一、引言

2007 年，生物大分子国家重点实验室各项工作成绩斐然。

实验室新增各类科研项目 30 项，其中：科技部项目 6 项，国家基金委项目 14 项，中科院知识创新工程重要方向项目 10 项。在 SCI 收录的刊物上发表论文 94 篇，其中 IF 〉10 的论文 12 篇，篇均 IF=4.72。申请国内发明专利 12 项，国外发明专利 2 项，有 2 项专利被授权。梁伟研究员“肿瘤靶向的新型纳米药物输送系统”成果入选 2007 年中国十大科技进展。

实验室始终坚持人才是第一资源的理念，在各级领导和主管部门的大力支持下，引进了一批杰出的中青年科学家。2007 年引进“百人计划”2 名，实验室目前已初步建成一支由国际著名或知名科学家领衔的，老中青相结合，规模适度、结构合理、充满活力的高素质创新科技队伍。实验室现由 35 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 5 名；“长江学者奖励计划”特聘教授 2 名）。在读研究生 301 名，其中 135 名博士生，162 名硕士生。获得博士学位 27 名，24 名博士后。

2007 年，经过各方积极不懈的努力，生物物理所蛋白质与分子生物医学科研楼正式破土动工，预计将于 2008 年中完成土建工程，2008 年底投入使用，这将大大改善实验室的科研用房条件。

2007 年末，中科院第 12 次院长办公会审议并原则通过了中国科学院蛋白质科学平台二期建设实施方案，这是继生物物理所于 2005 年底完成了研究平台的一期建设后，科学院大力支持科研条件建设的又一重大举措，平台二期建设是一期建设的跨越式提升，通过持续的平台建设，最终将建成大规模、高产出、国际一流的蛋白质科学研究平台，为提升我国生命科学的自主创新能力、不断产出国际水平的原始创新成果、保障经济社会可持续发展做出历史性贡献。

科技部批准以生物大分子国家重点实验室为基础建设“蛋白质科学国家实验室”。目前，在所领导和全室同仁共同努力和积极推进下，蛋白质科学国家实验室的筹备工作已全面启动。

先进的价值理念，良好的文化生态，和谐的科研氛围，已经成为现代实验室核心竞争力的重要源泉。展望 2008 年，将是实验室发展至关重要的一年。我们将积极配合研究所推进科研条件建设，着力打造蛋白质研究国家基地；完善技术支撑体系建设，以技术创新推动科学创新；加强学科方向的研讨，凝练出若干世界科学难题，组织力量开展攻关，力争为我国生命科学发展作出历史性贡献；加强国际合作与交流，着力推进与国际一流研究机构建立长期稳定的战略合作伙伴关系，不断提升实验室在国际同行中的学术地位。

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委会主任：

一、 Introduction

In 2007 the National Key Laboratory of Biomacromolecules had many excellent academic achievements. Not only has our Lab published high quality papers, but the standard of scientific research in our Lab has improved continuously. Ninety four papers were published in SCI journals, of which 12 had impact factors greater than 10. The average impact factor per paper was 4.72. The Lab applied for 11 domestic patents and two overseas patents, two of which were granted. Professor Wei Liang's, 'New Nano Drug Delivery System for Targeting Tumors' was selected as one of the 'Ten Outstanding Science and Technology Achievements of China' in 2007.

In recent years, the competitive strength and overall ability of the Lab to undertake important national research programs has improved remarkably. In 2007, the Lab undertook about 30 new science research projects, including 6 projects from the Ministry of Science and Technology, 14 projects from the National Natural Science Foundation of China, and 10 projects from the Knowledge Innovation Program of the Chinese Academic of Sciences.

The Ministry of Science and Technology authorized IBP to establish the National Laboratory of Protein Science on the foundations laid by the National Key Laboratory of Biomacromolecules. Thanks to the efforts of the Directors of IBP and the members of the Lab, preparations for the establishment of the National Lab of Protein Science are already underway.

The National Key Laboratory of Biomacromolecules insists that talent is its greatest resource. With the strong support of the Directors and administration staff, the Lab has attracted a group of outstanding young and middle-aged scientists. In 2007, the Lab recruited two scientists in the 'One hundred talents program'. Our Lab has a good-sized, well-structured team of top-level young，middle-aged and older scientific researchers led by internationally famous scientists. There are 36 professors, of which seven are members of the CAS, 19 are members of CAS's 'One hundred talents program', five are winners of 'National Outstanding Youth Foundation' grants, and two have professorial chairs as part of the 'Chang Jiang Scholars Program'. There are 301 graduate students in the Lab, of which 135 are students pursuing PhD degrees, and 162 students are pursuing Master's degrees. Twenty-seven researchers in the Lab have PhD degrees, and 24 are currently doing postdoctoral research.

In 2007, thanks to unrelenting efforts on each side, IBP started to build the Protein and Molecular Medical Sciences Research Building. It is expected to be finished in the middle of 2008, and will be in use by the end of 2008. This will greatly improve our scientific research facilities.

The second phase of the construction and implementation plan for the CAS protein sciences platform was discussed and approved by the CAS President's Office at the end of 2007. This represents a further investment by CAS to improve the scientific research environment at IBP following on from the establishment of the protein science platform at the end of 2005. The second phase of construction will deliver further improvements on the foundation established by the first phase, giving rise to a large scale, high output and internationally top level protein science research facility which will make an historic contribution to improving the innovative ability of national life sciences, produce high level and original

innovative scientific achievements and contribute to the sustainable development of the economy.

Advanced values, a healthy work culture, and a harmonious scientific research environment have already become an important source of our Lab's core competitive ability. 2008 will be a very important year in the development of the Laboratory. In cooperation with the Institute to improve scientific research conditions, we will build a national research base for protein science, improve the technology support system, promote scientific innovation through technology innovation, strengthen consultation over research directions, organize scientists to unravel a number of the world's difficult science problems, and make an historic contribution to the development of the life sciences in China. The Lab will aim to promote international academic exchanges and collaborations, and establish steady and long term relationships with advanced international scientific research institutes, so that the Lab will continually improve its high academic reputation among other international scientific research institutes in its field.

National Laboratory of Biomacromelecules Director: Tao Xu

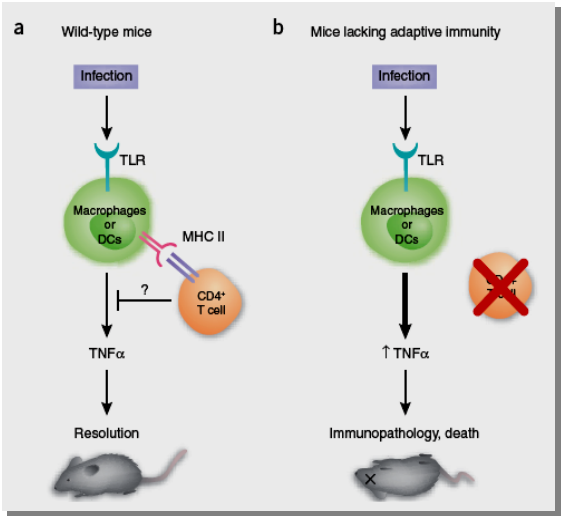
Academic Council Chairman: Chih-chen Wang

二、代表性成果 （Selected Achievements）

1、T 细胞控制天然免疫细胞产生的炎症反应

Adaptive immune cells temper initial innate responses.

NATURE MEDICINE 2007,13(10):1248-1252



唐宏研究组和付阳心研究组发现在肝炎病毒感染的极早期(<2 天)，未被激活的 T 细胞对于控制天然免疫细胞产生的炎症反应期至关重要的抑制作用。病毒感染适应性免疫系统缺陷的裸鼠或剔除 T 细胞的小鼠后，小鼠因天然免疫系统被激活导致的炎症因子飙升而剧烈死亡，过继性输入 T 细胞或者进一步剔除自然杀伤细胞（NK）后小鼠重新存活，炎症反应也得到了有效抑制。研究成果加深了人们对于炎症反应的认识，并提出了 T 细胞参与天然免疫反应的负性调控的新理论。对于临床上深入了解病毒性感染的炎症反应和病毒清除机理，免疫低下病人(新生儿，老年人，器官移植患者或艾滋病人)机会性感染的控制具有极高的理论价值。

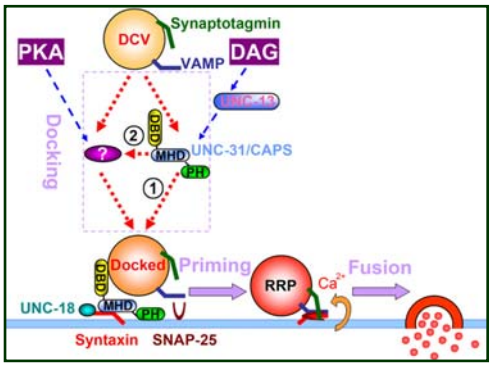
The joint research by Drs. Hong Tang and Yang-xin Fu's labs has shown that T cells of the adaptive immune system suppress overzealous early innate responses-"cytokine storm"-to infection that usually lead to severe immunopathology and high death rates. They have been able to show, through the depletion of $CD4^+$ and $CD8^+$ T cells in wild-type mice or by adoptive transfer of T lymphocytes into Rag-1 deficient mice (lack of T cells), that T cells are both necessary and sufficient to temper the early innate response. They further demonstrated that viral infection or administration of a synthetic, RNA virus genome mimickery compound, poly (I:C), led to cytokine storm in T-cell-deficient mice in NK cells and tumor necrosis factor (TNF) dependent manner. They also found that, in addition to the conventional inhibitory T cells (Treg cells), close contact of resting non-Treg ($CD4^+CD25^-Foxp3^-$) or $CD8^+$ T cells with innate cells could also suppress the cytokine surge in an antigen-independent fashion. These findings therefore suggest that early innate immunity requires the adaptive immunity in check to maintain the appropriate immune responses. These findings may also provide a novel mechanism of immunopathology during acute infections and potential anti-inflammation regime.

2、UNC-31 蛋白调控线虫致密核心囊泡锚定的机理

PKA Activation Bypasses the Requirement for UNC-31 in the Docking of Dense Core Vesicles from C. elegans Neurons. *Neuron* 2007，56:657－669

线虫是很好的研究遗传和发育的系统，但其在细胞生物学特别是囊泡转运与分泌领域的贡献却

十分有限，其主要原因是缺少高时空分辨的研究手段。2007年11月21日，《Neuron》发表了徐涛研究组在该领域的最新成果。他们克服了研究手段上局限，发展了模式生物线虫的单细胞分离和培养方法，首次在线虫单神经元上用膜电容检测技术记录到胞吐和胞吞过程，结合改进的碳纤微电极技术和囊泡转运的显微成像技术等先进的生物物理方法，将高时空分辨的分泌检测技术应用在线虫上，建立了在线虫细胞水平研究调控型分泌的技术平台。利用该技术平台，证明了核心致密囊泡的胞吐过程需要一种称为UNC-31(CAPS在线虫中的同源蛋白)的蛋白，阐明了该蛋白参与囊泡锚定的作用机制，并发现了UNC-13（Munc13-1在线虫中的同源蛋白）与UNC-31 蛋白之间存在相互作用。该工作开辟了利用线虫模式生物研究囊泡分泌的新方向。

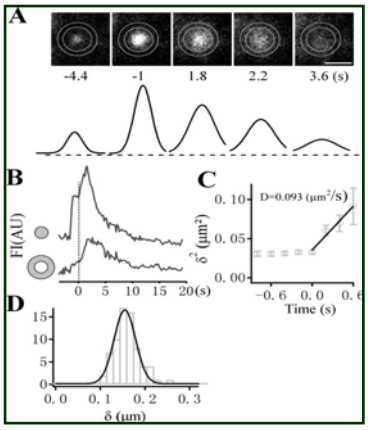


The nematode C. elegans provides a powerful model system for exploring the molecular basis of synaptogenesis and neurotransmission. However, the lack of direct functional assays of release processes has largely prevented an in depth understanding of the mechanism of vesicular exocytosis and endocytosis in C. elegans. For the first time, we establish a high spatial-temporal method to monitor secretion from neurons. We developed direct electrophysiological assays, including membrane capacitance and amperometry measurements, in primary cultured C. elegans neurons. In addition, we have succeeded in monitoring the docking and fusion of single dense core vesicles (DCVs) employing total internal reflection fluorescence microscopy. With these approaches and mutant perturbation analysis, we provide direct evidence that UNC-31 is required for the docking of DCVs at the plasma membrane. Interestingly, the defect in DCV docking caused by UNC-31 mutation can be fully rescued by PKA activation. We also demonstrate that UNC-31 is required for UNC-13-mediated augmentation of DCV exocytosis. This work represents both a significant technical advance in the analysis of regulated exocytosis in an important genetic system, C.elegans, but also uncovers new insights into the mechanisms underlying secretion.

3、脂肪细胞 GLUT4 贮存囊泡 GSV 的锚定

Dissecting multiple steps of GLUT4 trafficking and identifying the sites of insulin action.

CELL METAB 2007，5:47-57



徐涛研究组开发了一种分辨脂肪细胞GLUT4贮存囊泡GSV与细胞质膜融合过程中锚定、启动、融合等关键调控步骤的方法，发现了胰岛素在提高GSV囊泡锚定速率的同时，更关键的调控步骤是在囊泡锚定在细胞膜下之后使囊泡具有融合能力的启动过程。研究还发现胰岛素激活的PI3K及其下游效应物AS160调控了囊泡的锚定过程。研究组同时利用全内反射荧光显微成像方法发现和研究GLUT4贮存

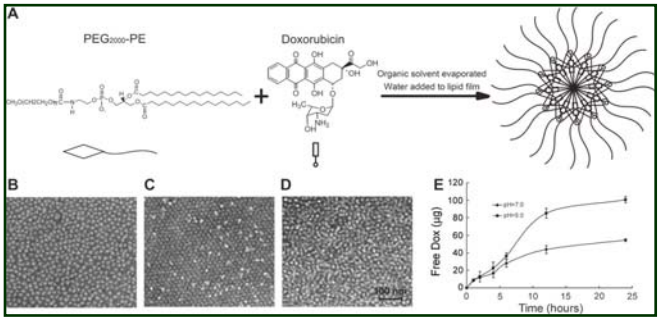
囊泡的调控作用，挑战了之前的GLUT4转运调控过程，为研究胰岛素信号途径提供了重要资料。2007年1月 《Developmental Cell》发表的评论文章认为：该研究方法有利于解决胰岛素怎样调控GSV囊泡与质膜融合等重要科学问题，有利于将胰岛素对GSV调控机制的研究重点转向囊泡与质膜融合这一关键步骤。

Insulin-stimulated GLUT4 translocation is central to glucose homeostasis. Functional assays to distinguish individual steps in the GLUT4 translocation process are lacking, thus limiting progress toward elucidation of the underlying molecular mechanism. First we have developed a robust method, which relies on dynamic tracking of single GLUT4 vesicles in real time, for dissecting and systematically analyzing the docking, priming, and fusion steps of GLUT4 vesicles with the cell surface in living adipocytes. Using this method, we have shown that the preparation of GLUT4 vesicles for fusion competence after docking at the surface is a key step regulated by insulin, whereas the docking step is regulated by PI3K and its downstream effector, the Rab GAP AS160. These data show that Akt-dependent phosphorylation of AS160 is not the major regulated step in GLUT4 trafficking, implicating alternative Akt substrates or alternative signaling pathways downstream of vesicle docking at the cell surface as the major regulatory node.

4、PEG-PE 聚合物胶束与阿霉素的自组装过程与其性质

Improving penetration in tumors with nanoassemblies of phospholipids and doxorubicin. ***J NAT CANCER INST.*** 2007, 99(4):1004-1015

梁伟研究组的工作表明：聚乙二醇衍生化磷脂与抗肿瘤化疗药物-阿霉素可自组装形成纳米尺度的新型输送载体，提高阿霉素在肿瘤组织中的富集和对深层组织细胞的渗透，进而增强了阿霉素的抗肿瘤效果并降低了毒性。研究首次证明了包载阿霉素的聚乙二醇衍生化磷脂纳米胶束可以选择性地在肿瘤组织蓄积并渗透到深层肿瘤组织提高肿瘤细胞内药物浓度，从而显著增强阿霉素的细胞毒性、抑制肿瘤的生长、延长小鼠的生存时间和降低药物的毒性，为临床治疗肿瘤提供了新的有效手段。该技术已申请国际专利，具有自主知识产权。同期杂志配发评论指出，这是一个简单但能有效地将药物和合适的载体整合起来产生很好效果的例子，也许药理学概念上的抗肿瘤药物由于不能正确识别它们的靶标而错伤病人的时代将会结束。

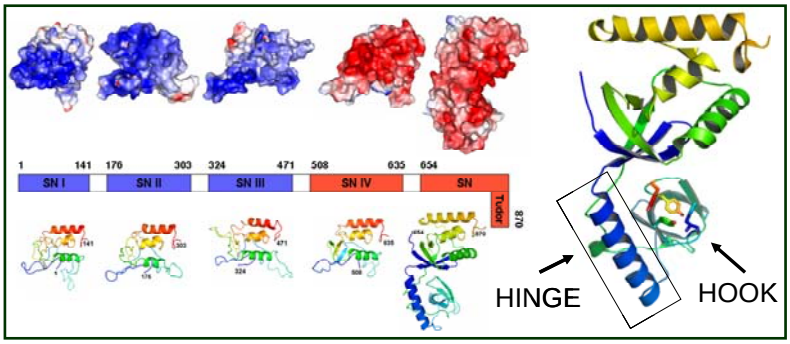


The study by Wei Liang's group has indicate that PEG-PE and doxorubicin self-assemble to form a novel nano-carrier, which improves the antitumor activity of doxorubicin and reduces its toxicicity by enhancing the accumulation and penetration of doxorubicin in the cells located in the deep-layers of the tumor. This is first time to prove that the doxorubicin-loaded PEG-PE micelles selectively accumulate and penetrate in the deeper tumor tissue to increase the intracellular drug concentration in tumor. Thus, doxorubicin loaded

PEG-PE micelles greatly enhances the cytotoxicity of doxorubicin, inhibits the tumor proliferation, prolongs the survival time of tumor-bear mice and reduces the drug systemic toxicity. This drug packaging technology may provide a new strategy for design cancer therapy. Meanwhile, this technology has been applied for international patent with our own intellectual property rights. The editorial in the J Natl Cancer Inst has pointed out: this study is a simple but effective demonstration of the benefits of integration of a drug with an appropriate carrier to yield a striking gain in efficacy. May the days of pharmacologic missiles that miss their target and friendly fire that kills patients soon be over.

5、人源多功能转录共激活因子 p100 的三维精细结构

The multifunctional human p100 protein 'hooks' methylated ligands. *Nat Struct Mol Biol* 2007,14(8):779-784



刘志杰课题组报告了人源p100这种多功能转录共激活因子的三维精细结构，解释了多功能转录共激活因子p100在转录和剪接中的不同作用，有利于进一步了解p100蛋白的功能和作用机制。表明多功能转录共激活因子p100及与其特异性结合的多蛋白复合体在人体免疫反应的IL-4 信号传导通路中起着非常重要的转录、调控和激活作用。研究还发现多功能转录共激活因子p100的一种全新的钩状结构域分布方式并将其命名为TSN结构域。

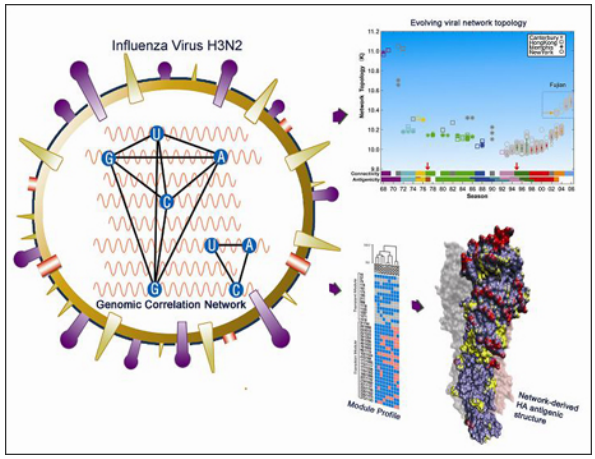
The human p100 protein is a vital regulator of cellular transcription processes. p100 has been shown to physically bridge promoter specific activators with the basal transcription machinery resulting in an increase in the level of gene transcription. Here, we demonstrate interaction between the tudor domain of p100 and the U snRNP complex, thus suggesting a role for p100 in the processing of pre-mRNA. We determined the crystal structure of p100 SN-Tudor domain in order to delineate the molecular basis of the proposed functions for p100. The interdigitated structure resembles a hook, with a hinge controlling the movement and orientation of the hook. Our studies suggest a conserved aromatic cage hooks methyl groups of snRNAs and anchors the p100 to the spliceosome. The findings of this study provide important structural insights that partly explain the distinct roles of p100 in transcription and splicing.

6、模拟流感演化的计算机新模型的建立

Evolution. *GENOME RESEARCH* 2007,

了解流感病毒的演化规律对防治流感起着非常重要的意义。尽管流感基因组看似简单，但流感变化分子规律却难以捕捉。蒋太交研究员实验室首次提出了利用网络模型来描述共进化的基因组信

息，创造性地将每个病毒表示为一个基因组元件相关性网络。该研究工作还引进几个网络特性参数（连接度K、连接度变化R以及表征片断间协同进化程度的量C），定量地描述出流感进化中的很多重要特征：抗原演化及其结构基础，流感片断间的功能联系及片断间的重组。该文章的三个评审专家都认为这个新方法将推动流感演化的分子机制的了解。同时他们认为该新颖的网络模型是研究流感病毒全基因组演化的重要方法，代表了该领域的重要进展。



Understanding the evolution of influenza A virus, which poses a global challenge to public health, is of special significance for its control and prevention. Although the genome structure of the virus is seemingly simple, their evolutionary patterns and molecular mechanisms are difficult to reveal.

The recent availability of full genomic sequence data for a large number of human influenza A (H3N2) virus isolates over many years have provided an opportunity to analyze its evolution by considering all gene segments simultaneously. However, such analysis requires new computational models that can capture the complex evolutionary features over the entire genome.

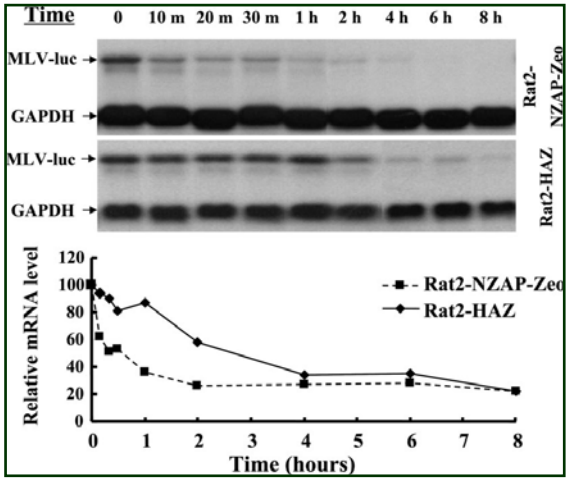
As being reported online by *Genome Research* on 21 November, a research group headed by Prof. Jiang Taijiao with the CAS Institute of Biophysics has set up a new computational model to depict many epidemiological characteristics of the A (H3N2) virus.

By analyzing the co-occurrence of the nucleotides in the entire genome of the virus, Prof. Jiang and colleagues have developed a network model to describe its evolutionary patterns and dynamics. The network model can effectively identify the antigenic features of the virus at the whole-genome level and accurately distinguish the complex patterns in the viral evolution between different gene segments. Their work further shows that the co-occurring nucleotide modules apparently underpin the dynamics of the H3N2 viral evolution. Moreover, the network model allowed them to identify key amino acid substitutions that dictate the antigenic evolution of human H3N2 virus. The study demonstrates that the network of nucleotide co-occurrences presents a promising method for tracking down the route of the viral evolution.

The idea that a network can model its evolution is a streamlined approach to further understand and predict the patterns of global epidemics and will be a great step forward in virus biology," according to a reviewer of the paper. This work is also highly appreciated by another reviewer, "Few papers on novel methods for the analysis of large collections of influenza genomes have been published to date, and this paper represents a significant advance.

7、ZAP 通过招募 RNA 外切酶加工复合体降解靶 RNA

The zinc-finger antiviral protein recruits the RNA processing exosome to degrade the target mRNA。 *PNAS* 2007，104(1)：151-156

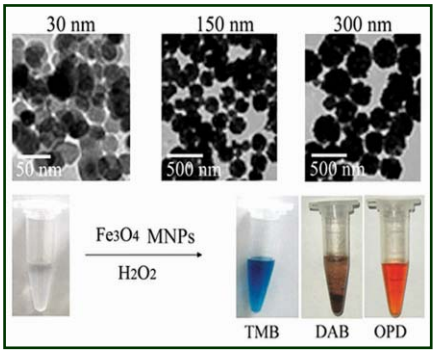


宿主抗病毒因子锌指结构抗病毒蛋白（ZAP）能够通过防止病毒 mRNA 在细胞质中的积累从而特异性抑制小鼠白血病病毒和辛德比斯病毒的复制。高光侠课题组以前的工作表明，ZAP 直接结合特异性的靶 mRNA。本文中，提供一些证据表明 ZAP 招募 RNA 外切酶加工复合体（Exosome）降解靶 RNA：在蔗糖或甘油梯度离心中 ZAP 与 Exosome 共迁移；ZAP 的免疫沉淀可以共沉淀下来 Exosome 组分；体外结合实验结果表明 ZAP 直接与 Exosome 组分 hRrp46p 相结合，ZAP 与之结合的功能域定位在 224－254 氨基酸；利用 RNAi 方法将 Exosome 组分 hRrp46p 或 hRrp41p 敲低后 ZAP 的活性被减弱。上述结果表明 ZAP 是一种调控 mRNA 稳定性的反式作用因子。

The zinc finger antiviral protein (ZAP) is a host antiviral factor which specifically inhibits the replication of Moloney murine leukemia virus and Sindbis virus by preventing accumulation of the viral mRNA in the cytoplasm. In previous studies, we demonstrated that ZAP directly binds to its specific target mRNAs. In this report, we provide evidence indicating that ZAP recruits the RNA processing exosome to degrade the target RNA. ZAP co-migrated with the exosome in sucrose or glycerol velocity gradient centrifugation. Immunoprecipitation of ZAP coprecipitated the exosome components. In vitro pull-down assays indicated that ZAP directly interacted with the exosome component hRrp46p and that the binding region of ZAP was mapped to amino acids 224-254. Depletion of the exosome component hRrp41p or hRrp46p with small interfering RNA significantly reduced ZAP's destabilizing activity. These findings suggest that ZAP is a type of *trans*-acting factor modulating mRNA stability.

8、氧化铁纳米颗粒具有类似过氧化物酶的催化活性

Intrinsic peroxidase-like activity of ferromagnetic nanoparticles. *NATURE NANO* 2007，2:577-583



阎锡蕴研究组研究发现氧化铁纳米颗粒具有过氧化物酶的催化功能。研究组还利用纳米颗粒模拟酶的这一新特性，设计了多种免疫检测方法，实现了对乙肝病毒表面抗原和肌钙蛋白的检测。同期杂志上还刊登了中佛罗里达大学(University of Central Florida) 纳米科学技术中

心J.Manuel Perez教授写的述评：《氧化铁纳米颗粒：蕴藏的功能》。该述评称阎锡蕴、柯莎及其课题组成员首次发现氧化铁纳米颗粒具有类似过氧化物酶的催化活性，并提出了氧化铁纳米颗粒模拟酶的概念。虽然如何在生物技术和医疗领域更好地利用纳米材料的催化活性还有待探索，但氧化铁纳米颗粒催化活性的发现将使人们对此产生更多的关注。

Prof. Xiyun Yan's group reported that magnetite nanoparticles possess an intrinsic enzyme mimetic activity similar to natural peroxidases. Based on the novel findings, they developed a novel immunoassay using the multi-function of antibody-modified nanoparticles (targeting, separation and catalysis). A commentary article in the same issue of Nature Nanotechnology noted that Yan, Perrett and colleagues' results show for the first time that iron oxide nanoparticles can function as peroxidase nanomimetics. Although the potential wide applications of the peroxidase-like activity of iron oxide nanoparticles in medicine and biotechnology remain to be explored, the 'ready-made' simplicity of catalytic activity in iron oxide nanoparticles will certainly attract a lot of attention.

三、组织机构 （Organization）

（一）室务委员会

实验室主任： 徐 涛 研究员

实验室副主任： 龚为民 研究员

阎锡蕴 研究员

唐 宏 研究员

（二）学术委员会

学术委员会主任： 王志珍 院士

学术委员会成员：（按姓氏拼音排序）

姓名	职称	工作单位
常文瑞	院士	中科院生物物理所
郭爱克	院士	上海生科院神经所/中科院生物物理所
贺福初	院士	军事医学科学院
蒋华良	研究员	中科院上海生科院药物所
李家洋	院士	中国科学院
李 林	研究员	中科院上海生科院生化所
林其谁	院士	中科院上海生科院生化所
强伯勤	院士	中国医学科学院
秦志海	研究员	中科院生物物理所
饶子和	院士	南开大学/中科院生物物理所
施蕴渝	院士	中国科技大学
田志刚	研究员	中国科技大学
王大成	院士	中科院生物物理所
徐 涛	研究员	中科院生物物理所
于 军	研究员	中科院基因组所
张先恩	研究员	科技部基础司

（三）实验室成员（按姓氏拼音排序）

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	江 涛	蒋太交	焦仁杰	柯 莎	梁栋材	梁 伟
刘迎芳	刘志杰	马 跃	苗 龙	秦 燕	秦志海	饶子和	孙 飞
唐 宏	唐 捷	王大成	王江云	王盛典	王志珍	王志新	徐 涛
阎锡蕴	杨福愉	殷勤伟					

四、管理 （Management）

（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。

五、研究进展 （Research Progress Report）

（一）蛋白质三维结构与功能研究

1、常文瑞组

在光合膜蛋白研究方面，我们完成了黄瓜 LHCII 晶体结构的测定工作，发现 LHCII 分子中两个 Lutein 分子的构象差异，提出这种构象改变可能与光淬灭位点的形成有关；发现不同存放期的 LHCII 晶体的晶胞参数和光谱特征有所改变，推测这种变化可能与其分子构象变化有关，并将可能为研究其光能传递和光保护提供新的信息，部分研究结果已经发表（*Biochem. Biophys. Res. Commun.*），后续研究工作正在进展之中。另外我们已成功获得高等植物光系统 II 中几种光合膜蛋白及其复合物的样品，其中数种样品已获微晶，晶体质量正在改善和优化之中。

在可溶性的重要功能蛋白研究方面，我们成功地用基于Br的SAD法测定了马来酰丙酮酸异构酶MPI高分辨率晶体结构，这是第一个MSH依赖性酶的晶体结构（*J. Biol. Chem.*）。并解析了人源S100A13蛋白的晶体结构，发现一些独特的结构特征（*Biochem. Biophys. Res. Commun.*）。解析了人胞质磺酰基转移酶SULT1A2与PAP复合物的晶体结构，研究结果已经投送国际核心杂志。解析了硫氧化还原酶 (SOR)的两种不同晶型的晶体结构，研究结果正在总结之中。此外还分别测定了蚯蚓纤溶酶三种组分：EFE-b、EFE-c、EFE-g和牛胰蛋白酶抑制剂aprotinin的复合物的晶体结构。并获得人源DPY-30的晶体，正在进行重原子衍生物的制备工作。

1、Prof. Chang W.R.

We have solved LHC-II crystal structure from cucumber at 2.66Å resolution. It was found that two lutein molecules have different conformations. We proposed that the conformational change might relate to formation of non-photochemical quenching site based on the structure analysis. We also discovered that the dehydration of the LHCII crystals resulted in a notable shrinkage of the crystal unit cell dimensions, which was accompanied by a red-shift of the fluorescence emission spectra of the crystals. These phenomena suggest the changes in the crystal packing during dehydration might be the cause of internal conformational changes within LHCII. Part of the results was published (*Biochem. Biophys. Res. Commun.*). Moreover, we have successfully harvested some amount of several membrane proteins and complexes from higher plant photosystem II, and gain microcrystals of some samples, now we are trying to optimize the crystal growth conditions.

On the other projects, we have solved high resolution structures of MPI, which is the first example of MSH-dependent enzyme, using SAD method (*J. Biol. Chem.*). And we have solved crystal structure of human S100A13 and found some unique structural features (*Biochem. Biophys. Res. Commun.*). In addition, crystal structure of SULT1A2 complexed with PAP, crystal structures of sulfur oxygenase reductase (SOR) in two crystal forms, three structures of EFE components complexed with inhibitor were also solved, the results were submitted or in preparation. And we have successfully crystallized human DPY-30, the screening of heavy atom derivatives are in progress.

发表文章：

1、 Wang R, Yin YJ, Wang F, Li M, Feng J, Zhang HM, Zhang JP, Liu SJ, **Chang WR**. Crystal structures and site-directed mutagenesis of a mycothiol-dependent enzyme reveal a novel folding and molecular basis for mycothiol-mediated maleylpyruvate isomerization. ***J Biol Chem.*** 2007；82(22):16288-294.

2、 Li M, Zhang PF, Pan XW, **Chang WR**. Crystal structure study on human S100A13 at 2.0 A resolution. ***Biochem Biophys Res Commun.*** 2007；356(3):616-21.

3、 Yan H, Zhang P, Wang C, Liu Z, **Chang WR**. Two lutein molecules in LHCII have different conformations and functions: Insights into the molecular mechanism of thermal dissipation in plants. ***Biochem Biophys Res Commun.*** 2007；355(2):457-63.

2、龚为民组

目前主要集中在蛋白质翻译起始、生物膜转运等相关的蛋白质复合体和膜蛋白的结构生物学研究，建立了膜蛋白和蛋白质复合体的表达纯化体系，形成了相关功能研究的稳定合作伙伴。在真核翻译起始复合物及其与核糖体相互作用方面取得重要进展，共解析其中四个真核翻译起始因子亚基的晶体结构，表达纯化了eIF3和mini-MFC两中复合体，纯化了酵母核糖体并完成了亚基拆分，为后续解析起始复合体的三维结构和研究起始复合体与核糖体的相互作用打下了基础。根据生物膜转运的功能研究，筛选并大量可溶表达出22种膜转运相关的人源未知结构蛋白，完成了TRAPP复合体中synbindin蛋白的晶体结构和NMR结构，研究了其与syndecan的相互作用。表达纯化出三种人源膜蛋白，其中一种已获得微晶。另外我们还完成了一些酶催化机制的结构生物学研究。

2、Prof.Gong W.M.

Our research interests are the structural biology studies of proteins and protein complexes involved in translation initiation, vesicle trafficking. We have set up some expression and purification systems for membrane proteins and protein complexes and established stable collaborations with other groups on related functional studies. We have already made significant progress on the sample preparation of eukaryotic translation initiation complexes and yeast ribosome. Four crystal structures of eukaryotic initiation factor subunits have been solved in our lab. Based on the functional studies, we selected and purified 22 human vesicle trafficking related proteins with unknown structures in soluble form. The structure of synbindin, a component of TRAPP complex, has been solved by crystallography and NMR. We also have expressed and purified three human membrane proteins, one of which has been crystallized as a micro-crystal. Besides, we have finished other structural biology studies on enzyme catalytic mechanisms.

发表文章：

1. Hou X, Liu R, Ross S, Smart EJ, Zhu H, **Gong W**. Crystallographic Studies of Human MitoNEET. ***J Biol Chem***. 2007；282(46):33242-6.

2. J Li, C Zhang, X Xu, J Wang, H Yu, R Lai, **W Gong**. Trypsin inhibitory loop is an excellent lead structure to design serine protease inhibitors and antimicrobial peptides. ***FASEB J***. 2007；21(10):2466-73.

3. Wang M, Liu L, Wang Y, Wei Z, Zhang P, Li Y, Jiang X, Xu H, **W Gong.** Crystal structure of homoserine O-acetyltransferase from Leptospira interrogans. ***Biochem. Bioph. Res. Co***. 2007；363(4):1050-6.

4. X Hou, Y Wang, Z Zhou, S Bao, Y Lin, **W Gong**. Crystal structure of SAM-dependent O-methyltransferase from pathogenic bacterium *Leptospira interrogans* .***J. Struc. Biol.*** 2007；159(3):523-8.

5. X Li, Z Wei, M Zhang, X Peng, G Yu, M Teng, **W Gong**. Crystal structures of E. coli laccase CueO at different copper concentrations.***Biochem. Bioph. Res. Co.***. 2007；354(1):21-6

6. Z Cheng, L Sun, J He, **W Gong** . Crystal structure of human mu-crystallin complexed with NADPH. ***Protein Sciences***, 2007；16(2):329-35

7. C Zhang, L Liu, H Xu, Z Wei, Y Wang, Y Lin, **W Gong**. Crystal structures of human IPP isomerase new insights into the catalytic mechanism. ***J Mol Biol***. 2007；366(5):1437-46

3、江涛组

2007 年我们一共完成了包括神经生长因子，神经营养因子与其受体 $P75^{NTR}$ 复合物, P2 蛋白，Mastoparan 以及钙调蛋白-靶肽复合物等五种蛋白的晶体结构解析工作，并获得多种重要蛋白的晶体。

1、 神经营养因子对于神经系统的发育具有重要的意义。 研究发现，其细胞表面受体之一 $p75^{NTR}$ 与神经营养因子的直接相互作用与神经系统退行性疾病关系密切。但是二者间的相互作用方式一直存在争议。我们最近完成了神经营养因子 NT-3 与 75^{NTR} 2：2 复合物 2.8 Å 分辨率晶体结构解析，揭示了神经营养因子与其受体 $P75^{NTR}$ 天然的结合模式，因此具有重要的科学意义。

2、 Mastopran 是蜂毒中一种具有多种生物学功能的多肽，我们利用晶体学手段解析了这种多肽 1.2 Å 分辨率的晶体结构。通过与核磁结构比较，并结合生物化学实验的结果，我们对其结构功能关系进行了论述。

3、 P2 蛋白是外周髓鞘中的重要蛋白。迄今其功能未知，但有实验证明 P2 能诱导实验性过敏神经炎(EAN)，可作为研究人类 Guillain-Barré 综合症的模型。我们解析了猪的硬脊髓根部神经中的 P2， 获得分辨率为 1.8 Å 的晶体结构。根据电子密度图在 P2 结合口袋处发现其天然脂类配体，初步推断为 γ-亚麻酸（GLA，18:3n-6)。这一发现为 P2 的功能研究提供了新的思路。

4、 膜受体Fas与其配基FasL的相互作用与人类癌症的发生关系密切以往的研究表明，钙调素与Fas死亡结构域之间存在着直接的相互作用。我们最近完成了CaM与Fas肽复合物的晶体结构解析，该结构有助于人们深入了解CaM与Fas受体间的相互作用方式。

3、Prof. Jiang T.

In 2007, we determined five protein structures including nerve growth factor, NT3-P75 complex, Mastoparan, Calmodulin complex and P2 protein.

1) NTs are key factors for the development and maintenance of the mammalian nervous system. The binding of NTs to the $p75^{NTR}$ receptor induces either cell survival or apoptosis. $p75^{NTR}$ also plays a very important role in Alzheimer's disease, and tumor development and metastasis. In spite of this knowledge, the fundamental mechanism of interaction between p75 and NTs is not clear. Here we report the crystal structure of a 2:2 symmetrical complex of NT-3 and $p75^{NTR}$ at 2.8A resolution. This structure revealed the detailed interaction mode between p75 with NT-3. This structure provides a basis to understand diverse $p75^{NTR}$ functions and facilitate the therapeutic utility of neurotrophins as clinical agents.

2) Mastoparans are the major peptides in social wasp venoms and possess a variety of biological activities. Here we report the first crystal structure of mastoparan from Polistes jadwagae (MP-PJ) at 1.2 Å resolution. Together with biochemical results, we propose that the interactions between mastoparan molecules serve an important role in forming the α-helix conformation which is highly related to their biological activities.

3) The P2 protein is a small basic protein found in peripheral myelin. Its function has not been established, but it is known that P2 could induce experimental allergic neuritis(EAN) in rats, a model of Guillain-Barré syndrome in humans. Structure of P2 protein purified from intradural spinal roots of pig was determined to 1.8 Å. The structure contains some extra electron density in the binding cavity. It is very likely that this is the density of P2 protein's natural lipid ligand. The density is quite suitable for the molecular of γ-linolenic acid (GLA，18:3n-6)，which was not reported previously.

发表文章：

Liu SQ, Wang F, Tang L, Gui WJ, Cao P, Liu XQ, Poon WS, Shaw PC. Crystal structure of mastoparan from Polistes jadwagae at 1.2 angstrom resolution. *JOURNAL OF STRUCTURAL BIOLOGY* 2007; 160(1):28-34

4、梁栋材组

1) 在甘油的代谢过程中，甘油磷酸二酯磷酸二酯酶（GDPD）催化甘油磷酸二酯，水解成一个醇类和一个三磷酸甘油。它的产物参与到很多的生化途径中，起到重要的作用。我们解析了来自于T. tengcongensis 的GDPD（ttGDPD）的1.9埃的结构。ttGDPD单体分子通过一个分子间的二硫键以及其他一些氢键结合形成二体，二体很可能是作为它的功能单位。通过对ttGDPD同源蛋白的一级序列比对以及三维结构叠合，我们在活性位点周围确定了一些保守残基，可能和ttGDPD的催化机制有密切关系。通过对这些残基的单点突变研究，i）我们首次确定了GDPD是一个金属依赖酶；ii）确定了ttGDPD的活性残基，并提出了ttGDPD的可能的催化机制；iii）根据同源蛋白1zcc的结构中活性位点结合的硫酸根离子，通过把它模拟成GDPD底物中的磷酸半族，分析了ttGDPD底物分子甘油磷酸二酯分子和ttGDPD的实际结合情况。

2) 细菌通过趋化系统来控制自身运动方向，从而对有益或有害化学信号的梯度变化做出响应。两组跨膜蛋白复合物参与了细菌对外界环境和自身生理信号的感应、增益和反馈控制。CheW是第一组复合物中的重要因子。它与CheA和MCP结合，在细胞极点上对稳定MCP－CheA的结合起到了至关重要的作用。 在2.2 Å分辨率下，我们运用分子置换法解析了来源于腾冲嗜热菌中蛋白TtCheW的三维结构，结构分析发现在CheW上存在一个保守motif“NxxGxIxP”，对CheW-CheA的结合起了重要作用。我们根据已有的CheW单点突变实验和对TtCheW分子中蛋白质相互作用区域预测，推测TtCheW与MCP的结合区域是位于复合物结构模型中TtCheW和CheA P4 domain结合所产生的凹槽内。

3) 完成了二种重要功能酶的三维结构研究。①利用SAD方法解析了Tfdx蛋白的2.15 Å的三维结构。Tfdx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αβ/βα 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。文章已投送国际期刊。②利用SIRAS方法解析了来自生防芽孢杆菌的甘露聚糖酶 BCman 1.45 Å的三维结构。通过功能研究与结构分析揭示了BCman 催化特性和耐热性。

4、Prof. Liang D.C.

1) Glycerophosphodiester phosphodiesterase catalyzes the hydrolysis of a glycerophosphodiester to an alcohol and glycerol 3-phosphate in glycerol metabolism. It has an important role in the synthesis of a variety of products that participate in many biochemical pathways. We report the crystal structure of the Thermoanaerobacter tengcongensis GDPD (ttGDPD) at 1.9 Å resolution. The ttGDPD dimer with an intermolecular disulfide bridge and two hydrogen bonds is considered as the potential functional unit. To elucidate the catalytic mechanism, we used site-directed mutagenesis to make a series of converted residues. We have characterized ttGDPD as a metal ion-dependent enzyme, for the first time. We have also identified the residues participating in the catalysis, and we propose the catalytic mechanism of ttGDPD too. There is a sulfate ion in the active site of homologous structure GDPD from A. tumefaciens (1zcc), which is equivalent to the phosphate moiety of the substrate, allowing us to study the true substrate-binding mode of ttGDPD.

2) Chemotaxi senables bacteria to control their movements in response to gradients of beneficial and toxicchemicals. Two transmembrane protein complexes from bacteria exhibit remarkable sensitivity, through gain and feed back control, to the external environment and internal physiology. CheW is an essential component of the first complex. It interacts with both CheA and the cytoplasmic domain of MCP and links their activities. The crystal structure of the scaffolding protein CheW from Thermoanaerobacter tengcongensis (TtCheW) is solved with a resolution at 2.2A ˚using molecular

replacement. Based on the crystal structure， we found that the conserved motif ‘‘NxxGxIxP’’ from CheW plays an important role in CheA binding. The coincidence of the reported mutation sites related to CheW–MCP binding, and the predicted protein interaction region with in the TtCheW molecule, suggest that CheW–MCP binding sites lie in the groove-shaped area between TtCheW and the CheA P4 domain with in the assembled model.

3） Solved the crystal structure of two important function enzymes. ①We have solved the 2.15Å crystal structure of Tfdx using single SAD. Tfdx belong to a metal hydrolyze family, which have the β-inneracylammoniase domain. The Tfdx molecule exhibits fold of αβ/βα. Its metal binding site plays an important role in the course of hydrolyzes covalent bond. Article to be contributed. ②We have solved the 1.45Å crystal structure of BCman using SIRAS. Structure and function studies revealed Catalytic Substrate Specificity and Thermostability Displayed. Article to be contributed.

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WangYao, Liang Shi, **Dong-Cai Liang**. Crystal structure of scaffolding protein CheW from thermoanaerobacter tengcongensis. ***Biochemical and Biophysical Research Communications*** 2007；361：1027-1032.

5、刘迎芳组

本课题组今年的工作进展主要集中在凋亡细胞的吞噬和泛素蛋白酶体两大途径。在线虫中凋亡细胞的吞噬主要由两条信号通路介导，第一条为CED-14/CED-1/CED-6/CED-7，第二条信号通路为CED-2/CED-5/CED-10/CED-12。目前我们已经解析了CED-14和CED-2的晶体结构，它们都在凋亡细胞的吞噬方面起着非常重要的作用，结构的解析，为疾病的研究提供了新的思路。底物泛素化主要包括E1 泛素激活酶，E2泛素转移酶，E3泛素连接酶和近年发现的多泛素连接因子E4。DCN1是一种参与泛素-蛋白酶体途径泛素化修饰过程的蛋白，结构表明它可能是E3连接酶酶复合物的一种结合接头蛋白，用以连接泛素化蛋白与底物蛋白。DOA1是E4家族成员中的一员，它能与泛素和CDC48直接结合，从而帮助CDC48招募泛素来行使它的功能，从结构上分析，它在蛋白质泛素降解途径中起到非常重要的作用，阐明了泛素蛋白质降解途径中泛素来源问题。另外，本课题组承担了国家自然科学基金重大项目“禽流感病毒主要蛋白质的结构和功能研究”，并获得了其中RNA聚合酶亚基的晶体，结构正在进一步解析中。

5、Prof. Liu Y.F.

Our lab mainly focused on the cell death engulfment and ubiquitin-proeasome pathway this year. 1, Dying cells engulfment and aging research: Two signal transduction pathways that act redundantly to control engulfment in C elegans have been identified in the past reports. Components of the cell-corpse recognition system of one pathway includes the CED-14/CED-1/CED-6/CED-7; The second pathway contains CED-2/CED-5/CED-12. Now we have solved the structures of CED-14 and CED-2. The structures of these proteins implicate their mechanisms for cell corpse engulfment processes. Protein ubiquitination, a processes that covalently link ubiquitin or ubiquitin-like proteins to protein substrates, involve in E1(ubiquitin activating enzyme),E2(ubiquitin conjugating enzyme), E3(ubiquitin-proein ligase) and E4(ubiquitin elongating factor). DCN1 participates in modification of protein substrates by Nedd8 in ubiquitin-proeasome pathway. The structure of DCN1 illustrates that DCN1 could be a scaffold protein in an E3 ligase compelx. DOA1 is a member of E4,which can bind ubiquitin and CDC48 to help CDC48 recruit ubiquitin to facilitate their function. DOA1 plays a key role during ubiquitin dependent protein degradation based on structure analyses and is the major source of ubiquitin during ubiquitin dependent protein degradation process. We also took part in the structural and functional study of the main protein of avian influenza virus and obtained the crystal of RNA polymerase subunit and structure determination is undergoing.

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Yang X, Zhou J, Sun L, Wei Z, Gao J, Gong W, Xu RM, Rao Z, **Liu Y**. Structural basis for the function of DCN-1 in protein Neddylation. ***J Biol Chem***. 2007；282(34):24490-4.

6、刘志杰组

本课题组过去的一年中，在所各级领导的关怀和结构生物学中心、及平台各位老师的帮助下，带领课题组成员们顺利实施了获得资助的几个研究课题并且进展顺利，取得了一些阶段性的研究成果，2007年共发表研究论文12篇，包括Nat Struc Mol Biol, Cell, Proteins 等。同时又争取到了5项研究基金，总之各项工作稳步进行。在科研经费申请方面，获得我院“知识创新工程重要方向项目”和与韩国KIST合作的资助项目各一项；与英国Leeds大学的Stephen Baldvin 教授合作获得访问学者交流基金一项；从院国际合作局获得与俄罗斯科学院生物物理所Eugene Vysotski教授合作的国际交流资助一项；我组副研究员Neil Shaw获得国家自然科学青年基金资助一项。在合作与交流方面，积极参加了多个结构生物学方面的国际会议并作邀请报告。接待多位海外科学家的到访。主办了“International Symposium on Synchrotron Radiation and Biology”。在研究所建设方面，积极参与平台二期建设，负责蛋白质平台二期“自动化克隆和小规模表达可溶性筛选机器人”和“蛋白质晶体生长机器人”筹备工作，该工作已基本完成。 在新的一年中，本人将继续带领研究组成员在院和研究所的政策方针指导下，进一步加强自主创新能力和核心竞争力的培养，争取取得更大成果。

6、Prof. Liu Z.J.

In 2007, our team made many significant achievements.

1. Papers: 12 research papers were published in high impact factor journals, including Nat. Struc. Mol. Biol. 2007,14(8), 779-84;Cell 2007,129, 747-759; Proteins 2007(1),263-267

2.Grants: ①fund from CAS, ②fund of KIST project, ③fund from CAS-RAS, ④fund from NSFC.

3. Awards: Doctor Neil Shaw Won the Top Prize at the 6th TICPS international conference .

4.International cooperation: ①organized International Symposium on Synchrotron Radiation and Biology, ②attended several international conferences on Structural Biology.

5. Research platform development: Automated cloning & small-scale expression testing using robotics, protein crystallization at nanoliter scale using robotics implemented.

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2． Shaw, N., Tempel, W., Chang, J., Yang, H., Cheng, C., Ng, J., Rose, J., Rao, Z., Wang, B. C. & **Liu, Z. J***. (2007b) Crystal structure solution of a parb-like nuclease at atomic resolution. Proteins, Doi: 10.1002/prot.21641. (Correspondence)

3． Shaw, N., Cheng, C., Tempel, W., Chang, J., Ng, J., Wang, X. Y., Perrett, S., Rose, J., Rao, Z., Wang, B. C. & **Liu, Z.J***,. (NZ)CH...O Contacts Assist Crystallization of a Par B –like Nuclease, ***BMC Struc Biol***. 2007；7: 46. (Correspondence)

4． Shimada, A., Niwa, H., Tsujita, K., Suetsugu, S. Kyoko, H.S., Akasaka, R.,Nishino, Y., Toyama, M., Chen, L., **Liu, Z.J,** Wang, B.C., Yamamoto, M., Terada, T., Miyazawa, A., Shirouzu, M., Tanaka, A., Sugano, S., Takenawa, T., and Yokoyama, S. Curved EFC/F-BAR domain dimers are joined end to end into a filament for membrane invagination in endocytosis. ***Cell***. 2007；129: 747-759.

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Biochem Biophys . 2007；463, 68-77. (Correspondence)

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7． Takuya B. Hiyama, Min Zhao, Yu Kitago, Min Yao, Shun-ichi Sekine, Takaho Terada, Chizu Kuroishi, **Liu, Z. J.**, John P. Rose, Seiki Kuramitsu, Mikako Shirouzu, Nobuhisa Watanabe, Shigeyuki Yokoyama, Isao Tanaka, and Wang, B.C.. Structural basis of CoA recognition by the Pyrococcus single-domain CoA-binding proteins. ***J Struct Funct Genomics***, 2007；7: 119-129.

8． Gerwe, B., Kelley, L. L., Dillard, B. D., Lai, T., **Liu, Z. J.**, Tempel, W., Chen, L., Habel, J., Lee, D., Jenney, F. E., Jr., Sugar, F. J., Richardson, J. S., Richardson, D. C., Newton, M. G., Wang, B. C., Adams, M. W. & Rose, J. P. Structural and transcriptional analyses of a purine nucleotide-binding protein from pyrococcus furiosus: A component of a novel, membrane-bound multiprotein complex unique to this hyperthermophilic archaeon. ***J Struct Funct Genomics***, 2007；8(1), 1-10.

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10． Kanaujia, S.P., Ranjani, C.V., Jeyakanthan, J., Baba, S., Chen, L., **Liu, Z.J**., Wang, B.C., Nishida, M., Ebihara, A., Shinkai, A., Kuramitsu, S., Shiro, Y., Sekar, K., and Yokoyama, S. Crystallization and preliminary crystallographic analysis of molybdenum-cofactor biosynthesis protein C from Thermus thermophilus. ***Acta Cryst F*** 2007；63, 27-29.

11． Kelley, L. L.; Dillard, B. D.; Tempel, W.; Chen, L.; Shaw, N.; Lee, D.; Newton, M. G.; Sugar, F. J.; Jenney, F. E., Jr.; Lee, H. S.; Shah, C.; Poole, F. L., 3rd; Adams, M. W.; Richardson, J. S.; Richardson, D. C.; **Liu, Z.** J.; Wang, B. C.; Rose, J. Structure of the hypothetical protein PF0899 from Pyrococcus furiosus at 1.85 Å resolution. ***Acta Cryst F*** 2007；63, 549-552.

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7、王大成组

1. 2006-2007 年完成 4 种蛋白质及复合物的晶体结构研究,2007 年内已发表和被接受发表论文 2 篇。

2. 2007 年内完成动物病原菌三型分泌系统蛋白质效应物 SpvC 及其活性多肽底物三维结构及其与功能关系的研究，发现全新的蛋白质结构，阐明 SpvC 与致病通路中关键激酶 MAPK 相互作用，进而阻断宿主天然免疫应答的机理。由于这类病原菌效应物同时存在于动植物中，因而具有重要意义。有关论文已发表在 Molecular Cell。

3. 完成3种Cul3介导的泛素连接酶复合物的体外构建，其中2种已获得可溶表达和纯化样品，一种获得初步结晶。

7、Prof. Wang D.C.

In 2006-2007, four crystal structures have been determined and 2 papers published or accepted in 2007 (see paper list). Among others, crystal structures of SpvC, an effector of TTSS of bacterial pathogens, and its complex with phosphopeptide substrate, revealed a novel protein structural type and provides insights into the molecular mechanism of the inactivation of the pathogenic MAPK. The results have been published in Molecular Cell. Besides, 3 human Cul3 ubiquitin ligase complexes has been constructed. Among them 2 recombinant complexes have been expressed and purified, one crystallized preliminary.

发表文章：

Yongqun Zhu, Hongtao Li, Chengzu Long,Liyan Hu, Hao Xu, Liping Liu, She Chen, **Da-Cheng Wang**, Feng Shao. Structural Insights into the Enzymatic Mechanism of the Pathogenic MAPK Phosphothreonine Lyase. ***Molecular Cell***, 2007；28：899－913

（二）蛋白质功能与折叠原理研究

1、陈畅组

细胞的氧化还原调控失衡与衰老、神经退行性疾病、炎症、糖尿病等都密切相关，其分子机制有待阐明。我们的研究方向为细胞氧化还原调控的分子机制:氧化还原依赖的蛋白质翻译后修饰在细胞命运和疾病发生中的作用。重点研究一氧化氮对蛋白巯基的亚硝基化修饰及作用。

1. 致力于蛋白质巯基亚硝基化方法学的原始创新：发现了维生素 C 在亚硝基化检测过程中引起假阳性信号；解决了高通量检测蛋白亚硝基化方法中表面活性剂对质谱的干扰和实验重复性差的问题；创建了蛋白亚硝基化的胶内快速直接可见检测方法;已建立高通量定量组学检测内源亚硝基化方法。

2. 发现一氧化氮引起的蛋白质亚硝基化修饰失衡在细胞死亡中的关键作用，并首次阐述了蛋白质亚硝基化修饰与细胞氧化还原状态的定量依赖关系。

3. 发现一氧化氮通过蛋白亚硝基化修饰诱导核酸内切酶 APE1-REF1 核输出，首次揭示了一氧化氮通过蛋白亚硝基化修饰特异机制实现对细胞蛋白核输入和核输出系统的调控。一氧化氮通过蛋白质巯基亚硝基化修饰调控 SUMO 修饰 E3 连接酶 PIAS3 稳定性，首次揭示了蛋白亚硝基化修饰、泛素化修饰及 SUMO 化修饰三种翻译后修饰的相互作用。

4. 在研究单个蛋白亚硝基化对其功能调控的基础上，结合本课题组建立的蛋白亚硝基化修饰的定量组学方法和系统生物学思想，进行多靶点蛋白亚硝基化修饰作用网络的分析和动态变化研究。

1、Prof. Chen C.

We are interested in investigating the mechanism and the cellular effects of the redox-based post-translational modification of proteins, particularly on the S-nitrosylation of proteins induced by nitric oxide. Some progress in 2007 is as following:

We found that nitric oxide causes global hyposumoylation in mammalian cells, promoted Pias3 degradation by facilitating its interaction with tripartite motif-containing 32 (Trim32), a ubiquitin E3 ligase. This study reveals a novel crosstalk between S-nitrosation, ubiquitination, and sumoylation, which may be crucial for NO-related physiological and pathological processes.

We found that nitric oxide controls nuclear export of APE1/Ref-1 through S-nitrosation of Cysteines 93 and 310. Our finding provided the first evidence that nitrosative stress regulated APE1 by subcellular translocation through S-nitrosation mechanism.

We proposed a novel mechanism underlying the susceptibility of neuronal cells to nitric oxide: the occurrence and regulation of protein S-nitrosylation is the checkpoint.

We developed a detergent-free biotin switch method and combined with LC-MS/MS to identify the S-nitrosylated targets. The LC-MS performance for the proteomic analysis of S-nitrosylated proteins was greatly ameliorated and the repeatability of experiments was greatly improved. Furthermore, the amount of sample was also significantly reduced.

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3. Jie He, Tiepeng Wang, Peng Wang, Peiwei Han, **Chang Chen***, A novel mechanism underlying the susceptibility of neuronal cells to nitric oxide: the occurrence and regulation of protein S-nitrosylation is the checkpoint. ***Journal of Neurochemistry,*** 2007; 102: 1863–1874

4. Shaojin Duan, **Chang Chen ***, S-nitrosylation/Denitrosylation and Apoptosis of Immune Cells. ***Cellular & Molecular Immunology.*** 2007；Vol.4(5): 353－358.

2、柯莎组

在2007年度完成的工作主要有五方面：

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不同程度缺失的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）不同酵母来源Ure2的对比研究

有研究表明Saccharomyces. paradoxus Ure2p (SpUre2p)Sacharomyces cerevisiae Ure2p (ScUre2p) 有很高的同源性，但体内实验表明，SpUre2p并没有prion形成的能力。为此，我们和法国Cullin教授的实验室合作，分别从体外和体内做实验来寻找原因。我们的体外实验证明，SpUre2p同ScUre2p一样，在体外都有着很强的成纤维的能力，但SpUre2p的纤维有着更好的机械强度。于是我们推测，可能正是因其高机械强度，SpUre2p的纤维不容易被打断产生种子传播prion，导致prion的丧失。

5）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。

2、Prof. Perrett, S.

Protein Misfolding and Disease

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 activation. 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) *Conservation of Ure2 Prion Behaviour in Different Yeast Species*

While Ure2 in the yeast species *Saccharomyces cerevisiae* (*Sc*Ure2) behaves as a prion, its homologue (*Sp*Ure2) in the closely related yeast *S. paradoxus*, does not. In order to investigate the structural basis for this, we collaborated with Prof. C. Cullin, Bordeaux, France, to compare the properties of the proteins *in vitro* and *in vivo*. Surprisingly, we found that *Sp*Ure2, like *Sc*Ure2, readily forms amyloid-like fibrils *in vitro*. Further, the biochemical properties of the two proteins are identical. However, we observed greater resistance to fragmentation for *Sp*Ure2 fibrils. The results suggest that the failure of *Sp*Ure2 to act as a prion stems from its inability to propagate transmissible prions *in vivo*, rather than a fundamental difference in amyloid structure.

5)*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. 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.

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3、秦燕组

克隆表达并纯化出大肠杆菌LepA和EF-G的全长与缺失体蛋白，测定了它们的GTPase活性，正在检测它们的分子伴侣活性；已获得LepA全长蛋白的晶体，正在优化条件；发酵得到大量对数期大肠杆菌菌体，并通过区带密度梯度离心方法制备出足够多的重组核糖体，测定其具有体外活性；制备并纯化得到LepA蛋白与核糖体L2蛋白的多克隆抗体，正在制备LepA蛋白的单克隆抗体；合成特定的氨酰tRNA与mRNA，构建体外翻译体系，为进一步实验提供了良好基础；通过大肠杆菌野生型与LepA缺陷型在极端条件下的生长曲线对LepA蛋白的功能作出提示，正在对LepA蛋白进行细胞定位；正在制备敲除lepA同源基因的果蝇；表达纯化得到大肠杆菌RRF蛋白，蔗糖密度梯度离心获得大肠杆菌多聚核糖体，准备进行多聚核糖体breakdown实验。

3、Prof. Qin Y.

Escherichia coli full-length and truncated protens of LepA and EF-G have been cloned, expressed and purified, and their GTPase activity has also been tested. The chaperone activity of this two proteins as well as their truncations are under test. We have obtained the crystal of LepA, but its growth condition is still in optimization. Plenty of recombinant ribosome has been extracted from *E. coli* in exponential phase and has been separated and purified by zonal density gradient centrifugation. Ribosome activity *in vitro* has been ascertained. Polyclonal antibodies of LepA and ribosome protein L2 are available. LepA monoclonal antibody is under preparation. Specific aminoacyl-tRNA and mRNA have been prepared and *in vitro* translation system has been constructed, which provides a convenient foundation for future study. The growth curve results of *E. coli* wide type and *lepA* knock-out strains have given us some clues of LepA function *in vivo* under extreme growth conditions. Localize LepA *in vivo*. And we are trying to knock out the homologous gene of *lepA* in fruit fly. Protein RRF of *E. coli* has been expressed and purified and polysome has also been separated, so that the breakdown assay of polysome is going to be carried out.

4、王志珍组

1. α-synuclein (AS)在大肠杆菌的转运

α-synuclein (AS)是帕金森氏病患者大脑神经元中淀粉样斑块的主要成分。确认了在大肠杆菌表达的无信号肽的 AS 转运到周质腔定位。鉴定其 C 端 99-140 是与转运相关的关键序列，可能起到类似信号肽的作用；N 端 1-60 序列对其转运没有贡献。发表在 2007 年 J.Bacteriol.。

2. ERp44 的晶体结构解析

人内质网滞留蛋白ERp44是PDI家族成员，也是ER内蛋白质质量控制的重要成员。解析了2.6埃分辨率人ERp44的晶体结构，登录PDB(ID：2r2j)。这是迄今唯一获得的人PDI家族成员全长分子的晶体结构。发现柔性的C末端尾巴挡住结合底物蛋白的疏水口袋和CRFS基序周围的疏水表面。切除C端使酶活性、分子伴侣活力和结合内源性蛋白能力明显增强。

4、Prof. Wang C.C.

1. Translocation of α-Synuclein expressed in *Escherichia coli*.

α-synuclein (AS) is a major component of Lewy bodies in Parkinson's disease. We report for the first time that recombinant AS with no signal sequence produced in *E. coli* mostly localizes in the periplasm. The C-terminal 99-to-140 sequence is the main part responsible for the translocation of AS. The N-terminal 1-to-60 region is not required for translocation of AS into the periplasm. Published in J. Bacteriol (2007).

2. Study on the crystal structure of ERp44

As a member of the human protein disulfide isomerase (PDI) family, ERp44 plays an important role in the endoplasmic reticulum (ER) protein quality control. We solved the crystal structure of ERp44 at 2.6 A, which has been deposited to PDB (ID: 2r2j). This is the first full length structure of the human PDI family members. A flexible C-terminal tail turns back to the b' and a domains, shielding a hydrophobic pocket in domain b' and a hydrophobic patch close to the -CRFS- motif in domain a. Removal of the C-tail significantly increases the enzyme and chaperone activities, and the fraction of ERp44 that forms mixed disulfides with endogenous proteins at steady state.

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（三）生物膜与膜蛋白功能结构研究

1、姬广聚组

FK506 结合蛋白对β-细胞钙释放及胰岛素分泌的影响研究及钙释放受体在发育期心肌胞的表达、功能及与先心病发生发展的可能关系均取得突破性进展;FKBP12.6 基因敲除对心肌细胞 Ca2+ 释放受体功能的影响研究已成文；干细胞高效分化及应用研究取得阶段性进展。

1、Prof. Ji G. J.

During the year 2007 all the research projects we carry out have been made great progress. Besides the functional study on FKBP12.6 binding proteins in Cardiac, smooth myocytes, and pancreatic beta-cells, the most exciting things is that we make significant progress in protein ERP 44 study. We find that the ERP 44 is not, as reported, a IP3R subtype I selective inhibitor, but it possesses also markedly effect on RYRs in smooth muscle. This encourages us to generate knockout mouse model to investigate the ERP 44 in deeply and broadly further. Another exciting event in our research is that we have successfully construct and expressed specifically the G-CAMP2, a unique Ca2+ indicator, in cell nucleus. This is very important for us to investigate the role of nuclear in handling Ca2+ signaling for some genetic diseases. Additionally, we also make remarkable progress in our embryo heart study. We find for first time that a “switch” of function of RYRs and IP3Rs during heart development exsits.

2、焦仁杰组

1）证明 WRN 是 CAF-1 行使功能所必须（*Oncogene, 2007*）。2）证明 *dCAF-1-p180* 在染色质结构的建立与维持中至关重要（*Dev. Biol., 2007*）。目前正在研究该基因在表观遗传调控中的分子作用机制，已有一些很有意义的发现；同时我们也正在研究 *p180* 与 *p55* 的关系。3）我们已得到 *small boy* 基因的果蝇突变株。该基因的纯合突变果蝇幼虫期致死，同龄幼虫个体比野生形小很多；而杂合突变果蝇寿命减短。目前正在检测它的抗氧化能力变化、细胞生长及其与 Insulin 等信号通路的关系。4）我们已获得果蝇 *dRecQ4* 和 *dRecQ5* 的突变株。*dRecQ4* 突变株对特异 DNA 损伤敏感，内复制（Endo-replication）减少，细胞周期发生变化，*dRecQ5* 突变影响 DNA 双链断裂的修复能力，它可能直接参与同一染色体内同源重组的调控，而对染色体间的同源重组不重要。5）合作项目包括：（a）Bcd 调节基因表达的新机制；*Branching* 基因与细胞生长的关系。（b）dCAF-1 等蛋白复合物的结构解析。（c）dHDAC6 与蛋白清除及 Parkinson's 病的关系。我们已获得 dHDAC6 的 LOF 及 GOS 果蝇模型。（d）5HTs 与 Octopamine 受体（GPCRs）在睡眠、侵略性及抑郁症等行为方面的功能。为此，我们正在制备 6 个受体突变株果蝇（已获得两个）。

2、Prof. Jiao R.J.

The Jiao lab is focused on the research of epigenetic regulation of chromatin plasticity and genome stability using *Drosophila* as a model system. In the last two years, (1) We demonstrated that WRN is required for CAF-1 in response to DNA damage (2) *dCAF-1-p180* is essential for *Drosophila* development and maintenance of epigenetic memory (3) Loss of function of *dRecQ4* affects particular DNA damage sensitivity, endo-replication and cell cycle while *dRecQ5* may be essential for homologous recombination in the same chromosome (4) *small boy* gene has multiple roles in cell growth, anti-oxidative stress and aging. In addition, we are collaborating with several labs within China and the world trying to understand (a) the role of *branching* gene (b) the structure of dCAF-1 (c) the role of dHDAC6 in the process of protein clearance (d) the roles of GPCRs in sleep, aggression and depression etc.

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3、苗龙组

本研究组以线虫精子为研究对象，研究细胞运动的调控机理。结合运用 *Ascaris suum* 精子细胞的无细胞体系在生化上的可操作性以及 *C. elegans* 在遗传学上的可操作性，研究在精子发生过程中的信号转导。运用反向遗传学结合细胞生物学观察，发现在 *C. elegans* 精子细胞活化及运动的过程中，小 G 蛋白和磷酸酶可能扮演重要角色，目前我们正在研究精子细胞活化过程中其信号转导通路。我们也利用 *Ascaris suum* 精子的无细胞体系研究发现，其精子的活化过程与 *C. elegans* 精子活化高度同源，来自 *C. elegans* 的识别膜状体（Membranous Organelle, MO）的抗体，也特异性地识别 *Ascaris suum* 精子细胞中的膜状体。生化分析结合免疫荧光观察表明，该抗体标记的分子可能是一种膜结合蛋白，精子活化时，在膜状体与质膜融合的过程中，被释放到精子细胞表面。在精卵识别的过程中，该分子可能起重要作用。

3、Prof. Miao L.

My group is studying the amoeboid cell motility using sperm of nematodes *Ascaris suum* and *C. elegans*. Combining the biochemical accessibility of *Ascaris suum* sperm and genetics advantages of *C. elegans*, we are now studying the signal transduction during the worm spermatogenesis (including meiosis and sperm activation). Using the genome wide screening for infertility, we found that GTPases and phosphatases may play pivotal roles during *C. elegans* spermiogenesis and sperm motility. We also found that the sperm activation in *Ascaris suum* is very similar to that in *C. elegans.* The antibody recognizing the MO（Membranous Organelle）structure in *C. elegans* also labeled the MOs of *Ascaris suum* specifically. Further biochemical and immunofluorecence studies suggested that the antigen recognized by MO antibody is probably a membrane associated protein. During the MO fusion to plasma membrane, it may be released to the outside of plasma membrane to act as an important signal for sperm-egg recognition.

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4、徐涛组

胰岛素在GLUT4 转运过程中的关键作用位点的识别和确认

胰岛素刺激下脂肪和肌肉细胞中的葡萄糖转运体4（GLUT4）会被大量转运到膜上，对维持血糖平衡起着很重要的作用。一直以来，局限于传统的生化手段，GLUT4转运的具体步骤没能很好的区分和定义开来。我们发展了单个GLUT4储存囊泡的标记和识别技术，在活细胞中实现了对其动态循环过程的跟踪。依靠该技术我们确定了胰岛素调控GLUT4上膜的关键步骤是在囊泡锚定到细胞膜之后，主要是增强GLUT4储存囊泡与脂膜的融合能力。我们还发现PI3K以及它的下游效应分子AS160参与调控囊泡的锚定步骤，初步揭示GLUT4储存囊泡与细胞膜锚定的分子机制。

应用模式生物线虫研究调控型分泌的分子机制

模式生物线虫是很好的研究遗传和发育的系统，但其在细胞生物学特别是膜转运领域的贡献却十分有限。主要的原因是缺少高时空分辨的功能研究手段。我们克服了这个技术局限，首次将高时空分辨的分泌检测技术应用在线虫上，建立了在线虫细胞水平研究调控型分泌的技术平台。利用该技术平台，我们证明了核心致密囊泡的胞吐过程需要一种称为UNC-31的蛋白，阐明了该蛋白参与囊泡锚定的作用机制，并发现了UNC-13（Munc13-1 在线虫中的同源蛋白）和UNC-31 蛋白存在相互作用。该工作开辟了利用线虫模式生物研究囊泡分泌的新方向。

4、Prof. Xu T.

GLUT4-containing Vesicle Ranslocation in Adipocytes

We developed method to dissect different steps along the translocation and fusion of GLUT4-containing vesicles in live adipocytes. Using this method, we identified the key step of GLUT4 vesicle translocation that is regulated by insulin (Bai et al., Cell Metabolism, 2007).

Novel Insights of Dense Core Vesicle Docking from Studies on C. elegans Neurons

We advanced techniques in recording exocytosis at high temporal- and spatial-resolution from C. elegans neurons. Using these techniques, we investigated the requirement of UNC-31 protein in the release of dense core vesicles and revealed a novel interaction between UNC-31 and UNC-13 in the docking of dense core vesicles. This work represents a new hallmark of using C. elegans to study the basic mechanism of regulated exocytosis (Zhou et al., Neuron, 2007).

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5、杨福全组

完善了高灵敏和高通量的多维蛋白质鉴定系统，在低丰度蛋白质、膜蛋白质以及蛋白质复合物鉴定中形成特色。

建立复杂生物样品目标蛋白质的分离、鉴定方法。成功鉴定了疾病相关的潜在的蛋白质生物标志物。

利用 SILAC 策略研究 L6 成肌细胞分化前后的蛋白质表达水平的变化。共定量分析了 894 个蛋白质。其中 267 个蛋白质的表达水平上调，20 个表达水平下调。主要包括细胞信号转导、蛋白质生成与降解、物质代谢、分子伴侣、细胞黏附、细胞结构与运动、物质转运等相关蛋白。

利用 SILAC 策略研究胰岛素短时刺激下 L6 骨胳肌细胞从内膜系统向细胞膜转位的蛋白质动态变化。定量分析胰岛素短时刺激下的 L6 骨胳肌细胞膜、低密度囊泡（LDM）组份中蛋白质组变化。

研究高糖状态下胰岛 β 细胞功能改变及其线粒体的蛋白质组学变化。高糖处理后的 INS-1 细胞，其线粒体变圆、线粒体肿胀、线粒体比重增加、线粒体嵴减少、线粒体呼吸功能下降，INS-1 细胞氧自由基生成增加，凋亡明显增加，ATP 生成明显减少，胰岛素生成与分泌减少。结果表明代谢相关蛋白、呼吸链相关蛋白、线粒体生成相关蛋白以及 ROS 相关蛋白发生了表达下调或上调。

MALDI-TOF-MS 检测磷酸化肽段的技术方法的优化。利用 SILAC 定量策略对胰岛素短时间刺激作用前后 L6 肌管细胞中可溶性磷酸化蛋白质组变化进行研究。共鉴定到 171 个磷酸化蛋白，387 个磷酸化位点，其中 353 个为未报道的磷酸化位点。

开展了脂质分析检测方法的初步研究。建立了生物样本中脂质的分类提取、分离方法以及基于质谱的检测方法。

5、Prof. Yang F.Q.

1) Optimized the sensitive and high through-put multidimensional protein identification technique system and widely used for the identification of low abundant protein and membrane proteins and protein complex.
2) Established methods for the purification and identification of target proteins from complex biological sample and successfully identified several potential protein biomarkers.
3) Preliminary quantitative profile of differential expression between rat L6 myoblasts and myotubes by SILAC. 894 proteins were quantified. 267 of them were up-regulated and 20 of them were down-regulated。These differentially expressional proteins are mainly involved in inter- or intracellular signaling, protein synthesis and degradation, molecular chaperone，cell adhesion and extracelluar matrix，cell structure and motility, metabolism，substance transportation，etc.
4) SILAC quantitative proteomic method was applied to analyze proteins dynamic change from intracellular membrane compartments to plasma membrane of L6 skeletal muscle cells after rapid insulin stimulation.
5) Study on proteomic changes of mitochondria of pancreatic β cells after treated by high glucose.
6) The morphology and function of mitochondria of rat derived Ins-1 cells were found altered significantly after treated by high glucose. Such as round profiles, increased density, decreased ridges and increased bubbles of mitochondria, decreased membrane potential and respiratory control rate of mitochondria, gradually accumulated oxygen free radicals in Ins-1 cells, increased apoptosis of ins-1 cells, decreased ATP formation and insulin secretion of Ins-1 cells. The quantitative proteomic result indicated that the expression level of some mitochondrial proteins such as substrate metabolism, respiratory chain, mitochondria genesis, apoptosis and ROS formation related proteins, changed. The study presented more clues for impaired insulin secretion or mitochondria function failure in diabetic’s

pancreatic β cells.

7) Optimized the method for the analysis of phosphopeptides by MALDI-TOF-MS. Study on phosphoproteomics of rat L6 myotubes cell after insulin stimulation for short time by SILAC. 171 phosphoproteins and 387phosphorylation sites were identified. Among the identified phosphorylation sites，353 were reported for the first time.
8) Primary study on the analysis and identification of lipids by MALDI-TOF-MS and LC-MS/MS.

6、杨福愉组

系统研究了胰凝乳蛋白酶在细胞内的定位，并研究了其参与调控细胞凋亡的机制，发现胰凝乳蛋白酶定位在多种细胞的溶酶体中，并在细胞凋亡信号的刺激下从溶酶体中释放出来，其主要作用底物为 Bid 和 Calcineurin；胰凝乳蛋白酶可将 Bid 剪切为 tBid，tBid 可快速诱导线粒体释放细胞色素 c，并激活凋亡酶 3 依赖的细胞凋亡通路，启动细胞凋亡。胰凝乳蛋白酶可将 Calcineurin 剪切为具有磷酸酶活性的大片段，且剪切后的 Calcineurin 其磷酸酶活性不再受钙信号调控。

研究了脂筏结构调控 PMCA 活性及 PMCA 与其他蛋白相互作用的机理，发现 PMCA 与 nNOS 存在部分共定位；在静息态细胞中，PMCA 与 nNOS 不发生蛋白质相互作用；当细胞被钙信号激活后，PMCA 与与 nNOS 发生蛋白质相互作用，，且该相互作用依赖于脂筏结构；转染外源 PMCA 后，细胞 nNOS 活性显著降低，NO 生成受抑制，提示 PMCA 可去活化 nNOS；PMCA 对 nNOS 的去活化作用依赖于脂筏结构。

发现脂筏结构是调控典型纳米颗粒的跨膜运输的关键因素。细胞主要通过 clathrin-coated pits 运输富勒烯纳米颗粒；富勒烯纳米颗粒进入细胞后富集在溶酶体中，并可增强溶酶体的稳定性。

6、Prof. Yang F.Q.

The intracellular localization of lysosomal chymotrypsin B was investigated, and its involvement in apoptosis regulation was explored. Chymotrypsin B were localized in the lysosomes of various cell types, and could be released into the cytosol upon apoptotic stimuli. Its potential substrates include Bid and Calcineurin. Upon activation by chymotrypsin-catalyzed cleavage, tBid could induce the rapid release of mitochondrial cytochrome c, which activates the caspase-30dependent apoptotic pathways, and induces apoptosis. Also, calcineurin could be activated by chymotrypsin-catalyzed cleavage.

The regulation of lipid rafts on PMCA activity was investigated. PMCA co-localizes with nNOS in neuronal cells. In silent cells, PMCA shows no protein-protein interaction with nNOS; upon calcium activation, PMCA interacts with nNOS in a lipid-raft dependent manner. Exogenous PMCA inactivates cellular nNOS and inhibits the synthesis of NO, suggesting that PMCA is a regulator of PMCA. The inactivation of nNOS by PMCA depends on the integrity of lipid rafts.

Lipid raft plays important roles in the transmembrane trafficking of nanoparticals. Cells uptake nanoparticals via a clathrin-coated pits mechanism. Lysosomes are the intracellular pool for nanoparticals, and the integrity of lysosomal membrane could be stabilized by nanoparticals.

发表文章：

Melatonin impairs NADPH oxidase assembly and decreases superoxide anion production in microglia exposed to amyloid-1-42. ***J. Pineal Res.***

（四）计算与系统生物学

1、毕利军组

DNA 损伤是基因突变的诱因，导致基因组的不稳定性。细胞依赖各种修复系统对其损伤进行修复。已有证据显示人类 DNA 修复失活导致基因组 DNA 的高突变率，并引起多种癌症的发生，但具体的修复机制、各种修复途径、细胞周期调控及凋亡如何协同作用以保持基因组的稳定性和防止癌症的发生还远不清楚。结核病是由结核杆菌引起的全球性传染疾病。由于基因突变导致的耐药性使人类对其防治更加困难。结核杆菌缺乏明显的错配修复基因、具有高突变率和易形成耐药性，目前还不了解这三个特征是否存在内在联系。课题组围绕上述问题开展研究，主要工作概括为四个方面：

1）DNA 修复机制：完成了修复蛋白 MutS 寻找错配位点和 UvrD 的解螺旋功能可视化研究；研究修复蛋白 MutL 与 DNA 聚合酶 III 的相互作用揭示了 DNA 错配修复与复制系统的协同作用机制。2）结核杆菌 DNA 修复与耐药性：完成了吡嗪酰胺酶的鉴定及其突变情况调查工作；开展 Gyrase B 结构与功能研究；建立 DNA 修复蛋白库并开展 DNA 修复和耐药性的研究。
3）非编码 RNA 与 DNA 修复：垂钓 ncRNA 的靶蛋白并研究其功能；研究 ncRNA 对 DNA 修复功能的调控；开展结核杆菌 ncRNA 的标注。4）分析生物技术：开展蛋白激酶检测肽芯片和基因突变检测等方法研究。

1、Prof. Bi L.J.

DNA repair system takes an important role in keeping stability of genome and its defect in the mammalian pathway is associated with a strong predisposition to tumor development. So far, detail mechanism is less understood. 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 work has been focused on the mechanism of DNA damage repair and the relationship between DNA repair and drug-resistance. Further details are given below:
1) DNA repair system: (a) these studies on the mechanism of MutS searching for a mismatch site and Visualization and kinetic analysis of DNA binding and unwinding by Helicase II (UvrD) have been done. (b) We find the strong evidence to support the notion that DNA replication and MMR are highly associated with each other. 2) DNA repair and drug-resistance of MTB: (a) Characterization of PncA and research on the relationship of its mutation and drug-resistance have been finished. (b) Studies on structure and function of Gyrase B have been developed. (c) We are constructing a library composed of DNA repair proteins of MTB and doing the relative works on DNA repair and drug-resistance. 3) Non-coding RNA and DNA repair: (a) we are baiting the target protein of ncRNA in the C. elegans and further to discover their functions. (b) Research on regulation of ncRNA on DNA repair function in human is doing. (c) we are focusing on finding ncRNAs and discovering their functions in mycobacterium tuberculosis. 4) Analytical methods: they inclu

2、陈润生组

研究组从事的非编码基因和系统生物学两个方面的研究工作都是国际的热点领域，本组又有多年的研究积累，所以进展顺利。2007 年已在国际 SCI 杂志上正式发表研究论文 8 篇，其中 IF 大于 5 的有 4 篇。以通讯作者和生物物理所为第一单位发表的有 4 篇，其中包括：Genome Research 一篇，Nucleic Acid Research 一篇，BMC *Molecular Biology* 一篇，*PROTEINS*.一篇。以署名作者发表的 ***Molecular Cell*** 一篇等。

2、Prof. Chen R.S.

Our group focus on the research of non-coding RNA and systematic biology. The two areas are both the international hotspots. Meanwhile,we have accumulated many years of research experiences about these fields. So the work is now going smoothly.

In the year of 2007,we published eight pieces of research papers on the SCI magazine. The address are all theI Institue of Biophysics. The Impact Factor of four pieces of them are morn than 5. Moreover, four pieces of papers published respectievly on *Genome Research*, *Nucleic Acid Research*, *BMC Molecular Biology* and *PROTEINS*. The coorespondent author of these papers is Dr.Chen and primacy adress is the Institue of Biophysics. Also Dr.chen is the byliner of one paper in *Molecular Cell*. The detail is in the following paper list.

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3、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。该文已发表于 Genome Research 上。

2．与流感中心舒跃龙教授和 MIT 的陈建柱教授合作，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。

3、Prof. Jiang T.J.

Computational analysis of human influenza evolution and its molecular mechanism

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 has been published on Genome Research. In a collaborative work with Professor Yuelong Shu at China CDC and Professor Chen Jianzhu at MIT, we elucidated the molecular basis that underpins the influenza outbreak in 03-04 influenza season. This work is also being prepared for publication.

发表论文：

XJ Du, Z Wang, AP Wu, L Song, HY Hang, **TJ Jiang**. Networks of Nucleotide Co-occurrence Capture Characteristics of Human Influenza Evolution. ***Genome Res.***

4、饶子和组

本课题组研究重点之一是重要病毒（如：SARS、MHV、IBV、HCoV 等冠状病毒及其他与人类疾病相关病毒）和与人类重大疾病相关的蛋白质，开展三维结构与功能研究以及相关抑制剂药物研发。本年度解析 MHV-A59 毒株非结构蛋白 nsp4 C 端结构域、IBV 主蛋白酶及其与 N3 抑制剂复合物以及 nsp3 的 ADRP 结构域的三维结构；解析诺罗病毒表面抗原 P 结构域、结核杆菌丙二酰辅酶 A 转酰基酶以及 SIV 中 Mamu-A*01 与两类主要表面抗原决定簇复合物的晶体结构；已获得 N3、N24、N27、H6、H16、H23 及 H24 这些抑制效果较好的抑制剂，为相关药物的开发提供了实验依据。

人体重要生物活性酶的结构与功能研究是另一重点研究方向。解析了人源半胱氨酸双加氧酶、人源异戊烯焦磷酸异构酶、RSCUT、长链烷烃羟化酶 LadA、类 ParB 蛋白核酶及其与底物或辅因子的复合物结构。

开展细胞周期、转录调控及信号转导相关蛋白的结构与功能研究。解析了减数分裂纺锤体相关蛋白 spindlin 1、人源 APPL1N 端 BAR－PH 结构域、酵母 DCN-1 晶体结构。

2007 年，在国际学术刊物上发表研究论文 21 篇，申请发明专利 5 项，获得国家发明专利 2 项。

4、Prof. Rao Z.H.

In 2007, the main research focus of our group involved three-dimensional structure, function, protein engineering and novel drug design studies of target proteins related to important viruses and human diseases.

The structure, function and related inhibitor design studies of non-structural proteins and associated replication-transcription machinery from coronaviruses, including SARS-CoV, MHV, IBV, HCoV-HKU1.We determined the three dimensional structure of the C-terminal cytoplasmic domain of MHV A59 non-structural protein 4 (nsp4-C), IBV M^{pro} and its complex with an inhibitor N3, ADRP domain of nsp3, P domain of the norovirus capsid, Mamu-A*01 in complex with two immunodominant epitopes and MtMCAT. There was significant progress on the discovery of wide-spectrum inhibitors. Of the inhibitors we have designed, N3, N24, N27, H6, H23 and H24 all show strong inhibition effects, thus providing a solid basis for the development of effective anti-coronavirus drugs.

Another key focus of our research is the structural and functional study of human enzymes with important biological activities. We determined the three-dimensional structures of human cysteine dioxygenase, human IPP isomerase, RSCUT, long-chain alkane monooxygenase LadA, Par B nucleases, or in complexes with their substrates and co-factors. The results provide a structural basis for further insights into the catalytic mechanisms of human enzymes.

We seek to carry out structural and functional studies upon important proteins in cell cycle, transcription regulation and signal transduction. Crystal structure determination of human spindlin1, human APPL1 N-terminal BAR-PH domain motif and yeast DCN-1 provides biochemical basis for cell cycle regulation and other functions.

A total of 21 research papers were published in international journals, 5 invention patents were applied for and 2 were accepted as national patents.

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5、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。

目前的研究内容包括：1.线粒体呼吸链复合物 II 的电子传递机制；2.线粒体呼吸链复合物 I 同源蛋白——大肠杆菌 NDH－1 的结构研究；3.细菌脂蛋白合成通路上重要膜蛋白的三维结构研究；4.古菌二型分子伴侣的冷冻电镜和晶体学研究；5.线粒体呼吸链相关的解耦联蛋白 UCP 的三维结构研究；6.帕金森氏病相关蛋白 LRRK2 的晶体结构研究（与许挚恒合作）；7 真核生物染色质重组蛋白因子的结构研究；8 兔出血症病毒衣壳三维结构研究；9 细胞内吞作用的再循环过程相关蛋白 ACAP1 的结构研究。

研究进展主要有：完成线粒体复合物 II 与两种抑制剂的复合物晶体结构解析；获得了细菌脂蛋白合成通路上两个重要膜蛋白的晶体；获得了细胞内吞作用的再循环过程重要蛋白 ACAP1 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；与范祖森研究组合作解析了人源颗粒酶 M 及其底物多肽的晶体结构，目前正在进行总结；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。

5、Prof. Sun F.

Research Projects

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

We have already begun several structural research projects: 1. Mitochondrial respiratory Complex II structural electron transfer mechanism; 2. Structural study of mitochondrial respiratory Complex I homology – E.coli NDH-1; 3. 3D research of important bacterial lipoprotein synthesis pathway related membrane proteins; 4. 3D research of second type of chaperon from archaeal; 5. Structural research on mitochondrial respiratory related uncoupling protein UCP. 6. Crystal structural research on Parkinson diseases related protein LRRK2 (collaborated with Zhiheng Xu). 7. Structural study of chromatin assembly factor complex in *Drosophila* 8. Structural study of rabbit hemorrhagic disease virus (RHDV)；9 Structural research on ACAP1 involved in endocytic recycling.

Research Progress

We have already successfully solved two crystal structures of mitochondrial respiratory Complex II with two inhibitors. We obtained the crystals of two important membrane proteins relating with bacterial lipoprotein synthesis pathway. And we have obtained the crystal of ACAP1. Besides, with collaboration from Prof. Wang C.C., we solved the first crystal structure of human ERp44 relating with protein quality control system in endoplasmic reticulum. We had the collaboration with Prof. Fan Z. and solved the crystal structure of human GzmM and its complex structure bound to peptide. Finally, we successfully reconstructed the 3D structure of archaeal type II chaperon α by negative stain method, revealing two different confirmations in one complex, and then we also obtained crystals of chaperon α and chaperon β; Further work on cryoEM and X-ray crystallography is now going.

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（五）感染与免疫的分子基础研究

1、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。同时我们还对 *rta* 基因自激活及受病毒颗粒蛋白激活的具体调控机理进行了研究。

（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。首次发现细胞转录因子 NF-Y 在病毒基因组复制中起重要作用，并对其作用机理展开了详细研究。

（3）病毒包装：结合遗传学，蛋白质组学，结构学及电子显微镜技术选择性地对 MHV-68 的间质蛋白 ORF33 和 ORF52 在病毒颗粒的组装和出胞过程中的作用和机理进行了研究。

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，构建了携带 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。

3）通过构建鼠肝炎病毒/人丙肝病毒嵌合病毒，研究丙肝病毒慢性感染的机制。

1、Prof. Deng H.Y.

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 directions:

1) 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 are also dissecting the mechanisms governing activation of the *rta* promoter by virion components as well as RTA protein itself.
2) 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 involved in mediating viral DNA replication. We have shown that a cellular transcription factor NF-Y plays an important role in this process. To our knowledge, this is the first time that NF-Y has been implicated in mediating DNA replication. We are further investigating the detailed mechanisms.
3) Virion morphogenesis and egress. We combine genetics, proteomics, structural biology and electron microscopy approaches to study viral tegument proteins (currently focusing on ORF33 and ORF52) and their role in virion packaging and egress.

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

We investigate the mechanisms responsible for chronic/persistent infection of HCV through constructing chimeric MHV-A59/HCV viruses and studying the immune responses in vivo.

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2、范祖森组

阐明了颗粒酶 M 介导靶细胞凋亡机制

在发现颗粒酶 M 引起 DNA 双链断裂为特征的靶细胞凋亡的基础上（Journal of immunology，2006）。我们继续研究发现颗粒酶 M 进入靶细胞后直接作用线粒体，从而引起活性氧的产生。热休克蛋白 75（HSP75）具有抑制活性氧产生的功能。研究发现颗粒酶 M 进入靶细胞后，随即切割 HSP75 蛋白并破坏了其相应的抗氧化功能，打破了细胞氧化平衡体系，从而决定细胞走向凋亡的命运。该研究成果刚被 JBC 杂志接受发表。我们表达了具有高度活性的颗粒酶 M，获取了其大量均一的表达。与孙飞课题组合作通过优化晶体生长条件，获取了颗粒酶 M 的晶体。收取了高分辨率的衍射数据，解析了颗粒酶 M 的结构。正在探索结构与功能的关系。

揭示了颗粒酶 H 在 NK/CTL 介导肿瘤杀伤中的作用

我们研究发现颗粒酶 H 进入肿瘤细胞后介导了快速的靶细胞凋亡。磷脂酰丝氨酸外翻、染色体凝集、核形态发生变化及 DNA 双链断裂为颗粒酶 H 介导靶细胞死亡的主要特征。颗粒酶 H 介导的靶细胞死亡依赖于 Caspase 的激活，以及 CAD 活性的释放。并发现颗粒酶 H 能水解 Bid 为 tBid, 引起线粒体肿胀和破坏，引起 cytochrome c 的产生，致使细胞走向凋亡。我们正在从结构和功能的基础上，深入探明颗粒酶 H 介导肿瘤杀伤中的作用底物和机理。

2、Prof. Fan Z.S.

Get insight into the mechanisms of granzyme M-mediated target cell apoptosis

We recently demonstrated that GzmM induces caspase-dependent apoptosis with DNA fragmentation through direct cleavage of inhibitor of caspase-activated DNase (ICAD). However, the molecular mechanisms for GzmM-induced apoptosis is unclear. We found GzmM causes mitochondrial swelling and loss of mitochondrial transmembrane potential. Moreover GzmM initiates reactive oxygen species (ROS) generation. Heat shock protein 75 (HSP75) acts as an antagonist of ROS and protects cells from GzmM-mediated apoptosis. GzmM cleaves TRAP1 and abolishes its antagonistic function to ROS resulting in ROS accumulation. ROS accumulation is in accordance with the release of cytochrome c from mitochondria and enhances GzmM-mediated apoptosis. We obtained its crystal of granzyme M and analyzed its structure in collaboration with Sun's Lab. We are investigating the functions of granzyme M based on its structure.

The functions of granzyme H in NK/CTL-mediated cell death

Granzyme H (GzmH) plays a pivotal role in NK cell mediated cytolysis. However GzmH is defined as an orphan granzyme and its function has less been defined. Here we demonstrate GzmH can induce rapid apoptosis of target cells, which is dependent on caspase activation and mitochondrial damage. GzmH-induced death is characterized by phophatidylserine externalization, nuclear condensation, DNA fragmentation, caspase activation and cytochrome c release that are hallmarks of typical apoptosis. GzmH can directly cleave ICAD to unleash CAD for DNA fragmentation. Moreover, GzmH directly processes Bid to produce the active form tBid leading to cytochrome c release. We are further investigating its mechanisms of granzyme H-mediated target cell apoptosis.

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2. Hua G, Zhang Q, **Fan Z***. Heat shock protein 75 (TRAP1) antagonizes reactive oxygen species generation and protects cells from granzyme M-mediated apoptosis. ***J Biol Chem.*** 2007；282(28):20553-60.
3. Zhao T, Zhang H, Guo Y, **Fan Z***. Granzyme K directly processes Bid to release cytochrome c and endonuclease G leading to mitochondria- dependent cell death. ***J Biol Chem.*** 2007； 282(16):12104-11

3、高光侠组

本课题组主要研究以 HIV 为代表的逆转录病毒与宿主相互作用的分子机理,锌指结构抗病毒蛋白（ZAP)的作用机理是本实验室的研究重点。我们前期的工作发现 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病毒 RNA，并招募 RNA 降解机器实现对靶 RNA 的降解。本年度取得主要成果如下：1）分析了 RNA 降解机器 Decapping 和 Deadenylation 复合物与 ZAP 之间的相互作用关系，发现 ZAP 与 PARN 有直接的相互作用，用 RNAi 方法敲低 PARN 可明显减弱 ZAP 的活性。同时发现，5'-3'外切酶 XrnI 参与 ZAP 介导的 RNA 降解。2）改进了鉴定 ZAP 复合物组分的方法，鉴定出多个可能参与调控 ZAP 功能的细胞因子。根据作用机理，大致可将其分为三类。第一类是为 ZAP 实现其功能所必需的，如 RNA 解旋酶 p72；第二类参与调控 ZAP 的控能，如 TRIM25；第三类通过结合 ZAP 作用的靶 RNA 拮抗 ZAP 的功能，如 YB1。3）利用 RNAi 方法敲低 p72、TRIM25 都可明显减弱 ZAP 的活性；过表达 YB1 也会明显减弱 ZAP 的活性。上述结果表明这些细胞因子在 ZAP 功能中发挥着重要作用，具体的作用机理正在研究中。

3、Prof. Gao G.X.

Our research mainly focuses on the molecular mechanism of the interaction between retroviruses and their hosts. Specifically, we work on the mechanisms of the host antiviral factor ZAP, which inhibits virus infection by specifically degrading viral mRNAs.

Our previous studies reveal that ZAP specifically eliminates the viral mRNA in the cytoplasm. Our current working model is that ZAP directly binds to the target viral mRNA through the zinc-finger motifs, and recruits the cellular RNA degradation machineries. Analyses of the involvement of the RNA degradation machineries revealed that ZAP recruits deadenylase PARN to shorten the polyA tail. The 5'-3' exoribonuclease XrnI is also involved in ZAP-mediated mRNA degradation. In addition to studying the interaction of ZAP with the known components of the RNA degradation machineries, we used various methods to identify proteins associated with ZAP. A handful of candidate proteins have been identified, several of which have been confirmed to be involved in ZAP-mediated RNA degradation. Based on the mechanisms by which these proteins affect ZAP's activity, they can be roughly classified into three groups. The proteins in group I, such as TRIM25 and GSK3, modulate ZAP's activity through binding to or modification of ZAP. The proteins in group II, such as YB-1 and IMP1, seem to antagonize ZAP's activity through binding to ZAP's target RNA and thereby prevent the RNA from ZAP-mediated RNA degradation. The proteins in group III, such as DEAD box RNA helicase p72, function as cofactors of ZAP. The current working model is that ZAP binds to the target RNA through the zinc-finger motifs, recruits the RNA helicase p72 to unwind the RNA and recruits the RNA degradation machineries to degrade the RNA. Detailed mechanisms of these proteins in ZAP-mediated RNA degradation are currently under investigation.

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Guo X., Ma J., Sun J., and **Gao G***. The Zinc-finger Antiviral Protein Recruits the RNA processing Exosome to Degrade Target RNAs.***Proc Natl Acad Sci USA.*** 2007; Vol. 104 (1): 151-6

4、秦志海组

本研究组主要运用转基因动物研究细胞因子对肿瘤间质细胞的作用及其机制，研究发现细胞因子介导的抑制血管新生是重要的抗肿瘤免疫效应机制。主要进展如下：1）天然免疫细胞是肿瘤排斥过程中 IFN-γ 的重要产生者，而 T 细胞起辅助作用。我们运用 IFN-γ$^{-/-}$及 Rag1$^{-/-}$小鼠构建了只有天然免疫细胞才具有 IFN-γ 产生能力的骨髓嵌合小鼠。研究显示 T 细胞并不是必不可少的 IFN-γ 产生者，天然免疫细胞可以产生足够量的 IFN-γ，而且其产生 IFN-γ 的能力只有在 T 细胞存在的情况下才能激活。T 细胞和天然免疫细胞之间的相互作用可能由 IL-2 介导。为了进一步研究 IFN-γ 在抑制血管新生中的重要作用，我们还成功构建了组织特异性 IFN-γ 受体转基因小鼠，这一模型将有助于进一步阐明 IFN-γ 的作用机制。2）肿瘤坏死因子 TNF-α 通过巨噬细胞来源的一氧化氮抑制肿瘤内血管形成。肿瘤坏死因子（TNF）有两个受体，但是关于 TNFR2 的作用研究甚少。本组研究首次证明 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、Prof. Qin Z.H.

Using transgenic animals, we have investigated the effects of cytokines on tumor stromal cells and the underlying mechanisms. Our results indicate that cytokine mediated angiostasis is the major immunological mechanism for tumor rejection. We found: 1) Innate immune cells are the major producer of IFN-γ, and T cells cooperate with innate immune cells for IFN-γ-mediated tumor rejection. By using various bone marrow chimeric mice, we show here that IFN-γ essential for tumor immunity is solely produced by hemopoietic cells. Surprisingly, IFN-γ derived from T cells was not necessary for tumor immunity in this model. In the immunized mice, in which only innate immune cells have the IFN-γ-producing potential, tumors were efficiently rejected. The innate immune cells, such as NK1.1^{+} cells and CD11b^{+} cells, can provide sufficient amounts of IFN-γ which requires, however, the help of T cells. The close cooperation between T cells and innate immune cells during tumor regression is likely mediated by IL-2. 2) Tumor necrosis factor inhibits tumor angiogenesis via macrophages-derived nitric oxide. Tumor necrosis factor (TNF) binds to two different receptors. Although most of its functions are attributed to TNF receptor 1 (TNFR1), the independent role of TNFR2 is still largely unknown. Our results show for the first time that TNFR2 expressed on host innate immune cells is sufficient to mediate the antitumor effect of TNF, and NO is necessary for this process, possibly by inhibition of angiogenesis in the tumor.

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2. Li, Z., P. Felicia, B. Li, S. Liu, and **Z. Qin**. Crosstalk between T cells and innate immune cells is crucial for IFNγ-dependent tumor rejection. ***J Immunol***. 2007；179(3):1568-76.

5、唐宏组

研究炎症反应中的信号转导机制，细胞凋亡机理,病毒感染的天然免疫调控机理。2006-2007 年的研究工作已发表高水平论文多篇。

5、Prof. Tang H.

Major research interests focus on signal transduction mechanism in inflammation reaction, apotosis mechanism, virus infection and innate immununе regulation.

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3. Lei pan，Shuyi Chen，Changjiang Weng, Gerald call,Deng xiao Zhu, **Hong Tang** and Ting Xie, Stem cell aging is controlled both intrinsically and extrinsically in the drosophila ovary, ***Cell Stem Cell.*** 2007；1:458-469

6、唐捷组

目前本课题组在下面三个方面取得阶段性进展：

1） 发现 MIF 在 LPS 诱导的 iNOS 上调中的关键作用。同时发现 MIF 内吞对其信号转导具有关键作用，MIF 可以直接进入细胞核，影响 Jab1 的细胞定位。

2） 发现 CLM 家族蛋白在 LPS 诱导的 TNF-alpha 分泌中的作用。

3） 发现在类风湿关节炎病人中清除 B 细胞后，引起 T 细胞和巨噬细胞功能的改变。

6、Prof. Tang J.

We made progress in the following aspects:

1) MIF function is important for LPS induced iNOS up-regulation. MIF endocytosis is essential for its signal transduction and it enters nucleus to interact with Jab1.

2) CLM family receptors are involved in LPS induced TNF-alpha secretion

3) B cell depletion in rheumatoid arthritis patients led to T cell and macrophage function changes.

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2. Identification of eight novel alternative splicing forms of CD72 and their differential expression in a mouse model of SLE. ***Prog. Biochem. Biophys.*** 2007；34 (11): 1175-1181
3. MIF regulates TNF Alpha Receptor Type II Expression in RAW264.7 ***Cells. Prog. Biochem. Biophys.*** 2007；34 (6):580-584

7、王盛典组

实验室的研究工作主要集中在免疫调节分子，主要是共刺激分子在慢性病毒感染、肿瘤等疾病中的免疫调节作用。其中与他人合作研究发现，慢性乙肝病人 mDC 上的 B7-H1 分子表达增高，可抑制抗 HBV 的 T 细胞免疫反应；抗共刺激分子 B7-H1、CTLA-4 抗体可增强肿瘤疫苗的抗肿瘤效果，这些成果分别发表在 J Immunol（2007）（共同通讯作者）；Immunol. Lett (2007) (共同通讯作者）和 J. Clin.Immunol (2007).

通过基础研究与临床资源和需求的紧密结合，我们研究发现 4-1BB 共刺激信号途径在慢性乙肝的发生和发展中起重要作用；CD24 基因的单核苷酸多态性与慢性乙肝病人的肝硬化和肝癌发生有相关性，动物实验结果也显示 CD24 分子可促进 HBV 转基因小鼠肝癌的发生。此外，发现 PD-1、B7-H3 分子在慢性乙肝免疫耐受中有重要调控作用。

通过与协和肿瘤医院的密切合作，我们已对 20 多例结肠癌组织和前哨淋巴结中，重要免疫细胞和分子的功能进行了全面研究，结合体外及动物实验，初步获得了有关 B7-H1/PD-1 信号途径、Treg 和 MSC 细胞在肿瘤免疫耐受中作用的重要发现。

经过一年多的努力，终于从美国合作实验室获得了 Rag γ cDKO 免疫缺陷小鼠，目前正通过协和动物所从国外运送，下一年的另一项重点工作是利用该小鼠，建立人源化的慢性乙肝和肿瘤模型，这一模型的建立将显著提升实验室的科研水平。

7、Prof. Wang S.D.

Our studies focus on the regulatory functions of molecules, especially co-signaling molecules in the immune responses against chronic virus infections and tumors. We found in collaboration with other groups that the expression of B7-H1 on mDC of PBMC is increased in patients with chronic HBV infection compared with healthy controls, and the B7-H1 expressed on mDC inhibit T cell-mediated response against HBV infection. Monoclonal antibodies against B7-H1 or CTLA-4 enhance the anti-tumor effects of tumor vaccine. These results were published in J Immunol (2007) (co-responding author); Immunol. Lett (2007) (co-responding author) and J. Clin.Immunol (2007).

Combined our basic study with clinical resource and requirement, our studies showed that co-signaling of 4-1BB play a important role in incidence and development of chronic hepatitis B; The single nucleotide polymorphisms of CD24 is related with developing of cirrhosis and hepatocellular carcinoma in patients with chronic HBV infection, and CD24 molecule can promote the development of liver cancer in HBV transgenic mice. In addition, we found that co-signaling molecules of PD-1 and B7-H3 may have an important roles in regulation of immune tolerance in chronic hepatitis B.

Collaborating with Cancer Institute affiliated with Peking Union Medical College, we studied the functions of important lymphocytes and molecules in tumor tissues and draining lymph nodes from more than 20 colorectal cancer patients and has some interesting discoveries about the functions of B7-H1/PD-1 co-signaling pathway, Treg and MSCs in tumor-induced immune tolerance.

At last we got permission for Ragγ_CDKO immune deficient mice from one of our collaborating labs in US through one year of hard work. One of the important works for next year is to establish the modes of humanized mice with chronic hepatitis B and tumors, which is very important for dramatically raising the levels of scientific research in our lab.

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2. Chen L, Zhang Z, Chen W, Zhang Z, Li Y, Shi M, Zhang J, Chen L, **Wang S***, Wang FS*. B7-H1 upregulation on myeloid dendritic cells significantly suppresses T-cell immune function in patients with chronic hepatitis B. ***J. Immunol.*** 2007；178(10):6634-41.
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8、阎锡蕴组

肿瘤新靶点及新功能抗体作用机理：(1) 继续深入研究 CD146 分子及其抗体抑瘤作用机制，在活细胞上观察 CD146 二聚体与肿瘤化的相关性（BBA-molecular cell research 1773 :513,2007）；(2) 用 Confocal 观察到 CD146 分子具有类似细胞膜受体介导内吞的内在化现象；（3）继续寻找 CD146 天然配体，发现 CD146 的胞内区通过 moesin 的介导，与 actin 和 vimentin 等形成复合体，将相关信号传递下去；（4）构建抗 CD146 的人源化抗体，开发肿瘤抗体药物。

新型免疫检测方法: 把肿瘤靶分子或抗体与纳米材料结合创造新型免疫磁珠。在国际上首次报道磁性纳米颗粒具有类似过氧化物酶活性，提出纳米材料模拟酶的新概念，并利用其新特征建立一种新型免疫检测方法。研究结果发表在 **Nature Nanotechnology**，同期杂志《新闻与观点》栏目配发了评论文章,称"这一发现不仅为惰性金属材料在纳米尺度具有催化活性的学说提出了新的证据，而且拓展了磁性纳米材料的应用"。随后美国 Science 杂志（Science News，172:174,2007），美国 Nanowerk（Nanowerk, Oct.18th,2007）发表评述文章。

8、Prof. Yan X.Y.

The mechanism study of anti-tumor antibody: We have established a differential screening platform for specific tumor-targeting antibodies; and discovered several tumor biomarkers. Importantly, we have found that CD146 is a novel target on tumor blood vessels and involved in tumor angiogenesis. The function and mechanism of CD146 and its antibody AA98 have been extensively studied: (1) We found that CD146 dimerization was up-regulated by tumor conditional medium through the NF-kappa B pathway and down-regulated by mAb AA98.（BBA-molecular cell research 1773 :513,2007）. (2) We observed the endocytosis of CD146 by using TIRFM (Single-molecule) in living cells, suggesting the regulability of the quantity of CD146 on plasma membrane and its significance in regulating signal transduction.（3）We found that CD146 interacted with actin and vimentin via moesin, which might be an important pathway to transfer the signal downwards. （4）We have constructed the humanized CD146 antibody, and the invention has been licensed by an industrial partner for developing antibody-based tumor drug.

Antibody-based biosensor. We construct novel-structures of antibody combined with nano-material and nano-technology to make new biosensor for diagnosis. During running this project, we found that magnetic nanoparticles (MNPs) have a peroxidase-like activity. Based on this finding, we have developed a novel immunoassay using the multi-function of antibody-modified MNPs (targeting, separation and catalysis). This work has published in *Nat Nanotechnol, 2:577, 2007* and received highly positive comments from international colleagues: "A catalytic property widely used for laboratory tests and the treatment of waste water has been discovered in iron oxide nanoparticles and could lead to many applications in medical diagnostics." ***(Hidden talent, Nat Nanotechnol, 2:535, 2007).***

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（六）蛋白质药物与多肽药物

1、梁伟组

揭示了肿瘤发生发展的新机制： 我们的研究发现，组织的纤维化为肿瘤细胞的生成和发展提供了有利的微环境，纤维化可促进正常细胞向肿瘤细胞转化及增值；纤维化为肿瘤细胞提供了适宜其定居和生长的微环境并促进肿瘤转移灶的形成。TGF-β/Smad3 信号通路在这一过程中起到关键作用可以作为药物筛选的新靶点。发现了柚皮素和柚皮苷可以特异性干预 TGF-β/Smad3 信号通路起到预防和治疗纤维化及癌症作用。

提出了肿瘤化疗的新观点和新思路：大多数化疗药物的作用靶点在细胞内，如阿霉素和顺铂等作用于细胞核的DNA，紫杉醇和长春新碱等作用胞浆的微管；或已具有耐药性的肿瘤细胞，通过外排机制将药物泵出细胞外，细胞内的药物浓度不足以抑制细胞的增殖。仅仅将药物输送到肿瘤组织（组织靶向）是不够的，在提高肿瘤组织选择性基础上，如何提高药物的组织渗透性及对肿瘤细胞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。我们提出了利用纳米药物输送系统既实现肿瘤组织的靶向渗透性又实现肿瘤细胞内的靶向富集，为临床治疗肿瘤提供新的有效手段和策略。

1、Prof. Liang W.

Revealing a new mechanism of tumor genesis and progression

Based on our research, we find that tissue fibrosis provides a special microenvironment which is beneficial for the proliferation of tumor cells. Fibrosis can promote the malignant transformation of normal cells into tumor cells. Fibrosis also offers a beneficial microenvironment that can promote tumor growth and metastasis. TGF-b/smad3 signaling pathway plays a crucial role in these processes and can be a new target for drug design and development. Naringenin and Naringin can specifically inhibit TGF-b/smad3 signaling pathway and consequently can be used for prevention and therapy of fibrosis and cancer.

Proposing a new viewpoint toward chemotherapy for cancer

The targets of most chemotherapeutic drug were located in the intra-cells, such as doxorubicin and cisplatin intercalate into double helix of DNA in the nucleus, and paclitaxel and vincristin disrupt the microtubes in the cytoplasma. However, resistant tumor cells can pump drugs out of the cells through some specific efflux mechanisms. Therefore, concentration of the drug in cells can not reach the critical level to inhibit tumor cell proliferation or kill tumor cell. In order to overcome these problems, it is not enough only to deliver drug to the tumor tissue (tissue target), but the drug need to be delivered into tumor cells. Penetration into the depth of tumor tissue and into tumor cells reaching effective concentration of drug in the tumor cells is very important for chemotherapy. We have developed a novel nano-sized drug delivery system to fit for the requirements of penetration into the depth of tumor tissue and into tumor cells. This strategy could have important clinical applications for cancer therapy.

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2、马跃组

目前在人源化细胞外基质的研究中取得一定的进展，初步得到了一种可用于人胚胎干细胞培养的人源细胞外基质。这对人胚胎干细胞的培养，移植具有一定的意义。目前我们正在进一步的鉴定和优化。

2、Prof. Ma Y.

We recently developed a humanized EMC for human embryonic stem cell culture. This EMC are all human protein, and can avoid animal protein containmination if applied on human ES cell culture. We are currently working on characterization of this EMC.

3、殷勤伟组

基础研究方面

与中科院计算机所合作，研发了新的软件在曙光 4000H 生物信息处理的应用专用计算机上从 2 万 1 千多个人编码蛋白基因的内含子中发现了 1 千多个内源性 shRNAs （short hairpin RNAs），它们不同于现已发现的其它小 RNAs 如 miRNAs，piRNAs， rasiRNAs， siRNAs 等，是一类新的小 RNAs，详细的研究成果正在整理、分析和发表过程中。

用这些新发现的小 RNA 和已发现的 miRMNA 研制成了小 RNA 组合芯片，已检测了 6 对正常的组织细胞和肿瘤细胞间的表达差异，发现它们也许是一种优良的标志物，可用于临床的诊断。对此，已与其他研究组（如乐家昌研究员）合作进一步研制用于临床诊断的小 RNA 分子马达检测仪。

通过小 RNA 组合芯片，我们能够筛选出一些有重要功能的 shRNAs，它们可通过多种方式来调控基因的表达和细胞的生长和分化。对此，与中国协和医科大学合作，正在研究人内源性 shRNA 对人间充质干细胞的自我更新和生长分化的调控作用。结果是令人兴奋的，第一阶段的研究成果正在整理、分析和发表过程中。

同时，我组也在小 RNA 与 DNA 甲基化方面作了一些研究工作，有关的研究论文正处于投稿阶段。

此外，我们也正在扩展和深入对这些新发现的小 RNAs 的功能和作用机制的研究，力争能做出一些原创性的重要发现

3、Prof. Yin Q.W.

Basic Research

1. With the cooperation with the institute of computing technology, we have found more than 1000 novel small RNAs from human introns of protein-coding genes. They are different from those known small RNAs such as miRNA, tncRNA, rasiRNAs, piRNAs ad others.

2. Using these novel RNA sequences, we have developed an integrative microarrays that contain known miRNAs and new predicted sRNAs. Based on this type of arrays, we assayed 12 different samples including normal and cancer cells. Furthermore, we are developing a new molecular engine-driven small RNA assay instrument with other labs.

3. By using small microarrays, my lab has selected some important sRNAs that can regulate the differentiation and growth of cells. For example, of them two sRNAs can modulate the proliferation and differentiation of haematopoietic stem cells.

4. We also conducted some investigations in sRNAs and DNA methylation. The research data are being prepared for publication.

5. More importantly, my lab is going to make deeper and broader study on the biogenesis and cellular functions of these newly discovered sRNAs.

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六、研究成果（Achievements)

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2、2007 年申请专利 (2007 Patents)

序号	申请号/授权号	名称	完成人
1	PCT/CN2007/001651	鼠抗人巨噬细胞迁移抑制因子单克隆抗体及其应用	唐捷
2	PCT/CN2007/001652	针对自身抗原和/或种属间高度保守抗原的抗体及其制备方法	唐捷
3	200710065245.2	从中药等天然产物混合物备选库中筛选 HCV NS5B 蛋白的抑制剂的新方	饶子和
4	200710087457.0	从中药等天然产物混合体系中高效、快速获取靶分子与靶蛋白复合体精细三维结构的新方法	饶子和
5	200710065119.7	从中药等天然产物混合物备选库中筛选 SARS 冠状病毒主蛋白酶抑制剂的新方法	饶子和
6	200710090647.4	一组抗人 CD146 分子单克隆抗体及其在检测 CD146 中的应用	阎锡蕴
7	200710081203.5	磁性纳米材料降解苯酚及其在治理环境污染中的应用	阎锡蕴
8	200710118872.8	一种制备蒽环类抗肿瘤抗生素的纳米胶束制剂的方法	梁伟
9	200710118871.3	柚皮素和柚皮苷作为转化生长因子-β1 信号通路抑制剂的应用	梁伟
10	200710064381.X	用于检测葡萄糖转运蛋白 4 上膜的探针和方法	徐涛
11	200710100124.9	检测过氧化氢含量的新试剂和新方法	阎锡蕴
12	EP2007/008961	The protein factor LepA (EF4) as a new target for antibiotics against bacteria	秦燕

3、2007 新增国家、院级重要主持项目 (2007 Projects)

序号	项目来源	项目编号	项目/课题名称	主持人
1	创新研究群体	30721003	膜蛋白与蛋白质复合体的结构生物学研究	常文瑞
2	海外青年学者合作研究	30728004	生物化学和分子生物学	朱海宁 龚为民
3	海外青年学者合作研究基金	30728006	免疫学	程根宏 唐宏
4	国际合作重点	2007DFC30190	表型组学技术：病毒感染免疫应答机制中的应用	唐宏
5	863 重大项目	2006AA02A245	肿瘤抗体药物	阎锡蕴
6	863 重大项目	2006AA02A106	心血管疾病干细胞临床治疗技术与产品的研发	马跃
7	863 重大项目	2006AA02A314	癌症相关蛋白质的三维结构研究	刘迎芳
8	863 重大项目	2006AA02A319	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
9	院重大项目	KSCX1-YW-02-1	2 型糖尿病致病机制及新药靶	徐涛
10	院重大项目	KSCX1-YW-10	艾滋病和病毒性肝炎新型疫苗和新药研究	唐宏
11	院重大项目	KSCX1-YW-13	冷冻电镜三维重构原始数据集	孙飞
12	院方向性项目	KSCX2-YW-R-120	逆转录病毒与宿主相互作用机理研究	高光侠
13	院方向性项目	KSCX2-YW-R-121	肿瘤抗体药物	阎锡蕴

14	院方向性项目	KSCX2-YW-R-123	物质运送、能量转换相关膜蛋白的结构与功能研究	常文瑞
15	院方向性项目	KSCX2-YW-R-125	HOPS 蛋白复合体在线虫细胞凋亡中作用的分子机制研究	刘迎芳
16	院方向性项目	KSCX2-YW-R-126	冷冻电子断层三维成像技术建立及其应用	孙飞
17	院方向性项目	KSCX2-YW-R-127	动化高效率晶体结构解析系统的研究和构建	刘志杰
18	院仪器研制改造项目	Y20634	高通量、高灵敏度蛋白质组学研究系统	杨福全
19	院仪器研制改造项目	YZ200751	光纤型 ATP 马达生物传感器 miRNA 分析仪器的研制	殷勤伟

七、研究生培养 （Training）

（一）博士后

2007 年在站人博士后：24 人

2007 年出站人博士后：3 人

名单：闫小雪、徐平勇、张志栋

（二）博士生

2007 年在读博士生：139 人

2007 年取得博士学位：27 人

名单：马静、张佰茹、耿勇、白宝艳、卜鹏程、曹鹏、曹晟、陈桂芳、韩佩韦、韩伟、郝蕊、侯强、黄文涛、霍霞、李梅、连惠勇、刘涛、吕红霞、欧先金、曲静、苏华、孙红、孙阳、宛佳、王铁鹏、殷雷、张红、朱小蓬、朱永群

（三）硕士生

2007 年在读硕士生：162 人

2007 年取得硕士学位：4 人

名单：张玲、李琳、李绍娟、李文奇

（四）学生获奖

卜鹏程、刘光慧、孙红	院长优秀奖
曲静	刘永龄奖
何云、谢韬	地奥奖学金一等奖
牛玉琼、王峰	地奥奖学金二等奖
赵学强	研究生院 BHP Billiton 学生奖学金
庄洁	第九届复旦大学谈家桢基金九源奖学金一等奖
王琰、赵洁、贺子轩、林金钟、孙红	第九届复旦大学谈家桢基金九源奖学金三等奖

八、学术交流 （International Exchange）

（一）承办的学术会议

1、中国科学院结构生物学战略研讨会

时间：2007-4-5

地点：北京

2、基础与应用免疫生物学国际研讨会

时间：2007-10-1

地点：天津

（二）学术交流

参与国内外学术会议：76 人次，会议报告：41 人次

国内外来室讲学：56 人次

国内外来室访问：42 人次

九、2007 年度大事记 （ 2007 Events）

一月

1.17　古巴科学院院士、中巴双边生物技术工作组组长、古巴神经科学中心主任 Mitchell Valdes-Sosa 博士在古巴驻中国大使馆一等秘书 Hector Conde Almeida 先生的陪同下到生物物理研究所进行学术访问并参观了实验室。

1.21　第六届中国十大女杰评选活动在京揭晓，中国科学院院士、发展中国家科学院院士、生物大分子国家重点实验室学术委员会主任中国科学院生物物理研究所研究员王志珍同志光荣当选。

二月

2.15　中国科学院副院长陈竺看望了全国政协委员、九三学社中央副主席、中国科学院院士、第六届中国十大女杰获得者、生物大分子国家重点实验室学术委员会主任王志珍院士。

三月

3.20　在 2007 年 1 月召开的北京市科学技术协会第七次代表大会上，生物大分子国家重点实验室学术委员会主任王志珍院士当选为北京市科协第七届委员会委员、副主席。

3.20　中国科学院青年联合会二届三次常委会议在北京召开，会议增补了生物大分子国家重点实验室主任徐涛研究员为第二届中科院青联副主席。

3.22　德国科学基金会（DFG）化学学部主任 Dr. Karlheinz Schmidt 在德国科学基金会赵妙根主任的陪同下访问生物物理研究所并参观了实验室。

3.22　科技部国际合作司马林英副司长在中科院国际合作局曹京华副局长、科技部国际合作司综合与计划处张健处长、美大处王强处长的陪同下视察生物物理研究所参观唐宏研究员的课题组。生物物理研究所党委书记杨星科、副书记实验室副主任龚为民等参加了接待。

四月

4.10　来自 17 个国家的 30 余位驻华使馆科技官员和国际组织驻华代表到生物物理研究所和实验室进行参观访问。

4.14　由生物物理研究所和生物大分子国家重点实验室共同承办的“中国科学院结构生物学战略研讨会”在香山召开。陈竺院士、饶子和院士、徐涛研究员担任本次会议执行主席，来自海内外的 30 多位知名结构生物学家以及物理学、化学等领域的专家参加了本次会议，科技部、基金委等部门的领导应邀出席了会议。

4.19　蛋白质科学国家实验室筹备办公室正式挂牌。

五月

5.19　第七届全国科技活动周和中科院第三届公众科学日活动开幕式在北京奥运村中科院动物所开幕。当日，由生物物理研究所主办的以“关注生命科学，共建和谐社会”为主题的第四届“公众科学日”同时拉开帷幕。实验室承接了来自科研院所、大学、中小学及社会各界群众 200 余人参加。

六月

6.11　我室徐涛研究员承担中科院仪器改造项目“膜蛋白实时相互作用的荧光共振能量转移动态检测系统”顺利通过院综合计划局专家组验收。

6.21　德国马普学会科学家代表团到生物物理研究所和生物大分子国家重点实验室进行学术访问。

七月

7.4　国际著名学术期刊 Journal of the National Cancer Institute 以“Article”形式发表了生物物理研究所梁伟研究组“磷脂—阿酶素自组装纳米胶束促进对肿瘤的渗透性”的研究论文。这一最新发现表明：聚乙二醇衍生化磷脂与抗肿瘤化疗药物-阿霉素可自组装形成纳米尺度的新型输送载体，提高阿霉素在肿瘤组织中的富集和对深层组织细胞的渗透，进而增强了阿霉素的抗肿瘤效果并降低了毒性。

7.15　《自然·结构和分子生物学》杂志发表了我所刘志杰研究组在多功能人源蛋白钓取甲基化的配基研究方面取得的突破性进展。该研究表明多功能转录共激活因子 p100 及与其特异性结合的多蛋白复合体在人体免疫反应的 IL-4 信号传导通路中起着非常重要的转录、调控和激活作用。

八月

8.27　《自然·纳米技术》在线刊发了我所阎锡蕴研究员主持完成的《氧化铁纳米颗粒具有过氧化物酶活性》论文。评论文章认为，阎锡蕴、柯莎及其课题组成员首次发现氧化铁纳米颗粒具有类似过氧化物酶的催化活性，并提出了氧化铁纳米颗粒模拟酶的概念。虽然如何在生物技术和医疗领域更好地利用纳米材料的催化活性还有待探索，但氧化铁纳米颗粒催化活性的发现将使人们对此产生更多的关注。

九月

9.4　英国生化期刊及生化学会代表团到生物物理研究所及实验室进行交流访问，徐涛所长参加接待。

9.11　中科院副院长、党组成员李家洋院士莅临生物物理研究所调研、视察,并在图书馆报告厅与院士、科研人员和管理骨干代表进行座谈，会后参观了实验室。

9.23　《自然·医学》杂志在线发表了生物物理研究所唐宏研究组和海外团队付阳心研究组在 T 细胞抑制天然免疫细胞炎症反应方面取得的突破性进展。该成果对于临床上深入了解病毒性感染的炎症反应和病毒清除机理，免疫低下病人(新生儿，老年人，器官移植患者或艾滋病人)机会性感染的控制具有极高的理论价值。

十月

10.10　国际干细胞权威杂志、《Cell》系列刊物《Cell Stem Cell》发表了生物物理研究所唐宏课题组和美国斯道尔研究所(Stowers Institute) 解亭课题组合作完成的研究论文“果蝇卵巢内干细胞的衰老是由内源和外源的因素共同调控的”。

10.18　科技部万钢部长在中科院秘书长李志刚等人的陪同下到生物物理研究所进行工作视察并参观了实验室

10.25　我室刘志杰研究员、李雪梅研究员承担的“十一五”863 重大项目“功能基因组和蛋白质组”

的“重要致病微生物蛋白质的三维结构研究”课题和“肝脏及肝病相关蛋白质的三维结构研究”课题顺利通过科技部生物技术发展中心专家组检查验收。

10.26　国家自然科学基金委国际合作局韩建国局长访问我所，并为研究组长们作了题为“科学基金国际合作介绍”的专题报告；随后与研究组长们进行了友好座谈。

十一月

11.2　由常文瑞院士牵头的“膜蛋白和蛋白质复合体的结构生物学研究”群体获得国家自然基金委员会创新研究群体科学基金资助。

11.21　生物物理研究所蒋太交研究组在 Genome Research 杂志在线发表了一项研究成果，此成果建立了模拟流感演化的计算机新模型，即网络模型。他们研究表明利用网络模型可以揭示流感演化及流行病学中的很多重要特征。

11.21　国际著名期刊《Neuron》发表了生物物理研究所徐涛研究组在囊泡转运与分泌领域的最新成果：“PKA activation bypasses the requirement for UNC-31 in the docking of dense core vesicles from C.elegans neurons”。该工作开辟了利用线虫模式生物研究囊泡分泌的新方向。

十二月

12.22　“2007 海外学人回国创业周——中国科学院行”在生物物理研究所举图书馆报告厅举行。中共团中央统战部副部长、中国青年科技工作者协会秘书长阳向东等团中央领导和近百位来自美国、日本、澳大利亚、加拿大、德国、英国、法国、韩国等不同国家各类科研机构和大学的留学人员参加了此次活动。会后参观了实验室。

12.27　中国科学院生物物理研究所“2007 年度生物物理研究所学术年会暨生物大分子国家重点实验室学术年会”在学术报告厅召开。科技部基础司张先恩司长和中科院计划局科研基地处侯宏飞副处长应邀出席了会议，施蕴渝院士、杨福愉院士、王志珍院士、郭爱克院士、王大成院士、陈润生院士，中科院上海生科院生化细胞所所长李林研究员、中科院上海药物所副所长蒋华良研究员、美国纽约大学许瑞明教授、美国西北大学吴瑛教授和生物物理研究所研究组长、资深科学家、科研人员和研究生 400 余人参加了学术年会。徐涛所长作生物大分子国家重点实验室 2007 年度的工作总结报告。

12.27　中国科学院发布《中国科学院 2007 年院士增选和外籍院士选举结果的公告》，我所陈润生研究员当选为中国科学院院士。