DAY 1

Keynote Forum

Euroscicon Conference on

MEDICINAL CHEMISTRY AND BIOSIMILARS

March 25-26, 2019 | Budapest, Hungary

Thomas D Bannister et al., Der Pharmacia Sinica 2019, Volume:10
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Thomas D Bannister, Laura M Bohn, Cullen L Schmid, Nicole M Kennedy, Nicolette C Ross, Kimberly M Lovell, Zhizhou Yue, Jenny Morge weck and Michael D Cameron

The Scripps Research Institute, USA

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ADDRESSING THE OPIOID CRISIS WITH SAFER OPIOID PAIN RELIEVERS: IS IT POSSIBLE?

For thousands of years humans have used opioids acting at the mu opioid receptor (MOR), such as morphine, for pain relief and for their euphoric effects. Poppy-derived compounds, and especially their modern synthetic cousins such as fentanyl, deliver not only robust pain relief but also elicit a host of unwanted side effects. These include respiratory failure, a life-threatening outcome that sadly we see far too often in the global opioid crisis. The Bohn-Bannister research team has succeeded in dramatically improving respiratory safety in new pain relievers and are now studying whether properties such as addiction potential, constipation and drug tolerance can also be eliminated. These probe molecules will help untangle the mechanistic details of MOR signalling and its pharmacological effects. Respiratory safety appears to require robust G-protein-mediated MOR signalling with almost no measurable beta arrestin involvement. We have identified functionally biased and drug-like MOR agonists with this specific profile. Further, they are robust and respiratory-safe pain relievers in mice. These potentially safer opioids may be one of the tools that are badly needed to combat the opioid abuse epidemic.

Biography

Thomas D Bannister is a Senior Scientific Director of Molecular Medicine at Scripps Research in Jupiter, Florida. Scripps is a world leader in non-profit biomedical research. He has received his scientific training at Wabash College (A.B.), Yale University (M.S., M.Phil.), and finally at Indiana University (Ph.D.), where he studied natural products synthesis under the direction of William R. Roush. He then worked in the pharmaceutical industry as a Drug Discovery Medicinal Chemist for 14 years. In 2005, he came to Scripps Florida and built a highly collaborative research group that provides medicinal chemistry expertise to several project teams focused on the discovery of potential new drug and molecular probes. In particular, the group is now targeting various cancers, neurological disorders, and pain. The contributions of Dr. Bannister and co-workers to medicinal chemistry are reflected in over 85 published papers and patent applications. His work in collaboration with Laura Bohn, to be discussed here, is aimed at the discovery, evaluation, and optimization of safer pain relievers as part of an overall strategy to help combat the global opioid abuse epidemic.

tbannist@scripps.edu

Mitsuji Yamashita et al., Der Pharmacia Sinica 2019, Volume:10
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Mitsuji Yamashita[1], Hiroko Hasegawa[1], Kazutaka Hirakawa[1], Reiko Makita[1], Michio Fujie[2], Satoki Nakamura[2], Tatsuo Oshikawa[3], Junko Yamashita[1], Mitsuo Toda[1], Kazunori Ohnishi[2], Haruhiko Sugimura[2], Sophie Laurent[4] and Robert N Muller[4]

[1]Shizuoka University, Japan, [2]Hamamatsu University School of Medicine, Japan
[3]Numazu National College of Technology, Japan, [4]University of Mons, BE

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PRECLINICAL RESEARCHES ON TUMOR ACCUMULATIVE NOVEL SUGAR DENDRITIC GD-DTPA COMPLEX MRI CONTRAST AGENTS AND IER5/CDC25B TAGETED NOVEL PHOSPHA SUGAR MOLECULAR TRGETED ANTITUMOR AGENTS TO INNOVATE IN CANCER THERAPY

Innovative and strategic materials against tumor to decrease sharply the number of people died by tumors are desired eagerly. To innovate in medical technologies of diagnosis and cure for various kinds of cancers by novel medicinal materials, i.e., sugar dendritic Gd-DTPA complex MRI contrast agent (DEN-OH) and IER5/Cdc25B targeted novel molecular targeted phospha sugar antitumor agents (e.g., TBMPP) were prepared and evaluated in vitro and in vivo methods, and then these novel medicinal materials were revealed preclinically to have excellent characters against tumor cells. Sugar dendritic Gd-DTPA complex (DEN-OH) was prepared by introduction of protected sugar dendritic parts to diethylenetriamine pentaacetic acid (DTPA) ligand followed by the successive complex formation with Gd (III) and hydrolysis. The prepared DEN-OH for MRI contrast agent (1/10 Gd concentration compared with Magnevist) showed quite clearer images of quite early stage of cancer (Figure 1). Phospha sugar derivatives, one of pseudosugar derivatives (Figure 2), were prepared via traditional or newly developed synthetic pathway to construct the compound library. Deoxybromophospha sugar derivatives (e.g., TBMPP) prepared from phospholenes were first found to exert quite effective and wide spectral antitumor activities by in vitro evaluation against various kinds of leukemia cells such as K562 and U937 cell lines as well as solid cancer cells (stomac, lung, and skin cancers), where normal cells were not suffered from any damages. Mechanistic studies of phospha sugar (TBMPP) on leukemia cells by Western blotting showed that the phospha sugar enhanced the expression of IER5, and then suppressed the expression of Cdc25B in the cell cycle of tumor cells. As the results, tumor cells might selectively and specifically might be induced apoptosis at the mitosis step of the tumor cell cycle. In vivo evaluation for TBMPP was successfully performed by using a nude mouse transplanted by K562 cells on the skin (Figure 3)

Biography

Mitsuji Yamashita has completed his PhD from Nagoya University, Japan, and Postdoctoral studies from Toyota Science and Chemistry Research Center, Japan, and Iowa State University, USA, as well as a Visiting professor of University of Massachusetts, USA, and a Visiting researcher of Oxford University, UK. He was a Professor of Shizuoka University, Japan, and he was retired at his age of 65 years old followed by the university regulation. After the retirement, he was a Special Professor and Guest Professor of Shizuoka University. He is now a Professor Emeritus of Shizuoka University and a part time Lecturer of Shizuoka Science and Engineering University, Japan, and established a private research institute named "Research Institute for Innovative and Strategic Materials of Medicinal Technology against Tumors". He has published more than 180 papers in journals and patents (more than 80 open patents and 38 registered patents).

myama44@yahoo.co.jp

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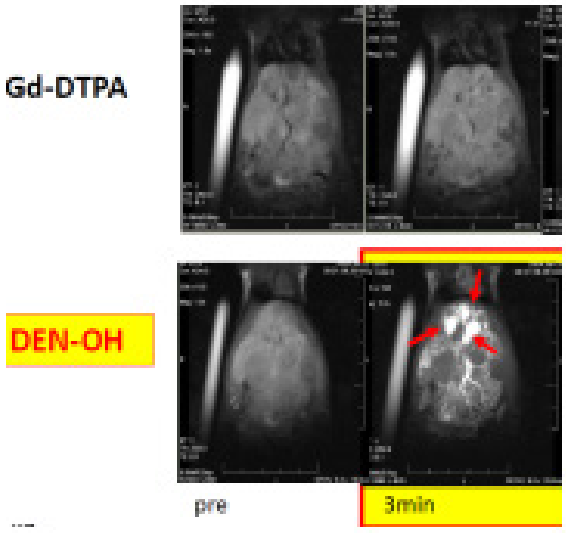

Figure 1: MRI of liver cancer of a Rat with Gd-DTPA (Magnevist) (Top) and DEN-OH (Bottom)

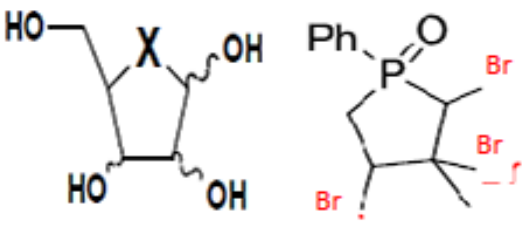

Figure 2: Pseudo sugars (X = NH, P (O) R, etc. (Left)); Branched deoxytribromo-phospha sugar TBMPP (Right).

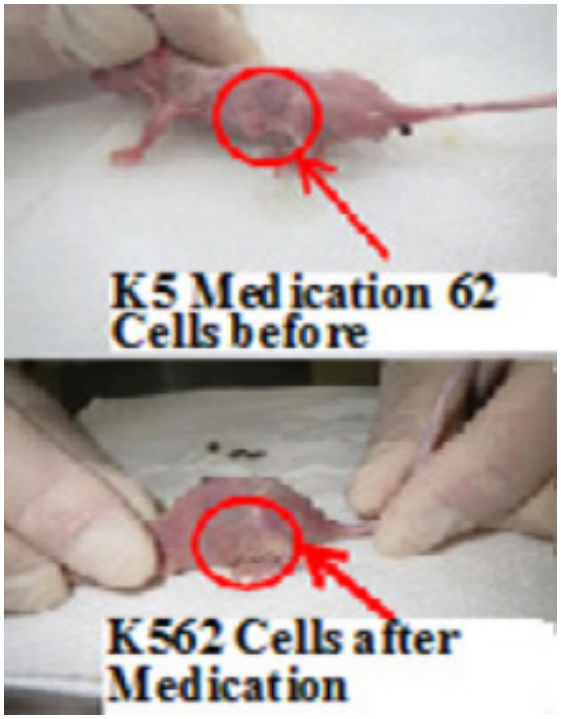

Figure 3: *In vivo* evaluation for TBMPP

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MT Den Hartog
Bioceros BV, Netherlands

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USING SPOT™ AND SLIM™ TECHNOLOGY AND UPSTREAM PROCESS MODULATION TO REDUCE COST OF GOODS OF BIOSIMILARS

Innovative cell line generation and early process development is the cornerstone of the success of a biosimilar antibody, since costs of goods (COGs) needs to be very low. To achieve this, high producing cell lines in combination with a modulatory USP strategy to meet similarity to the originator without limiting productivity are obligatory. The major strategy generally used in USP to optimize productivity, is elevation of viable cell density (VCD) in the fermenter. This USP solution however creates difficulties in DSP, since clarification will be difficult and in addition host cell related impurities will be high. Therefore, we increase specific productivity (Qp) using our SPOT™ technology, already during cell line generation. In addition, upstream process modulation can be used to increase Qp while at the same time improving biosimilar product quality. The high Qp values facilitate high volumetric productivity at low VCD, which enables an efficient DSP process. Alongside we observed that irrespective of the VCDs, cell lines with a high productivity had a very high demand for nutrients and oxygen. Because of the high oxygen requirements, a high-power input is necessary in bioreactors, resulting in hardware limitations, i.e. maximum gas flow and agitation rates. In turn, these hardware limitations ultimately limit innovations that increase productivity further. To avoid this issue, we applied metabolic engineering and developed the SLIM™ technology on our CHOBC® platform. The SLIM™ technology decreases oxygen and feed consumption and therefore decreases gas flow and agitation rates in the bioreactors. Together, SPOT™ and SLIM™ technology in our CHOBC® platform reduce cost of goods of biosimilars.

Biography

MT Den Hartog received his PhD in Molecular Biology at the University of Amsterdam (NL). Subsequently, he carried out a Post-doctoral Fellowship at the The Palo Alto Institute of Molecular Medicine (Mountain View, US). Thereafter, he was involved in the startup of PanGenetics where he was responsible for Molecular Biology and Protein Expression. In 2003, he was one of the Founders of Bioceros, where he currently holds a position of Director of Cell Line Development. He is Author/Co-author of over 20 papers in international scientific journals in the field of Biotechnology.

m.denhartog@bioceros.com