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CHINA LOOKS WEST

Chinese pharma chemical industry seeks greater global role

AUGUST 2015

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China's Pharma Chemical Industry: Ambitions, Challenges, Opportunities

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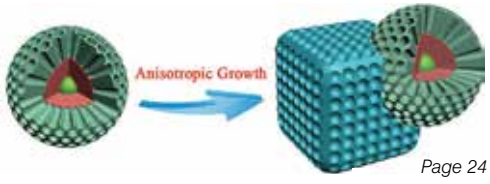

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PUBLISHER'S NOTE

China Looks West

IN THIS, OUR THIRD C&EN supplement for 2015, we are taking a different approach by focusing on a country whose role and influence in the global chemistry enterprise just keep intensifying—China. It should come as no surprise that both the quality and volume of Chinese research are growing at a remarkable rate.

We see this in the contributions from Chinese researchers in the pages of American Chemical Society journals and in the growing prominence and prestige of Chinese technology organizations, including the likes of Shanghai Fosun Pharmaceutical Group, which has proposed to merge with U.S.-based biotech company Ambrx. I have also been struck by the rapid growth of organizations and outreach of organizations such as WuXi AppTec and BGI (formerly the Beijing Genomics Institute), both of which have acquired American companies in the past couple of years to expand their technological capabilities and global footprint.

The theme of this supplement is "China Looks West"—a close look at the state of the pharmaceutical chemical industry in China, with a view to understanding how Chinese companies are raising their profiles and growing their businesses in high-value markets in North America, Europe, and elsewhere. Under the guiding hand of Maureen Rouhi, Director of Editorial & Business Development for C&EN in Asia, we have commissioned articles—from a European fine chemicals expert and from Chemical Abstracts Service—that shed some fascinating light on the current state of the pharmaceutical enterprise in China. Maureen provides a nice summary of the contents on page 3. We believe this supplement will be of interest not only to regular subscribers of C&EN but also to attendees at upcoming events in the U.S., Europe, and Asia, where it will have bonus distribution.

In addition to acknowledging Maureen, who served as managing editor for this issue, we thank C&EN's Digital Production Manager Renee Zerby and her team for production and Web Analytics Manager Senol Akay for helping to gather the most popular pharma-related papers authored by Chinese groups in ACS journals over the past 12 months.

We are already gearing up for our next supplement—The Top 20 Drugs in the Pipeline—which will be published in September. If you are interested in participating in future C&EN supplements or any of our print, digital, or lead-generation media offerings, please visit the C&EN media site at http://acsmediakit.org/.

Best wishes,

Kevin Davies PhD
Publisher, C&EN
Email: k_davies@acs.org

For the record: The editorial content in this supplement was created without direct involvement of C&EN reporters or editors, with the exception of the articles reprinted from C&EN.

CHINA'S SUMMER ROLLER COASTER

A. Maureen Rouhi, Ph.D.

THE EARLY WEEKS of summer saw the Chinese stock market tumbling, obliterating more than $3 trillion in value in the final days of June. The Chinese government pulled no punches in implementing measures to halt the free fall, and as of mid-July the efforts seemed to be having the intended effects. Many investors were shocked and angry, but the debacle is unlikely to derail China's growing ambitions to be a global leader in many areas, including the pharmaceutical industry.

That ambition is the central theme of this C&EN supplement: China Looks West.

The cover story describes the changing pharmaceutical chemical landscape in China and the challenges Chinese companies face, not only in raising the quality of products but also in expanding capacity to serve both global and local markets. They include the long-standing criticism by Western pharma chemical trade groups of unscrupulous Chinese producers making substandard, sometimes dangerous, products. These challenges in turn present opportunities for businesses and service providers that can help Chinese companies make the investments to improve R&D, regulatory compliance, processes, and plant design.

Complementing the cover story are contributions from the American Chemical Society's publication and information services. One article describes trends in Chinese patents in the pharmaceutical arena. China's global pharma ambitions are supported by robust development of intellectual property (IP), as revealed by the databases of our colleagues at Chemical Abstracts Service. The data reveal the areas of strength of Chinese IP in the pharma field. Patent readers will also appreciate the addition of PatentPak in SciFinder. The new module reduces the time it takes to get to the chemistry in patents.

Rounding up the content are trends in Chinese pharma-related research in the journals of the American Chemical Society, as well as stories first published in *Chemical & Engineering News* about Chinese higher education also "looking West"—adopting Western models of higher education—to raise innovation.

The Scene From Shanghai

Even as Chinese stock prices were sinking in June, the mood at CPhI China 2015 (June 24–26) was positive. According to the organizer, UBM Sinoexpo, the convention in Shanghai attracted some 2,700 exhibitors, up 5% from last year, and almost 30,000 visitors, up 2% from 2014. The event featured three national pavilions, with Russia joining Korea and India for the first time.

CPhI China is an ideal event for a quick look at the pharma chemical landscape of the country: lots of producers of active pharmaceutical ingredients and intermediates, but only a few with products that can be sold to the highly regulated Western markets. As this supplement suggests, however, it is only a matter of time before Chinese pharma chemical producers raise their game and increase their share of high-value markets. The Chinese government is helping by, among other things, fostering innovation.

Coincidentally, in mid-July the McKinsey Global Institute released a preview of "The China Effect on Global Innovation," a research bulletin to be published in full later this year. It concludes that China has "the potential to become a global innovation leader," given the investments the country has made in R&D and education.

UBM Sinoexpo

Show Time
The opening ceremony of CPhI China 2015, in Shanghai, concluded with a shower of confetti.

"Chinese innovators are not waiting," the report says. "They are trying to do things differently by leveraging China's scale and speed advantages in scientific research and filling talent gaps. They are attempting to defy convention about how to do science. If they succeed, they may offer lessons for companies around the world that depend on science-based innovation."

Similarly, this supplement suggests advances ahead for the pharma chemical producers, custom manufacturers, and contract research organizations in China. More than ever, industry players are aware of international standards of product quality they must meet, the level of customer service they must provide, and the quality of business relationships they must cultivate to achieve recognition as quality and trustworthy domestic suppliers as well as global players. There will be bad actors, to be sure, but their numbers will quickly diminish as government regulations are strictly enforced and demand for good-quality, safe, and effective pharmaceuticals continues to rise.

A. Maureen Rouhi is director of editorial and business development for C&EN in Asia. She served as the managing editor of this supplement. ■

PHARMACEUTICALS LEAD CHINESE PATENT APPLICATIONS IN 2014

Matthew J. McBride & Roger J. Schenck, Chemical Abstracts Service

CHINESE PATENTING ACTIVITY has been growing at a staggering rate. Since 2004, patent applications reported by the **State Intellectual Property Office of the People's Republic of China**, also known as the Chinese Patent Office, have been increasing at an annual rate of more than 25%. That is the highest growth rate among the world's five major patent offices—the other four are the patent offices of the U.S., Europe, South Korea, and Japan—covered by Chemical Abstracts Service (CAS). Altogether CAS analyzes and indexes patents from 63 authorities in its databases.

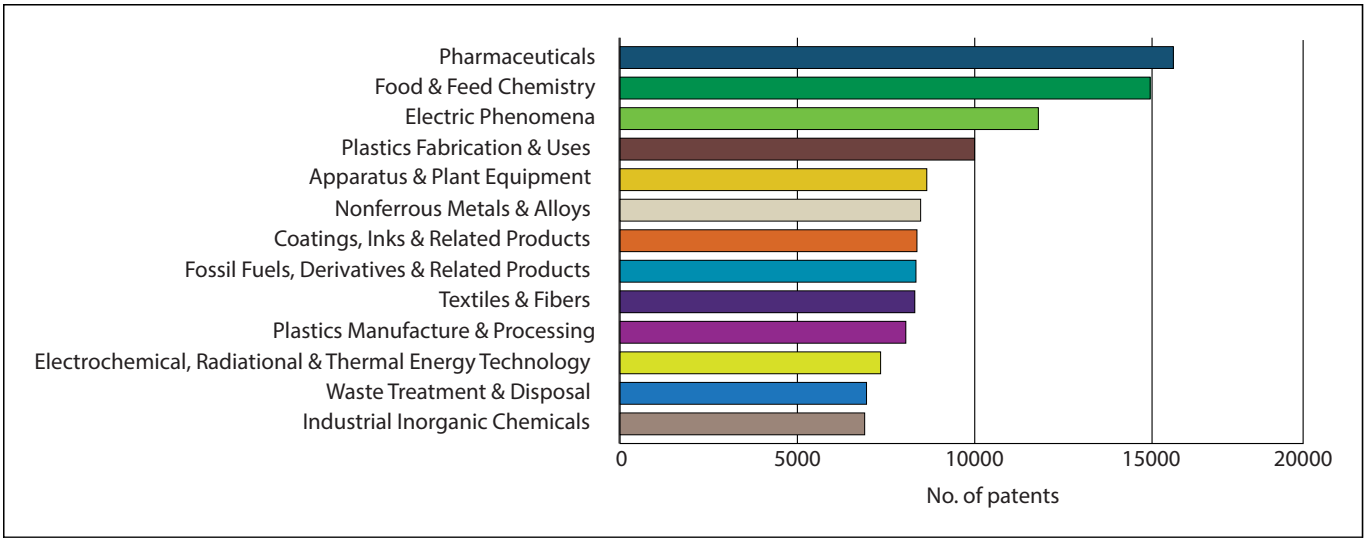
Patent publications, as covered by CAS, show that the top three areas of Chinese intellectual property (IP) activity in 2014 were pharmaceuticals, electric phenomena, and food and feed. As the largest consumer of energy in the world, China's electricity consumption doubled over the 7-year period ending in 2013 and has shown few signs of slowing. Information in the CAS databases shows that IP concerning fuel cells, insulators, and rare-earth resource impacts were among some of the drivers behind patenting activity about electric phenomena.

For a country as large as China, it is not surprising that patents in pharmaceuticals, food, and feed lead the charge. The Chinese government must ensure that the country's vast population is both well-fed and healthy, and it likely heavily supports research that helps achieve those goals. That research is reflected in Chinese patent application activity.

ChemPartner

Prolific Researchers
R&D in China is yielding many pharmaceutical patents.

Of the patent applications submitted to the 63 patent authorities covered by CAS databases, 50% of the pharmaceu-

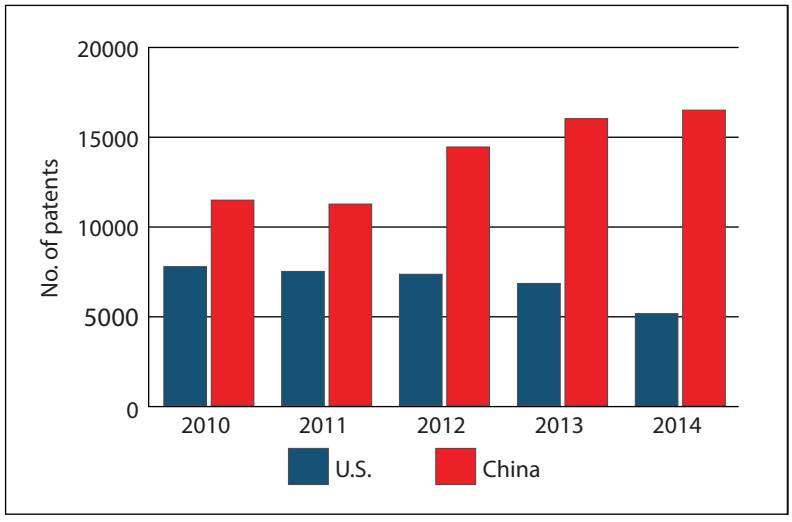


2014 Chinese patents by chemistry category

NOTE: Chinese patents appeared in 80 categories; only those with at least 6,000 patents are shown.
SOURCE: CAS

ticals and drug-related applications in 2014 came from China. Growing steadily from nearly 11,500 pharmaceutical-related patents in 2010 to more than 16,500 last year, China's activity in this patent field is outpacing that of all other patent authorities, including the U.S.'s. Overall, the number of Chinese pharmaceutical patent applications is growing year-over-year, whereas that of the U.S. is declining. Many factors likely contribute to this trend, including the outsourcing of research and development to China.

For Chinese pharmaceutical patents, the percentage of new substances disclosed relative to the total number of substances mentioned in patent documents averaged 11% in the period 2010-2014. For the same period, the corresponding average for U.S. pharmaceutical patents was 9%.



Chinese vs. U.S. pharmaceutical patents, 2010-2014
SOURCE: CAS

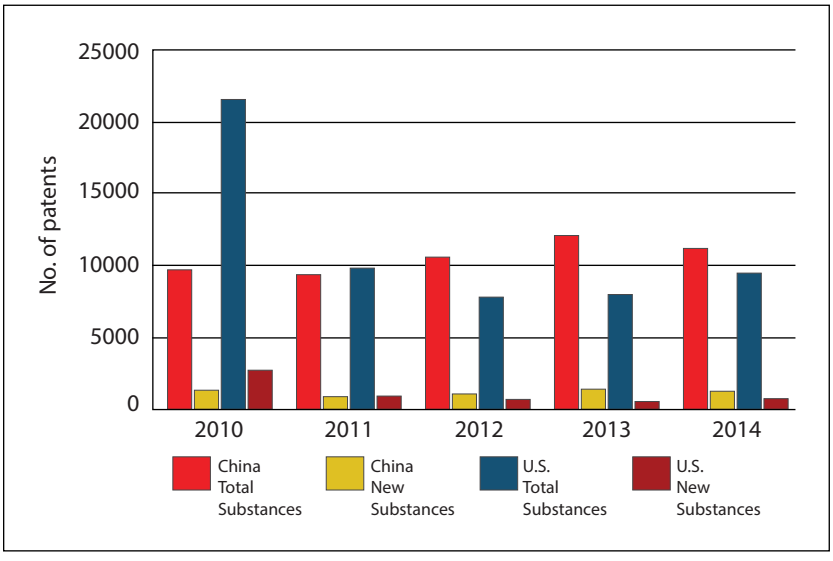
In CAS databases, pharmaceutical patents are categorized in eight subsections. Majority of Chinese pharmaceutical patents fall in the categories of biologics, pharmacognosy, pharmaceutics, formulation and compounding, and prosthetics and medical goods. Formulations and devices have been traditional strengths of Chinese pharmaceutical patents. Noteworthy in 2014 was a spike in the pharmacognosy area, which covers medicinal uses of natural products.

Most Chinese patent applications are in the area of formulation and compounding. These patents typically don't contain new chemical entities. Instead they cover new ways to deliver previously patented compounds to achieve the desired therapeutic effect more effectively than older formulations. This category includes combination therapies, which are formulations of two or more drugs that together increase the intended effect of each drug when administered separately. Also covered here are new therapeutic uses for known drugs.

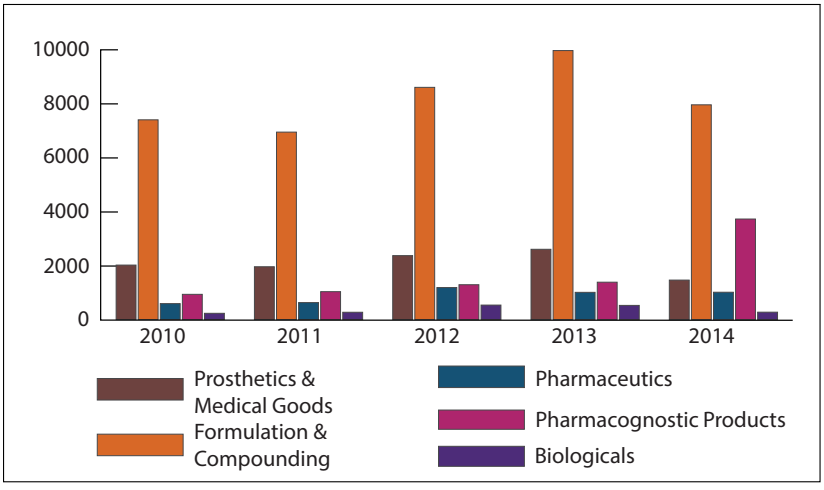
Pharmacognostic product patents focus on the medicinal uses of natural products and bioactive substances isolated from terrestrial plants and animals, as well as marine organisms. China has a long history of using traditional medicines. Some patents in the area show innovative therapeutic approaches based on integrating Chinese traditional medicines with Western drugs.

For example, a 2013 patent application from **Taicang Shengzhou Biotechnology Co.** claims a combination therapy (CN 103169807) as an effective treatment for B-cell lymphoma. The treatment combines the Western cancer drug suberoylanilide hydroxamic acid (SAHA, also known as Vorinostat) and a Chinese medicine extracted from the bark of the roots of *Sophora flavescens, Scrophularia ningpoensis,* and *Paeonia suffruticosa* plants. This combination inhibits the cancer at a higher rate than does SAHA or the Chinese extract alone.

The spongelike loofah, popularly used as a bath or kitchen scrubber, comes from a plant in the cucumber family (Cucurbitaceae) that has many uses. The spongelike material consists of the fibrous skeleton of the mature fruit that has been allowed to dry. The young fruit is popular as a food in many Asian countries, including China. Researchers at **Zonhon Biopharma Institute** claim that loofah seeds or seed capsules can be used to treat diabetes and its complications (CN 103181945). The inventors claim that



New substances vs. total substances in U.S., Chinese pharma patents, 2010-2014
SOURCE: CAS



Areas of pharma patenting in China, 2010-2014
SOURCE: CAS

the loofah seeds or seed capsules can reduce a patient's blood glucose levels. When loofah seeds or seed capsules are given to patients together with conventional diabetes drugs, the combination reduces blood glucose levels more significantly than can conventional diabetes drugs alone. Loofah seeds or seed capsules may also prevent patients with a genetic disposition for diabetes from developing the disease, the researchers suggest.

With so much pharmaceutical patenting activity occurring in China and elsewhere, finding the relevant chemistry can be time-consuming. Researchers worldwide often need quick access to the substances reported in the patents. CAS now provides a direct route to those substances in SciFinder, through PatentPak.

When a search in SciFinder brings up research disclosed in a patent, users have the option of going directly to the patent document, which is the traditional way. Now, they can gain access to the patent document through the PatentPak module in SciFinder. The module provides the user both the patent document and a list of substances mentioned in the patent and their respective locations in the document. Clicking on a substance on the list takes the searcher directly to the substance within the document.

With some patents consisting of dozens if not hundreds of pages, PatentPak enables searchers to significantly reduce their time spent studying patent documents by providing instant access to hard-to-find chemistry.

About the Authors

Matthew J. McBride *manages the Science IP ResearchTeam of Chemical Abstracts Service (CAS). The team comprises highly-trained scientists who are also expert patent searchers with specialized knowledge in many areas of science and technology.*

Roger J. Schenck *is the manager of the CAS Content Planning Department. He provides analyses and insights into CAS content to develop communications for CAS marketing.*

CAS is a division of the American Chemical Society and the world's authority on chemical information. The CAS team of highly trained scientists finds, collects, and organizes all publicly disclosed substance information, creating the world's most valuable collection of content that is vital to innovation worldwide. ■

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CHINA'S PHARMA CHEMICAL INDUSTRY WANTS MAJOR GLOBAL ROLE

Achieving the goal faces obstacles, but presents great opportunities

Roger LaForce, Ph.D., LaForce Business Solutions

CHINESE PHARMACEUTICAL CHEMICAL suppliers are poised for the next big step: They are now aiming to be major suppliers of active pharmaceutical ingredients (APIs) to the lucrative markets of the developed world. These ambitions could be stymied by the need to provide high-quality medicines to China's own population. The challenge for Chinese pharma chemical companies is to raise manufacturing capacity and quality simultaneously.

Selling products to the developed world would be far more profitable than supplying only the domestic market, a prospect not lost on Chinese pharma players. Manufacturers like **Zhejiang Hisun Pharmaceutical Co.** and **Zhejiang Huahai Pharmaceutical Co.** started supplying generic APIs to highly regulated markets years ago. Many others are getting in the act.

According to the IMS Institute for Healthcare Informatics, China is already the world's second largest pharmaceutical market, after the U.S. (1). But per-capita spending on pharmaceuticals in China is just 9% that of the U.S. and trails those of Japan, Canada, and the European top five: Germany, France, Italy, Spain, and the U.K.

Drug Master Files (DMFs) from Chinese suppliers now make up 13.7% of submissions to U.S. regulatory authorities, compared with 40.7% from Indian suppliers and 13.5% from U.S. suppliers; the rest comes from Canada, France, Germany, Israel, Italy, Japan, Germany, Spain, and Switzerland (2). However, Chinese submissions of Abbreviated New Drug Applications (ANDAs) for prescription generic drugs still lag far behind: only 15 from China in 2014, versus 1,430 from the U.S., 1,190 from India, and 290 from Europe (2).

Today, the Chinese pharma chemical industry is a key link in the global supply chain of medicines. China now dominates the supply of pharma chemicals in the Asia-Pacific region, except Japan, and in Europe and Russia. The country now ranks first in exports of generic APIs to Western Europe, with 34.1 % of the $3.56 billion market in 2014 (2).

The U.S. market for generic APIs—worth $4.98 billion in 2014—depends largely on imports of APIs and advanced intermediates. Italy used to supply up to 70% of generic APIs to the U.S., but its overall market share has plunged to 33%. India follows, with 22%; domestic U.S. suppliers, 16%; and Spain and China, each 12% (2). The rest comes from other foreign suppliers with slim market shares.

In Japan, China's market share of pharma chemicals is a measly 2% (2). Chinese producers have a great incentive to increase market share in both Japan and the U.S.

UBM Sinoexpo

Prominent Display

Fosun Pharma, a major exhibitor at CPhI China 2015, is one of many Chinese companies aggressively expanding in Western markets.

The Chinese government itself wants to raise the quality of China's pharma chemical enterprise. It is waging a campaign to raise quality and accountability across the healthcare infrastructure, including anti-corruption investigations of multinational pharma companies (3). The **China Food & Drug Administration (CFDA)** has been increasing its scrutiny of domestic manufacturing plants to raise manufacturing quality to the international standards. In addition, Chinese leaders want China to become a world leader in technology and innovation (4). No doubt, the government will provide the means for the Chinese pharma chemical industry to become a world-class player.

China's 2011-2015 five-year plan aimed to develop at least five pharma companies with annual sales of at least RMB 50 billion (about $8.05 billion) and at least 100 more with annual sales of at least RMB 10 billion (about $1.61 billion). Toward these goals, the government is encouraging companies to merge, acquire, integrate or consolidate to optimize the value chain and increase efficiency (5). These goals will not be achieved in 2015, but the groundwork has been laid to attain the results within the next five-year plan, 2016-2020.

For example, one of the top 20 Chinese pharma companies, **Shanghai Fosun Pharmaceutical Group Co.**, announced its intention to use acquisitions to expand overseas and to invest RMB 5 billion (about $805 million) in the next five years to develop drugs, Bloomberg reported last month (6). Accord-

Chinese pharma chemical suppliers dominate all major markets except those of the U.S. and Japan

Country of Origin of Pharmaceutical Chemicals	Asia-Pacific except Japan		U.S.		Western Europe		Japan		Russia		Eastern Europe	
	Market Share, %	Value, $ million	Market Share, %	Value, $ million	Market Share, %	Value, $ million	Market Share, %	Value, $ million	Market Share, %	Value, $ million	Market Share, %	Value, $ million
Italy	NA	NA	32.8	1,631.00	25.8	920.00	57.5	535.00	NA	NA	6.0	43.00
Spain	NA	NA	11.7	580.00	7.2	255.00	17.2	160.00	NA	NA	3.8	27.00
India	37.4	3,625.00	22.2	1,105.00	27.1	967.00	3.5	33.00	17.9	135.00	16.8	120.00
China	60.3	5,850.00	11.7	580.00	34.1	1,215.00	2.2	20.00	33.1	250.00	29.9	214.00
Poland	NA	NA	0.5	27.00	0.3	10.00	0.4	4.00	12.8	97.00	17.5	125.00
Hungary	NA	NA	0.5	23.00	0.6	20.00	0.2	2.00	15.9	120.00	14.3	102.00
Others	2.3	220.00	20.6	1,029.00	4.9	173.00	19.0	176.00	20.3	153.00	11.7	84.00
Total value per market		**9,695.00**		**4,975.00**		**3,560.00**		**930.00**		**755.00**		**715.00**

NOTE: Data are APIs and cGMP intermediates for the "merchant market," which excludes amounts produced for in-house use of companies. Highest share for each market is shown in red.
SOURCE: Adapted with permission from Competition in the World APIs Market, 2015 Edition.

ing to Bloomberg, Fosun has been an active acquirer in China's healthcare industry, having made 17 deals worth $1.6 billion since 2010. Fosun expects to increase the share of its overseas revenue from 12% today to 40% in five years. Recently, the group joined three investors to purchase the U.S. biotech company **Ambrx**.

Speed Bumps Along The Way

Speed bumps line the road to world-class status. Foremost is regulatory compliance, which stakeholders are addressing on multiple fronts. U.S. and European regulators are working with CFDA to enforce current Good Manufacturing Practices (cGMP). The **U.S. Food & Drug Administration (USFDA)** has implemented measures to ensure the quality of pharmaceutical products arriving in the U.S. from China. It has set up offices in Beijing, Shanghai, and Guangzhou (7). It is also beefing up staffing to ensure the safety, quality, and efficacy of regulated products made in China. And it is supporting the training of local inspectors of manufacturing facilities.

The task is huge, with more than 4,000 registered Chinese companies making APIs, finished dosage forms, and medical devices. In 2013, USFDA conducted only 84 inspections in China. The good news is that the number of USFDA inspections is increasing.

Meanwhile, CFDA faces a huge challenge. It has to balance the roles of central and provincial authorities, build sufficient technical and scientific knowledge, and train its own staff. CFDA inspectors are now regularly observing USFDA inspections at Chinese manufacturing plants.

CFDA must also contend with noncompliant producers peddling poor-quality products. These rogues succeed because cGMP enforcement is not yet universal in China. Legitimate manufacturers claim that they are undermined when unscrupulous producers are allowed to thrive.

CFDA takes the problem seriously. China has affiliated with international organizations—such as the **Pharmaceutical Inspection Convention** and the **Pharmaceutical Inspection Co-Operation Scheme**—that aim to eliminate noncompliant producers and establish a level playing field for legitimate manufacturers. Chinese authorities know the importance of raising compliance. The challenge is ensuring that this understanding is shared by manufacturers throughout the supply chain.

Western industry associations are also decrying rogue producers. Among them is the **European Fine Chemicals Group (EFCG)**. According to EFCG President **Heinz Sieger**: "Since its formation in 2004, EFCG's main objective has been the creation of a legally enforceable, GMP level-playing field worldwide for all manufacturers and distributors of pharma raw materials—APIs and excipients—and final dosage forms to protect patient safety. EFCG's main driver was the existence of many thousands of unregulated manufacturers in China supplying the European and U.S. markets."

Historically, most China-based manufacturers of pharma raw materials were not inspected by CFDA, which focused only on local manufacturers serving the local market. That changed with the heparin tragedy of 2007-08, resulting in dozens of deaths from adulterated heparin sourced from China (8). As a result, European and U.S. authorities issued new laws—the Generic Drug User Fee Amendments (GDUFA) of 2012; the Food & Drug Administration Safety & Innovation Act (FDASIA); and Directive 2011/62/EU, the European Union legislation on falsified medicines. These new regulations, and Western pharma industry's increased auditing of Chinese facilities, have cut the number of Chinese exporters to the West.

Ultimately, the work of foreign regulatory agencies and stakeholders in China and the CFDA's reform of Chinese domestic regulations to meet international standards will push Chinese pharma chemical manufacturers to adapt their manufacturing and quality systems to Western standards. Upgrades

of Chinese facilities will require investments. And the ability to make those investments will determine companies' success, or failure.

Another challenge is changing labor costs in China, which are predicted to double, or even triple, by 2020. In developed markets, rising labor costs are often neutralized by automation. According to **Asa Cox**, CEO and founder of **The Pharma Partners (TPP)**, Chinese manufacturers will need to invest in more automation to stay competitive. TPP is a consulting firm that connects healthcare companies and investors in China with new technologies and products from Europe and North America.

Service Providers Lend A Hand

To achieve international regulatory compliance, Chinese producers still seek expertise and assistance from outside China, in companies such as **Pharma Quality Europe (PQE)**. Headquartered in Reggello, Italy, near Florence, PQE is a rapidly growing provider of regulatory and compliance services, with offices worldwide, including in Shanghai.

Chinese companies need partners to build capacity and reputation for quality and compliance and to gain in-depth knowledge of foreign markets, say **Francesco Amorosi**, worldwide business director and partner, and **Frederick Qiu**, PQE consultant in the Shanghai office. Partners also help bridge cultural differences when locals work with foreigners.

For example, management of Chinese companies is heavily hierarchical, unlike in the West where decision making is diffuse. It can be confounding to Western teams in China when relatively simple decisions have to come from the top. Doing business with the Chinese can sometimes feel like hitting a brick wall because transparency is not the norm. Service providers can help Chinese companies understand the Western way of doing business.

Service providers also can advise local companies in making purchasing decisions for machinery and other equipment needed to upgrade quality and capacity. Chinese manufacturers want to catch up with the best in pharma chemical production, Amorosi says. And that represents a tremendous opportunity for service providers.

Pharma chemical producers want to be part of the supply chain of major multinational pharma companies. (MNCs). These global players seek suppliers with exceptional ability to meet their requirements and a good track record with Western regulatory authorities. Despite language barriers, Chinese companies have the advantage over European and other Asian pharma chemical suppliers because they have access to capital to invest in upgrades to meet MNCs' requirements. Capital is generated primarily by initial public offerings (IPOs) of stocks by Chinese companies.

Meanwhile, MNCs are under pressure to provide medicines at prices people all over the world can afford. They need suppliers who can innovate to cut production costs. The U.S., Europe, and Japan will continue to lead in technology, but some improvements must come from emerging economies. Innovation or adoption of new manufacturing technologies, especially involving automation, could catapult China to the top ranks of leadership in pharmaceutical technology.

A model for automation comes from **Fermion Oy**, whose fully automated API plant in Hanko, Western Finland, runs parallel production of three APIs. The 100-m^3 plant requires a staff of at most four people, compared with up to 15 operators for an equivalent standard facility.

Many Routes To The Prize

As China's economy grew by leaps and bounds, it was inevitable for the world to come to China and for China to spread its wings. In the pharma chemical sphere, the East/West confluence has played out primarily in three ways.

Monthly wages in China and India are rising at a faster pace than those in the U.S. and Western Europe

Country	Average monthly wage of workers in the pharma chemical industry, $	Index, U.K. = 100	Comment
U.K.	12,750.00	100.00	Oscillating in past years
Switzerland	11,990.00	94.00	Oscillating in past years
Japan	10,450.00	82.00	Stable
U.S.	10,210.00	80.10	Stable, slightly decreasing in recent years
Germany	9,950.00	78.00	Stable
France	8,780.00	68.90	Increasing at an average of 0.4% per year in past years
Spain	8,100.00	63.50	Decreasing in past years
Italy	7,605.00	59.60	Increasing at 1-2% per year in recent years
Hungary	1,320.00	10.30	Oscillating, rising at 4-4.5% per year in the past two years
Poland	1,200.00	10.10	Oscillating, rising at 4-4.5% per year in the past two years
China	1,080.00	8.50	Increasing by 14-15% per year on average since 2006. The European Union Chamber of Commerce predicts that Chinese wages could double or even triple by 2020, but even at that rate, Chinese wages would still be about one-third those of Europe or the U.S., which are expected to grow by only 1-2% per year during the same period.
India	470.00	3.70	No specific growth rate for pharma chemicals; for manufacturing industries as a whole, wages are expected to increase 7% per year.

NOTE: Qualitative and quantitative descriptions of wage fluctuations take into account inflation rates.
SOURCE: Adapted with permission from Competition in the World APIs Market, 2015 Edition.

Chinese companies selling to U.S. and European markets need strong sales and marketing teams on the ground. Typically, the teams themselves are Americans or Europeans, their expertise due in part to belonging to the societies of the target markets. This East-goes-West model is an exciting opportunity for young professionals who can switch back and forth between the hierarchy of Chinese companies and the collaborative quality of Western business practice. Facility with Mandarin would be a huge advantage—and formidable when blended with business skills.

The complementary model, West-goes-East, is exemplified by fine pharma chemical companies setting up operations in China. They include **Lonza** (Switzerland), **DSM** (the Netherlands), **Flamma** (Italy), and **Siegfried** (Switzerland). **Chiral Technologies**, a specialist in enantioselective chromatography with operations worldwide, recently opened a center in Shanghai. **Irvine Pharmaceutical Services Inc.**, based in California, has commissioned new labs in China. And **Sagent Pharmaceuticals**, headquartered in Illinois, just invested in a Chinese injectable facility to supply both the domestic Chinese and the U.S. markets. For big pharma companies, operations in China offer opportunities to develop, test, and manufacture products also for the local market.

For these companies and others running plants in China, the challenge has been to harmonize the operations of their geographically distant facilities. That MNCs no longer worry about geography as long as quality and cost are good indicates that companies going East have met the challenge.

In addition, Western companies that have gone East have demonstrated to locals the importance of long-term relationships and putting the customer first. Local companies seeking only a quick buck may soon be gone as Chinese pharma chemical players begin to see pharma manufacturing as a service with steady, reasonable returns on investment.

The View From Three Companies

Porton Americas Inc. is the U.S.-based subsidiary of **Porton Fine Chemicals Ltd.**, a Chinese company based in Chongqing, China. In 2014, Porton Fine Chemicals posted sales of approximately $160 million, up from $20 million in 2008, when it began operations. The Porton Americas subsidiary is privately held by Porton Fine Chemicals and does not report revenue or financial results. **Steven Spardel**, the general manager of Porton Americas, cites two success factors: availability of investment capital and full compliance of Porton's manufacturing plants in China with the quality, health, and environmental standards of Western customers.

In addition, the company's culture helps forge successful collaboration with Western customers. Although service to others is intrinsic in Asian cultures, few Chinese companies can get business-to-business relationships right. For this reason, only about 10 Chinese providers are seriously competing in Western markets, Spardel says. He adds that a service attitude and customer focus are essential to success. For this reason, Porton promotes a modern management culture, through training of employees, and creates a learning organization, both of which are business practices embraced by Western companies.

Siegfried, a well-known pharma chemicals player based in Switzerland, recently built a new GMP plant in Nantong, in Jiangsu Province. As **Marianne Späne**, executive vice-president of business development, marketing, and sales explains, Chinese regulations are approaching U.S. and European standards, and the Nantong plant was designed with the new regulations in mind.

Siegfried sought advice on integrating the distinct cultures of the local and Western teams. One key decision was to have a local team led by a local, well-educated bilingual Chinese who is supported by the Western management team.

China wants to be a technology leader. Beyond investments, she says, culture and mind set must fit, too. Managers with English proficiency and applying modern management practice will help. As labor costs rise, the USFDA encourages new manufacturing processes. Engineers trained for sophisticated machines and processes—which are typically Western and will remain for some time—are crucial.

Flamma, an Italian company, started its activities in China in 2004 with just an R&D lab in Shanghai. In 2008 the company moved its China operations to Dalian, in Liaoning Province. In Dalian, they built a non-cGMP plant, which now produces starting materials and intermediates for the company's Italian cGMP plants and for third parties.

Gian Paolo Negrisoli, Flamma's president and CEO built Flamma into a cGMP manufacturer of advanced intermediates and APIs with 2014 revenues of $55 million. The company decided to build its own plant in China to exercise full control over operations and to build its own presence in the Chinese domestic market, which is growing at phenomenal rates.

Chinese pharma chemical plants will have to meet the same design and regulatory standards as those in the West do. Being fully compliant with the regulations of the Western target markets, Negrisoli says, "is a no-brainer."

Negrisoli thinks that the availability of cash, strong support from the Chinese government, and relatively lower labor cost—compared with the U.S. and Europe—will render China more competitive in Western markets. Although the labor cost is rising in China, it is unlikely to reach the levels in the U.S. or Europe in the next 10 years.

Also working well is the mixed model: individuals or groups in Europe or the U.S. with knowledge, customer contacts, and knowhow to translate pharma-sourcing requirements into R&D and manufacturing operations of their Chinese clients operating pharma chemical plants. For example, **Ash Ingredients** in the U.S., **ACIC** in Canada, and **Midas Pharma** in Germany provide such facilitation, as do independent experts with good knowhow and relationships.

According to **James Bruno**, of the New Jersey-based consultancy **Chemical & Pharmaceutical Solutions**, large groups like **Qilu Pharmaceutical Co.** and **CSPC Pharmaceutical Group** want to become big global players. They are considering going public in the Chinese stock market to raise funds for expansion, or merging with Western companies. **Tony Chu**, president of California-based **Eastar Chemical Corporation** and a partner of TPP, points out that IPOs have generated large amounts of investment funds for Chinese pharma chemical companies.

Meanwhile, smaller firms may look for agents and distributors in the West, Bruno says, because they do not yet have a good grasp of development costs, customers' qualification procedures, or the total cost of doing business in Western markets. Chinese-born managers with both Chinese and foreign language skills, he believes, may best ensure close collaboration and smooth communication.

TPP's Cox, on the other hand, believes that China will follow the Indian example: starting with API sales offices and offering contract-manufacturing for finished dosage forms (FDFs). Chinese companies are aiming to acquire profitable API and FDF companies in Europe or the U.S., he believes.

Unlike the Indians, however, the Chinese have a language disadvantage. Furthermore, many Chinese companies are inexperienced in international business, and Chinese management decisions are often based on personal relationships and "gut feel". These factors may delay the full flowering of Chinese pharma chemical companies outside of China, until a new generation of managers with better language and management skills takes over.

Joint ventures could leverage the strengths of both Western and Chinese companies, Cox says. The West still has a lot of technology and know-how that China lacks. Cash-rich Chinese companies are eager to go West. They aim to bring technology to China through investments in the West, and the Chinese government is promoting the country's modernization by giving incentives to deals that allow importation not only of products but also of new technologies. The Chinese government is also pushing domestic manufacturers to improve their quality by granting premium pricing for products manufactured in a U.S.- or Europe-approved facility.

What companies will do to achieve China's dream of being the world's pharma chemical supplier

- Comply with international regulatory standards; accelerate collaboration with U.S. and European regulatory bodies
- Implement compliant plant designs; adopt manufacturing innovations, such as continuous manufacturing
- Promote the East-West exchange of young professionals to close cultural gaps, eliminate language barriers
- Promote the learning of Chinese language and culture by foreign pharma professionals to facilitate East-West collaborations

Who benefits from new opportunities due to China's dream

- Non-Chinese or Chinese-born professionals with Western training and education who have Mandarin proficiency to connect two distinct cultures
- Service providers and technical experts to help Chinese companies transform for high-value markets
- Professionals to harmonize functions of foreign companies and their China operations or China-based partners
- Technology developers to help the country become a global technology leader

What Lies Ahead

Driven by the need to raise quality and production capacity and the ambition to be a global player in pharma chemicals, China has to become a global technology leader. Product quality must comply with international standards. Manufacturing capacity needs to rise to meet domestic demand and export goals. Perhaps China will lead in heeding USFDA's calls for manufacturers to switch from batch manufacturing to continuous systems (9).

To become a global player, China's pharma industry must cover domestic demand, now growing annually at double-digit rates, as well as export pharmaceutical products. In the less-regulated markets of Latin America and the Asia-Pacific Rim, China already is a key supplier of APIs, yet the growth potential for the entire Chinese pharma industry in these markets is still immense.

Moreover, therapeutic categories for which Chinese companies are making APIs have expanded to cancer, diseases of the central nervous system, hypertension and cardiovascular diseases, obesity, and diabetes, consistent with the Chinese citizen's changing lifestyle.

Chinese API manufacturers will likely organize themselves to serve the internal market and enter the regulated markets. These two goals represent opportunities but also challenges. Each company must decide its priorities. And the West stands to gain by helping China achieve its dreams.

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Courtesy of Roger LaForce

About the Author

Roger LaForce *is a Switzerland-based expert on the business of pharmaceutical fine chemicals with extensive executive experience in Europe. After receiving a Ph.D. in biotechnology at the Swiss Federal Institute of Technology, Zurich (ETH, Zurich), he began his professional career by doing contract research in enzyme technology, food and flavors, bioinsecticides, and recombinant organisms. For more than two decades, LaForce served in three of Western Europe's best known pharmaceutical fine chemical companies: Helsinn, in Switzerland; Fabbrica Italiana Sintetici (FIS), in Italy; and Zach System, also in Italy. In 2014, he founded LaForce Business Solutions, offering expertise in international business-to-business development for supply chain management, R&D, fine chemicals, active pharmaceutical ingredients, and final dosage forms. La Force speaks German, English, French, Italian, and Serbian.* ■

SHANGHAITECH AIMS TO RAISE THE BAR FOR HIGHER EDUCATION IN CHINA

A. Maureen Rouhi, C&EN Asia

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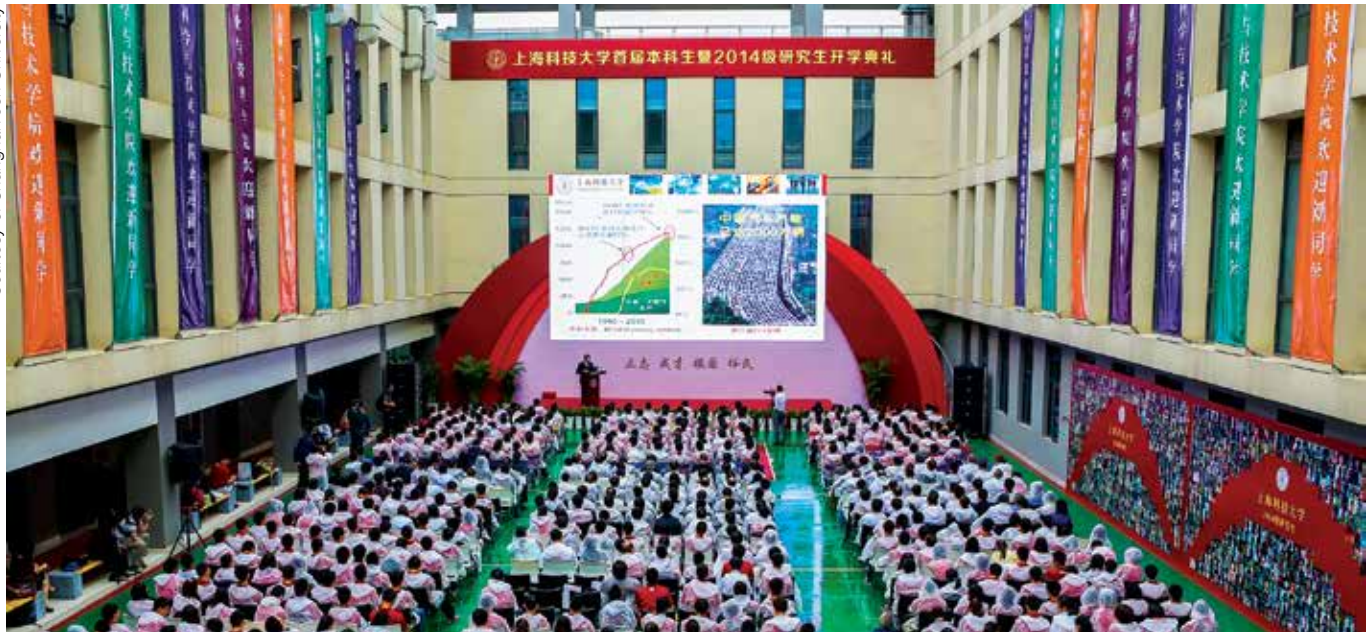
Courtesy of ShanghaiTech University



Undergrads' First Day

ShanghaiTech opened its doors to undergraduates for the first time on Sept. 30, 2014.

Even as China is poised to lead the world in R&D spending by 2019, the quality of the country's scientific output still trails that of developed economies. China's government is acutely aware of the gap and has been taking diverse measures to narrow it.

Among them is the establishment of a "research ecosystem" in the country's most populated city, Shanghai. Last year, China opened its newest academic research institution there: ShanghaiTech University. Established by the Shanghai municipal government and the Chinese Academy of Sciences, ShanghaiTech aims to be both an exemplary institution of higher education and an engine of innovation that supports Shanghai's dynamic economy and provides solutions to China's needs and to global challenges. It hopes to achieve these goals through an academic system new to China.

The university's buildings are now rising in the Zhangjiang Hi-Tech Park, also known as Zhangjiang InnoPark, in Pudong, the Shanghai district east of the Huangpu River just across from Shanghai's historic center in Puxi. In the 1990s, the Pudong landscape rapidly transformed from farmland into iconic skyscrapers, free-trade zones, and high-technology parks. When completed this year, ShanghaiTech will be within easy reach of global R&D-based companies.

Since the 1990s, Shanghai's economy has boomed through manufacturing and exports. The local government knew that the city could not forever depend on these activities and determined that it should foster innovation in high-technology industries to maintain its economic vibrance, according to ShanghaiTech President Mianheng Jiang. He observes that hotbeds of innovation, such as Route 128 around Boston and Silicon Valley outside of San Francisco, thrive in places with easy access to world-class research universities, which Pudong lacked. Locating the university amid global industrial R&D centers, Jiang says, was a deliberate move to fill a gap in Shanghai's high-technology enterprise.

Before the university could rise, another key ingredient had to be in place: a network of R&D facilities with infrastructure that would attract researchers from around the world, thereby ensuring a constant influx of new people and ideas to the area and catalyzing collaborations across multiple disciplines. This network comprises three facilities built with major support from the Shanghai government.

First is the Shanghai Synchrotron Radiation Facility, a third-generation synchrotron radiation light source that has been attracting thousands of users locally and globally each year since it became fully operational in 2009. Next is the Shanghai Advanced Research Institute, which was inaugurated in 2009. The institute undertakes research and trains students in areas critical to China, such as communication technology, energy efficiency, greenhouse gas management, and advanced technologies for chronic diseases and regenerative medicine. And third is the National Center for Protein Science Shanghai, which opened in June 2013 and aims to be "an advanced global technology platform and an internationally competitive research center for protein science."

"The leadership of the local government was forward-looking," Jiang says. The hope is that these three research resources around ShanghaiTech would raise the quality of science, promote cross-pollination, and boost the probability of translating research into innovation.

As ShanghaiTech drew inspiration from U.S. innovation hubs for its research ecosystem, it has been drawing upon foreign expertise and partnerships to help build its human capital and advance its goals.

Jiang recruited University of California, Berkeley, chemist and materials scientist Peidong Yang to help build ShanghaiTech's School of Physical Science & Technology (SPST). Foremost among his tasks is to select panels of experts, typically from the faculty of UC Berkeley and Stanford University, to interview faculty candidates for ShanghaiTech in the U.S. Because everyone in the panel has "very high standards," Yang says, the caliber of ShanghaiTech's faculty hires is "very high."

In turn, Yang enlisted UC Berkeley chemists Christopher J. Chang and Michelle C. Chang to help with the materials bioresearch center, one of SPST's three research centers. Among other things, the Changs, who are married to each other, advise young faculty and help them get their independent careers off the ground. Yang also convinced Stanford materials scientist Yi Cui to chair SPST's international advisory board. "Helping China build its best research university," Cui says, "is like my payback to China for educating me."

Yang, the Changs, and Cui are palpably excited about the chance to help shape what could be China's premier research university. Whether that dream will come true is uncertain, but the university is implementing practices that could lead to success.

For example, all faculty are on a tenure track. Chinese universities typically have a professoriat organized like the system in Europe, where most faculty do research under the supervision of a senior professor. In the tenure-track system, faculty do independent research from the get-go, and only those who earn tenure are retained. Some Chinese universities have adopted tenure tracks for specific academic units, but ShanghaiTech is the first to apply the practice systemwide.

"Innovation can happen anywhere, but the tenure track may be the best system to encourage innovation in academia," Cui says. "It picks the best people and makes good people become even better. Evaluation is based on creativity, originality, and innovation."

Implicit in the excitement about tenure track is an acknowledgment of the quality of Chinese academic research. "China does not have enough quality of higher education," says Jiang, ShanghaiTech's president.

The quality of higher education is a top priority in China, notes Jay Siegel, dean of the School of Pharmaceutical Science & Technology at Tianjin University, about 700 miles northwest of ShanghaiTech. He himself was hired to bolster Tianjin University's efforts on this front. International programs with foreign hires, English as the language of instruction, and tenure-track-like options are just some of the ideas taking hold all over China, Siegel says.

Other features that ShanghaiTech hopes will ensure success are a low student-to-faculty ratio, at most 12 to 1; interdisciplinary schools and institutes instead of departments based on traditional fields; and broad cooperation with international partners in academia and industry.

The university has already signed memorandums of understanding with

ABOUT SHANGHAITECH

Origin: Established by the Shanghai municipal government and the Chinese Academy of Sciences; opened to graduate students on Sept. 30, 2013

Concept: Small-scale research university with tenure-track faculty where research and education combine to support local economy, solve global challenges

ENROLLMENT

2013: 296 graduate students

2014: 432 graduate students and 207 undergraduates

Projected: 4,000 graduate students and 2,000 undergraduates

SCHOOLS & INSTITUTES

School of Physical Science & Technology Founding Dean: Peidong Yang, University of California, Berkeley.

School of Life Science & Technology Founding Dean: Haifan Lin, Yale University.

School of Information Science & Technology Founding Dean: Cher Wang.

School of Entrepreneurship & Management Dean: R. May Lee.

Shanghai Institute for Advanced Immunochemical Studies Founding Director: Richard A. Lerner, Scripps Research Institute. Focus on antibody research.

iHuman Institute Founding Director: Raymond C. Stevens, University of Southern California. Focus on human cell signaling research.

SOURCE: ShanghaiTech University

UC Berkeley and the University of Chicago, says Jin-kang Gong, a university vice president and SPST professor. Among other things, these agreements support what ShanghaiTech is calling its 3 + 1 + N Program: If third-year ShanghaiTech students (3) complete a fourth year at a partner school (+ 1), the students will be admitted to the partner school's graduate program (+ N), provided they meet the requirements. Gong says ShanghaiTech is pursuing similar agreements with other U.S. and European universities, including Massachusetts Institute of Technology and the University of Oxford.

ShanghaiTech plans to have 2,000 undergrads and 4,000 graduate students once it's at full capacity. So far, SPST has hired 10 faculty and has 15 more hires in negotiation, UC Berkeley's Yang says. The school alone plans to recruit 120 faculty over 10 years, he adds.

On top of its own hires, ShanghaiTech also enjoys the service of faculty from other universities, especially those in Shanghai. This arrangement promotes even more cross-pollination, Gong says. Also important, it gives students the benefit of the best teachers available. For example, he explains, undergrads are getting their general education economics lectures from an economics professor at nearby Fudan University.

With support from two powerful institutions—the Chinese Academy of Sciences and the Shanghai government—ShanghaiTech is poised to take flight. But progress could be impeded by external factors. A looming question is the sustainability of financial support from the city of Shanghai, which now provides 100% of the university's operating budget. "We need to look in the private sector for support," says Jiang, the university's president. "Successful entrepreneurs will want to invest in education."

Jiang has been intimately involved in the planning for ShanghaiTech for more than a decade. His scientific credentials are solid: He earned a Ph.D. in electrical engineering from Drexel University, worked at Hewlett-Packard, was a Chinese Academy of Sciences vice president for many years, and still runs a research group. But being the son of Jiang Zemin, China's president from 1993 through 2003, opens him to unusual scrutiny. Unfazed, the younger Jiang says, "I'm just doing my job."

By 2018, the first batch of undergrads at ShanghaiTech will graduate, and measuring success can then begin. "At minimum, we expect our graduates to get good jobs," Jiang says. "We would like to see them become leaders in business and academia. Eventually, we would like to have Nobel Prize winners." ■

AMERICAN CHEMIST TAKES CHARGE IN TIANJIN

Jean-François Tremblay, C&EN Hong Kong

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In an unusual development for the Chinese academic world, a prominent American scientist has taken charge of a school at a major university in China. Until recently, Californian organic chemist Jay S. Siegel was based in Switzerland, but since June, he has been dean of the School of Pharmaceutical Science & Technology at Tianjin University.

Siegel is not just lending his name to Tianjin and visiting for a few weeks every year. He has moved to the Chinese city and has started a profound overhaul of the school. His vision—one that he says the leaders of the university entirely support—is to turn Tianjin's school of pharmaceutical science into a world-class fundamental drug research center staffed by faculty who may or may not be Chinese-born and where the language of education is English.

If Siegel's efforts are successful, they will mark another milestone in China's steadily improving ability to invent and develop new drugs. The precedent will also signal that foreign academics can function normally in China as researchers, professors, or administrators, just as foreign academics do in many other countries. "As far as I know, I am the first non-Chinese dean of a science school in China in at least 60 years," Siegel says.

The idea that he might lead Tianjin University's school of pharmacy first came up, casually, a little more than two years ago during a dinner in Tianjin when he was in China as a visiting professor, he says. At the time, Siegel was a professor and codirector of the Institute of Organic Chemistry at the University of Zurich (UZH) as well as director of its laboratory for process chemistry research. "It took two years of talks, but the university administration and I came up with a common vision."

Siegel comes to Tianjin with a vast web of international connections from having worked for years on both sides of the Atlantic. He earned his Ph.D. at Princeton University in 1986 under the supervision of Kurt Mislow and did a postdoc at Louis Pasteur University in Strasbourg, France, in Jean-Marie Lehn's lab. He was at the University of California, San Diego, where he became full professor of chemistry in 1996, for 17 years before moving to Zurich.

After his arrival at Tianjin University, he immediately boosted international exchanges. A group of six Chinese students are currently on a two-month exchange program at his UZH labs to get more familiar with how Western labs are equipped, operated, and managed. Soon after their return to China, four of Siegel's students who are still at Zurich will come to Tianjin, mostly to complete their Ph.D. studies but also to get a taste of life in China.

A deeper change for Tianjin will be the hiring of international faculty. In coming years, Siegel foresees that the pharmacy school will hire about 80 new faculty, about 30 of whom, he estimates, would not be natives of China. The school currently employs about 30 academic staff. "We can offer internationally competitive packages that not many schools worldwide can outdo," he says.

Jean-Francois Tremblay/C&EN

Singular Case

Nonethnic Chinese deans such as Siegel are currently a rarity at Chinese universities.

Siegel envisions a school that will contain several centers of excellence in the broad field of drug discovery and development. He imagines an "Institute for Drug Innovation & Development," an "Institute for Molecular Design & Synthesis," and other centers focused on other areas, including traditional Chinese medicine. Students will be exposed to the entire drug discovery and development process, Siegel claims.

To complement Siegel's vision, the school will be guided by international advisers who will meet periodically in Tianjin. This advisory board initially comprises Michael A. Marletta, president and chief executive officer of Scripps Research Institute; Donald Hilvert, head of the organic chemistry lab at the Swiss Federal Institute of Technology (ETH), Zurich; Chris Abell, a biological chemistry professor at the University of Cambridge; William L. Jorgensen, Sterling Professor of Chemistry at Yale University; Shaomeng Wang, professor of medicinal chemistry at the University of Michigan, Ann Arbor; and Thomas J. Meade, a chemistry professor at Northwestern University.

"This school in Tianjin will do basic science, and basic science is what leads to new drugs," Meade says. "Jay is combining under one roof multiple disciplines that will work together for a common purpose." The idea, Meade says, is to implement at the Tianjin school of pharmaceutical science some of the best practices that administrators of research institutes and university departments have implemented worldwide in recent years. A priority will be to avoid setting up at the school "silos"—such as organic, inorganic, and computational chemistry—that do not interact with each other, Meade says.

Over the next few years, the school of pharmaceutical science will hire medicinal chemists, pharmacologists, pharmacokineticists, plant biologists, formulation scientists, and scientists from other related fields, Siegel envisages.

Siegel's wife, Kim K. Baldridge, is one of the first international recruits. She will move to Tianjin in 2014. Like Siegel, she is the beneficiary of a Chinese government program called 1000 Talents that encourages accomplished scientists to move to China. An American computational chemist, Baldridge is director of the Grid Computing Competence Center at UZH.

Beyond science and technology, the school will teach and research regulatory affairs, ethics, and drug economics. The comprehensiveness of Tianjin's program "will address a complaint among companies hiring scientists for drug discovery and development that Chinese grads aren't knowledgeable about the field," Siegel says.

Located a mere 80 miles southeast of Beijing, Tianjin may seem like a backwater compared with the Chinese capital or major cities such as Shanghai or Guangzhou. Yet, with a population of 13 million, it offers what one would expect to find in any major city around the world, Siegel claims. Tianjin, he says, has first-class restaurants, theaters, museums, large parks, and sports facilities. In the early decades of the 20th century, he notes, many foreigners lived in the city.

In the eyes of potential faculty recruits, the opportunity to work in a world-class school led by Siegel will carry more weight than whether the quality of life in Tianjin is on par with Shanghai, says Fraser Stoddart, a chemistry professor and the director of the Center for Chemistry of Integrated Systems at Northwestern University.

"Jay is a highly regarded and respected scientist, recognized in his research as a world authority on stereochemistry and physical organic chemistry with an enviable reputation as both a teacher and an administrator," he says. "I don't see him having the least difficulty in attracting top faculty to Tianjin University either as visiting faculty or as newly appointed assistant professors."

Courtesy of Jay Siegel

Peiyang University

A student poses at the original gate to Tianjin University, built when it was still called Peiyang University.

Stoddart himself is discussing a collaboration with Tianjin, which may involve supervising students there. His students may also go to Tianjin. "There is no doubt that members of my present research group will jump at opportunities to go and spend some time in the new research laboratories that Jay is creating." About a third of Stoddart's group of 35 researchers are from China.

In line with the rising faculty headcount, the student population at Tianjin's pharmacy school is set to increase. In coming years, the intake of Ph.D. students will grow from the current 30 or so to about 100, Siegel says. Master's degree candidates will number 150 in a few years, up from about 50 now. And the school will accept 200 undergraduates annually, up from about 60 now, Siegel foresees.

That the language of instruction is English will not be a problem, expects Libing Yu, CEO of Alputon, a Shanghai-based contract research firm servicing the pharmaceutical industry. More and more students in China attend high schools that teach in both Chinese and English, he says. The school could play a useful role in raising China's drug discovery and development capabilities, he further notes. "It will be a positive development to teach ethics and integrity as well as science and technology," he says.

To accommodate a larger population, the school is expanding and upgrading its facilities. The renovation of 32,000 sq ft of lab space started last summer is scheduled for completion early next month. Once that is finished, Siegel says, a second phase

Courtesy of Jay Siegel

Upgrade In Progress

A large reconstruction effort is under way at the School of Pharmaceutical Science & Technology of Tianjin University.

of renovation will involve rebuilding an additional 130,000 sq ft of lab and office space. In addition, the planned construction of a new building will provide 85,000 sq ft of new space. "We're looking at 2,000 sq ft of brand new lab space on average for each new faculty," Siegel says.

Siegel's appointment is making waves in China's academic world. The director of the Shanghai Institute of Organic Chemistry, Kuiling Ding, says that he was extremely surprised when he heard the news. Scientists such as Siegel are people whom Chinese students seek for postdoc positions at labs abroad, not in China. To have Siegel leading a school in the country is remarkable, he says.

At the same time, Siegel is likely to face formidable challenges at Tianjin, Ding expects. "I suppose Tianjin has already considered this, but a foreigner administering a Chinese school will face language problems, cultural differences, and difficulties to communicate externally, with government officials for instance."

Siegel says that he will be able to operate effectively because Tianjin University officials are letting him operate the school of pharmaceutical science as a "free zone" where experimentation in research, teaching, and administration will be fostered. More important, the president of Tianjin University, Jiajun Li, wholeheartedly champions the overhaul of the school.

"It's rare that someone is given the freedom I have gained, this mandate to create a new institute," Siegel says. "It's an irresistible proposition." ■

ABOUT TIANJIN UNIVERSITY

Student population: 29,000
Faculty and staff: 4,500
History: The university was founded in 1895 by Xuanhuai Sheng, an intendant of customs, and Charles Daniel Tenney, an American educator who was living in China at the time. The school's initial name was Peiyang University.
University Motto: "Seeking truth from facts."
SCHOOL OF PHARMACEUTICAL SCIENCE & TECHNOLOGY: Founded in 2000, the school employs about 30 faculty currently.
TIANJIN'S OTHER PROMINENT UNIVERSITY: Nankai University, adjacent to Tianjin University.

POPULAR PHARMA-RELATED PAPERS FROM ACS JOURNALS

ONE MEASURE of scientific productivity is publication in scholarly journals. In terms of published articles in American Chemical Society journals, China is outpacing the rest of the world. Chinese scientists' papers in ACS journals increased at a compound annual growth rate of 10.8% during 2008–2014, faster than those from China's BRICKS comrades: Brazil, Russia, India, South Korea, and South Africa.

In pharma-related scientific fields, the following 10 papers in ACS journals were among the most accessed during the period May 2014–April 2015. Nine papers come from the *Journal of the American Chemical Society,* in which most Chinese chemical scientists aspire to be published.

At the top of the list, however, is a paper from *Biomacromolecules,* about a means to repair damaged bones. Such research reflects the attention Chinese researchers pay to solving health problems and finding treatments for diseases that afflict many among China's population. For example, according to the International Osteoporosis Foundation, about 70 million Chinese who are more than 50 years old have osteoporosis, resulting in close to 700,000 hip fractures each year.

Five of the 10 papers are related to diagnosis and treatment of cancers. The incidence of cancer in China is rising. In 2012, the latest year for which data are available, the risk of getting cancer before the age of 75 was on average 20% for men and 13% for women, according to the International Agency for Research on Cancer. For anyone who has experienced the particulate pollution in Beijing and other Chinese cities, it is not surprising that lung cancer is the most frequently encountered type of cancer in China.

Two other studies describe new methods to image disease-related phenomena. One describes a sensor to detect hypoxia, a condition associated with malignant tumors. The second reports a way to visualize cardiac glycans, enabling their study during pathophysiological responses.

Consistent with the long tradition of herbal medicines in China, one of the publications describes the discovery and structural elucidation of a new family of bioactive natural products isolated from a plant. Members of the family exhibit immunosuppressive effects, inhibiting the proliferation of T and B lymphocytes, which are specialized defender cells in the human body.

Rounding up the collection is a report on mesoporous silica nanocomposites designed for bimodal, controlled drug release. ■

In Situ Controlled Release of rhBMP-2 in Gelatin-Coated 3D Porous Poly(ε-caprolactone) Scaffolds for Homogeneous Bone Tissue Formation

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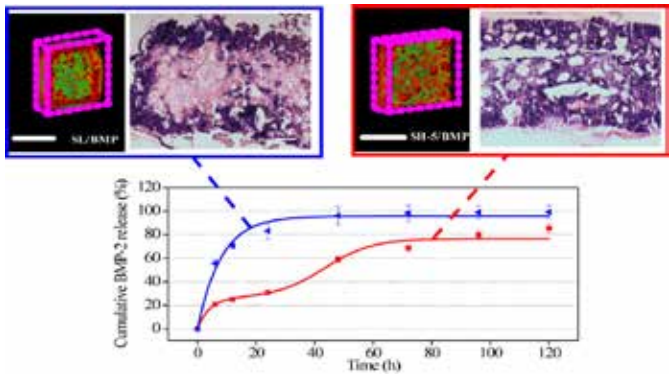
In tissue engineering, incorporation of bone morphogenetic protein-2 (BMP-2) into biomaterial scaffolds is an attractive strategy to stimulate bone repair. However, suboptimal release of BMP-2 remains a great concern, which may cause unfavorable bone formation as well as severe inflammation. In this study, genipin-cross-linked gelatin entrapped with recombinant human BMP-2 (rhBMP-2) was exploited to decorate the interior surface of three-dimensional porous poly(ε-caprolactone) (PCL) scaffolds. With gelatin-coating, PCL scaffolds demonstrated enhanced water uptake and improved compressive moduli. Intriguingly, a unique release profile of rhBMP-2 composed of a transient burst release followed by a sustained release was



achieved in coated scaffolds. These coated scaffolds well supported growth and osteogenesis of human mesenchymal stem cells (hMSCs) in vitro, indicating the retaining of rhBMP-2 bioactivity. When hMSCs-seeded scaffolds were implanted subcutaneously in nude mice for 4 weeks, better bone formation was observed in gelatin/rhBMP-2-coated scaffolds. Specifically, the spatial distribution of newly formed bone was more uniform in gelatin-coated scaffolds than in uncoated scaffolds, which displayed preferential bone formation at the periphery. These results collectively demonstrated that gelatin-coating of porous PCL scaffolds is a promising approach for delivering rhBMP-2 to stimulate improved bone regeneration. ■

Phainanoids A–F, A New Class of Potent Immunosuppressive Triterpenoids with an Unprecedented Carbon Skeleton from *Phyllanthus hainanensis*

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Phainanoids A–F **(1–6)**, six highly modified triterpenoids with a new carbon skeleton by incorporating two unique motifs of a 4,5- and a 5,5-spirocyclic systems, were isolated from *Phyllanthus hainanensis*. Their structures with absolute configurations were determined by spectroscopic data, chemical methods, and X-ray crystallography. Compounds **1–6** exhibited exceptionally potent immunosuppressive activities in vitro against the proliferation of T and B lymphocytes. The most potent one, phainanoid F **(6)**, showed activities against the proliferation of T cells with IC_{50} value of 2.04 ± 0.01 nM (positive control CsA = 14.21 ± 0.01 nM) and B cells with IC_{50} value of <1.60 ± 0.01 nM (CsA = 352.87 ± 0.01 nM), which is about 7 and 221 times as active as CsA, respectively. The structure–activity relationships of **1–6** are discussed. ■

Near Infrared Laser-Induced Targeted Cancer Therapy Using Thermoresponsive Polymer Encapsulated Gold Nanorods

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External stimuli, such as ultrasound, magnetic field, and light, can be applied to activate in vivo tumor targeting. Herein, we fabricated polymer encapsulated gold nanorods to couple the photothermal properties of gold nanorods and the thermo- and pH-responsive properties of polymers in a single nanocomposite. The activation mechamism was thus transformed from heat to near-infrared (NIR) laser, which can be more easily controlled. Doxorubicin, a clinical anticancer drug, can be loaded into the nanocomposite through electrostatic interactions with high loading content up to 24%. The nanocomposite's accumulation in tumor post systematic administration can be significantly enhanced by NIR laser irradiation, providing a prerequisite for their therapeutic application which almost completely inhibited tumor growth and lung metastasis. Since laser can be manipulated very precisely and flexibly, the nanocomposite provides an ideally versatile platform to simultaneously deliver heat and anticancer drugs in a laser-activation mechanism with facile control of the area, time, and dosage. The NIR laser-induced targeted cancer thermo-chemotherapy without using targeting ligands represents a novel targeted anticancer strategy with facile control and practical efficacy. ■

Programmable and Multiparameter DNA-Based Logic Platform For Cancer Recognition and Targeted Therapy

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The specific inventory of molecules on diseased cell surfaces (e.g., cancer cells) provides clinicians an opportunity for accurate diagnosis and intervention. With the discovery of panels of cancer markers, carrying out analyses of multiple cell-surface markers is conceivable. As a trial to accomplish this, we have recently designed a DNA-based device that is capable of performing autonomous logic-based analysis of two or three cancer cell-surface markers. Combining the specific target-recognition properties of DNA aptamers with toehold-mediated strand displacement reactions, multicellular marker-based cancer analysis can be realized based on modular AND, OR, and NOT Boolean logic gates. Specifically, we report here a general approach for assembling these modular logic gates to execute programmable and higher-order profiling of multiple coexisting cell-surface markers, including several found on cancer cells, with the capacity to report a diagnostic signal and/or deliver targeted photodynamic therapy. The success of this strategy demonstrates the potential of DNA nanotechnology in facilitating targeted disease diagnosis and effective therapy. ■

Combination of Small Molecule Prodrug and Nanodrug Delivery: Amphiphilic Drug–Drug Conjugate for Cancer Therapy

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DOI: 10.1021/ja505212y

All drugs for cancer therapy face several transportation barriers on their tortuous journey to the action sites. To overcome these barriers, an effective drug delivery system for cancer therapy is imperative. Here, we develop a drug self-delivery system for cancer therapy, in which anticancer drugs can be delivered by themselves without any carriers. To demonstrate this unique approach, an amphiphilic drug–drug conjugate (ADDC) has been synthesized from the hydrophilic anticancer drug irinotecan (Ir) and the hydrophobic anticancer drug chlorambucil (Cb) via a hydrolyzable ester linkage. The amphiphilic Ir–Cb conjugate

self-assembles into nanoparticles in water and exhibits longer blood retention half-life compared with the free drugs, which facilitates the accumulation of drugs in tumor tissues and promotes their cellular uptake. A benefit of the nanoscale characteristics of the Ir–Cb ADDC nanoparticles is that the multidrug resistance (MDR) of tumor cells can be overcome efficiently. After cellular internalization, the ester bond between hydrophilic and hydrophobic drugs undergoes hydrolysis to release free Ir and Cb, resulting in an excellent anticancer activity in vitro and in vivo. ■

An "Enhanced PET"-Based Fluorescent Probe with Ultrasensitivity for Imaging Basal and Elesclomol-Induced HClO in Cancer Cells

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DOI: 0.1021/ja505988g

Reactive oxygen species (ROS) and cellular oxidant stress have long been associated with cancer. Unfortunately, the role of HClO in tumor biology is much less clear than for other ROS. Herein, we report a BODIPY-based HClO probe (BClO)

with ultrasensitivity, fast response (within 1 s), and high selectivity, in which the pyrrole group at the meso position has an "enhanced PET" effect on the BODIPY fluorophore. The detection limit is as low as 0.56 nM, which is the highest sensitivity achieved to date. BClO can be facilely synthesized by a Michael addition reaction of acryloyl chloride with 2,4-dimethylpyrrole and applied to image the basal HClO in cancer cells for the first time and the time-dependent HClO generation in MCF-7 cells stimulated by elesclomol, an effective experimental ROS-generating anticancer agent. ■

Cocoon-Like Self-Degradable DNA Nanoclew for Anticancer Drug Delivery

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A bioinspired cocoon-like anticancer drug delivery system consisting of a deoxyribonuclease (DNase)-degradable DNA nanoclew (NCl) embedded with an acid-responsive DNase I nanocapsule (NCa) was developed for targeted cancer treatment. The NCl was assembled from a long-chain single-stranded DNA synthesized by rolling-circle amplification (RCA). Multiple GC-pair sequences were integrated into the NCl for enhanced loading capacity of the anticancer drug doxorubicin

(DOX). Meanwhile, negatively charged DNase I was encapsulated in a positively charged acid-degradable polymeric nanogel to facilitate decoration of DNase I into the NCl by electrostatic interactions. In an acidic environment, the activity of DNase I was activated through the acid-triggered shedding of the polymeric shell of the NCa, resulting in the cocoon-like self-degradation of the NCl and promoting the release of DOX for enhanced therapeutic efficacy. ■

Glycan Imaging in Intact Rat Hearts and Glycoproteomic Analysis Reveal the Upregulation of Sialylation during Cardiac Hypertrophy

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In the heart, glycosylation is involved in a variety of physiological and pathological processes. Cardiac glycosylation is dynamically regulated, which remains challenging to monitor in vivo. Here we describe a chemical approach for analyzing the dynamic cardiac glycome by metabolically labeling the cardiac glycans with azidosugars in living rats. The azides, serving as a chemical reporter, are chemoselectively conjugated with fluorophores using copper-free click chemistry for glycan imaging; derivatizing azides with affinity tags allows enrichment and proteomic identification of glycosylated cardiac proteins. We demonstrated this methodology by visualization of the cardiac sialylated glycans in intact hearts and identification of more than 200 cardiac proteins modified with sialic acids. We further applied this methodology to investigate the sialylation in hypertrophic hearts. The imaging results revealed an increase of sialic acid biosynthesis upon the induction of cardiac hypertrophy. Quantitative proteomic analysis identified multiple sialylat-

ed proteins including neural cell adhesion molecule 1, T-kininogens, and α_2-macroglobulin that were upregulated during hypertrophy. The methodology may be further extended to other types of glycosylation, as exemplified by the mucin-type O-linked glycosylation. Our results highlight the applications of metabolic glycan labeling coupled with bioorthogonal chemistry in probing the biosynthesis and function of cardiac glycome during pathophysiological responses. ■

Ultrasensitive Nanosensors Based on Upconversion Nanoparticles for Selective Hypoxia Imaging in Vivo upon Near-Infrared Excitation

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Hypoxia is a distinct feature of malignant solid tumors, which is a possible causative factor for the serious resistance to chemo- and radiotherapy or the development of invasion and metastasis. The exploration of nanosensors with the capabilities like the accurate diagnosis of hypoxic level will be helpful to estimate the malignant degree of tumor and subsequently implement more effective personalized treatment. Here, we report the design and synthesis of nanosensors that can selectively and reversibly detect the level of hypoxia both in vitro and in vivo. The designed nanosensor is composed of two main moieties: oxygen indicator $[Ru(dpp)_3]^{2+}Cl_2$ for detection of hypoxia and upconversion nanoparticles for offering the excitation light of $[Ru(dpp)_3]^{2+}Cl_2$ by upconversion process under 980 nm exposure. The results show that the nanosensors can reversibly become quenched or luminescent under hyperoxic or hypoxic conditions, respectively. Compared with free $[Ru(dpp)_3]^{2+}Cl_2$, the designed nanosensors exhibit enhanced sensitivity for the detection of oxygen in hypoxic regions. More attractively, the nanosensors can image hypoxic regions with high penetration depth because the absorption and emission wavelength are within the NIR and far-red region, respectively. Most importantly, nanosensors display a high selectivity for detection of relevant oxygen changes in cells and zebrafish. ■

Anisotropic Growth-Induced Synthesis of Dual-Compartment Janus Mesoporous Silica Nanoparticles for Bimodal Triggered Drugs Delivery

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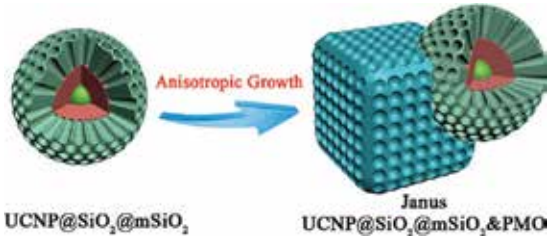
Multifunctional dual-compartment Janus mesoporous silica nanocomposites of UCNP@SiO_2@mSiO_2&PMO (UCNP = upconversion nanoparticle, PMO = periodic mesoporous organosilica) containing core@shell@shell structured UCNP@SiO_2@mSiO_2 nanospheres and PMO single-crystal nanocubes have been successfully synthesized via a novel anisotropic island nucleation and growth approach with the ordered mesostructure. The asymmetric Janus nanocomposites show a very uniform size of ~300 nm and high surface area of ~1290 m^2/g. Most importantly, the Janus nanocomposites possess the unique dual independent mesopores with different pore sizes (2.1 nm and 3.5–5.5 nm) and hydrophobicity/hydrophilicity for loading of multiple guests. The distinct chemical properties of the silica sources and the different mesostructures of the dual-compartments are the necessary prerequisites for the formation of the Janus nanostructure. With the assistance of the near-infrared (NIR) to ultraviolet/visible (UV–vis) optical properties of UCNPs and heat-sensitive phase change materials, the dual-compartment Janus mesoporous silica nanocomposites can be further applied into nanobiomedicine for heat and NIR light bimodal-triggered dual-drugs controllable release. It realizes significantly higher efficiency for cancer cell killing (more than 50%) compared to that of the single-triggered drugs delivery system (~25%). ■



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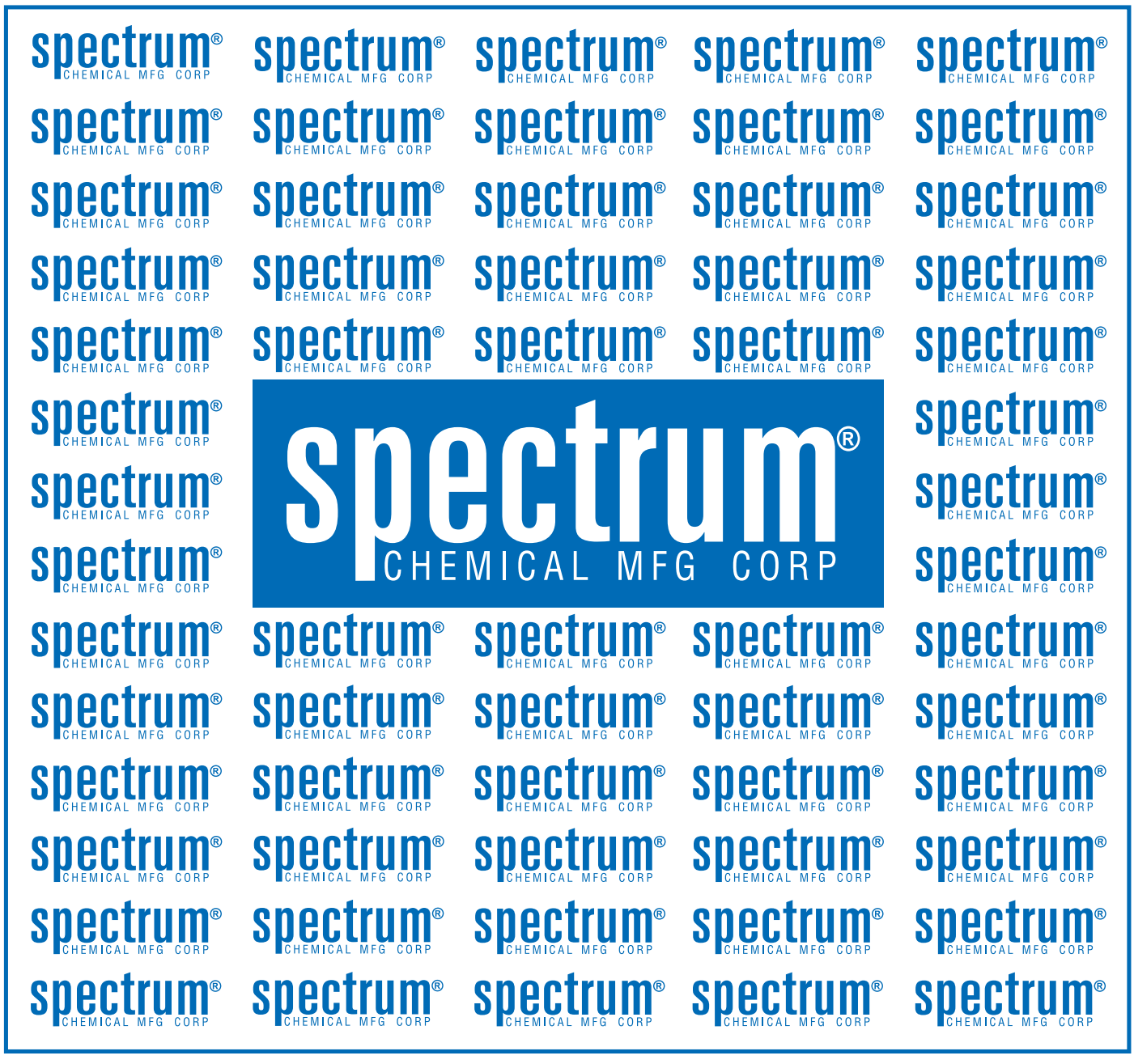

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