【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Development of Novel Anti-Infectious Drugs Exhibiting Therapeutic Effects

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Research Project Number: 15H05783 Researcher Number: 90126095
Research Area: Environmental and hygienic pharmacy
Keyword: Microbiology and infectious diseases, Pathogenicity

【Purpose and Background of the Research】

The development of novel anti-infectious drugs with therapeutic effects is urgently needed to establish effective strategies against multidrug-resistant pathogens. Current strategies, however, are inadequate and the number of newly discovered drugs has dramatically decreased, resulting in a very limited number of anti-infectious drugs with novel mechanisms. One possible reason for this is that the behavior of pathogenic bacteria in test tubes differs considerably from that in hosts. In this project, we will focus on gene products of pathogens that are necessary for pathogenesis in the host environment. To achieve this goal, we will identify the genes in pathogens necessary for pathogen proliferation and pathogenesis in host animals. Based on the findings, we will establish screening systems to identify inhibitors against the gene products and establish a method for developing antibacterial agents with novel mechanisms of action. Our project also aims to elucidate the molecular aspects of bacterial pathogenesis.

【Research Methods】

1. Screening of pathogenic genes in bacteria using silkworms
We have established silkworm infectious disease models with human pathogenic bacteria. Using this model, we will identify deletion mutants of pathogenic bacteria whose pathogenesis is decreased compared with the wild-type strain. We will also identify bacterial genes whose expression is appreciably increased in mouse organs compared with that in test tubes. The decreased pathogenesis of the gene deletion mutants will be confirmed in mouse infection models.
2. Establishment of an assay system to screen novel antibacterial agents
We will then establish methods for biochemical analysis of the enzymes encoded by the pathogenic genes identified in this study. Using these methods, we aim to elucidate the functions of the enzymes. The assay systems we develop will then be used to screen for inhibitors.

【Expected Research Achievements and Scientific Significance】

1. Understanding bacterial pathogenesis
Based on comprehensive analyses of data obtained in this project, we will identify novel genes responsible for bacterial pathogenesis. Biochemical analysis of the functions of the products of the responsible genes will allow us to uncover networks of gene expression involved in bacterial pathogenicity. These findings will contribute to our understanding of bacterial pathogenesis in the host.
2. Development of novel anti-infectious drugs
This project will identify novel genes necessary for bacteria to survive in the host environment. Evaluating the products of these novel genes will lead to potential targets for drug development. Bacterial growth inhibitors obtained by screening will be useful seed compounds for anti-infectious treatments.

【Publications Relevant to the Project】

1. Hamamoto H, Urai M, Ishii K, Yasukawa J, Paudel A, Murai M, Kaji T, Kuranaga T, Hamase K, Katsu T, Su J, Adachi T, Uchida R, Tomoda H, Yamada M, Souma M, Kurihara H, Inoue M, Sekimizu K: ***Nat Chem Biol***, 11, 127-133, 2015
2. Kaito C, Saito Y, Ikuo M, Omae Y, Mao H, Nagano G, Fujiyuki T, Numata S, Han X, Obata K, Hasegawa S, Yamaguchi H, Inokuchi K, Ito T, Hiramatsu K, Sekimizu K: ***PLoS Pathog***, 9, e1003269, 2013
3. Kaito C, Kurokawa K, Matsumoto Y, Terao Y, Kawabata S, Hamada S, Sekimizu K: ***Mol Microbiol***, 56, 934-944, 2005

【Term of Project】

FY2015-2019

【Budget Allocation】

154,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~bisei/