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Eleanor Roosevelt Institute

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For nearly 40 years, the Eleanor Roosevelt Institute (Fig. 1) has pioneered basic biomedical research in the effort to understand, treat, and eliminate disease. The Institute was founded on the belief that research is the most effective and cost-efficient long-term approach to the eventual conquest of human afflictions. Our long tradition of innovative science and dedicated scientists led to remarkable molecular advancements in understanding cell structure and function. Today that pioneering spirit thrives in our explorations of birth defects like Down syndrome, cancers, genetic diseases like amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), and premature aging. Beyond the bench science, the Institute continues to be a leader in the examination of the legal, social, and ethical implications of genetics and genetic research as well as a resource to our local community.

Founding of the Institute

Eleanor Roosevelt was deeply moved by the growing problem of cancer among the people of the world, and so she ensured that provisions for cancer research were in place prior to her death. The Eleanor Roosevelt Cancer Foundation, Inc. was responsible for the establishment and the initial funding of the Institute in 1961. Mrs. Roosevelt captured the founding concept when she said that, "it will strive to destroy the scourge of cancer for the benefit of all people who live in our one small world."

In the last 40 years the world has gotten much smaller and research has expanded exponentially. However, the Institute remains close to Mrs. Roosevelt's founding principles by pursuing one of the most important intellectual endeavors ever undertaken—to understand the processes of life.

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The Eleanor Roosevelt Institute operates as an independent research institute, alleviating the constraints often found in a traditional academic environment with the sole objective to produce a useful product: new knowledge about human genetics and disease. This is advantageous in our efforts to bring together a small group of outstanding biomedical and genetic scientists who work interactively in the field of human biology, cell biology, and cancer biology.

Scientific Achievements

In the mid-1960's the researchers of the Institute, led by Theodore Puck, Ph.D., were curious about a new approach to genetic analysis in multi-cellular organisms. The question of how to expedite the concepts of molecular genetics to a human population fueled many of the scientific achievements that were made under the roof of the Eleanor Roosevelt Institute.

The following is an excerpt from an article written by Dr. Puck for GIT - Biology Galleys entitled "The New Biology and Its Human Implications" as it relates to this quest that eventually resulted in the development of somatic cell genetics. The basic concept involved study of mammalian genetics. Instead of mammalian reproduction, which involves mating of the germ cells, reproduction of cells from other parts of the body was utilized. Since each of the somatic (i.e., body) cells contains a nucleus that houses the chromosomes on which the genes are carried, it seemed reasonable to sample these cells, to grow them into large populations in glass vessels by the methods of tissue culture, and then to study the genetics of such cell populations as though each cell were an independent microorganism like *E. coli*. Such a discipline required the following achievements:

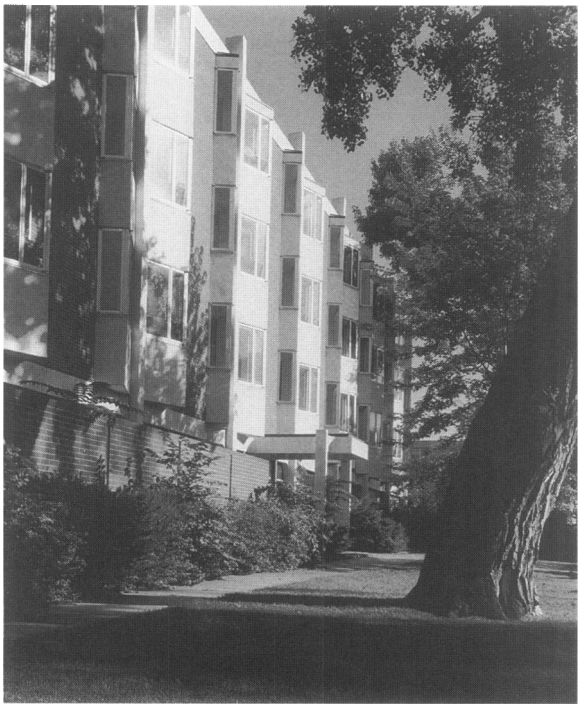

Fig. 1. Eleanor Roosevelt Institute.

(1) Development of a method for taking samples of living cells from the skin (or any other organ) and growing these cells into a large population by methods of tissue culture in a process that would be simple, reliable, and inexpensive.
(2) Development of a means whereby single cells from such a culture could be deposited in a vessel and grown in the incubator under conditions such that each cell multiplied in isolation produces a large visible colony. Such colonies arising from single cells are called clones and constitute a genetically uniform population. Since all cells of a clone are identical, it becomes easily possible to recognize mutant clones and to isolate them to form new cell stocks. Such mutants are essential for genetic studies, because mutations furnish genetic markers which illuminate the operations of the genetic process.
(3) Identification of the human chromosomes. Until 1956, not even the correct number of human chromosomes was known. Their exact identification is a necessary step to the building of systematic human genetics. The identity of each of the human chromosomes was first established by means of cell growth in culture in 1958, and then Denver System for classification of the human chromosome developed in 1960. This classification system, achieved by a self-appointed study group meeting in Denver, Colorado, is still the one in use today and has made possible many fundamental discoveries in human genetics, as well as recognition of the chromosomal basis of many human diseases.
(4) Development of the single cell survival curve by which the effects of any physical, chemical, or biological agent on the multiplication of mammalian cells could be quantitatively measured. This methodology for the first time offered quantitative measurement of the effects of agents on the reproductive capacity of mammalian cells. For example, it greatly improved the power of radiotheraphy by substituting accurate information about the amount of radiation needed to destroy tumors. It also made possible isolation and characterization of many kinds of mutants needed for a variety of genetic studies.

These four basic developments, which owe a considerable debt to earlier studies in tissue culture and to microbial genetic concepts, were carried out in our laboratories and initiated a new discipline of somatic cell genetics.

Today, we herald a new age of biomedical and genetic research where discoveries are made by the minute. In response to this revolution, the Institute has taken a proactive approach in positioning the organization for the future.

Current Research

Current scientific research programs at the Eleanor Roosevelt Institute are a mixture of mature and new studies. Genetics and biochemistry are the basis of our research methods.

Down syndrome

A major center for Down syndrome research is located at the Institute and is headed by David Patterson, Ph.D, President and Senior Fellow of the Eleanor Roosevelt Institute. The mission of this effort is to carry out medical research focused on generating the knowledge which will

allow mitigation of the symptoms of Down syndrome and to use this knowledge to devise and test strategies for mitigation of these symptoms.

Down syndrome is caused by the presence of an extra copy of chromosome 21, the smallest human chromosome.

The research programs of the center address the challenge to identify genes overexpressed in people with Down syndrome to determine which of them contributes to particular phenotypes, and to counteract the effects of having three copies of the genes on chromosome 21. Largely through the last 15 years of work done by the Eleanor Roosevelt Institute's scientists and collaborators, the time is right to undertake this challenge.

Recently, the Institute was awarded a 5-year grant by the National Institute of Child Health and Human Development to study the genes possibly responsible for the neurological and cognitive characteristics of people with Down syndrome.

"Dr. Patterson's research team is addressing an area of research that is of high program relevance to the Mental Retardation & Development Disability Branch of the National Institutes of Child Health and Human Development," said Felix F. de la Cruz, Chief of the Mental Retardation and Developmental Disability Branch. "The scope of the research embraces studies from the cellular level to analysis of cognitive development in individuals with Down syndrome including development and characterization of animal models of Down syndrome, biochemical studies, and molecular biological studies."

This program is a wonderful example of the Institute's principal investigators that seems to be truly devoted to sharing concepts, approaches, technology, and systems. The following is a description of the research program outlined by Dr. Patterson.

GENE IDENTIFICATION. The goals of this research are to identify genes on human chromosome 21 which lead to the pathology of Down syndrome. To carry this out, individual genes have to be identified and characterized using the information generated here and around the world about chromosome 21. Characterization includes understanding the role each gene might play in the development of mental abilities and why having an extra copy of this gene should cause some of the features of Down syndrome. Often, but by no means always, it is possible to make hypotheses regarding how a particular gene might lead to a particular aspect of Down syndrome. Katheleen Gardiner, Ph.D., a Senior Fellow at the Eleanor Roosevelt Institute, is a world recognized expert in this technology and will play the lead role in this critical aspect of the project.

GENE FUNCTION: ANIMAL MODELS. Once genes are identified and characterized, we shall test whether they cause features reminiscent of Down syndrome when introduced into an experimental animal, the laboratory mouse. Recent work by us and by our collaborators has clearly demonstrated the feasibility and usefulness of this approach. Miles Brennan, Ph.D., a Junior Fellow at the Institute, has produced a number of mice carrying genes suspected of involvement in Down syndrome. However, many more are essential for a full understanding of the syndrome.

In addition, Dr. Brennan is developing a method which will allow the creation of extremely specific mouse models of Down syndrome unlike any of the ones currently available because the precise nature of the genetic alteration will be known. Dr. Brennan will produce mice with extra copies of the genes identified by Dr. Gardiner and will produce additional mice using this new approach. These are highly complementary approaches. Drs. Brennan and Gardiner will both analyze the mice.

GENE REGULATION. Once genes which produce features reminiscent of Down syndrome in mice are identified, it will be essential to determine whether the actions of these genes can be blunted so that the features of Down syndrome are lessened, prevented, or reversed. Dr. Patterson will be heavily involved in this aspect of the work and will start immediately to analyze mice already engineered by Dr. Brennan and other collaborators. Dr. Brennan has begun experiments to develop a general way to reduce the expression of any gene on human chromosome 21 regardless of its function. In this way, the three copies of any gene present in people with Down syndrome will be made to function at the same level as the two copies present in individuals without Down syndrome.

CLINICAL RELEVANCE. There are a significant number of drugs and other compounds for which it is possible to devise a rational reason to attempt therapy of aspects of Down syndrome. Before these can be ethically tried in clinical studies, it is important to test them in animal models. The best available animal models currently are mice in which regions of chromosome 21 are present in extra copies. The most well

characterized mouse currently is the Ts65Dn mouse. This mouse has one extra copy of a part of mouse chromosome 16 which is the equivalent to about 75% of the human chromosome 21. The mouse has a set of symptoms which is reminiscent of Down syndrome, although it clearly does not have all the features of Down syndrome.

As part of the Center's activities, we propose to establish a testing facility in which the effects of compounds for which there is a rational basis for believing they might mitigate some of the symptoms of Down syndrome, especially the cognitive deficits, will be tested to determine their effect on the features reminiscent of Down syndrome which are seen in the Ts65Dn mouse. The work on mice will be essential before human clinical studies can be carried out. The studies on mice will be guided by definition of the precise learning strengths and weaknesses of children with Down syndrome, which will be carried out by our project collaborators and other scientists. A Community Advisory Board is assembled to assist the Institute in these efforts.

INFORMATION DISSEMINATION AND EDUCATION. The Eleanor Roosevelt Institute is developing a World Wide Web page, which makes the results of research and clinical efforts available to Down syndrome researchers, clinical care givers, and their patients and families. Components of this website include the most up-to-date computer analysis of the 40 million bits of genetic information currently being decoded by the international consortium established for this purpose. Please visit the website at: www-eri.uchsc.edu. In addition to the technological information provided, the Institute offers public lectures regarding this effort.

The Institute's investigators also conduct independent research. The following list is not exhaustive but represents the major efforts of the Institute.

ALS

Eleanor Roosevelt Institute scientists were among the lead researchers in the breakthrough discovery that pinpointed the alterations of an enzyme (SOD1) that causes ALS in certain families. The gene for SOD1 lies on human chromosome 21. Identifying the role of this gene in the familial form of ALS may be helpful in further identifying the causes of all forms of ALS, an always fatal disease characterized by progressive paralysis. More recent discoveries at the Eleanor Roosevelt Institute promise to reveal new insights about ALS and other diseases of the nervous system.

Alzheimer's Disease

Scientific investigators at ERI have participated in collaborative efforts which demonstrate that chromosome 21 contains genes which may cause the biochemical changes seen in the brains of individuals affected by this form of progressive, and fatal, dementia.

Human Genome Initiative

The Institute is a state-designated Center for Human Genome Research, working in concert with the University of Colorado Health Sciences Center. The mapping conducted at the Institute is primarily associated with chromosomes 3, 12, and 21.

While much of the scientific community realizes the importance of this international effort, the Institute garnered the support of the legislative community in Colorado while presenting a House Joint Resolution that created a Colorado center for human genome research. "This center will lead the state in increasing understanding of the role of genes in human health and disease," said Rep. Faatz. "And its designation by the state as a center will formally recognize one of the state's great resources—its scientific community."

Leukemia

Eleanor Roosevelt Institute researchers have located a damaged gene responsible for a most deadly form of leukemia: acute myelogenous leukemia (AML). In finding this gene on chromosome 21, there is hope that diagnosis of AML could be earlier and more accurate. Eleanor Roosevelt Institute investigators are also actively involved in searching for genes on chromosome 3 that are linked to leukemia.

Recombinant 8 syndrome

Recombinant 8 syndrome (Rec8 syndrome) is one of the few identified chromosomal disorders that impacts a specific ethnographic population. Rec8 syndrome is found in the population of the San Luis Valley of southern Colorado and Northern New Mexico. Sharon Graw, Ph.D., Junior Fellow at the Eleanor Roosevelt Institute, is working to characterize the chromosomal rearrangement which leads to Rec8 syndrome in great detail at the molecular level. The region of the chromosome within which the rearrange-

ment must lie is narrowed down to about 1% of the total chromosome region. Once this 1% has been analyzed, the laboratory will devise a rapid, inexpensive, and sensitive assay to detect the inversion 8 chromosome in unaffected individuals at risk for having a child with Rec8 syndrome.

Again, the Eleanor Roosevelt Institute recognizes the need to work closely with the Hispanic and health care communities in these studies. To foster communication between the Institute and these groups, a Rec8 Advisory Board was assembled to examine the ethical administration of issues surrounding this syndrome.

Ethical, Legal, and Social Studies

The Eleanor Roosevelt Institute is exploring the often uncharted waters of the legal, ethical, and social implications of genetics and genetic research. The Institute is also concerned with the responsible stewardship of genetic information. All research programs address ethical issues prior to submitting grant requests, and all community outreach programs contain information about these issues. One example of how the Institute is involved in the responsible stewardship is the work of Lynda M. Fox, J.D., the former Vice-President and Senior Fellow of the Institute. She worked with legislators to draft one of the first six pieces of legislation in the nation that protects an individual's genetic information privacy.

Funding

The Institute's major research grants come from the National Institutes of Health, the Department of Energy and national health organizations. The Institute is proud to recognize these supporters, as their funding is a watermark for the quality of the Eleanor Roosevelt Institute's sciences and the Institute's financial viability.

For the balance of funding necessary to fulfill our mission, the Eleanor Roosevelt Institute relies on private dollars. These donations provide the primary, and sometimes only, means for the Eleanor Roosevelt Institute to recruit new faculty, to support promising young investigators, to provide seed money for innovative but untested research ideas, to provide transition support for established investigators, and to fund ongoing projects that otherwise might incur expensive shutdown and start-up costs, and to acquire, maintain, and renovate the first-rate laboratory space essential for the biomedical research mission of the Institute.

Gifts from the private sector also help us to leverage grants from national sources and help support our community educational programs.

Scientific Advisory Committee

Senior Faculty

Bronwyn Bateman, M.D., Genetics of Eye Disease Laboratory

Linda Crnic, Ph.D., Behavioral Neuroscience Laboratory

Katheleen Gardiner, Ph.D., Genetic and Metabolic Regulation Laboratory

Fa-Ten Kao, Ph.D., Human Genome Structure and Mapping Laboratory

Charles Kirkpatrick, Ph.D., Cytokine Sciences Laboratory

Loris McGavran, Ph.D., Colorado Genetics Laboratory

David Patterson, Ph.D., Thomas G. & Mary M. Vessels Laboratory for Molecular Biology

Theodore T. Puck, Ph.D., Cyclic AMP, the Cytoskeleton and Cancer Laboratory

Arthur Robinson, M.D., Clinical Application of Somatic Cell Genetics Laboratory

Junior Faculty

Miles Brennan, Ph.D., Molecular Genetics Laboratory

Sharon Graw, Ph.D., Genetic and Metabolic Regulation Laboratory