Interview: Guochuan Emil Tsai MD PhD MAS – Founder & CEO, SyneuRx, Taiwan

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With more than 100 peer-reviewed articles published and more than ten thousand citations, Guochuan Emil Tsai, founder and CEO of SyneuRx and Professor at the department of Psychiatry and Behavioral sciences at the University of California, Los Angeles (UCLA), is an internationally reputed scientist in neurosciences and brain disorders, whose main area of focus is the enhancement of the NMDA system. As CEO of SyneuRx, he provides an overview of the company's extremely promising R&D pipeline and the seven groundbreaking CNS treatments that will undergo late stage trials in 2017; two of these products having already been granted breakthrough designations by the US FDA.

You were the first scientist to report the therapeutic efficacy of N-methyl-D-aspartate (NMDA) receptors enhancement for a wide variety of CNS disorders; setting the tone for a novel line of neurological treatments. As an introduction to our international readers, could you explain how you ended up founding SyneuRx in 2013?

As a psychiatrist and CEO of a drug development company, my main driver is science and – more precisely – when science truly benefits patients. In academia, the closest you can get to this objective is through translational medicines, which never actually reach the patients. As a result, the only way forward for me was to embark on drug development, prompting me to found SyneuRx in 2013 in order to ensure that patients around the world could fully benefit from the learning and expertise accumulated through 20 years of research.

In the mid-1990s, I started working on translational studies focused on NMDA enhancement at the Massachusetts General Hospital (MGH), the largest teaching hospital of Harvard Medical School and one of the best biomedical research facilities in the world. Only two years after I started conducting these studies, the first results I had gathered were already particularly interesting. My research supervisor then advised me to fill a patent for this product, which was actually granted in 1999. In academics, the traditional thinking is to concentrate your efforts on basic research and license-out to pharmaceutical companies such patents – an unfortunate decision for which I paid a high price, as my commercial partner left it on the shelf for ten years. This terrible decision somehow highlights the huge gap that still lies between promising academic findings and industry's strategic decisions.

During these ten years, I was however accumulating more and more evidences that this treatment would work. In 2010, a patient's family approached me after all existing treatments had failed to cure a patient affected by psychosis. After having studied this patient's history, I identified that the only option likely to work was a shock treatment. Nevertheless, the regulations in California, where I was based at this time, do not allow shock treatments for patients under 16 years old – unless it is approved by a court decision, which is extremely hard to obtain. Given how desperate the situation was, I suggested testing my compound as part of an experimental treatment. The results we obtained for this patient were almost miraculous. The exact same year, the company to which I had licensed-out my patent ten years before decided to return it to the MGH. I then decided to license it out and founded SyneuRx, in 2013, with the ambition to develop by myself the product I have been working on for 20 years.

Although it is particularly rare in the CNS field, two of your products (SND 13 and SND 12, in schizophrenia) have already been granted breakthrough designations by the US FDA, in December 2014 and November 2015 respectively. You now plan to apply NMDA enhancement to a vast array of brain disorders. Could you provide us with an overview of the mechanism that makes NMDA enhancement therapeutic such a promising option for CNS diseases?

In a way, NMDA mechanism can be considered the molecular foundation of the brain. For example, deactivating a subject's NMDA system will make him lose all his memories and completely block the capacity of the brain to further develop through cognitive learning and experience, to the extent that neuronal cells may even start to drop out. Overall, the NMDA system plays a fundamental role in neural activation, as 80 percent of all synapses use glutamic acids, whose receptor is mainly the NMDA system.

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Based on the evidence we held that blocking the NMDA system would make a patient psychotic, I predicted – in the late 1990s – that enhancing it could in turn allow the treatment of psychosis. When testing NMDA enhancers as part of the translational studies I just mentioned, I also realized that psychotic patients' depression was improving. Further studies then proved that we had also identified a primary mechanism for the treatment of depression and suicidal thoughts, and that positive outcomes for depression were not only due to the treatment of these patients' psychosis.

Although it can be compared to a Prozac-like mechanism, the clinical studies of our products have been displaying remission rates two times higher than with this treatment, while also greatly reducing suicidal tendencies. In this regard, we are now designing the protocol for the phase III trial protocol of the first ever anti-suicidal drug.

You set up SyneuRx to ensure patients could eventually benefit from ground breaking CNS treatments based on NMDA enhancement. In light of this objective, how have you been progressing in the advancement of your promising R&D pipeline?

Our mission now is to further confirm the groundbreaking results we obtained during the first phases of the clinical development of our products. Overall, in 2017, seven treatments will be in phase II/III study, encompassing critical indications. Our R&D pipeline indeed comprises two first-in-new-class products for major and refractory major depression (SNG-12 and SNA-1), two new indications, first-in-new-class products for early and mild dementia (SND-14 and SND5), and three first-in-new-class products in schizophrenia, namely SND-11 (adolescent schizophrenia, orphan drug), SND-12 (orphan drug, combinational therapy for refractory schizophrenia with US FDA breakthrough therapy designation) and SND-13 (an add-on therapy of schizophrenia which was also granted a FDA breakthrough designation).

At the moment, we are focused on advancing the development of the two schizophrenia products that received breakthrough therapy designations, which are particularly rare in the CNS field. As part of this breakthrough designation program for expedited development, we will get an additional access to the FDA in order to support a quicker path to a NDA application and discuss the most reasonable and efficient way to develop these two highly needed drugs. We now expect to start the phase II/III trial of these drugs in March 2017, while we still own the global rights for all our products. In this regard, we are currently discussing some licensing opportunities with potential partners, but nothing has been officially signed yet.

Considering the fundamental role of the NMDA system and the broad spectrum of CNS diseases it can impact, what are the new treatments that you plan to develop?

Although our current pipeline already holds some game-changing treatments, the future products we envision are even more exciting!

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For example, one of our early stage product (SND-3) targets amyotrophic lateral sclerosis (ALS), a neuro-degenerative disease which causes the death of neurons controlling voluntary muscles. We also hold a product focused on metabolic syndromes (SND-7), as more than 50 percent of the patient population taking antipsychotics also display metabolic disorders. SND-7 is an improved version of two breakthrough therapies, targeting both psychosis and metabolic syndromes. This product actually required a lot of work on the chemistry side in order to develop a co-crystal structure: one of this product's component being an antipsychotic, the other aiming to lower cholesterol and sugar rates.

Leveraging my clinical experience, I believe that brain development issues, whether they are caused by early childhood trauma, parental deprivation, or genetic predispositions, provoke a broad spectrum of illnesses and diseases that go beyond the CNS field. Considering NMDA enhancement stands as mechanism operating at the brain development level and my twenty years of study of this mechanism, I would not be surprised if we can prove that NMDA enhancement therapeutics can work for so many different conditions. Nevertheless, my experience leads me to pay extra attention to some specific conditions, such as dementia and bipolar disorders for example, for which we designed different studies and selected different candidates.

Finally, we also hold a product in our pipeline, SND5, specifically targeting the Chinese market. In China, traditional Chinese medicine still make up around 30 percent of the market, which prompted us to adopt a completely different R&D strategy than for the US and the EU. In this regard, we found that one of our compounds could be developed as a TCM, although it is developed as a NCE in US/EU.

Overall, SyneuRx's drug development approach is based on chemistry, biology, medicine and IP but also on regulatory aspects, as we strive to identify the best pathways to market for all our products, depending on the country considered. In the US, we are then leveraging the orphan drug and breakthrough designations we received, while, in China, the TCM approach could allow us to bring our products to the market more swiftly and efficiently.

One of the main challenges in the CNS field relates to the execution of clinical studies. As CEO of the company and a reputed expert in the CNS field, what are your priorities to overcome the challenges that you identify as the company is about to run seven late-stage trials in the next few years?

We worked on the design of these trials for more than a year, and we looked at implementing a lot of novel design when conceiving their protocols. The placebo response in CNS treatment trials is notoriously high. The problem does not lie in placebo response: placebo response is real – and some patients, just by being closely followed by physicians over the course of the trial, may truly feel better. The only problem is that the signal-to-noise for most CNS treatments is extremely narrow: when the placebo arm traditionally displays a high response rate of around 30-40 percent, the response rates displayed by most innovative drugs do not exceed 50 percent.

Nobody knows how to deal with the placebo response, but we have been trying to implement novel approaches to cope with this issue, such as two successive randomizations: after the first randomization, only placebo non-respondents will continue to the second randomization. On the other hand, this approach implies eliminating a large number of participants, as – after the first randomization – we will have to eliminate around 40 percent of our initial subjects. Nevertheless, I truly believe it is worth it, and I expect we will get a much better signal thanks to this approach.

In the meantime, we have to cope with cultural differences in case ascertainment: for example, chances are that a same patient will be diagnosed for schizophrenia in one country and for bipolar disorders in the other – and this example has already been documented by scientific literature. As a result, we identified that it is absolutely crucial to build a solid monitoring system and a robust rating system for our trials, while many global trials failed in the past because of the lack of consistency among the 1000 raters that may hold a four-continent, 3000-patient global trial, for example. In our trials, we ensure that every single subject enrolled is recorded, monitored and approved before it is randomized. During our trials, we also run algorithms to detect abnormal inconsistencies among the different sites and raters and prevent these problems from contaminating the entire study.

Moving forward, what do you identify as the most important success factors for SyneuRx?

As we will start seven late-stage clinical trials in the coming years, our treatments are now on the brink of reaching the market – and our key markets obviously are the US, EU and China. Considering the size of our domestic market, it is absolutely crucial for Taiwan-based biotech

companies to become active on the global stage, whatever it takes to reach this objective: acquisitions, licensing agreements or strategic partnerships.

> “Science is fundamental, but – as a Taiwan-based company – the capacity to internationalize our business is probably even more important.”

Science is fundamental, but – as a Taiwan-based company – the capacity to internationalize our business is probably even more important. This aspect cascades down to the execution of clinical trials, as a true global capacity is needed to conduct multi-center phase III studies. If you content yourself with delegating a CRO to conduct challenging trials on your behalf, it is very likely that you will never get the results you envisioned. I personally designed and now supervise all our trials, because I believe that when it comes to bringing an innovative drug onto the global market, the main success factor is the quality of execution. At this stage, it is not about science any longer, but about being able to build the conditions that will clearly showcase the scientific outcomes that you have identified.

What is your vision for the development of SyneuRx?

We hold top-rated scientists and will become a world-class CNS company over the next five years. If our two breakthrough therapies reach the market, they will instantly raise our profile within the industry and among regulatory stakeholders. In CNS, the competition is particularly limited, while 30 percent of all repositioned drugs are CNS treatments – there is clearly a lack of new, innovative treatments coming to the market. When you consider that 70 percent of CNS drugs used in the US are off-label, our promising treatments undoubtedly hold huge market prospects.

Our positioning and ambitions are extremely clear: SyneurRx is a science-based company focused on high-impact, novel CNS drugs, whose benefits target both the patients and their families. I am a physician, my first and foremost objective is to do the things right for the patients – the rest will follow if this condition is truly fulfilled.

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