Customer case study | Taiwan
Featured field bioinformatics scientist: Louis Tang

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Taiwan's effort to advance personalized health care relies on the expertise of a dedicated field bioinformatics scientist

From the initiation of the original Human Genome Project in the 1980s through today's advancements in understanding the impact of genetics on disease, Applied Biosystems™ technologies have been at the forefront of the effort to learn how our genes shape who we are. And all along this journey, the unsung heroes of the Thermo Fisher Scientific global services and support team have enabled researchers to get the most from these technologies, driving important discoveries at the dawn of the era of personalized health care.

Two years ago, Thermo Fisher launched an effort to highlight the hard work and dedication of our service heroes who support every aspect of life science research, from genetics and cell therapy to combatting viruses and global climate change. Leveraging feedback from our customers about the global services and support team members who have gone above and beyond in providing world-class support for their important projects, the Guardians of Your Science program honors and rewards these outstanding individuals around the world for their tireless effort to advance science.

This month, Thermo Fisher celebrates the extraordinary work of Louis Tang, a field bioinformatics scientist supporting Applied Biosystems™ Axiom™ microarray design, optimization, and data analysis in the Taiwan region. Louis has been instrumental in providing support to the Taiwan Precision Medicine Initiative (TPMI), a key research project in the field of predictive genomics: the study of 1 million participants to develop algorithms to aid in the future prediction of disease risk and drug response that can help focus the future of health care resources on improving outcomes and managing costs.

We spoke with Louis about his work for the TPMI project and then with his customer, Dr. Ling-Hui Li, PhD, a geneticist and senior researcher for the project, about the excellent support Louis has provided her team.

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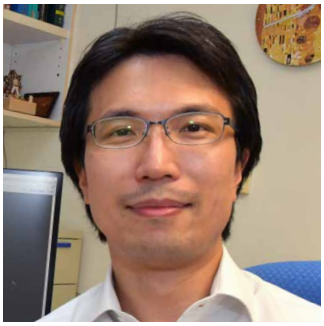
Interview with Louis Tang

Louis received his MSc in Computing Science from Newcastle University in the UK and his BSc in Agricultural Chemistry from National Taiwan University in Taipei. After working for over a decade as a researcher at Taiwan's National Center for Genome Medicine (NCGM), Academia Sinica, Louis joined Thermo Fisher in 2018 and returned to the NCGM to support their use of microarray technologies for the TPMI.



Louis Tang
Field Bioinformatics Scientist

Can you tell us about how your role supporting the TPMI came about?

After working as a research associate in academia doing mainly next-generation sequencing (NGS) data analysis at Taiwan's National Genotyping Center, I came to Thermo Fisher three years ago. The TPMI project had been established, and it gave me the opportunity to change my career to support this project from the other side (since I had already been a part of the TPMI team). It was a good opportunity for me to change my path and join the commercial world to experience things differently—and my former supervisor supported the idea. In fact, he encouraged me to do it, so they'd have someone they knew and trusted to support the project from the commercial side.

So you were able to bring some of that insight to your support of the project?

Yes, because of the connections I had with the TPMI, I knew what it felt like if we had any challenges—I understood the team's emotions, wishes, and needs, which helped me better manage their expectations.

What was the main focus of your work at that time?

The NCGM had become the primary genotyping center supporting the project, genotyping around 80% of the samples for TPMI. So, after I joined Thermo Fisher, I was fully focused on supporting TPMI—even though I'm a field bioinformatician and would normally support all kinds of bioinformatics problems across many different product lines, including Ion Torrent™ NGS technologies, microarray products, and various Sanger sequencing technologies. Because of this position that opened just for the TPMI project, my supervisor and I agreed that I should focus on this project and only support other projects if I had any free time. So TPMI became my whole world; almost everything I did was for the project. As for our other regional customers, we have a great support team, so I just provided some consultation for my team members who helped support these other projects.

> "TPMI became my whole world; almost everything I did was for the project."

Can you explain TPMI a bit more?

TPMI is an initiative to implement precision medicine in Taiwan. An Applied Biosystems™ Axiom™ microarray was designed for analyzing the DNA of Taiwanese people. The goal is to use this microarray to genotype one million participants. By analyzing a million people's genotype data and medical records, TPMI can look to create models to help predict the people's risk for common diseases and adverse drug reactions. With these models at hand, this project may be able to aid in future development of tailored medical treatments and health management for all Taiwanese people.

To implement this sort of precision medicine study in any country, you need to do two things: one is to collect information about the phenotypes of the entire population of the country, which in this case would be via electronic medical records. And the other thing is to collect the genotypes of the whole population of the country.

In Taiwan, we already have national health care and insurance that apply to 23 million people, so the phenotype part is already done. The problem is that we simply didn't have the genotyping results of a large percentage of the population. TPMI aims to genotype one million Taiwanese people in order to form the foundation of the precision medicine study by combining the phenotypes and genotypes of these Taiwanese. That will provide the basis for doing analysis and creating models to help aid in the future customization of medical treatment or health management suggestions for them. If the project is successful, hopefully the Taiwanese government will expand the genotyping to cover all the people in Taiwan.

> "This project can help the nation develop tailored medical treatments and health management for all Taiwanese people."

Has TPMI collected the genotypes from the million people yet?

Not yet, but they have recruited 400,000 participants and genotyped 300,000 of them so far; hopefully they can achieve the 1,000,000 goal by the end of 2023.

It's impressive to have done that during the pandemic.

Yes, indeed. That was really challenging when COVID-19 was so widespread worldwide, but we were lucky that in Taiwan the case numbers were relatively low. So TPMI was able to continue recruiting patients in hospitals to join the project.

How was TPMI able to recruit people to give their personal health information?

Well, that's the tricky part. As far as I know, the genotyping analysis is done for free, so that's one of the incentives. The other thing is that TPMI participants are told that if they provide a blood sample to join this project, they will receive information about the relevance of the study.

What is your specific role in supporting TPMI?

As a field bioinformatician supporting Axiom microarray products, I am responsible for three things:

1. Microarray design

The human genome has more than one billion known SNPs (single-nucleotide polymorphisms, used to measure genetic variation) while the maximum capacity of an Axiom microarray is 800,000. How to properly select the target SNPs and design the detecting probes to meet customers' needs is the key to success. Though Thermo Fisher has a dedicated array design team to create the custom arrays, it is my job to make sure that the design details meet the customers' needs and that the customers have a reasonable expectation for the performance of this design.

2. Microarray optimization

The same microarray may provide different levels of performance for different populations; microarrays have a collection of adjustable parameters to cope with this issue. It is my responsibility to collaborate with customers and optimize the microarrays for the target populations.

3. Microarray data processing

The primary output of microarray analysis is genotype/CNV (copy number variation) calls. For small to medium-sized projects, we have a user-friendly application to process microarray data and get the corresponding genotype/CNV calls. For large projects with more than 100,000 samples, we provide a collection of utilities for customers to build their own data processing pipeline. I am responsible for training customers to use these applications and helping them establish their genotyping pipeline if necessary.

The customer obviously appreciates your work. How do you feel about being selected for the Guardians of Your Science award?

My supervisor nominated me because of what I did over the past several years to serve the customer, and that's great, and I am still supporting them and focused on meeting their needs today.

Interview with Dr. Ling-Hui Li

Dr. Li is assistant director at the National Center for Genome Medicine, Academia Sinica. She received her PhD in developmental biology in the graduate program of Molecular and Cellular Biology, SUNY at Stony Brook in New York, and did her postdoctoral work in Taiwan at the Institute of Genetics, National Yang-Ming University; the Division of Molecular and Genomic Medicine, National Health Research Institutes; and the Institute of Biomedical Science, Academia Sinica, Taiwan, where she is now a research scientist.

Dr. Ling-Hui Li
Assistant Director at the National Center for Genome Medicine, Academia Sinica

Can you tell us about yourself, your lab, and your role with the TPMI?

I was trained as a geneticist, and studied embryo development of *Drosophila melanogaster*, which you know as the common fruit fly. It is used as a model organism to study human diseases like neurodegenerative disorders since about 75% of the genes responsible for human diseases have homologs in this fly. So that was the focus of my PhD work.

To perform genetic experiments directly in humans is impossible, but we can perform genetic engineering with fruit flies—any kind of gene you can think of—so they provide a very good model for genetic research. But I switched to human genomics for my postdoc work. So the TPMI fits my expertise, and that's why I'm involved in this project.

When I came back to Taiwan to do my postdoc, I started to be involved in the Human Genome Project. I was involved in sequencing a segment of chromosome 4 of the human genome, which was a milestone for genomics in Taiwan. I was then recruited to the Institute of Biomedical Sciences, Academia Sinica, in Taiwan; that's where the TPMI project started. There is a center called NCGM, and I am the supervisor of the genotyping team there, so when they started the TPMI project, they thought I should supervise the genotyping platform.

Doctor Pui-Yan Kwok, the director of the Institute of Biomedical Sciences, initiated this project about three years ago. In the beginning, of course, we did things slowly because even though I had supervised microarray genotyping for more than 10 years when I joined the TPMI project, we hadn't done such high-throughput genotyping before.

Can you tell us more about the goal of TPMI?

Yes, the goal of the TPMI is to work toward developing risk prediction algorithms to aid in identifying individuals with a high risk of common diseases and offer them optimal health care strategies to reduce that risk. The reason we intend to study the genetic profiles and clinical data from 1 million participants in Taiwan is so that we have sufficient data to develop these algorithms.

The idea is that if we can identify those who are at high risk of developing cancer at an early age, for example, they can be screened for cancer at a younger age than that for the general population. For those who are likely to develop adverse drug reactions to particular medications, alternative medication or dosing can be used to mitigate the risk. Once reliable disease risk prediction algorithms are developed, health care can be personalized and focused on disease prevention, early disease screening, and optimized use of medication.

Already successful in Taiwan is the prevention of adverse drug reactions. Some people develop severe adverse reactions to specific types of drugs that can be predicted by their genotype. It turns out that genetic risk factors for several severe adverse drug reactions are HLA types found only in the Han Chinese. Routine screening for these HLA types prior to prescribing the medication in question has completely eliminated these adverse drug reactions in Taiwan. This points to the need for us to generate our own data and conduct our own studies, because results from other populations often do not apply to our population.

Genetic profiling for common disease risk prediction and preemptive genotyping for genetic variants that affect drug response will usher in the era of precision medicine in Taiwan.

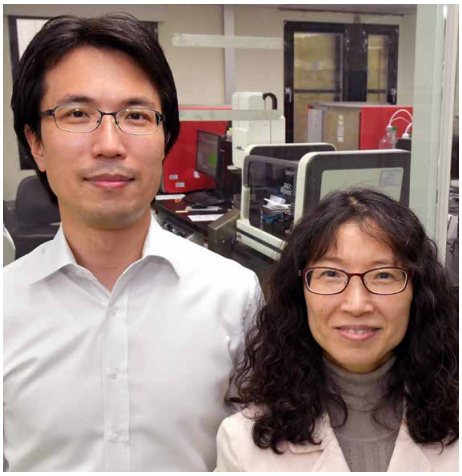
Can you tell us about the use of microarray technology for the research and how Louis Tang helped you?

Doctor Kwok proposed that we should have our own Taiwan-specific SNP chip instead of using the existing one. We hoped that the chip would eventually have clinical-use value. We developed that backbone SNP chip, and we also collected SNPs from our partner hospitals. There are so many sources of SNPs because TPMI is a very big project. And it's from there that Louis joined us and provided his help and support. He did the coordination of the SNP array content.

As I said, there was a lot of information coming in, so of course we had someone here to coordinate it, but we still relied on Louis to compile all the data before handing them off to the Thermo Fisher array design team. That's tough and tedious work. Louis did a really good job compiling all this information and then transferring it back to the design team and transferring the results from the design team back to us, facilitating the ongoing discussion until we had the finalized version of the SNP array. From the very beginning of this project, Louis has made a major contribution by helping us finalize the SNP array.

Then after we started the high-throughput genotyping, we did encounter some problems. Louis helped us with every different type of challenge we encountered—and, by the way, I'd like to mention something about Louis himself, because I think personality is quite important. He is helpful and thoughtful. His attitude is quite good. He doesn't just take this as a job. He really makes himself seem like a part of our team, and whenever we report a problem, he provides a very quick response and visits my office as soon as possible.

Once he came to me to clarify the problem, and I shared some data with him to explain it, and he took it very seriously. He always takes notes, you know. And then after I explained what we faced, he double-confirmed the data with me to make sure they were ready to bring to Thermo Fisher to solve. That's his greatness: he catches the real problem and tries to find the solution for us. And he's always quite gentle and listens well.



"From the very beginning of this project, Louis has made a major contribution by helping us finalize the SNP array."

You said you kicked off TPMI in 2019. How much were you affected by COVID-19 and how far along are you toward meeting the project's goals?

We have 14 partner hospitals that we needed to have agreements with regarding sample collection and how we report results, so the logistics took some time.

Even though we have more than 300,000 genotypes, we are still slow. Some of our partner hospitals have been severely affected by the pandemic. That really slows down the recruitment process, and it has also affected the genotyping at those sites—because in addition to the genotyping performed in the National Center for Genome Medicine here at Academia Sinica, we also have instruments installed in five of the partner hospitals. So the pandemic actually affected the productivity of the genotyping at some of those hospitals. But here at Academia Sinica, we don't see patients. We have just routinely kept working through everything. Of course, there was a period where we had level-three regulations for the pandemic, so we had to take turns working in the lab, which affected our productivity a bit, but it was just for about two months. So, we are still okay here, but for the partner hospitals, yes, the interference has been bigger.

"He doesn't just take this as a job. He really makes himself seem like a part of our team."

How does Louis work when faced with problems? Has he helped you navigate these challenging times?

For Louis, I think the pandemic hasn't slowed him down—because most of the time we have been able to still meet and discuss problems. After some genotyping was done, for example, we figured out that there were some issues with the genotype calling.

Louis was, in fact, my colleague before. He worked in the same center with me. He is a very good bioinformation scientist and highly motivated to learn new things: new techniques, technologies, and knowledge. When I think back on what we have done to advance this project together, I think about his strong motivation to learn. Indeed, when he was working with me as a colleague here, he learned a lot of biology from me. So, he not only knows information, he knows biology.

So when we reported that the genotype call is not what we expected—missing data and so forth—he mentioned that there is a way to solve this problem. He recommended another Thermo Fisher scientist who had experience at UK BioBank, who knew how to implement this solution—but he needed to access the data generated by TPMI, and it was locked. In this place, no one can get remote access. Thermo Fisher proposed sending that scientist here to implement what they called the biobanking pipeline to adjust the SNPs that were problematic.

But because TPMI would take a long time, and we already had a plan to revise the array to create a version 2 and version 3, we really needed to have someone that could routinely perform this work in Taiwan. Louis is quite active in this field and, as I said, highly motivated. He said he could learn and then perform it himself. So that expert from Thermo Fisher in the United States was here for two weeks to teach Louis how to perform the analysis, and soon after that, Louis was able to do this on his own. He was so dedicated. I think he worked very late every day in our lab. He was the first field scientist on the whole global team for Thermo Fisher to perform the biobank pipeline outside Thermo Fisher headquarters—and did it using a different server, different hardware, and a different system. With minimal training, he quickly learned the hardware and the server structure. I don't know how he achieved that, but I know that he worked so hard that I believe he was often the last one left in our lab. The implementation of the biobank pipeline was important for us because some SNPs are critically important.

What do you hope to achieve next?

There are two parts to what we want to achieve. One is to screen for the already known SNPs that can be applied to potential future use, and the other part is for research: we would like to perform a genome-wide association study with these data and find even more SNPs that are potentially clinically useful. So that's why we have a second version of the array. And since Louis now has experience performing the biobank pipeline, he can work on that immediately after we have collected enough data. That has really helped us a lot because for the TPMI project we asked for a very high quality of SNP genotyping. In general, people think that for research the successful rate for genotyping—the professional term is "call rate"—is about 95%, but for our project we asked for a much higher rate than that; we didn't want to miss too many SNPs, and I think Louis' implementation of the biobank pipeline really helped us to increase the call rate. We have achieved a rate of about 99.7%. Louis did the pipeline process to make sure the data analysis could achieve that.

On the other hand, we still experienced some difficulties with array quality, and Louis also helped us communicate with the global professionals at Thermo Fisher to recognize the problem. As I said before, Louis had a very good habit of taking thorough notes, and he would send a memo to me to make sure what we discussed had been recorded correctly. Then he would communicate with the global team, so the global team could ask him to ask us for other information they needed to help us. I think he did a great job in this communication aspect too.

Any additional thoughts on the future of the project?

Of course, this project is quite promising, but we really need to reach a critical threshold of samples so we can see its impact. I think the unique homogeneity of the genetics of Han Chinese makes it much easier to do this kind of project in Taiwan because in places where the genetic background is quite mixed, it's hard. Like I said earlier, the reason we had a successful study of linking adverse drug reactions and genotypes is because we are Han Chinese. So that's why we are quite eager to build our own database and not just use UK BioBank data or other population studies like from the US. The achievement of this project will not only benefit people in Taiwan but also Han Chinese around the world because the foundation of TPMI is genetics. And I'd also mention that because of the scale of the study, microarray is a fast, useful, and cost-effective tool for studying a large, homogeneous population.

"Louis had a very good habit of taking thorough notes, and he would send a memo to me to make sure what we discussed had been recorded correctly."