

Transitioning to large-scale sequencing

The early years of the Human Genome Program have been remarkably successful. Critical resources and infrastructures have been established, and technologies have been developed for producing several useful types of chromosomal maps. These gains are supporting the project's transition to the large-scale sequencing phase. Some highlights and trends in the U.S. Department of Energy's (DOE) Human Genome Program after FY 1993 are presented in this section.

Clone Resources for Mapping, Sequencing, and Gene Hunting

The demands of large chromosomal mapping and sequencing efforts have necessitated the development of several different types of clone collections (called libraries) carrying human DNA. Three generations of DOE-developed libraries are being distributed to research teams in the United States and abroad. In these libraries, human DNA segments of various lengths are maintained in bacterial cells.

NLGLP Libraries

The first two generations are chromosome-specific libraries carrying small inserts of human DNA (15,000 to 40,000 base pairs). As part of the National Laboratory Gene Library Project (NLGLP) begun in 1983, these libraries were prepared at Los Alamos National Laboratory (LANL) and Lawrence Livermore National Laboratory (LLNL) using DOE flow-sorting technology to separate individual chromosomes. Library availability has allowed the very difficult whole-genome tasks to be divided into 24 more manageable single-chromosome projects that could be pursued at separate research centers. Completed in 1994, NLGLP libraries have provided critical resources to

genome researchers worldwide (<http://www.bio.llnl.gov/genome/html/cosmid.html>). Very high resolution chromosome maps based principally on NLGLP libraries were published in 1995 for chromosomes 16 and 19. These are described in detail in the Research Narratives section of this report (see LLNL, p. 27, and LANL, p. 35).

PACs and BACs

The third generation of clone resources supporting chromosome mapping is composed of P1 artificial chromosome (PAC) and bacterial artificial chromosome (BAC) libraries. A prototype PAC library was produced by the team of Leon Rosner (then at DuPont) many years ago, but more efficient production began with improvements introduced by the DOE-supported teams headed by Melvin Simon at Caltech (BACs) and Pieter de Jong at Roswell Park (PACs).

In contrast to cosmids, BACs and PACs provide a more uniform representation of the human genome, and the greater length of their inserts (90,000 to

DOE Genome Research
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<http://www.ornl.gov/hgmis/research.html>

Research Narratives

Separate narratives, beginning on p. 25, contain detailed descriptions of research programs and accomplishments at these major DOE genome research facilities.

- Lawrence Livermore National Laboratory
- Los Alamos National Laboratory
- Lawrence Berkeley National Laboratory
- University of Washington Genome Sequencing Laboratory
- Genome Database
- National Center for Genome Resources

Research Abstracts

Descriptions of individual research projects at other institutions are given in *Part 2, 1996 Research Abstracts*.