US-based Neuro-Horizon Pharma licenses promising compounds from NTU Singapore to combat multidrug-resistant tuberculosis

02/08/2022 Nanyang Technological University, Singapore

With multidrug-resistant tuberculosis (TB) causing outbreaks in both developing and developed nations, new treatments are urgently required to tackle this infectious disease.

A series of chemical-based compounds which could be potential drug candidates in the fight against TB have been developed in Singapore.

The compounds are developed by a joint team from **Nanyang Technological University, Singapore (NTU Singapore)** and the **Experimental Drug Development Centre (EDDC)**, a national drug discovery and development platform hosted by the **Agency for Science, Technology and Research (A*STAR)**.

Neuro-Horizon Pharma LLC (NHP), a US-based drug development company, has licensed the compounds for commercialisation from NTU's innovation and enterprise company, **NTUitive**, which had filed patent applications for the compounds.

The World Health Organisation[1] estimates that over 1.5 million people die from TB worldwide, making it thesecond leading infectious disease killer after COVID-19.

Caused by the bacterium*Mycobacterium tuberculosis*, TB is an infectious disease that has plagued humankind formore than 70,000 years[2], with an estimated 10 million new cases of tuberculosis annually.

Earlier in June, the Ministry of Health announced that 170 people had tested positive for TB in a large cluster[3] in Singapore. TB is endemic in the developed city state and the prevalence of tuberculosis infection can be as high as 29% among those aged 70 to 79 years.

Founder and CEO of NHP Dr Vladimir Marshansky, said: "We are pleased to partner with NTU Singapore to develop compounds for treating pulmonary tuberculosis, which remains a public health crisis today."

"Current regimens for treating tuberculosis are lengthy and suffer from toxicity issue while drug-resistant strains of the respiratory disease are becoming more prevalent, with only 1 in 3 people suffering from drug-resistant TB having access to treatment," added Dr Marshansky.

This discovery was made possible through a transdisciplinary platform called **TOPNet** (Targeting Oxidative Phosphorylation Network) that is supported by the **National Research Foundation Singapore [4](NRF Singapore)**.

TOPNET is led by **NTU Professor Dr Gerhard Grüber** in collaboration with EDDC and **Prof Thomas Dick** from the **Center for Discovery and Innovation Hackensack Meridian Health (CDI)** in the US.

Prof Grüber said that developing innovative solutions to tackle some of humanity's greatest challenges, like the ever-evolving infectious diseases, is a key pillar of the NTU 2025 Strategic Plan.

"This partnership between NTU Singapore and NHP is a great example of how basic fundamental research at the University can yield great results years later, such as drug compounds that have a big impact on public health. When we started our research, it was imperative that we understood all the key processes needed for the survival of the TB bacterium. With that done, only was it then possible to identify key targets of the adenosine triphosphate (ATP) processes that could stop multidrug-resistant tuberculosis bacterium from proliferating and replicating, opening up the potential fpr new treatment options," explained Prof Grüber.

These small molecule compounds were shown to inhibit a key enzyme used by the TB bacterium to produce ATP, an important molecule that is the primary source of energy for living cells.

At the molecular level, this ATP-producing enzyme is akin to a nano-sized Wankel[5]-like rotary motor that turns to convert energy from one type to another type. If the ATP-enzyme stops running, the ATP production process and the resulting energy supplied to the TB bacterium will be disrupted. This can be likened to how a car comes to a halt when its engine stops.

The path to the discovery and design of these small molecules was paved by earlier NTU studies on the metabolism of drug-resistant TB, done by **Prof Grüber**, **Assoc Prof Roderick Wayland Bates**from theSchool of Physical and Mathematical Sciencesand**Assoc Prof Kevin Pethe**, Provost's Chair in Infectious Disease at the Lee Kong Chian School of Medicine.

The researchers then combined their expertise in structural biology, mycobacterial physiology, bioenergetics, and drug discovery, with EDDC's expertise and experience in drug design and medicinal chemistry, to successfully develop the lead series of small molecule inhibitors.

Professor Damian O'Connell, Chief Executive Officer of EDDC, said, "As Singapore's national drug discovery and development platform, EDDC works with key players in the local ecosystem to translate R&D into medicines that address unmet needs, and drive better health outcomes for society. EDDC is proud to partner with NTU in the development of these small molecule inhibitors, and we look forward to NHP progressing these molecules as drug candidates for tuberculosis patients."

END

[1] World Health Organization. (n.d.). Tuberculosis (TB). World Health Organization. Retrieved July 5, 2022, from https://www.who.int/news-room/fact-sheets/detail/tuberculosis

[2] Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg. 2017 Mar;58(1):E9-E12. PMID: 28515626; PMCID: PMC5432783.

[3] Chew, E. (2022, June 25). Singapore Widens Tuberculosis Checks After Large Cluster Emerges. Bloomberg.com. Retrieved July 6, 2022, from https://www.bloomberg.com/news/articles/2022-06-25/singapore-widens-tuberculosis-checks-after-large-cluster-emerges

[4] NRF Research Grant Number: NRF–CRP18–2017–01

[5] https://en.wikipedia.org/wiki/Wankel_engine

https://www.ntu.edu.sg/news/detail/new-compounds-to-kill-multidrug-resistant-tb