Principal Researcher	Akihito YAMAGUCHI	**Number of Researchers**	3
Research Institution・Department・Title	Professor, Institute of Scientific and Industrial Research, Osaka University	**Location of Institution**	Osaka

Title of Project	Postogenomic Approach for Bacterial Gene Resources of Xenobiotic Exporters and Elucidation of Novel Multidrug Resistance Mechanisms
Abstract of Research Project	On the basis of genome sequence analysis of Escherichia coli, 37 ORFs were presumed to encode putative xenobiotic exporters. We clone all of these ORFs into multicopy plasmid, and they were expressed in E. coli strain KAM3 which lacks its major xenobiotic exporter gene *acrAB*. As a result, we identified that 19 different genes actually encode exporters for some drug and toxic compounds. Among them, 11 genes encode MFS type transporters, 2 encode SMR ones, 5 encode RND ones, and 1 encodes ABC one. The ATP-hydrolyzing drug exporter MacAB is the first one as ABC-type drug exporters identified in Gram-negative bacteria. It is a macrolide antibiotic-specific exporter. It contains 4 putative transmembrane segments and one NBD domain. It co-operates with an outer membrane channel and exports drugs directly out of the cells bypassing periplasm. All five RND-type exporters require TolC as an outer membrane channel and export drugs directly out of the cells bypassing periplasm. To be surprised, an outer membrane channel co-operating with MacAB is also TolC. In addition, two other MFS-type transporters also require TolC. These TolC-dependent drug exporters seems not to form permanent complex with TolC, but rather temporarily recruit TolC only when they transport drugs. The intrinsic presence of such a lot of drug efflux transporters in bacterial chromosomes must be a serious threat for our future chemotherapy.
References	1. Nagakubo, S., Nishino, K., Hirata, T., and Yamagichi, A. The putative response regulator BaeR stimulates multidrug resistance of *Escherichia coli* via a novel multidrug exporter system, MdtABC. *J Bacteriol.* **184** : 4161-4167（2002） 2. Nishino, K., and Yamaguchi, A. EvgA of the two-component signal transduction system modulates production of the YhiUV multidrug transporter in *Escherichia coli*. *J Bacteriol.* **184** : 2319-2323（2002） 3. Nishino, K., Yamaguchi, A. Analysis of a complete library of putative drug transporter genes in *Escherichia coli*. *J Bacteriol.* **183** : 5803-5812（2001） 4. Kobayashi, N., Nishino, K., Yamaguchi, A. Novel macrolide-specific ABC-type efflux transporter in *Escherichia coli*. *J Bacteriol.* **183** : 5639-5644（2001） 5. Nishino, K., and Yamaguchi, A. Overexpression of the response regulator evgA of the two-component signal transduction system modulates multidrug resistance conferred by multidrug resistance transporters. *J Bacteriol.* **183** : 1455-1458（2001）
Term of Project	Fiscal years 2001-2005（5 years）

Budget Allocation (in thousand of yen)	FY2001	FY2002	FY2003	FY2004	FY2005	Total
	19,700	20,000	20,000	20,000	15,200	94,900

Homepage Address	under construction