# Of Mice and Molecules: Research with Genetically Modified Mouse Models

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During the first century of the development of the mouse as a model organism for biological research, mouse models were inbred with the goal of achieving genetic homogeneity within strains (Lowy and Gaudilliere 1998) and standardization at the locus of the gene (Rader 2004). Beginning in 1910, these mouse models "crossed the threshold of laboratories to replace human bodies," where they were investigated not as mice but as "living instruments" for the study of the human diseases (Lowy and Gaudilliere 1998). Inbred strains were first developed and promoted for cancer genetics research; however, by the 1930s, they were circulated widely as "'pure' biological reagents for . . . diverse lines of medical research" (Rader 2004). After World War II, such mice featured prominently in research on the effects of ionizing radiation conducted by scientists in the Biology Division at Oak Ridge National Laboratory in Oak Ridge, Tennessee (Rader 2004). Standardized strains of mice (along with their rodent brethren the Fischer rat) have served as the "work horses" of research at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) in Research Triangle Park, North Carolina, where scientists have used them to study environmentally associated disease etiology and progression and to develop bioassays to evaluate the toxicity and carcinogenicity of hundreds of substances.

However, beginning in the 1970s, NIEHS and NTP research agendas in genetic toxicology, molecular carcinogenesis, and mechanisms of toxicity contributed to the demand for mouse models modified at the locus of the gene. Genetically modified mouse models appealed to NIEHS and NTP scientists as research tools with potential applications as carcinogen bioassays and in

*Scientists at the NIEHS and the NTP developed genetically modified mouse models as "living instruments" to analyze the effects of environmental exposures* in vivo, *to incorporate mechanistic research in the rodent carcinogenicity bioassay, and to study human genetic variation.*

mechanistic research. As such, genetically modified mouse models served as "boundary objects" (Star and Griesemer 1989), facilitating efforts to "bridge" *in vivo* and molecular biological approaches to toxicological research. The multiple nature of genetically modified mice—that is, that they are simultaneously molecular tools and whole animals—also contributed to their appeal in regulatory settings, where they have been identified as an alternative to traditional carcinogenicity testing for pharmaceuticals.

Over time, the ability of genetically modified mouse models to serve as living instruments for both *in vivo* and molecular research has earned them a prominent niche in contemporary efforts to integrate genetics and genomics with classic toxicology. As such, the history of these models may provide insight into the future of environmental health.

## Materials and Methods

This analysis is based on oral history interviews with scientists who have worked at the NIEHS and/or the NTP ($n$ = 23), archival documents, and articles published both in the popular press and in the scientific literature. Oral history interviews, conducted between October 2003 and June 2004, were audiotaped in their entirety and professionally transcribed. Archival documents were obtained from the files and records of NIEHS and NTP researchers and from their scientific advisors. Literature was identified using electronic databases, including PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi), LexisNexis (http://www.lexisnexis.com/), and F-D-C Reports (http://www.fdcreports.com/). These data were analyzed using the general principles of grounded theory (Glaser and Strauss 1967; Strauss 1987; Strauss and Corbin 1998).

## From Environmental Mutagenesis to Environmental Carcinogenesis

During the 1970s and 1980s, a number of scientists left their positions in the Biology Division of the Oak Ridge National Laboratory for the laboratories of the NIEHS and the NTP (established in 1969 and 1978, respectively). What many of these scientists had in common was a deep interest in genetic toxicology, that is, "the potential of chemicals to induce heritable changes in germ cells that lead to genetic disorders in subsequent generations" (Shelby MD, interview with author, 2004). Many also shared an interest in developing short-term tests to "study the mechanisms of chemically induced DNA damage and to assess the potential genetic hazard of chemicals to human" (Tennant et al. 1987). In 1972, under the direction of Dr. Frederick J. de Serres, these interests were institutionalized in the NIEHS Laboratory of Environmental Mutagenesis; the objective of this laboratory was to address "most issues associated with the emerging fields of environmental mutagenesis and carcinogenesis (as it related to mutagenesis)" in organisms "ranging from microbes to mammals" (Malling 1999).

As these scientists established laboratories and research agendas at the NIEHS, scientific interest in environmental mutagenesis increasingly converged with research on environmental carcinogenesis. Several factors contributed to this process. First, both fields shared a substantive focus—the effects of environmental chemicals on genes. Environmental mutagenesis originally focused primarily on the threat of environmental chemicals to future generations (i.e., via germ cell mutations); however, the effects of environmental exposures on somatic cells was a

closely related concern (Frickel 2004). At the NIEHS "from its inception" genetic damage was "identified as a component of environmental hazards"; NIEHS scientists did "some of the early work *in both carcinogen metabolism . . . and in mutagenesis* [emphasis added]" (Barrett JC, interview with author, 2004).

Second, evidence was accumulating in support of the somatic mutation theory of carcinogenesis, which strengthened the links between the study of mutagenesis and that of carcinogenesis. The theory that mutagenesis was associated with carcinogenesis had existed for decades. Indeed, some of the first evidence that supported this theory came from Hermann J. Muller's experiments in the 1920s, in which he demonstrated that ionizing radiation, already known to be a carcinogen, is also a mutagen (Knudson 1995; Muller 1927). That chemicals could cause mutations was demonstrated in the work of Charlotte Auerbach and John M. Robson in the 1940s, and by the 1960s scientists had observed that some chemical carcinogens interact with DNA (Auerback and Robson 1944, 1946; Schull 1962). However, in the early 1970s, the work of Bruce Ames and his colleagues made a strong connection between mutagenesis and carcinogenesis and provided a relatively easy mutagenesis bioassay—the *Salmonella* test—to identify carcinogens (Ames et al. 1973). In a relatively short time, short-term tests for mutagenesis were "enshrined in regulatory requirements and in biomedical research more generally as carcinogenicity screens" (Frickel 2004).

That the predictive value of the Ames test was overstated (Frickel 2004) only served to stimulate the development of short-term, *in vitro* tests for carcinogenicity. Indeed, through the 1970s and 1980s, the elegance of the Ames imperative, combined with the increasingly apparent limitations of the *Salmonella* bioassay, led to burgeoning efforts to develop *in vitro* carcinogenicity bioassays:

> In an effort to try to resolve the Ames imperative, people . . . kept evolving more and more tests because the initial tests just didn't quite cut it; they missed a lot of carcinogens. [The logic was] if carcinogens are mutagens, then we need better mutagenicity assays, so let's try this or let's try that. But . . . there was always a residue of chemicals that slipped through. So . . . anybody who had a bright idea would try to create a new model system. (Tennant RW, interview with author, 2004)

In the 1980s, NIEHS and NTP scientists led the efforts to evaluate short-term, *in vitro* tests of carcinogenicity: "A great deal of the activity over 15 or 20 years involved trying to figure out the best combinations of organisms and end points for genetic tox tests . . . to predict the potential carcinogenicity of a compound" (Shelby MD, interview with author, 2004). Scientists at the NIEHS, including Fred De Serres, Mike Shelby, Errol Zeiger, Carl Barrett, and Bill Suk, engaged in research collaborations organized by the International Programme on Chemical Safety of the World Health Organization to "attempt to validate all the short-term *in vitro* and *in vivo* tests for mutagenicity with regard to their ability to detect environmental carcinogens" (Malling 1995).

At the NTP, Dr. Raymond Tennant, then director of the Cellular and Genetic Toxicology Branch, and his colleagues compared the results for 73 chemicals tested in the 2-year rodent bioassays and in four *in vitro*, short-term tests. The results of this study, published in *Science* in 1987, highlighted the limitations of these tests for predicting chemical carcinogenicity in rodents. The study found that "not all rodent carcinogens are *in vitro* mutagens nor are all *in vitro* mutagens rodent carcinogens" (Tennant et al. 1987). When using short-term, *in vitro* tests,

> it turns out that in fact you miss a large number of carcinogens. The way it works out is, approximately 70% of everything that is a mutagen is also a carcinogen. That means 30% of the things you might identify as a mutagen don't cause tumors even when they're put into animals for 2 years. On the other hand, 50% of the agents that were tumorogenic weren't mutagens. (Tennant RW, interview with author, 2003)

The clear implication of these evaluation efforts was that there was a need for animal models that could identify nonmutagenic carcinogens. NIEHS and NTP scientists increasingly suspected that extant *in vitro* models were insufficient to understanding the action of nonmutagenic carcinogens: "it was our conviction that in order to understand how nonmutagenic carcinogens cause tumors, we would have to look at whole animals" (Tennant RW, interview with author, 2003). Thus, the work of genetic toxicologists highlighted the need for new models for carcinogenesis research (Tennant 1999).

## Molecular Carcinogenesis and Mechanisms of Action

At the same time that genetic toxicologists were evaluating short-term tests as screens for carcinogenicity,

the NIEHS was also developing a research program in molecular carcinogenesis. As Carl Barrett recalled, "There was not much of an emphasis in the early days, the first decade of the NIEHS, on cancer because there was a cancer institute. So there was . . . an intentional focus away from cancer to distinguish NIEHS from NCI [National Cancer Institute]." However, beginning in the late 1970s, "there was a growing interest and involvement in cancer [research] within the institute" (Barrett JC, interview with author, 2004). Barrett established the Environmental Carcinogenesis Group within Paul Nettesheim's Laboratory of Pulmonary Function and Toxicology.

In 1987, at the request of Martin Rodbell, then the scientific director of NIEHS, Barrett founded the Laboratory of Molecular Carcinogenesis, the first laboratory at the NIEHS dedicated entirely to carcinogenesis research. The mission of the Laboratory of Molecular Carcinogenesis was to "elucidate the genes involved in the [cancer] process and use that information to understand how the environment impacts it." Across the life sciences at this time, there was a burgeoning interest in the genetics of cancer. As Barrett recalled, "There was a lot of excitement. Bishop and Varmus a few years earlier had cloned the first cellular oncogenes. Weinberg had cloned the *ras* oncogene, which was activated by chemicals and that was being studied by a number of different laboratories . . . There was a lot of sense that we knew now the molecular causes of cancer" (Barrett JC, interview with author, 2004; Bishop 1982, 1983; Sakaguchi et al. 1983; Weinberg 1983, 1991). The research of Barrett and his colleagues incorporated these advances but also complicated them by demonstrating that environmental carcinogenesis is a complex, multistage, molecular process that includes both initiating events (e.g., mutagenesis) and other mechanisms (e.g., promotion) that cause an initiated cell to proliferate unchecked. Their research highlighted the need for models that would enable investigation of tumor promotion. NIEHS researchers during this time also called attention to the absence of animal models for late-acting environmental carcinogens:

> One of the chemicals that we had looked at was arsenic—a very well known human carcinogen. The epidemiology is quite clear . . . arsenic induces cancer in a wide variety of tissues in the human population. . . . But it seemed to affect a later stage in the process . . . the epidemiology said it was working late. Arsenic is unquestionably a human carcinogen and there was no animal model. It was not carcinogenic in any animal model. That said to me that the animal models were wrong, and we really needed to have a better way of looking at these later effects. (Barrett JC, interview with author, 2004)

Thus, NIEHS research again pointed to the need for new models for studying the entirety of the process of carcinogenesis.

In the 1980s, research on molecular mechanisms of carcinogenicity also emerged as a focus at the NTP. The NCI's Carcinogenesis Bioassay Program had been transferred to the NTP in Research Triangle Park, North Carolina, in 1981; at that time, the 2-year rodent cancer bioassay was established as one of NTP's central activities. In the years that followed, NTP scientists developed a standardized study design for the 2-year rodent cancer bioassay that has been used to evaluate 600 chemicals. At the same time, there have been persistent concerns that although the 2-year rodent bioassay is widely accorded credibility in identifying carcinogens, it may be "insufficient to produce data from which accurate human health assessments can be made" (Boorman et al. 1994). Indeed, the bioassay was originally designed primarily for qualitative identification of potential human carcinogens and additional experiments are often required in order to inform quantitative risk assessment (Fung et al. 1995). Additionally, given the expense, time, and number of animals required to evaluate a chemical using the standard 2-year rodent bioassay, the NTP has maintained a strong interest in developing reliable methods for testing agents for carcinogenicity that would require a shorter period of time and use fewer animals (Eastin 1998; Tennant et al. 1995). This was also concordant with the NTP mission of evaluating agents of public health concern "by developing and applying tools of modern toxicology and molecular biology" (NTP 2002).

In 1984 the NTP Board of Scientific Counselor's Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation report recommended that the NTP "establish a goal of better understanding mechanisms by developing a battery of short-term tests that measures the widest possible number of end points (including promotion, transformation, and chemical interaction with oncogenes)" (NTP 1984). Then again, in 1992, a scientific review panel convened to evaluate the NTP reported that the program "places too much emphasis on testing per se" and not enough on understanding

the underlying mechanisms (Stone 1993). As a consequence of growing recognition of the complexity of the process of carcinogenesis and the limits of *in vitro*, short-term tests (Tennant et al. 1987), the NTP increasingly sought to identify and elucidate mechanisms of carcinogenicity and toxicity *in vivo*. Genetically modified mouse models provided scientists with one means of pursuing these goals.

## Genetically Modified Mouse Models

Scientists began to create genetically modified mice in the 1980s (Gordon and Ruddle 1981; Palmiter and Brinster 1985). The first genetically modified mice contained randomly inserted transgenes and were used in studies of gene function in the whole animal. In the late 1980s, a convergence of advances in developmental, reproductive, and molecular biology made it possible for scientists to mutate or cause a loss of function in specific genes (Gordon 1989). Using targeted mutations in transgenic mice, scientists began to develop knockout mouse models of human disease to test the role of specific genes in disease etiology and progression (Eddy 1993; Smithies and Kim 1994).

A variety of genetically modified mouse models were developed at the NIEHS and the NTP, primarily in the Laboratory of Environmental Carcinogenesis and Mutagenesis (LECM). The goal of the LECM was to "bridge the task of identifying environmental agents that may be of potential harm to humans . . . and the task of studying the basic biological mechanisms that underlie such effects, in order to ultimately make them more predictable" (NIEHS 2003). The mouse models alone contributed significantly to creating this "bridge," as the altered molecular pathways in their whole, living bodies make genetically modified mice suitable tools for both classic toxicological and molecular biological research. Thus, genetically modified mice enabled LECM researchers to proceed simultaneously at both the whole animal and the molecular level:

> [With these mice] you can have models and hypotheses and actually test them, and that's pretty exciting because there are not many systems where you actually can go in with a molecular laser and actually change a pathway . . . and look at the effect *in vivo* in a living animal. That just doesn't happen very often." (Cannon RE, interview with author, 2003).

In the LECM, interdisciplinary teams of toxicologists and molecular biologists worked together to develop and evaluate genetically modified mouse models (Tennant 1994, 1997, 1998; Tennant et al. 1995, 1996, 1998). Two models may serve as illustrations:

### The Tg.AC Mouse

The Tg.AC mouse was created in the FVB/N mice by pronuclear injection of a v-Ha-*ras* transgene linked to a fetal zeta-globin promoter and an SV40 polyadenation/splice sequence (Leder et al. 1990). The transgene is transcriptionally silent unless it is activated by wounding, radiation, or chemical exposure (Cannon et al. 1997; Pritchard et al. 2003; Spalding 1993, 1999). The Tg.AC model provides a reporter phenotype—skin papillomas—in response to both nongenotoxic and genotoxic chemicals (Pritchard et al. 2003). The Tg.AC mice "behave like genetically initiated mice . . . rapidly developing epidermal carcinomas in response to topical tumor promoter or carcinogen treatment" (Eastin 1998). Scientists at the NIEHS and the NTP have been particularly interested in the potential of Tg.AC as a tool for identifying and studying nongenotoxic chemicals.

Over time, the applicability of the Tg.AC model for risk assessment has been questioned because research suggests that the chemicals that produce a neoplastic response in the Tg.AC mouse do so through activation of the zeta-globin promoter region in the v-Ha-*ras* transgene (Bucher 1998). As noted by the NTP Board of Scientific Counselors, this complicates "the conceptual relationship between the ability to activate this particular promoter" and "the broader ability to induce cancer" (Bucher 1998). However, the Tg.AC's reporter phenotype may still be used to identify nongenotoxic chemicals of concern for further toxicological investigation research, thus helping to identify tumor promoting chemicals that often elude identification in short-term, *in vitro* tests.

### The p53(+/–) Mouse

The p53(+/–) mouse has one functional wild-type allele and one inactivated allele of the tumor suppressor gene *p53*. The p53 mouse model came to the NIEHS from the Baylor School of Medicine in Houston, Texas (Donehower et al. 1992; Harvey et al. 1993a, 1993b). The p53(+/–) model was of interest to LECM researchers as potential rapid screen for

mutagenic chemicals; because p53(+/–) mice offered a single target for mutagens, scientists hoped that it would require less time than the 2-year rodent bioassay to detect mutagenic carcinogens. The model was also attractive because it has a low background tumor incidence in its first 12 months. Therefore, tumors appearing within the first year of exposure to a chemical could be more reliably attributed to the exposure of interest, thereby minimizing the confounding effects of the development of "early sporadic tumors in the rodent models, which often didn't have any direct relevance to human malignancies" (French JE, interview with author, 2003).

Perhaps most compellingly, because of the extensive scientific evidence associating the *p53* gene with forms of human cancer, the p53(+/–) mouse enabled scientists to explore, at the molecular level, the relevance of a specific mechanism of carcinogenesis in the mouse to a known cancer pathway in humans. *p53* is a tumor suppressor gene that contributes to the prevention of aberrant cell growth, division, and neoplastic formation (Dunnick et al. 1997). It is highly conserved between humans and mice (Harris 1996) and has been strongly associated with human carcinogenesis, including lymphomas. The p53 protein is mutated or dysfunctional in 50% of all cancers and in 55% of childhood lymphomas (Donehower et al. 1992; Dunnick et al. 1997; Hollstein et al. 1991). Therefore, as French noted, the p53 mouse

> gave us a focus on the pathway of [the] tumor in the mouse and a means of generating hypotheses about the similarity of that pathway in humans. . . . This helped us to remove some of the uncertainty between trying to extrapolate between rodents and humans. (French JE, interview with author, 2003)

The power of this approach was demonstrated in 1997, when the Food and Drug Administration (FDA) decided to ban phenolphthalein, an active ingredient in laxatives for almost 100 years. The FDA decision was based, in part, on evidence from studies conducted by NIEHS and NTP scientists with the p53(+/–) mouse, which demonstrated that phenolphthalein induced thymic lymphomas accompanied by a loss of the *p53* wild-type allele, within just 4 months (Dunnick et al. 1997). That is, using the p53(+/–) mouse model, scientists were able to make powerful linkages between a molecular pathway in the mouse (*p53*) and a specific cancer phenotype (thymic lymphomas) thought to be highly relevant to human cancer risk. In April 1997, the FDA review committee determined in a nearly unanimous (15–1) decision that "human cancers are known to be associated with alterations in the *p53* gene . . . thus there appears to be a potential risk for humans" (Wall Street Journal 1997).

## The Regulatory Context

The interest of pharmaceutical researchers and regulators in genetically modified mouse models also provided a significant impetus to their development. In 1996, the International Conference on Harmonization (ICH) Expert Working Group on Safety ruled that carcinogenicity testing in an alternative model, such as a genetically modified mouse model, and bioassays in one other rodent species (e.g., the rat) could replace the previous requirement for bioassays in two rodent species for assessing the carcinogenicity of new pharmaceuticals (ICH 1997). The ICH is a joint regulatory/industry project "to improve, through harmonization, the efficiency of the process for developing and registering new medicinal products in Europe, Japan, and the United States and to make these products available to patients with a minimum of delay" (ICH 2000). Their 1996 ruling stimulated international interest in developing alternative models of carcinogenicity testing, including genetically modified models.

In response to the ICH ruling, the International Life Science Institute (ILSI), an international consortium of pharmaceutical companies, with participation from public research institutions and regulatory agencies, formed a technical committee to coordinate research on alternatives to carcinogenicity testing. Evaluating the ability of three genetically modified models, p53(+/–), Tg.AC, and H*ras*2, to provide useful information for human risk assessment was one of the first major initiatives of this committee. Evaluation of the models required the development of standardized protocols to allow reproducibility and comparability of data obtained across multiple laboratories (Robinson and MacDonald 2001). In evaluating the effort, the leaders of the ILSI committee argued that "the database from these studies represents an important contribution to the future application of new models for human cancer risk assessment" (Robinson and MacDonald 2001). They noted also that "beyond the

data, the collaborative process by which the models were evaluated may also represent a prototype for assessing new methods in the future" (Robinson and MacDonald 2001). Indeed, this process has been drawn upon for the assessment of additional molecular technologies in toxicology, including DNA microarrays.

## ERKO and Environmental Genetics: Modeling Genetic Variations

Throughout the 1990s, research at the NIEHS focused increasingly on genetic mechanisms that are affected by environmental exposures. As a result, the uses of genetically modified mice by NIEHS scientists has expanded dramatically.

The estrogen receptor knockout, or ERKO, mouse models were made by Dr. Kenneth Korach and his collaborators to study the estrogen signaling system, both in "normal" development and in hormonal carcinogenesis (Korach 1994). At the time that Korach and his colleagues made a knockout model for estrogen receptor alpha, the conventional wisdom was that it would be impossible to do so. Indeed, as Korach recalled,

> if you looked in the literature and what people were taught in graduate school and medical school, the belief was that mutations in the estrogen receptor were lethal . . . [so] people just felt that was not going to be a worthwhile endeavor.

Korach disagreed, reasoning that even if the ERKOs proved not to be viable, important information about the function of estrogen could be gleaned from the attempt. As such, the first "big surprise" in the development of the ERKO models was that they were viable: "We made these mice and everybody in the endocrine field . . . couldn't believe it, because the knockout was supposed to be lethal." After developing the ERKO model, Korach and his colleagues used them "to study various aspects of the biology of estrogen action and . . . [to] explore the possibility . . . that they could be used for evaluation of environmental agents that have hormonal activity" such as diethylstilbestrol and dioxin (Hall and Korach 2002). A second big surprise for Korach and his laboratory came when researchers in Sweden identified a second estrogen receptor, now called ER-beta. In response to this discovery, Korach and his colleagues developed an estrogen receptor-beta knockout mouse model (Krege et al. 1998), as well as a double knockout model. Unique insights have been generated by subsequent research with each these models concerning the role of estrogen in male and female development and fertility (Couse and Korach 1999; Couse et al., 1999; Meuller et al. 2002; Ogawa et al. 2000; Schomberg et al. 1999); the estrogen receptor alpha model also played a key role in diagnosing the only known human case of a genetic mutation resulting in a living person who is hormonally insensitive to estrogen (Smith et al. 1994). Korach and his colleagues are now crossing the ERKO models with other mouse models that contain genetic modifications specific to carcinogenesis in particular tissues, in order to investigate the role of estrogen signaling in mammary cancers, including the effects of DES, dioxin, and other nongenotoxic environmental chemicals.

Genetically modified mice have also been created to model known human genetic variations suspected to be relevant to how persons differ in their responses to environmental exposures. The uses of genetically modified mice as models of human genetic susceptibilities to environmental exposures was highlighted by NIEHS Director Dr. Kenneth Olden in his testimony before Congress in 2001 when he announced the development of the Comparative Mouse Genomics Consortium:

> Today, I am announcing our intent to support the development of Comparative Mouse Genomics Centers that will make use of all available DNA sequence variation data generated in the Environmental Genome Project to produce novel transgenic and knockout mouse models which will mirror specific polymorphic variants of human environmental response genes found in the general population. (Olden 2001)

Genetic modifications enable scientists to "humanize mice" and to model human genetic variation (Wilson SH, interview with author, 2004). For example, scientists may insert a human gene into a mouse through transgenic knock-in and then study the function of a human protein in the mouse background. Alternatively, a mouse gene may be altered so that it has the same variation as the human gene of interest, and then the mouse is examined to determine the function of the altered mouse gene or gene product. In the Comparative Mouse Genomics Centers, "all this work is conducted in the context of toxicology, from the standpoint of understanding the effect of the gene variation on a toxicant dose–response relationship"

(Wilson SH, interview with author, 2004). Again, genetically modified mouse models here serve as a bridge between traditional toxicology and mechanistic approaches.

## Conclusions

The interest of NIEHS and NTP scientists in developing genetically modified mouse models for toxicological research derived originally from their research in the areas of genetic toxicology, molecular carcinogenesis, and mechanistic research. Specifically, in the 1970s and 1980s, NIEHS scientist highlighted the need for animal models for identifying nongenotoxic and tumor-promoting chemicals. At the NTP, scientists were also interested in the potential of genetically modified mouse models to serve as carcinogenicity bioassays that would simultaneously generate both mechanistic and phenomenological data. Across the institute and its programs, genetically modified mouse models have been taken up, in part, because they provided scientists with "living instruments" for investigating molecular mechanisms *in vivo*. That they have met with some acceptance by international regulatory agencies, especially for the evaluation of pharmaceuticals, has further stimulated research on their applications.

As the director of the NIEHS, Dr. Olden has been a strong advocate of incorporating advances in genetics and molecular science into environmental health research. This commitment is evident in the programs launched during "the Olden years," such as the Environmental Genome Project and the National Center for Toxicogenomics. Genetically modified mouse models occupy a pivotal niche in these programs, where they serve as standardized models of human genetic variation. As such, just as they sit at the boundary between classic toxicology and molecular genetics/genomics, genetically modified mouse models may represent a crucial bridge between the past and what Dr. Olden has envisioned as the future of environmental health.

## Summary

The development of genetically modified mouse models at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) is an important component of emerging genetic and genomic research agendas in the environmental health sciences. Scientists at the NIEHS and the NTP developed genetically modified mouse models as "living instruments" to study the effects of environmental exposures *in vivo* and to incorporate mechanistic research in the rodent carcinogenicity bioassay. These genetically modified mouse models bridged traditional toxicological approaches and emerging molecular foci within the institute, leading to new collaborations and innovative approaches to environmental health research. This historical overview locates the emergence of genetically modified mouse models in the history of the NIEHS and NTP research on environmental mutagenesis and carcinogenesis, while exploring their consequences for the future of environmental health.

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## Notes

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