Interview: Ming-Kuei Jang – Founder & CEO, Aprinoia, Taiwan



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19.05.2017

Tags: Taiwan, Aprinoia, CNS, R&D, Partnerships, Biotech, Pharma

Ming-Kuei Jang, founder and CEO of Aprinoia, a very promising Taiwan-based company focused on the development of groundbreaking imaging tracers and therapeutics targeting tau-related neurodegenerative diseases, provides insights into the company's rapid development over the past two years, its R&D strategy, and its eagerness to partner with both academia and the industry to bring life-changing and affordable products to CNS patients around the world.

Could you walk us through the main milestones of your career that led to the creation of Aprinoia in May 2015?

I studied chemistry at National Taiwan University and obtained my PhD in Pharmacology and Neuroscience from Boston University School of Medicine. After completing two postdoctoral trainings at Northwestern University and Columbia University in neurophysiology, I decided to join the pharmaceutical industry. I first worked as a Senior Research Biologist for Merck's neuroscience drug discovery laboratories, where I was managing Alzheimer's disease drug and biomarker discovery programs as well as academic and industrial collaborations. I then moved to GlaxoSmithKline in Shanghai where I was appointed Associate Director in their Neurodegeneration Discovery Performance Unit and was responsible for formulating and executing therapeutic strategies for Alzheimer's disease.

Prior to returning to Taiwan in 2015, I spent two years at the MD Anderson Cancer Center in Houston leading a newly established Alzheimer's drug discovery consortium, which gathered researchers from MIT, Baylor and MD Anderson. Following an initial funding of USD 25 million, this unique research program raised an additional USD 25 million to develop both imaging devices and therapeutics.

Through my experiences at GSK and MD Anderson, I got the opportunity to closely partner with the National Institute of Radiological Sciences (NIRS), a radiology and nuclear medicine research center located in Japan. One of NIRS' research teams was notably working on new imaging tracers for neurological diseases, targeting both psychiatric disorders and *tau*-associated neurodegenerative diseases such as Alzheimer's disease *[tau proteins stabilize microtubules and are particularly abundant in neurons of the central nervous system, e.d.]*. In 2014, NIRS' principal investigator, Dr. Makoto Higuchi and I came to the conclusion that we could more rapidly develop this promising technology by bringing it into the private sector.

I then founded Aprinoia in 2015 and in-licensed the global development and marketing rights of these revolutionary tracers from the NIRS, as part of our plan to bring them as swiftly as possible to patients, clinicians, and drug development companies around the world.

Founded only in 2015, Aprinoia is now advancing the development of the aforementioned imaging tracers as well as groundbreaking therapeutics and antibodies for Alzheimer's disease and other *tau*-related diseases. How would describe the company's R&D strategy?

We are following a different strategy than most companies involved in the CNS field – an area that has remained desperately static in recent decades, despite dramatic unmet needs.

In neurological diseases in general and for Alzheimer's in particular, FDA's assessment of clinical results is essentially based on the drug's capacity to trigger cognitive modulations and improvements, which can take a very long time to materialize or being difficult to identify – even when the drug tested is truly engaging its molecular target. As a result, many researchers around the world have been working on developing new biomarkers, including new imaging tracers, as surrogate clinical readouts for pathological changes. The latter would allow monitoring the evolution of the disease at the molecular level, providing a precise assessment of the drug's efficacy way before cognitive improvements are noticeable.

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Furthermore, these new tracers would also improve the current diagnostic capacity. Most neurological pathologies start spreading through patients' brains way before the first signs of cognitive impairment actually appear. For Alzheimer's disease for instance, Amyloid betas sometimes start to aggregate up to fifteen years before physicians can detect the first symptoms of the disease. As a result, the medical and research communities cannot start treating patients at the early stage of the disease development, which however stands as the most effective treatment window for neurodegenerative diseases.

As a result, Aprinoia is committed to a two-fold mission: first, developing the tracers that will allow us to truly monitor *tau* pathologies at the molecular level; and, by leveraging the heightened visibility that these tracers would offer, developing the small molecules and antibodies targeting these pathologies.

So far there is no FDA-approved *tau*-tracer in the market. We however see a global effort from both academia and the industry to develop innovative tracers for *tau*-related diseases. What sets Aprinoia' *tau* tracers apart?

The development of Alzheimer's disease is notably driven by *tau* proteins that have become defective and no longer stabilize microtubules properly. It has been found that *tau* proteins are also involved in the development of other non-Alzheimer's brain disorders, including progressive supranuclear palsy (PSP), an uncommon brain disorder that causes serious problems with walking, balance and eye movements.

In 2015, we decided to in-license NIRS' technology, called PBB3, which has already been clinically tested on more than 200 patients throughout its development. Over the past two years, we have been concentrating our efforts on addressing this product's remaining rooms for improvements. For example, the first generation of tracers had a half-life of 20 minutes, rendering impossible to use them in large-scale clinical trials. We also worked on improving the photo sensibility of these products, which had to be manufactured and administered in the dark or by using dimmed light. We then managed to convert the carbon 11 at the core of this first generation of tracers into a longer lasting compound, F-18. This new generation of tracers, F18-PM-PBB3, just completed an exploratory clinical study.

F18-PM-PBB3's clinical results are extremely promising, especially in comparison to those developed by leading pharmaceutical companies in the world. While some of those tracers are only targeting *tau* aggregations involved in the development of Alzheimer's disease, our tracers have proven being efficient in a diverse neurologic diseases, which truly stands as our technology's

competitive edge. Furthermore, our technology's imaging capacity boasts a level of precision that is absolutely unrivalled, especially for the motor area of the brain, which is critical for PSP. Finally, our second generation of tracers can be used in both animal studies and clinical development, which is – again – a very interesting specificity that most of our competitors' products do not hold.

Following the promising phase I results of Aprinoia's tracer F18-PM-PBB3, what are the next development steps that you envision?

When it comes to clinical trials, PSP's patient's population is more homogenous than for Alzheimer's disease, while clinical trials for Alzheimer's disease require to invest in large patient number, longer-lasting phase III trials – making PSP a great staging disease to test our tracers and therapeutics. In the meantime, *tau* pathologies truly stand as the main driver of PSP, while multiple factors are usually involved in the development of Alzheimer's disease. As a result, we are now conducting in the US a phase 0 exploratory trial on two different diseases, Alzheimer's and PSP, while we expect both trials to be completed by the end of March 2017.

We are also about to initiate a phase I/II trial in Taiwan, in which we will test our tracer in different diseases to better define its therapeutic scope. In the meantime, our partner NIRS is conducting a PI-initiated study in Japan, a country where we are about to open an office. We notably want to get more involved in *tau*-related research in this country, as the Japanese government announced the set up of a holistic, tau-focused research consortium including both companies' and academia laboratories, which could tremendously benefit from our tracers.

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In the meantime, our third generation of tracers which are selected from our focused chemical library (>500 diverse new compounds) that we design and generated, will start a first-in-human trial before the end of 2017. In addition to those tau tracers, interestingly, some of the compounds in our chemical library do not bind to tau proteins any more, but show ability to detect alpha-synucleins aggregates that form insoluble fibrils in Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. We are particularly eager to move forward on the development of those compounds, as no tracer under development has proven being able to detect alpha-synuclein aggregates.

Besides Aprionoia's contribution to this research program in Japan, to what extent do you consider partnering with other pharmaceutical companies that could be interested in using your tracers to develop their own products?

We are currently talking to several potential partners around the world which could use our tracers in both preclinical and clinical settings. Overall, we plan to leverage our upcoming clinical data to trigger a more aggressive partnership approach.

Looking at the different forms that these potential partnerships would take, we are particularly flexible – although our company's philosophy is to ensure that our tracers can benefit to the largest patient population possible. In this regard, one of our main objectives is to offer cost-efficient and affordable products. In this vein, our ability to form comprehensive partnerships with pharmaceutical and hardware companies as well as with governments will be absolutely critical to make our tracers both affordable and widely accessible.

Although strategic partnerships hold a central importance in our growth strategy, we already have great institutional investors supporting the development of our company. We completed our Series A round in 2016 and now hold three major investors from Taiwan, Japan, China, including the Daiwa Taiwan-Japan Biotech Fund Investment [*Japan's largest biotech fund targeting both Japanese and Taiwanese biotech companies*] as well as Shangpharma Corporation, a Shanghai-based service and investment company which also stands as crucial and generous partner in the development of our compounds. We are now preparing a series B round, which we want to complete before the end of 2017.

In the meantime, how are you advancing on the development of your tau-inhibitor and tau-antibody?

We have identified chemical compounds that can cross the blood-brain barrier, and change aggregation status of pathological tau proteins. The preclinical development has been extremely promising and we now plan to prepare for a US FDA's IND in 2018.

In the meantime, we are also working on an anti-tau antibody. *Tau* pathologies display a very unique development pathway: while *Tau* proteins are only located within neurons in healthy patients, pathological tau species in patients could be released between neurons to other parts of the brain when a patient develop a tau-related disease such as Alzheimer's. The evolution of the disease then reflects the gradual contamination of successive parts of the brain by *tau* pathologies. This is why we think antibodies would stand as an interesting therapeutic option: they could capture released pathological *tau* species and confine these pathologies to infected neurons or brain regions, preventing them from spreading to the rest of the brain.

We are not the only company working on these promising products: leading biopharmaceutical companies like Eli Lilly and BMS are also developing anti-tau antibodies. What sets our R&D

approach apart is that we are apply novel technologies and screening strategies to generate antibody libraries with antibodies with diverse properties and potentially with abilities to recognized various form of pathological *tau* species and aggregates – offering divers and efficient therapeutic options.

Where will the company be in five years?

Our imaging tracers and therapeutics (i.e. *tau*-inhibitor and *tau* antibody) will be well advanced in their clinical development. In five years, I expect we would have completed phase II trials for our therapeutic drugs, including both our small and large molecule products.

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I also hope a large number drug development companies and research institutes will be using our imaging tracers and that Aprinoia will play a very central role in helping researchers around the world to develop new *tau*-related drugs. As a company, we are not only focused on building our own success, and it is a priority for us to see our tracers contributing to the promising development of other companies’ therapeutics products.

In the grand scheme of things, I also hope that more companies will take the risk to invest in the clinical development of CNS drugs. In 2050, as many as 135 million people globally may have Alzheimer’s diseases, while – in the US alone – the total annual payments for health care, long-term care and hospice care for people with Alzheimer’s or other dementias are projected to increase from USD 259 billion in 2017 to more than USD 1.1 trillion in 2050. Medical needs in this area are huge and keep on tremendously increasing year after year, as – in countries like Taiwan for example – population is rapidly aging.

In this regard, any company that holds a drug able to modulate the disease should be supported. As Aprinoia, we will continue to push the development of our own, promising products and tracers, while in the meantime, we are ready to partner and to help any ambitious company that wants to make a real difference in this crucial field.

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