CARNA BIOSCIENCES

September 20, 2018
Carna Biosciences, Inc.

# Research Paper on Discovery of Carna Novel BTK inhibitor Published in Journal of Medicinal Chemistry

Carna Biosciences announces that the medicinal chemistry and its biological data to discover a series of novel BTK inhibitors have been published in Journal of Medicinal Chemistry.

The publication in Journal of Medicinal Chemistry describes the details of Carna's medicinal chemistry efforts to develop novel kinase inhibitors targeting Bruton's tyrosine kinase (BTK). The Journal of Medicinal Chemistry is an international scientific journal published by the American Chemical Society, and one of the most well-established scientific journal covering research in medicinal chemistry. Carna is currently conducting preclinical studies of two selective BTK inhibitors targeting autoimmune diseases and cancer, and initiation of Phase 1 clinical trials are expected in 2019.

"We are pleased to demonstrate outstanding skills of our medicinal chemistry team to develop a new drug candidate," said Dr. Kohichiro Yoshino, President and CEO of Carna Biosciences. "Our talented drug discovery team identified highly selective and non-covalent BTK inhibitors utilizing Carna's powerful kinase drug discovery engine, and we are proud that the discovery story has been published in Journal of Medicinal Chemistry," added Masaaki Sawa, Ph.D., Chief Scientific Officer, Head of Research and Development.

The Company conducts research and development of kinase inhibitors focused on the therapeutic areas with high-unmet medical needs including cancer and autoimmune diseases.

**Abstract of the paper**

BTK is a member of the Tec family of non-receptor tyrosine kinase that is essential for B-cell maturation by mediating the B-cell receptor (BCR) signaling, and also plays a crucial role in macrophages and mast cell activation via the highly-affinity IgE receptor (FcεRI). Therefore, BTK is a promising drug target for the treatment of multiple diseases such as blood cancer and autoimmune diseases (Figure 1). Ibrutinib, the first FDA-approved covalent BTK inhibitor, has demonstrated impressive response rates in patients with leukemia, and several second generation covalent BTK inhibitors are currently being evaluated in clinical trials. However, since most BTK inhibitors in clinical trials are covalent inhibitors, there is still a high demand for non-covalent BTK inhibitors to treat non-oncology diseases. In addition, it is significantly important to optimize kinase selectivity for producing safer drugs.

In order to generate a highly selective non-covalent BTK inhibitor, the drug discovery team developed novel drug discovery technology using two conformationally different BTK proteins, an activated form of BTK (BTK[A]) and an unactivated form of BTK (BTK[U]) (Figure 2). Using this novel technology, the drug discovery team successfully identified a new lead compound showing a stronger inhibitory potency for BTK[U] than for BTK[A] (Figure. 3.) Subsequent lead optimization led to the discovery of compound **4b** having strong inhibitory potency for BTK[U] with high kinase selectivity in a non-covalent manner. With strong inhibitory potency for the BCR activation in B-cells and significant efficacies in vivo models,

compound **4b** was selected as a clinical candidate compound and is currently under preclinical development.

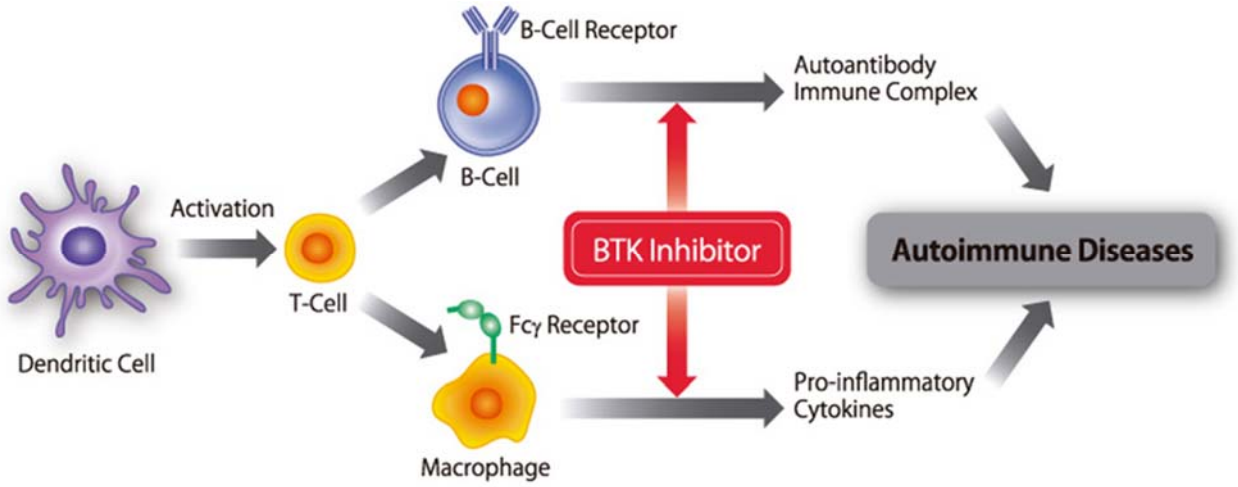


**Figure 1.** BTK mediated signaling pathway in autoimmune diseases

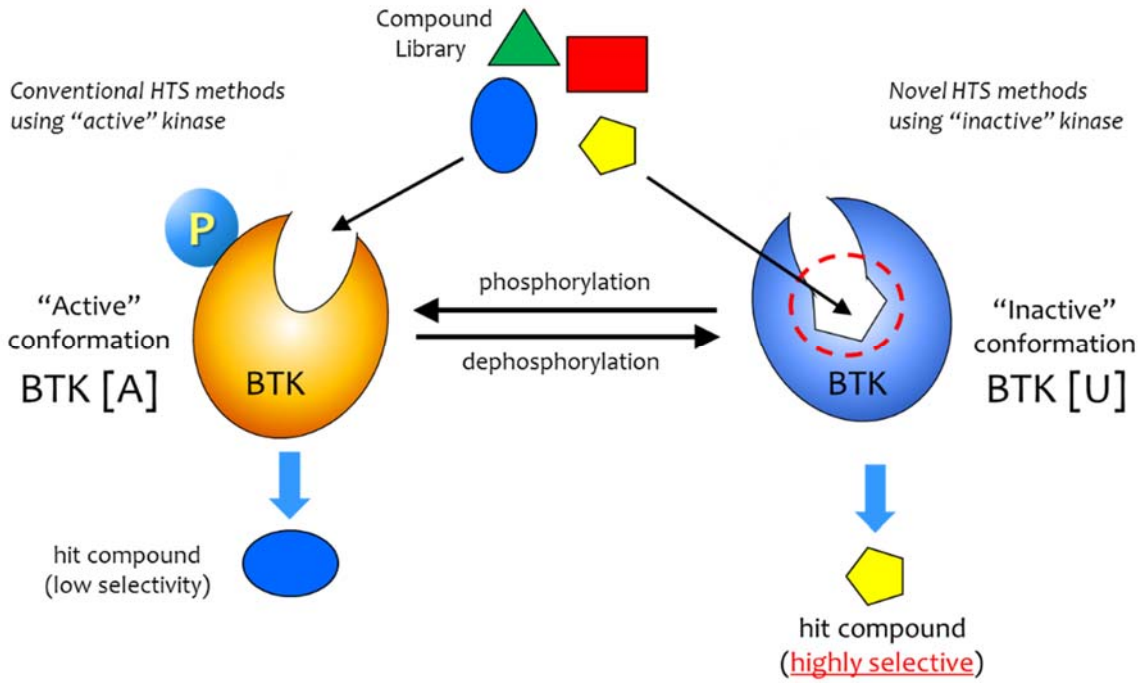


**Figure 2.** Novel screening method using an unactivated conformation of kinase

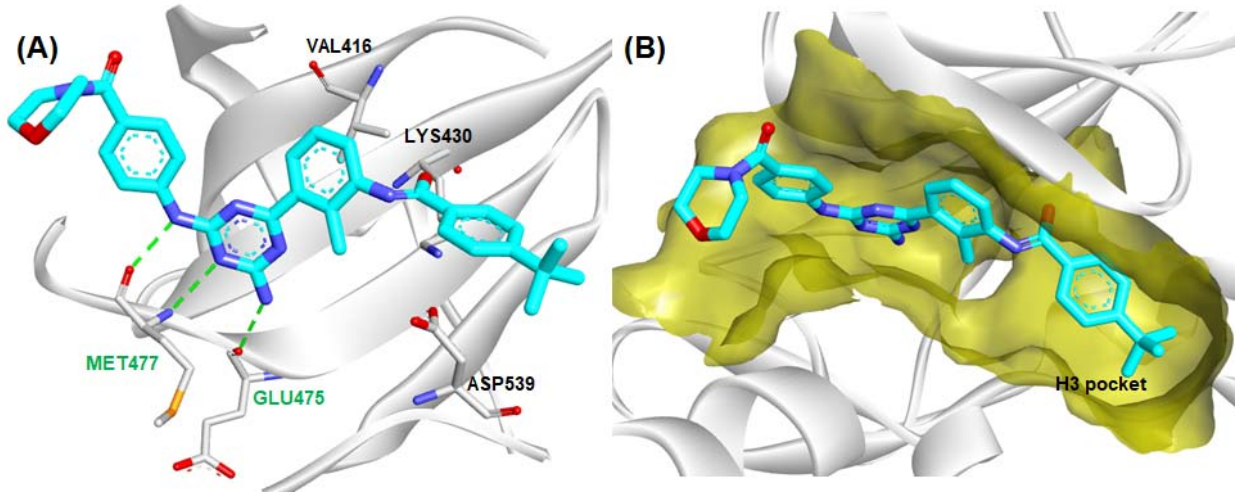


**Figure 3**. X-ray co-crystal structure of BTK complexed with **2e**

**Publication**

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| Journal: | Journal of Medicinal Chemistry |
| Title: | Design and Synthesis of Novel Amino-triazine Analogs as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis |
| Author: | Wataru Kawahata, Tokiko Asami, Takao Kiyoi, Takayuki Irie, Haruka Taniguchi, Yuko Asamitsu, Tomoko Inoue, Takahiro Miyake, Masaaki Sawa |
| DOI: | 10.1021/acs.jmedchem.8b01147 |

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