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Press Release

Tübingen researchers develop inhibitors for autoimmune-relevant enzyme

Highly selective new JAK3 inhibitors may offer new treatments for autoimmune conditions

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University of Tübingen researchers have developed new inhibitors which act on a special enzyme known as the Janus kinase 3 (JAK3). Janus kinases carry out important intracellular functions in many organs - for instance, activating key signal pathways in the systems which form new blood cells. But mutations in Janus kinase genes can cause alterations in these processes, leading to a number of blood and immune diseases. Because many cytokines use Janus kinases to carry their signals during inflammation, these molecules also play a major role in inflammatory autoimmune disorders such as rheumatoid arthritis and psoriasis. If researchers can inhibit the function of Janus kinases, they may be able to find better treatments for a number of diseases. The researchers have published their findings in the latest edition of *Cell Chemical Biology*.

“For ten years, medicine has been looking for the right inhibitors to control the effect of JAK3,” says Stefan Laufer, Professor of Pharmaceutical Chemistry at the University of Tübingen. “Because JAK3 has such an isolated role in the immune system, we believe that inhibiting it will lead to a suppression of immune responses which could be used to treat autoimmune disorders like psoriasis and rheumatoid arthritis. All the agents which are currently available - and have been approved as medication in some countries - inhibit several Janus kinases at the same time.” That may be the cause of undesirable side effects observed in patients treated with JAK inhibitors. The JAK inhibitors developed in Tübingen exploit small differences in the amino acid sequences of the four types of Janus kinases. They bond with a cysteine amino acid which only occurs in JAK3 - thereby blocking this enzyme but not the other Janus kinases.

“There are more than 500 kinases in the human body; and many of them are essential building-blocks of life,” Laufer explains. “So it is of vital importance that a JAK inhibitor has a very selective effect.” The

promising properties of the new inhibitors saw them registered in the Structural Genomics Consortium's Chemical Probe program. The Structural Genomics Consortium is a global network of research universities and pharmaceutical companies which focuses on research into genetically-determined disorders and communicates findings to researchers around the world. An important contribution has been made to it by Professor Stefan Knapp of the University of Frankfurt am Main. The Consortium also has long had ties with the University of North Carolina in Chapel Hill, one of Tübingen's partner universities in the US. "Making our inhibitors available could take basic research and the understanding of JAK signal pathways and their role in guiding the immune system a big step further in the future," Laufer says.

Publication:

Michael Forster, Apirat Chaikuad, Silke M. Bauer, Julia Holstein, Matthew B. Robers, Cesear R. Corona, Matthias Gehringer, Ellen Pfaffenrot, Kamran Ghoreschi, Stefan Knapp, Stefan A. Laufer:

Selective JAK3 Inhibitors with a Covalent Reversible Binding Mode Targeting a New Induced Fit Binding Pocket.

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