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″Structure and chemical biology approaches to understand type IV secretion system function and inhibition″

Prof. Christian Baron

Department of Biochemistry and Molecular Medicine, Faculty of Medicine, Université de Montréal

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北海道大学 理学部 6 号館 204−02

The resistance to antimicrobial drugs keeps increasing and we therefore need to develop alternative strategies to treat infectious diseases. The classical approach for the design of antibiotics is to target essential metabolic functions in order to either kill bacteria or stop their growth. This strategy was very successful in the past, but the strong selection pressure by antibiotics has contributed to the increasing occurrence of multi-resistant bacteria. The goal of our work is to develop a novel alternative to antibiotics: Anti-virulence (anti-infective) drugs that target bacterial virulence factors. These molecules will disarm pathogens so that they can be eliminated by the immune system. Since such drugs would not target essential metabolic processes, the selection for resistance will be reduced as compared to classical antibiotics. Anti-virulence drugs alone, or given as combination therapy with antibiotics, would constitute a major advancement for the treatment of infectious diseases.

We are pursuing this approach using bacterial type IV secretion systems as targets. These systems are essential for the virulence of many bacterial pathogens such as *Brucella* species*, Bordetella pertussis*, *Helicobacter pylori* and *Legionella pneumoniae*, and they are likely required for the virulence of *Coxiella* and *Rickettsia* species. The specific targets of our work are VirB8 from the select agent *Brucella*, and CagV and CagL from *H. pylori,* type IV secretion proteins that are essential for bacterial virulence. High-throughput screening using a bacterial two hybrid system-based *in vivo* system identified specific small-molecule inhibitors of VirB8. One of these molecules was a potent inhibitor of the intracellular replication of *Brucella* in a macrophage infection model. The binding site of inhibitors on VirB8 was identified by X-crystallography, docking and by structure-function analysis of the binding site. A first round of structure-activity relationship analysis defined key features of active inhibitors, and we have further improved these molecules by medicinal chemistry.

We are also conducting structure- and fragment-based screening approaches to identify inhibitors of *H. pylori* proteins CagV and CagL. Ultimate goal of this work is to find inhibitors of the virulence of this important human pathogen that is present in the gastric mucosa of about 50% of the world's population. *H. pylori* causes persistent inflammation and conditions such as gastric or duodenal ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. For this reason, *H. pylori* was classified as a Class 1 carcinogen by the World Health Organization (WHO). Drug resistance is increasing in this organism and new treatment strategies are therefore urgently needed.

連絡先：北海道大学大学院理研究院化学部門 坂口和靖

(Tel: 011-706-2698, Mail: kazuyasu@sci.hokudai.ac.jp)