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A knockout mouse resource for the biomedical research community

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Abstract

The Knockout Mouse Project (KOMP) Repository archives and distributes vectors, embryonic stem cell clones, frozen germplasm, and live mutant mice for 8,500 knockout genes. Here, we describe the creation and functions of the KOMP Repository.

Keywords

genetically altered mice; knockouts; gene targeting; ES cells

Since its inception in the mid-1980s, gene targeting by homologous recombination in mouse embryonic stem (ES) cells has transformed the ability to functionally assess individual genes in mice for the study of systems biology in health and disease.¹ Just a few years ago, the National Institutes of Health (NIH) discovered that after awarding hundreds of millions of dollars over two decades to individual laboratories, large and small, only ~4,000 unique mouse strains had been generated, and even fewer, 700 or so, were publicly available without restriction. In response, and to capitalize on newly sequenced whole genomes, improvements in construct and vector design, and technological advances in gene targeting and ES cells, a recently coordinated program² involving projects in the United States³ and Europe⁴ has used unconventional high-throughput approaches to derive a comprehensive library of ES cells with loss-of-function alleles, covering nearly every protein-coding gene in the mouse genome.⁵ The close homology between the mouse and human genomes⁶ and the promise for identifying genetic factors in mice that may inform human disease pathogenesis is a compelling rationale for converting the entire ES cell resource into mice. Further, these facts provide convincing evidence for the scientific value of a concerted effort to strategically analyze the resultant knockout mouse resource.

To extend the benefit of these large-scale efforts to knockout the entire mouse genome to the worldwide community of biomedical researchers, repositories have been created to archive and distribute the newly generated materials and data, and to make them available and accessible to any and every scientist. One of these repositories is made up of a consortium

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Conflicts of interest

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between the University of California Davis (UCD) and Children's Hospital Oakland Research Institute (CHORI), which serves as the repository for all products generated in the NIH Knockout Mouse Project (KOMP) Mutagenesis Program. As the lead institution, UCD archives, maintains, conducts quality assurance, and fulfills orders for ES cell clones, live mouse lines, and frozen embryos and sperm, whereas CHORI fulfills similar requests for targeting vectors. The repository ensures the viability, genotype, pathogen-free status, and chromosome count of all KOMP products.

To date, the repository has imported 75,302 targeted ES cell clones for 6,909 unique genes from the two teams (CHORI–Sanger–UCD Consortium and Regeneron, Inc.) participating in the KOMP Mutagenesis Program. After quality assurance testing, 70,754 ES cell clones for 6,503 genes have been made available for ordering and distribution. Eventually, products for 8,500 knockout targeted genes, most conditional ready, will be available. Since initial operations began four years ago, the repository has fulfilled 2,770 (84%) of 3,316 orders received for ES cell clones, doing so by aiming to respond to orders within 8–12 weeks of a request. The repository now receives and fulfills on average of more than 150 orders per month for vectors, ES cell clones, and mice (Fig. 1). Most investigators use KOMP ES cells and/or chimeras obtained from the KOMP Repository to generate mutant mouse colonies to use for hypothesis-driven scientific study.

The repository also provides valuable services, such as microinjection, to convert ES cells to mice. To date, the repository has injected 938 unique clones into either BALB/c or B6D2F1 $\times$ C57BL/6 host blastocysts to produce chimeras for germline transmission testing. Of 659 clones for which testcrosses have been completed, 446 (68%) successfully transmitted through the germline. These data suggest that injection of three clones per gene will ensure a $>96\%$ likelihood ($1 - [0.32 \times 0.32 \times 0.32]$) of achieving germline transmission. All KOMP Repository products and services are available to both academic and commercial entities for a modest cost. Because the NIH intended the resource to become self-sustaining, fees charged to obtain KOMP products are used to ensure continued maintenance and operation of the repository. Special pricing packages are available to reduce costs to researchers. For example, instead of purchasing an individual ES cell clone for US\$648, a customer can save by purchasing a “premium ES cell package” for US\$2,801, which includes up to three injectable clones per gene and guaranteed quality control assurance, including growth and viability testing, genotyping confirmation, pathogen screening, and chromosome count. Alternatively, investigators can purchase a premium microinjection service for US\$10,691, which guarantees production of at least one $>50\%$ male chimera or there is no charge. By creating a myKOMP account and registering interest in specific KOMP genes, investigators will be sent email notification announcing that products on their interest list are available and can be ordered from the repository. To date, more than 6,000 scientists from around the world have created accounts and expressed interest in over 3,200 genes.

In an effort to seek feedback on the scientific utility of KOMP products, the repository conducts surveys of their researcher clients and requests feedback on their success using KOMP ES cells. For example, in response to an email questionnaire to 524 investigators who had ordered 454 clones, 209 (42%) respondents reported that 227 (83%) of 273 clones injected in their labs had resulted in the birth of chimeras. Of these, 117 (63%) of 185 clones

that have completed germline transmission testing had been successful. In another survey of 70 customers who had ordered microinjection and delivery of chimeras, 52 (74%) reported that 34 (71%) of 48 clones that produced chimeras had successfully transmitted through the germline. Once completed, NIH-funded investigators can fulfill their obligations under the NIH Sharing Policy by depositing into the repository mice made in their laboratory from KOMP products. Under the KOMP Sharing Plan, researchers who return at least two germline-confirmed, heterozygous KOMP mutant male mice on a congenic C57BL/6N genetic background within one year of purchase of ES cell clones and/or chimeras will receive an immediate cash refund of 50% the cost of purchasing ES cells or US\$1,000 refund of the cost of microinjection. Mutant mice sent to the KOMP Repository and passing stringent quality assurance procedures are made available for distribution to other investigators and are cryopreserved as frozen germplasm for safety, security, and distribution.

The repository maintains an easily navigable website (www.komp.org) where users can search, browse, and order products and services from the online catalog. In addition, users can access and download protocols, contact customer and technical services (1-888-KOMP-MICE, service@komp.org), read news updates, follow the KOMP blog, view FAQs, and more. Besides ensuring the utility, longevity, and vitality of this unique resource, the KOMP Repository is key to the success of KOMP-Phase 2, which seeks to conduct comprehensive, high-throughput phenotypic screening to functionally annotate all protein-coding genes in the mammalian genome.⁷

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Figure 1.

Orders for gene-targeted ES cell clones generated by the KOMP Mutagenesis Program and archived and distributed by the KOMP Repository. The steady increase in orders (average ~150/month over the last six to nine months) from the global research community demonstrates the scientific value and promise of this resource to facilitate the study of the genetic basis of disease.