叠中间态，目前我们正在研究一系列 C 端缺失突变体的折叠机制。

（2）Ure2 的酶学分析

我们首次证明了天然态和纤维化 Ure2 都具有谷光甘肽依赖性的过氧化物酶活性。为了进一步发现其反应机制和确认催化活性的必需残基，我们正在进行一系列相关突变体的构建以及功能与结构关系的研究。

（3) 淀粉样聚集物的细胞毒性研究

培养不同种类的哺乳动物细胞，加入天然态 Ure2 及不同种类的 Ure2 聚集体，研究 Ure2 及其成纤维不同阶段聚集体的细胞毒性。原初纤维的细胞毒性最大，其次是成熟纤维，天然态的 Ure2 几乎没有细胞毒性。分子伴侣对 Ure2 聚集体细胞毒性的影响正在研究中。

（4）分子伴侣与 Ure2 的相互作用

在细胞内影响 prion 化的因素包括分子伴侣 Hsp70、Hsp40 和 Hsp104。这些分子伴侣已被纯化并用于探索他们对 Ure2 折叠和纤维化的影响。最近的结果表明 Hsp40-Ydj1 能和 Ure2 直接相互作用，并且特异性的在 Ure2 成纤维的早期抑制 Ure2 的纤维形成。其他分子伴侣 Ssa1-Hsp70 和 Hsp104 也能抑制 Ure2 的纤维形成。

(4) Protein Misfolding and Disease

Sarah Perrett Group

1) Molecular mechanism of Ure2 prion formation

The yeast prion protein Ure2 forms amyloid-like structure in vivo and in vitro. Mutants in either the N-terminal prion domain (PrD) or the C-terminal region of Ure2 are found to affect prion formation *in vivo*. In order to shed light on the mechanism of prion formation, we have studied the properties of a series of PrD deletion mutants. We found that the N-terminal PrD plays an important role in the nucleation of amyloid-like structure, while the folding properties of Ure2 are determined by the C-terminal region. We have also carried out a detailed kinetic and thermodynamic analysis of Ure2 folding, identifying at least three folding intermediates, and we are currently studying the folding mechanism of a series of C-terminal deletion mutants.

2) Enzymatic activity of Ure2

We have demonstrated that Ure2 possesses glutathione-dependent peroxidase activity. Interestingly, we found that peroxidase activity is maintained in amyloid-like fibrils of Ure2. In order to gain further insight into the reaction mechanism and to identify the residues required for catalytic activity, we are currently carrying out mutagenesis studies. Based on inspection of the published crystal structure, and sequence alignments of Ure2 with related enzymes, we have mutated residues that appear to be important for substrate binding or activitation. The mutants have been purified and their enzyme kinetics characterized. A picture is now emerging of the residues important for the enzyme activity of Ure2.

3) Identifying the toxic species in the process of amyloid formation

We have isolated intermediates that appear at different stages during the process of Ure2 amyloid fibril formation and tested their affect on mammalian cells in culture. We found that both small aggregates and mature fibrils were able to enter mammalian cells, but only early aggregation intermediates were toxic to the cells.

4) Interaction of chaperones with Ure2

Factors that affect Ure2 prion formation in the cell include the molecular chaperones Hsp70, Hsp40 and Hsp104. These chaperones have been purified and we are investigating their effect upon folding and fibril formation of Ure2. Recent results have demonstrated a direct interaction between these chaperones and Ure2. Further, we found that each of these chaperones is able individually to reduce the formation of amyloid-like aggregates of Ure2. A detailed characterization of the interaction with Hsp40 indicates that it inhibits fibril formation by binding to the native state of Ure2 prior to the onset of oligomerisation.

5、蛋白-蛋白和蛋白-DNA 相互作用的 NMR 研究

王金凤组

（1）确定了一个人源 c10orf70 (c10orf70[31-108])蛋白质的三维结构，这是一个相互交叠的二体蛋白，是具有新结构类型的人线粒体的 2Fe-2S 蛋白。它的 Fe-S 簇的几何结构以及 Fe-S 簇结合位的结构不同于其它的已知 2Fe-2S 蛋白。 经分析 c10orf70[31-108])蛋白质可能是一个糖尿病药物 Thiazolidinediones (TZDs)在人线粒体中的潜在靶分子。

（2）确定了[P62A]Ssh10b 二聚体的三维结构，运用 GdmSCN 的变性实验和 NMR 的 H/D 交换及蛋白骨架酰氨氮弛豫研究了[P62A]Ssh10b 及其突变体热稳定性的结构基础及热稳定性的分子机制。指出了在桶状疏水核心的疏水堆积与蛋白质中的肽链间和肽段间的氢键以及离子对间的协同相互作用决定了[P62A]Ssh10b 的热稳定性，而盐键网中的静电相互作用对蛋白质的高度热稳定性起了关键作用。

（3）研究了金黄色葡萄球菌酶（SNase）的β-与 α-亚结构域片段(SNase121 与 SNaseα3 片段)在 SNase121-SNaseα3 复合体中的折叠机制及相互识别的机制，确定了 SNase121-SNaseα3 复合体的溶液三维结构,得出了β亚结构域和α亚结构域两个片段在复合体中相互作用，相互诱导，不断地调整结构，最后组装成天然态的酶，说明了在全酶折叠过程中β亚结构域和α亚结构域的折叠有高度地协同性和依赖性。

（4）运用异核多维 NMR 解析了其它三个人源基因编码蛋白质的三维结构，正在对这些蛋白的相关功能进行研究。正在进行[P62A]Ssh10b-DNA 和 SNase-DNA 复合物的异核多维 NMR 实验，以最终确定复合物的溶液三维结构。

6、内源 NO 介导神经元内质网应激的分子机理

陈畅组

建立内外源一氧化氮 NO 诱导神经细胞内质网应激模型。阐明神经细胞内质网应激过程中 NO 对功能蛋白的巯基亚硝基化修饰的机理及与细胞氧化还原状态的关系，以及该过程中细胞内氧化应激和亚硝基化应激的时序关系。揭示细胞中重要的控制蛋白合成的细胞器内质网发生应激对神经细胞损伤的新的作用机理，为蛋白沉积类疾病机理提供新线索。为通过监测细胞内总体亚硝基化修饰水平新指标来诊断脑疾病提供理论依据。并进一步研究 NO 供体 S-亚硝酰基谷光甘肽（S-nitrosoglutathione，GSNO）的调控机制，为开发新的 NO 供体类药物奠定基础。

(5) Protein-Protein and Protein-DNA Interactions Studied by NMR Methods

Jinfeng Wang Group

The 3D structure of the soluble domain of human c10orf70 (c10orf70[31-108]) has been solved which reveals a novel iron-sulfur protein in human mitochondria, presenting as an intertwined dimer. The geometry of the [2Fe-2S] cluster and the structure of the cluster-binding site are novel among other [2Fe-2S] iron-sulfur proteins. c10orf70[31-108] can be postulated as a potential target for Thiazolidinediones (TZDs) in human mitochondria.

The 3D structure of [P62A]Ssh10b dimer was determined. The amide hydrogen exchange in the absence and presence of different concentrations of GdmSCN and backbone ^{15}N relaxation detected by NMR experiments were used to provide a basis for interpreting the stability of [P62A]Ssh10b in a structurally correlated fashion. The results indicate that the cooperative interactions of hydrophobic packing in the barrel-shaped hydrophobic core with the cross-strand and cross-segment hydrogen-bonding and ion-pairing determine the thermal stability of [P62A]Ssh10b. The electrostatic interactions are thought to be crucial to higher thermal stability of the protein structure.

The 3D structure of the complex of SNase121 and SNaseα3 was determined, which are the two fragments of staphylococcal nuclease (SNase) representing β- and α-subdomains, respectively. The folding mechanism and recognition mechanism of two SNase fragments in the SNase121-SNaseα3 complex have been analyzed. The 3D structure of the SNase121-SNaseα3 complex is very similar to the native structure of SNase. The tertiary folding of two fragments in the complex is induced by the long-range interactions between them and proceeds cooperatively.

Structures of the other three human proteins were determined by heteronuclear multidimentional NMR experiments, and study of the related physiological functions is in progress. Determination of 3D structures of [P62A]Ssh10b-DNA and SNase-DNA complexes by heteronuclear multidimentional NMR methods is in progress.

(6) The mechanism of ER stress in neuronal cells involved in endogeneous nitric oxide (NO)

Chang Chen Group

This project is trying to build models for endoplasm reticulum stress (ER stress) induced by endo- and exo-nitric oxide (NO) in neural cells. On this basis, we are trying to reveal the mechanism of NO S-nitrosylation modification of key functional proteins and the relationship of this effect with the redox status of cells during ER stress. Besides this, we are also interested in the spatial and temporal relationship between oxidative stress and nitrosative stress in this cascade. By this work we are trying to get better understanding about the mechanism of neural cell damage from a new aspect, namely ER stress, which is an important organelle response related to protein function. The results of this research may cast light on the pathology of diseases involved in protein over-accumulation, supply evidence to obtain new parameters for use in diagnosing brain diseases according to the nitrosylated level of proteins. Further study will focus on the regulated effects of S-nitrosoglutathione (GSNO) on ER stress for the development of NO donor drugs.

（三）生物膜和膜蛋白功能结构研究

1、膜脂－膜蛋白相互作用的研究

杨福愉组

（1）与张旭家合作，研究‘脂筏’对肌浆网膜 Ca^{2+}-ATP 酶（SERCA）和质膜 Ca^{2+}－ATP 酶（PMCA）的影响，‘脂筏’组分－胆固醇、神经鞘脂对 SERCA 的 PMCA 活性的影响。对‘脂筏’对 NOS 基因表达及酶活性的调控作用。

（2）胰凝乳蛋白酶 B（CtrB）在溶酶体中的定位及其对细胞凋亡的影响。

一般认为 Ctr B 是由胰腺分泌的一种具有消化功能的水解酶，我们发现它也是细胞内溶酶体中的一个成员，在一定条件下可以从溶酶体中泄漏并通过线粒体中介参与细胞凋亡过程。

2006 年通过:

① Ctr B 在溶酶体中的定位;

② 在 TNFα诱发下 CtrB 从溶酶体移位至细胞质;

③ CtrB 水解 Bid 导致线粒体的释放;

④ 如果将 CtrB 与其抑制剂 TPCK 同时处理，TNFα诱导细胞凋亡就会显著降低等等都进一步验证细胞中溶酶体 CtrB 的存在及其参与细胞凋亡的作用。

除此之外 CtrB 是否对细胞还有其它功能正准备进一步研究。

2、囊泡钙库的动态调节及其与分泌的关系

徐涛组

我们成功的在INS-1细胞上同时检测到$[Ca^{2+}]_i$ 和$[Ca^{2+}]_{Lu}$变化，并通过直接证明用GPN消除酸性钙库后不影响ER钙库内的钙变化过程，证明它们为不同的细胞内器官。

我们进一步研究了胰腺β细胞上酸性囊泡钙库的特性，发现它会在生理条件下激活，因此具有生理意义。例如，我们发现，长时间去极化细胞会导致囊泡钙库的释放，含胰岛素大囊泡与细胞融合后释放出来ATP也会促进囊泡钙库的释放，起一个正反馈的作用。我们同时证明囊泡膜上存在不同的钙释放受体，如IP3受体和NAADP受体等。

研究成果如下:

（1）我们证明外源ATP刺激胰腺β细胞后会促进囊泡通过IP3受体的释放Ca^{2+}，从而增强胰岛素分泌，结果发表在Traffic上。

（2）我们证明长时间去极化刺激胰腺β细胞后也可以促进囊泡钙库通过NAADP受体释放Ca^{2+}，从而影响葡萄糖刺激后细胞的动作电位振荡和Ca2+振荡的动力学，结果也发表在Traffic上。

3. Membrane Biology and Membrane Protein Function and Structure

(1) Interaction between lipids and membrane proteins

Fuyu Yang Group

1) In collaboration with Dr. Xujia Zhang's group, the effects of lipid rafts on SR Ca^{2+}-ATPase and plasma membrane Ca^{2+}-ATPase have been studied. Moreover, the effects of cholesterol and gangliosides, which are the major components of lipid rafts were also studied. NOS expression and enzymatic activity regulated by lipid rafts were of interest.

2) Chymotrypsin B (CtrB) localizes at lysosomes and is involved in apoptosis

Although CtrB is usually accepted as a protease secreted from pancreas, our results demonstrated that it localizes at lysosomes and is involved in apoptosis after leakage from lysosomes in response to stress. We have shown that 1) CtrB localizes at lysosomes; 2) TNFα induced the translocation of CtrB from lysosomes to the cytosol; 3) the truncated Bid by CtrB lead to the release of cytochrom c from mitochondria; 4) TPCK, the specific inhibitor of CtrB attenuated the TNFα inducted apoptosis. Moreover, the study of possible other functions of CtrB are underway.

(2) Dynamic Regulation of Vesicle Ca Store and Its Relationship with Exocytosis

Tao Xu Group

Many cells show a plateau of elevated cytosolic Ca^{2+} after a long depolarization, suggesting delayed Ca^{2+} release from intracellular compartments such as mitochondria and endoplasmic reticulum (ER). Mouse pancreatic β-cells show a thapsigargin-sensitive plateau ('hump') of Ca^{2+} after a 30 s depolarization but not after a 10 s depolarization. Surprisingly, this hump depends primarily on compartments other than the mitochondria or ER. It is reduced by only 22% upon blocking mitochondrial Na^{+}–Ca^{2+} exchange and by only 18% upon blocking ryanodine or IP3 receptors together. Further, the time course of ER Ca^{2+} measured by a targeted cameleon does not depend on the duration of depolarizations. Instead, the hump is reduced 35% by treatments with the dipeptide glycylphenylalanine β-napthylamide, a tool often used to lyse lysosomes. We show that this dipeptide does not disturb ER functions, but it lyses acidic compartments and releases Ca^{2+} into the cytosol. Moreover, it induces leaks in and possibly lyses insulin granules and stops mobilization of secretory granules to the readily releasable pool in β-cells. We conclude that the dipeptide compromises dense-core secretory granules and that these granules comprise an acidic calcium store in β-cells whose loading and/or release is sensitive to thapsigargin and which releases Ca^{2+} after cytosolic Ca^{2+} elevation.

3、肌浆网脂筏结构调控肌浆网 Ca2+-ATPase 的功能

张旭家组

脂筏结构不仅存在于质膜，在高尔基体、膜蛋白运输通路中的内质网囊泡膜中也有类似的结构微区。肌质网是骨骼肌细胞中特化的内质网，其功能主要在于维持胞内的 Ca^{2+} 平衡。我们利用蔗糖密度梯度漂浮的方法，从基本上无质膜和线粒体等细胞器污染的肌质网膜中分离了低密度的，低温下不溶于非离子去垢剂 Triton X-100 的膜微区，即肌质网膜的不溶于去垢剂的组分---SRIC，并对其进行了性质的鉴定，发现它富含鞘磷脂和胆固醇，并富集脂筏的标志分子 GM1。Caveolin-3 （Cav-3）是 Caveolae 的结构和标志蛋白，定位于肌细胞的质膜。我们利用免疫荧光显微镜技术，证明 Cav-3 也存在于肌质网膜上。另外免疫印迹的结果显示 Cav-3 在 SRIC 微区中富集。上述结果进一步提示肌质网膜中可能也具有“脂筏”结构。

对肌质网 Ca^{2+}-ATPase 蛋白及其活性在膜上的分布情况进行了分析，肌质网 Ca^{2+}-ATPase 既存在于 SRIC，又存在于肌质网膜的溶于去垢剂的组分，即 SRSC 微区中，但是只有位于 SRIC 中的肌质网 Ca^{2+}-ATPase 才表现出很高的 Ca^{2+} 依赖的 ATP 水解活性和 Ca^{2+} 转运活性，这说明肌质网 Ca^{2+}-ATPase 与 SRIC 的结合对于其功能活性是必需的。利用不同的去垢剂，CHAPS 和 OG 溶解肌质网膜，不同去垢剂提取的 SRIC 结构组成并不等同，但均支持肌质网 Ca^{2+}-ATPase 只有与 SRIC 结构结合，才具有功能活性。用 MβCD 去除肌质网膜的胆固醇，破坏了 SRIC 结构，使得分布于 SRIC 组分的肌质网 Ca^{2+}-ATPase 移向 SRSC，并导致酶活力的丧失。以上结果提示肌质网膜中的“脂筏”结构对 Ca^{2+}-ATPase 活性的表现具有重要的作用。

(3) Lipid microdomains residing at the sarcoplasmic reticulum are required for the SR Ca^{2+}-ATPase

Xujia Zhang Group

Lipid rafts are not only restricted to the plasma membranes, but indications for the existence in the Golgi complexes, and endoplasmic reticulum (ER) membranes along the secretory pathway have been reported. Upon the isolation of SR without apparent contaminations from other organelles, we characterized detergent-resistant membranes (DRM) from SR membranes isolated by using 1% Triton X-100 and sucrose density gradient flotation. These SR-derived detergent-insoluble complexes (SRICs) had a low buoyant density and were highly enriched in sphingomyelin and cholesterol. Marker glycolipid of DRM, such as GM1 was also concentrated in SRICs. Caveolin-3 (Cav-3) is the structural and characteristic protein of caveolae, and located on the sarcolemma. The results of immunofluorescence microscopy of SR vesicles showed the presence of Cav-3 and SERCA on the SR membranes and suggested their colocalization. Furthermore, the results of western blot showed the concentration of Cav-3 in SRICs. These results suggest that 'lipid rafts' may exist in SR membranes.

The functional distribution of SERCA protein was observed. It was found SERCA partitions into both SRICs and SR-derived detergent-soluble complexes (SRSCs), but only the enzyme in SRICs was fully functional, which suggests that the SERCA associates with SRICs and the inclusion of the enzyme into SRIC is critical for its activity. We also used other detergents, such as CHAPS and OG to isolate SRICs, and found that SERCA was soluble in the zwitter ionic detergent, CHAPS, but only partially soluble in the non-ionic detergent, OG, just as in Triton X-100. The detergents differed considerably in their abilities to selectively solubilize membrane proteins and lipids, but the results obtained here support the importance of SRIC association of SERCA to its activity. Disruption of SRICs upon depeletion of SR cholesterol by Methyl-β-cyclodextrin (MβCD) resulted in the redistribution of SERCA into SRSCs, and the loss of enzyme activity. Together, these findings suggest that the association of SERCA with SRICs may represent a mechanism for regulating the enzyme activity, that is, 'lipid rafts' in SR membranes are important to SERCA activity.

4、蛋白质组学新方法研究与应用

杨福全组

（1）研制了新型一维、二维高效毛细管液相色谱柱，设计加工了液-质联用接口平台，建立了经济、高灵敏和高通量的多维蛋白质鉴定系统，并成功应用于蛋白质复合体的鉴定以及蛋白质组学研究。

（2）以大鼠线粒体膜蛋白为研究对象，选择和优化了膜蛋白的溶解、富集和酶解的最佳条件，建立了膜蛋白质组学技术平台，并成功应用于：大鼠 β 细胞中胰岛素储存囊泡蛋白质组分析；人 NK 细胞中溶酶体的蛋白质组分析；小鼠肝脏中脂滴蛋白质组分析；GSV 分泌相关的蛋白质复合体的分析鉴定。

（3）建立了基于 SILAC 定量蛋白质组学技术方法，成功应用于：L6 骨骼肌细胞分化前后蛋白质表达差异分析；Insulin 对 L6 肌管细胞长效作用前后蛋白质表达差异分析等。

（4）开展了磷酸化蛋白质组学新技术新方法的研究与应用。

（5）开展了肿瘤死亡预警蛋白生物标志物、白血病相关蛋白生物标志物的分离鉴定工作，并取得重要进展。

（6）完成了微型逆流色谱仪及液-质联用接口的研制，并初步开展了人类血清肽组学的研究。

(4) Study and Application of New Proteomic Methods

Fuquan Yang Group

(1) A sensitive, high-throughput multidimensional protein identification technology (MudPIT) platform was set up by developing new single phase (C18) and two phase (SCX+C18) capillary HPLC columns and designing a new LC-ESI-MS interface. The MudPIT platform has been applied to the identification of protein complexes and proteomics.

(2) A membrane proteomic platform has been set up by selection of the optimal conditions for the dissolution, enrichment and digestion of membrane proteins. This platform has been applied to proteomic analysis of insulin storage vesicles from rat β cells; proteomic analysis of lysosomes from human NK cells; and proteomic analysis of lipid droplets from mouse liver.

(3) A SILAC (stable isotope labeling by amino acids in cell culture) based quantitative proteomic platform has been set up and applied to the quantitative profile of expressional differentiation between L6 myoblasts and myotubes, and the quantitative profile of expressional differentiation of myotubes before and after stimulation with insulin.

（4）Development and application of new phosphoproteomic techniques and methods.

（5）A new countercurrent chromatographic instrument has been developed and applied to the human serum peptidomics.

（四）计算与系统生物学

1、DNA 错配修复系统作用机制研究

毕利军组

（1）DNA 错配修复（Mismatch Repair，MMR）系统研究

① 利用纳米/分子生物传感器开展 MMR 系统中 MutS 蛋白与错配 DNA 分子的作用行为研究，揭示 DNA 错配修复过程中错配碱基的识别机制;

② 通过研究 DNA 错配修复蛋白与复制酶亚基之间的相互作用，建立 DNA 修复和复制系统中多个蛋白间相互作用网络，揭示 DNA 错配修复与复制过程的耦联机制;

③ 完成了 MMR 系统中解螺旋酶 UvrD 与不同类型 DNA 分子的动力学研究，在单分子水平上观测到 UvrD 的 DNA 解螺旋过程。完成了四种核酸外切酶的克隆、表达和功能鉴定。通过上述研究揭示错配修复终止分子机制;

④ 通过利用错配修复蛋白 MutS 对体外分子进化中突变子的高效分离和富集，提高突变或重组的比例，从而减少筛选的工作量，并提高有意义突变的比例，此研究已经获得初步结果;

⑤ 基因组信息学研究显示，结核杆菌中未发现在其它生物中普遍存在的 DNA 系统的同源基因。我们通过确定结核杆菌中是否存在错配修复系统，然后利用垂钓等方法寻找错配修复蛋白组分，从而回答结核杆菌中是否有 DNA MMR 系统，如果存在，其组成和作用机制是什么？如果不存在，结核杆菌又是通过那种途径来维护其基因组稳定性的，其效率又如何等问题。

（2）结核杆菌耐药性机理研究

结核病是严重的全球性传染疾病。结核杆菌的各种基因突变导致相应的耐药性，其 DNA 旋转酶作为药物靶点的研究越来越受到重视。我们在晶体结构学的基础上，进一步揭示了结核杆菌 DNA 旋转酶 A 亚基的 C 端结构域在该酶催化反应中的作用，鉴定了 DNA 旋转酶 A 亚基的 C 端结构域中的 DNA 结合位点，并提出该结构域是结核分枝杆菌中潜在的药物设计的作用部位。同时开展了结构与功能的相关性研究。目前已经得到 DNA 旋转酶 B 亚基的 C 末端晶体，衍射收到一套数据，正在解析结构。

4. Computational and Systems Biology

(1) Function mechanism of DNA mismatch repair system

Lijun Bi Group

1) DNA mismatch repair (MMR)

The DNA mismatch repair system plays an important role in maintaining the stability of the genome and defects in the mammalian pathway are associated with a strong predisposition to tumor development. So far, the detailed mechanism of interaction between MMR proteins is poorly understood. Our recent interests include multi-MMR protein interactions and MMR protein-DNA interactions, and exploring MMR molecules as biosensor recognition elements for effective detection of DNA mutations. The progress in the past year is as follows:

(i) Studies on interaction of MutS and DNA using atomic force microscopy (AFM);

(ii) Interactions of MMR proteins and DNA polymerase III subunits;

(iii) Kinetic analysis of DNA binding and unwinding of Helicase II (UvrD);

(iv) Application of DNA mismatch repair protein MutS in molecular evolution;

(v) Molecular mechanism of TB MMR.

2) Drug-resistance mechanism of *Mycobacterium tuberculosis*

Tuberculosis is one of the most deadly and common infectious diseases, whose global spread is further complicated by the ubiquitous appearance of drug-resistant strains. Our group has focused on the structure and function of gyrase A and gyrase B and developed drug design and selection based on the gyrase structure. We have used site-directed mutagenesis of these conservative polar residues according to conservation mapping and the crystal structure of *B. burgdorferi* C-terminal domain of GyrA (GyrA-CTD). The results show that the DNA-binding sites in GyrA-CTD mostly lie on the surface of the third and fourth blades, and these sites also have a role in relaxation activity, despite also influencing the DNA-binding and supercoiling activity.

2、基因组 DNA 稳定性研究

杭海英组

（1）采用小鼠条件基因敲除技术，发现细胞周期监控点基因 *Rad9* 是抑癌基因。*Rad9* 敲除纯合小鼠皮肤不会自发长瘤。但涂抹癌诱变剂 BMDA 在 *Rad9* 敲除纯合小鼠皮肤上高频诱发乳头瘤（13/14），而野生小鼠的肿瘤发生率则要低得多（3/14）。同时还检查到 *Rad9* 敲除的皮肤角质细胞基因组变得不稳定。基因组变得不稳定可能是 *Rad9* 敲除纯合小鼠易发癌症的内在原因;

（2）用免疫共沉淀与质谱相结合，发现 Rad9 蛋白与多种参与 DNA 修复、细胞周期调控及染色质重塑蛋白质因子相互作用。用酵母双杂交和 pulldown 证明这些相互作用直接的。正在对这些相互作用的功能意义进行研究。

3、非编码基因及其相关的调控网络

陈润生组

总的是发现新的非编码 RNA，研究它们的生物学功能，发现其表达调控的新规律，构建有非编码 RNA 参与的新的生物网络。具体是:

（1）在以前的工作中我们已在线虫上发现了 100 个全新的非编码 RNA(*Genome Research* 16: 20-29, 2006; NCBI accession number: AY948555-- AY948719），并证实其中很多基因是在线虫发育的不同时期表达的。因此我们的第一个任务是确定这些新非编码 RNA 的功能及其表达调控的规律;

（2）拟以人类为对象发现更多的非编码 RNA;

（3）迄今为止尚未见包含非编码 RNA 的生物网络研究，我们的第三个研究内容就是要构建由蛋白质和非编码 RNA 两类物质为节点的新网络（简称：双色网络），并研究其性质。

(2) Genomic DNA stabilization

Haiying Hang Group

(1) Created *Rad9* skin-conditional knockout mice. Experiments using the mouse model demonstrated that *Rad9* is a tumor suppressor gene. Homozygous *Rad9* deletion did not spontaneously yield tumors. When treated with BMDA (a tumor inducing chemical), there is a higher tumorigenesis rate on *Rad9-/-* mouse skin (13/14) than on wild type mice (3/14). This result indicates that *Rad9* plays a role in tumor suppression. We have also found that the genome in mouse *Rad9-/-* keratinocytes is highly unstable.

(2) We have found by combining co-immunoprecipitation and mass-spec that Rad9 protein interacts with a group of proteins involved in cell cycle control, DNA repair and chromotin remodeling. Further work using yeast two-hybrid and protein pulldown indicates that the interactions are direct. More experiments are underway to reveal the functions of these interactions in maintaining DNA stability.

(3) Non-coding RNA genes and the related controlling networks

Runsheng Shen Group

Our work has been focused on finding new non-coding RNAs, discovering their functions, exploring how they are expressed and controlled, and constructing new bio-networks in which the non-coding RNAs are involved. Further details are given below:

(1) Previously, we found 100 new non-coding RNA genes in *the C. elegans* genome (*Genome Research* **16:** 20-29**,** 2006; NCBI accession number: AY948555-AY948719), and confirmed that many of these genes are expressed at different developmental stages. So, our first task was to discover the functions of these new non-coding RNA genes and find out how they are expressed and controlled.

(2) Our second task was to find new non-coding RNA genes in the human genome.

(3) To date, no studies on bio-networks containing non-coding RNA have been reported. The third component of our research was therefore to construct new bio-networks containing two kinds of nodes (proteins and non-coding RNAs, so we called them two-color networks) and to study the properties of these networks.

4、染色质可塑性与基因组稳定性

焦仁杰组

（1）我们证明在人类细胞中 WRN 与 CAF-1 大亚单位 hp150 存在功能相互作用（文章已发表在 Oncogene）;

（2）我们已经证明 dCAF-1-p180 在组织染色质结构中至关重要。dCAF-1-p180 对果蝇发育至关重要。它的突变可以通过影响染色质的构建而影响基因的表达和基因组的稳定性；dCAF-1-p180 的功能改变还与果蝇的生殖能力有关；dCAF-1-p180 缺失或过多表达会使细胞停止生长或执行 apoptosis。（文章已提交）dCAF-1 另外两个亚基的突变株正在制备中。

（3）我们已得到 *CG9613* 基因的果蝇突变株。初步结果显示该基因可能与细胞生长和抗氧化能力有关。目前正在检测它与 Insulin 信号通路的关系;

（4）我们已获得果蝇 *dRecQ4* 和 *dRecQ5* 的突变株，它们在维持基因组稳定性中的可能功能正在研究中;

（5）合作项目包括:

① 我们的实验结果表明 Bcd 的调节基因表达的活性可能与 HDAC 等染色质重构因子有关;（马骏）

② dCAF-1 等蛋白复合物的结构解析；（孙飞）

③ dHDAC6 如何质控α-synuclein 及其与 Parkinson’s 病的关系；（王志珍）

④ 5HT 酪氨酸受体激酶在睡眠、好斗及抑郁症等行为方面的功能；（饶毅）

⑤ Knock-in Dos 点突变研究它与 14-3-3 的体内相互作用；（罗金才） ⑥ RNAi 转基因果蝇库的建立。（Barry Dickson）。

(4) Chromatin plasticity and genome stability

Renjie Jiao Group

1) We have demonstrated that WRN physically and functionally interacts with the largest sub-unit of CAF-1 in human cells (paper published in *Oncogene*).

2) We have shown that dCAF-1-p180 is crucial in chromatin organization. It is essential for *Drosophila* development. Its mutation alters gene expression via changing the chromatin structural state. dCAF-1-p180 mutant animals show an unstable genome. Loss of partial function of dCAF-1-p180 causes male sterility. Loss of or ectopic dCAF-1-p180 expression in the eyes leads to apoptosis (submitted). Generation of mutant flies for the other two sub-units of dCAF-1 is in progress.

3) We have obtained the *CG9613* mutant which shows a small larvae phenotype. Preliminary results indicate that this gene is involved in cell growth and anti-oxidation. Currently we are examining its relationship with the insulin signaling pathway.

4) We have obtained *dRecQ4* and *dRecQ5* mutant flies and are currently investigating their possible roles in maintaining genome stability.

5) Collaborative projects: (a) Relationship of Bcd and chromatin modifying factors such as HDACs in controlling gene expression during *Drosophila* early development (Dr. Jun Ma). (b) Structural analysis of dCAF-1 and other protein complexes (Dr. Fei Sun). (c) How dHDAC6 controls α-synuclein and its role in the development of Parkinson's disease (Prof. Chih-chen Wang). (d) Functions of 5HT tyrosine kinase receptors in sleep, aggressiveness and depression etc. (Dr. Yi Rao). (e) In vivo interaction investigation of Dos and 14-3-3 via Knock-in point mutations (Dr. Jincai Luo). (f) Generation of RNAi transgenic fly library (Barry Dickson).

5、钙跨膜转运的分子机制及调节

姬广聚组

（1）细胞膜和胞内的许多受体/通道及其调节蛋白（如 RYRs、 IP3Rs、 FKBP、cADPR 及 PKA 等）在细胞的信息传递、生理功能的保持等方面发挥着重要作用。位于肌质网(SR)和内质网 （ER）上的 Ca^{2+} 释放受体由 Ryanodine 受体(RYR)和 IP3 受体(IP3R)组成。 这些受体(或通道)调控细胞内 Ca^{2+} 的释放， 进而调节着细胞的多种生物学效应，如肌肉收缩、卵细胞受孕、 激素分泌以及细胞凋亡等。FKBP12.6 为 FK506 的结合蛋白，我们的研究结果表明， FKBP12.6 选择性与心肌 SR 上 RYR2 结合，对心肌钙诱发的钙释放(CICR)发挥重要的调节作用。我们发现，在平滑细胞上 FKBP12.6 同样对 RYR2 的钙释放功能发挥着重要调节作用。同时，我们的预实验也提示所有钙释放受体的亚型在胰岛均有表达。

（2）目前我们在 RYR(ryanodine receptor)调节蛋白 FKBP12.6 基因敲除对心肌、平滑肌细胞 Ca2+ 释放受体功能影响、钙释放受体在发育期心肌细胞的表达及功能、 FK506 结合蛋白对β-细胞钙释放及胰岛素分泌影响、以及胚胎干细胞分化心肌细胞一些受体/蛋白的表达和功能研究方面， 已取得大量的实验数据，并获得一些非常有意义的新发现， 发表论文 3 篇（见后）。

6、利用人胚胎干细胞进行心肌组织工程修复

马跃组

本研究的目标是创建一个以人胚胎干细胞为基础的心肌细胞移植方法来治疗心力衰竭。通过用移植的心肌细胞来修复和替代坏死心肌组织，以达到改善损伤心脏的功能的目的。为了达到这一目标，我们将主要解决以下技术问题:

（1）如何高效的将人胚胎干细胞分化成心肌细胞;

（2）如何从分化的人胚胎干细胞中分离纯化心肌细胞;

（3）如何将心肌细胞移植到心脏并使之存活;

（4）如何对细胞移植的患者（或动物）进行生理评估;

（5）如何确保细胞移植的安全性。

（6）如何大规模培养人胚胎干细胞，并诱导分化成心肌细胞。

(5) The molecular mechanism and regulation of Ca^{2+} trans-membrane movement in mycoytes

Guangju Ji Group

Receptors / channels and their regulatory proteins on cell membranes (including intracellular membranes) play a major role in signaling conduction and physiological function maintenance of cells. The Ca^{2+} release receptors/channels on sarcoplasmic reticulum (SR)/ endoplasmic reticulum (ER) consist of ryanodine receptor (RYR) and the inositol 1,4,5-trisphosphate receptor (IP3R). These channels (receptors) control intracellular Ca^{2+} release, which in turn regulates diverse cellular processes such as muscle contraction, oocyte fertilization, hormone secretion and apoptosis etc. cDNA cloning studies have defined three subtypes of RYR (RYR1, RYR2, and RYR3) that are coded by distinct genes in vertebrates. Three forms of IP3R (IP3R1, IP3R2, and IP3R3) have also been identified and cloned. Our studies indicate that the FK506 binding protein 12.6 (FKBP12.6) selectively associates with RYR2, which plays a vital role in regulation of Ca^{2+} induced Ca^{2+} release (CICR) in myocytes. We have already made significant progress in the study of the effect of FKBP12.6 deletion on the expression and function of Ca^{2+} release channels/receptors in both myocytes and pancreatic beta cells. Three papers related to this study have been published so far.

(6) Myocardial tissue engineering repair using human embryonic stem cell

Yue Ma Group

The target of this research is to establish a heart failure therapeutic method, on the basis of the transplantation of myocardial cells derived from human embryonic stem cells. The transplanted cells can repair and replace the degeneration of myocardial tissues. To attain this target, we will mainly resolve the following technique problems:

1) How to derive myocardial cells from human embryonic stem cells efficiently;

2) How to select and isolate myocardial cells from differentiated human embryo stem cells;

3) How to transplant myocardial cells into the heart and ensure their survival;

4) How to evaluate the physiological level of the sufferer (or animal) treated by cell transplantation;

5) How to ensure the safety of cell transplantation;

6) How to culture human embryo stem cells on a large scale, and induce them to differentiate into myocardial cells.

7、基于离子通道的新型生物传感器的研究

靳刚组

随着各领域对检测灵敏度和精度要求的不断提高，目前的生物传感器已越来越不能满足需要。我们的研究工作针对离子通道这一特殊膜分子进行改造，偶合特意感应部分，构建成一种具有特意感应和自身放大功能的分子耦合器件，为发展新型的生物传感器奠定研究基础。

（1）构建 Kv2.1-xyz 离子通道，膜片钳技术检测其功能。

（2）拼接出 hKcsA 基因，构建 hKcsA 离子通道。

（3）构建 SBP-Kv1.2,SBP-linker-Kv1.2, SBP-Kv1.2-30AA,SBP-linker-Kv1. 2-30AA, Kv1.2-SBP,Kv1.2-linker-SBP,Kv1.2-30AA　SBP, Kv1.2-30AA-linker-SBP 离子通道，检测以上通道的可调控性。

（4）构建 Kv1.2-cmyc 离子通道。

（5）构建 Kv1.3-xyz 离子通道，膜片钳技术检测其功能。

（6）构建 Kv1.3 C 端缺失型离子通道，和 Kv1.3-Cter　cmyc 融合离子通道。

（7）构建 cmyc-Kv1.4 离子通道。

（8）负责平台原子力显微镜的管理工作。在进行技术支持的同时，主要进行了 DNA 与蛋白的相互作用、端粒 DNA 以及特殊蛋白的形貌及结构的研究工作。通过原子力显微镜力谱技术的应用为所内外的许多研究课题提供了积极的帮助。

测定脑脊液(CSF)中 tau 蛋白的含量可能是有前途辅助 AD 早期诊断以及预测 MCI 转归的生物学标志物之一。靳刚、赫荣乔课题组合作开展 CSF-tau 的研究，利用自主研制的无标记蛋白质芯片技术，探讨 CSF-tau 蛋白对于痴呆的早期诊断、鉴别诊断等作用。

同时，为推进所内纳米生物学研究工作的开展，开展协助和合作。

8、流感进化的规律及分子机制的计算生物学模拟

蒋太交组

（1）利用流感的全基因组序列，我们建立了模拟流感演化的新模型。这个模型对预测流感流行，疫苗制备和防治流感将会发挥重要作用。而且，通过模型的分析，我们发现流感流行的新规律。目前该文在送投中。

（2）与流感中心合作，通过计算机建模，我们发现导致 03-04 年人流感严重致病性的分子机制。该文正在准备之中。

(7) Research on a new type of biosensor based on an ion channel

Gang Jin Group

Current biosensors are increasingly unable to meet the ever more exacting requirements now seen in various fields. Our research work involves the transformation of an ion channel, which is a specific membrane protein, to construct a type of coupled ion channel with specific selectivity. This lays the foundation for a new type of biosensor with higher sensitivity and higher selectivity.

1) Construct Kv2.1-xyz ion channel and examine its function by patch-clamp technology.

2) Synthesize hKcsA gene and construct the hKcsA ion channel.

3) Construct SBP-Kv1.2, SBP-linker-Kv1.2, SBP-Kv1.2-30AA, SBP-linker-Kv1.2-30AA, Kv1.2-SBP,Kv1.2-linker-SBP, Kv1.2-30AA–SBP and Kv1.2-30AA-linker-SBP ion channels and examine the regulatory function of these channels.

4) Construct Kv1.2-cmyc ion channel.

5) Construct Kv1.3-xyz ion channel and examine its function by patch-clamp technology.

6) Construct Kv1.3 ion channel free of C terminal and Kv1.3-Cter–cmyc ion channel.

7) Construct cmyc-Kv1.4 ion channel.

8) Manage the AFM facility of the Institute of Biophysics. We not provide technical support and maintenance of the AFM, but also carry out our own research work, mainly focussed on DNA-protein interactions. By using AFM technology, we contribute to the work of many groups.

Measurement of protein tau in cerebrospinal fluid (CSF) is a useful method to diagnose AD and predict the state of MCI in clinical samples. The groups supervised by Jin Gang and Rongqiao He are cooperatively involved in this project. The measurement of CSF-tau from patients using an unlabeled-protein microarray is attempting to study the relationship between CSF-tau and early diagnosis and identification for AD.

At the same time, we are developing cooperations in nanobiotechnology.

(8) Computational analysis of human influenza evolution and its molecular mechanism

Taijiao Jiang Group

We proposed a novel model to interpret the evolutionary patterns of human influenza based on its whole genome sequence, and discovered new evolutionary characteristics of human influenza viruses. This work is being submitted for publication. In a collaborative work with China CDC, we elucidated the molecular basis that underpins the influenza outbreak in the 2003-04 influenza season. This work is also being prepared for publication.

9、coiled-coil 相互作用组的研究

蒋太交组

coiled coil 是一个相对简单的蛋白质超二级结构，由 2 个或以上的α螺旋组成的超螺旋结构。在自然界中，coiled coil 是一个介导蛋白质相互作用或形成蛋白质骨架的非常通用的结构域。许多研究表明，尽管 coiled coil 的链都是α螺旋，但它们之间的相互作用的专一性非常高。功能研究表明，coiled coil 的专一性的相互作用在病毒传染、膜融合和基因转录等生理途径中发挥重要作用。我们的研究目标是通过计算与实验相结合的方法在整个蛋白质组水平上预测由特定结构域，coiled coil 介导的蛋白质之间相互作用。在理论计算部分，我们已经综合数据挖掘的一般方法构建了一个由 coiled-coil 蛋白参与的蛋白质网络；目前正在发展预测 coiled coil 专一性相互作用的方法。在实验部分，我已经从酵母的基因组中克隆了近 600 个 coiled coil 链，并利用酵母双杂交分析了 coiled-coil 蛋白质相互作用对中的 coiled coil 相互作用。目前，正在发展荧光蛋白片断重组和蛋白质芯片等方法来实验确证酵母双杂交的结果。这是我实验室目前在系统生物学方面开展的一个大课题。

(9) Mapping the coiled-coil interactome

Taijiao Jiang Group

The coiled coil, a relatively simple protein supersecondary structure, consists of 2 or more α-helices that form a superhelical bundle. It is a generic motif or domain in nature, which mediates protein-protein interactions and forms a protein structure scaffold. Although coiled-coil strands are all α-helices, their associations are very specific, which plays an important role in many biological pathways including viral infection, membrane fusion and gene transcription regulation. Our research goal is to understand the specific interactions between coiled coils in a proteome-wide mode using both computational and experimental approaches. In the computational part, we constructed a coiled-coil protein network via data integration, and currently, are developing algorithms to predict the specific interactions for those coiled coils whose proteins were observed to interact. In the experimental part, we cloned over 500 coiled-coil strands from the yeast genome, and, in a yeast two-hybrid assay, tested the potential interactions between those coiled coils whose proteins were observed to interact. We are now utilizing fluorescent protein fragment complementation and protein assay methods to confirm the positives in a yeast two-hybrid assay.

（五）感染与免疫的分子基础

1、MTMR4 对 TGF-β信号通路的抑制性调控

唐宏组

转化生长因子β (TGF-β) 超家族由大量结构相关的多肽生长因子组成，是迄今为止了解的功能最为多样性的细胞因子，在细胞生长、分化、凋亡、基质形成、机体免疫、组织修复、组织分化、早期胚胎发育及肿瘤发生等过程中具有广泛的生物学作用。对 TGF-β信号通路的研究已经有了近 20 年的时间，这条信号通路也已经被研究的比较透彻，主要是 TGF-β与含有丝氨酸/苏氨酸激酶活性的膜受体结合，导致 II 型受体与 I 型受体形成复合体并使 I 型受体活化。活化的 I 型受体识别胞内相应的 Smads (R-Smads)，并使之发生磷酸化。磷酸化的 R-Smads 进而与 Smad4 (Co-Smad) 形成复合体而转移到细胞核中，与其他转录激活或者转录抑制因子的共同作用下，指导特异靶基因的转录。虽然这条信号通路相对比较简单，但是它可以呈现完全不同，甚至相反的调节功能。这种信号传导的多样性和复杂性是由于胞内不同蛋白对这条信号通路调节的结果。我们所研究的蛋白 MTMR4 就在 TGF-β信号通路中起到抑制性调控的作用。MTMR4 属于 myotubularin 家族，具有 FYVE 结构域和 PTP 结构域。我们研究发现 MTMR4 定位于早期内涵体，并且可以与 TGF-β受体 I 和 Smad3 相互结合。在细胞中过量表达 MTMR4 可以抑制 Smad3 磷酸化的发生，并且减弱了 Smad3 与 Smad4 复合体的形成，抑制了 Smad3 的核转位。进一步的 TGFR 和 Smad3 特异的报告基因实验的结果表明，MTMR4 对 TGF-β信号通路的下调有可能是直接作用于 Smad3 使其去磷酸化而发生的。

2、 肿瘤抗体及其靶分子作用机制研究

阎锡蕴组

1. 揭示 CD146 参与的细胞信号传导途径，阐明其介导内皮细胞迁移、血管生成和肿瘤转移过程的作用机制。

我们的研究表明，含有多种细胞因子及促血管生成因子的肝癌细胞培养上清可上调血管内皮细胞黏附分子 CD146 的表达，从而促进内皮细胞的迁移和血管生成；而抗 CD146 的单克隆抗体 AA98 可以通过与 CD146 的结合，抑制这种促血管生成作用。对其分子机制的研究表明，肝癌细胞培养上清可通过 p38 MAPK 上游途径激活 NF-B，使 MMP-9 活性上调，从而促进内皮细胞迁移，实现对血管生成的促进作用；而 AA98 可通过与内皮细胞表面的 CD146 分子的相互作用抑制 p38 MAPK 的磷酸化，从而抑制 NF-B 的激活，使血管生成过程得到抑制。我们的研究从正反两方面证实了 CD146 分子作为细胞膜受体参与血管内皮细胞信号传导过程，首次报道了 CD146 分子细胞信号传导过程涉及 NF-B 途径，揭示了 CD146 分子在血管生成中发挥作用的分子机制。

2. 利用荧光共振能量转移，发现 CD146 的二聚体化等膜表面结构特征。

为阐明 CD146 分子与其配体的相互作用介导的内皮细胞信号传导过程中的分子识别、构象变化和单分子行为，我们利用 FRET 等手段在单个活细胞水平上研究了 CD146 分子的二聚化现象。结果表明，在血管内皮细胞膜表面表达的 CD146 分子以单体和二聚体两种形式存在，而且，肿瘤细胞培养上清不仅提高 CD146 表达量，而且还促进 CD146 分子的二聚化，使细胞中二聚体形式比例增加。这一现象提示我们，CD146 的二聚体形式是介导与其配体相互作用，促进血管生成的功能性分子构象。

5. Molecular mechanisms of infection and immunity

(1) MTMR4 inhibits TGF-β signaling by dephosphorylation of Smad3

Hong Tang Group

TGFβ signaling controls diverse normal developmental processes and pathogenesis of diseases including cancer and autoimmune and fibrotic diseases. A key step in TGFβ signaling is ligand-induced phosphorylation of receptor-activated Smads catalyzed by the TGFβ type I receptor kinase. Myotubularin related protein 4 (MTMR4) is a FYVE domain-containing dual specificity protein phosphatase that dephosphorylates phosphotidylinositol 3-phosphate (PI3P), which belongs to the myotubularin family, a large eukaryotic group within the tyrosine/dual-specificity phosphatase super-family (PTP/DSP). Recently research suggests MTMR4 could homodimerize or heterodimerize with MTMR3, a homologue of MTMR4, in association with EGF receptor trafficking and degradation. We show that MTMR4 protein could inhibit the TGFβ-mediated signaling pathway in PAE cell lines as determined by reporter gene assay. To further investigate the role of MTMR4, we examined the protein/protein interaction between MTMR4 and TGFβ signal transducers. In vivo binding data showed that MTMR4 protein directly interacted with TGFβ receptor I (TβR-I) in 293T cell lines but not with TGFβ receptor II (TβR-II) and Smad3. We also found that MTMR4 protein co-localized with TβR-I in the early endosomes of PAE cells and inhibited TGF-β-mediated nuclear translocation of Smad3. Furthermore, we demonstrate that MTMR4 protein abrogated the phosphorylation of Smad3 and the heterodimerization of Smad3 and Smad4. To further explore the mechanism of MTMR4 down-regulation of TGFβ signaling pathway, we examined the phosphorylation level of TβRI in the present of MTMR4 with TGFβ stimulation. We show that MTMR4 could dephosphorylate P-TβRI. The PTP_motif and FYVE domain both play the critical role in the dephosphorylation function of MTMR4. We show that TβRI could not be dephosphorylated by MTMR4C407S and MTMR4ΔFYVE, because PTP_motif has the function of protein tyrosine phosphatase and the FYVE domain decides the localization. These results indicate that MTMR4 modulates TGFβ signaling through interaction with TβR-I and Smad3, which takes place in the early endosomes, and the dephosphorylation of Smad3 mediated by MTMR4 is an effective mechanism for governing negative feedback in TGFβ signaling.

(2) Mechanistic studies of an anti-tumor antibody

Xiyun Yan Group

1) Anti-CD146 monoclonal antibody AA98 inhibits angiogenesis via suppression of nuclear factor-KB activation

Our previous study showed that an anti-CD146 monoclonal antibody (mAb), AA98, which inhibited cell migration, angiogenesis, and tumor growth. However, the underlying mechanism was not elucidated. The objective of our study was to understand the mechanism by which mAb AA98 inhibits the endothelial cell migration and angiogenesis. Our data showed that the engagement of mAb AA98 with membrane protein CD146 inhibited p38 mitogen-activated protein kinase phosphorylation, suppressed NF-KB activation, and downregulated matrix metalloproteinase 9 and intercellular adhesion molecule 1 expression, suggesting that the suppression of NF-KB is a critical point for the inhibitory function of mAb AA98 on endothelial cell migration, angiogenesis, and tumor metastasis. These results will provide clues for a better understanding of the mechanisms underlying tumor angiogenesis as well as antiangiogenesis therapy.

2) Visualization of CD146 dimerization and its regulation in living cells

The adhesion molecule CD146 is over-expressed on activated endothelium as an angiogenesis marker. However, the CD146 molecular organization on the cells is unknown. Here we found that the dimerization of CD146 occurs in both normal and tumor cells. However, the dimer/monomer ratio was higher in tumor cells than in normal cells. Moreover, we found that CD146 dimerization was up-regulated by tumor conditional medium through the NF-kappa B pathway and down-regulated by mAb AA98. To further confirm that CD146 dimerization occurs in living cells, we used fluorescence resonance energy transfer (FRET) with melanoma Mel888 cells co-expressing CFP/YFP-tagged CD146 fusion proteins. We observed a strong FRET signal produced by these two fluorescence-tagged proteins. The FRET efficiency reached 20.1%. Our data provide the first evidence that CD146 dimerization occurs in living cells and is regulated within the tumor microenvironment, implying that dimerization of CD146 may be associated with malignancy.

3、细胞因子介导的肿瘤间质细胞之间的相互作用及其对肿瘤生长与排斥的影响

秦志海组

（1）虽然 IFNγ在肿瘤免疫中的重要作用无可置疑，但是人们对其来源以及它是如何被诱导的还了解甚少。我们通过对多种骨髓嵌合小鼠的研究表明，肿瘤免疫中所必需的 IFNγ主要是由造血细胞产生的。令人惊讶的是，T 细胞产生的 IFNγ对肿瘤免疫不是必需的。在经过免疫的-R>-骨髓嵌合小鼠中，仅天然免疫细胞具有分泌 IFNγ的能力，肿瘤的生长仍能够被有效抑制。进一步实验证明天然免疫细胞如 $NK1.1^+$ cells 和 $CD11b^+$细胞在 T 细胞的辅助下可以分泌足够量的 IFNγ。T 细胞和天然免疫细胞之间的相互作用可能是 IL-2 介导的。我们的结果阐明了 T 细胞如何与天然免疫细胞相互作用通过 IFNγ介导肿瘤的排斥，这无疑对肿瘤免疫治疗的进一步完善有重要的提示作用。

（2）肿瘤坏死因子（TNF）存在两个受体，以前的工作认为 TNF 的大部分功能都是通过受体 1（TNFR1）来实现的，而关于 TNFR2 所介导的作用研究甚少。利用 TNF 受体单敲除和双敲除小鼠作为动物模型，我们发现无论在正常或是在 T、B 淋巴细胞缺陷的情况下，TNFR2 在体细胞的单独表达都能有效地介导 TNF 的抗肿瘤作用。免疫组化分析表明，TNF 可以通过 TNFR2 招募大量巨噬细胞对肿瘤组织的侵润并且强烈地抑制肿瘤内的血管新生。在体外，TNF 能够激活 TNFR1 缺失的巨噬细胞产生大量的 NO。在肿瘤生长早期，用 NO 合成抑制剂 L－NAME 处理小鼠可以全部去除 TNF 对血管新生和肿瘤生长的抑制作用。结果首次证明 TNFR2 在机体天然免疫细胞上的表达可以独立介导 TNF 的抗肿瘤作用，而 NO 及其对肿瘤血管新生的抑制是这一过程所必需的。

4、肿瘤发生的分子基础和免疫活性细胞介导的肿瘤清除机制

范祖森组

（1）新抑癌基因 pp32 的抑癌机制

我们发现新抑癌基因 pp32 与 SET 等蛋白形成 SET 复合体，参与颗粒酶 A 介导的细胞凋亡。以 pp32 为诱饵蛋白，采用酵母双杂交系统筛选出 8 个与 pp32 相作用的蛋白，其中组蛋白 H3, RYBP 和 TRAP1 与 pp32 的相互作用已被证实。研究证实 pp32 通过调节组蛋白 H3 的乙酰化和磷酸化抑制基因的转录而控制细胞生长。这些研究成果已发表在 *Cell Death Differ* 杂志。正进一步研究 pp32 如何通过其作用蛋白 TRAP1 参与 TNFR 信号及 pRb 调节途径调控细胞生长分化。并与龚为民教授课题组合作解析 pp32 及其作用蛋白的结构，从结构与功能的关系上，以期阐明 pp32 抑制细胞生长的机制。

（2）免疫活性细胞介导的肿瘤清除机制

我们正在探明孤儿颗粒酶（K、H 和 M）在 CTL/NK 介导的靶细胞杀伤中的作用。首次发现颗粒酶 K 介导了快速的 caspase 非依赖性的以 DNA 单链断裂为特征的靶细胞凋亡，论文刚被 *Cell Death Differ* 接受发表。同时研究发现颗粒酶 K 能够切割 Bid 为其活性形式 tBid, 攻击线粒体使其释放 ROS 和细胞色素氧化酶 C，加速靶细胞的死亡。我们研究证实颗粒酶 M 能够引起 caspase 依赖的 DNA 双链断裂的靶细胞凋亡，研究成果发表在 *JI* 杂志。我们首次阐明了颗粒酶 H 能够导致 caspase 依赖性的具典型凋亡特征的靶细胞死亡。还与饶子和院士和孙飞教授课题组合作以期解析穿孔素和一些颗粒酶的结构。在结构和功能的基础上，深入探明颗粒酶 K、M 和 H 在 CTL/NK 介导肿瘤杀伤中的作用。

(3) Cytokine-mediated interaction of tumor stroma cells and its effects on tumor growth and rejection

Zhihai Qin Group

(1) Although the importance of IFNγ in tumor immunity has been well demonstrated, little is known about its source and how it is induced. By using various bone marrow chimeric mice, we show here that IFNγ essential for tumor immunity is solely produced by hematopoietic cells. Surprisingly, IFNγ derived from T cells is not necessary for tumor immunity. In the immunized mice, in which only innate immune cells have the IFNγ-producing potential, tumors were efficiently rejected. The innate immune cells, such as $NK1.1^+$ cells and $CD11b^+$ cells, can provide sufficient amounts of IFNγ, which requires, however, the help of T cells. The close co-operation between T cells and innate immune cells during tumor regression is likely mediated by IL-2. Together, our results clearly illustrate how T cells co-operate with innate immune cells for IFNγ-mediated tumor rejection and this may have important indication for clinical trials of tumor immunotherapy.

(2) Tumor necrosis factor (TNF) binds to two different receptors. While most of its functions are contributed to TNF receptor (TNFR) 1, the independent role of TNFR2 is still largely unknown. Using TNFR single or double knockout mice, we show here that the expression of TNFR2 alone on host cells was sufficient to suppress the growth of TNF secreting tumors in both immune competent and T/B lymphocyte-deficient SCID mice. Histological studies showed that TNF recruited via TNFR2 large numbers of macrophages and efficiently inhibited angiogenesis in the tumor. In vitro, TNF activated TNFR1-deficient macrophages to produce nitric oxide (NO). Treatment of TNFR1 knockout mice with L-NAME, a specific NO synthase inhibitor, almost completely eliminated TNF-induced angiostasis and tumor suppression. Our results demonstrate for the first time that TNFR2 expressed on host innate immune cells is sufficient to mediate the anti-tumor effect of TNF and NO is necessary for this process, possibly by inhibition of angiogenesis in the tumor.

(4) The molecular mechanisms of tumorigenesis and the killing mechanisms of tumor cells by NK and CTL

Zusen Fan Group

1) The molecular mechanisms of tumor suppression by the new suppressor pp32

The new tumor suppressor pp32 and SET forms SET complex that involves in GzmA-mediated cell death. We identified 8 pp32-associated protein candidates and verified pp32 interaction among histone H3, RYBP, TRAP1. We found pp32 specifically binds to histone H3 and blocks its acetylation and phosphorylation leading to growth arrest. We next want to determine how pp32 inhibits cell growth through interaction with TRAP1 and further investigate its inhibitory action by its crystal analysis via collaboration with Dr. Gong's Lab.

2) Killing mechanisms of tumor cells by NK and CTL

Granule-mediated cytolysis is the major pathway for killer lymphocytes to kill pathogens and tumor cells. We found human GzmK triggers rapid cell death independently of caspase activation with single stranded DNA nicks that is similar to GzmA. GzmK can also induce rapid reactive oxygen species (ROS) generation and collapse of mitochondrial inner membrane potential ($\Delta\Psi m$). We recently demonstrated that GzmM induces caspase-dependent apoptosis with DNA fragmentation through direct cleavage of ICAD. We first verified GzmH induces caspase-dependent death with DNA fragmentation. We next want to elucidate the functions of orphan Gzms based on their structures by collaborating with Drs. Rao's and Sun's Labs.

5、逆转录病毒与宿主细胞相互作用机理研究

高光侠组

本实验室的主要研究方向是逆转录病毒与宿主细胞相互作用关系，包括两方面:

（1）利用体细胞遗传学方法筛选克隆具有抗 HIV 活性的宿主细胞因子: 在与病毒长期共存过程中，宿主进化产生了多种抗病毒机制，其中一种机制是表达宿主限制性因子。宿主限制性因子可以作用于病毒复制周期的不同环节。我们建立以一种体细胞遗传学筛选方法，用于筛选具有抗 HIV 活性的宿主细胞因子。

（2）宿主细胞抗病毒蛋白 ZAP 作用机理研究: ZAP 是我们利用体细胞遗传学筛选方法克隆的具有抗病毒活性的宿主细胞限制性因子，能够特异性地抑制几种病毒的复制，包括小鼠白血病病毒、辛德比斯病毒、埃波拉病毒。通过对 MLV、SIN 受抑制机制的研究，发现 ZAP 通过特异性地降低细胞质中病毒 mRNA 的稳定性从而抑制病毒的复制。ZAP 本身不具有 RNA 酶的活性，但具有反式作用因子的功能，能够直接结合特定的靶 RNA，并招募 RNA 外切酶复合体 Exosome 实现对靶 RNA 的降解。ZAP 抗病毒机制的研究不仅可能为病毒的防治提供新的策略和技术手段，也将有助于我们更深入了解 RNA 稳定性的调控机理。

6、共刺激信号途径的免疫调节作用研究

王盛典组

（1）以 HBV 转基因小鼠为基础建立慢性乙肝动物模型，建立 HBV 特异 T 细胞克隆和 TCR 转基因小鼠，通过增强或阻断 4-1BB、LIGHT 和 PD-1 共刺激分子受体的信号通路来研究这些共刺激信号途径对 HBV 感染免疫耐受的调节作用,尤其对 HBV 特异性 T 细胞功能和肝脏慢性炎症反应的调控作用。此外，与 302 医院合作研究慢性乙肝病人不同发病阶段共刺激分子的表达，以及共刺激信号途径对外周血免疫细胞功能的调节作用。

（2）以肿瘤肝转移、肺转移，和皮下移植肿瘤为模型，通过建立表达不同功能共刺激分子的肿瘤细胞系，给小鼠注射抗共刺激分子抗体、和表达共刺激分子的表达载体，研究 B7-H1/B7-DC—PD-1 共刺激信号途径对机体抗肿瘤免疫反应的调控作用，以及调控该信号途径对肿瘤的治疗作用。

（3）用化学诱变剂在共刺激分子 CD24 基因缺陷小鼠上诱发肿瘤发生，研究 CD24 对肿瘤发生和发展的影响及作用机制。同时，用该原发肿瘤小鼠模型研究共刺激信号途径对肿瘤免疫反应的调控作用和调节机制。

（4）比较高致病性和底致病性禽流感病毒感染 DCs 和 MΦ细胞后，细胞功能的差异，主要是 IL-1、IP-10、TNF-α等炎症因子产生的差异，进而探讨它们在高致病性禽流感病毒感染导致的肺部病理损伤中的作用及致病机制。

（5）制备抗多种共刺激分子单克隆抗体，以期筛选出具有不同功能特性的单抗，为共刺激信号途径的免疫调节作用研究提供更多研究工具。

(5) Studies on the mechanisms underlying retrovirus-host interaction

Guangxia Gao Group

The main interest of our laboratory is in the molecular mechanisms underlying retrovirus-host interaction. Current research is focused on the following aspects:

1) Cloning of cellular anti-HIV factors: vertebrates have evolved multiple mechanisms to prevent virus infection. For retroviruses, one mechanism is through host restriction factors, which target various steps of the viral life cycle. To identify novel anti-HIV factors, we have developed a somatic cell genetic screening method. This project is ongoing.

2) Mechanistic studies on ZAP: the zinc-finger antiviral protein (ZAP) is a host factor we recently cloned that inhibits the replication of Moloney murine leukemia virus, Sindbis virus and Ebola virus by preventing the accumulation of viral mRNA in the cytoplasm. Our previous studies revealed that ZAP directly binds to specific viral RNA sequences through the zinc-finger motifs. Recently, we demonstrated that ZAP recruits the RNA processing exosome, a multiple-component exoribonucleases complex, to degrade the target RNA. Furthermore, we identified a cellular DEAD box RNA helicase that is required for ZAP's activity. The long term goal of this project is to construct a framework of the proteins involved in ZAP-mediated mRNA degradation.

(6) The roles of co-signaling pathways in regulation of immune responses

Shengdian Wang Group

(1) We establish mouse mode of chronic HBV hepatitis based on HBV transgenic mice, and prepare HBV-specific T cell clones and HBsAg peptide-specific TCR transgenic mice, manipulate the immune responses by enhancement or blockade of signals of 4-1BB, LIGHT, and PD-1 co-signaling receptors to study the regulatory roles of co-signaling pathways in immune tolerance of chronic HBV infection, particularly in the functions of HBV-specific T cells and chronic inflammation in liver. In addition, we collaborate with 302 hospital to study the expression of co-signaling molecules in different stages of chronic HBV hepatitis, and the regulatory roles of co-signaling pathways in function of periphery immune cells in patients.

(2) We establish stable tumor cell lines which express the co-signaling molecules with different co-stimulatory functions, treat the mice with liver or lung tumor metastasis, or subcutaneously transplanted tumor with injection of anti-costimulatory molecules antibodies, or expression vectors of cositmulatory molecules to study the regulatory roles of B7-H1/B7-DC—PD-1 pathway in anti-tumor immune response and therapeutic effects of manipulation of this pathway.

(3) We induce formation of tumor in CD24 knock-out mice by inoculation of carcinogen to study the effects of CD24 on initiation and development of tumor. Meanwhile, we utilize this premary tumor model to study the effects and mechanism of co-signaling pathways on regulation of anti-tumor immune responses.

(4) We analyze the difference of the functions of DCs and MΦ between infected with high pathogenic and low pathogenic avian flu virus, particularly the difference of production of inflammatory cytokines, such as IL-1, IP-10 and TNF-α. We will further investigate the roles of these cytokines in pathogenesis of lung during infection of high pathogenic avian flu virus.

(5) We prepare kinds of anti-co-signaling molecules mAbs, and select out the mAbs with different specific functions in order to provide more researching tools for the studies of immunological roles of co-signaling pathways.

7、病毒感染、复制及与宿主相互作用的机理

邓红雨组

（1）以小鼠疱疹病毒-68（MHV-68)为肿瘤相关疱疹病毒的模型，本课题组从以下几个方面对该病毒的复制机理展开了研究:

① 基因表达的转录调控及表观遗传学: 病毒编码的复制和转录因子 RTA 在 MHV-68 生命周期中起着分子开关的重要作用。我们的研究表明，*rta* 基因启动子上组蛋白的乙酰化能激活 MHV-68 从潜伏期进入裂解期。我们还发现，除自激活外，*rta* 基因还受病毒颗粒蛋白的调控，具体机理正在研究中。

② 基因组复制: 鉴定了 MHV-68 基因组的左端复制子，并详细研究了相关的顺式元件与反式因子。

③ 蛋白功能与相互作用：结合遗传学与蛋白质组学选择性地对 MHV-68 的若干蛋白进行了研究，目前主要研究两个病毒间质蛋白 ORF33 和 ORF52（属于病毒颗粒蛋白）。

（2）以鼠肝炎病毒（MHV-A59）为急性感染和免疫的模型，通过靶向重组，构建携带 T 细胞表面抗原的重组病毒，研究病毒感染后小鼠 T 细胞的各种反应。

(7) Mechanisms of viral infection, replication and virus-host interactions

Hongyu Deng Group

1) We investigate the replication mechanisms of murine herpesvirus-68 (MHV-68) as a model for tumor-associated herpesviruses. Specifically, we have carried out research in the following 3 areas:

(i) Transcriptional and epigenetic regulation of MHV-68 gene expression. We have focused on regulation of the RTA gene, whose product is the "molecular switch" for MHV-68 life cycle. We have shown that histone acetylation plays an important role in mediating reactivation of MHV-68 from latency. We have also demonstrated that the *rta* promoter is activated by virion components as well as RTA protein itself. We are currently dissecting the detailed mechanisms.

(ii) Viral genome replication. We have identified a 1.1-kb origin of lytic replication (*ori*Lyt) located toward the left viral genome. Through a systematic approach, we have identified the critical cis-elements and cellular factors involved in mediating viral DNA replication. We are further studying the role of viral proteins in this process.

(iii) Functions of viral proteins and protein-protein interactions. We combine genetics and proteomics approaches to study the function of viral proteins and their interaction with other viral and cellular partners. We are currently studying two viral tegument proteins, ORF33 and ORF52.

2) We employ murine hepatitis virus-A59 (MHV-A59) as a model system to study acute viral infection and immunity. Through targeted recombination, we are generating a mutant MHV-A59 that carries T-cell epitopes to study T cell responses to coronavirus infection in vivo.

（六）蛋白质药物与多肽药物

1、纳米胶束增强抗肿瘤药物活性和疗效的机制研究

梁伟组

肿瘤细胞的转移和扩散及其耐药性是肿瘤治疗的最大障碍，如何提高药物对肿瘤组织选择性和渗透性，尤其提高药物对肿瘤细胞的选择性并能跨膜输送至细胞内达到有效浓度已成为肿瘤治疗的新的挑战。构建高效低毒的、理想的、即实现组织靶向渗透又实现细胞靶向的药物纳米载体受到国内外的广泛重视。本项目拟构建基于 PEG-PE 胶束装载蒽环类抗肿瘤药物的纳米载体, 采用亚细胞器标记定位、单分子测定等生物物理技术，系统地研究它们的组装机制、结构特性与体内外抗肿瘤活性的关系，阐明载药纳米颗粒的材料、尺度、结构对药物发挥其药理活性和疗效的影响，为合理设计和构建用于疾病治疗的药物纳米输送载体提供最新的策略和途径，为建立科学的药物纳米输送载体的质量评估体系提供理论依据。

2、调控黑色素形成的分子机制的研究

殷勤伟组

虽然已有许多有关 MITF 和 MC1R 对黑色素形成的调控研究，但潜在的分子机制的解析乃有待进一步深入。对此，我们采用 RNA 干扰技术，来研究抑制恶性黑素瘤细胞株 A375 的 MC1R、MITF 基因表达后，MC1R 和 MITF 基因之间的调控关系以及他们与黑色素形成的靶基因之间的相互作用。方法: RT-PCR 检测 MC1R、MITF、TYR、TYRP-1 基因 mRNA 水平的变化，利用测定黑色素含量检测蛋白水平的改变。用台盼蓝活细胞计数法检测其对细胞增殖的影响。结果: RT-PCR 检测表明 MITF-siRNA 能显著下调 MC1R、MITF、TYR 和 TYRP-1 基因的表达，而 MC1R- siRNA 却只能抑制 MC1R、TYR 和 TYRP-1 基因的活性。此外，这两个小 RNA 都能引起黑色素含量的明显降低，此结果揭示 MC1R 和 MITF 独自都不能维持正常的黑色素形成，TYR 和 TYRP-1 基因的激活需要操纵子的 M 盒子中 CREB 和 MITF 分子的相互作用。进一步的分子分析试验在进行中，同时我们也发现脂质体包裹的 siRNA 对 A375 细胞的毒性远比现在临床常用的色斑去除剂小的多。更令人感兴趣的是 MITF-siRNA 可抑制恶性黑素瘤的生长，导致癌细胞的凋亡。提示这种小 RNA 具有成为治疗恶性黑素瘤的潜在药物的可能。

6. Protein and Peptide Drugs

(1) Improving penetration in tumors with nano-assemblies of phospholipids and doxorubicin

Wei Liang Group

Solid tumors account for more than 85% of cancer mortality. To obtain nutrients for their growth and to metastasize to distant organs, cancer cells in solid tumors utilize two strategies: (1) growth around existing vessels and (2) stimulation of vessel formations. These new vessels are abnormal in structures characterized by leakage, tortuousness, dilation, and a haphazard pattern of interconnection. The abnormal tumor structure and blood flow is one of major factors that plague the treatment of solid tumors. To reach cancer cells in optimal quantities, a therapeutic agent must be able to run through its imperfect blood vasculature to the tumor, to cross vessel walls into the interstitial, and to penetrate multiple layers of solid tumor cells. Recent studies have demonstrated that poor penetration and limited distribution of doxorubicin in solid tumor are main causes of clinical resistance to cancer therapy.

Strategy to reduce tumor interstitial pressure by modulation of vascular endothelial barrier function to improve chemotherapeutic drug penetration in tumor have been developed, this approach could enhance the antitumor activity of chemotherapeutic drug, with no evidence of increased toxicity. The three dimensional penetration of macromolecules, depending on their molecular weight, into tumor interstitium from the vascular surface has been studied using the dorsal skin fold window chamber model, with laser-scanning confocal microscopy, indicating that increasing molecular weights significantly decrease penetration into tumor from vascular surface, but increase retention time, dextrans with a molecular weight between 40 and 70 kDa provide the greatest tumor penetration and accumulation. Based on these findings, an optimal nano-carrier of chemotherapeutic drug can be designed for treatment of solid tumors.

We investigate whether PEG-PE micelles could enhance the penetration of DOX in tumors, and then improve its efficacy. The PEG-PE molecule consists of both hydrophilic PEG and hydrophobic PE segments, which is a good amphiphilic co-polymer for forming micelle. PEG-PE micelles have a low critical micelle concentration (CMC) and small size (approx. 10 nm), which make PEG-PE micelles as appropriate nano-carriers of drug. We demonstrate that DOX can be packed tightly with PEG-PE, thus enhances its cellular uptake and cytotoxicity, and alters its cellular distribution, mainly located in lysosomes. We provide evidence that M-DOX can efficiently penetrate into tumor and increase the amount of DOX that reaches cancer cells, resulting in strong inhibition of tumor growth with reduced drug-related toxicities.

(2) Cooperation of MC1R and MITF is required for maintenance of normal outputs of tyrosinase and melanin

Qinwei Yin Group

Although it is known that both MC1R and MITF are related to the regulation of melanin synthesis, the underlying mechanisms remains poorly elucidated. In this study, using a siRNA-mediated gene silencing technique, we showed clearly that MC1R-siRNA could effectively silence the expression of MC1R gene and induce a remarkable reduction in the tyrosinese (TYR) and tyrosinase-related protein 1 (TRP1) levels. Similar gene silencing results were observed with MITF-siRNA. However, the MC1R-siRNA could not cause a detectable change in the MITF mRNA while the MITF-siRNA significantly resulted in the down-regulation of MC1R gene. These findings suggest that neither MC1R nor MITF alone maintains the transcriptional level of TYR and (TRP1) genes. Moreover, these two siRNAs could separately result in an obvious inhibition of melanin synthesis. Compared with chemical depigmenting agents such as kojic acid and arbutins, the both siRNAs were characterized with high efficiency, low dose and no cytotoxicity. In addition, MITF-siR has been shown to inhibit the proliferation of melanoma cells. Thus, the present results indicate that MITF plays important roles in melanin synthesis and melanoma inhibition. Therapeutic application of high potent MITF-siRNA may provide a novel strategy for the prevention and treatment of hyperpigmentation disorders and malignant melanoma.

3、免疫相关疾病中细胞因子治病机理研究

唐捷组

巨噬细胞迁移抑制因子（MIF）是早期发现的细胞因子之一, 在固有性免疫系统中有着重要的作用。 MIF 有两条可能的信号转导通路。 一条是 CD74 受体介导通路，激活 ERK-1/2，另一条通路与 MIF 的内吞有关，MIF 通过与 Jab1 的相互作用增加 p27Kip1 的水平，从而对细胞周期进行调节。我们的研究发现: MIF 的胞吞是由其受体 CD74 介导的，MIF 可以直接通过胞吞进入细胞核内，MIF 将 Jab1 滞留在核内，阻止其将 p27Kip1 带出核外降解。这些发现将改写目前公认的 MIF 信号转导模型，完善生物学界对 MIF 信号转导通路的认识。 一篇论文正在整理中。

MIF 的高水平生成在急性感染中是有害的。在动物模型中，抑制 MIF 的作用对于败血症具有明显的治疗效果。开发针对 MIF 的单克隆抗体的主要困难在于人源与鼠源的 MIF 有 95%以上的同源性，小鼠将人源的 MIF 抗原当作自身抗原而产生免疫耐受，无法得到高质量的抗体。 我们为此开发了一个新方法，得到了高亲和力的抗 MIF 抗体，在细胞水平上能够拮抗 MIF 的生物学功能， 并能够在小鼠的败血症模型中表现出很好的疗效。目前已申请了方法学和抗体序列的专利。

强制性脊柱炎是一种常见的慢性炎症性风湿性疾病，近年来尝试应用抗TNFα生物制剂治疗取得非常好的疗效，但TNF-α在强制性脊柱炎中起的作用还不是很清楚。解放军301医院风湿科进行了TNF-α拮抗剂治疗强制性脊柱炎的临床实验，我们利用Elispot, FACS等免疫检测方法，对病人治疗前后外周血中多种细胞功能的变化进行了深入研究，发现TNF拮抗剂治疗后病人的T细胞活性降低, 伴随着调节性T细胞增加和DC细胞数量增加。这些发现提示了巨噬细胞—— TNF-α——DC细胞——调节性T细胞——T细胞活性——免疫病理的相关性，具有很强的创新性，一篇论文正在写作中。

(3) Pro-inflammatory cytokines and immune-related diseases – basic mechanism and applications

Jie Tang Group

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that plays an important role in macrophage activation. We studied its signal transduction pathways in macrophage cell line Raw264.7. It was known that MIF can initiate signaling cascade through its receptor CD74. There were also studies indicating its interaction with Jab-1, an intracellular protein that traffic between cytoplasm and nucleus. We found that MIF can enter cell through receptor mediated endocytosis. It goes through endosome-lysosome pathway and ends up in the nucleus. MIF interacts with Jab-1 in the nucleus preventing it from going out to the cytoplasm. The retention of Jab-1 in the nucleus leads to accumulation of p27, a cyclin inhibitor and induces cell cycle arrest of the cell. The above novel observations will change the current model of MIF signaling. A manuscript is in preparation.

MIF is also a good drug target for sepsis, due to its function in the later stage of inflammatory cascade. We are developing monoclonal antibody agaisnt MIF to treat sepsis and the auto-immune diseases. Since the human and mouse MIF proteins are highly conserved, it is hard to raise good antibody against the human antigen in mice. We developed a novel method to break immune tolerance towards highly conserved antigen in mice and got high affinity and neutralizing monoclonal antibody against MIF. We are in the process of humanizing the antibody and express it in mammalian cell line. Two patents have been filed to cover the novel method of antibody development and the sequence of the MIF neutralizing antibody.

Anti-TNF-alptha therapy has been successfully applied to ankylosing spondylitis patients. We used patient serum samples before and after TNF-alpha antagonist treatment to study the cellular effects of TNF-alpha blockage. Our data indicated that T cell reactivity has been reduced after TNF-alpha antagonist treatment. This change is corelated with increasing number of circulating MHC Class II dendritic cells and regulatory T cells. We proposed a model in which TNF-alpha antagonist treatment blocks the maturation of antigen presenting cells and this in turn reduced the T cell reactivity. The accumulation of semi-mature antigen presenting cells may promote the generation of regulatory T cells, which in turn suppressed the T cell function. A manuscript is in preparation.

五、人才培养

（一）博士后:

在站: 闫小雪 许凌峰 龚 勇 王新宇 徐平勇 尹长城 张金华 米志强 赵同标
张志栋 李香群 杜刚军 张发云 李玉明

出站: 张春玲 张红梅 李 辉

（二）博士

2006 年取得博士学位 25 人

王占新 汪 涛 望 超 严汉池 王 睿 朱德裕 范成鹏 李德峰 刘 琳 程中军
黄春娟 李升建 王 敏 张英豪 段建发 卢宏超 张治华 张 卓 高利增 张佰茹
陈亚丽 纪 昕 刘兴军（代培） 缺杨福愉 2 名博士名单

2006 年在读博士生 169 人

（三）硕士

2006 年取得硕士学位 8 人

王 杰 郭晓芸 张 勇 石宝晨 李志强 陈 芳 唐 昱 张勇琴

2006 年在读硕士生 108 人

（四）学生获奖

柳振峰	2006 年度全国优秀博士学位论文奖
朱永群	院长优秀奖
殷 雷	刘永龄奖学金
高利增	地奥奖学金一等奖
李德峰	地奥奖学金
朱德裕	BHP Billiton-CAS 奖学金
陈舜梅	第四届国际结构基因组大会最佳墙报奖
江 轶	九源奖学金二等奖
张勇、吴涛、王洁	九源奖学金 三等奖

V. Training

1. Post-Doctoral

Current: Xiaoxue Yan Lingfeng Xu Yong Gong Xinyu Wang Pingyong Xu
Changcheng Yin Jinhua Zhang Mi Zhiqiang Tongbiao Zhao Zhidong Zhang
Xiangqun Li Gangjun Du Fayue Zhang Yuming Li

Completed: Chunling Zhang Hongmei Zhang Hui Li

2. Doctoral Students

Students Conferred with the PhD Degree in 2006

Zhanxin Wang Tao Wang Chao Wang Hancai Yan Rui Wang Deyu Zhu
Chengpeng Fan Defeng Li Lin Liu Zhongjun Cheng Chunjuan Huang Shengjian Li
Min Wang Yinghao Zhang Jianfa Duan Hongchao Lu Zhihua Zhang Zhuo Zhang
Lizeng Gao Bairu Zhang Yali Chen Xinji Liu Xingjun Liu

The National Laboratory of Biomacromolecules currently has 169 Doctoral students.

3. Master's Students

Students Conferred with the Master's Degree in 2006

Jie Wang Xiaoyun Guo Yong Zhang Baochen Shi
Zhiqiang Li Fang Chen Yi Tang Yongqin Zhang

The National Laboratory of Biomacromolecules currently has 108 Master's students.

4. Student Awards

Zhengfeng Liu	National Outstanding PhD Dissertation
Yongqun Zhu	CAS President's Award
Gao Lizeng	Diao Scholarship (First Class)
Defeng Li	Diao Award
Lei Yin	Liu Yonglin Award
Deyu Zhu	BHP-CAS Scholarship
Yi Jiang	Fudan University, Tan Jiazhen Fund, Life Science Jiuyuan Scholarship (Second Class)
Yong Zhang, Tao Wu, Jie Wang	Fudan University, Tan Jiazhen Fund, Life Science Jiuyuan Scholarship (Third Class)

（五）导师获奖

获奖人	奖励名称
常文瑞	中国科学院研究生院优秀教师
王大成	中国科学院研究生院优秀教师
陈润生	中国科学院研究生院优秀教师
范祖森	“新世纪百千万人才工程”国家级人选

5. Graduate Student Supervisor Awards

Prof. Chang Wenrui	CAS Outstanding Supervisor Award
Prof. Wang Dacheng	CAS Outstanding Supervisor Award
Prof. Runsheng Chen	CAS Outstanding Supervisor Award
Prof. Zusen Fan	National Award for “Outstanding Individuals of the New Century”

六、获奖统计

集体奖

获奖名称	奖励类别	等级	获奖人	获奖时间
全国杰出专利工程技术评审预展	发明专利	优秀	阎锡蕴,杨东玲,沈毅,冯静,林芸等。	2006．5

个人奖

获奖人	奖励类别	获奖时间
饶子和	2006 年度陈嘉庚科学奖	2006
饶子和	2006 年的里雅斯特科学（医学）奖	2006
徐涛	第十届中国青年五四奖章	2006
常文瑞	中国科学院研究生院优秀教师	2006
王大成	中国科学院研究生院优秀教师	2006
王志珍	全国三八红旗手	2006
陈畅	“SFRR Asia Award for 2006” the 13th International Congress of the Society for Free radicals, Davos, Switzerland.	2006
阎锡蕴	中国科学院五好文明家庭	2006

VI. Achievements

1. Group Awards

Prize	Type	Level	Awardee	Year
National Outstanding Patent Award	Patent	Excellent	Yan Xiyun, Yang Dongling, Shen Yi, Feng Jing, Lin Yun et al.	2006

2. Individual Awards

Awardee	Grade	Year
Zihe Rao	Chenjiageng Science Awards	2006
Zihe Rao	The Trieste Science Prize	2006
Tao Xu	The 10th Chines Youth “WUSI” Award	2006
Wenrui Chang	Outstanding Graduate Student Supervisor Award of CAS	2006
Dacheng Wang	Outstanding Graduate Student Supervisor Award of CAS	2006
Chih-chen Wang	Woman Pace-Setter Award	2006
Chen Chang	“SFRR Asia Award for 2006” the 13th International Congress of the Society for Free radicals, Davos, Switzerland.	2006
Yan Xiyun	Chinese Academy of Sciences Exemplary Family Award	2006

中科院研究研究生院优秀教师：Excellent Teacher of Graduate University of Chinese Academy of Scineces"

刘勤瑞版

七、国际交流

（一）主办国际学术会议

1. 北京国际纳米生物医药技术与结构生物学研讨会

时间：2006 年 6 月 30 日

地点：北京

2. 第四届国际结构基因组学大会（ICSG 2006）

时间：2006 年 10 月 22-26 日

地点：北京

（二）参加学术会议

张旭家　名称：Gordon Conference on “Glycolipid & Sphingolipid Biology”

时间：1 月 8-13 日

地点：Ventura, USA

报告题目：Activation of sarcoplasmic reticulum Ca2+-ATPase requires association with lipid microdomain at sarcoplasmic reticulum

饶子和　名称：The 3rd Intl. Symposium of the Austrian Proteomics Symposium

时间：2006 年 1 月 16-19 日

地点：Seefeld，奥地利

报告题目：Structural insights into SARS coronavirus proteins

饶子和　名称：Asian Research Forum on Emerging and Reemerging Infections-2006

时间：2006 年 2 月 18-20 日

地点：Tokyo

报告题目：Structural insights into SARS coronavirus proteins

饶子和　名称：UK-CHINA Workshop on Synchrotron Radiation

时间：2006 年 2 月 20-22 日

地点：上海

报告题目：SARS protein structure, function and anti-viral drug discovery

王志珍　名称：“中国梦与和谐世界”研讨会

时间：2006 年 4 月 2 日

地点：北京，中国

报告题目：中国科学梦与和谐世界

VII. International Exchange

1. Organization of International Meetings

1) Symposium of Nanobiomedical Technology and Structural Biology

Time: 30 June 2006

Venue: Beijing

2) 4th International Conference on Structural Genomics（ICSG 2006）

Time: 22-26 October 2006

Venue: Beijing

2. Participation in International Mettings

Xujia Zhang	Meeting:	Gordon Conference on "Glycolipid & Sphingolipid Biology"
	Time:	8-13 January 2006
	Venue:	Ventura, USA
	Talk Title:	Activation of sarcoplasmic reticulum Ca2+-ATPase requires association with lipid microdomain at sarcoplasmic reticulum
Zihe Rao	Meeting:	The 3rd Intl. Symposium of the Austrian Proteomics Symposium
	Time:	16-19 January 2006
	Venue:	Seefeld, Austria
	Talk Title:	Structural insights into SARS coronavirus proteins
Zihe Rao	Meeting:	Asian Research Forum on Emerging and Reemerging Infections-2006
	Time:	18-20 February 2006
	Venue:	Tokyo, Japan
	Talk Title:	Structural insights into SARS coronavirus proteins
Zihe Rao	Meeting:	UK-CHINA Workshop on Synchrotron Radiation
	Time:	20-22 February 2006
	Venue:	Shanghai, China
	Talk Title:	SARS protein structure, function and anti-viral drug discovery
Chih-chen Wang	Meeting:	Seminar "China Dream and a Harmonious World"
	Time:	2 April 2006
	Venue:	Beijing, China
	Talk Title:	China Dream of Scientists and a Harmonious World
Chih-chen Wang	Meeting:	The 7th National Conference on Phosphorus Chemistry and Industry
	Time:	8-12 April 2006
	Venue:	Zhengzhou, China
	Talk Title:	Macromolecules assisting protein folding: chaperones and foldases

王志珍　　名称：第七届全国磷化学化工暨第四届海峡化学生物学、生物技术与医药发展讨论会

时间：2006 年 4 月 8-12 日

地点：郑州，中国

报告题目：Macromolecules assisting protein folding: chaperones and foldases

靳刚　　名称：9th World Congress on Biosensors

时间：2006 年 5 月 10-12 日

地点：Toronto, Ontario, Canada,

报告题目：Kinetic process study for biomolecule interaction with biosensor based on total internal reflection imaging ellipsometry

姬广聚　　名称：第六届全国鈣信号和细胞功能研讨会

时间：2006 年 5 月 22-23 日

地点：青岛

报告题目：Ca^{2+} induced Ca^{2+} release through localized Ca^{2+} uncaging in smooth muscle

姬广聚　　名称：第十届全国生物物理学术会议

时间：2006 年 5 月 24-26 日

地点：青岛

报告题目：ANP regulates L-type Ca2+ channel in ES cell derived cardiaomyocytes

王大成　　名称：第十届全国生物物理学术会议

时间：2006 年 5 月 26 日

地点：青岛

报告题目：蛋白质结构空间的基本特征：从特征折叠到蛋白质的不同结构与功能（特邀报告）

刘志杰　　名称：第十次中国生物物理学术大会

时间：2006 年 5 月 23-28 日

地点：青岛

报告题目：基于 Coelentrazine 的生物发光蛋白分子的结构及发光机理的研究

陈畅　　名称：第十次中国生物物理学术大会

时间：2006 年 5 月 23-28 日

地点：山东青岛

报告题目：TGaseII protects neural cells from death by maintaining cellular TrkB content（特邀报告）

Zihe Rao	Meeting:	Applied Biological Science and Biology Engineering
	Time:	17-19 April 2006
	Venue:	Qingdao, China
	Talk Title:	Structural insights into SARS coronavirus replication machinery
Xiyun Yan	Meeting:	Nanobioscience and Nanomedicine Conference
	Time:	29 April – 3 May 2006
	Venue:	Suzhou, China
	Talk Title:	Development of Nanobiology
Gang Jin	Meeting:	9th World Congress on Biosensors
	Time:	10-12 May 2006
	Venue:	Toronto, Ontario, Canada,
	Talk Title:	Kinetic process study for biomolecule interaction with biosensor based on total internal reflection imaging ellipsometry
Xiyun Yan	Meeting:	10th Annual Meeting of the Biophysical Society of China
	Time:	23-28 May 2006
	Venue:	Qingdao, China
	Talk Title:	The mechanism of Antibody AA98 inhibit tumor angiogenesis
Weimin Gong	Meeting:	10th Annual Meeting of the Biophysical Society of China
	Time:	23-28 May 2006
	Venue:	Qingdao, China
Zhijie Liu	Meeting:	10th Annual Meeting of the Biophysical Society of China
	Time:	23-28 May 2006
	Venue:	Qingdao, China
	Talk Title:	Structural and Functional Study of Coelenterazine-dependent Bioluminescent Proteins
Chang Chen	Meeting:	10th Annual Meeting of the Biophysical Society of China
	Time:	23-28 May 2006
	Venue:	Qingdao, China
	Talk Title:	TGaseII protects neural cells from death by maintaining cellular TrkB content
Tao Xu	Meeting:	10th Annual Meeting of the Biophysical Society of China
	Time:	23-28 May 2006
	Venue:	Qingdao, China
	Talk Title:	Calcium signalling in pancreatic beta cells

徐涛　　名称：第十届中国生物物理大会

时间：2006 年 5 月 23-28 日

地点：青岛

报告题目：胰腺 β 细胞上的钙信号系统

张旭家　　名称：第十次中国生物物理学术大会

时间：2006 年 5 月 23-28 日

地点：青岛

报告题目：溶酶体促进细胞凋亡因子的研究

杨福全　　名称：第十次中国生物物理学术大会

时间：2006 年 5 月 23-28 日

地点：青岛

报告题目：磷酸化蛋白质组学新技术研究与应用

阎锡蕴　　名称：第十次中国生物物理学术大会

时间：2006 年 5 月 23-28 日

地点：青岛

报告题目：抗 CD146 抗体抑制肿瘤血管新生的机理

王志珍　　名称：第一届纳米生物学技术与结构生物学国际会议

时间：2006 年 6 月 24-28 日

地点：成都，中国

报告题目：Dimerization bestows chaperone and isomerase activities

陈润生　　名称：第五届世界华人物理学大会

时间：2006 年 6 月 27-30

地点：台北

报告题目：Organisation of the *Caenorhabditis elegans* small non-coding transcriptome

阎锡蕴　　名称：中国药学大会

时间：2006 年 7 月 29-31

地点：黄山

报告题目：肿瘤抗体药物

Chih-chen Wang	Meeting:	First International Conference of Nanobiomedical Technology and Structural Biology
	Time:	24-28 June 2006
	Venue:	Chengdu, China
	Talk Title:	Dimerization bestows chaperone and isomerase activities
Runsheng Chen	Meeting:	The 5th Joint Meeting of the Chinese Physicists Worldwide
	Time:	27-30 June 2006
	Venue:	Taipei, Taiwan
	Talk Title:	Organisation of the *Caenorhabditis elegans* small non-coding transcriptome
Zhihai Qin	Meeting:	Fragrant Hills Protein Research Conference
	Time:	4-5 July 2006
	Venue:	Xiangshan Restaurant, Beijing, China
	Talk Title:	Mechanisms of the Immunosurveillance
Xiyun Yan	Meeting:	The Symposium of Hangzhou Science Committee
	Time:	6-9 July 2006
	Venue:	Hangzhou, China
	Talk Title:	Antibody in disease diagnosis and therapy
Hongyu Deng	Meeting:	9th International Workshop on Kaposi’ s Sarcoma Associated Herpesvirus (KSHV) and Related Agents
	Time:	12-15 July 2006
	Venue:	Cape Cod, USA
Zihe Rao	Meeting:	Hawaii Conference
	Time:	22-27 July 2006
	Venue:	Hawaii, USA
	Talk Title:	Structural insights into SARS coronavirus replication machinery

秦志海　　名称：蛋白质研究香山科学会议第 280 次学术研讨会

时间：2006 年 7 月 4-5 日

地点：中国 北京 香山饭店

报告题目：肿瘤免疫监视机理研究

饶子和　　名称：应用生物科学和生物工程（中英双边会议）

时间：7 月 17-19 日

地点：青岛

报告题目：Structural insights into SARS coronavirus replication machinery

饶子和　　名称：夏威夷会议

时间：7 月 22-27 日

地点：夏威夷

报告题目：Structural insights into SARS coronavirus replication machinery

王志珍　　名称：20th Annual Symposium of The Protein Society

时间：2006 年 8 月 5-9 日

地点：加利福尼亚，美国

墙报题目：Dimerization bestows chaperone and isomerase activities

蒋太交　　名称：十四届分子生物学智能系统国际年会

时间：8．6-8．13

地点：Fortaleza, 巴西

报告题目：Parallel residue adaptation drives the divergent evolution of human H3N2 infectivity

杨福全　　名称：第四次逆流色谱国际会议

时间：2006.8.8-8.11

地点：美国 NIH, Bethesda, MD

报告题目：逆流色谱在人血清肽组学中的应用研究

陈畅　　名称：The 13th International Congress of the Society for Free radicals International,

时间：15-19 August 2006

地点：瑞士，Davos

报告题目：Nonspecific S-nitrosation in spinach chloroplasts induced by GSNO in vitro based on proteomic analysis

Chih-chen Wang	Meeting:	20th Annual Symposium of The Protein Society
	Time:	5-9 August 2006
	Venue:	California, USA
	(Poster)	Dimerization bestows chaperone and isomerase activities
Taijiao Jiang	Meeting:	14th international conference on intelligent systems for molecular biology
	Time:	6-13 August 2006
	Venue:	Fortaleza, Brazil
	Talk Title:	Parallel residue adaptation drives the divergent evolution of human H3N2 infectivity
Fuquan Yang	Meeting:	4th International conference on CCC
	Time:	8-11 August 2006
	Venue:	NIH, Bethesda, MD, USA
	Talk Title:	Application of high-speed countercurrent chromatography in human serum peptidomics
Chen Chang	Meeting:	13th International Congress of the Society for Free Radicals International
	Time:	15-19 August 2006
	Venue:	Davos, Switzerland
	Talk Title:	Nonspecific S-nitrosation in spinach chloroplasts induced by GSNO in vitro based on proteomic analysis
Zihe Rao	Meeting:	ICCBM11 Conference
	Time:	17-21 August 2006
	Venue:	Quebec, Canada
	Talk Title:	Structural proteomics of the SARS coronavirus: insights into the replication machinery
Chih-chen Wang	Meeting:	The First Symposium of The Chinese Protein Society
	Time:	24-27 August 2006
	Venue:	Xiamen, China
	Talk Title:	Dimerization bestows chaperone and isomerase activities

饶子和　　名称：ICCBM11 Conference

时间：8 月 17-21 日

地点：Quebec, Canada

报告题目：Structural proteomics of the SARS coronavirus: insights into the replication machinery

王志珍　　名称：第一届全国 “跨学科蛋白质研究”学术讨论会

时间：2006 年 8 月 24-27 日

地点：厦门，中国

报告题目：Dimerization bestows chaperone and isomerase activities

饶子和　　名称：the second meeting of the Global Structural Proteomics Initiative

时间：8 月 27-29 日

地点：Scotland，UK

报告题目：Structural proteomics of the SARS coronavirus: insights into the replication Machinery

焦仁杰　　名称：中国遗传学会七届二次青年研讨会

时间：2006 年 8 月

地点：武夷山

报告题目：Functional characterization of dCAF-1-p180, the gene that encodes the largest subunit of Drosophila CAF-1

焦仁杰　　名称：第四届发育生物学研讨会

时间：2006 年 8 月

地点：昆明

报告题目：Potential role of CG9613 gene in Drosophila

饶子和　　名称：第三世界科学院院士大会暨的里雅斯特科学奖颁奖

时间：2006 年 9 月 2-6 日

地点：里约热内卢，巴西

靳刚　　名称：3rd Germany-China Workshop on Microgravity & Space Life Sciences

时间：2006 年 10 月 9-11 日

地点：Berlin, Germany

报告题目：A Space-rated Biosensor for Kinetic Process Study of Biomolecule Interaction

Tao Xu	Meeting:	2nd Asian Pacific Diabetes and Obesity Study Group
	Time:	25-28 August 2006
	Venue:	Kobe, Japan
Zihe Rao	Meeting:	2nd Meeting of the Global Structural Proteomics Initiative
	Time:	27-29 August 2006
	Venue:	Scotland, UK
	Talk Title:	Structural proteomics of the SARS coronavirus: insights into the Replication machinery
Zihe Rao	Meeting:	TWAS 10th General Conference & 17th General Meeting TWNSO 9th General Assembly
	Time:	2-6 September 2006
	Venue:	Rio De Janeiro, Brazil
Gang Jin	Meeting:	3rd Germany-China Workshop on Microgravity & Space Life Sciences
	Time:	9-11 October 2006
	Venue:	Berlin, Germany
	Talk Title:	A Space-rated Biosensor for Kinetic Process Study of Biomolecule Interaction
Tao Xu	Meeting:	RUI-JIN International Endocrine Symposium On Pancreatic Beta Cell Dysfunction in Diabetes
	Time:	14-15 October 2006
	Venue:	RUI-JIN Hospital, Shanghai, China
	Talk Title:	Munc13-1 Is Required For The Second Phase of Insulin Secretion From Mouse Pancreatic Beta Cells
Chen Chang	Meeting:	海峡两岸自由基与天然抗氧化剂暨氧化压力之分子检验学术研讨会
	Time:	20-21 October. 2006
	Venue:	Changgeng University, Taiwan
	Talk Title:	蛋白质巯基亚硝基化修饰检测方法分析与改进
Tao Jiang	Meeting:	4th International Conference on Structural Genomics
	Time:	Main conference October 22-26
	Venue:	Beijing

徐涛　　名称：RUI-JIN International Endocrine Symposium On Pancreatic Beta Cell Dysfunction in Diabetes

时间：2006.10.14-10.15

地点：上海瑞金医院

报告题目：Munc13-1 Is Required For The Second Phase of Insulin Secretion From Mouse Pancreatic Beta Cells

陈畅　　名称：海峡兩岸 自由基與天然抗氧化劑暨氧化壓力之分子檢驗 學術研討會

时间：2006 年 10.20-21

地点：长庚大学, 台湾

报告题目：邀请报告：蛋白质巯基亚硝基化修饰检测方法分析与改进

刘志杰　　名称：第四届国际结构基因组学大会

时间：2006.10.22-26

地点：北京

报告题目：中国人类肝脏结构基因组学研究

孙飞　　名称：2006 国际结构基因组会议

时间：2006 年 10.22.

地点：北京友谊宾馆

报告题目：Crystal Structure of Mitochondrial Complex II from porcine heart

阎锡蕴　　名称：香山科技会议－纳米医药与纳米生物学前沿

时间：2006.11

地点：北京

报告题目：磁性纳米材料的酶催化功能研究

范祖森　　名称：第 7 届国家杰出青年基金学术会议

时间：2006.11

地点：昆明

报告题目：抗肿瘤的效应机制

姬广聚　　名称：全国生理学大会

时间：11.3-7

地点：北京

报告题目：Ca2+ signaling in smooth muscle

Zhijie Liu	Meeting:	The 4th international conference of structural genomics
	Time:	22-26 October 2006
	Venue:	Beijing, China
	Talk Title:	Human liver structural proteomics in China
Fei Sun	Meeting:	ICSG-2006
	Time:	22 October 2006
	Venue:	Beijing Friendship Hotel, China
	Talk Title:	Crystal Structure of Mitochondrial Complex II from porcine heart
Zihe Rao	Meeting:	The joint conference of the Asian Crystallographic Association (AsCA) and the Crystallographic Society of Japan (CrSJ)
	Time:	20-22 November 2006
	Venue:	Tsukuba, Japan
	Talk Title:	Structural proteomics of the SARS coronavirus: insights into the replication machinery
Fei Sun	Meeting:	AsCA/CrSJ-2006
	Time:	23 November 2006
	Venue:	Tsukuba, Japan
	Talk Title:	Crystal Structure of Mitochondrial Complex II from porcine heart
Xiyun Yan	Meeting:	Fragrant Hills Science Meeting: Nano Medicine and Frontiers of Nano Biology
	Time:	27-30 November 2006
	Venue:	Beijing, China
	Talk Title:	Biological Function of Nanomaterials
Sarah Perrett	Meeting:	EU COST Working Group Meeting on High Pressure Tuning of Biochemical Processes: Protein Folding and Molecular Diseases
	Time:	30 Nov.-1 Dec. 2006
	Venue:	University of Girona, Spain
	Talk Title:	Investigating the Molecular Mechanism of Prion and Poly-Q Diseases

饶子和　　名称：The joint conference of the Asian Crystallographic Association (AsCA) and the Crystallographic Society of Japan (CrSJ)　(AsCA’ 06/CrSJ)

时间：11.20-22.

地点：Tsukuba, Japan

报告题目：Structural proteomics of the SARS coronavirus: insights into the replication machinery

孙飞　　名称：2006 亚洲晶体学会暨日本晶体学联合会议

时间：2006 年 11 月 23 日

地点：日本国筑波市国际会议中心

报告题目：Crystal Structure of Mitochondrial Complex II from porcine heart

王大成　　名称：第二届全国脑与认知科学学术会议

时间：2006.11.28

地点：桂林

报告题目：蝎神经毒素生物活性的分子基础（特邀报告）

柯莎　　名称：EU COST Working Group Meeting on High Pressure Tuning of Biochemical Processes: Protein Folding and Molecular Diseases

时间：2006 年 11 月 30 日-12 月 2 日

地点：西班牙 Girona 大学

报告题目：Investigating the Molecular Mechanism of Prion and Poly-Q Diseases

高光侠　　名称：艾滋病研究国际研讨会

时间：2006 年 12 月 6 日

地点：上海

报告题目：Inhibition of viral mRNA production by ZAP

Guangxia Gao	Meeting:	HIV and AIDS
	Time:	Dec. 6, 2006
	Venue:	Shanghai
	Talk Title:	Inhibition of viral mRNA production by ZAP
Haiying Hang	Meeting:	Annual Meeting of the American Society of Cell Biology
	Time:	8-12 December 2006
	Venue:	Los AngeLes

（三）对外合作与交流

1. 来访

2006.3.0－4.17	英国 Glasgow 大学 Karen McLuskey and Mads Gabrielsen
2006.4.2－4	德国科隆大学生理研究所 Juergen Hescheler
2006.4.3	Duke University Medical Center　Dr. Youwen He
2006.4.10	美国俄亥俄州立大学 Peng Wang
2006.4.13	Sir William Dunn School of Pathology Dr. George Brownlee
2006.5.8－6.3.	爱尔兰国立大学 Harriet Loovers 博士
2006.5.22－25	Yale Sidney Altman
2006.5.29	University Oklahoma Health Sci Ctr Dr. Xiaohong Sun
2006.6	法国 Sanofi Aventis 公司 Shiv Krishnan，Gaurav Laroia Renata Lee，Tai-he Xia
2006.6.15.	Inst Virol, Univ Hospital Essen, Germany　Dr. Mengji Lu
2006.6.16.	University of Tennessee，USA 余美祥 教授
2006.6.21	UCSF　Dr. Jason Cyster
2006.6.28	美国马里兰大学医学院　ZHOU Xing-wang 副教授
2006.7	纽约大学医学院　许瑞明教授
2006.7	University of Southern California 韩原平博士
2006.8.20－9.18	意大利 Verona 大学　Matteo Ballotari
2006.9	Children’ s Hospital, University of Cincinnati　Dr. Jun M
2006.10	加拿大 Institute for Biological Sciences, National ResearchCouncil of Canada Prof. Jinbin Zhang
2006.10	Institute of Molecular Biology, University of Zurich Dr. Werner Boll
2006.10.	英国 Warwick 大学 Robert Freedman 教授的学生 Ateesh Sidhu
2006.10.13	CalTech Dr. Melvin I. Simon
2006.10.19－24	法国巴黎大学分子心血管生理药理研究所 Rodolphe Fischmeister
2006.10.22	美国佐治亚大学　Bi-Cheng Wang
2006.10.23	哥伦比亚大学　Prof. Tong Liang
2006.10.31－11.2	Northwestern medical center Pinghui Feng
2006.11	法国 Institute Albert Bonniot, INSERM U578 Prof. Jean-Luc Coll
2006-11	加拿大多伦多大学　Tak Wah Mak
2006.11	NIH　Dr. Linggang Wu
2006.12.22	瑞典卡罗林斯卡研究所 Jan Sedzik　教授
2006.12.27	美国 Scripps 研究所　Du Li-Lin 博士

3. Visits

1) Visitors to the Institute

2006.3.0 − 4.17	Karen McLuskey and Mads Gabrielsen, Glasgow University, UK
2006.4.2 − 4	Juergen Hescheler, Inst. of Neurophysiology, U. of Cologne, Germany
2006.4.3	Dr. Youwen He, Duke University Medical Center, USA
2006.4.10	Peng Wang, Ohio State University, USA
2006.4.13	Dr. George Brownlee, Sir William Dunn School of Pathology, Oxford, UK
2006.5.8 − 6.3.	Dr. Harriet Loovers, National University of Ireland, Maynooth, Ireland.
2006.5.22 − 25	Sidney Altman, Yale University, USA
2006.5.29	Dr. Xiaohong Sun, University of Oklahoma Health Sci. Ctr., USA
2006.7	Shiv Krishnan, Gaurav Laroia Renata Lee and Taihe Xia, Sanofi Aventis, France
2006.6.15.	Dr. Mengji Lu, Inst. Virology, Univ Hospital Essen, Germany
2006.6.16.	Dr.Meixiang She University of Tennessee，USA
2006.6.21	Dr. Jason Cyster, UCSF, USA
2006.6.28	Dr. Xingwang Zhou, Medical Institute, U. of Maryland, USA
2006.7	Dr.Ruiming Xu New York UniversityMedical Centre, USA
2006.7	Dr. Pingyuan Han, University of Southern California, USA
2006.8.20 − 9.18	Matteo Ballotari, U. of Verona, Italy
2006.9	Dr. Jun M, Children's Hospital, University of Cincinnati, USA
2006.11	Prof. Jinbin Zhang, Inst. for Biological Sci., National Research Council of Canada
2006.10	Dr. Werner Boll, Institute of Molecular Biology, University of Zurich, Switzerland
2006.10.	Ateesh Sidhu (student of Prof. R. Freedman), U. of Warwick, UK
2006.10.13	Dr. Melvin I. Simon, CalTech, USA
2006.10.19 − 24	Rodolphe Fischmeister, Lab. of Cell. & Molec. Cardiology, U. of Paris-Sud, France
2006.10.22	Bi-Cheng Wang, U. of Georgia, USA
2006.10.23	Prof. Tong Liang, Columbia University, USA
2006.10.31 − 11.2	Pinghui Feng, Northwestern Medical Center, USA
2006.11	Prof. Jean-Luc Coll, Institute Albert Bonniot, INSERM U578, France
2006-11	Tak Wah Mak, U. of Toronto, Canada
2006.11	Dr. Linggang Wu, NIH, USA
2006.12.22	Prof. Jan Sedzik, Karolinska Institute, Sweden
2006.12.27	Dr. Lilin Du, Scripps Institute, USA

2. 出访

2005.10.1-2006.3.31	柯莎博士到英国剑桥 Hutchison/MRC 研究中心访问工作
2005.12.21-2006.2.26	张平峰、望超到意大利 Verona 大学访问工作
2006.1	王盛典研究员到 Johns Hopkins University 和 University of North Carolina-Chapel Hill 参观访问
2006.1－3	阎锡蕴研究员到日本大阪大学访问工作
2006.1－4	卫涛涛博士到英国 MRC 短期工作
2006.1.13	柯莎博士到英国 Kent 大学生命科学系参观访问
2006.2.2	柯莎博士到英国利兹大学 Astbury 研究中心参观访问
2006.2—4	孙飞研究员到英国牛津大学短期工作
2006.2.17	柯莎博士到英国 Leicester 大学生物化学系参观访问
2006.2.24	柯莎博士英国 Warwick 大学生物系和化学系参观访问
2006.3.14	柯莎博士英国剑桥医学研究所（CIMR）参观访问
2006.3.29	柯莎博士英国剑桥大学生物化学系参观访问
2006.4	高光侠研究员到瑞士罗氏公司参观
2006.5	秦志海柏林自由大学参观访问
2006.5.8－14	张旭家研究员俄罗斯莫斯科大学参观访问
2006.6	靳刚研究员到 Linkoping Univeristy 参观访问
2006.7－9	杨福全到美国 Scripps 研究所短期工作
2006.8.16－9	唐宏研究员到 Australia Phenomic Center 访问工作
2006.9.10	徐涛研究员到法国巴黎第五大学参观访问
2006.11.13	柯莎博士中国预防医学科学研究院病毒研究所参观访问
2006.11.14—21	孙飞研究员到日本筑波高能粒子加速器光子中心短期工作
2006.12.4	柯莎博士到英国 Bristol 大学生物化学系参观访问
2006.12.8	柯莎博士到英国剑桥大学药物学系参观访问
2006.12	杭海英研究员到 University of Southern California 参观访问
2006.12	邓红雨研究员到加州大学参观访问

2) Visits by Members of the NLB

Oct 2005-Mar 2006	Dr. S. Perrett	Hutchison/MRC Research Centre, Cambridge, UK
Dec 2005-Feb 2006	Dr. PF Zhang Dr. C Wang	University of Verona, Italy
Jan 2006	Dr. S.D. Wang	Johns Hopkins University & University of North Carolina-Chapel Hill, USA
Jan-Mar 2006	Dr. X.Y. Yan	Osaka University, Japan
Jan-Apr 2006	Dr. T.T. Wei	MRC, UK
13 Jan 2006	Dr. S. Perrett	Dept. of Biosciences, University of Kent, Canterbury, UK
2 Feb 2006	Dr. S. Perrett	Astbury Centre, University of Leeds, UK
Feb-Apr 2006	Dr. F. Sun	University of Oxford, UK
17 Feb 2006	Dr. S. Perrett	Dept. of Biochemistry, University of Leicester, UK
24 Feb 2006	Dr. S. Perrett	Dept. of Biological Sciences and Dept. of Chemistry, University of Warwick, UK
14 Mar 2006	Dr. S. Perrett	CIMR, Cambridge, UK
29 Mar 2006	Dr. S. Perrett	Dept. of Biochemistry, University of Cambridge, UK
Apr 2006	Dr. G.X. Gao	Roche Diagnostics, Switzerland
May 2006	Dr. Z.H. Qin	Berlin Free University, Germany
8-14 May 2006	Dr. X.J. Zhang	Moscow University, Russia
June 2006	Dr.G. Jin	Linkoping Univeristy, Sweden
July-Sept 2006	Dr. F.Q. Yang	The Scripps Research Institute, USA
Aug-Sept 2006	Dr. H. Tang	Australia Phenomic Center
10 Sept 2006	Dr. T. Xu	Université René Descartes (Paris 5), France
13 Nov 2006	Dr. S. Perrett	Prion Laboratory, Institute of Virology, China CDC, Beijing
14-21 Nov 2006	Dr. F. Sun	Photon Factory, Japan
4 Dec 2006	Dr. S. Perrett	Dept. of Biochemistry, University of Bristol, UK
8 Dec 2006	Dr. S. Perrett	Dept. of Pharmacology, University of Cambridge, UK
Dec 2006	Dr. H.Y. Hang	University of Southern California, USA
Dec 2006	Dr. H.Y. Deng	University of Califonial,USA

3. 国际合作

国家	合作单位	项目名称	课题负责人
意大利	Verona 大学	Agreement of Scientific and Technological Cooperation between CNR and CAS CNR/CAS Joint Projects 2005/2007	常文瑞院士
德国	慕尼黑理工大学	蛋白质错误折叠与分子伴侣	柯莎博士
爱尔兰	爱尔兰国立大学	分子伴侣对 Prion 传播机制的影响	柯莎博士
俄罗斯	莫斯科大学	线粒体与细胞凋亡	杨福愉院士
美国	University of Southern California	Rad9 and Fen1 interaction	杭海英研究员
德国	科隆大学生理研究所	胚胎干细胞生物学研究	姬广聚研究员
美国	康奈尔大学生物医学系	Ca2+ 转运的分子机制研究	姬广聚研究员
加拿大	Institute for Biological Sciences, National Research Council of Canada	禽流感抗体组学研究	阎锡蕴研究员
法国	Institute Albert Bonniot, INSERM U578	标记抗体在裸鼠体内的肿瘤成像	阎锡蕴研究员
日本	大阪大学	活细胞单分子探测细胞膜蛋白 CD146 与其配体的分子识别和信号传导机制	阎锡蕴研究员
加拿大	大多伦多大学	肿瘤间质细胞的相互作用机制	秦志海研究员
美国	UCLA, U Chicago	冠状病毒 MHV-A59 天然免疫机制	唐宏研究员

3) International Cooperation

Country	Institution	Project Title	PI
Italy	Verona University	Agreement of Scientific and Technological Cooperation between CNR and CAS CNR/CAS Joint Projects 2005/2007	Prof. W.R. Chang
Germany	Technical University of Munich	Protein misfolding and molecular chaperones	Dr. S. Perrett
Ireland	National University of Ireland, Maynooth	Effect of chaperones upon prion propagation	Dr. S. Perrett
Russia	University of Moscow	Mitochondria and apoptosis	Prof. F.Y. Yang
USA	University of Southern California	Rad9 and Fen1 interaction	Dr. H.Y. Hang
Germany	University of Cologne	Embryonic stem cell biological study	Dr. G.J. Ji
USA	Cornell University	Molecular mechanism of Ca2+ movement in SM	Dr. G.J. Ji
Canada	Institute for Biological Sciences, National Research Council of Canada	Study of Avian influenza virus specific antibodies	Dr. X.Y. Yan
France	Institute Albert Bonniot, INSERM U578	Optical imaging of tumor blood vessels by antibody AA98 *in vivo*	Dr. X.Y. Yan
Japan	Osaka University	Single-molecule behavior of CD146 in living cells	Dr. X.Y. Yan
Canada	University of Toronto	Stroma cell interactions in tumorigenesis	Dr. Z.H. Qin
USA	UCLA, U Chicago	Innate immune response against the infection of coronavirus MHV-A59	Dr. H. Tang

附　　录

1、2006 年实验室新增课题

（一）2006年新增国家部委科研项目

（1）新增基金委资助重点项目

序号	项目种类	项目名称	负责人	起止时间
1	重点项目	囊泡转运及其与细胞膜融合分子机理研究	徐　涛	2007.01-2009.12
2	重点项目	线虫和人的非编码 RNA 及其功能研究	陈润生	2007.01-2009.12
3	重大研究计划重点项目	纳米胶束增强抗肿瘤药物活性和疗效的机制研究	梁　伟	2007.01-2010.12
4	优秀重点实验室项目	通过基因敲除和三维结构来揭示重要蛋白复合物的体内功能	焦仁杰	2007.01-2010.12
5	海外学者合作研究基金	生物分子的结构与功能、合成机理及调节过程	许瑞明 刘迎芳	2007.01-2009.12
6	中加合作项目	应用 FRET 技术研究 SNARE 蛋白-钾离子通道相互作用及其对胰岛素分泌的调控作用	徐涛	2007.01-2009.12

(2)2006 年新增科技部资助项目

序号	项目种类	课题名称	负责人	起止时间
1	973 计划项目	重要疾病相关蛋白质相互作用通路	王大成	2006.09-2011.08
2		光合作用系统膜蛋白复合物的结构与功能	常文瑞	2006.09-2011.08
3		线粒体呼吸链分子机器的结构与功能	孙　飞	2006.09-2011.08
4		荧光标记分子影像在小动物模型中的应用	梁　伟	2006.09-2011.08
5		宿主限制性因子抑制病毒复制作用机理的研究	高光侠	2006.09-2011.08
6		细胞因子在感染免疫病理中的作用机制研究	秦志海	2006.09-2011.08
7		病原微生物感染的免疫耐受和免疫逃逸机制	王盛典	2006.09-2011.08
	蛋白质研究计划	项目名称：重要功能蛋白质复合体的功能与结构研究 项目首席：王志珍		2006.09-2011.08
		项目名称：重要功能膜蛋白的功能与结构研究 项目首席：陈畅		2006.09-2011.08
8		能量转换相关膜蛋白结构及调控机制	陈畅	2006.09-2011.08
9		重要免疫调节蛋白质的功能与结构研究	唐捷	2006.09-2011.08

10		基因损伤修复机理研究	杭海英	2006.09-2011.08
11		细胞内膜转运相关蛋白质相互作用机理研究	蒋太交	2006.09-2011.08
12		蛋白质翻译、折叠与讲解	秦燕	2006.09-2011.08
13		神经系统相关重要蛋白质复合物的结构与功能研究	戚智	2006.09-2011.08
14	纳米研究计划	导向性纳米药物载体增强血管活性药物疗效及机制的研究	张春玲	2006.09-2011.08
15	生殖与发育研究计划	人胚胎干细胞心肌细胞移植方法研究	马跃	2006.09-2011.08
16	863 专题项目	原发性肝癌固有免疫耐受基因谱的筛选鉴定及对疾病的早期预警研究	范祖森	2006.09-2009.10
17		研究人内源性 siRNA 的结构、发生和功能的关键技术	张洪杰	2006.09-2009.10
18	863 重点项目	诊断试剂关键原料	高光侠	2006.11-2010.12
19	863 重大项目	肿瘤抗体药物	阎锡蕴	2006.11-2011.12
20		心血管疾病干细胞临床治疗技术与产品的研发	马跃	2006.11-2011.12
21		肝脏代谢及肝病相关蛋白质的三维结构研究	刘志杰	2006.09-2011.10
22		重要致病微生物蛋白质的三维结构研究	李雪梅	2006.09-2011.10
23		心血管、神经与免疫系统重大疾病相关蛋白的三维结构研究	江涛	2006.09-2011.10
24		癌症相关蛋白质的三维结构研究	刘迎芳	2006.09-2011.10

(3) 2006 年新增院创新项目

序号	项目名称	项目负责人	起止时间
1	SARS 冠状病毒转录与复制机理的结构基础	饶子和	2006.10-2009.12
2	生物大分子药物高效输送系统的关键技术研究	梁　伟	2006.10-2009.12
3	抗肿瘤的免疫效应机制	范祖森	2006.10-2009.12
4	胚胎干细胞定向高效分化及移植治疗的研究	姬广聚	2006.10-2009.12
5	蛋白质翻译起始和延伸过程中关键蛋白质复合物研究	龚为民	2006.10-2009.12
6	DNA 错配修复系统作用机制研究	毕利军	2006.10-2009.12

2、2006年实验室发表论文索引

1. **FAN ZS**, YU P, WANG Y, WANG YG, FU ML, LIU WH, SUN YL, FU YX, NK-cell activation by LIGHT triggers tumor-specific CD8(+) T-cell immunity to reject established tumors. *BLOOD*, 2006, 107(4):1342-1351.

2. KANG LJ, HE ZX, XU PY, FAN JM, BETZ A, BROSE N, **XU T**, Munc13-1 is required for the sustained release of insulin from pancreatic beta cells. *CELL METAB*, 2006, 3(6):463-468.

3. ZHANG ZH, WU T, **CHEN RS**, LIU CN, SKOGERBO G, ZHU XP, LU HC, CHEN L, SHI BC, ZHANG Y, WANG J, Dynamic changes in subgraph preference profiles of crucial transcription factors. *PLOS COMPUT BIOL*, 2006, 2(5):383-391.

4. **FAN Z**, ZHANG H, ZHANG Q, Tumor suppressor pp32 represses cell growth through inhibition of transcription by blocking acetylation and phosphorylation of histone H3 and initiating its proapoptotic activity. *CELL DEATH DIFFER*, 2006, 13(9):1485-1494.

5. S Kannan, H Pang, DC Foster, Z Rao, M Wu, Human 8-oxoguanine DNA glycosylase increases resistance to hyperoxic cytotoxicity in lung epithelial cells and involvement with altered MAPK activity. *CELL DEATH DIFFER*, 2006, 13(2):311-323.

6. SUN H, SKOGERBO G, **CHEN RS**, Conserved distances between vertebrate highly conserved elements. *HUM MOL GENET*, 2006, 15(19):2911-2922.

7. GUO YC, ZHOU YF, **ZHANG XE**, ZHANG ZP, QIAO YM, BI LJ, WEN JK, LIANG MF, ZHANG JB, Phage display mediated immuno-PCR. *NUCL ACID RES*, 2006, 34(8):.

8. You-Yi Huang, Jiao-Yu Deng, Jing Gu, Zhi-Ping Zhang, Anthony Maxwell, Li-Jun Bi, Yuan-Yuan Chen, Ya-Feng Zhou, Zi-Niu Yu, **Xian-En Zhang**, The key DNA-binding residues in the C-terminal domain of Mycobacterium tuberculosis DNA gyrase A subunit (GyrA). *NUCL ACID RES*, 2006, 34(19):5650-5659.

9. HE HS, TAO Y, ZENG HP, AFTAB MN, CUI Y, LIU GZ, **CHEN R**, CAI L, SKOGERBO G, DENG W, LIU T, ZHU XP, WANG YD, JIA D, ZHANG ZH, Profiling Caenorhabditis elegans non-coding RNA expression with a combined microarray. *NUCL ACID RES*, 2006, 34(10):2976-2983.

10. BAI L, ZHU D, ZHOU KM, ZHOU W, LI DD, WANG Y, ZHANG RY, **XU T**, Differential properties of GTP- and Ca2+-Stimulated exocytosis from large dense core vesicles. *TRAFFIC*, 2006, 7(4):416-428.

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