

Prof. Dr. Katsuhiko Murakami

Department of Biochemistry and Molecular Biology
Pennsylvania State University

will give a presentation entitled

„Structures of bacterial RNA polymerase in complex with inhibitors toward understandings of their mechanism of action, resistance and new antibiotic development “

Thursday(!), March 27, 2014, at 17:00h s.t.
in Blg E1.3, Lecture Hall 003

Host: Prof. Dr. Rolf Hartmann

There is opportunity to talk with the speaker before the talk.
There will be a follow-up session (Nachsitzung).

For details and for making appointments please contact:
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Guests are welcome!

Summary

Tuberculosis (TB) is one of the most significant global challenges to human health. For over four decades, Rifampin (Rif), a semi-synthetic derivative of Rifamycin, has been used as a first line antibiotic treatment of tuberculosis and is the cornerstone of current short-term tuberculosis treatment. The mode of action involves tight Rif binding to a beta subunit of bacterial RNA polymerase (K_d is sub nanomolar) to inhibit RNA transcription. Although many Rif resistant (Rif^R) strains with mutations in the Rif-binding pocket can be isolated in bacterial culture, only three specific Rif^R mutations account for over 80 % of *Mycobacterium tuberculosis* (MTB) Rif^R strains in clinical isolates due to Rif^R associated fitness costs.

Recently, we have shown that RNA polymerase from *Escherichia coli* can be prepared from a convenient overexpression system and its structure can be determined by X-ray crystallography. The *E. coli* RNA polymerase structural study has enabled us to further characterize bacterial RNA polymerase mutants including antibiotic-resistant RNA polymerases. In the current study, we have determined the X-ray crystal structures of the *E. coli* RNA polymerase Rif^R mutants each having one of three major Rif^R mutations found in clinical isolates. Each Rif^R RNA polymerase structure shows a unique conformation of the Rif binding pocket and their structural deviations from the wild-type Rif binding pocket are consistent with their Rif resistances suggesting that the Rif^R results from alternating the shape complementary between the Rif binding pocket and Rif rather than disrupting their hydrophilic and hydrophobic interactions. This study provides an important step for understanding the structure–activity relationship of Rif against Rif^R RNA polymerase inhibition and toward developing superior Rif analogues for Rif^R MTB.

Song, T. et al, (2014). Fitness costs of rifampicin-resistance in *Mycobacterium tuberculosis* are amplified under conditions of nutrient starvation and compensated by mutation in the β' subunit of RNA polymerase. *Mol. Microbiol.*, on-line publication.

Molodtsov, V., I.N. Nawarathne, N.T. Scharf, P.D. Kirchhoff, H.D.H. Showalter, G.A. Garcia and K.S. Murakami (2013). X-ray crystal structures of the *Escherichia coli* RNA polymerase in complex with Benzoxazinorifamycins. *J. Med. Chem.* **56**, 4758-4763.

Murakami, K.S. (2013). The X-ray crystal structure of *Escherichia coli* RNA polymerase Sigma70 Holoenzyme. *J Biol Chem.*, **288**, 9126-9134.

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Education

Graduate University for Advanced Studies, Japan

Ph.D., 1997, Department of Genetics, School of Life Science

Thesis Title: “*Functional analysis of the carboxyl-terminal transcription regulation domain of Escherichia coli RNA polymerase α subunit*”
 Advisor: A. Ishihama

Yamaguchi University, Yamaguchi, Japan

Master of Chemistry, 1994, Department of Chemistry

Yamaguchi University, Yamaguchi, Japan

Bachelors of Chemistry, 1992, Department of Chemistry

Experience

2009 - present	Pennsylvania State University , College of Science, University Park, PA, Department of Biochemistry and Molecular Biology	Associate Professor
2003 - 2009	Pennsylvania State University , College of Science, University Park, PA, Department of Biochemistry and Molecular Biology	Assistant Professor
1998 - 2003	The Rockefeller University New York, NY Postdoctoral Fellow - Supervisor: S.A. Darst	
1997 - 1998	National Institute of Genetics Mishima, Shizuoka, Japan Postdoctoral Fellow - Supervisor: Y. Shirakihara	