

COMPUTATIONAL BIOLOGY

Finding Genes, Predicting Protein Structure

ORNL's computational biology researchers played an important role in the Human Genome Project. In 2001, special issues of *Science* and *Nature* that included the draft of the human genome made reference to ORNL's bioinformatics research. ORNL's Frank Larimer, Jay Snoddy, and Ed Uberbacher are listed as co-authors on the lead paper of the *Nature* issue. The GRAIL gene-finding tool, developed by Uberbacher and Richard Mural, was used for the work, and it is mentioned on *Science's* human genome program timeline.

Ying Xu and Dong Xu developed the Protein Structure Prediction and Evaluation Computer Toolkit (PROSPECT), computational tools for predicting three-dimensional structures of proteins from their amino acid sequences. Knowledge of these specific three-dimensional structures is vital to disease research and drug discovery. PROSPECT can determine a protein's geometry in a few hours, rather than the months required by traditional experiments. PROSPECT has been ranked among the world's best protein-structure prediction tools.

the reproductive potential of prize cattle. The embryo cryopreservation technique, used in Oak Ridge and at the Jackson Laboratory in Bar Harbor, Maine, allows the affordable maintenance of genetic lines of mice and provides a method for obtaining virus-free lines of mice with known genetic traits.

In 1979, Willie Lijinsky showed in rats that nitrites from food preservatives react with amines from food and drugs to form cancer-causing nitrosamines during digestion in the stomach. Walderico Generoso discovered that the genetic makeup of the unexposed female mouse is critically important for determining the amount of genetic damage passed to offspring by males exposed to certain chemicals. Bill Russell discovered that ethylnitrosourea (ENU) is the most effective chemical for inducing mutations in mice. Subsequently, it was found that this chemical generates primarily "point" mutations (DNA base substitutions rather than deletions), and ENU is now in widespread use as the gold-standard reagent for the discovery and cloning of genes associated with human diseases.

In 1986 Generoso discovered that exposure of newly fertilized mouse embryos within the mother to certain chemicals increases the possibility of specific late-fetal birth defects. This work upset teratology dogma that exposure only during the formation and development of organs poses a significant risk.

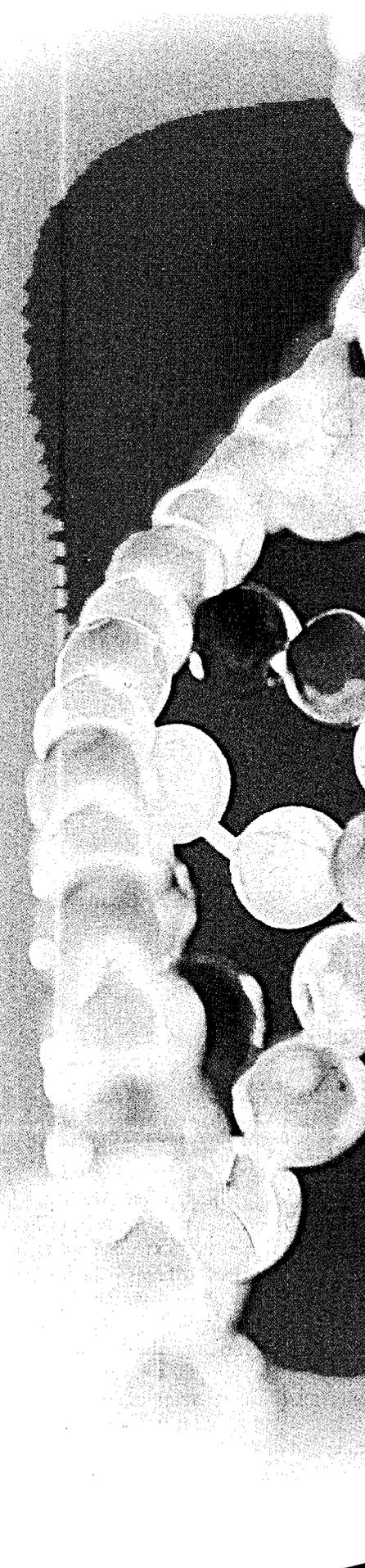
By the 1990s, numerous studies led by Liane Russell on the nature and frequency of chemically induced mutations concluded that germ-cell-stage exposure to a mutagen is more important than the mutagen itself in determining the nature of a heritable mutation. Thus, it was possible to find suitable chemicals and exposure protocols for making certain classes of mutations "to order."

In 1992 Scott Bultman, Ed Michaud, and Rick Woychik identified and cloned the mouse agouti gene, which causes altered fur color, obesity, diabetes, and cancer in mice and has a human counterpart. In 1993 Gene Rinchik helped identify the human and mouse pink-eyed dilution gene that enables normal pigmentation in mammals. In 1994, using mice, Woychik and his associates generated an insertional mutation exhibiting polycystic kidney disease and identified the gene responsible.

In 1995 Cymbeline Culiat and Rinchik demonstrated that deficiency of a neurotransmitter receptor leads to cleft palate in mice, resulting in tests by human geneticists. Gerald Bunick produced the seeds of DNA-protein crystals that were grown in space aboard the space shuttle and an orbiting space station.

In 1998 Audrey Stevens was elected to the National Academy of Sciences for her successes in identifying numerous proteins involved in RNA metabolism. In 2001 Dabney Johnson, Culiat, and Rinchik proved they had developed mouse models for the acute and the chronic forms of the human disease hereditary tyrosinemia, enabling laboratory tests that might lead to therapies.

Today ORNL biologists are looking forward to conducting research at the new Mouse House, scheduled to open in July 2003, to further advance the field of mammalian genetics.



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