中国科学院深圳先进技术研究院
SHENZHEN INSTITUTE OF ADVANCED TECHNOLOGY
CHINESE ACADEMY OF SCIENCES

SIAT IBT

Information Technology and Biotechnology

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Message from the President

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Only first–class environment can attract top–notch talents. Shenzhen Institutes of Advanced Technology (SIAT) inspires to create an enabling scientific and cultural environment that is appealing to researchers. Through the establishment of advanced human resource system, competitive incentive measure, innovative culture, and technology transfer mechanism, our institute seeks to attract and cultivate first class talents for collaborative innovation. By making strategic, forward–looking and fundamental contributions to sciences and technology, SIAT is endowed with the responsibility to boost China's advanced manufacturing and service industries, and promote new industries with independent intellectual property rights. In the fields of biomedicine, biomedical engineering, integrated technology, advanced computing, new materials and new energy, SIAT has emerged as a premier institute in the world and a power horse in China, and has profound influence on the advanced manufacturing enterprises in Guangdong and Hong Kong. We play a leading role in Shenzhen–Hong Kong Innovation Circle, and make significant contribution to innovating China into a world manufacturing power.

About SIAT

The Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Science (CAS) was jointly established by CAS, the Shenzhen municipal government and the Chinese University of Hong Kong in February 2006. SIAT aims to enhance the innova-tive capacity of the equipment manufacturing and service industries in the Guang-dong-Hong Kong region, promote the development of emerging industries possessing their own proprietary intellectual property, and become a world-class industrial research institute.

SIAT focuses on the multi-disciplinary integration development of Information Technology and Biotechnology. It mainly includes 8 sub-institutes(57 research centers): Shenzhen Institute of Advanced Integration Technology (SIAIT); Institute of Biomedical and Health Engineering (IBHE); Institute of Advanced Computing and Digital Engineering (IACDE); Institute of Biomedicine and Biotechnology (IBB); Institute of Brian Cognition and Brian Disease (IBCBD, collaborated with MIT McGovern Institute); Institute of Synthetic Biology; Institute of Advanced Electronic Materials (IAEM); Institute of Technology for Carbon Neutrality (ITCN). It is also home to 11 national innovation labs, 34 key labs and platforms at the provincial level and 79 key labs and platforms at the municipal level.

SIAT has staff over 2300, including 156 full-time national talents, 77 faculty members are among the World's Top 2% Scientists by Stanford University, as well as more than 2799 postgraduate students. 34 international academicians and fellows are invited as chief scientists part-time working in SIAT. Oriented to be the industrial research institute, SIAT makes efforts to the scientific and technological transforming and has incubated 1853 companies (365 shareholding) in the fields of emerging industries such as low-cost healthcare, service robots, electric vehicles, cloud computing, digital cities, nano-medi-cine, new energy and new materials.

SIAT established global partnership across 54 countries and districts, on nearly 500 programs in 98 institutions including MIT, Stanford University, UCL, UBC, UCLA, EPFL, HU Berlin etc. 45.2% of SIAT annual publications are resulted from international collaboration.

SIAT is already a leading research institute in Southern China and innovative reforming model in China, as is reflected by the consistency with our high-quality papers and contri-bution to industries. However, we still have a long way to go for our ultimate goal as the top-tier ' E(Engineering) - T(Technology) - S(Science)' institute around the world.

Information Technology

Focusing on the integration of intelligence and biotechnology, it is all along committed to providing new methods, tools and materials in the realm of life and health.

1 Big Data and Machine Intelligence

Before the current buzz around big data, the volume of data continues increasing over time (e.g., 5000 years). According to the Oxford English Dictionary, the term “information explosion” was first used in 1941. In the following years, the volume of data experiences a more and more rapid rate to generate. Computers are used to process and store the data, which in turn makes data generate even faster than ever before. In 2008, the term “big data” was coined, indicating traditional computing systems failed to process the data generated by today. This difficulty comes by the four features of big data: (1) volume, (2) velocity, (3) value, and (4) variety. These features require innovations from the full stack of a computing system.

The full-stack research includes computer architecture, compilers, operating systems, a wide range of algorithms, and applications.

In architecture level, heterogeneous and intelligent processor architectures including CPUs, GPUs, and FPGAs, and their systems are needed to be explored. In the OS level, IACDE focuses on cloud operating systems.

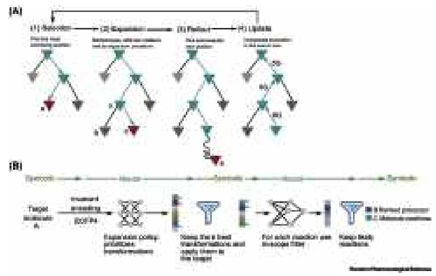
Institute of Advanced Computing and Digital Engineering(IACDE) focuses studying as well as developing new technologies in the digital computing area, primarily serving for the industry requirements of Shenzhen City, Guangdong province, and China southern area. IACDE has developed a software-defined cloud operating system named Chameleon which can be used in a wide range of different cases such as cloud and edge computing. In the algorithm level, IACDE focuses on deep learning and data mining algorithms. For example, IACDE has developed a number of efficient and powerful deep learning algorithms such as small samples learning. In addition, IACDE also developed many high performance data mining algorithms. In the application level, we are working in many interesting areas including city transportation, bio-information, geographic information, meteorology, and so on. The lower levels such as architecture can efficiently support the research of the upper levels while the upper level applications can reversely drive the innovation of the lower levels. Therefore, IACDE is a wonderful place for the research of digital techniques. We always solicit highly self-motivated researchers to join IACDE. Let’s cross fingers and work together to pursue as well as realize the Chinese dream.

Go! Drug Discovery with Artificial Intelligence 2

For a long time, GO had been regarded as the last board game in which computer cannot surmount human, because the territory controlled by each player during the game is highly abstract to evaluate. When AlphaGO overwhelmingly defeated the topmost human player Sedol Lee from Korea in 2016, its underlying principle “artificial intelligence” (AI) was immediately in the spotlight of public attention. It is interesting to note that, in the live commentary, the professional GO players were often caught out by the moves from AlphaGO and not able to explain its ‘intention’. It seems now human needs the inspiration from a computer to play better GO!

One may ask, “Can AI show the same game-changing power in science, say drug discovery?” First, one needs to understand how the AI “magic” works. AI comprises various algorithms that process a huge amount of data, identify the relevant features and transform them mathematically, in order to relate the initial features to certain outcomes. After this step, an AI model is “trained” for making predictions. For example, AlphaGO has played numerous games with itself during the “training”, from which it finds the move that would increase the chance of winning in each scenario. Later, when played against a new player, AlphaGO effectively predicts the best move in each turn, based on its past “knowledge” of GO. Nowadays, scientists benefit largely from the improved computational capacity, and manage to implement the AI concept in many different research areas.

Drug discovery is a lengthy and costly process. Its complexity is no simpler than playing a GO game. A traditional workflow includes the following stages: 1) identifying the malfunctioned protein or biochemical pathway, 2) selecting active compounds from huge databases for chemical modifications, 3) syntheses of these compounds for safety tests, and 4) clinical trials in human patients for efficacy. Regulatory bodies like FDA would review the validity of these data, before approving the commercialization of a drug. This whole pipeline is estimated to cost USD 2.6 billion on average and takes over 12 years to complete. Therefore, speeding up projects at reduced costs remains a key challenge for all pharmaceutical companies. AI-based methods are increasingly used in various stages of the process to improve time- and cost-efficiency.

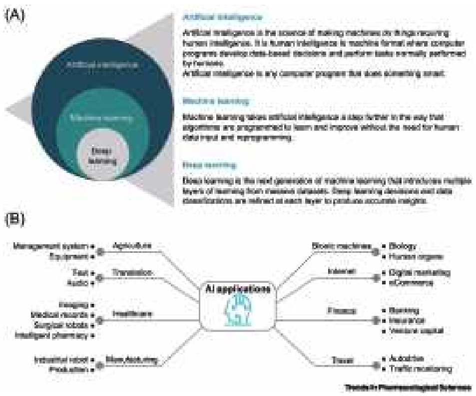


(A) The four iterative phases in planning retrosynthesis. (B) The implementation of "Expansion" phase, which converts the target molecule into fingerprint and obtains the probable reactants via a policy network. The possible reactions are predicted and filtered by the in-scope filter, based on predicted probability.

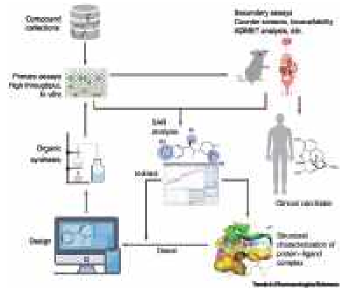
Various representations of a 3D protein structure predicted by AI method

Very often, scientists can easily acquire the 1D amino acid sequence of a disease–related protein, but not necessarily its 3D structure. However, the latter offers more important information on how a potential drug molecule can bind. Can scientists predict the unknown 3D protein structure from its amino acid sequence? The answer is yes! In a recent contest, an AI–based method AlphaFold made successful predictions in nearly 60% of the test cases. The next best method only had a hit rate of less than 10%. AI once again demonstrates its superiority over traditional methodologies.

When the 3D topology of a drug target can be predicted with fairly high confidence, scientists turn their attention to searching potentially bioactive molecules. This task is again not easy. Databases may contain millions molecular structures. Testing the bioactivities of all these molecules is practically impossible. One should not forget these molecules require further chemical modifications for better bioactivities. Thus, scientists have to shortlist the molecular candidates, based on their physical chemical properties and their interactions with the target protein. AI based methodologies link the chemical information of molecules (or alongside the 3D chemical environment of a protein) to the measured properties and bioactivities — or even to the predictions from quantum mechanical calculation, which undergoes a lengthy iterative process in solving a complicated equation. The advantage of the last model is that it can predict the properties of novel molecules at the accuracy of quantum mechanical calculation but at a significantly lower time cost.



(A) The relationship between artificial intelligence, machine learning, and deep learning. (B) Diverse applications of AI in different areas.



The workflow of drug discovery

After narrowing down the number of plausible molecules, scientists need to synthesize them for testing. However, planning a cost–effective and efficient synthetic pathway is another great hurdle. Technically, scientists need to think “backward” for the possible precursor molecules and reaction that would have led to the current molecule at hand. For larger molecules that require multiple reactions, the number of possible synthetic routes may increase exponentially! In this context, AI method can comprehensively compile published synthetic reactions, through which the algorithm fragments the target molecule into smaller and smaller precursor molecules in a stepwise manner. During the AI training step, scientists can bias the selections of reaction pathways, according to the reported yield, the cost of the reaction and the commercial availability of the precursor molecules. The powerful feature of this AI based model is the terrific speed in finding a sensible solution out of an astronomical number of possibilities. The traditional methods may not even reach a solution within the same calculation timeframe!

Having tried hard to synthesize a novel molecule, scientists are keen to know if it really possesses the desired bioactivity. A possible option is to examine its impact on cells. AI model can be trained with the images of cells that response to a test molecule and those that show no response. Scientists take advantage of the AI model for rapid identification of responded cells, and further develop an experimental platform that is able to sort mechanically the two cell types from a jet of flowing cells.

All and all, AI based methods have shown a strong potential in hastening drug discovery process in many aspects. Scientists in SIAT are dedicated to incorporate and renovate these technologies in the existing drug discovery pipeline. Yet, there are still untouched topics in this area. Can AI model predict the movement of a drug within our body? Can AI model relate drug efficacy to patients’ genomes? Or more outrageously, will AI one day replace scientists in designing new drugs? To the last question, we are confident that scientists need not worry still. Indeed, AI excels the ability to uncover hidden trends and patterns at a horrific speed. But the essence of science resides in our creativity and curiosity that cannot be replaced with machines.

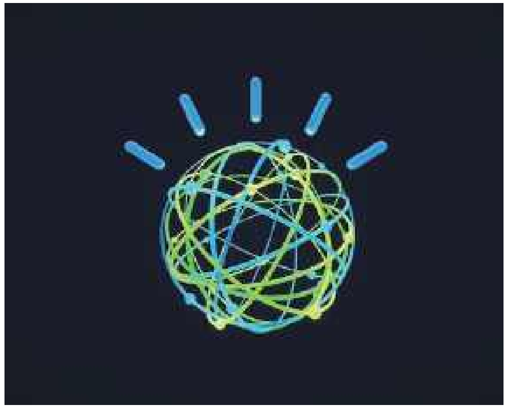
3 Health Informatics in the Artificial Intelligence Era

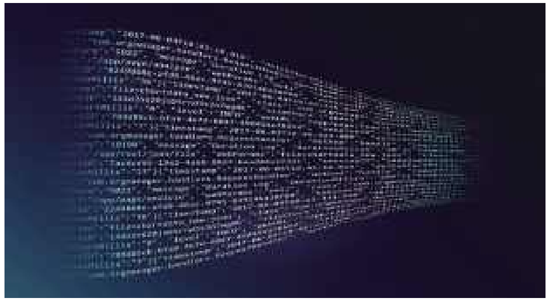

SCIENCE

Reasoning Foundations of Medical Diagnosis

Healthcare informatics was a natural ally to artificial intelligence over a long history. As early as in 1950's, soon after the dawn of the information age, biomedical researchers began to create computer-aided systems for medical diagnosis, which gradually led to the development of expert systems — a milestone in the artificial intelligence history. In early 1970's, MYCIN was release as one of the earliest expert systems, which diagnoses bacterial infection diseases and recommends antibiotics. MYCIN claimed to achieve competitive qualities with human experts (JAMA 1979). After that, health informatics continued to serve as a major incubator for new artificial intelligence technologies.

In 2013, IBM's Dr. Watson question-answering computer system began to provide decision support for lung cancer treatments, after winning the "Jeopardy!" TV competition over human players. Three years later, the success of Google Deep Mind's AlphaGo raised up a tide for adopting the new-generation artificial intelligent technologies, featured by deep learning, on an extensive range of real-world problems. Especially, lots of progresses have been made on the applications of machine learning technologies to biomedical fields, including automatic diagnosis from medical images, mining electronic health records, discovering of disease-related biomarkers and medicines, etc.





Despite the remarkable achievements, understanding healthcare problems still poses a major challenge for artificial intelligence techniques. Unlike board games, for most healthcare tasks there are no explicit mathematical expression of the problems, the state space, or the complete list of controllable variables. In many cases, there are even no "golden-standard" answers or reliably labelled data. Hence, accurate formulation of the problems, curation and extraction of reliable sample information play the same important role as problem solving. Moreover, healthcare problems require interactions between human doctors and AI programs. In addition to making wise decisions or predictions, an explainable presentation of the AI model would be also critical for efficient delivery of the solution.

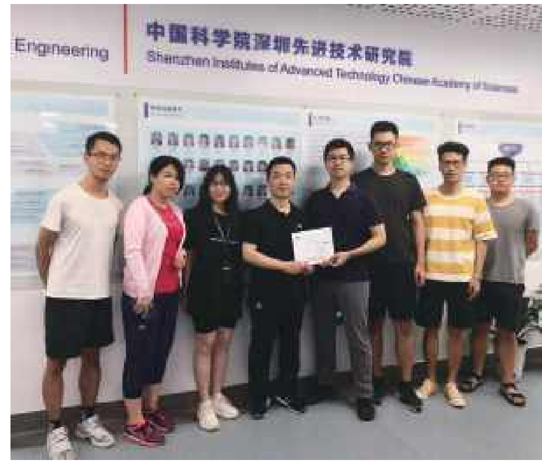
In SIAT, we aim at developing computational technologies that help with extending the power of artificial intelligence to medical fields with the aid of big data and biomedical informatics. High-quality preprocessing, accurate pattern recognition, efficient feature extraction and representation learning are the essential issues for improving the performance of the final models, which in-turn demanded advanced machine learning methods that are tailored for diversified medical data. With the combination nature language processing (NLP) and knowledge engineering, we converted unstructured electronic health record data into machine-readable knowledges, which helped with building accurate prediction models for understanding future trends of diseases. With new bioinformatic algorithms, we transformed DNA sequencing data into gene biomarkers that efficiently explains the molecular mechanism of diseases. Recognition of abnormal patterns from wearable ECG signals, medical images and gait test provided very useful signs for real-time and long-term disease risk alarms. We have delivered our computational solutions together with our wearable medical devices and healthcare APPs to serve a wide range of citizens in Shenzhen and all over the country, which formed a prototype of precision health that would benefit everybody with affordable cost in the future.

To understand where artificial intelligence is heading, we must first know where artificial intelligence is coming from. In the summer of 1956, scientists such as McCarthy and Minsky met at Dartmouth College in the United States to discuss "how to use machines to simulate human intelligence." The concept of "Artificial Intelligence (AI)" was first proposed, which marked artificial The birth of intelligent science.

Artificial intelligence is a branch of computer science that attempts to understand the essence of intelligence and create a type of intelligent machine that can respond in a similar way as human intelligence. In general, a major goal of artificial intelligence research is to enable machines to perform tasks that normally require human intelligence Complex work. Researches in this area include robotics, language recognition, image recognition, Natural language processing, expert systems etc. Since the birth of artificial intelligence, the theory and technology have become more and more mature, and the application field has also expanded. It can be imagined that artificial intelligence technologies will revolutionize our society and industry. Artificial intelligence studies can also help to understand the information process of human consciousness and thinking. Artificial intelligence is not just human intelligence, but humans and may exceed human intelligence in certain aspect.

Like steam engines in the steam age, generators in the electrical age, computers and the Internet in the information age, artificial intelligence is becoming a decisive force in pushing humans into the intelligent age. The global industry fully recognizes the significance of artificial intelligence technology to lead a new round of industrial transformation, and has transformed and developed one after another to lay out the artificial intelligence innovation ecology. The major developed countries in the world regard the development of artificial intelligence as a major strategy to enhance national competitiveness and maintain national security, and strive to take the lead in international competition in science and technology.

4 Multimedia Integrated Technologies



After more than 60 years of development, artificial intelligence has made important breakthroughs in "three calculations" such as algorithms, computing power (computing power), and data (data). But there are still many bottlenecks to being "easy to use".

Center for multimedia integrated technologies (CMIT) in SIAT mainly focuses on the research and development in the areas of computer vision, deep learning, multimedia, and intelligent robots. The team published over 200 papers in international journals and conferences such as PAMI, TIP, IJCV, CVPR, ICCV, ECCV, AAAI etc, and won the first prize multiple times in international challenges such as ChaLearn, LSun, ActivityNet and EmotionW 2017. In addition, CMIT won the first and second place in two sub-challenges in EmotiW2018. The published papers have been cited more than 20,000 times (Google Scholar).

CMIT has develop a series novel methods to promot the technologies of video processing and understanding, such as multi-category video behavior classification, ultra-large-scale portrait recognition, and complex scene classification, greatly improving the recognition accuracy on these tasks, and forming large-scale industrial applications. The technologies developed by the team have been successfully transferred to industry leaders like Huawei, ZTE, Tencent, SenseTime, etc.

1 Materiobiology in Tissue Regeneration

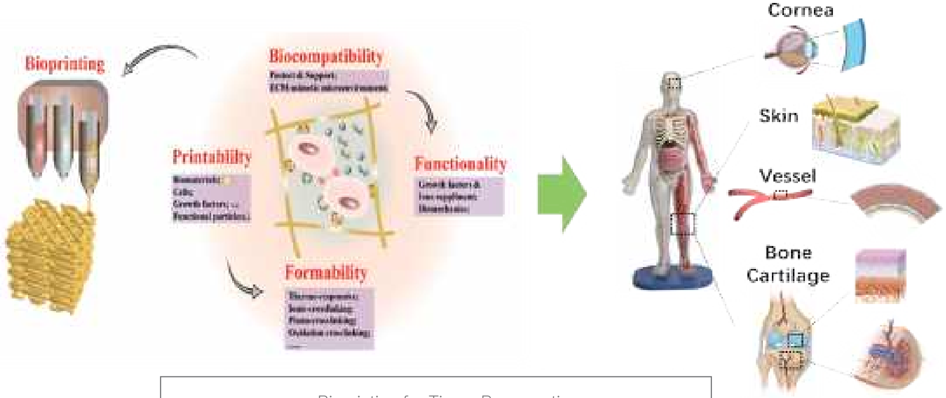
Tissue engineering (TE) is poised to revolutionize health care by replacing or restoring the function of damaged organs. Organ shortage continues to be one of the significant problems in global healthcare. The emerging technique of bio-printing allows for the precise tailoring of cell-laden constructs to simulate real human tissues, which shows great potential for the individual-ized therapy of organ defects and drug screening.

Researches for tissue regeneration in the Research Center for Human Tissue and Organs Degeneration (HTOD) at SIAT focus on fabricating new materi-als, cell-laden constructs, organoids, and even living tissues. 3D bioprinting, for example, has the potential to fabricate complex, sophisticated, and biomimetic tissue constructs. The advantages of 3D bioprinting are high precision, geometrical freedom, customizability, reproducibility, and repeat-ability.

Supported by the National Key R&D Program of China, the key laboratory of Guangdong, and the key laboratory of Shenzhen, Prof. Haobo Pan, and HTOD PIs lead a team over 100 people, including postdocs, RAs, and students. With the background of TE, biomaterials, molecular biology, stem cell bioengineering, and biomechanics, we can develop a series of bio-inks for 3D bioprinting, explore the biological questions, and even generate living tissues such as bone, cartilage, blood vessel, nerve, cornea and so on.

HTOD focus on, but not limited, the following goals:

- Stem cell differentiation and regulation
- Novel biodegradable materials
- Multifunctional bio-inks for bioprinting and tissue generation
- Surface modification of biomedical devices
- Clinical translation of biomedical technique and products



Bioprinting for Tissue Regeneration

Group photo of Principal Investigators in HTOD

2 Biomaterials Research in Translational Medicine Research and Development

Biomaterials research in the center for translational medicine research & development (TMC) at SIAT targets major orthopaedic problems with huge global socioeconomic and healthcare burdens, such as osteoporosis and bone defects. With the rapid development and acceleration of aging process in human society, more and more people are suffering from musculoskeletal disorders, which are the most common causes of severe long term pain and physical disability, affecting hundreds of millions of people around the world. It was agreed that there was an urgent need for positive action. In order to improve the health related quality of life for people with musculoskeletal disorders throughout the world, the World Health Organization (WHO) designated the first decade of the new millennium 2000-2010 as the Decade of the Bone and Joint.

The mission of TMC is to build up a bridge between fundamental research and clinical applications. Based on skeletal physiology and pathophysiology, TMC research team focused on seeking of osteogenic bioactive materials and found that magnesium, an essential mineral element of our bone matrix, is an ideal candidate for bone fracture fixation and regeneration. Mg is a kind of biodegradable material, which doesn't require removal as conventional rigid metal orthopaedic implants do. Moreover, Mg exhibits very prominent bioactivity for promoting bone regeneration. Collaborating with local and international colleagues, TMC researchers have developed pure magnesium implants, as well as alloys and hybrid systems for safe application in bone fracture fixation and bone defect repair enhancement.

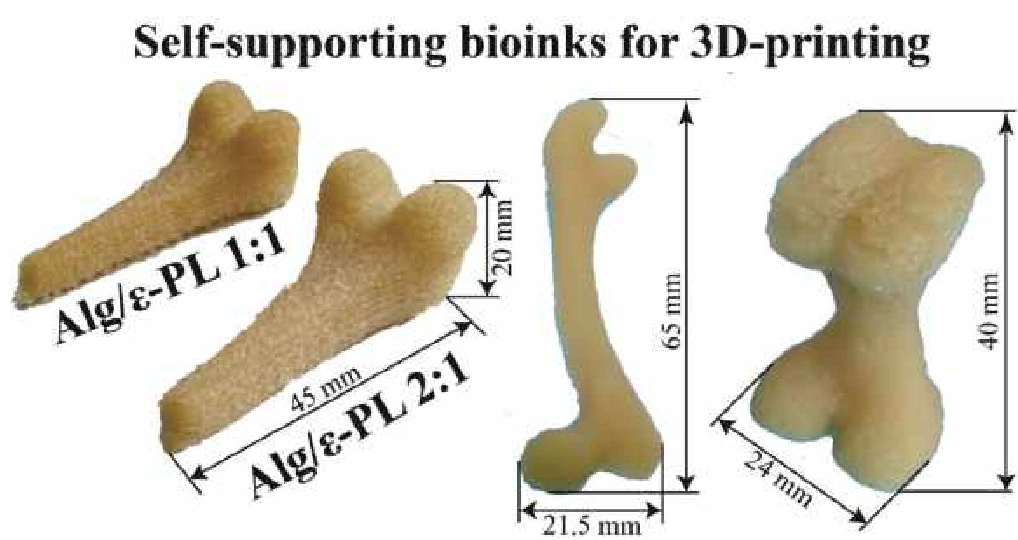
The multidisciplinary team also looks at the potential healing mechanisms of magnesium ions after implant degradation. In 2016, based on animal model studies, they showed, for the first time, that magnesium-induced osteogenesis or bone formation is mediated by local neuronal production of calcitonin gene-related peptide 1 (CGRP1), a calcium-lowering peptide. Joint research with orthopaedic surgeons has led to the very first clinical trial to use magnesium screws for fixation in reconstructive hip surgeries. These findings have been published in Nature Medicine, Biomaterials and other leading journals, and have led to numerous patents and awards.

Personalized medicine emerges as an innovative and promising trend for future health-care, featuring as the tailoring of medical treatment to the individual characteristics of each patient. There are special needs for personalized therapy in the field of orthopae-dic treatments, because the bone defects of patients vary from case to case in many aspects, such as the geometries and mechanistic properties. The advent of additive manufacturing technologies (also known ad 3D printing) provides great opportunities for personalized bone tissue engineering. 3D printing was developed in the mid-1980s, providing the required ability to deliver a high level of control over the architecture of the construct and the flexibility to scale-up fabrication, whilst guaranteeing the standardization and reproducibility of the manufacturing process. This technology possesses huge advantages to provide customized scaffolds with precise geometries, components and porosity for use in replacing damaged or diseased tissues.

The TMC researchers pioneered in using 3D printing technology for fabrication of biodegradable bone scaffolds. From 2007, the team developed an innovative low-temperature rapid prototyping (LT-RP) technology to fabricate customized bone scaffolds with precise control of the geometries, porosity and mechanistic properties. Complex structures can be created based on medical imaging and computer-aid design to perfectly match the bone defects. Biodegradable and biocompatible polymers serve as the matrix with incorporation of bioactive components to further achieve improved bone regeneration efficiency. Several kinds of composite scaffolds were fabricated by incorporating Mg powder or phytomolecules (such as icariin) as the bioactive ingredients. Previous mechanism studies by TMC team have comprehensively revealed the osteogenic activities of Mg and phytomolecules. By introducing the novel 3D printing technology, highly bioactive and biodegradable bone scaffolds were created and patented. These innovative products have drawn a lot of attentions and earned important awards in international invention shows, including gold medal of 2nd International Warsaw Invention Show (IWIS) and silver medal of 45th International Exhibition of Inventions of Geneva (IEIG).

To realize the final goal of clinical translation, in 2012, a spin–off company was founded based on these patents and technologies by corporations with medical devices industry. 3D printing scaffolds are produced strictly according to the good manufacturing practice (GMP) standards for comprehensive pre–clinical evaluations. In 2018, our product "Mg–containing bone repair scaffold" was listed in the special approval procedure for innovative medical devices by Chinese Food and Drug Administration (CFDA). This indicates that this product has entered the fast lane for clinical trial and final licensing procedure. Hopefully, we expect it to be approved by CFDA and applied to clinical use in the near future.

In 2013, Prof. Qin in TMC founded the Journal of Orthopaedic Translation (JOT) as an international platform for orthopaedic community to share innovations and advancement in both academic and industrial collaborations. JOT also provides support for clinical and translational researchers in data sharing, adoption of good laboratory and clinical practices, and effective use of informatics. JOT is the official peer–reviewed journal of the Chinese Speaking Orthopaedic Society (CSOS) and the International Chinese Muscu–loskeletal Research Society (ICMRS). After 6 years of successful development, JOT has been indexed in Science Citation Index and gained an impact factor of 3.06 in June 2019. JOT will continue its mission to be an international platform for accelerating innovations towards clinical applications and a healthy society.



3 Photonics and Energy Materials (PIE)

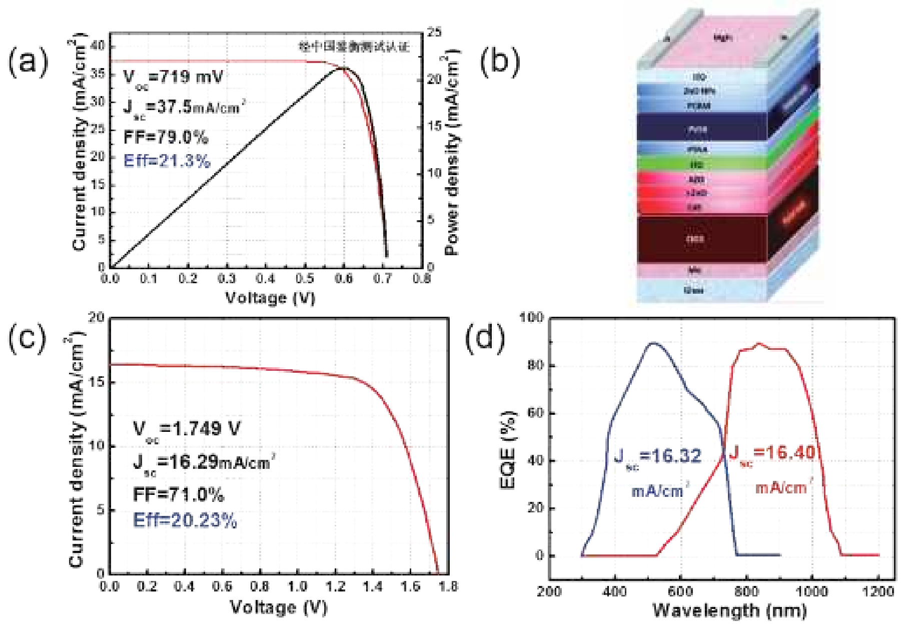


Figure 1: (a) J–V curve of a CIGS solar cell device with 21.3% efficiency, (b) Schematic of a tandem perovskite/CIGS combination, (c) J–V curve of a tandem perovskite/CIGS comobination, (d) EQE of a CIGS and perovskite solar cell.

(1) High efficiency CuIn1-xGaxSe2 (CIGS) thin film solar cells

With the rapid development of social economy, the demand for energy utilization continues to increase. The prominent energy shortage and environmental deterioration caused by the excessive use of traditional resources has become the main contradiction restricting the sustainable development of human society. It is urgent to seek and develop clean renewable energy resources. Solar energy has attracted worldwide attention for its advantages of clean, environmentally friendly and renewable. Among all kinds of solar cells, thin film solar cells have attracted much attention due to their advantages of low cost, large–scale production and fabrication of multi–junction series battery modules. And CuIn1–xGaxSe2 (CIGS) thin film solar cell has been recognized as the one of the most efficient and promising thin–film solar cells, which is fabricated on both rigid substrates such as glass and on flexible substrates such as polyimide (PI) and stainless steel. With these advantages such as low pollution, good weak light absorption, and strong radiation resistance, CIGS solar cells exhibits the extensive application prospects including military, civil, aerospace, BIPV.

In recent years, a large amount of progress has been achieved by PIE team. To be more specific, the center for Information Photonics and Energy Materials (PIE), founded in 2008, focuses on the growth of high performance optoelectronic thin film materials and the fabrication of photovoltaic energy conversion devices, energy storage devices, sensors and imaging device. Research topics of the group includes but not limited to: (1) CIGS, CZTS thin film photovoltaic devices; (2) visible and near infrared broad band photo–detector; (3) Scanning probe microscopic characterization; (4) lithium ion battery; (5) x ray flat panel detector. They completed the record conversion efficiency of CIGS thin film solar cell from 2012 to 2016 consecutively and fabricated the first CIGS solar cell with certified efficiency above 20% in our country. The highest efficiencies of CIGS solar cell and perovskite/CIGS tandem solar cells are 21.3% and 20.23%, respectively; Moreover, we have designed and constructed a CIGS pilot line with a production capacity of 2 MW/year (substrate size: 60 cm×40 cm). They have basically mastered the core equipment manufacturing capability, design, integration and operation capability for large–scale production line of CIGS.

(2) Novel semiconductor thin film for high performance photodetector towards CMOS compatible broadband imaging sensor

Photodetectors (PDs) convert light photons into current via photoelectric effect, and achieve continuous research interest and wide applications in the fields of biological imaging, communication, environmental monitoring spectroscopy, etc. Commercially available photodetectors are typically made from GaP, Silicon and InGaAs; based on their band gaps, the above materials sense the ultraviolet (UV), visible and NIR regimes, respectively. In the case of broadband wavelength detection beyond the individual detector' s detectable range, such as the modern multispectral detection and ultraviolet to near–infrared digital camera, multiple data measurement segments and data correction have to be performed during which measurement error and image distortion can happen. To address this, photodetectors with broadband spectral response and high detectivity at room temperature are urgently needed. Over the past few decades, dramatic advances in broadband photodetectors (PDs) technology have been achieved by the introduction of new materials such as PbS quantum–dots, organic semiconductors, two–dimensional layered materials, etc. Photoconductive PbS quantum dots detectors possess tunable band gap and achieved remarkable detection sensitivity of up to 1 × 1013 Jones in visible and IR range. Two–dimensional materials have presented excellent electronic and optoelectronic properties including ultrafast carrier dynamics, layer–dependent energy band–gap, tunable optical properties and high mobility. Until now, InGaAs detectors still serve as the only commercial IR detector, and new IR detection materials and devices are highly needed to address InGaAs's limiting characters of high manufacture cost, incompatible with Si substrate and narrow detection range.

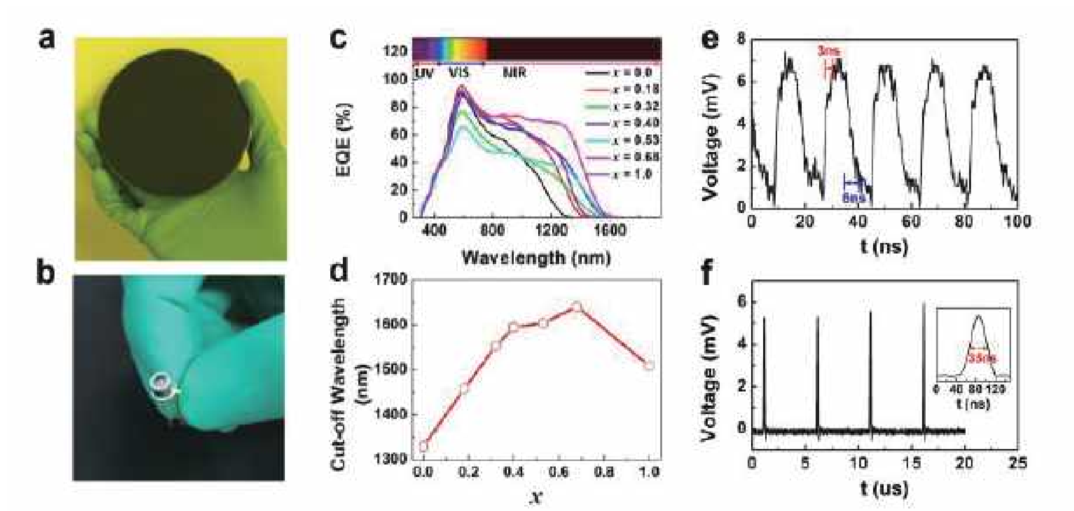


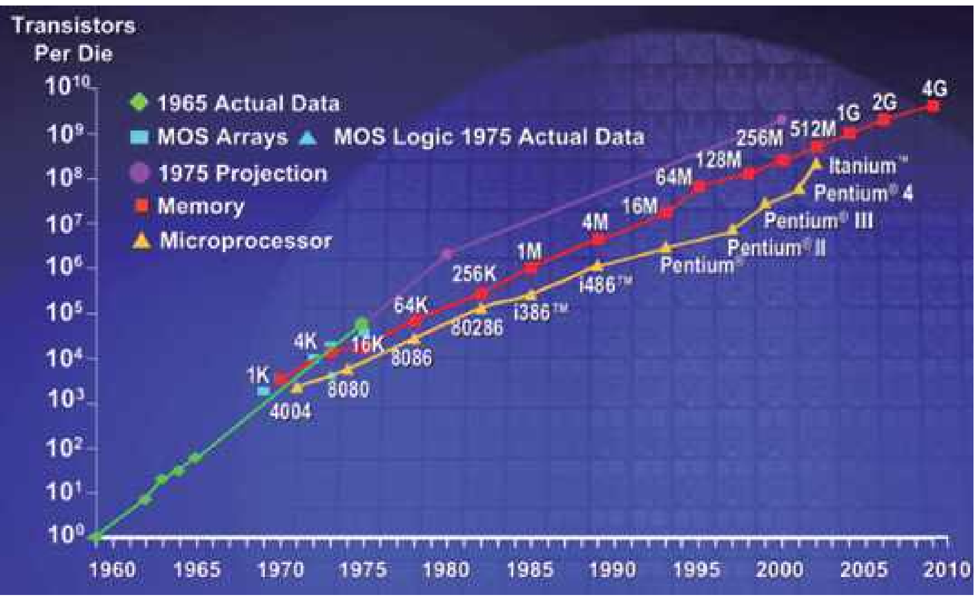
Figure 2: Photograph of a Cu2CdxZn1–xSnSe4–based photodetector and the corresponding performance

Researchers at the PIE designed a novel semiconductor film (Cu2CdxZn1–xSnSe4) for IR detection based on first principle calculations and fabricated the broadband photodetector of Cu2CdxZn1–xSnSe4 for the first time. The responsivity and detectivity of the presented photodetector are investigated in the range from 305 nm to 1640 nm and the maximum values of 0.849 W/A and 2.33 × 1012 Jones, respectively. Cu2CdxZn1–xSnSe4 has remarkable fast response of 3 ns which is beneficial for high–resolution devices. Our results show that the direct band gap of CCZTSe compounds can be effectively tuned through the Cd concentration and with optimized band gap this material can be used as new type ultra–fast response broadband IR detector.

4 Advanced electronic materials, from lab to industry

IC packaging revolution

The packaging form of integrated circuit (IC) changes from two-dimension to three-dimensional heterogeneous integration, and raises the challenges of high density, miniaturization, thinning, high performance, multifunction, high reliability, and low cost. With the failure of Moore's law, the advancement of Integrated Circuit highly depends on the innovation of electronic packaging technology, whereby advanced electronic packaging materials play an important role.

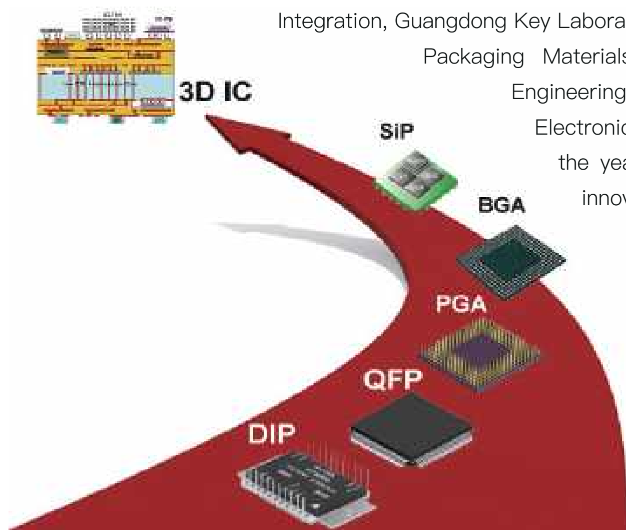


From CAMR to IAMSE

In 2006, a small group headed by Prof. Sun Rong founded the Center of Advanced Material Research (CAMR) at SIAT. The center dedicated to developing advanced electronic packaging materials including polymeric materials, electronic interconnection materials, interfacial adhesions, nano-functional material syntheses and characterizations, materials interface, information photonics and energy materials, both for fundamental researches and industrial applications. In 2012, CAMR organized the Advanced Electronic Packaging Materials Innovation Team of Guangdong Province. This team focuses on developing key materials for the IC high density 3D wafer level and system-in package technologies. After a decade of efforts, the group has grown up to 242 by the end of 2019, consisting of Academicians, Professors, Researchers, Engineers, PhD and Master students. The center has become Member of the "National Engineering Laboratory for Advanced Electronic Packaging Materials" and renamed as Institute of Advanced Materials Science and Engineering, SIAT (IAMSE).

Scientific and technology achievements

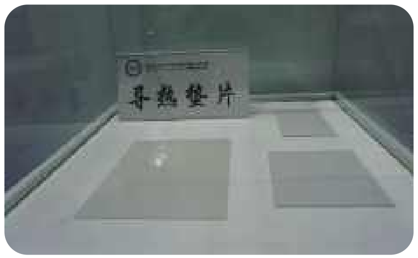
IAMSE has been actively participating in more than 100 national scientific and industrial programs, published 450 SCI journal papers and filed over 380 patents. Because of its outstanding researches, IAMSE has been authorized to be Shenzhen Key Laboratory of Key Technologies for High Density Electronic Packaging and Device Integration, Guangdong Key Laboratory of High Density Electronic Packaging Materials, and National Local Joint Engineering Laboratory of Advanced Electronic Packaging Materials. Over the years, IAMSE has spinned off 3 innovative material companies.



Industrial application development

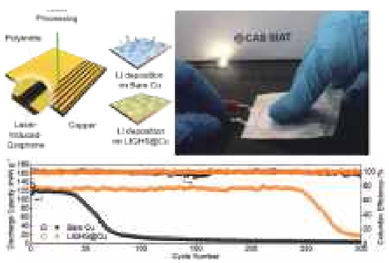
With advanced electronic packaging materials and complete process as the core, IAMSE focuses on industrial application key issues such as electrical, thermal and mechanical properties of electronic packaging materials, including key materials for high density flip chip, high performance thermal interface materials, wafer level packaging materials, key materials for 3D IC interconnection integration, embedded functional materials, high density high frequency substrate base materials. A couple of prototypes have been validated by industrial customers and some products already entered into market.

Temporary bonding materials with thermal sliding and UV laser debonding technique for ultrathin wafer processing.



Thermal slip debonding material

Microencapsulated Phase Change Material– no formaldehyde release, latent heat value >190J/g, from a few microns to dozens of microns in size, phase change temperature adjustable.



High Performance Quasi–Solid Lithium–Metal Batteries, a novel method to tune the deposition kinetics of lithium metal using laser–induced–graphene so as to control lithium electrodeposition

Spinoffs

Case– Samcien Semiconductor Materials

Samcien is the first spinoff of IAMSE, setted up in 2016. The company focuses on wafer level advanced packaging materials and systematic solutions. For example, the product of UV laser debonding material is developed to meet the ultrahin wafer separation requirement at room temperature without stress. The bonding pair with UV release layer can go through a serial backside processes, such as thinning, lithog–raphy, etching, passivation, electroplating and then be radiated by UV laser, which induced photochemical reaction and breakdown the release layer to decrease the adhesion strength and realize the high efficiency, stress free separation, and the use of auxiliary cleaning agent to remove organic matter residue on the wafer.

FEATURES

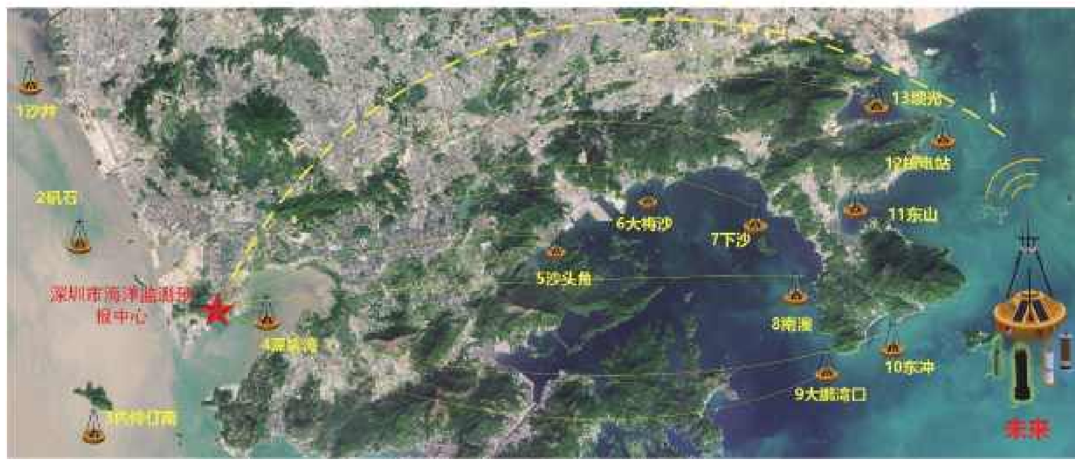
- Spin Coating or Spray Coating
- Strong Absorption at 308 or 355nm–UV
- Transparent Glass for Support Carrier
- Separated at Room Tempera–ture without Stress
- Unit Per Hour (UPH) > 60 for Laser De–bonding
- Good Corrosion Resistance of Acid, Alkali and Polarity Organic Solvent
- Separated after High Temperature Process
- Low Temperature Storage > 6 months.

1 Photonics and Energy Materials (PIE)

Sensing open and coastal oceans, including the littoral zone, is the key foundation for comprehensive understanding and prediction of long– and short–term climates, assessment of resources and environments, as well as applications for defense and security. With the development in advanced technology, more and more traditional ocean research techniques are widely augmented today with advanced in situ sensor technologies deployed in various ocean observation platforms.

Scientists and engineers at SIAT are actively working on developing new sensors and instruments for in situ ocean sensing. Supported by the National Key R&D Program of China, Dr. Jianping Li and his team from the center for optoelectronic engineering and technology are developing a series of optical sensors that can work underwater for ocean observation, including underwater fluorimeters for chlorophyll a (Chl a) concentration and BOD (biochemical oxygen demand) measurement, underwater spectrophotometers for COD (chemical oxygen demand) measurement, and underwater imaging system for plankton monitoring, respec–tively. “Chl a, BOD, COD and plankton are essential and routine variables for moni–toring seawater pollutants. Traditionally, their measurement is dependent on seawater collection and manual analysis following certain protocols. This is very labor–intensive and time–consuming. In comparison, the sensors we are developing will measure these variables directly in seawater under a buoy in real time. This would not only reduce sampling and analysis cost, but would also increase the observation frequency to reflect the seawater situation in a timely manner.” Dr. Li introduced.

Once the technology proved feasible, the idea can be extended to integrate more sensors under more buoys setting up networks covering larger and denser area for seawater monitoring. “The Shenzhen Ocean Monitoring and Forecasting Center has already deployed 13 buoys along the city’s coast, but neither the number nor the type of sensors were enough. We will help them to gradually improve the network, as ocean sensing must provide not only timely and accurate data, but also offer insights forecasting future environmental condi–tions. This is not only for the satisfaction of scientific curiosity, but also for the benefit and well–being of the people!” emphasized Dr. Li.



Dr. Li and his team firmly believe that cutting-edge technologies from multiple disciplines will strengthen the capabilities of next-generation ocean sensors. These include robotics, artificial intelligence, heterogeneous computing, IoTs and more, which are also focused areas that SIAT is strong and targets. “Thanks to SIAT’s diverse and multidisciplinary research atmosphere, we can easily collaborate with colleagues with various expertise internally to nurture future ocean sensing technologies. These vibrant research and development areas can be complementary to generate many brilliant ideas to promote ocean sensor technology towards ever smarter technology, and deeper the ocean!” predicted Dr. Li.

Just as the ocean connects all the continents and bring the world people together, SIATers are also clearly aware that the R&D of marine high-tech requires an open environment and spirit. Hence, it becomes necessary to collaborate nationally and internationally. We aim to bring together research and technical personnel, as well as managers from industry, governments, and academia, to foster cooperation and to reduce the gap between legacy ocean sensing techniques and breakthroughs in other disciplines. Now SIAT teams start to establish more and more collaborations with top universities, research institutes, industry partners and government departments in ocean management in China as well as worldwide.

Exploring the ocean and utilizing its resources need more new and advanced technologies in sensors, robotics, AI, and etc. SIAT will continue taking good usage of her strengths in IT and BT to nurture and develop future smart equipment on this endeavor.

2 Applications of Robotics

Industrial application development

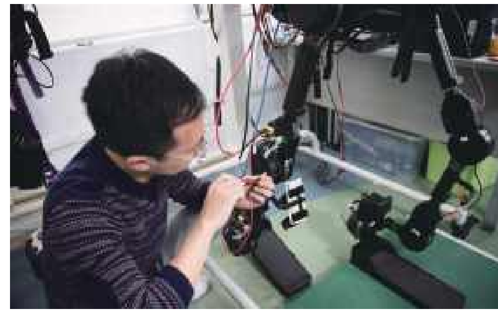
The Neural Engineering Laboratory takes a multidisciplinary approach to medical research, incorporating medical and surgical knowledge and engineering capability to develop techniques and advanced medical devices for neuromodulation. Recently, the neural controlled exoskeleton investigated from the Neural Engineering Lab received the 1st Prize in Human–machine Synergy in Super Heroes Competition organized by PLA armaments in 2019.

The mission of the Neural Engineering Laboratory is to relieve human suffering by developing the knowledge and technology needed to effectively modulate central nervous system function.

Many people don't have time for sports. But we think it's good to do exercise especially for people who sit in the office all day. If we have no time to go outside, we can use i–dong in home. We have designed this equipment, i–dong, cooperated with Shenzhen Taihan Technology Corporation.

The Neural Engineering Laboratory works toward the following goals:

- Understand the biological mechanisms of action for neuromodulation
- Invent lasting bioelectrical technologies and create devices and procedures for neuromodulation in human patients
- Pioneer less invasive neurosurgical techniques
- Translate gained knowledge into medical practice



3 Applications of Robotics


The real microscopic cataract surgery environment.

Cataract surgery simulator needs to simulate the interaction between various surgical instruments and eye anatomical structures in the main procedures, such as corneal incision, capsulorhexis, nucleus delivery and paracentesis port suturing. It's a challenging task to robustly and efficiently simulate all these procedures on high accurate eye anatomical models. Moreover, existing simulator mainly focus on the training of intracapsular operation due to limitation of human–computer interface.

Hardware Interface

We presents a virtual cataract surgery simulator with high fidelity human–computer interface and deeply immersive virtual environment. In the system, HTC Vive is employed to simulate the microscopic view during real surgery, and Geomagic Touch X connected to the forceps is used to track the position of surgical instruments in the virtual scene, thus constructing an immersive micro–surgical environment. With our training platform, surgical apprentices can be observed the simulated surgical scene through HTC Vive helmet, while adjusting the virtual microscopy with HTC Vive handle.

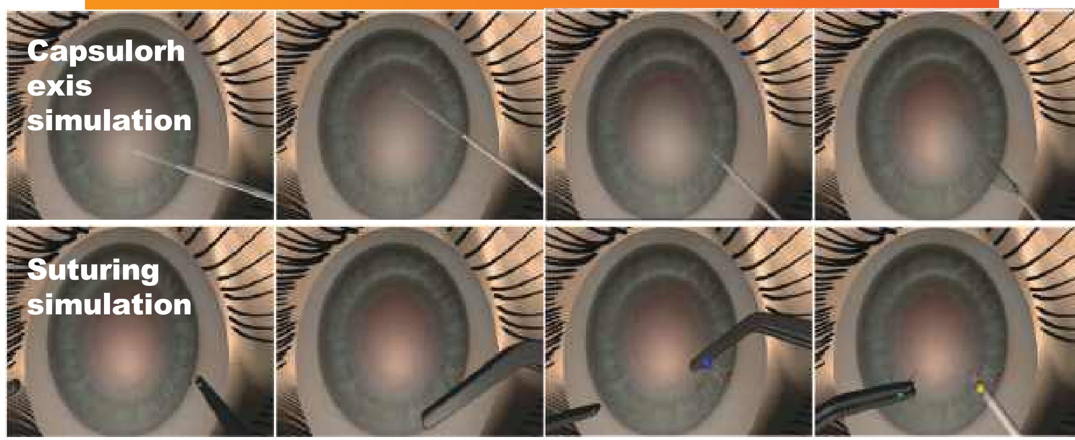

The hardware interface for virtual cataract surgery training.

and practicing their skills with real forceps connected to Geomagic Touch X. Our system can be divided into the following three parts: microscopic display, microscopic adjustment and surgical interface.

Interactive Surgery Simulation

To achieve efficient and unconditionally stable capsulorhexis simulation, the system simulates tearing of lens capsule with PBD on a triangle mesh and constraint the fracture path on existing triangle edges.

During the suturing procedure, the suture will affect the position of the corneal PBD particles around the perforation, resulting in deformation of the cornea. Besides, at the end of the suture, the tightening of the suture causes the incisions to approach each other. To handle this issue, we first detect whether the forceps is gripping the suture needle. Then, suture needle is modelled as a rigid body connected end to end. When the suture needle starts to move to the soft body for suturing, the collision detection will be performed between the needle and the surface of the soft body.



4 Robotic-implementation

Under the new wave of global technological revolution and industrial transformation, the economy of China has been accelerated greatly and the traditional industries have been extensively updated, especially with the breakthrough and penetration of "artificial intelligence" technology. From 2018 to 2020, the average annual sales growth of industrial robots remains between 15% and 20%. It is expected that in the next few years, the robot industry will maintain a rapid growth in the Chinese market.

Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (SIAT–CAS) has focused on the robotic fields, taking great effort in all kinds of the robots, which are summarized as follows.

Service robot

Service robots can be widely used in the public service industry, retail industry and financial industry, which is the most potential development direction of the industry.

Service robots have achieved small–scale production and application in the fields of pension service, rehabilitation, social services and disaster relief, etc. The core technology of the new generation of robots has made a breakthrough; some products have been exported; the new generation of robot prototype has been successfully developed. In 2025, service robots will have achieved large–scale production, began to be widely used in people's life, social services and national defense construction.

Medical robots

Medical robots form a variety of series products such as nursing robots, rehabilitation robots, medical distribution robots, medical auxiliary robots, etc., and are involved in the fields of medical rehabilitation, surgical assistance, hospital logistics, intelligent pension, and intelligent disability assistance.

At present, the SIAT–CAS has its own developed medical robot and intelligent robot, especially in the research of minimally invasive surgery robot for spine, which is in the leading position in China. The research in medical robot and automation is gradually going to clinical, and undertakes many major scientific research projects related to National Fund of China, Chinese Academy of Sciences, Guangdong Province and Shenzhen, and with a number of hospitals and enterprises to achieve strategic collaboration.

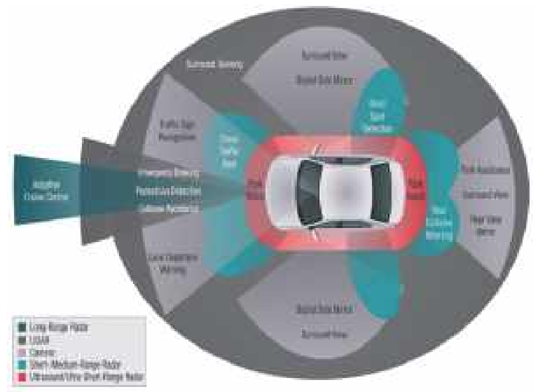
Exoskeleton robot can significantly improve the user's physical capability. In the medical field, exoskeleton robot is mainly used in paraplegia patients, stroke, spinal cord injury and cerebral palsy patients. The application of exoskeleton will completely change the rehabilitation treatment and daily life of patients with lower extremity paralysis.

Spinal surgery guiding system

Robotic Spinal Surgery System

5 Robotic-implementation

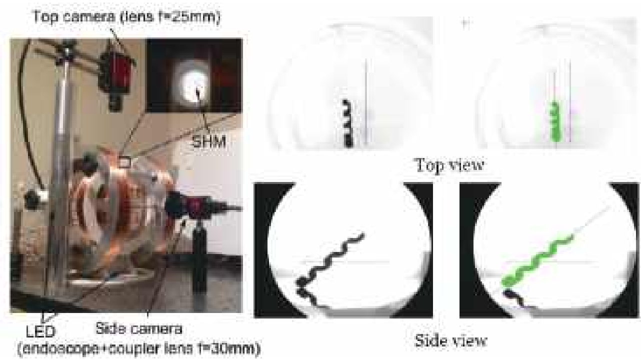
Multi–functional artificial limb neural control and human–computer interaction technology can achieve flexible and natural artificial limb control, and provide effective help for amputees to restore limb function. The team in SIAT–CAS has made a series of progress in neural control multi–functional prosthetic system relying on the Key Laboratory of human–machine intelligent cooperative system, Chinese Academy of Sciences. The advanced prosthesis and prosthesis control system can improve the control performance of prosthesis, and provide many amputees with high–performance, intelligent and multi–functional prosthesis.



Autonomous driving

There is huge potential growth in autonomous driving, while the environmental perception is the core technology to achieve the function. It mainly involves precise detection and recognition of road surface, static objects and dynamic objects. This research focuses on the information fusion technology of vehicle radar and machine vision, as well as the three–dimensional information construction technology in vision detection and measurement technology.

Micro-robots



Because of their small scale, micro robots can work in complex and narrow space, so they have great application potential in clinical medicine, bioengineering, environmental governance and so on. The bionic micro robot can be made by imitating the non–reciprocating reversible motion of microorganism in nature. A magnetic micro robot with a rigid spiral tail is driven by a rotating magnetic field, which can be controlled in the liquid.

Biotechnology

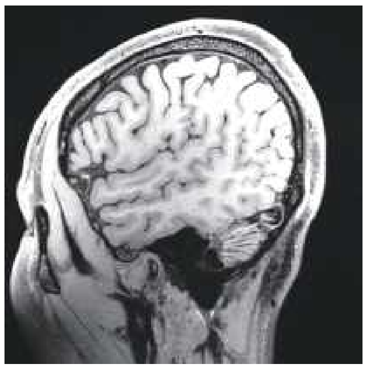
Focusing on the integration of intelligence and biotechnology, it is all along committed to providing new methods, tools and materials in the realm of life and health.

1 MRI (Magnetic Resonance Imaging)

Paul C. Lauterber (1929–2007) was an American chemist, known as "the father of magnetic resonance imaging". He was born in Ohio and received his bachelor's degree from Case Western Reserve University. His doctorate degree was from the University of Pittsburgh in 1962. Lauterber first proposed to use heterogeneous magnetic fields to mark the spatial coordinates of magnetic resonance signals for imaging in 1971 and obtained the first results of magnetic resonance imaging experiments in 1973, which was known as magnetic resonance imaging. Because of that, he was awarded the 2003 Nobel Prize in physiology or medicine. To encourage China to develop medical imaging technology, Prof. Lauterber donated his Nobel MEDALS to Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences. In the same year, the Paul C. Lauterbur Research Center for Biomedical Imaging was established by Prof. Zhi–Pei Liang from the University of Illinois at Urbana–Champaign as a founder.

Lauterbur Center is committed to build an international top–level research center, shouldering the mission and adhering to the spirit of "academic guidance, industry driven". By pooling senior talents, promoting the development of medical imaging and biomedical engineering, and breaking through new methods, technologies, components and system equipment of MR medical devices, we are combining various imaging experts with their backgrounds and expertise, developing and applying imaging technology to solve the problems in the field of health care, and promoting our understanding of life science. In the next five years, the key goal of high–end medical imaging device of magnetic resonance imaging is to develop a human body 7T magnetic resonance imaging system, focus on building an internationally advanced medical magnetic resonance innovation platform, serving the development of medical device industry and satisfying the healthcare needs of all people. Lauterbur Center devotes to promote innovation of biomedical imaging technology, research and development systems and equipment of biomedical applications.

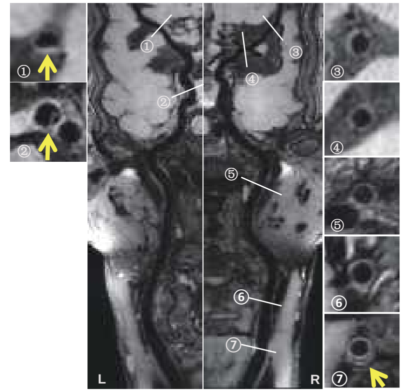
Magnetic resonance is a physical process in which the magnetic moment of the nucleus is not zero, the spin energy level is split under the action of the external magnetic field, and the energy level transition is generated by absorbing the radio frequency (RF) electromagnetic wave of a specific frequency. When revoking the specific frequency RF electromagnetic wave, the nucleus releases the same frequency electromagnetic wave due to the unstable energy level. The electro–magnetic wave can be received for imaging through signal processing.



Magnetic resonance imaging (MRI) is the most rapidly developed advanced medical imaging technol–ogy in the past 30 years. It has considerable advantages in many aspects, such as no trauma, no radiation, multi–parameter, high resolution, high contrast and arbitrary azimuth cross section imaging. The reason for the rapid development is not only the principle of magnetic resonance itself, but also the advances in low–tempera–ture superconductivity technology, electronics, data acquisition, signal processing and image reconstruc–tion. At present, the main research direction of magnetic resonance imaging is fast imaging and high signal–to–noise ratio image, which requires not only hardware support but also research on imaging meth–ods.

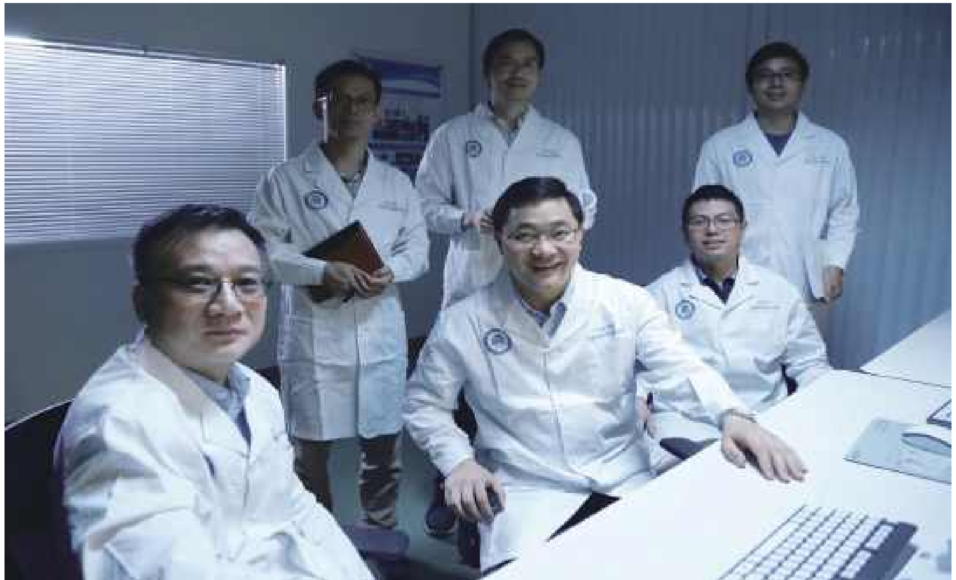
The MRI image of the human brain in the sagittal plane with compressed sensing fast imaging algorithm. Acceleration factor = 5, scan time = 5 mins.

The development of magnetic resonance needs to be guided by clinical needs, closely related to the development direction of the world's hot–spot disease diagnosis, and constantly achieve breakthroughs in technology and application. In the Lauterbur Center, doctors and scholars with many years of medical experience have made the research closer to the clinical requirements of the Center team, we have carried out a series of academic studies, such as vascular plaque imaging, brain functional imaging, heart imaging, fetal imaging, artificial intelligence imaging, PET–MRI imaging, and compressed sensing reconstruction algorithm. And with the unremitting efforts of our research team, we have overcome a number of problems in the fields of brain functional imaging,



The MRI image acquired by head and neck combination coil, the blood vessel wall from the common carotid artery to the middle cerebral artery can be fully and clearly displayed

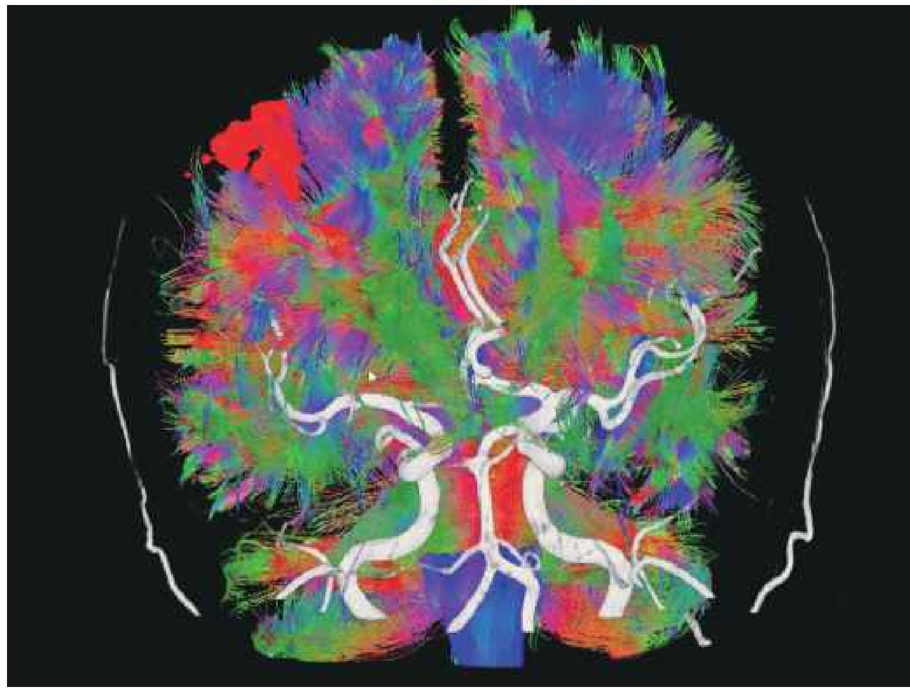
real–time cardiac imaging, cerebrovas–cular imaging, carotid plaque imaging and other high–end imaging. Our team has developed the international advanced commercial 3.0T human MRI scanner products.



In recent years, the incidence of ischemic stroke (cerebral infarction) increased significantly, stroke related to vascular bed atherosclerotic plaques of fast magnetic resonance imaging and intelligent diagnosis research is important for early prevention and the cause for cerebral apoplexy. Hence, we have studied a new method of rapid magnetic resonance imaging and intelligent diagnosis of vascular plaques in ischemic stroke. In order to solve the problem of unstable image quality and long acquisition time, a novel 3D vascular wall imaging sequence and a fast reconstruction algorithm based on the compressed sensing framework were studied and developed. In view of the difficulty in reading and quantification of plaque images, a new technology of rapid and accurate quantitative intelligent diagnosis of plaque vulnerability based on deep learning was also researched and developed. These works provide new tools for stroke risk assessment and prediction.

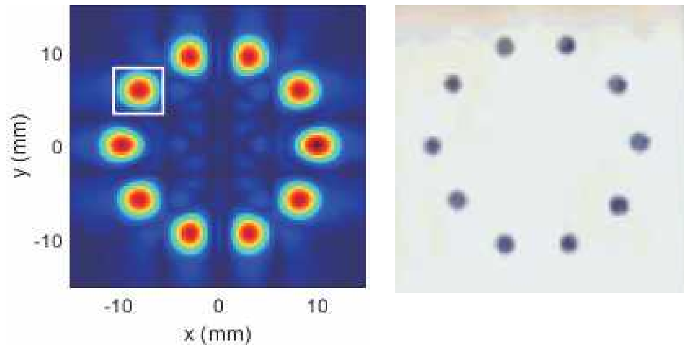
These achievements have also translated into industry and reflected in the social and economic benefits. Such as, we participated in the incubation of Shanghai United–Imaging medical technology co., LTD., and jointly developed the first commercial 3.0T human MRI scanner system with independent intellectual property rights in mainland China, which has been installed in hundreds of hospitals and greatly reduced the social healthcare cost. Since now, its MRI scanner sales have exceeded 3 billion RMB.

In addition, the MRI research achievements have been continuously industrialized through the Shanghai United–Imaging, and more and more scientific research achievements have been applied in the medical disease diagnosis of the people.

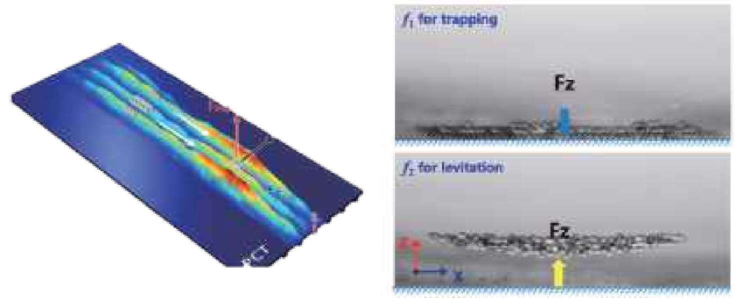


2 Ultrasound

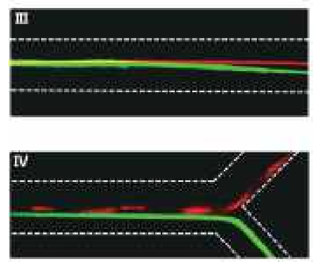
Ultrasound is sound waves with frequencies higher than 20 kHz and B–mode, Doppler color ultrasound imaging has been widely used in disease diagnosis due to the scattering effects. Simultaneously, ultrasound as a mechanical wave also has the mechanical effects. Owing to objects in the acoustic filed absorbing, scattering, and reflecting an acoustic wave, an exchange of momentum and energy between the particles and the acoustic wave will occur, resulting in the generation of an acoustic radiation force (ARF) on the objects. Our lab focus on ARF, develop ARF–based ultrasound imaging and neuromodulation equipment and carry out a series of academic research on acoustic tweezers, ultrasound neuromodulation, ultrasound elastography and ultrasound drug delivery.



(a) Complexandtunableacoustic fieldsynthesisusinganareaarrayand3Ddynamical manipulationofparticles.

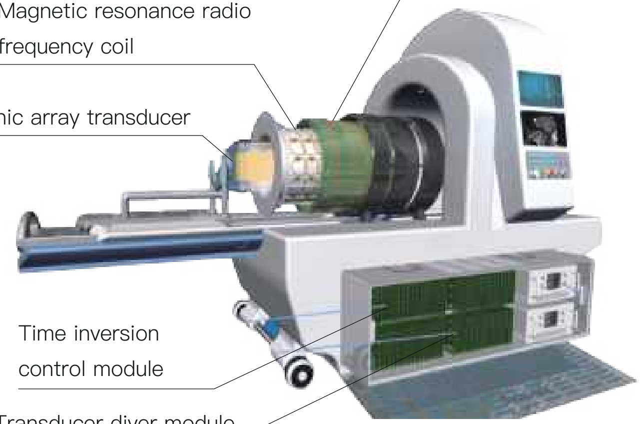


(b) Phononiccrystalmodulated acousticfieldandtrappingandlevitatingparticlesby switchingthedrivingfrequency



(c) Acousticsoringofcirculating tumorcells(green)fromredblood–cells(red)based ontheacousticsurfacewave.

Drawing on the concept and methodology of optical tweezers, objects in a strong-gradient acoustic field could be effectively manipulated by the ARF, and the technique is termed acoustic tweezers. Acoustic tweezers have the advantages of high throughput, label-free operation, noninvasiveness, and biocompatibility, and thus it is anticipated that acoustic tweezers may serve as a powerful tool for a wide range of applications. We developed various phononic-crystal-based acoustic devices, acquiring highly localized acoustic radiation force induced by the resonance transmission of an acoustic wave. The particles can be aligned, trapped and transferred according to their size or mass density, all in a tunable manner. Surface acoustic wave (SAWs), on the other hand, propagates along the surface of the piezoelectric substrate and its energy is strongly confined to the surface of the substrate. We also fabricated interdigital transducers (IDTs) to manipulate the single cells. By modulating the relative phase between two IDTs, the positions of pressure nodes of the standing wave in the microchannel change linearly resulting in the transportation of a single cell. The resolution of the transportation is approximately 2.2 μm. This device can be used for manipulation of bioparticles, cell sorting, tissue engineering, and other biomedical applications.



Animal Experiments on Mouse and Monkey

Large-scale ultrasound radiation force system for neurostimulation and Large-scale array ultrasonic transducer

Recently, an abundance of evidence has accumulated showing that ultrasound is also useful for non-invasively modulating brain circuit activity. Stimulation and modulation of neural circuit are among the fundamental ways of neuroscience to probe the neural mechanisms from molecular to behavioral levels, embedding the scientific and technological prospects to effectively treat entities including Parkinson disease, epilepsy and depression. We developed three types of ultrasound stimulation system to investigate the neurons, C. elegans, mice and NHP. When the HEK cell was transfected with Piezo1 and stimulated by the ultrasound, the membrane current of the cell changed immediately in response to ultrasound recorded by the whole-cell voltage clamp recordings. Calcium imaging also shows that the Ca2+ transients were triggered and fluxed into neurons in response to the stimulation by ultrasound. In motor cortex, ultrasound-stimulated neuronal activity was sufficient to evoke mice motor behaviors. By stimulation of the deep brain nucleus, motor behavior in a subacute mouse model of PD can be improved significantly. The results suggested that ultrasound wave could be used to modulate the animal behaviors and its interactions with the protein of cell membranes leads to the opening of mechanosensitive ion channels. We further develop the neuromodulation tool of “sonogenetics” method aimed to provide non-invasive, specific, safe, precise and reliable deep brain stimulation.

3 Novel Optical Microscopy

Benefiting from the ability of accessing biological processes in live tissue, optical microscopy has revolutionized biomedical research in the past few decades. However, observation of cellular and subcellular dynamics and functions in deep live tissue within highly complex and heterogeneous environments is still difficult to obtain. There is a need for the development of novel optical microscopy methods to improve the imaging quality such as the spatial resolution, temporal resolution, field of view and pentation depth.

In 2017, a group led by Dr. Wei Zheng in the Research Center for Biomedical Optics and Molecular Imaging collaborated with National Institute of Biomedical Imaging and Bioengineering in US succeeded in developing a super–resolution two–photon microscopy imaging system. This system combines structured illumination and adaptive optics to break the resolution limit of conventional two–photon microscopy even at the depth of ~250 μm beneath the sample surface (Fig.1). Using this novel technique, the group realized super–resolution imaging in living biological systems, such as nematode larvae and embryos, drosophila brain, and zebrafish embryos.

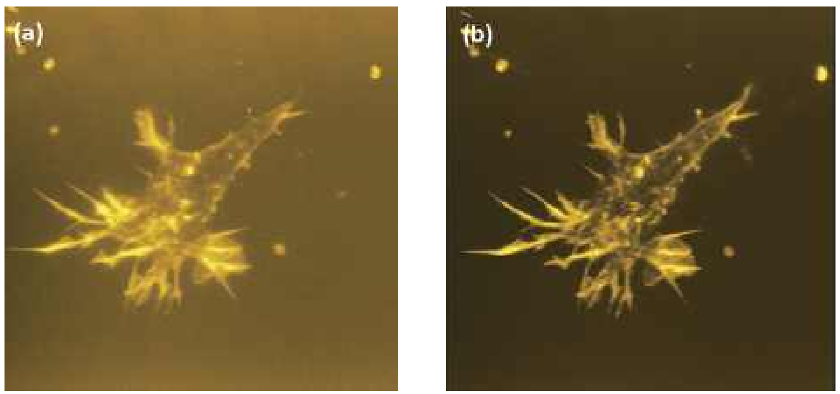


Fig.1 Three dimensional imaging comparison between (a) conventional two–photon microscopy and (b) super–resolution two–photon microscopy. The imaging area is 40 x 40 um2

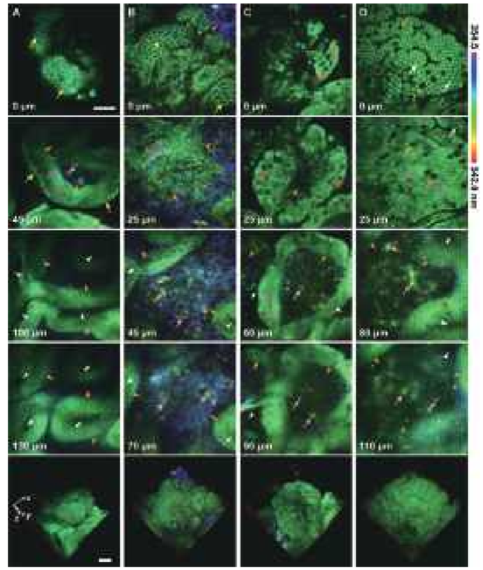


Fig.2 Spectrum–coded 3D structures of the normal and diseased human gastric antrum mucosa: (A) normal; (B) chronic gastritis with erosion; (C) chronic gastritis with intestinal metaplasia; (D) intestinal–type adenocarcinoma. The spectrum–coded images with different depths (transverse view) and corresponding 3D images are shown in the first four rows and the fifth row, respectively.

In 2018, the same group developed a time– and spectra–resolved two–photon microscopy by integrating fluorescence spectrum and lifetime detection techniques into two–photon microscopy. Using this technique, they quantitatively characterized the process of human gastric carcinogenesis merely based on endogenous biomarkers (Fig.2). This technology shows significant potential for noninvasive, label–free, real–time histological and functional diagnosis of digestive tract tumors.

In 2019, they proposed another approach to speed up the volumetric imaging rate of two–photon microscopy by an order of magnitude. It harnesses the point spread function engineering to avoid axial scanning during imaging. Benefiting from the rapid volumetric imaging speed, the technique is highly suitable for longitudinal tracking of biological events in vivo. They captured the processes of macrophage phagocytosis and C. elegans embryos development.

Within the same research center, Wei's colleague, Dr. Chengbo Liu and Dr. Xiaojing Gong are leading a research team working on photoacoustic imaging, a revolutionary technique that breaks the limit of conventional optical imaging in terms of both resolution and depth. Unlike fluorescence imaging, photoacoustic detects chromophores with and without fluorescence emissions. The harnessed optical energy is converted into acoustic waves within the sample, resulting in significantly improved penetration depth and imaging resolution.

In one of their recent works, they reported the world's fastest multiscale photoacoustic microscopy. The system is capable of obtaining multicolor information at different resolutions and depths by simply switching the laser sources. A line speed of 100 KHz was achieved, which is the highest among the reported same kind systems. The system would find significant applications in biological research such as study of tumor angiogenesis and brain function. By probing the inherent absorption property of endogenous hemoglobin molecules, the system is also highly suitable for vascular imaging.

To push the clinical translation of photoacoustic imaging, the same group also established a handheld photoacoustic imaging method based on a clinical ultrasound scanner. A unique photoacoustic detection design was implemented to achieve high imaging sensitivity and meanwhile maintain the compactness of the handheld detector for user-friendly purpose. The system is capable of imaging human body at multiple centimeter depth with micron resolution and real time imaging speed, which is highly suitable to be used in clinical settings for applications such as disease screening, metabolism assessment and intraoperative guidance. Pre-clinical studies are currently being conducted in Liu's group to investigate the feasibility of the system for clinical translation. The group members are working closely with clinical physicians to get the system ready for clinical use.

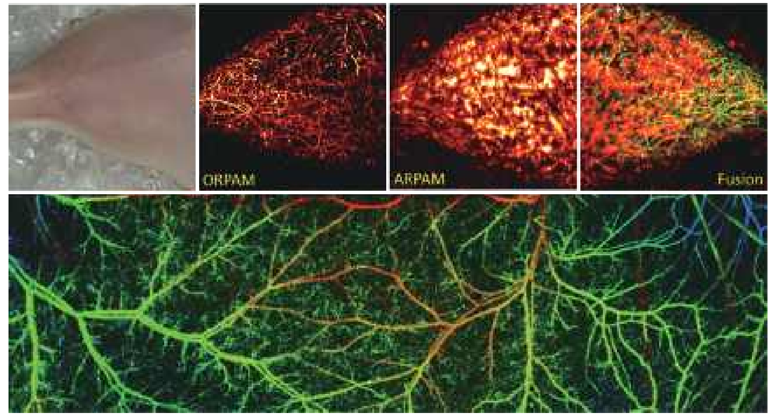


Fig.3 The top row is the imaging results with multiscale photoacoustic imaging system. From left to right are photo of the imaging sample, imaging result of high resolution mode, imaging result of large depth mode, and fusion of two different imaging modes. The bottom row is the dorsal vascular imaging result of photoacoustic imaging.

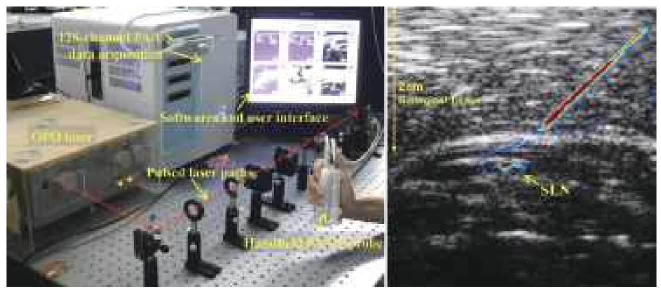
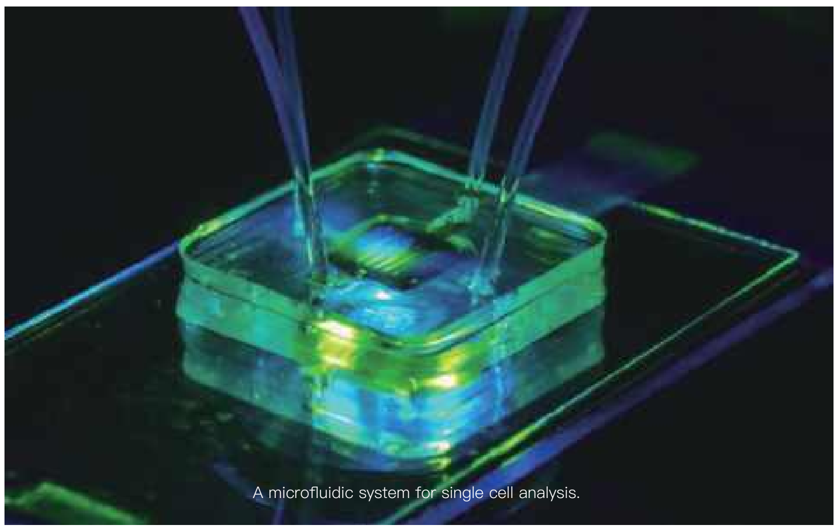


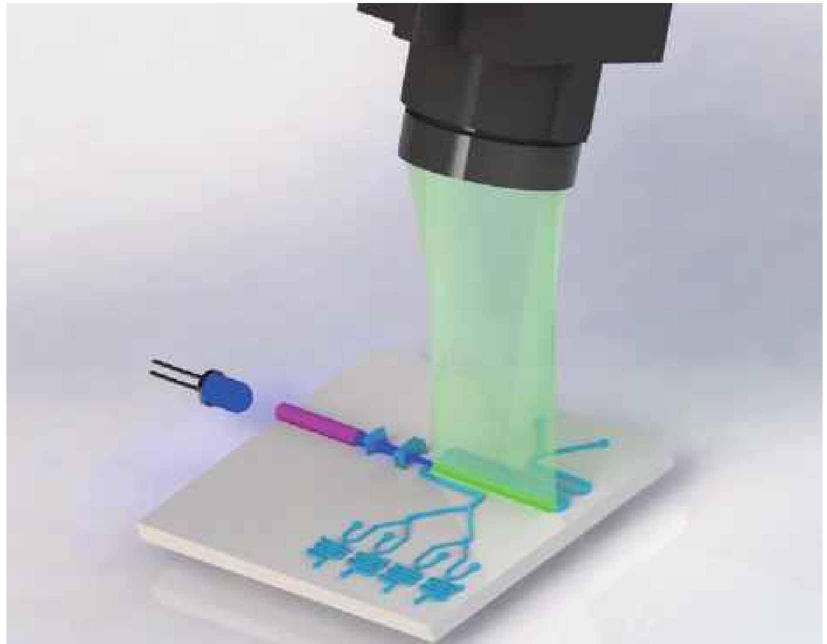
Fig.4 The left panel is the photo of the handheld photoacoustic detector and the imaging system for clinical translation. The right panel is the imaging result for guiding sentinel lymph node (SLN) biopsy. The gray image shows the morphological background information provided by ultrasound imaging, and the color image shows the SLN and biopsy needle acquire by photoacoustic imaging.

4 Microfluidics,NanotechnologyandInVitro Diagnostics

There is a significant demand for high–throughput biomolecular analysis tools to assist diagnosis in research and clinical applications. A strong interest for the devel–opment of chemical and bio–sensing platforms with fully integrated, automated functions and equipped with user friendly interfaces started to evolve in the late 1990s. The operation of these miniaturized devices often relied on the science of ''Micro–Electro–Mechanical Systems'' (MEMS) (equivalent term for ''microsystems'', preferred in Europe) and microfluidics. Over the last decade, a fast–growing interest was noticed for developing microdevices that integrate one or several functionalities (e.g. sample preparation, reaction, separation, and detection) onto a single chip, the latter being of only millimeter size up to a few square centimeters in size. These microdevices can be used either to perform a certain type of chemical analysis, or more generally, for other non–analytical lab processes like sample pre–treatment, and they are known as ''Micro Total Analysis System (microTAS)'' or ''Lab–On–a–Chip (LOC)'' devices.

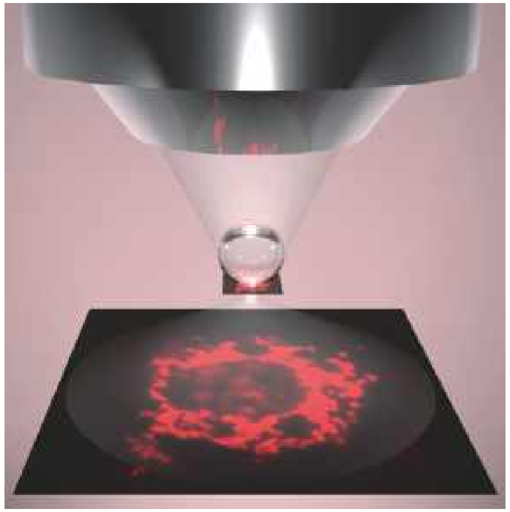


A microfluidic system for single cell analysis.



An integrated optofluidic platform comprises microfluidic and micro–optical components.

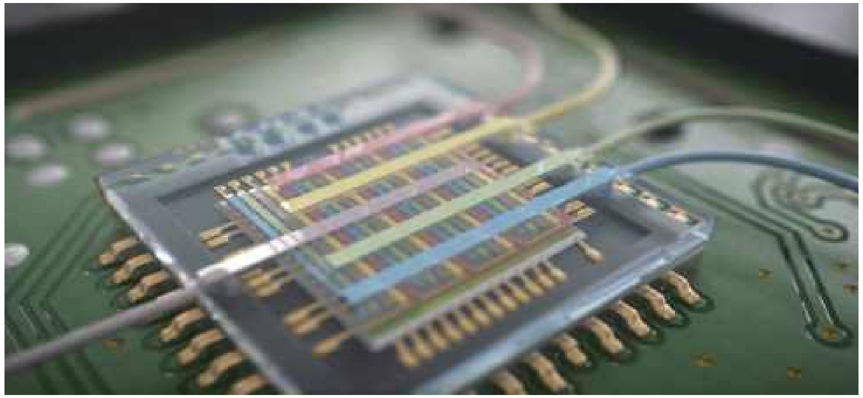
A microTAS or LOC is in general an integrated microfluidic device or a platform that provides a set of fluidic unit operations and allows the imple–mentation of complete (bio–)chemical processes, including sample collec–tion, preparation, processing and analysis, in an easy and flexible way. A microfluidic platform typically offers miniaturization, integration, automa–tion and parallelization of (bio–)chemical processes.

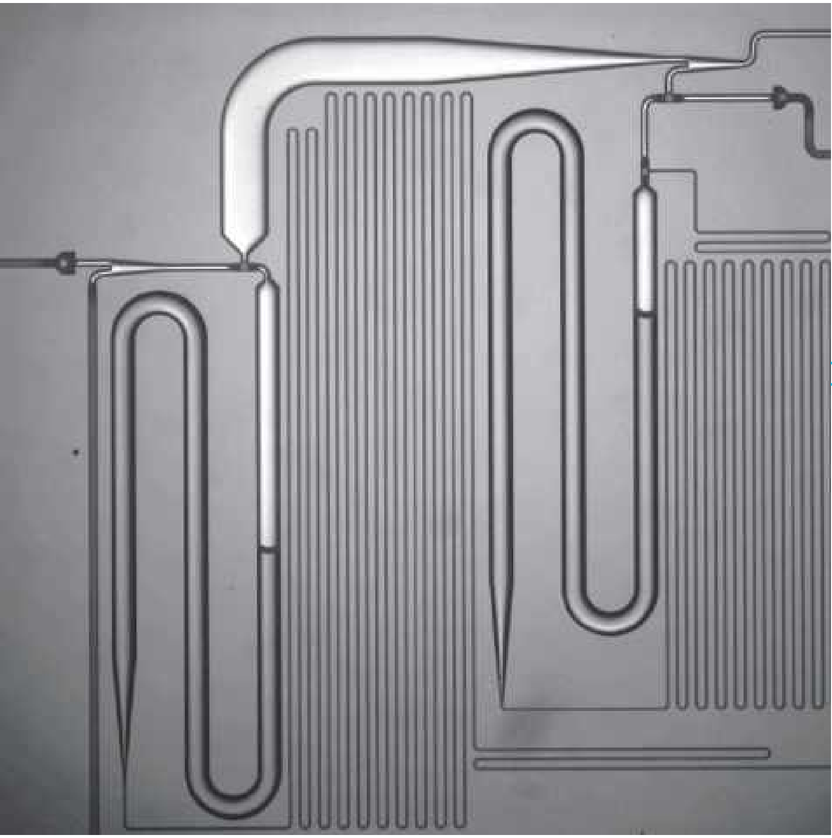


The detection of biomarkers (molecules that indicate the onset and status of disease) is the most promising strategies for the early diagnostics of various diseases. Early diagnosis can lead to a cure at a fraction of the cost of currently ineffective treatments for late-stage disease. It is predicted that the development of new biomarker diagnostic technologies will simultaneously improve survival rates and quality of life, while significantly reducing health care costs. For example, early diagnostics can give a cancer patient a up to 90 percent chance of surviving beyond five years. There are close to one million medical institutions in China, of which there are 20,400 hospitals, and the rest are primary health institutions at the township level and below. Large-scale biochemical testing equipment for biomarkers detection is only suitable for testing a large number of samples due to its expensive price and complicated maintenance process, which requires professional personnel to operate. Basic-level medical institutions, community health centers, township health centers, and clinics cannot afford such testing equipment because of the limited samples amount, so patients can only perform blood biochemical tests in the hospital if needed. In 2007, SIAT established the Research Center for Biosensors and Medical Instruments, and its goal is to have the detection system directly on the microfluidic chip and to realize portable microdevices with high sensitivity and fast response, so that they can be potentially used for early cancer diagnostics in limited resource settings. To date, microfluidic devices with various detection techniques including optical detection, electrochemical detection, mechanical detection, mass spectrometry and others have been developed in SIAT

The completion of the human genome project heralded a new era of molecular and genetic based medicine. Molecular diagnoses bring out major opportunities for individuals affected by a wide variety of illness such as cancer, diabetes, heart disease, auto-immune disease, as well as many infectious diseases. In 2017, SIAT's new Center for Bionic and Intelligent Sensing was founded, Professor Tingrui Pan and Associate Professor Hui Yang and their research groups focus on developing new diagnostic technologies involving accurate and sensitive determination of marker molecules associated with disease and found in small amounts of biological samples, which combines varied disciplines to work together on applications in preventive and personalized medicine, the researches include: • novel microsystems and nanodevices for in vitro diagnostics; • novel technologies on single molecule sensing and imaging; • novel approaches to manipulate biosamples and biofluids at the microscale and nanoscale; • microtechnology and nanotechnology devices for capturing extracellular vesicles and circulating nucleic acids (cell-free DNA and microRNAs).

So far, 3 research centers and 9 research groups have been established in SIAT to study various aspects related to the development of biosensors and microfluidics for point-of-care diagnostics. The teams are highly multidisciplinary, bringing together scientists from areas such as microtechnology, nanotechnology, molecular biology, biochemistry, pathology and medicine. Microfluidic technologies integrated with nanotechnology largely demonstrated potential to dramatically improve many aspects of analytical research by providing superior performance when compared to the traditional labor-intensive analytical procedures.





A microfluidic circuits for human blood pretreatment and test.

SIAT researchers' leadership has been recognized by publishing their research works in high impact journals such as: Chemical Society Reviews, Advanced Materials, Advanced Functional Materials, ACS Nano, Nano Letters, Angewandte Chemie International Edition, and so on. Researchers have collaborations over 12 countries and have forged links with leading national organizations, such as Mindray, Beijing Genomics Institute (BGI), Snibe and Wondfo. Four in vitro diagnostics start-up companies have been established based on SIAT discoveries and innovations, with 120 million RMB of equity being raised. SIAT researchers have 60 patents related to microfluidics, biosensing and in-vitro diagnostics. Highlights on education and training include attaining 40 postdoctoral researchers and research higher degree students, as well as hosting more than 10 international conferences and workshops.

SIAT's approach to achieving excellence in research has embedded in its ability to demonstrate discovery-to-translation pathways. Our mission is to develop improved point-of-care diagnostics from the benchtop to bedside, with the goal of significantly enhancing patient outcomes and helping to transition of the medical system towards early disease detection and personalized treatment.

A China–U.S. joint research team reported the generation of germline–transmittable cynomolgus macaques with Shank3 mutations, known to cause a form of autism. A macaque model of SHANK3 mutation exhibits neurological phenotypes similar to patients with autism and Phelan–McDermid Syndrome.

The prevalence of autism in the US and UK population is greater than 1%, yet there are currently no available therapeutics that target the underlying pathology. "The human brain is an extremely complex network system, the pathogenesis and cause of autism and other mental diseases are not clear, so the treatment is very difficult."says Zhou Huihui who is an neuroscientist of Shenzhen Institutes of Advanced Technology, and one of the senior authors of the study. He says that behavior training is the most common treatment at present, but it can only improve some patients, and the training effect is difficult to predict. According to the report on the development of China's autism education and rehabilitation industry, at present, there are more than 10 million autistic patients in China, including more than 2 million children aged 0 to 14 years old. In recent years, the prevalence rate is still on the rise. According to Zhou huihui, the visual attention of autistic patients is different from that of normal people. It is an important aspect of the project to identify whether there is abnormal behavior and cognition of patients with similar diseases in animal models.

1 Neuroscientists develop a primate model for autism by genome-editing

Autism Spectrum Disorders (ASD) is complex developmental disorders with a strong genetic basis. Scientists have identified hundreds of genetic variants associated with ASD, many of which individually confer only a small degree of risk. Scientists have identified hundreds of genetic variants associated with autism spectrum disorder, but most of them have little impact on autism. The researchers focused on one gene with a strong association, known as Shank3. The Shank3 gene mutation is highly related to the onset of autism. The protein encoded by Shank3 is found in synapses — the junctions between brain cells that allow them to communicate with each other. It is particularly active in a part of the brain called the striatum, which is involved in motor planning, motivation, and habitual behavior. Shank3 mutations show some of the traits associated with autism, including avoidance of social interaction and obsessive, repetitive behavior.

Although mouse studies can provide a great deal of information on the molecular underpinnings of disease, there are drawbacks to using them to study neurodevelopmental disorders. The rise of rodent models targeting identified risk genes for autism has generated a renewed interest in the search for a pharmacological therapy. However, the spectrum of behavioral disturbances associated with autism have been difficult to model in rodents that display clear differences in cognitive and social strategies. Additionally, the development of biomarkers using resting–state functional magnetic resonance imaging (MRI) has been difficult to adapt to preclinical rodent models."

Biotechnology

Brain Science

Neuroscientists develop a primate model for autism by genome-editing

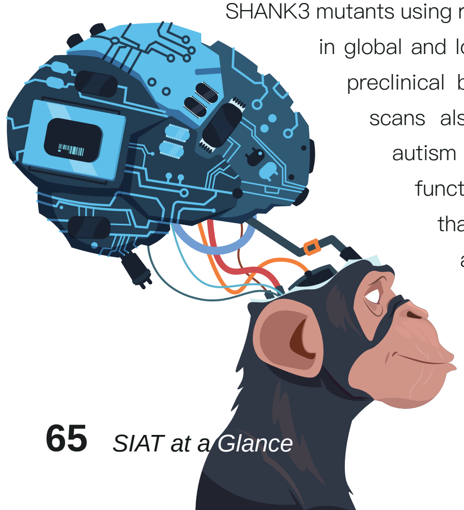
In particular, mice lack the highly developed prefrontal cortex that is the seat of many uniquely primate traits, such as making decisions, sustaining focused attention, and interpreting social cues, which are often affected by brain disorders. The primate model is close to humans in evolution and has many similarities to humans in brain structure. For exam–ple, the prefrontal cortex in nonhu–man primates is well developed, which plays important roles in decision–making, attention and social interactions. Deficits in these cogni–tive functions have been associated with brain disorders including autism. Therefore, ”nonhuman primates are hopeful to become an ideal animal model for simulating some human brain diseases,” Zhou Huihui says.

To tackle these problems, the China–U.S. joint research team has created a primate model of autism by introducing germline mutations in the SHANK3 gene of macaques (Macaca fascicularis) using CRISPR–Cas9 genetic editing. The study, published in Nature, is conducted by scientists from the Shenzhen Institutes of Advanced Technology (SIAT) of the Chinese Academy of Sciences (CAS), Massachusetts Institute of Technolo–gy, Sun Yat–Sen University and South China Agricultural University.

IThrough the study, we find that non–human primates carrying Shank3 mutation show similar behavioral characteristics in social interaction, face specific attention distri–bution and other aspects with autism, and there are abnormal brain connection patterns.” Zhou Huihui says that the non–human primate model is close to human in evolution and has many similarities with human in brain structure and function.”For example, the primate model has a relatively developed prefrontal cortex, which is the core of decision–making, attention and social behaviors. These behaviors are closely related to autism and other brain diseases. Therefore, non–human primates are expected to become an ideal animal model to simulate some human brain diseases. This project involves many aspects such as molecular biology, embryo operation, behaviorism, neurophysiology, brain imaging and so on. This project tackles key technical problems and the cycle is long.With the cooperation of all teams, the project steadily advances in the process of constantly overcoming various technical difficul–ties. ” Zhou Huihui says.

The recent development of the CRISPR genome–editing technique offered a way to engineer gene variants into macaque monkeys, which has previously been very difficult to do. CRISPR consists of a DNA–cutting enzyme called Cas9 and a short RNA sequence that guides the enzyme to a specific area of the genome. It can be used to disrupt genes or to introduce new genetic sequences at a particular location.

Through the genome–editing system CRISPR, they engineer macaque monkeys to express a gene mutation linked to autism and other neurodevelopmental disorders in humans. These monkeys show some behavioral traits and brain connectivity patterns similar to those in humans with these conditions. Mutations in SHANK3 are frequently associated with the development of autism and the neurodevelopmental disorder Phelan–McDermid Syndrome (PMS). Using a battery of behavioral tests, the authors show that macaques with SHANK3 mutations exhibit multiple behavioral phenotypes reminiscent of patients with autism or PMS. These include severe sleep disturbances, increased stereotypic behavior, impaired social interaction, and reduced vocalization. The macaques with Shank3 mutations show behavioral patterns similar to those seen in humans with the mutated gene. They tend to wake up frequently during the night, and they showed repetitive behaviors. They also engage in fewer social interactions than other macaques. In addition, video–based eye tracking revealed alterations in pupillary reflex and gaze fixation that are seen in children that develop autism. Together, the results suggest the SHANK3 mutant macaque model will be a valuable resource for modelling the disruptions in complex brain function seen in autism. Moreover, examination of SHANK3 mutants using resting–state functional MRI revealed alterations in global and local brain connectivity that may be useful as a preclinical biomarker. Magnetic resonance imaging (MRI) scans also revealed similar patterns to humans with autism spectrum disorder. Neurons showed reduced functional connectivity in the striatum as well as the thalamus, which relays sensory and motor signals and is also involved in sleep regulation. Meanwhile, connectivity was strengthened in other regions, including the sensory cortex.



The new type of model, however, could help scientists to develop better treatment options for some neurodevelopmental disorders," says Feng Guoping, who is the James W. and Patricia Poitras Professor of Neuroscience, a member of MIT's McGovern Institute for Brain Research, and one of the senior authors of the study. "Given the limitations of mouse models, patients really need this kind of advance to bring them hope." Feng says. Mouse models of ASD, due to their neural and behavioral differences from primates, haven't worked out very well. The reported behavioral and neural traits of Shank3 mutant primates provide new insights into the circuit–based pathophysiological model of ASD.

The development of primate models such as the SHANK3 mutant macaque is an advancement that may improve the predictive value of autism models. By introducing the SHANK3 gene variant associated with autism into monkeys, researchers hope to study treatment options for severe neurodevelopmental disorders. Now researchers can use this model to test the impact of potential therapeutic strategies on more complex behavioral symptoms and identify treatment–sensitive biomarkers that can be used for clinical trials. The main limitation of the study is a relatively small sample size that is likely due to the cost of creating and housing primate models. Although further studies are needed to determine the true advantages of using this macaque model, it is likely that primate models will accelerate autism research and enable the identification of more effective therapeutic strategies.

"We urgently need new treatment options for autism spectrum disorder, and treatments developed in mice have so far been disappointing. While the mouse research remains very important, we believe that primate genetic models will help us to develop better medicines and possibly even gene therapies for some severe forms of autism," says Robert Desimone, the director of MIT's McGovern Institute for Brain Research, the Doris and Don Berkey Professor of Neuroscience, and an author of the paper.

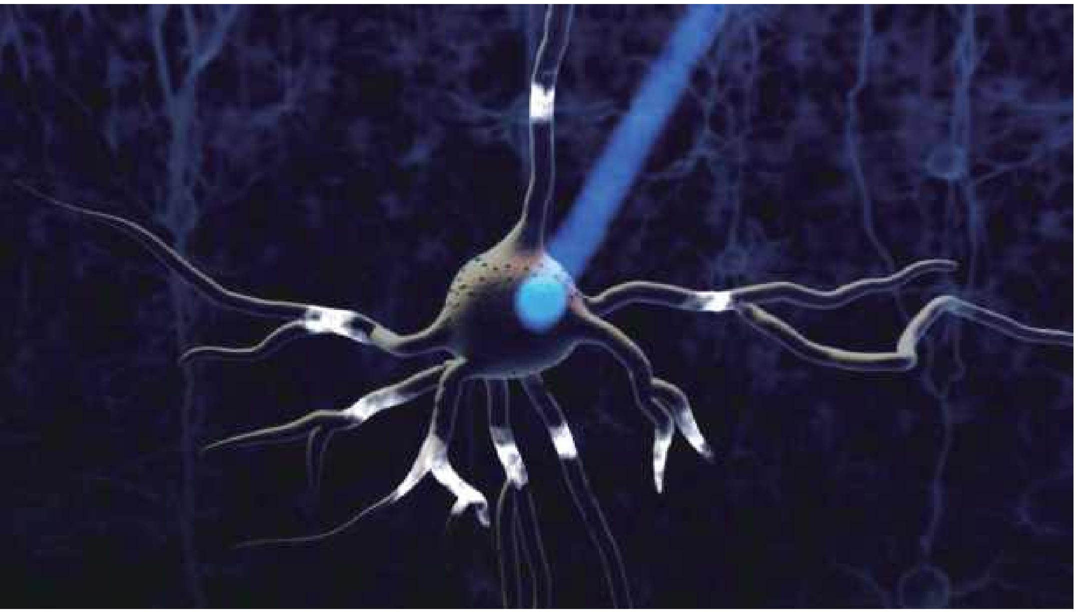
Neuroscientists develop a primate model for autism by genome-editing

The research is funded, in part, by the Shenzhen Overseas Innovation Team Project, the Guangdong Innovative and Entrepreneurial Research Team Program, the National Key R&D Program of China, the External Cooperation Program of the Chinese Academy of Sciences, the Patrick J. McGovern Foundation, the National Natural Science Foundation of China, the Shenzhen Science, Technology Commission, the James and Patricia Poitras Center for Psychiatric Disorders Research at the McGovern Institute at MIT, the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, and the Hock E. Tan and K. Lisa Yang Center for Autism Research at the McGovern Institute at MIT. The research facilities in China where the primate work is conducted are accredited by AAALAC International, a organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.

The Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) is a private, nonprofit organization that promotes the humane treatment of animals in science through volun-tary accreditation and assessment programs. SIAT received AAALAC accreditation in 2018 for its primate experiment platform, which laid a foundation for collaboration with international pharmaceutical companies to pursue new treatments of brain disorders in the future.

2 The story of Optogenetics

Understanding the working principles of the brain, revealing the pathophysiological mechanisms of neuropsychiatric diseases, and developing new "early diagnosis and optimized treatment" technologies are both major national needs and important scientific issues at the international frontier. To solve this problem, new techniques for high-temporal and precise neural circuit regulation are needed.
To study the functional significance of nervous system activity, multiple methods and techniques have been developed, in the past 50 years, electrical, genetic, and pharmacological interventions have been developed and applied to obtain related causal insights after artificial manipulation. Optogenetics, among all them, is one of the most shining stars.



Optogenetics leverages light-responsive proteins from microbes, such as halorhodopsin (HR), channelrhodopsin (ChR), bacteriorhodopsin (BR) and more. ChRs are naturally occurring light-gated ion channels. They are important for the motile algal cells to find suitable light levels for their living. Within nervous systems of behaving animals, these ion-conducting proteins, when expressed in neurons and being optically activated, can elicit light-dependent activation or inhibition of the neural activities. The use of light for perturbation can achieve fast, spatially controlled and minimally invasive modulation of neural activity, which conquered the lagged observation of activity manipulation before.

This technique is extremely charming because optical stimulation or inhibition of neurons expressing light-sensitive excitatory cation channels or inhibitory pumps can be achieved in a cell-type-specific manner either using viral vectors or transgenic rodent lines, also because it is manipulated the ion channels directly, it could activate or inhibit the cells at an acute time mode as milliseconds, which perfectly mimicking the electrophysiological rhythm of the nervous system. In this way, optogenetics enables direct targeting of specific neural circuit elements, which are neurons, for inhibition or excitation while spanning timescales from milliseconds to many days or more when light stimulation is continually provided. By including more proteins that are powerful and diverse in their ionic selectivity, spectral sensitivity, and temporal resolution, the optogenetic toolbox has broadly expanded and updated in the past ten to twenty years. Combined with sophisticated molecular techniques for transgenic and viral expression it can be used in rodents, zebrafish, flies, birds and non-human primates.

As one of the main contributors, Professor Liping Wang, now the director of Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, participated in research and development of Optogenetics, in the early years as a group member of Deisseroth Lab(Nature, 2007)., making it possible for people to perform functional analysis of specific neural circuits in milliseconds.

Optogenetics can be and has been proved to be a powerful tool in the research fields as it can be used to test the causal hypotheses with either "gain of function" manipulation by activation of these neurons or by "loss of function" by inhibition of these neurons, especially during behavior. Optogenetics was chosen to be Nature Methods' choice of Method of the Year 2010 "With the capacity to control cellular behaviors using light and genetically encoded light-sensitive proteins, optogenetics has opened new doors for experimentation across biological fields." — Editorial of Method of the Year 2010, Nature Methods.

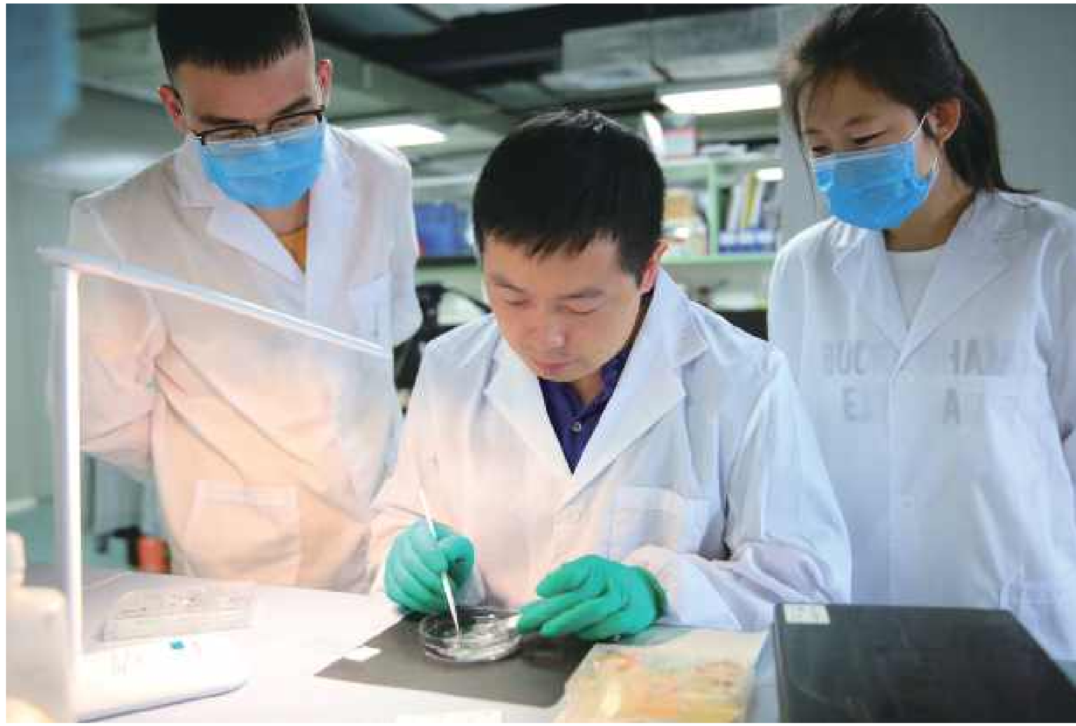
In recent years, with continuing technological developments, optogenetics has become a booming field in research, especially in neuroscience, including searching for light-sensitive proteins capable of controlling particular cellular behaviors; to stimulate moderately greater depths in large brains, avoiding local heating for direct light stimulation, wireless remote control of the stimulation and so on. This has yielded a diverse pool of tools with different functionalities and applications.

For example, based on the work done in Shenzhen, Wang group dissected two vital circuits underlying the innate defensive behavior of the mice (Nature Communications, 2015, Neuron 2019) and the circuitry basis of stress accelerated defensive response (Current Biology, 2018) and other neural circuits underlying innate or adaptive behaviors (Science Bulletin 2019, Neuroscience Bulletin, 2019, Nature Communications 2015, 2016). Optogenetics has made significant changes to how neuroscience studies are performed. The technique offers the capacity for multi-modal control of neuronal activity in specific cells and at timescales, most importantly, in the way relevant to the brain's in vivo physiology. This with the combined functions of optogenetics with other neuroscience tools, will yield more interesting and important findings.

Based on their work in Shenzhen, Guangdong, China, BCBDI research team established their platform and successfully develop several related technologies, including an implantable multifunctional photoelectrode array, the application of optogenetic technology in the analysis of peripheral nervous system functions; a wireless, remote-control, and programmable precision light stimulation system for in vitro light stimulation has been developed to study cell-to-cell and regulatory mechanisms of cellular signaling pathways. Related work was published in Biomaterials 2012, Journal of Neuroscience Methods 2014, Electrochemistry Communications 2017, Advanced Optical Materials, 2018, Glia, 2014, Cell Death & Disease, 2012, Cell Death & Disease, 2013, and other journals, and related technologies have authorized more than 20 national invention patents. With this technology, intensive research has been carried out on the structure and function of specific neural circuits in mental disorders with cognitive impairment.

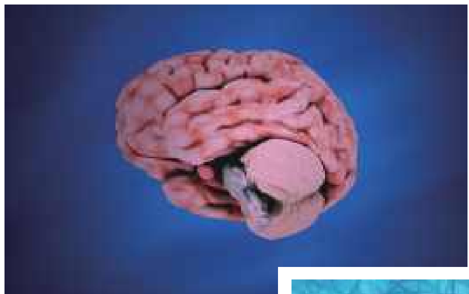
Wang group also used optogenetics and related techniques in the field of emotion study. Mental disorders defined as disruption in neural circuits (NIMH) cause abnormal thoughts, emotions and behavior, such as schizophrenia, depression, addiction, post–traumatic stress disorder and others, which are recognized as one of the leading global health challenges. Fear is a basic and highly conserved emotion. Fear circuits and their important implication in understanding human fear and anxiety disorders is an emerging field in emotion and behavior neuroscience research. However, little is known about the cross talk of the neural circuits between the innate fear, learned fear and anxiety. Dissection of functional neural circuits for fear and anxiety will help us to understand the mechanisms of mental disorders at neural circuit level, also, will lead us to search the identification of biomarkers and novel candidate drug targets, as well as the development of novel mechanism–based cognitive or behavioral interventions for mental disorders: Significant progress has been made in this field, including 1) determining the structure and function of brain specific neuronal subtypes control specific emotional behavior, including innate fear, learned fear and anxiety; 2) elucidating the modified neural circuits properties in mental disorders, such as schizo–phrenia and post–traumatic stress disorder.

Furthermore, in order to reduce the research and development costs of domestic counterparts and accelerate the overall domestic innovation process in this field in China, with the help of its own established platform, Wang group held eight consecu–tive national optogenetics training courses in Shenzhen from 2012 to 2019, radiating the self–developed optogenetics–related technologies to About 500 laboratories in the country. Till now more than 1,000 researchers in this field benefited from this training course.



3 The story of central-peripheral regulation involved in physiological functions and diseases

The involvement of the CNS in the regulation of basal functions of the peripheral organs has been studied for many years. Recent years have witnessed the rise of the neuro–peripheral interactions as a major topic of research interest in biology. For example, studies have revealed that the gut–brain axis influences normal physiology and contribute to various CNS diseases, such as Alzheimer's disease, Parkinson's disease, stress & depression and autism, et al. Accumulating data now indicate that the peripheral systems communicate with the CNS potentially through neural, endocrine and immune pathways — and thereby influences brain function and behaviors. Peers in our team have been focusing on the following research topics as discussed below.



Neuronal mechanisms of the gut-brain axis

The emerging area of researches on gut–brain axis is evolving quickly. Especially, the interaction between gut microbiota and the brain has gradually become the focus of neuroscience. Based on the evidence from animal and human studies, it has been well–recognized that gut microbiota affects the brain's physiological, cognitive and emotional functions and consequently the behavioral outcomes while the precise mechanisms have not yet been fully understood. Key studies in the past few years have given us a deeper understanding of the part played by the brain–gut–microbiota axis in disorders as diverse as depression, autism, obesity, ALS and neurodegenerations such as AD, PD.

The gut microbiota interact with the host through immune, neuroendocrine and neural pathways. Gut microbiota recruit bidirectional gut–brain network communication to modulate brain function. It was known that the development and bidirectional communication between the intestinal microbiota and HPA axis play key roles in human functioning, overactivation of the HPA axis can lead to increased release of stress hormones and neurotransmitters including norepinephrine which cause the change of microbiome(de Weerth, 2017). Meanwhile, work from Shulman Lab have shown that increased production of acetate by an altered gut microbiota in rats leads to activation of the parasympathetic nervous system, which, in turn, promotes increased glucose–stimulated insulin secretion, increased ghrelin secretion, hyperphagia and obesity(Perry et al., 2016). Gut microbiota mediate maternal high fat diet (MHFD)–induced social deficits and selective re–introduction of Lactobacillus (L.) reuteri reverses both the LTP in VTA DA neurons and social deficits in MHFD offspring(Buffington et al., 2016). A vagal gut–to–brain circuit linking sensory neurons in the upper gut to striatal dopamine release has been mapped by Araujo et al.(Han et al., 2018) and Han Seok Ko and colleagues recently show that gut–to–brain propagation of pathologic a–synuclein via the vagus nerve causes the degeneration of dopamine neurons and PD(Kim et al., 2019).

The brain–gut microbiota axis refers to a bidirectional information network between the gut microbiota and the brain, which may provide a novel therapeutic for neurological disorders.

Central nervous system-peripheral immune system crosstalk in neurological diseases

The function of immune system is not only pivotal for protecting mammals from pathogenic infection and invasion, but also indispensable for the homeostasis to maintain, especially in central nervous system (CNS). Classical concepts believe that the CNS is privilege from immune surveillance as it is isolated by barrier systems which the immune cells and factors cannot penetrate through. However, accumulating evidence shows that immune system participates in mediating the progression and restoration of numerous neurological disorders, such as in neural degenerative diseases and neural injury via the infiltration of cellular and molecular mediators from the circulating blood system. Moreover, many immune related signaling pathways functioning in glial or neuron are involved in modulating neural functions, and the dysregulation of these signaling pathways has been reported to correlate with neurological disorders such as autism, anxiety and addictive behavior.

On the contrary of regulating the CNS, immune system is being tightly controlled by CNS through circulating factors released by the neuroendocrine system, such as hormones, neuropeptides and neural transmitters. In addition to the soluble factors, innervation in immune organs forms synapse-like structure between sympathetic neuron and leukocyte that provide further signal port for CNS to regulate immune function in homeostasis or diseases conditions.

Thus, the relationship between peripheral immune cells and the peripheral system should be considered as an additional possible mechanism in neurological disorders, including neurodegenerative diseases and psychiatric disorders; and the immunotherapy can be an alternative therapeutic strategy in treating neurogenic peripheral dysfunction.

Neural regulation of bone remodeling

Recent work from our team has highlighted the influence of neural signals on bone metabolism, homeostasis, and diseases. The identification of neural pathways which participates in the regulation of bone modeling, is complementary to the endocrine activity. The characterization of neural receptors on bone cells can potentially affect the bony anabolic and catabolic activities. In particular, bone metabolism and homeostasis have been reported to be precisely modulated by the central neural signaling.

The central neuropeptides and neural factors have been confirmed to modulate bone metabolism and homeostasis, for example, the semaphorin-plexin system plays an important role in the cross-talk between osteoclasts and osteoblasts; and a complex system has also been identified and includes neuropeptide Y and cannabinoids. The bone tissue is under the dual control of the central and the peripheral neural system, and the central regulatory mechanisms correlate with other homeostatic networks such as the endocrine system and demonstrate an intricate and synergetic bone biology(Huang et al., 2019).

Central mechanisms for blood glucose homeostasis

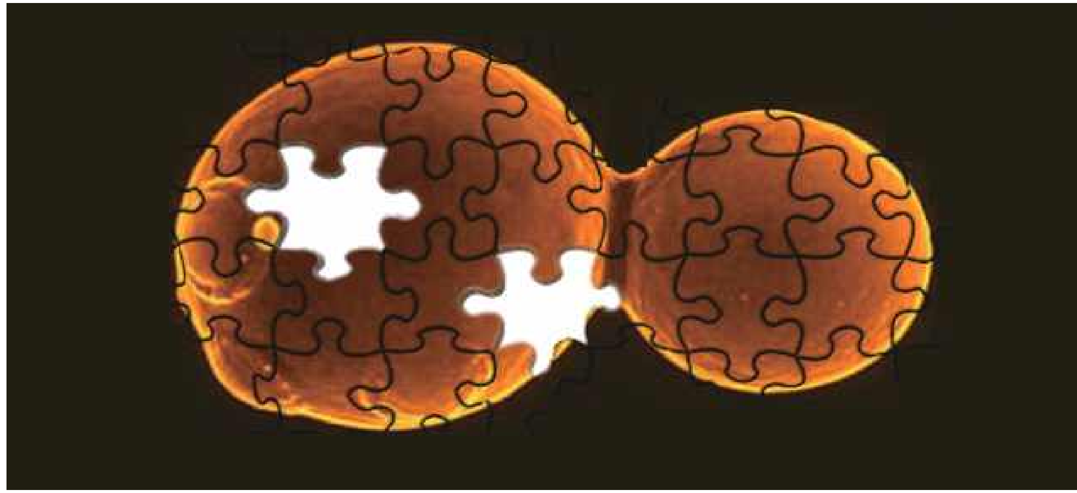
The primary focus of the diabetes research community has placed on the function of pancreatic islet and glucose metabolism in insulin-sensitive peripheral tissues. However, a growing body of evidences suggest that the central nervous system also play a key role in the control of blood glucose homeostasis.

First, studies in the 1960s found that there are glucose-sensitive neurons within the hypothalamus, and the firing rates of these neurons are affected by the change of ambient blood glucose levels. Central infusions of nutrients decrease blood glucose level by inhibiting hepatic glucose production. ICV a low dose of insulin can increase insulin sensitivity and infusions of insulin receptor antibodies into the third ventricle lowers hepatic insulin sensitivity, suggest that central actions of insulin signaling is required to maintain normal blood glucose level. Although the exact mechanism for how central insulin signaling affecting peripheral insulin sensitivity and hepatic glucose production is not clear, the vagal efferent fiber may be critical for this brain-peripheral indirect blood glucose control. Moreover, brain can regulate blood glucose clearance through non-insulin-dependent pathways. For example, central leptin administration lower blood glucose by increasing the uptake of blood glucose , which in turn lowers blood sugar levels, but does not affect insulin levels, and the same dose of leptin are ineffective when injected peripherally, suggesting that that the brain can regulate blood glucose level through insulin-independent mechanism.

Synthetic yeast genome

Synthetic biology is a multidisciplinary field of research which applies the engineering paradigm of systems design to biological systems to create useful novel functionalities that do not exist in nature. Researchers in the field are harnessing the power of synthetic biology to solve problems in manufacturing, medicine and agriculture. Synthetic genomics is a nascent field of synthetic biology that design, synthesis and implement whole genome of pre-existing organisms to create biological systems with new abilities. In the Center for Synthetic Genomics, researcher are focusing on improving the ability to synthesize DNA, the ability to precisely and accurately edit DNA, the ability to transfer entire chromosomes, the ability to design of genomes, as well as application of synthetic genomics in producing useful bio-products.

Saccharomyces cerevisiae, commonly known as baker's yeast, has been broadly used in daily life thousands of years, and it plays pivotal roles in the production of biopharmaceuticals. The advancement of DNA synthesis and assembly has enable to build a designer genome to address some fundamental biological questions. The international synthetic yeast genome project (Sc2.0) which aims to synthesize designer genome in yeast, is the first eukaryotic genome synthesis project. In 2017, 5 designer chromosomes were chemically synthesized in yeast. Researchers from the Center for Synthetic Genomics participated in Sc2.0 and successfully synthesized the longest one amongst 5 designer chromosomes. A new method to screen stress resistant robust strains was developed along the Sc2.0,which is synthetic chromosome rearrangement and modification by loxP-mediated evolution (SCRaMbLE). In 2018, researcher at the Center for Synthetic Genomics developed a versatile tool, called ReSCuES (reporter of SCRaMbLEd cells with efficient selection) to identify SCRaMbLEd cells. At the same time, researchers at Center for Synthetic Genomics and University of Manchester created a flexible combinatorial method, called SCRaMbLE-in, to optimize exogenous pathway expression and chassis engineering simultaneously. This method has great potential to promote metabolic engineering with synthetic yeast.



Researchers at Center for Synthetic Biochemistry are focusing on designing and building living factories (cells) to produce useful bioproducts efficiently and economically. They have developed an effective and automated workflow for a wide range of high-throughput screening campaigns targeting multistep enzymatic reactions in chemical engineering.

Cannabinoids are naturally occurring compounds found in the plant, and have been approved for certain human ailments treatment. With the increasing demand for their medical use, how to produce it more efficient and environmentally friendly is the challenge for the society. In 2019, researchers at Center for Synthetic Biochemistry collaborated with University of California Berkeley have created a yeast to produce cannabinoids with low cost sugar by introducing a novel metabolic network. This provides a crop-land free, energy saving, and low-carbon emission bio-factory (yeast) to manufacture cannabinoids.

Anti-tumor Therapy Based On Synthetic Microbial Circuits

The global cancer burden continues to rise. The WHO estimated that 2018 saw 18.1 million new cancer cases and 9.6 million deaths due to cancer. Evidently, existing cancer treatments are not sufficient in the fight against cancer and new therapies are urgently needed. The potential for microbial products as anti–cancer treatments has been known for years. Coley's toxin, a bacterial based anti–cancer therapy, was first used over 150 years ago, however it's use was limited by its unpredictable therapeutic effect and safety concerns due to potential toxicity. Current progress in biotechnology has allowed us to revisit bacteria–based cancer treatments. Engineered gene circuits allow us to design bacteria with a diverse range of diagnostic and treatment capabilities and limited adverse effects.

Recent developments in gene synthetic biology have allowed for the design and synthesis of a broad range of gene circuits with diverse functions. These gene circuits can then be integrated into bacteria to confer them with specific functions, including diverse potential cancer diagnostic and treatment functions, which could be ground–breaking in the fight against cancer.
Researchers at iSynbio (Institute of Synthetic Biology) of SIAT, led by Chenli Liu, are creating anti–tumor engineered bacteria. In engineered bacteria, several gene circuits can be combined in a module, giving them a highly specialized function, including but not limited to tumor targeting modules, regulatory modules and thera–peutic modules.

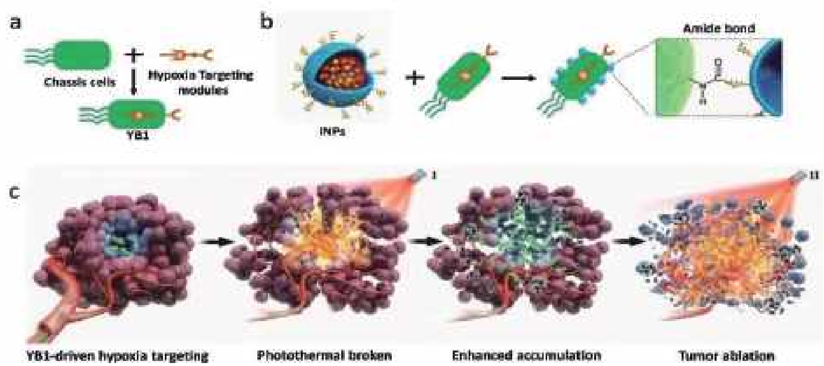
In tumor targeting modules, specific tumor cell biomarkers are used to design modules for cancer cell recognition. Hypoxia is a main characteristic of solid tumors and therefore a promising cancer target. In 2012, Jiandong Huang's group constructed a hypoxia targeting Salmonella strain YB1, which proved to be highly effective at targeting tumor cells. The engineered Salmonella were able to effec–tively colonize the tumor and inhibit tumor growth. Furthermore, there were no adverse effects on healthy tissue, as there the Salmonella were quickly cleared by the immune system.

Engineered regulatory modules allow for the design of bacteria that respond to various environmental signals such as light, heat and population density. Fan Jin's group integrated near–infrared regulated gene modules into Pseudomonas aerugi–nosa, which allows for fine tuning of Pseudomonas behavior.

When the near–infrared light intensity is low, the bacteria detach from surface of tumor cells. As the intensity increases, the bacteria attach to the tumor cells and once the light intensity reaches the threshold, the bacteria lyse themselves, releasing thera–peutic tumor–killing molecules. The ability to time the release of anti–cancer mole–cules allows for improved flexibility and targeting.

Therapeutic modules enable diverse molecules with cancer fighting capabilities to be loaded into bacteria in order to inhibit tumor growth. In 2019, Chenli Liu's group constructed an engineered YB1–INPs Salmonella strain with nano–photosensitizers (INPs) covalently attached to the surface. As YB1 colonizes the tumor cells, the INPs, which work as therapeutic agents, are delivered directly to the tumor. Under near–in–frared (NIR) laser irradiation, INPs exhibited a dependable and highly efficient photo–thermal tumor killing ability, effectively eradicating large solid tumors without relapse. Liu's joint team at SIAT is using iterative design to improve upon the first (like YB1) and second (like YB1–INPs) generation anti–cancer bacterial treatment in order develop an even more effective third generation. The therapeutic effect, safety, stability and clinical applicability of engineered bacteria are evaluated using both in vitro and in vivo models, as well as multiomics tools. For example, Nan Li's group used quantitative proteomics to study the nascent proteome of the engineered YB1 in mouse tumors to better understand their mechanism in vivo.

The overall goal is to create a safe and effective bacterial anti–tumor therapy founded on well–characterized, understood, and precisely controlled mechanisms. In the near future, we believe that synthetic microorganisms will be effective cancer therapies, helping to save millions of lives and bringing us one step closer to eradicating cancer.



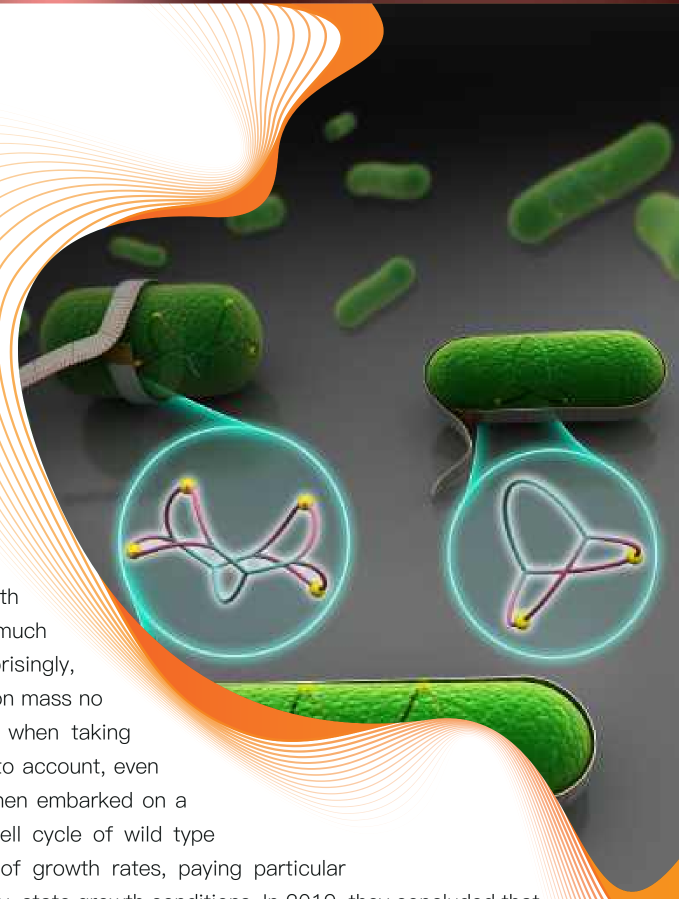
Quantitative Synthetic Biology

The bottom–up engineering approach of synthetic biology enables the construction of synthetic biological systems to test the predictions of quantitative biology,leading to new understanding. In turn, development of the basic theory of quantitative biology can establish principles for the rational design of synthetic living organisms.

The cross–fertilization of quantitative biology and synthetic biology will greatly promote the development of the biological sciences and help them to address major challenges facing human society. However, there are few studies in the world that closely connect these two subject areas. Chenli Liu' team encompasses research at the single–cell and multi–cell levels, to reveal the universal quantitative laws consistent with both natural and synthetic biological systems, and apply them to rational design and quantitative prediction of synthetic biological systems.

At the single–cell level, the cycle of cell growth, DNA replication plus sister segregation,and cell division is at the heart of living creatures. The foundation of bacterial cell cycle studies has long been two interconnected dogmas, the SMK growth law that relates cell mass to growth rate, and Donachie's hypothesis of a growth–rate–independent initiation mass. These dogmas have spurred many efforts to understand their molecular bases and physiological consequences.

In an example of "build–to–learn", in 2016, Chenli Liu' team interrogated basic principles of bacterial cell cycle regulation by actively manipulating cell diameter or length.This was achieved by employing synthetic gene circuits to finely tune the expression level of mreB or ftsZ. The initiation mass (i.e. added mass per origin between successive initiations) was found to remain constant in the face of significant cell dimension perturbations, in fast growth conditions. This study was a first demonstration that the tools of synthetic biology could be employed to study basic questions in quantitative biology, paving the way for new approaches to study the bacterial cell cycle.



As a follow–on to this initial publication, Chenli Liu' team began testing this finding in growth media that supported much slower growth rates. Surprisingly, they found that the initiation mass no longer remained constant when taking the slow growth regime into account, even for wild type cells. They then embarked on a systematic study of the cell cycle of wild type E.coli for a broad range of growth rates, paying particular attention to ensuring steady–state growth conditions. In 2019, they concluded that neither the SMK growth law nor the constant initiation mass hypothesis held across the range of growth rates examined. In their stead, a new linear relation was revealed between the cell mass and the number of cell divisions it takes to replicate and segregate a newly initiated pair of replication origins. Importantly, this relation held across both the slow– and fast–growth regimes, an achievement that had eluded investigators for more than five decades. Based on this newly discovered relation, they proposed a simple integral–threshold model with strong implications for possible bacterial cell division control mechanisms. This study provided a firm new foundation for the study of the bacterial cell cycle, while highlighting the importance of making quantitative measurements under carefully defined conditions to distinguish different theories or hypotheses.

At the multi–cell level, a basic observation is the universal occurrence of diversity. In this context, we asked a simple yet heretofore unanswered question: are there laws that govern how cells with different genetic backgrounds colonize a homogeneous solid environment? In 2019, our group completed a basic study in experimental evolution and synthetic biotechnology to systematically investigate phenotypical requirements for colonizing habitats of different sizes during range expansion by chemotaxing bacteria. Contrary to the intuitive expectation that faster is better, we first found that the expansion speed of the evolved strains become progressively faster for large habitats and progressively slower for small habitats through the course of evolution. Based on the expansion dynamics of two–strain competition experiments, we proposed a quantitative model that well–captured the outcomes of the competition process and revealed the underlying interaction, yielding the complete composition–dependent fitness landscape. Our analysis revealed a simple, evolutionarily stable strategy for colonizing a habitat of a specifc size: to expand at a speed given by the product of the growth rate and the habitat size. This study showed the power of the combination of quantitative biology and synthetic biology to reveal quantitative laws behind complex biological systems, which promises to be a powerful approach for rational design of complex living systems in the future. Published in Nature.

Bio: Chenli Liu is a Professor in Shenzhen Institutes of Advanced Technology (SIAT), Chinese Academy of Sciences, the Director of CAS Key Laboratory for Quantitative Engineering Biology, the Director of Shenzhen Institute of Synthetic Biology (iSyn–Bio), the Chief Scientist of Shenzhen Synthetic Biology Core Facility, the Deputy Director of Synthetic Biology Specialized Committee in Chinese Society of Bioengi–neering, and the Chairman of Shenzhen Synthetic Biology Association. He also serves as an Editorial Advisory Board member of journals ACS Synthetic Biology and Quantitative Biology. Liu obtained a Ph.D. in Biochemistry from the University of Hong Kong, and postdoctoral training in MCB, Harvard University. The research interest in his lab currently focuses on bacterial cancer therapy, the bacterial cell cycle, and directed evolution.

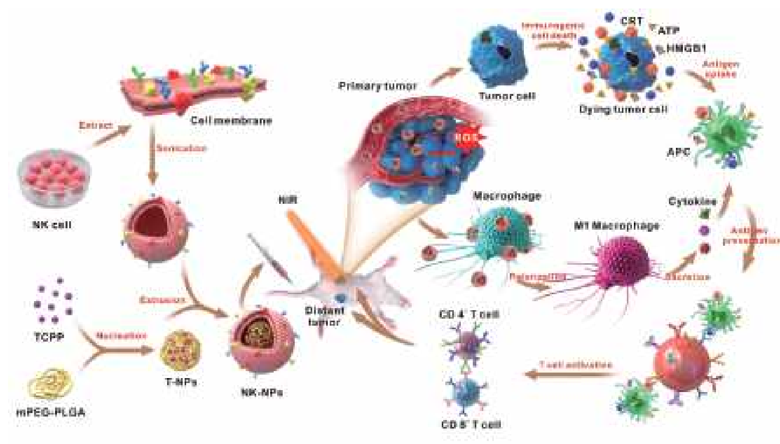
1 Nano-Biomedicine

Nano–Biomedicine and Nanotechnology Center of Institute of Biomedicine and Biotechnology (IBB) led by Prof. Lintao Cai is committed to the research of biomimetic drug delivery nanosystem, theranostic nanoplatform and nano–immunotherapy, including development of multifunctional nano–composite and nano–biological materials, exploration of molecular probes, molecular imaging, molecular diagnostics, targeted drug delivery nanotechnology, and construction of theranostics, and immunotherapy or transformation platforms applied for cancer prevention, diagnosis and treatment.

Biomimetic Drug Delivery Nanosystem. Recently, novel approach is developed by Prof. Cai's group to coat nanoparticles with cell membranes (i.e., cancer cells, NK cells, T cells), thus camouflaging them from detection by the reticuloendothelial system (RES) system and demonstrated specific homologous targeting to cancer (ACS Nano 2016, 10, 10049–10057; Adv. Funct. Mater. 2017, 1703197; ACS Nano 2018, 12, 12096–12108; Adv. Sci. 2019, 1900251). The biomimetic drug delivery nanosystem have emerged as a promising strategy for tumor–targeting, due to the retained complex natural properties of the source cells. These biomimetic nanoparticles provided great promise applied in efficient photothermal therapy, photodynamic therapy, chemotherapy and immunotherapy.

Theranostic Nanoplatform. Prof. Cai's group developed various theranostic nanodrug systems. NIR fluorescent ICG dye–doped lipid–polymer nanoparticles were constructed for tumor diagnosis and targeted imaging (ACS Nano 2013, 7(3), 2056–2067; ACS Nano, 2014, 8(12), 12310–12322; ACS Nano 2016, 10, 10049–10057). As one of the most promising theranostic optical nanomedicine, organic dots with aggregation–induced emission (AIE dots) are biocompatible nanoparticles with a dense core of AIE fluorogens (AIEgens) and protective shells. Aptamer–anchored AIE–dots has been developed to combine the diversity of aptamers with the rich category of AIEgens (CCS Chemistry, 2019, 1(3), 251–260). Different imaging probes, such as MRI contrast agents (T1 and T2 agents), fluorescent nanotags have also been developed in order to facilitate gaining information about the trafficking pathway, kinetics of delivery, and therapeutic efficacy (Anal. Chem. 2019, 91(11), 6996–7000; Chem.–Asian J. 2019, 14 (6), 770–774).

Nano–immunotherapy. Immunotherapy is revolutionizing the treatment of cancer. In recent study of Prof. Cai's group, human serum albumin was hybridized with hemoglobin by intermolecular disulfide bonds to develop a hybrid protein oxygen nanocarrier with chlorine e6 encapsulated (C@HPOC) for oxygen self–sufficient photodynamic therapy (PDT). Immunogenic PDT could destroy primary tumors and effectively suppress distant tumors and lung metastasis in a metastatic triple–negative breast cancer model by evoking systemic anti–tumor immunity (ACS Nano 2018, 12, 8633–8645; Biomaterials 2018, 177, 149–160). On the other hand, the unnatural cyclooctene (BCN) modified sugar (Ac4ManN–BCN) that can incorporated into surface glycans of various tumor cells were designed. This artificial targeting strategy can improve tumor–targeting ability by overcoming tumor heterogeneity (Small, 2019, 15, 1804383). Moreover, a "safe, efficient and universal" technique were developed based on bioorthogonal chemistry and glycol–metabolic labeling for viral–mediated engineered T cell manufacturing (Adv. Funct. Mater. 2019, 29, 1807528). In this strategy, the functional azide motifs were anchored on T cell surfaces via the intrinsic glycometabolism of exogenous azide–glucose. The complementary functional moiety dibenzocyclooctyne (DBCO)/–conjugated PEI1.8K (PEI–DBCO) was coated on the lentiviral surface, which strengthened the virus–T cell interaction through DBCO/azide bioorthogonal chemistry.

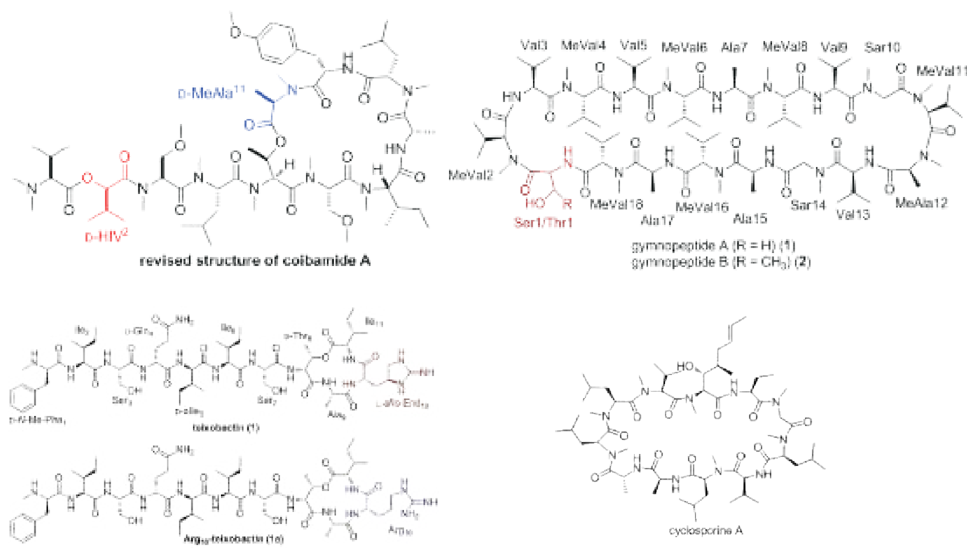


2 Peptides

Peptides, historically defined as polypeptides having 2–50 amino acids, play critical roles in human physiology, acting as hormones, neurotransmitters, growth factors, and antibacterial agents, inter alia. They have profoundly impacted the development of the modern pharmaceutical industry and have contributed significantly to the advancement of biological and chemical science. Basic studies in the first half of the 20th century aimed at exploring the structures and physiological role of peptide hormones such as insulin, oxytocin, gonadotropin–releasing hormone, and vasopressin have catalyzed many major advances in pharmacology, biology, and chemistry as well as other enabling technologies essential for what we now know as modern drug discovery.

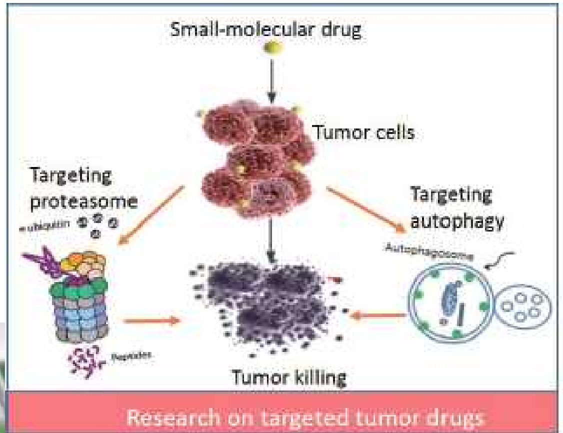
Peptides have gained increased interest as therapeutics during recent years. More than 60 peptide drugs have been approved worldwide, with several achieving significant market success, and several hundreds of novel therapeutic peptides are in preclinical and clinical development. Given their attractive pharmacological profile and intrinsic properties, peptides represent an excellent starting point for the design of novel therapeutics and their specificity has been seen to translate into excellent safety, tolerability, and efficacy profiles in humans. This aspect might also be the primary differentiating factor of peptides compared with traditional small molecules. Furthermore, peptide drugs are typically associated with lower production complexity compared with protein–based biopharmaceuticals and, therefore, the production costs are also lower, generally approaching those of small molecules. Thus, in several ways, peptides are in the sweet spot between small molecules and biopharmaceuticals.

There has been sustained interest in cyclic peptides as new modalities in medicinal chemistry research. In fact, macrocyclic peptides belong to the most attractive drug candidates, because they often combine highly favorable “drug–like properties”, such as a large surface area, high binding affinity, high activity, and target selectivity, improved stability in biological fluids, and cell permeability. We have an experienced research group focusing on the total synthesis, chemical modification and structure–activity relationship studies of naturally occurring bioactive cyclopeptides, such as coibamide A, gymnopeptides A and B, teixobactin, cyclosporin A and etc. We are also interested in the mechanism of biological activity of these peptides. We believe that the future development of peptide drugs will continue to build upon the strengths of naturally occurring peptides, with the application of traditional rational design to improve their weaknesses, such as their chemical and physical properties. We also expect that emerging peptide technologies, including multifunctional peptides, cell penetrating peptides and peptide drug conjugates, will help broaden the applicability of peptides as therapeutics.



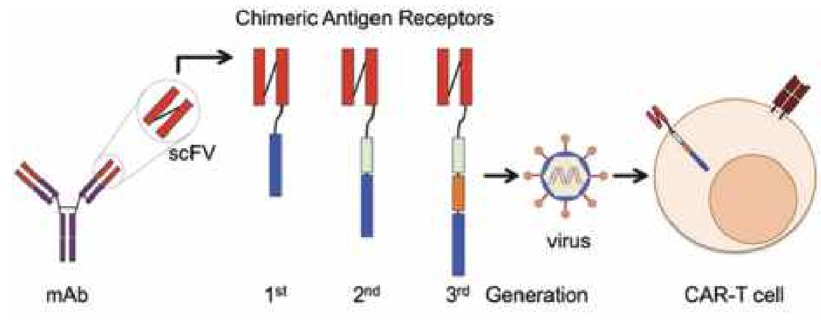
3 Protein and Cell-based Drugs

In 2011, Professor Xiaochun Wan established the Center for Protein and Cell-based Drugs in SIAT. The aim of the research center of protein and cell medicine is to develop self innovative protein medicine and cellular medicine for clinical diagnosis and treatment of malignant tumors, inflammation and autoimmune diseases, by using fully human monoclonal antibody technology with completely independent intellectual property rights and world-class immunocytotherapy technology, so as to enhance the competitiveness of China's biomedical industry.



Research on targeted tumor drugs


Recombinant human sDR5-immunoglobulin Fc (sDR5-Fc, code name: AS1501) fusion protein



China has the world's largest population of patients with hepatitis, and liver failure caused by hepatitis B virus infection is the most common cause of death of liver diseases in China. In western countries, excessive use of acetaminophen is the main cause of acute liver failure. At present, there is still a lack of effective therapeutic drugs for hepatitis, especially those with liver failure. Therefore, it is of great practical value and social significance to develop new drugs for the treatment of hepatitis and liver failure with high efficacy and low toxicity. Since cell death plays a fundamental role in almost all types of liver diseases, targeting apoptosis and necroptosis has become one of the major research directions for the treatment of liver diseases. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is one of the most important apoptotic molecules in humans and plays an important role in the initiation and development of various hepatitis. Death receptor 5 (DR5) is the TRAIL receptor with the highest affinity, and a soluble form of DR5 (sDR5) exists naturally, which can bind TRAIL, but cannot transmit signals, thus blocking TRAIL-mediated apoptosis. Prof. Wan's group produced a recombinant human sDR5-immunoglobulin Fc (sDR5-Fc, code name: AS1501) fusion protein, and studied its pharmacology, safety, pharmacokinetics, efficacy and mechanisms in mice, rats and cynomolgus monkeys. The results have proven that AS1501, as the first pharmaceutical TRAIL blocker, is safe and effective for the treatment of TRAIL-driven hepatitis or liver failure. The clinical study of AS1501 was approved by the State Drug Administration in November 2019.

Innovation System

Research

8 Affiliated Institutes

57 Research Centers

104 Labs

Education

Shenzhen Science and Technology University, CAS

Maker Institute

38 Joint Educational Cooperation

Capital

2 Angel Fund

3 Venture Capital

1 Merger Fund

Industry

3 Incubation Bases

1853 Spin-offs

365 Shareholding Enterprises

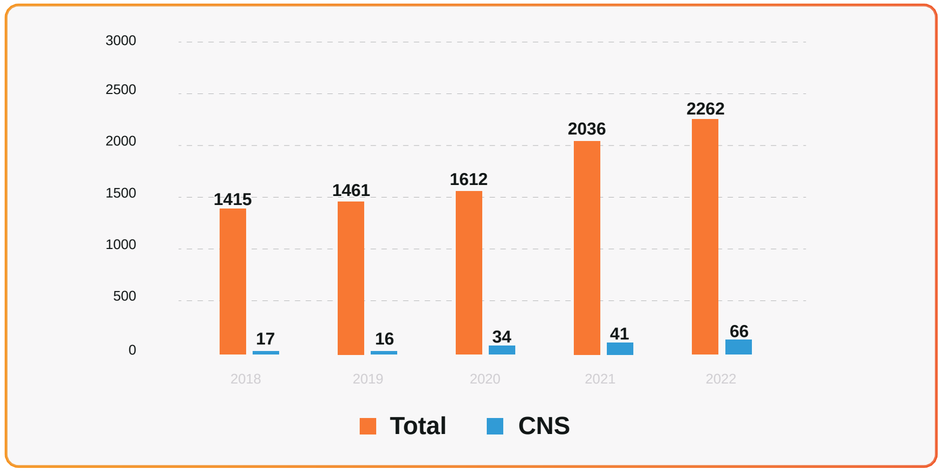
Figures and Facts

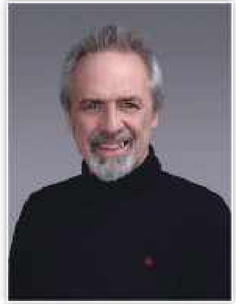
228 CNS(Nature\Science\Cell) and its series

45.2% of the published papers are the result of international cooperation

77 scholars made it to the “World's Top 2% Scientists 2023” (jointly released by Stanford University and Elsevier)."

PUBLICATION





John Speakman
United Kingdom

Horst Vogel
Switzerland

Diana Boraschi
Italy

Chinese Government Friendship Award (2020~2022)

156 Full-time national-level talents

24 NSFC Foreign Scholars Fund

176 CAS-PIFI Fellow

811 Returnee Employees (35%)

119 International Students

Advanced Biofoundry Shenzhen

"Advanced Biofoundry Shenzhen" is one of the key projects for the priority launch and layout of Shenzhen Science City. It is invested and constructed by the Shenzhen Government. Shenzhen Institutes of Advanced Technology, CAS is the lead unit for its construction, with the participation of Life Science Research Institute of BGI and Shenzhen Second People's Hospital. It aims to create a two-in-one synthetic biology research platform for the "cloud lab" of users and the "smart lab" of operators. It is not only open to the academic community, but also open to the industry.

Synthetic biology is an emerging interdisciplinary subject based on life sciences, engineering, information science and other quantitative basic sciences. Multiple research directions include bio-functional molecular synthesis, gene line synthesis, metabolic pathway synthesis, gene combination, primordial cell synthesis, multicellular systems, synthesis of non-natural elements, simulation of living systems and etc. The research goal is to use engineering design concepts to design, transform and even re-synthesize organisms to create artificial life bodies, that is, synthetic life. Synthetic biology is thought to bring the third biotechnological revolution following the "DNA double helix discovery" and the "human genome sequencing project".

The high complexity of synthetic living organisms determines that it still requires a large number of engineering trial and error experiments, that is, the closed loop of "design-synthesis-test-learn" needs to be completed quickly, at low cost, and in multiple cycles, ultimately achieving rational and predictable synthesis by design. This goes far beyond the scope of traditional labor-intensive research methods and requires a transformative research platform and approach. Based on this fundamental need, the major technology infrastructure for synthetic biology research will provide a basic research platform that combines rational design with engineering trial and error.

The key construction contents of Advanced Biofoundry Shenzhen include three platforms: design-learn platform, synthetic testing platform, and user testing platform.

The design-learn platform utilizes biological information, mathematical models, biosynthetic big data and artificial intelligence to provide experimental solutions for specific scientific needs, and to generate executable instructions for synthetic test platforms. Software tools and databases are mainly based on independent research and development.

The synthetic testing platform is mainly composed of five major systems, including large fragment DNA (assisted by Life Science Research Institute of BGI), phage, bacteria, yeast, and higher animal cell synthesis engineering system (assisted by Shenzhen Second People's Hospital). It will perform specific functions as a "function island" by building an automation module and achieve flexible integration of various types of "production lines" based on different demands.

The user detection platform integrates protein and metabolite analysis, chassis cell amplification cultivation, and advanced imaging three detection systems, to perform multi-modal cross-scale comprehensive testing of the synthesized products.

Large-Scale Scientific Facilities

Shenzhen Infrastructure for Brain Analysis and Modeling

Brain science is widely considered as one of the last frontiers of human knowledge and scientific research. According to the data from the WHO, diseases of the nervous system are one of the major disease categories that have cost our society a huge amount of financial and social resources. Nonetheless, therapeutic interventions for many brain disorders, such as autism, anxiety disorder, and Alzheimer's disease are still scarce. To promote brain science research and to develop new therapeutic solutions for brain disorders, the Shenzhen Municipal Government has started a new initiative to build the Shenzhen Infrastructure for Brain Analysis and Modeling. The initiative was proposed and led by Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences and other participating institutions include Southern University of Science and Technology, Hong Kong University of Science and Technology-Shenzhen Research Institute, Peking University Shenzhen Graduate School, and Shenzhen Institute of Neuroscience. The goal of this initiative is to build a world-class research facility for brain science and technology. The infrastructure is focused on supporting basic and clinical research for five major brain disorders: Alzheimer's disease, autism spectrum disorder, depression, stroke, and dyslexia.

The infrastructure features three modules: Brain Editing, Brain Analysis, and Brain Modeling. The Brain Editing Module will use technologies such as the CRISPR system to develop genetically modified brain disease models using multiple organisms, including rodents and monkeys. The Brain Analysis Module will employ a comprehensive set of analysis tools and technologies to probe phenotypic features of animals models for various brain disorders. And at last, the Brain Modeling Module will use true neurosignals to assist the development of artificial intelligence. The three modules will include state-of-the-art equipment including high field MRI, PET-MRI, PET-CT, VISoR for high-speed whole brain imaging, two-photon miniature microscope, gene-editing facilities, advanced facilities for rodents and non-human primates, etc. The infrastructure will be open to all scientists around the world with the goal to attract scientists from China and worldwide to tackle some of the most challenging topics in brain science and brain disorder research.

The initial proposal of the infrastructure was approved by the Development and Reform Commission of Shenzhen Municipality on Apr. 28th, 2018. The city will invest a total of 1 billion RMB to build the brain infrastructure. The infrastructure is located in Guangming District and will serve as one of the key components of the Guangming Science Park, an integrated national science center. The brain infrastructure is designed by Tongji Architectural Design Group and is currently under construction. The infrastructure is expected to start to provide service in late 2021.

中科创客学院
Maker Institute, CAS

中科创客学院
Maker Institute, CAS

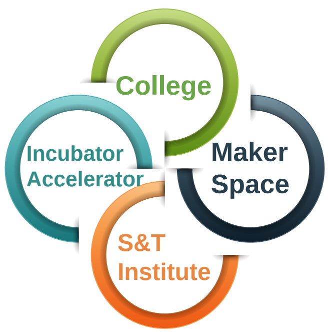
Maker Institute

Education
- Stimulation
- Mining
- Training
- Practice

Communication
- Salon
- Demo Day
- Competition

Support
- Technology
- Projects
- Service
- Capital

Incubation
- Projects Cultivation
- Start-ups Incubation



New Type of Maker Space

Professional mentorship of innovation and business.

Networked cooperation in research and education.

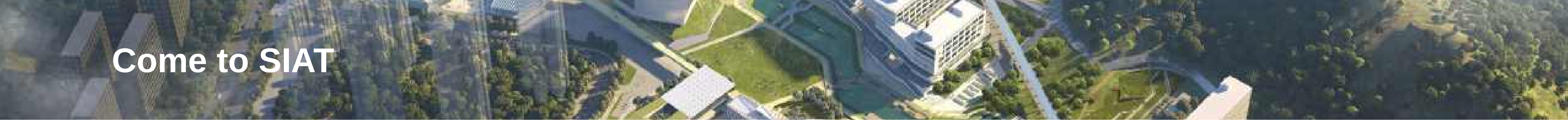
One-stop maker ecosystem like tadpole to frog.

Scientific resources of CAS develop Maker projects.

It is an ‘institute’ with no walls nor limit. Hope it will continue to spread the cultivation mode and to put out more energies with innovation and enterprise.

—— Prime Minister of PRC, Li Keqiang
Oct.19, 2015


Come to SIAT



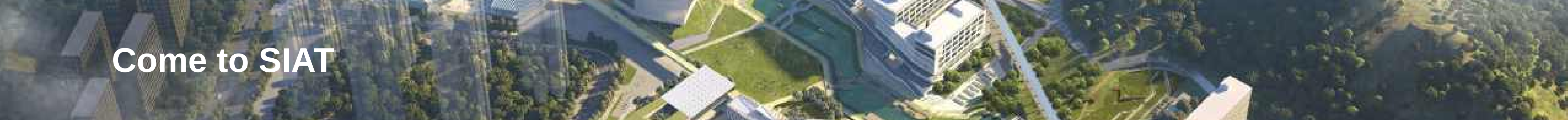
Come to SIAT

English is OK!

Many of SIAT's laboratories are completely bilingual with Chinese and non-Chinese scientists and technical staff working side by side to achieve common goals, and most scientific seminars are given in English. SIAT also offers a bilingual administrative environment that provides needed information in a timely fashion in both Chinese and English. Rest assured, you will be able to succeed in your research and enjoy life in China even if you don't speak the language when you arrive.

Friendly bilingual staff are on-hand at SIAT to provide information and support to help researchers deal with healthcare, housing, childcare and schooling, and the practical issues of daily life.

To help researcher focus on their work without having to worry about bringing their children off-campus, SIAT offers special leave, for caring for sick children or other family members.

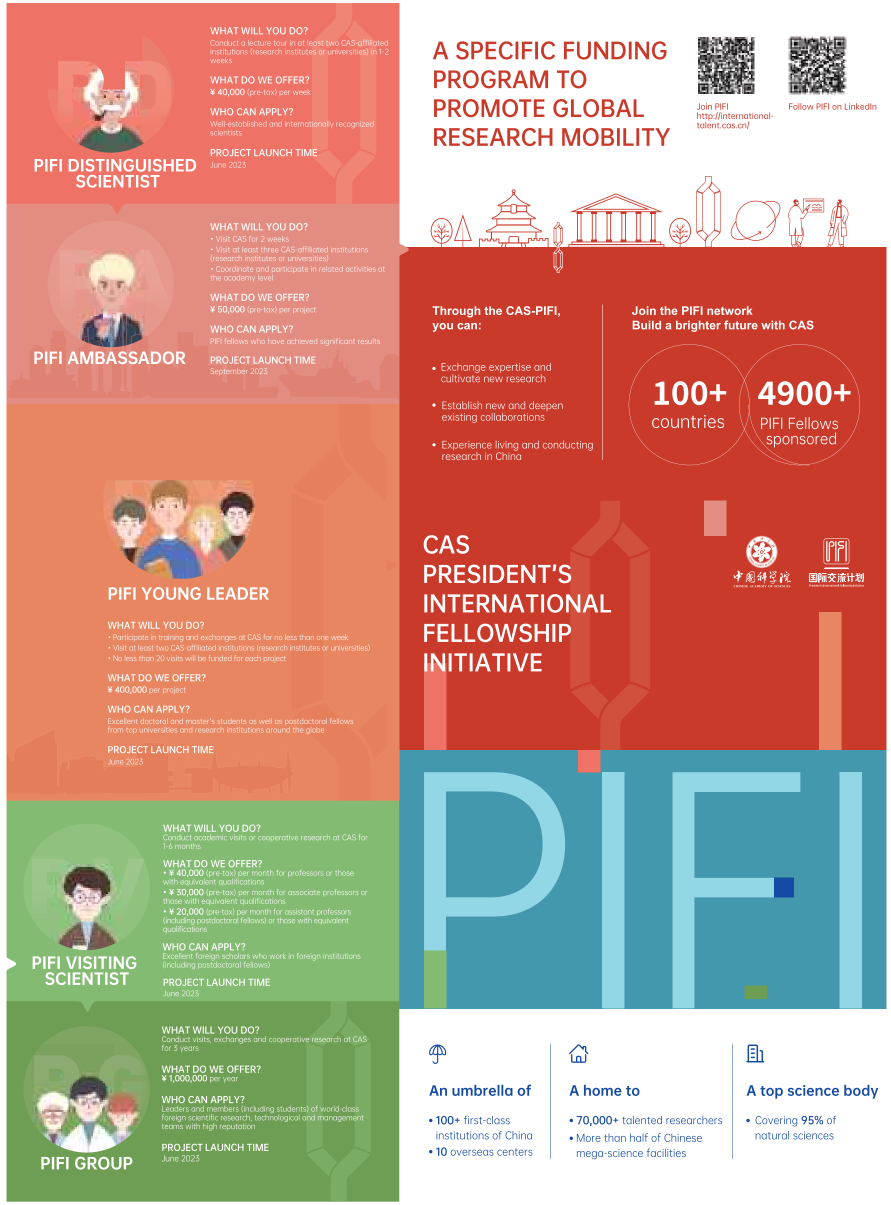


Come to SIAT

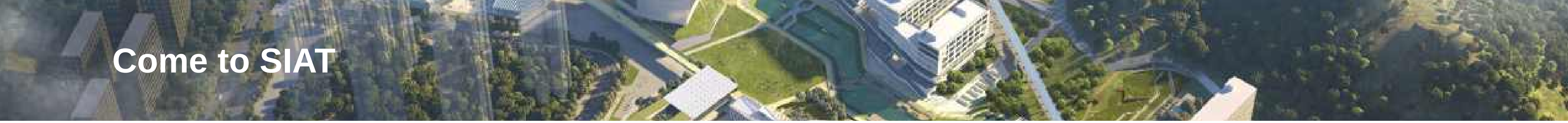
The CAS President's International Fellowship Initiative, PIFI, is a specific funding program to attract talented foreigners to CAS for scientific exchanges and research cooperation. It is open to scientific research personnel from around the globe, of the following seven types:

For more information, you can go to:
http://international-talent.cas.cn/front/pc.html#/bicsite/home

a specific funding program that attracts talents
from around the globe to CAS for
scientific exchanges and research cooperation



Come to SIAT



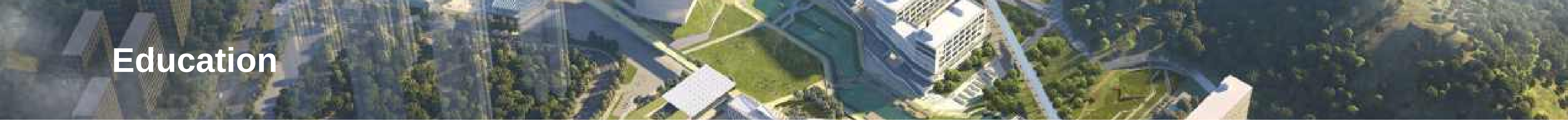
Oluwarotimi Williams SAMUEL, joined SIAT in January 2015,and commenced his research work under the supervision of Prof. Li Guanglin at the Center forNeural Engineering, SIAT. Now he is a Postdoctoral Research Fellow courtesy of the CAS–PIFI program.

He obtained the Outstanding Youth Fund of SIAT in 2019

Quentin Montardy, arrived in China from Europe (France) as a young post–doc, obtain the CAS–PIFI in 2017. “after a few years, I was able to begin to play the role I had set for myself: that of helping to build strong bridges between the scientific institutions of several countries. Obviously, this was the case with France and its prestigious institutions, the CNRS and INRA, and also with Australia.” he said.

Quentin was giving a lecture to the research scholar at SIAT in 2019.

Education



Education

1.Introduction to UCAS

University of Chinese Academy of Sciences (UCAS) is a university established with the approval of Ministry of Education of PRC, focusing on graduate education. Its predecessor was the Graduate University of Chinese Academy of Sciences (GUCAS), the first graduate school in China. It boasts many firsts in new China: the first doctorate in science, the first doctorate in engineering, the first female student awarded a doctoral degree, and the first research student awarded double doctoral degrees in China all graduating from this university.

2.Introduction to UCAS-Shenzhen

SIAT was authorized as a school campus for the graduate programs of UCAS since 2010. It has 328 tutors with international perspectives and excellent scientific research experiences and has cultivated more than 7000 graduates from 15 countries covering the fields of computer science and Technology, Control Science and Technology, Biology, Chemistry. SIAT focuses on training international and interdisciplinary talents with academic, innovation and entrepreneurship capabilities.

3.Majors

PhD and Master Programs in SIAT	
PhD	• Chemical Biology • Chemistry and Physics of Polymers • Physical Chemistry
	• Biochemistry and Molecular Biology • Microbiology • Neurobiology
	• Pattern Recognition and Intelligent Systems
	• Computer Applied Technology
	• Optical Engineering
Master	• Chemical Biology • Chemistry and Physics of Polymers • Physical Chemistry
	• Biochemistry and Molecular Biology
	• Pattern Recognition and Intelligent Systems
	• Computer Applied Technology
	• Optical Engineering

4.Contact info for international graduates enrollment

Email: yjsb@siat.ac.cn zf.qian@siat.ac.cn

Main Network Partners		
MIT	EPFL	Hanyang University
Stanford	CSIRO	Ben-Gurion University
University of Pennsylvania	Kyoto University	United Arab Emirates University
University of Manchester	Osaka University	CUHK
Goethe University Frankfurt	National University of Singapore	Hongkong University
INRA,France	Nanyang Technological University	Macau University

Affiliated Institutes

Institute of Advanced Integration Technology

Director: LI Guanglin
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Shenzhen Institute of Advanced Integration Technology (SIAIT) is one of the sub-Institutes at the Shenzhen Institutes of Advanced Technology (SIAT), Chinese Academy of Sciences (CAS). As the first sub-Institute of SIAT, SIAIT was jointly established by the CAS, the Shenzhen Municipal Government, and the Chinese University of Hong Kong in 2006. Currently, SIAIT includes 11 Research Centers/Labs and has 18 full professors, 37 associate professors, 140 staffs, and 309 graduate students and 9 foreign students. SIAIT concentrates on three main scientific research fields, Medical robotics and rehabilitation engineering, Human-Machine Interactions and Control, Intelligent Manufacturing and Energy Materials.

Institute of Biomedical and Health Engineering

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The Institute of Biomedical and Health Engineering (IBHE), established in August, 2007, is one of the largest research units in the area of biomedical engineering in China. IBHE focuses on the research and development of advanced diagnostic imaging systems, intelligent therapeutic biomedical devices, and innovative low-cost healthcare technologies. As a renowned research center in biomedical and health engineering, IBHE strives to accomplish breakthrough in strategic areas of medical imaging, neural engineering, micro-/nano-medical devices, mobile healthcare, bioinformatics and biomaterials. Our ultimate goal is to stimulate the modernization of clinical medicine, and to facilitate the excitingly fast growing of medical device industry.

Institute of Advanced Computing and Digital Engineering

Director: LI Ye
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Institute of Advanced Computing and Digital Engineering (IACDE) is dedicated to the advancement of basic theory, computational technology, software engineering, and the applications of digital engineering in social information services. IACDE strives to become a leader in basic and applied research, an interdisciplinary educational base for nurturing innovators with versatile skills, and a laboratory that generates advanced technologies with commercialization potentials.

IACDE consists of ten research centers and laboratories. Research scientists at IACDE are organized into three levels consisting of academicians, leading professors in various groups' research, and creative professors. And each scientific research group has a number of research scientists and research staff.

IACDE is equipped with a most advanced computing facility, including thousands of processor cores and petabytes of data storage. It also has access to the facility of National Supercomputer Center in Shenzhen.

Institute of Biomedicine and Biotechnology

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Institute of Biomedicine and Biotechnology (IBB), which was established in 2013, is oriented by clinical translation demand and industrial applications, and aims for the innovative solution to major diseases. The institute aims at seeking breakthroughs in core and cutting-edge technologies and innovative drugs development, creating first-class talents echelon formation, and deepening the regional biomedicine economy and clinical applications and benefiting people's health. In the coming future, the mission of IBB is to build a first-class scientists' studios and R&D team for biomedicine and biotechnology, and to develop international cooperation, therefore promoting the integration of production, teaching and research.

Affiliated Institutes

Institute of Brain Cognition and Brain Disease

Director: WANG Linping
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The Brain Cognition and Brain Disease Institute promotes collaboration between the Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences and scientists at the McGovern Institute at MIT. BCBDI focuses on brain cognition and brain disease, including Mechanisms underlying brain disorders, Neural basis of cognition and behavior, New tools and technology for brain research, Translational research: brain disease models for drug discovery.

Institute of Advanced Electronic Materials

Director: SUN Rong
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In 2006, a small group headed by Prof Sun Rong founded the Center of Advanced Material Research (CAMR) at SIAT. The center is dedicated to developing advanced electronic materials including polymeric materials, electronic packaging and interconnect materials, interfacial adhesions, nano–functional material syntheses and characterizations, materials interface, information photonics and energy mate–rials, both for fundamental researches and industrial applications. In 2012, CAMR established the Advanced Electronic Packaging Materials Innovation Team of Guangdong Province, led by Prof. Ching–Ping Wong, who is Member of US National Academy of Engineering, Foreign Academician Member of Chinese Academy of Engineering, IEEE Fellow and Founding Member of The Hong Kong Academy of Sciences. This team focuses on developing key materials for the IC high density 3D wafer level and system–in package technologies. After a decade of efforts, the group has grown up to 242 by the end of 2019, consisting of Academicians, Profes–sors, Researchers, Engineers, PhD and Master students. The center has become Member of the “National Engineering Laboratory for Advanced Electronic Packaging Materials” and renamed as Institute of Advanced Electronic Materials (IAEM).

Institute of Synthetic Biology

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Institute of Synthetic Biology (iSynBio) was launched in 2017, focusing on recon–struction of artificial life components, gene circuits, biological devices, and multicel–lular systems, and ultimately dedicated on deciphering the essence and fundamental laws of life. iSynBio has developed to be a young, dynamic, multi–disciplinary, and innovative team.

Institute of Technology for Carbon Neutrality

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Institute of Technology for Carbon Neutrality was launched in 2021 with committed to promote China’s energy revolution. The institute maily focuses on different aspects of carbon neutral areas, including renewable energy (solar energy, hydrogen power, thermal energy, fuel cell), energy storage (power battery, grid energy storage technology, hydrogen storage technology), smart city energy (energy internet, vehicle to grid and shared energy storage, smart multi–energy complementary system), carbon dioxide capture and conversion (efficient capture and conversion, real–time monitor), carbon neutral economy and urban development (low–carbon and carbon–free energy supply, low–carbon industrial chain, carbon neutral policy, carbon absorption and ecological cultivation, compensation and incentive mecha–nism).

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Thank you for your care and interest in SIAT!
Given that SIAT publishes thousands of research papers, it is a pity that we cannot present them all here in this brochure.

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More details about specific research center and laboratories can be found here:
http://english.siat.cas.cn

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