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**JB**

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### COVER:

#### Discovery in Japan

Anaplastic lymphoma kinase gene (*ALK*) was first identified as an oncogenic fusion to nucleophosmin (*NPM*) in anaplastic large-cell lymphoma, a relatively infrequent subtype of non-Hodgkin's lymphoma. While chromosome rearrangement-mediated oncogenesis was once presumed to be specific to haematological malignancies or sarcomas, Dr. Hiroyuki Mano and his colleagues discovered another fusion of *ALK*, *EML4-ALK*, in lung adenocarcinoma (1). *EML4-ALK* encodes a constitutively activated protein-tyrosine kinase with a marked oncogenic activity. Many *ALK* inhibitors are under clinical trials or preclinical experiments, and one of such compounds, crizotinib, has recently been approved by U.S. FDA as a therapeutic drug against lung cancer positive for *EML4-ALK*. During the phase I/II trial with crizotinib, Dr. Mano's group recognized a patient who had obtained partial response with crizotinib, but abruptly relapsed after 6 months of treatment. Comparison of the specimens before and after the relapse revealed two secondary non-synonymous mutations within *EML4-ALK* only in the latter specimen, each of which confers resistance against crizotinib (2).

These secondary mutations of *EML4-ALK* lead to amino acid changes within the kinase domain of the encoded protein, *i.e.*, Cys-to-Tyr at position 1156 and Leu-to-Met at position 1196. Here, the amino acid position of Cys<sup>1156</sup> is indicated as a pink sphere in the predicted three-dimensional structure model for the kinase domain of *ALK* (ID '3lcs' in the Protein Data Bank of Japan, <http://www.pdbj.org/index.html>). The  $\alpha$  helices and  $\beta$  sheets are shown in green and orange, respectively.

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**Hiroshi Manya, Keiko Akasaka-Manya, Ai Nakajima, Masao Kawakita and Tamao Endo:** Role of *N*-glycans in maintaining the activity of protein *O*-mannosyltransferases POMT1 and POMT2 (Vol. 147, No. 3, 337–344, doi:10.1093/jb/mvp170)

**Katsuyuki Iida, Junsei Mimura, Ken Itoh, Chikara Ohyama, Yoshiaki Fujii-Kuriyama, Toru Shimazui, Hideyuki Akaza and Masayuki Yamamoto:** Suppression of AhR signaling pathway is associated with the down-regulation of UDP-glucuronosyltransferases during BBN-induced urinary bladder carcinogenesis in mice (Vol. 147, No. 3, 353–360, doi:10.1093/jb/mvp169)

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**Takeshi Katsuda, Takumi Teratani, Takahiro Ochiya and Yasuyuki Sakai:** Transplantation of a fetal liver cell-loaded hyaluronic acid sponge onto the mesentery recovers a Wilson's disease model rat (Vol. 148, No. 3, 281–288 doi:10.1093/jb/mvq063)

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*<sup>1</sup>Department of Genetic Biochemistry, Kyoto University Graduate School of Pharmaceutical Sciences, Kyoto 606-8501, Japan; and <sup>2</sup>Department of Developmental Biology, Washington University School of Medicine, St Louis, MO 63110, USA (Vol. 149, No. 2, pp. 121–130)*

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## Pregnancy-associated homeostasis and dysregulation: lessons from genetically modified animal models

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**Tamaki Yano and Shoichiro Kurata**

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**Makoto Murakami, Yoshitaka Taketomi, Hiroyasu Sato and Kei Yamamoto**

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**Mika Shirasu and Kazushige Touhara**

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## **Signalling mechanisms of RhoGTPase regulation by the heterotrimeric G proteins G12 and G13**

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