A Chinese perspective on agchem R&D

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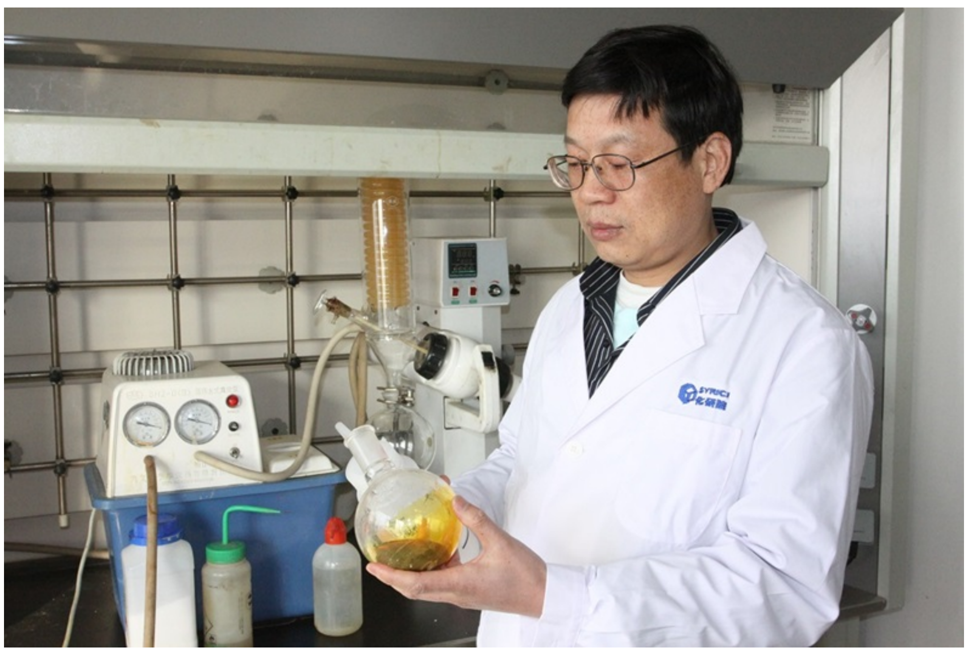
by Shuyou Han

Agrow's China correspondent, Dr Shuyou Han, interviews Dr Changling Liu - chief scientist at Sinochem International and R&D director at the Shenyang Research Institute of Chemical Industry (SYRICI).



Shuyou Han: *You are considered a pioneer in new active ingredient discovery in China and synthesised the first patent-protected fungicide, flumorph. How many new ai patents have you filed in China? How many of those have been commercialised? How many* patent co-operation treaty (*PCT) applications have you filed?*

Changling Liu: My efforts are the result of teamwork and I am fortunate to have the support of an able team. The discovery of a new ai is a costly process and was possible through funding from national, provincial, ministerial and Shenyang Research Institute of Chemical Industry (SYRICI) levels.

We have obtained more than 120 patents in China, and also more than 80 patents granted overseas, including in the US, the EU, Japan, Brazil, Canada, Australia, Argentina, South Korea and India. We applied for 27 PCTs.

We discovered flumorph fungicide, which shows preventive and curative activities against oomycete plant diseases. It got full registration from the Institute for the Control of Agrichemicals, Ministry of Agriculture (ICAMA) in 2006. Flumorph was the first pesticide that was patented in China, the US and the EU, and was awarded the golden prize for innovation in China. It has been widely used in Asia, Africa, and Latin America.

We discovered a series of strobilurin fungicides, such as pyraoxystrobin, coumoxystrobin, pyrametostrobin, and a strobilurin acaricide, pyriminostrobin during 1995-2007, all of those have been patented in the US, the EU and Japan. Coumoxystrobin has been registered by the ICAMA and is being used to control various plant diseases on vegetables, fruits, wheat, maize, rice and peanuts. Pyriminostrobin is in the process of being registered in China. More interestingly, pyraoxystrobin and coumoxystrobin function as insecticides, anti-virals, and plant growth regulators in addition to being fungicides.

Recently, we discovered the fungicides, SYP-4288 and SYP-5345, the insecticide, SYP-4380, and the herbicide, SYP-3301.

It is known that pyrimidinamine fungicides act effectively against downy mildew and powdery mildew, covering a global $1.5 billion downy mildew market and $2 billion powdery mildew market, which provide great business potential. As far as I know, Syngenta, Bayer, BASF, DuPont, Dow, many companies in Japan, and others have been active on pyrimidinamine research since the 1950s. They, however, could not address the higher acute toxicity issues (a hundred times higher than that of table salt). After exploring the issue for ten years, we have found the third generation of pyrimidinamines, such as SYP-2810, SYP-3730, SYP-4773, SYP-4777, SYP-9070 and SYP-9286. Their acute toxicities were even lower than that of table salt. Preliminary results showed that the novelty, creativity, and utility of pyrimidinamine molecules are advantageous due to their unique structure, mode of action, low toxicity, good efficacy and cost effectiveness.

SH*: Can you compare the differences between the big multinationals (MNCs) and Chinese new ai research teams in terms of research notions and equipment/research facilities?*

CL: China has had patent protection since the 1980s, which means that new ai discovery has been recognised and protected for over 30 years in China. But advanced countries, for instance, the US and the EU, started their pesticide ai innovation since the 1940s, 40 years earlier than us. They accumulated enriched research experiences on new ai discovery. In addition, there were over 20 research-oriented crop protection companies during the early 1980s, but only four big companies will be left soon (Bayer, Syngenta, Dow-Dupont and BASF). More research resources will make them unbeatable. In a word, there is a big gap between MNCs and Chinese research in terms of findings, market orientation, new ai databases, management skills, and ways of commercialisation. It is not only about lab work, but also about the whole pesticide production chain, ranging from the synthesis process in the lab, large scale production test in factories, formulations, registrations, procurement, supply chain and eventual shipment to farmers.

I do not think there is a big gap in terms of research facilities/hardware between China and other advanced countries. The biggest gap lies in the way of how a new compound is designed, or in other words, the methodology of new compound design. They adopt a market-oriented research system under which their new ais meet the requirements of end users by solving crop protection issues that farmers encounter. Based on my experience, our new ais must have the following features if we want to set up a joint project with MNCs: the molecular structure must be novel with no potential patent conflicts; the mode of action must be unique, which helps cope with resistance; and safety to crops, to the environment, high efficacy, low dosage, and cost-effectiveness both for synthesis and for farmers. It is a big challenge to discover one with all three features.

In China, most of research laboratories adopt "me-too" strategies because new ai discovery involves a big investment, long process and high risk. But the situation in China is of less funding and high pressure to get academic papers published. Some projects are initiated by researchers' interest rather than demands of the market. In fact, it is known that claimed scopes of the filed patents have become much wider than before, which narrowed down the opportunities to hunt for a brand new compound. You might have a novel compound but it is hard to say if its efficacy is superior to the patented ones.

SH: *Which MNCs have you been collaborating with? What have international scientific exchanges brought to your team?*

CL: I used to collaborate with Rohm and Haas/Dow during the years when I was doing my PhD degree, and I gained lots in terms of understanding the concept of innovation. Brand new ais are not only protected for 20 years, but they can also lengthen the future product life cycle, from which the relevant research companies could get paid off. On the other hand, one cannot control the product life cycle if the research is about generic products, or products with patent conflicts.

In order to penetrate markets, promising new ais must have one of three distinguishing features: complementarity, which allows you to differentiate the market; alternative structure, when there is no room to play with molecular structures and minor modifications on a chemical group could make a product more effective; or a revolution – a brand new structure with unclassified mode of action, which is the dream product that will surely lead the market. My research team and I have performed research work based on the above strategies since 2000.

SH: *Japan's new ai discovery teams are relative smaller but very productive. What are your views on that?*

CL: I keep in touch with Japanese researchers and have built up a good friendship with many of them. Japanese people in general work longer in labs, averaging 12 hours or even more per day. They design their crop protection compounds exactly based on target pests, which satisfies the features of complementarity, alternativeness and revolution.

SH: *Sinochem International has created the largest pesticide science and innovation centre. What does it mean for pesticide new ai research in China?*

CL: I think first class research outcomes will occur as we have first class research platform, facilities and researchers. I look forward to our platform and on communicating with researchers in MNCs.

SH: *How do you think ChemChina's acquisition of Syngenta will affect pesticide innovation in China?*

CL: Syngenta, the number one pesticide company, will become a part of ChemChina soon, which will provide us an insight into the global crop protection market. It will help make our new ai innovation more market oriented. Syngenta will open a door and pave a way for our ais to get access to the world's market. I think the acquisition of Syngenta will upgrade our new ai innovation capabilities.

SH: *You have often talked about Intermediate Derivatisation Methods (IDMs)? Why do you say it is an advanced research approach?*

CL: The objective of IDMs is to apply a wide variety of synthetic methodology on key intermediates resulting in an efficient route to innovative chemical structures. These structures, in conjunction with biological screening, become patentable leads or target compounds. There are three types of IDMs depending mainly on the functionality, namely Common Intermediate Method (CIM), Terminal Group Replacement Method (TRM) and Active compound Derivatisation Method (ADM).

The advantages of using IDMs to discover new ais are that IDMs offer us more flexibility to decrease risk of toxicity issues, shorten the ai development cycle, lower the complexity of the synthesis process by taking toxicity, raw material availability and derived diversity into considerations in advance. Furthermore, IDMs diversify molecular structures, thus making the intermediates novel structurally, which helps researchers obtain independent intellectual property and minimise potential patent conflicts. IDMs help make molecular design more reasonable, depending on the design notion, concept and objective.