Two Cultures Find Common Ground

Specialists in mouse and fruit-fly development come together to share their research results. They discover mutual interests in spite of their differences

A BILLION YEARS of evolutionary divergence separate the fruit fly and the mouse, and sometimes it has seemed as if the cultural divide between *Drosophila* and mouse researchers is nearly as wide. Last month, leaders of the Banbury Conference Center at Cold Spring Harbor Laboratory attempted to bridge that gap by bringing together under one roof about a dozen members of each band. The researchers could compare results and see how far findings on one organism might be applicable to the other.

The encounter was reported a success by many of the attendees. "The size of this meeting made it easier to exchange information," says the symposium organizer Mario Capecchi of the University of Utah in Salt Lake City. At large meetings, the mouse researchers tend to stick together as do the fruit-fly researchers. But the intimate atmosphere at the Banbury conference broke down these barriers. Everyone could hear all the talks and take part in the discussions.

And they found common ground. "People are beginning to pick up a whole series of genes from the fruit fly in the mouse," Capecchi points out. In the fruit fly, the genes regulate embryonic development. They presumably do the same in the mouse and in man, where they have also been found. Finding out how the genes work might therefore have ramifications for understanding birth defects and cancer.

The meeting may even have marked the beginning of a new respect for the mouse researchers on the part of fruit-fly group. "It's the first time that these *Drosophila* guys haven't been laughing at us," one mouse specialist was overheard remarking to another at the end of the meeting.

The fruit-fly researchers are buoyed by the knowledge that the development of their favorite organism is currently much better understood at the genetic and molecular level than is mouse development. But mouse research is beginning to gain, although a wait of a year or two might have made a big difference in what the mouse group could tell their fruit-fly counterparts about the parallels between the development of the two organisms.

"The meeting might have been more informative in a year," says Capecchi, who is himself a mouse man, "but I adopted [Cold Spring Harbor director] Jim Watson's philosophy that it is often good to have a meeting before things happen because then it may influence how things happen."

One discovery that brought the mouse and fruit-fly researchers together was the identification 5 years ago of the gene sequence called the homeobox because it occurs in the so-called homeotic genes of the fruit fly. Homeotic genes encode proteins that apparently work by regulating the expression of other genes that tell the cells in the various segments of the fruit-fly body to make their characteristic structures, whether these be antennae, legs, wings, or whatever.

At the time of the homeobox discovery, Frank Ruddle of Yale University, whose work focuses primarily on human molecular genetics, was spending a 5-month sabbatical leave in the laboratory of his friend Walter Gehring, one of the codiscoverers of the homeobox. (The other was Matthew Scott, working first with Thomas Kaufman at Indiana University in Bloomington and then at the University of Colorado at Boulder.)

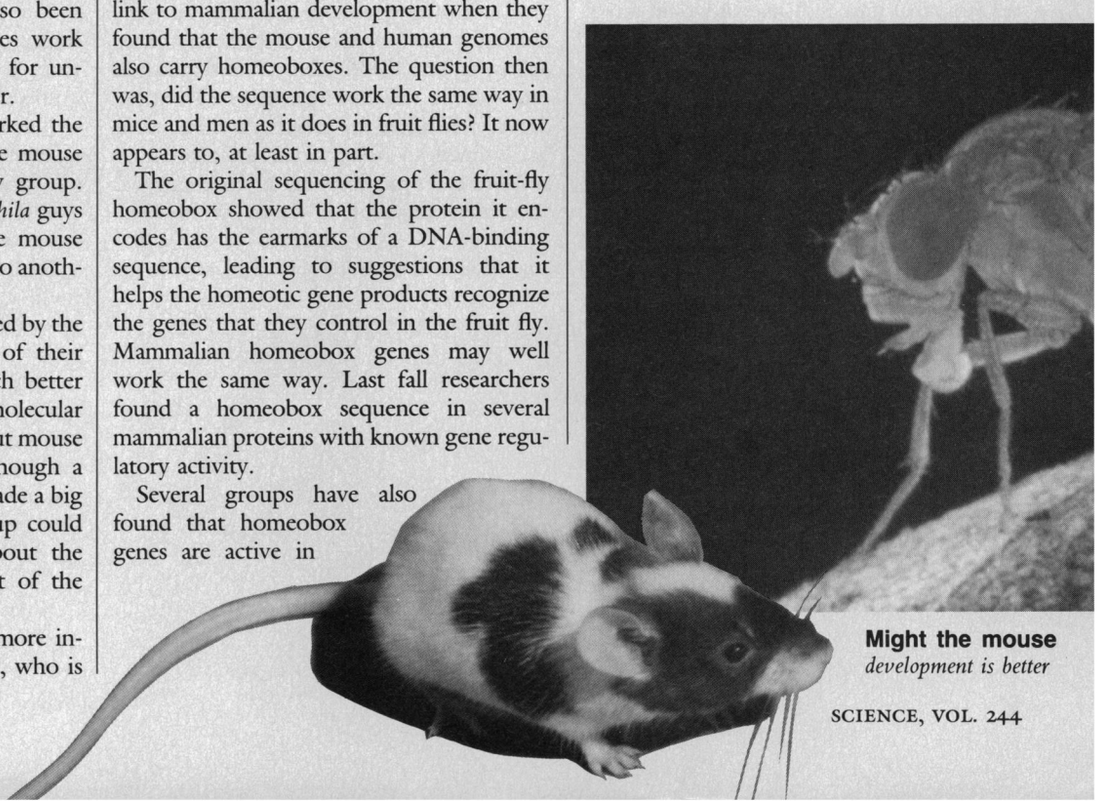
Ruddle and William McGinnis, then a postdoctoral fellow in the Gehring laboratory at the University of Basel, provided a link to mammalian development when they found that the mouse and human genomes also carry homeoboxes. The question then was, did the sequence work the same way in mice and men as it does in fruit flies? It now appears to, at least in part.

The original sequencing of the fruit-fly homeobox showed that the protein it encodes has the earmarks of a DNA-binding sequence, leading to suggestions that it helps the homeotic gene products recognize the genes that they control in the fruit fly. Mammalian homeobox genes may well work the same way. Last fall researchers found a homeobox sequence in several mammalian proteins with known gene regulatory activity.

Several groups have also found that homeobox genes are active in mouse embryos, although their developmental role may not be precisely the same as that of the fruit-fly genes. Recent work, described at the Banbury meeting by Denis Duboule of the European Molecular Biology Laboratory in Heidelberg, West Germany, by Robb Krumlauf of the National Institute for Medical Research in London, and by Ruddle shows, however, that the mammalian homeobox genes share one of the most remarkable features of the fruit-fly genes—a correspondence between the organization of the genes in the genome and the order in which they are expressed in the body.

Homeoboxes were first discovered in the genes of the Antennapedia and bithorax complexes, large multigene systems that are strung out along the long arm of chromosome 3 of the fruit fly. Early on, Edward Lewis of the California Institute of Technology in Pasadena, the classical geneticist who identified and mapped most of the bithorax complex genes, proposed that the order of expression of the genes along the head-to-tail axis of the fruit-fly embryo corresponded to the gene order in the complex.

In the past few years, investigators, including Scott, McGinnis, who is now at Yale University, Michael Levine of Columbia



Might the mouse *development is better*

University in New York City, and Welcome Bender of Harvard University have analyzed the actual pattern of expression of the Antennapedia and bithorax complex genes in fruit-fly embryos and found that, by and large, Lewis's prediction was correct.

The mouse and human homeobox genes are arranged in four multigene clusters, located on different chromosomes. Comparisons of the nucleotide sequences of the mammalian and fruit-fly homeoboxes show that the genes in all four mammalian clusters are lined up in the same order as the corresponding genes in the fruit-fly Antennapedia and bithorax complexes.

The results of Duboule, Krumlauf, and Ruddle now indicate that a correspondence, much like that seen in the fruit fly, exists between the chromosomal order of the mouse homeobox genes and where they are expressed along the head-to-tail axis of the mouse embryo. "What has impressed us all," Krumlauf says, "is that regardless of the cluster the general trend is holding."

All these similarities between the fruit-fly and mammalian homeobox clusters suggest that they may have had a common evolutionary ancestor and may still have common functions in controlling development. "I know of no other complexes of this size that have maintained this degree of similarity," says Ruddle.

Just how common the developmental functions are remains to be seen, however. Several participants in the Banbury meeting pointed to the inescapable fact that fruit-fly development is very different from that of the mouse. For example, the cells of the fruit-fly embryo become committed very early to specific fates.

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be envious of the fruit fly? *Because fruit-fly understood; but the mouse work is gaining.*

Not so in the mouse. "What characterizes mouse development is extremely slow development and extreme indecision until quite late on," says Rosa Beddington of the Imperial Cancer Research Fund Developmental Biology Unit in Oxford, England.

The fruit-fly homeobox genes come into play within the first 3 hours of fertilization when they help to establish the embryo's head-to-tail axis, and specify the borders and characteristics of its segments. The mammalian homeobox genes apparently kick on much later, around the ninth or tenth day of the mouse embryonic period. This raises the possibility that the mammalian genes do not act as the fruit-fly genes do to establish the embryonic body plan.

A billion years of evolution leaves plenty of time for the mammalian homeobox genes to have become adapted to new functions. With few exceptions, their sequences outside the homeoboxes themselves have turned out to be unlike those of the corresponding fruit-fly genes. "It seems to be that just the homeodomain is conserved, not the rest of the gene," observes Gail Martin of the University of California, San Francisco.

Determining just what the mammalian homeobox genes do in development is the problem. In this regard the fruit-fly work has it all over the mouse work, at least for now. Researchers have been so successful in identifying the fruit-fly developmental control genes because they were able to use the techniques of modern molecular genetics to isolate the genes corresponding to the wealth of developmental mutations identified over the years by classical geneticists.

But the mouse, as well studied as it is, does not come equipped with the fruit fly's bounty of genetic information. The mouse researchers are attempting to redress this deficiency by creating their own mutations in the mouse homeobox genes. One promising approach has hit what everyone hopes will be a temporary snag, however.

Last year, Capecchi's group and also those of Peter Gruss at the Max Planck Institute for Biophysical Chemistry in Göttingen, West Germany, and of Alexandra Joyner at the Mount Sinai Hospital Research Institute in Toronto, showed that they could use targeted gene transfer to knock out specific homeobox genes in mouse embryonic stem cells. The cells can then be introduced into early embryos that will develop into chimeric mice in which some of the tissues are derived from the genetically altered cells.

If the altered genes make it into the germline of the chimeras, they could be used to breed new strains of mice with defective homeobox genes. Germline transmission of the mutated genes does not seem to be occurring, however, although Capecchi had to destroy his animals before he could find out because they came down with a viral infection. The investigators are now exploring the possibility that germline transmission will occur if mouse embryos of another strain are used to make the chimeric animals.

According to Joyner, who collaborates with Janet Rossant at Mount Sinai, this may well work because it has happened in another set of experiments not involving mutant homeobox genes. In this set of experiments, the Toronto group showed that a transferred gene can be used to identify mouse genes that become active in the embryo, and are therefore potential developmental control genes.

Researchers are also trying to get a handle on the function of homeobox and other developmental control genes by introducing the genes into mice or fruit flies. In one such experiment, Gruss and his Max Planck colleague Michael Kessel found that the activity of a transferred homeobox gene in the embryonic head produced mice with cleft palates, a common human birth defect.

This shows that the gene had a developmental effect, Gruss says, but it does not necessarily provide any information about the true function of that particular homeobox gene, which is not expressed in the embryonic head area under normal conditions.

Although the Banbury Center meeting focused mainly on the homeobox genes of mice and fruit flies, these are not the only genes that the two species have in common. Some of the others have been identified as cancer-causing oncogenes in mammals.

The *int-1* gene, for example, was originally identified as an oncogene in mouse mammary tumors by Roel Nusse, now at the Netherlands Cancer Institute in Amsterdam, when he was working with Harold Varmus at the University of California, San Francisco. The *int-1* gene subsequently turned out to be the mouse equivalent of *wingless*, a developmental control gene of the fruit fly. Its pattern of expression in mouse embryos suggests that it also may have a regulatory role in mammalian development. The findings provide still more evidence for the already widespread view that cancer is development gone awry.

Although no follow-up meetings on the Banbury conference are currently planned, the growing number of genetic links between the mouse and the fruit fly will no doubt bring the two groups of researchers together again. "There is a lot to be learned from straight comparisons," Capecchi says. "Even when there are differences there might be common mechanisms underlying mouse and fruit-fly development."

■ JEAN L. MARX