清華大學 药学院
SCHOOL OF PHARMACEUTICAL SCIENCES
TSINGHUA UNIVERSITY

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清华大学药学院 2017 春季学期新闻简报

Newsletter

School of Pharmaceutical Sciences, Tsinghua University

目录

News Highlights ...

GHDDI's Inauguration Ceremony Held in Beijing

March 24 marked the official inauguration of the Global Health Drug Discovery Institute (GHDDI), a transformative drug discovery and translational platform with advanced biomedical research and development capabilities, jointly founded by Tsinghua University, the Bill & Melinda Gates Foundation, and the Beijing Municipal Government. GHDDI is the first independent and not-for-profit research institute of its kind in China, financed through an innovative Public-Private Partnership (PPP) model. It will bring together resources and expertise from academia and the pharmaceutical industry to streamline innovative drug development - from initial drug discovery to clinical development.

Under the leadership of Dr. DING Sheng, Institute Director of GHDDI, and Dean of the School of Pharmaceutical Sciences (SPS) of Tsinghua University, GHDDI aims to become an open and collaborative community of scientists and researchers around the world, and is currently recruiting top scientists from China and overseas with expertise in medicinal chemistry, computational chemistry, disease biology, structural biology, etc. The institute has already assembled a research team and initiated several projects in tuberculosis, malaria and cryptosporidiosis in collaboration with Tsinghua and its strategic and technological partner, the California Institute for Biomedical Research (Calibr).

The founding partners of GHDDI expresses significant expectation for the Institute. Dr. QIU Yong, President of Tsinghua University believes that GHDDI will drive innovative drug research in China and enhance Tsinghua's global impact. SUI Zhenjiang, Deputy Mayor of Beijing, encourages GHDDI to bring in international collaborations on global health. Bill Gates, Co-chair and Trustee of the Gates Foundation, hopes for GHDDI to leverage China's technology and R&D capacity to fight against diseases that harm those in most need globally.

Conference and Forum ...

Invitation to the 2017 Chinese Medicinal Chemistry Symposium sent

The 2017 Chinese Medicinal Chemistry Symposium will take place in Beijing from August 27 to August 30 at the Beijing National Conference Center. This year's theme is Global New Drug Research and Development: New molecules, New Technologies, and New Therapies. This symposium will gather scientists across the globe to inspire collaborative research and advance the field of medicinal chemistry. It will be a significant platform for scientists, researchers, experts and scholars to meet like-minded individuals, exchange ideas and build new connections. The symposium will feature presentations, poster sessions, open discussions and forums. Topics will focus on:

1. Progression of cell therapy research (including immune, stem cells, etc.)
2. New frontiers and trends in medicinal chemistry
3. Latest developments in critical diseases
4. New theories and methods of drug molecular design
5. New methods and technologies in medicinal materials and drug synthesis
6. Chemical biology and related fields
7. Frontiers of natural medicine and traditional Chinese medicine

In collaboration with the Chinese Pharmaceutical Association (CPA) and the European Federation of Medicinal Chemistry (EFMC), the symposium will be held together with the 2017 CPA-EFMC International Symposium on Medicinal Chemistry, during which the 20th Annual Servier Youth Pharmaceutical Chemistry Award will also be celebrated.

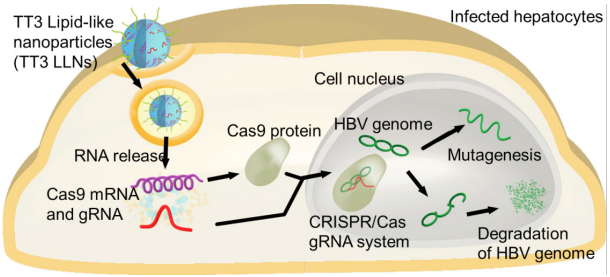
We hope the exchange of ideas and discoveries from researchers across different areas and disciplines will create new advances in this rapidly changing field of medicinal chemistry. We cordially invite experts and scholars in China and abroad to join us in this two-day presentations and discussions.

Scientific Discovery ...

1.TAN Xu research group examines in vivo targeted gene therapy

TAN research group, in collaboration with DONG Yizhou research group at the Ohio State University, published "A non-viral CRISPR/Cas9 delivery system for therapeutic gene targeting in vivo" in Cell Research.

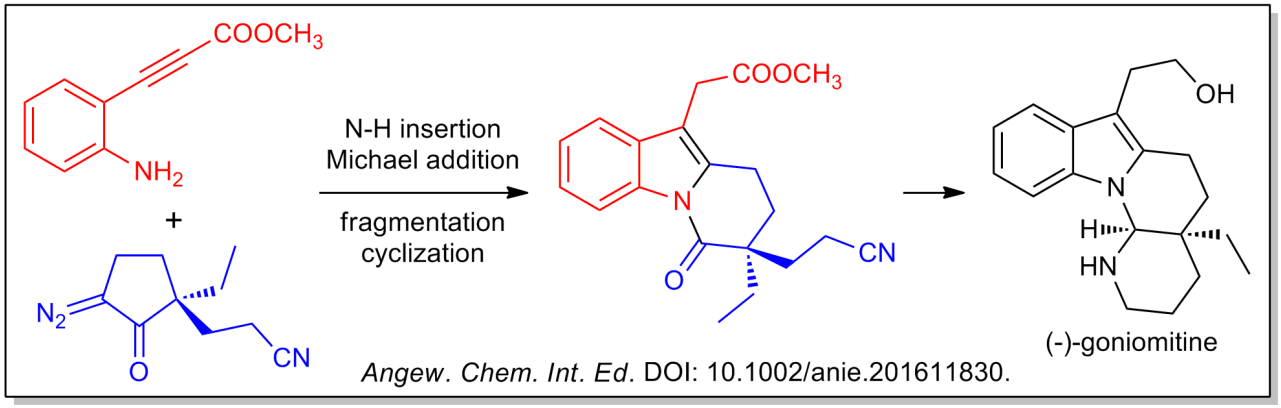
The clustered, regularly interspaced, short palindromic repeat (CRISPR)/CRISPR-associated protein (Cas) system has revolutionized biomedical research and facilitated the development of new therapies based on genome editing. A major roadblock to achieve the therapeutic potential of the CRISPR/Cas system is the lack of a safe and effecting in vivo delivery method. Adeno-associated virus (AAV)-assisted delivery of the CRISPR/Cas9 system has shown gene targeting efficacy in vivo, however, the long persistence and immunogenicity of AAV in the host prevent the wide therapeutic application of AAV-based CRISPR/Cas9 delivery



2. ZU Liansuo research group develops efficient synthesis of natural Goniomitine

ZU research group published “Bio-Inspired Fragmentations: Rapid Assembly of Indolones, 2-Quinolinones, and ( )-Goniomitine” in Angew. Chem. Int. Ed.

Inspired by the biogenetic origin of goniomitine, new synthetic bio-inspired fragmentation strategies for the synthesis of functionalized 2-quinolinones and indolones have been developed. Remarkable synthetic efficiency was achieved by telescoping several transformations into one-pot reactions, allowing for the direct coupling of 2-alkynyl-anilines and diazo ketones. The synthetic utility was demonstrated by the 5-step asymmetric total synthesis of (@)-goniomitine from 2-ethylcyclopentanone.

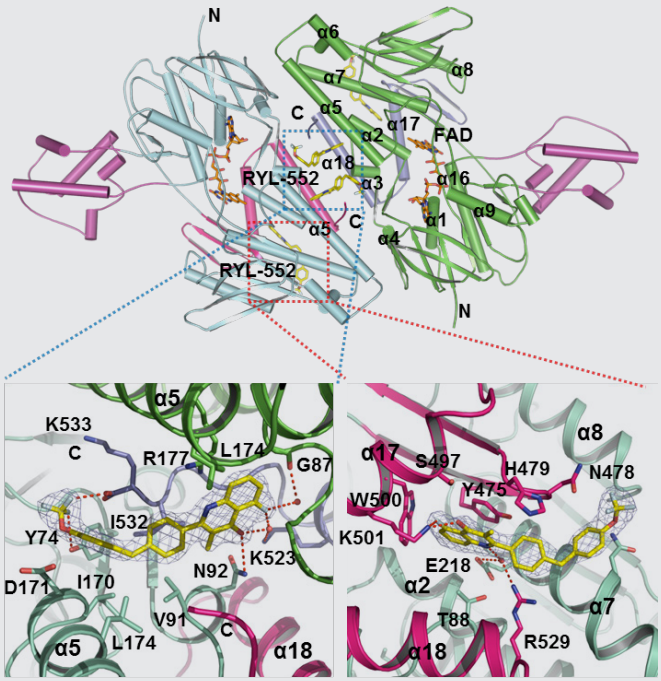


3.RAO Yu and YANG Maojun research groups examine the development and mechanism of high activity anti-malarial small molecule compounds

RAO research group, together with YANG research group at Tsinghua's School of Life Sciences published "Target Elucidation by Cocrystal Structures of NADH-Ubiquinone Oxidoreductase of Plasmodium falciparum (PfNDH2) with Small Molecule To Eliminate Drug-Resistant Malaria" in Journal of Medicinal Chemistry.

Recently, drug-resistant malaria strains have been emerging, which post a great challenge for global health. New antimalarial drugs with novel targeting mechanisms are urgently needed for fighting drug-resistant malaria. NADH-ubiquinone oxidoreductase of Plasmodium falciparum (PfNDH2) represents a viable target for antimalarial drug development.

However, the absence of structural information on PfNDH2 limits rational drug design and further development. We report high resolution crystal structures of the PfNDH2 protein for the first time in Apo-, NADH-, and RYL-552 (a new inhibitor)-bound states. The PfNDH2 inhibitor exhibits excellent potency against both drug-resistant strains in vitro and parasite-infected mice in vivo via a potential allosteric mechanism. Furthermore, the findings show that the inhibitor can be used in combination with dihydroartemisinin (DHA) synergistically. These findings are important for malarial PfNDH2 protein-based drug development and have broad implications for other NDH2-containing pathogenic microorganisms like Mycobacterium tuberculosis.

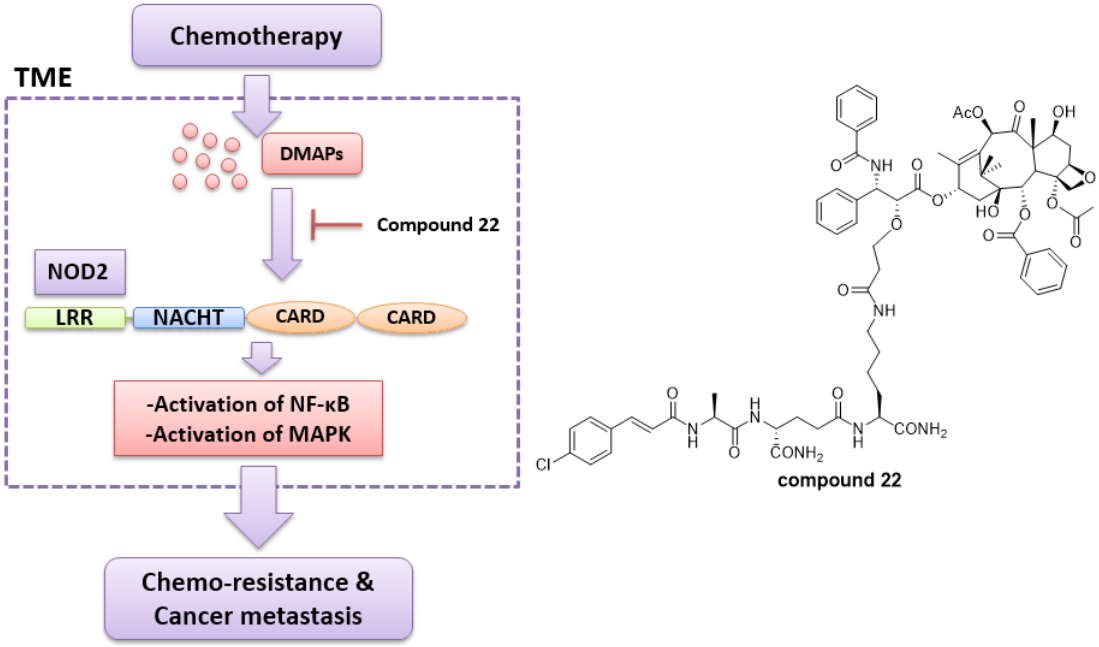


4. LIU Gang research group releases first report on NOD2 targeted tumor treatment

LIU research group published "Antagonizing NOD2 Signaling with Conjugates of Paclitaxel and Muramyl Dipeptide Derivatives Sensitizes Paclitaxel Therapy and Significantly Prevents Tumor Metastasis" in Journal of Medicinal Chemistry.

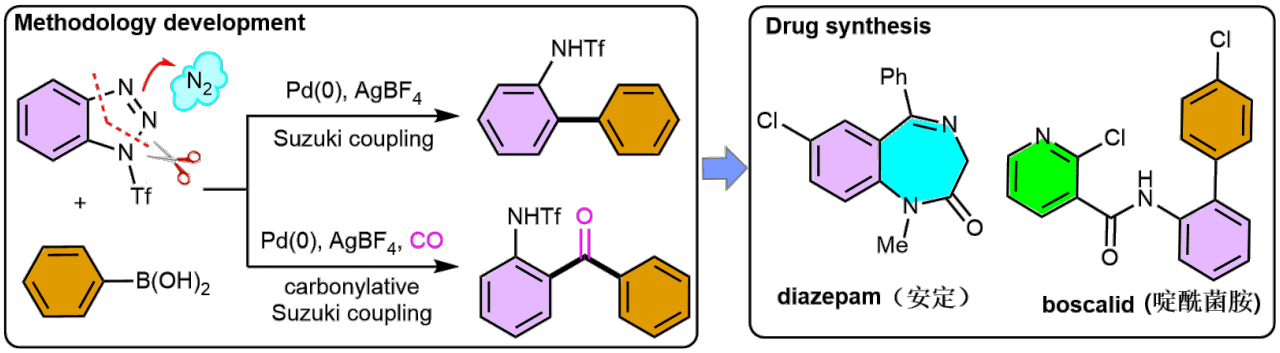
A noncleavable paclitaxel (PTX) and N-acetylmuramyl-l-alanyl-d-isoglutamine (MDP) derivative conjugate, 22 (DY-16-43), and its analogues were prepared and characterized as antagonists of NOD2 signaling. This conjugate enhanced the antitumor and antimetastatic efficacy of PTX in Lewis lung carcinoma (LLC) tumor-bearing mice.

This work first describes a molecular strategy that enables the sensitization of a chemotherapeutic response via antagonizing NOD2 inflammatory signaling and suggests NOD2 antagonist as potential adjunct in treating non-small-cell lung cancer (NSCLC).



5. TANG Yefeng research group discovers a new type of coupling reaction

TANG research group published "Denitrogenative Suzuki and carbonylative Suzuki coupling reactions of benzotriazoles with boronic acids" in Chemical Science.



Unprecedented palladium-catalyzed denitrogenative Suzuki and carbonylative Suzuki coupling reactions of benzotriazoles with boronic acids have been realized, leading to the possibility of structurally diverse ortho-amino-substituted biaryl and biaryl ketone derivatives. The key to this success is due to the development of a rationally designed strategy to achieve the ring opening of benzotriazoles with a synergistic activating–stabilizing effect, which enables the in situ generation of the corresponding ortho-amino-arenediazonium species. The present work opens up a new avenue to utilize benzotriazoles as synthetic equivalents of ortho-amino-arenediazoniums, which otherwise could not be directly accessed by existing synthetic methods.

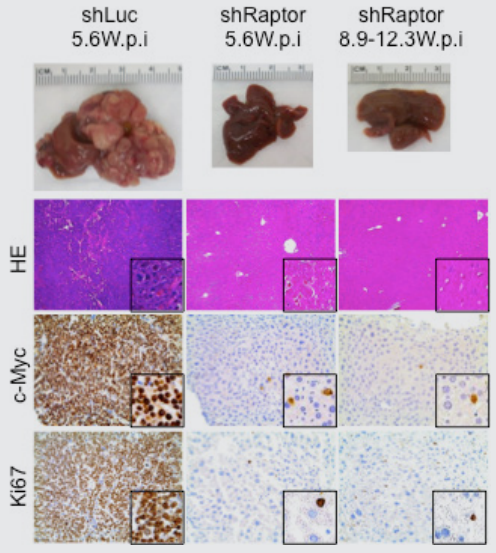
6.CHEN Ligong research group examines amino acid transporters as important regulatory factors in the process of liver cancer

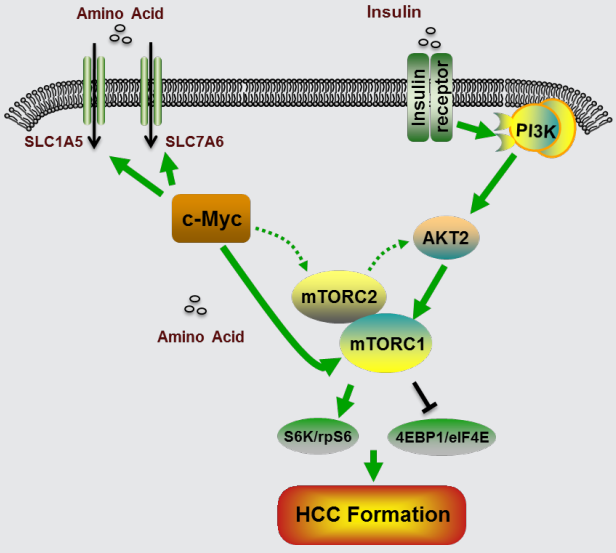
CHEN research group published “A "functional signaling indispensable is for c-Myc driven hepatocarcinogenesis" in Hepatology.

Amplification and/or activation of the c-Myc protooncogene is one of the leading genetic events leading to hepatocarcinogenesis. The oncogenic potential of c-Myc has been proven experimentally by the finding that its overexpression in the mouse liver triggers tumor formation. However, the molecular mechanism whereby c-Myc exerts its oncogenic activity in the liver remains poorly understood. Here, we demonstrate that the mammalian target of rapamycin complex 1 (mTORC1) cascade is activated and necessary for c-Myc dependent hepatocarcinogenesis.

Specifically, we found that ablation of Raptor, the unique member of the mTORC1 complex, strongly inhibits c-Myc liver tumor formation. Also, p70S6K/ribosomal protein S6 (RPS6) and eukaryotic translation initiation factor 4E-binding protein 1/eukaryotic translation initiation factor 4E (4EBP1/eIF4E) signaling cascades downstream of mTORC1 are required for c-Myc-driven tumorigenesis. Intriguingly, microarray expression analysis revealed the upregulation of multiple amino acid transporters, including SLC1A5 and SLC7A6, leading to robust uptake of amino acids, including glutamine, into c-Myc tumor cells. Subsequent functional studies showed that amino acids are critical for activation of mTORC1, as their inhibition suppressed mTORC1 in c-Myc tumor cells. In human HCC specimens, levels of c-Myc directly correlate with those of mTORC1 activation as well as of SLC1A5 and SLC7A6.

Conclusion: Our current study indicates that an intact mTORC1 axis is required for c-Myc-driven hepatocarcinogenesis. Thus, targeting mTOR pathway or amino acid transporters may be an effective and novel therapeutic option for the treatment of HCC with activated c-Myc signaling.



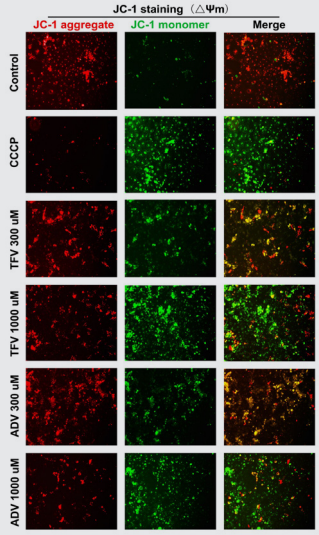


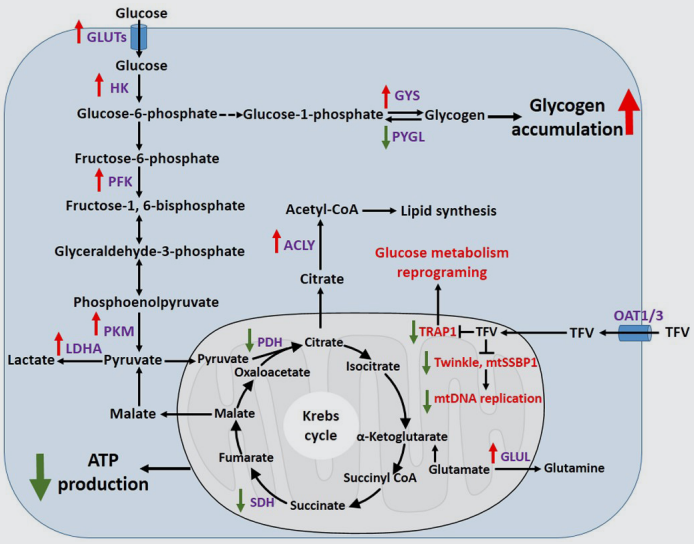
7.CHEN Ligong research group discovers the mechanism process of renal toxicity induced by adefovir and tenofovir

CHEN research group published "Tenofovir and adefovir down-regulate mitochondrial chaperone TRAP1 and succinate dehydrogenase subunit B to metabolically reprogram glucose metabolism and induce nephrotoxicity" in Scientific Reports.

Despite the therapeutic success of tenofovir (TFV) for treatment of HIV-1 infection, numerous cases of nephrotoxicity have been reported. Mitochondrial toxicity has been purported as the major target of TFV-associated renal tubulopathy but the underlying molecular mechanism remains unclear.

In this report, we use metabolomics and proteomics with HK-2 cells and animal models to dissect the molecular pathways underlying nephropathy caused by TFV and its more toxic analog, adefovir (ADV). Proteomic analysis shows that mitochondrial chaperone TRAP1 and mtDNA replicating protein SSBP1 were significantly down-regulated in TFV and ADV treated HK-2 cells compared with controls. Transmission electron microscopy (TEM) revealed that TFV and ADV-treated HK-2 cells had accumulated glycogen, a phenotype that was also observed in mice treated with TFV and ADV. Analysis of the proteins in TCA cycle showed succinate dehydrogenase subunit B (SDHB) was nearly depleted in glucose oxidative phosphorylation pathway however certain enzymes in the glycolysis and glycogen synthesis pathway had elevated expression in TFV and ADV-treated HK-2 cells. These results suggest that TFV and ADV may cause mitochondrial dysfunction in renal tubular cells and reprogramming of glucose metabolism. The resulting glycogen accumulation may partially contribute to TFV and ADV induced renal dysfunction.





Translational Research ...

Tsinghua University and Beijing Jialin Pharmaceutical Co., Ltd. collaborate on developing new cancer drugs

On January 13, Tsinghua University signed an agreement for a new drug development project with Beijing Jialin Pharmaceutical Co., Ltd. Dr. SHI Yigong, Vice-President of Tsinghua University and LIU Wei, President of Beijing Jialin Pharmaceutical Co., Ltd witnessed the signing. The collaboration aims to develop new cancer drugs.

SHI highlighted the rapid development in the past decade for life science, medicine and pharmaceutical sciences at Tsinghua University, which has been driven by the University's support, government funding and now the investment form the industry.

LIU pointed out that Jialin has been focusing on new drug development for cardiovascular diseases and cancers. The collaboration with Tsinghua will further enhance its R&D capabilities and drive the sustainable growth of the company.

Recently, Dr. HE Wei reached a significant technology transfer agreement with Beijing Jialin Pharmaceutical Co., Ltd. under favorable terms. This "BRM Inhibition Based New Cancer Drug Development Technology" will be further developed at the company for new drug discovery.

HE Wei, Ph.D.

Dr. He joined the faculty team at Tsinghua University in January 2011. His main research interests lie in the (nanostructure) metal catalysis and synthesis of drug molecules. Currently, he also serves as the Associate Editor for RSC Advances.

Talent Development...

1.SPS undergraduate selected to study at Stanford University

Stanford University's 2017 Undergraduate Visiting Research Program (UVGR) selected WU Muziyue, an undergraduate from Tsinghua SPS, as one of the 18 outstanding students across China to join the prestigious program this summer.

Students enrolled in UVGR will work with top professors on a ten-week research project at Stanford's Institute of Technology. The program aims to bridge China and the U.S. by building long-lasting, impactful relationships with students from China. Stanford hopes the program to serve a springboard for student exchange between China and the U.S.

WU will become a representative of Tsinghua SPS as she begins her summer at Stanford. This program will also bring her a unique opportunity to learn and grow, and to connect students in China and the U.S. by sharing her experiences at home and abroad.

2.Students enrolled in SPS' s pilot overseas programs return with enriched experience and high honors

On March 4, SPS students (Class 2011) who enrolled in the pilot overseas program at Melbourne Medical School celebrated their completion of the master's degree for research. YANG Haoyu, WANG Beinan and CHEN Sui from SPS are among the first cohort of the program to complete the two-year research program at University of Melbourne.

SPS has developed multiple pilot overseas programs across the world. The University of Pittsburgh's School of Medicine program started in 2012, and has three cohorts, a total of 12 students. The University of California - San Francisco (UCSF) program started in 2014, and has three cohorts, a total of 11 students. The University of Melbourne program has three cohorts.

To date, these students have participated in 11 international conferences and presented 10 oral and poster presentations. Their research work can be found in many top international journals, including 27 published papers and 2 accepted papers. WANG Yao has published her work in Plos Genetics as the co-first author. WU Jianchen also published a paper as the contributing author. MO Han received the Mary Anne Koda-Kimble Seed Award for Innovation (2016 and 2017).

Not only have these students achieved academic honors, they have also gained valuable experiences in laboratory research, a global perspective on science as well as new opportunities for their future endeavors.

Collaboration and Development ...

SPS strives to create an open and dynamic environment to encourage deep collaborations across various disciplines and sectors. We actively seek partnerships and sponsorships in the education, talent development, research, translational science and technology transfer spaces. Together with our partners, we are building a global ecosystem for biomedical research that can sustainably enable pharmaceutical breakthroughs and enhance the quality of life.

To date, we have already established partnerships with the Bill & Melinda Gates Foundation, Johnson & Johnson, Bristol-Meyers Squibb Company, Bayer, Roche, and Beijing Unisplendour Pharmaceutical etc.

Contact Us

With the generous support of SPS's advocates and through effective collaboration with SPS's partners we will be able to engage in more impactful educational and research activities to tackle the most pressing disease challenges.

If you are thinking about partnering with SPS or wishing to learn more about how to work with SPS, we welcome and value your inquiry sent to the Development Office at

tsps_d@tsinghua.edu.cn

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