**CCR5 Structure and Implications for Understanding HIV Infection Mechanism**

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Human immunodeficiency virus (HIV) has been well known to cause acquired immunodeficiency syndrome (AIDS). Since it was first clinically observed in 1981 in the US, AIDS has become a worldwide epidemic, and has caused about 30 million deaths to date. The first step of HIV infection is membrane fusion between the virus and the target cell, which is mediated through interactions of the viral envelope glycoprotein gp120 with the receptor CD4 on the cell and also with co-receptor, either CCR5 or CXCR4. A wealth of research is currently aimed at understanding the molecular mechanisms of HIV viral entry. This effort has been rewarded by several breakthroughs in structural biology, such as the structure determination of gp120-CD4 complex. But the structure-function relations of the co-receptors remains poorly understood, because both CCR5 and CXCR4 belong to the membrane protein family of G protein-coupled receptors (GPCRs), and structural studies of GPCRs are enormously challenging.

Our goal is to deepen the understanding of the molecular mechanisms of HIV viral entry by solving the crystal structures of the two co-receptors. The studies were started six years ago, when I worked as a postdoc in Dr. Stevens’ lab at The Scripps Research Institute (TSRI), La Jolla. With Dr. Stevens’ support, I managed to solve five independent crystal structures of human CXCR4 complexes with two different ligands in 2010. After I came to Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences building my research group in 2011, our research were continued to focus on the co-receptor CCR5. Since only a limited number of CCR5 inhibitors have been developed, the structural studies of CCR5 is particularly challenging compared with the other GPCRs with known structures. Our previous success of solving CXCR4 structures helped us to better understand the protein behavior of the more challenging CCR5 receptor. With support from Dr. Stevens and Dr. Qiang Zhao, our group has done a tremendous amount of work on CCR5 protein expression, purification and crystallization, together with efforts of computational modeling, compound synthesis and cell signaling assays from Drs. Hualiang Jiang, Hong Liu and Xin Xie’s groups, which led to the structure determination of the complex between CCR5 and a approved anti-HIV infection drug maraviroc.

There are two major findings in this study: firstly, solving the structures of both CCR5 and CXCR4 deepens our understanding of the exact molecular details and mechanism of HIV infection, and addresses specificity issues as well as factors that define viral gp120 binding. What is quite amazing about all proteins that exist in our bodies is that only a few amino acid side chain differences can have pronounced effects on the shape and molecular recognition properties of the binding pockets. Comparing the structures of CCR5 and CXCR4, we found out that the different characters of ligand binding pockets in the two receptors, such as charge distributions and steric hindrances, may be major determinants of HIV co-receptor selectivity. Secondly, the CCR5 structure reveals a ligand binding site of maraviroc that is distinct from the proposed major recognition sites for gp120. Maraviroc thus appears to work against HIV indirectly: not by physically blocking the virus, but by locking the receptor structure into an HIV-insensitive conformation. Structural characterization of ligand binding behavior of CCR5, along with knowledge that we gain from the CXCR4 structures, lays a foundation for carrying out next generation drug discovery aimed at inhibiting viral entry of different HIV strains.

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**CCR5的三维结构及其对于艾滋病毒感染机制研究的意义**

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人免疫缺陷病毒（艾滋病毒，HIV）的危害众所周知，人体感染该病毒可能导致艾滋病的发生。自1981年美国发现首例艾滋病患者以来，艾滋病迅速发展成全球规模的流行病，已导致全球约三千万人死亡。艾滋病毒感染人体细胞的第一步是病毒与细胞的膜融合，这一过程由病毒表面糖蛋白gp120与细胞表面的受体CD4以及共受体CCR5或CXCR4共同作用完成。为了阐明艾滋病毒侵入细胞的分子机制，科学家们进行了大量的研究。经过努力，研究人员在结构生物学领域取得了多项突破，其中包括gp120与CD4复合物的结构解析，但是由于共受体CCR5和CXCR4属于G蛋白偶联受体（GPCR）膜蛋白家族，其结构解析极具挑战性，因此这两种共受体的结构与功能关系一直未能被明确阐明。

我们希望通过解析这两种共受体的三维结构，从而深入理解艾滋病毒感染人体细胞的分子机制。六年前，当我在美国Scripps研究所Stevens教授的研究组从事博士后研究时就开展了相关工作。在Stevens教授的支持下，我于2010年成功解析了人源CXCR4受体蛋白与两种配体的复合物晶体结构，相关研究成果发表在《科学》杂志上。2011年，我加入中国科学院上海药物研究所组建研究团队，在药物所的支持下继续深入该项研究，进一步探索CCR5的三维结构。由于仅有少量CCR5抑制剂被成功研制，因此与其它结构已知的G蛋白偶联受体相比，CCR5的结构解析更具挑战性，但是，CXCR4结构测定的成功经验帮助我们更好地解决了在CCR5研究过程中出现的各种难题。在Stevens教授和赵强研究员的帮助和支持下，我的研究团队在CCR5蛋白的表达、纯化和结晶方面进行了大量的工作，同时与蒋华良、柳红和谢欣三位研究员的研究组在计算机模拟、化合物合成和药理功能筛选等方面开展合作，最终成功解析了CCR5与一种抗艾滋病毒药物——马拉维若复合物的蛋白质结构。

根据上述研究，我们获取了两个重要的发现：首先，解析CCR5和CXCR4这两种共受体的结构有助于我们深入理解艾滋病毒感染人体细胞的分子机制，以及决定病毒蛋白gp120结合的各种因素。人体内蛋白质的神奇之处在于，即使是极少数氨基酸的不同，也可能显著影响蛋白质结合区域的形状和分子识别能力。比较CCR5和CXCR4的结构，我们发现这两种受体分子的配体结合口袋在电荷分布和空间位阻等性质上的差异，可能是艾滋病毒对共受体具有选择性的主要原因。此外，CCR5的结构揭示了药物马拉维若在受体分子中的精确结合位点，该结合位点与公认的gp120结合位点不同，因此，马拉维若可能是通过间接机制抑制CCR5与艾滋病毒的结合，即不直接与病毒竞争结合CCR5，但通过其与CCR5的结合改变CCR5的分子构象，使其处于艾滋病毒非敏感状态，从而实现阻断CCR5与病毒结合的功效。CCR5与配体的相互作用模式，及CXCR4晶体结构信息，为研发抵抗不同类型艾滋病毒感染的新型药物打下了坚实的基础。

CCR5的研究获得了来自科技部“973计划”、美国国立卫生研究院、国家自然科学基金委和上海市科委的经费支持。同时，我衷心感谢上海药物研究所和美国Scripps研究所的所有同事给予我们的巨大支持，没有他们的帮助，我们无法在如此短的时间内取得这一重要成果。

**Return of GPCRs to SIMM**

Dr. Hualiang Jiang

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Discovering new drugs from TCM (Traditional Chinese Medicine) has been a major research endeavor of Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, since the founding of the Institute. Prof. Cheng-Gu Zhao (T.Q. Chou), the founder and the first director of SIMM, was a pioneer in this area. As early as 1920s, Prof. Zhao tried to find analgesics from Rhizoma Corydalis, a TCM that had analgesic activity. Through 8 years (1928-1936) of hard works, Prof. Zhao obtained the crystal samples of 13 alkaloids from Rhizoma Corydalis. However, he did not know which the main active compounds are because of the lack of screening models at that time. About 25 years later (1956-1964), Prof. Guo-Zhang Jin et al. at SIMM determined that the main active compound from Rhizoma Corydalis that has analgesic activity is Tetrahydropalmatine (Rotundine, l-THP). Prof. Jin also found that the tranquillizing effect of l-THP was mediated through its antagonist activities against monoamine receptors. In 1964, Rotundine was proved as an analgesic drug by CFDA. Based on the structure-activity relationship of l-THP, Prof. Jin discovered the new pharmacological functions for a series of berberine-like natural products such as Tetrahydroberberine and Stopholidine. In particular, in 1980s, Prof. Jin discovered that several berberine-like compounds could be used to treat schizophrenia by regulating multiple GPCRs including dopamine receptors and serotonin receptors. These discoveries formed a solid basis for the development of anti-schizophrenic and anti-depressant drugs.

In 1980s, Prof. Zhi-Qiang Chi led a team in SIMM to engage in discovering analgesics targeting opioid receptors. They discovered an extremely potent analgesic drug Ohmefentanyl (β-hydroxy-3-methylfentanyl) which selectively binds to the μ-opioid receptor. Thus, SIMM has a rich history in studying and discovering GPCR ligands from natural products (TCM) and developing them for therapeutic purposes.

SIMM should have a golden period for drug research targeting GPCRs when molecular biology revolutionized receptor identification during 1980-1999. However, the turmoil of culture revolution (1966-1976) and along with the retirement of the older generation scientists created a huge gap for GPCR research and related drug R & D at SIMM. Since 2007, several groups at SIMM have started the research of GPCR pharmacology and established a series of screening models for discovering GPCR ligands. During this period, we witnessed the fast development of GPCR structural biology. The leadership team of SIMM noticed that we need new talents of GPCR structural biology and SIMM has its luck! In 2010, Dr. Huaqiang Eric Xu was recruited to SIMM to establish a center platform for determining structures of pharmacologically important GPCRs. In 2011, two young scientists, Dr. Beili Wu and Qiang Zhao, joined SIMM, and their mentor Prof. Raymond C. Stevens also came to SIMM as a visiting professor. Under the guidance of Professors Stevens and Xu, GPCR structural biology is developing extremely fast at SIMM, in close collaboration with medicinal chemists, pharmacologists and computational biologists. Only after two years, SIMM has made striking progress on structure determination of GPCRs. Drs. Huaqiang Eric Xu and Raymond C. Stevens et al. published the X-ray crystal structures of two [serotonin](http://en.wikipedia.org/wiki/Serotonin) receptors (5-HT1B and 5-HT2B) in Science this March, and this July Drs. Raymond C. Stevens and Ming-Wei Wang published the X-ray crystal structure of glucagon receptor in Nature.

Today, we are witnessing another important event occurs at SIMM. Dr. Beili Wu and her collaborating team will publish the X-ray structure of the CCR5 chemokine receptor – HIV entry inhibitor maraviroc complex in Science. I am extremely happy for this milestone achievement for two reasons: First, I am happy because the Young talent like Dr. Beili Wu can find her success at SIMM, where we have stride to provide an intellectual enviroment for young people to succeed; secondly, I am happy because my colleagues and I were lucky enough to get directly involved in this project using our computational modeling. This research will speed up the discovery and development of anti-HIV-1 drugs. During the structural determination, Drs. Hong Liu and Xin Xie synthesized and screened many ligands in order to stabilize the structure of CCR5. Soon after Beili Wu team obtained the primary data of the structures, we had started to design, synthesis and screening new compounds. This tight collaboration is delightfully productive, and we have obtained drug lead compounds against HIV-1 infection. The antiviral efficacies of several compounds are even more potent than the clinical drug - maraviroc.

Now I am happy to announce that GPCRs have once again come back to SIMM, where we will work hard to make their homecoming exciting and long lasting. As today, I hope all of you are here to witness the beginning of another golden era of GPCR research and drug discovery at SIMM. Exciting time ahead, indeed!

**上海药物所GPCR研究的又一黄金时期到来**

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中国科学院上海药物研究所自建所以来，一直致力于基于中国特有的中草药及天然产物的新药研发工作，药物所的创始人兼首任所长赵承嘏院士即为该领域的先驱者。上世纪20年代，赵先生针对具有镇痛活性的传统中草药延胡索开展研究，希望可以确认其镇痛活性成分。经过八年（1928-1936)的艰苦研究，赵先生得到了13种延胡索成分生物碱样品晶体。然而，受制于当时的科技水平，缺乏合适的药理筛选模型，仍无法确认其具体活性成分。直到约25年后，药物所的金国章院士等科学家又经过八年（1956-1964）的潜心钻研方才确认了延胡索中镇痛活性成分为左旋四氢巴马丁（罗通定， L-THP ）。金先生还发现，L-THP可拮抗单胺受体活性，因此除镇痛作用外还具有安定作用。1964年，L-THP作为镇痛药物经药监局批准上市。基于对L-THP构效关系及其分子药理学的研究，金先生又发现了包括四氢小檗碱、左旋千金藤啶碱等在内的一系列小檗碱类天然产物的作用机制。特别是上世纪八十年代发现的可用于治疗精神分裂症的小檗碱类化合物，通过分子药理学研究，发现其可以调节包括多巴胺受体和5-羟色胺受体在内的多个G蛋白偶联受体（GPCR）活性，这些研究成果为抗精神分裂症和抑郁症的药物研发奠定了坚实的基础。

上世纪八十年代，池志强院士领导的科研小组在上海药物所开展以阿片受体为靶点的镇痛药物研究工作，他们发现了一种极其强效的镇痛药羟甲芬太尼（ β-羟基- 3 - 甲基），该配体分子可与阿片受体选择性特异结合。因此，药物所具有丰富的GPCR研究历史，包括其天然产物配体的发现及新药研发。

上世纪八九十年代，随着分子生物学的发展，GPCR受体分子的研究迎来了革命性的突破。然而，由于文革的动荡和老一代科学家的退休，药物所的GPCR研究及相关药物研发工作错过了此黄金时期。2007年以来，上海药物所陆续有多个研究组重新开始了GPCR药理学研究并建立了一系列的筛选模型。在此期间，我们目睹了GPCR结构生物学的飞速发展，药物所的领导班子意识到，我们亟需引进GPCR结构生物学人才。幸运的是，2010年，徐华强博士受聘于药物所筹建GPCR结构生物学平台；2011年，两位年轻的GPCR结构生物学家吴蓓丽博士和赵强博士加盟药物所；同时，他们的导师——国际GPCR结构生物学领军人物——Raymond C. Stevens教授也以客座教授身份加盟药物所。药物所GPCR结构生物学研究在Stevens教授和徐华强研究员的指导下，通过与药物所药物化学家、药理学家和计算生物学家的密切合作，取得了飞速发展，仅用了两年时间就取得重大科研成果，其中Stevens教授和徐华强教授合作解析了两个5-羟色胺受体结构，相关成果发表于今年三月份的《科学》杂志；Stevens教授和王明伟教授合作解析的胰高血糖素受体结构，相关科研成果发表于《自然》杂志。

今天，我们正在见证GPCR研究的又一重要事件——吴蓓丽研究员及其研究团队即将在《科学》杂志发表趋化因子受体CCR5与艾滋病毒抑制剂马拉维若复合物的X射线晶体结构。对于这一里程碑式的成果，我深感欣慰。首先，我为青年人才吴蓓丽研究员在药物所获得的成功感到高兴，药物所一直努力为青年科技人才提供良好的学术环境；同时，我也为我和我的团队可以有幸利用我们的计算模型直接参与此项研究工作而感到高兴。本项研究成果将加速抗艾滋病毒药物的研发。在药物所，我们多方紧密协作，在CCR5结构解析过程中，柳红研究员的科研团队和谢欣研究员的科研团队合成并筛选了多种配体分子以稳定CCR5蛋白分子结构；吴蓓丽研究员的科研团队获得CCR5的结构数据后，我们又立刻开始了基于CCR5结构的药物设计、合成及新化合物的筛选。由于这种紧密高效的合作，目前我们已经获得了数种抗艾滋病毒感染的先导化合物，且其抗病毒功效优于目前临床使用的药物马拉维若。

现在，我很高兴地宣布，药物所GPCR研究的辉煌再次重现！我们将不负老一辈科学家的期望，努力工作，传承药物所GPCR研究的光辉成就并将其发扬光大。今天，我希望大家可以在这里共同见证上海药物所GPCR研究和药物研发的另一个黄金时代的开始，未来药物所的GPCR研究将更加激动人心！

**GPCR Structure, Function, Drug Discovery and International Collaborations**

Dr. Raymond Stevens

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After 20 years of challenges with getting G-protein coupled receptor (GPCR) structure-function data, in 2007 the Stevens laboratory published the structure of the human β2-adrenergic receptor at 2.6 Å resolution in the journal Science. This study was rapidly followed up by Stevens and colleagues with the structure, structure-function, and drug discovery studies of the human adenosine A2a, dopamine D3, chemokine CXCR4, serotonin 5HT1B and 5HT2B, histamine H1, S1P1, glucagon, smoothened, kappa and delta opioid, and nociceptin receptors. To date, the Stevens laboratory has successfully conducted structure-function studies of 14 of the 21 published GPCRs. Highlights include the structure determination of the S1P1 receptor determined in collaboration with Receptos, a company started by the GPCR small molecule structure based drug design technology platform at The Scripps Research Institute. Receptos developed an S1P1 agonist to treat multiple sclerosis and inflammatory bowel disease in two different phase II/III human clinical trials and successfully completed a successful IPO in May 2013 on Nasdaq after only 4 years of startup. Crystal structures of GPCRs are providing a robust three-dimensional structural framework for computational modeling of receptor dynamics, as well as for ligand docking and virtual ligand screening (VLS). The growing number of structure-based VLS studies demonstrates encouragingly high hit rates (20–70%) in the identification of new ligand chemotypes as lead compounds for A2A adenosine, CXCR4 chemokine, D3 dopamine, and H1 histamine receptors, as well as in lead optimization. Obtaining structure-function data from closely related receptors such as the serotonin or opioid receptors is allowing for breakthroughs to occur in understanding how these receptors signal, particularly through specific biological pathways. Ultra high resolution crystallographic studies are now being conducted that are making new discoveries including allosteric control of GPCRs by molecules like cholesterol and sodium and NMR studies are uncovering biased signaling pathways through the membrane. Most recently, a second company called RuiYi has been established in Shanghai, China based on new technology to develop biologic therapeutics against GPCR drug targets to treat unmet medical needs that are difficult to address through small molecule drug discovery.

The above discoveries and accomplishments are significant, however the GPCR superfamily has 826 members and more than 300 at a minimum are considered to be critical drug targets to treat numerous diseases. At the current pace, it would take several decades to fully understand the GPCR family, which is the largest protein family in the human genome and the target of more than 40% of all drugs. This is unfortunate since the technology exists today to understand how these receptors work, and to develop new or best in class and safer therapeutics to treat many different human diseases. Related, the research is very expensive and the full financial burden of basic science should not fall on just one entity or country. International collaborations are critical for the future of science. To help recruit both the necessary funding support and talent to study the biomedically important family of proteins, an U.S.-China Biomedical Collaborative Research Program grant funded by National Institutes of Health and National Science Foundation of China was awarded to expand the PSI:Biology GPCR Network technology platform from The Scripps Research Institute in La Jolla, CA to the Shanghai Institute of Materia Medica. This effort was led by the newly appointed Professors Beili Wu and Qiang Zhao in Shanghai who trained at The Scripps Research Institute in the US, and Raymond Stevens in La Jolla, CA. With support from NIGMS and NIAID at the NIH, NSFC, and Director Jian Ding and Professor Hualiang Jiang at the Shanghai Institute of Materia Medica, the technology transfer was successfully completed and the CCR5 project initiated by Professor Wu who tirelessly pursued these studies with passion, dedication, and maintained the research at the highest quality level. The first of many results are now appearing and are being coordinated at the international level to avoid overlap of research efforts.

With the technology and collaborations now in place, we are seeing the needed difference and similarity details between closely related receptors. This information is critical for receptors that differ very slightly in the binding sites and recognize molecules like viruses, including HIV. The human CXCR4 and CCR5 structures are key breakthroughs for the field, and a long sought after goal. Perhaps most exciting is that with CXCR4 and CCR5 protein material available, the door is now open to using multiple biophysical studies and knowledge, to better understand how HIV infectivity occurs. With both the HIV co-receptor three-dimensional structures, it is likely we will see the next generation of HIV therapeutics.

**GPCR结构、功能研究、药物研发及国际合作**

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经过20年的艰苦研究，Stevens教授的研究组于2007年成功解析了人β2 -肾上腺素受体高分辨率晶体结构，该项研究成果发表于《科学》杂志。随后，Stevens教授和他的研究团队陆续在多个人源GPCR蛋白的结构生物学、结构-功能关系研究及药物研发方面取得到了突飞猛进的进展， 包括腺苷受体A2A、多巴胺受体D3、趋化因子受体CXCR4、5-羟色胺受体5HT1B和5HT2B、组胺受体H1、磷酸鞘氨醇受体S1P1、胰高血糖素受体、SMO受体、δ--阿片受体、κ-阿片受体及痛敏肽受体。迄今为止，已发表的21个GPCR蛋白晶体结构中有14个是由Stevens教授及其研究团队完成的。其中最重要的成果包括与Receptos公司合作解析的磷酸鞘氨醇受体S1P1结构，Receptos公司是由美国Scripps研究所基于GPCR结构的小分子药物研发平台发展而来，Receptos公司仅用了四年时间，就研发出一种可用于治疗多发性硬化症和肠炎的S1P1受体激动剂，并通过了临床二期和三期实验，该公司于2013年5月在纳斯达克上市。GPCR受体的晶体结构信息为包括受体动力学模拟、配体对接和虚拟配体筛选在内的药物研发提供了坚实的三维结构框架。在目前的新药研发中，基于结构的虚拟配体筛选和优化越来越显示出巨大优势，在针对腺苷受体A2A、趋化因子受体CXCR4、多巴胺受体D3、组胺受体H1等GPCR蛋白的先导化合物筛选优化工作中，小分子配体筛选的准确率高达20%-70%。同时，通过对相近GPCR蛋白进行结构-功能关系研究，如5-羟色胺受体和阿片受体，可以更清晰地了解其信号传导的分子机制，尤其是利用了何种生物学通路。此外，超高分辨率GPCR晶体结构研究对某些重要的生物学功能进行了新的探索，例如胆固醇和钠离子等对GPCR的变构调节机制。同时，利用核磁共振技术(NMR)，揭示了GPCR在跨膜信号传导中对信号通路的选择偏好性。最近，第二家基于GPCR结构生物学的药物研发公司——锐医在上海成立，公司主要致力于利用新技术开展以GPCR为靶点的新药研发工作，以期解决目前难以用小分子药物解决的医学难题。

GPCR相关研究虽然已经得到了飞速发展，然而，GPCR家族非常庞大，包括826个成员，其中与人类疾病相关的重要药物靶点至少有300余种，目前超过40%的上市药物以GPCR为靶点。以目前的科研水平，如果要全面地了解这个人体内最大蛋白质家族，至少需要几十年。并且，开展GPCR结构生物学研究及基于此的药物研发工作耗资巨大，仅靠一个国家的科研机构和科研经费支持无法完成，因此大力开展国际合作对未来该领域的发展至关重要。美国国立卫生研究院和中国国家自然科学基金委共同资助的一项中美生物医学合作研究项目，为GPCR蛋白的研究提供了科技人才和经费支持，此项目的启动加强了美国Scripps研究所GPCR网络中心与中国科学院上海药物研究所间的国际合作。此项工作是由上海药物研究所的两位年轻研究员吴蓓丽和赵强，以及Scripps研究所的Stevens教授领衔完成的，吴蓓丽研究员和赵强研究员曾在Stevens教授研究组接受过系统的GPCR结构生物学理论知识和实验技能训练。在美国国立卫生研究院、中国国家自然科学基金委、以及上海药物研究所的丁健所长和蒋华良副所长等的大力支持下，上海药物研究所已成功建立了GPCR结构生物学研究平台。利用该平台，吴蓓丽研究员领导其研究团队成功解析了艾滋病毒共受体CCR5的高分辨率晶体结构，这一成功与她长久以来的科研热情和孜孜不倦的钻研、奉献精神密不可分。目前，GPCR结构生物学研究领域保持着良好、紧密的国际协作关系，可以在全球范围内进行协调，避免重复浪费的科研力量投入。

利用先进的技术平台以及良好的合作基础，我们将侧重于研究CCR5和CXCR4这两种相近受体之间的细微异同之处，配体结合位点上的微小差异对于相近受体蛋白识别病毒等分子的机制研究至关重要。CXCR4和CCR5结构的成功解析是GPCR结构生物学研究的重要突破，也是长期不懈努力的结果。 同样重要的是，CXCR4和CCR5的高纯度蛋白样品的获得为运用其它生物物理手段进一步研究艾滋病毒感染机制铺平了道路。两种艾滋病毒共受体的三维结构的解析，为相关药物研发奠定了基础，新一代抗艾滋病毒药物的研究将很有可能取得突破性进展。