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## Series: Molecular Medicine Institutions

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### McLaughlin Research Institute

**George A. Carlson, Director**

Great Falls, Montana seems an unlikely spot for an independent biomedical research institute. This quiet town is certainly better known for the superb trout fishing in the Missouri River or as a jumping off point for the Bob Marshall Wilderness and Glacier National Park. There is no medical school in Montana and even the state's research universities are more than a three-hour drive from Great Falls. Yet for more than 40 years research coming from the McLaughlin Research Institute has belied its small size.

The Institute began in 1954 with the arrival of Dr. Ernst Eichwald, recruited as a pathologist by the Montana Deaconess Hospital. As a condition of accepting the position, Dr. Eichwald, who directed a research program at the University of Utah, stipulated that a portion of the Hospital's income from the clinical laboratory be set aside to help defray operating expenses and as a hedge against the day when NIH funding might become more difficult to obtain.

#### *Transplantation*

Ernst's work in the Laboratory for Experimental Medicine, as it was then known, focused on the young field of tissue transplantation. Lacking a university, Great Falls did not have a ready supply of biologists or chemists looking for jobs, so he hired a used-refrigerator salesman from Sears, Bud Silmsner, who seemed to be endowed with a good measure of common sense. In honing his skills at skin grafting using transplants within an inbred strain, Silmsner had an unusually high failure rate. These turned out not to be technical failures, however, but rather rejection of male

grafts by female mice—the discovery of the male-specific histocompatibility antigen, H-Y.

In addition to his clinical responsibilities and investigations into the genetics and immunobiology of transplant rejection, Ernst served as Editor of the journal *Transplantation Bulletin* and its successor, *Transplantation*, which had its editorial offices in Great Falls until 1967. Early work at the Institute by Eichwald and later by Dr. Jack Stimpfling played an important role in the eventual development of successful protocols for organ transplantation in humans.

#### *Experiments in Education*

Around 1956 an eager high school sophomore, Irving Weissman, approached Dr. Eichwald about the possibility of working in the lab. Irv was persistent and, after he made it clear that he didn't expect to be paid, was allowed to help clean and change mouse cages. He quickly became more and more involved in the lab, learning the process and excitement of research, inspiring him to a career in science. Dr. Weissman is now the Karel and Avis Beekhuis Professor of Cancer Biology at Stanford University and serves as Chairman of the Institute's Scientific Advisory Committee. In addition to after-school work, Irv spent much of his high school, college, and medical school summer vacations working on Dr. Eichwald's research projects. The obvious enthusiasm and accomplishments of the young Weissman at the Institute led to development of a summer program for promising young high school students, selected on a state-wide basis, to work and learn in the laboratory. This program continues today and has been supported since its inception by the Montana Division of the American Cancer Society. The summer interns are active participants in the research programs at the Institute and they learn, as no textbook can

teach, the questioning process by which new knowledge is obtained. Most participants in the program have gone on to productive careers in science or medicine.

The success of the summer high school program has led its recent expansion to include college undergraduates and to the development of a new initiative for area science teachers. All scientists at McLaughlin Institute serve as mentors in these programs. Service as an educational resource for the region is a vital part of McLaughlin Research Institute's mission. In addition to providing a start for the next generation of scientists, a basic understanding by non-scientists of the nature of scientific inquiry and its implications for society is crucial; it behooves all of us in research to devote some of our time and expertise to pre-college education.

#### *A Change in Venue*

In 1964, Ernst Eichwald recruited Jack H. Stimpfling from The Jackson Laboratory in Bar Harbor, Maine to join him in the Laboratory for Experimental Medicine. Jack also was a leader in transplantation immunogenetics and his work with future Nobel laureate George D. Snell was pivotal for the genetic dissection of the mouse major histocompatibility complex, *H2*. Ernst and Jack worked quietly but productively until 1966 when the Deaconess Hospital moved into a new building on the south edge of town designed to allow them to compete more effectively with their in-town rival, the Columbus Hospital. Promised research laboratory and mouse space in the new facility did not materialize, however, and the two scientists moved their research programs into two abandoned mom 'n' pop grocery stores, one of which is shown in Figure 1. The shelves served as adequate racks for mouse cages and the checkout counters worked as lab benches.

Through the urging of Great Falls physicians John Pfaff and Jack McGregor, Columbus Hospital under the Catholic Sisters of Providence realized that the orphaned laboratory presented an opportunity to support research (and perhaps provide the Hospital with a competitive edge in attracting patients). With support from local contractor John L. McLaughlin supplementing that of the Sisters, the McLaughlin Research Institute opened its doors in May 1967. The building provided excellent laboratory and mouse space for the two scientists, but soon after its opening Ernst Eichwald returned to the University of



**Fig. 1.** Drs. Ernst Eichwald (left) and Jack Stimpfling in front of one of two abandoned grocery stores that served as the temporary homes of the Laboratory for Experimental Medicine, predecessor to the McLaughlin Research Institute.

Utah where he became Chairman of the Department of Pathology. Although now "retired," Ernst continues daily work in his lab and is a valued friend and advisor to the McLaughlin Research Institute, as well as to his colleagues in Utah.

#### *Solo Science*

After Ernst's departure, Jack Stimpfling enjoyed his role as the sole scientist at the Institute, while making major contributions in immunology and immunogenetics. Jack devoted his career to the identification and characterization of *H2* recombinants, developing a panel of congenic strains with crossovers within the complex that were used by scientists worldwide during the golden age of immunobiology. By developing poly-

clonal, and later monoclonal, antibodies to identify the rare intra-*H2* recombinant mice, he added considerably to the value of the mouse resource. Jack's application of genetics towards isolating and understanding the functions of the many molecules encoded within the complex was exemplary and far-reaching in its impact. Although unique in his ability to work so productively in such isolation, Jack enjoyed scientific and philosophical discussions with his many visitors and collaborators. The "Montana Institute for Immunology" meetings on several occasions were combined with the Immunobiology Study Section sessions. In one instance, research grant applications were packed in for review on mules to remote cabins adjoining the Bob Marshall Wilderness, much to the chagrin of some NIH bureaucrats. During Jack's tenure, a cadre of scientists devoted to the Institute developed; in addition to Irv Weissman, this group included David Baltimore and Montana native Leroy Hood, both current members of McLaughlin's Scientific Advisory Committee.

#### *Expansion*

In 1987, Jack Stimpfling announced his intention to retire the following year. This raised an interesting problem. How could a one-man Institute continue in the emerging era of big science? The Columbus Hospital convened a committee to decide the fate of the Institute, and considered options including closing down or converting into a clinical lab. Fortunately, the committee included Irv Weissman, Lee Hood, and other scientists and community leaders who had the vision to recommend expansion. Realizing that replacement of Jack was impossible, two scientists (Peter Wettstein from the Wistar Institute and myself from The Jackson Laboratory) were recruited to direct the expansion. Among the attractions were the lack of administrative impediments to research and the outstanding mouse facility (not to mention the trout fishing). Expansion posed a number of problems, however. Most pressing was the fact the building was designed for two scientists and was rapidly filled to overflowing. In addition, the Institute had no endowment and no obvious source of funds for constructing a new facility.

Through the efforts of Institute and Hospital staff, community leaders, the state legislature, and Montana's congressional delegation, a combination of state and federal funding was obtained in 1991 for construction of a new research

laboratory (Fig. 2). Because of restrictions on grants from the State of Montana to sectarian institutions, McLaughlin Research Institute amicably separated from Columbus Hospital and incorporated as an independent not-for-profit research organization in 1989. Once again, however, the Institute became a single-scientist operation when Peter Wettstein accepted a position at the Mayo Clinic in Rochester. Recruiting began in earnest and by completion of the new facility in the summer of 1993, three scientists were on the staff.

#### *A Common Thread*

Although the research programs at McLaughlin Research Institute have diverse goals, they all take advantage of its historical strength in mammalian genetics. The animal facility is designed exclusively for mice, allowing efficient animal care, fewer demands for veterinary oversight, and, consequently, per diem rates lower than most other institutions. The mouse colony is maintained as a barrier facility and is free of viral pathogens; also included are quarantine rooms outside the barrier and an infectious disease area with individually vented cubicles. Animal technicians are active participants in the Institute's research programs, providing services such as tissue sampling, neurological testing, surgical procedures, and record keeping. This provides relief from the tedium of cage changing for the caretakers and develops a sense of responsibility for "their" mice. Current census is approaching the capacity of approximately 15,000 mice. McLaughlin Research Institute was fully accredited by the American Association for Accreditation of Laboratory Animal Care in 1995. J. Douglas Coffin, who joined the Institute in 1993 following postdoctoral training under Tom Doetschman in Cincinnati, successfully established a transgenic mouse facility with both pronuclear and blastocyst microinjection capabilities. To date, three genes have been ablated by Institute scientists using homologous recombination and numerous conventional transgenic lines have been produced. The shared application of mouse genetics to complex diseases and biological processes fosters interaction and collaboration among the scientists at the Institute.

#### *Alzheimer's Disease to Sex—Current Research Programs*

There are currently four research groups at the Institute. The most recent addition to the staff is



**Fig. 2. McLaughlin Research Institute.**

John A. Mercer, who was recruited from the University of Texas Southwestern Medical Center at Dallas. His research focuses on molecular motors. As a postdoctoral fellow under Scientific Advisory Committee members Neal Copeland and Nancy Jenkins at the National Cancer Institute, Frederick, he identified the non-muscle myosin gene underlying the dilute coat color mutation in mice. He has continued this line of research as an independent investigator and is particularly interested in the roles of unconventional myosins in the nervous system. The small size and geographical isolation of the Institute limits the breadth of expertise available, providing impetus to develop outside collaborations to enhance advancement of our research programs. Dr. Mercer provides an excellent example; he, Johns Hopkins electrophysiologist Peter Gillespie, and David Corey of Harvard have recently initiated a joint project to study the molecular motors responsible for hair-cell adaptation in hearing.

J. Douglas Coffin is the youngest member of the Institute, arriving immediately after completing his postdoctoral training in 1993. Regulation of angiogenesis forms the unifying theme of his research efforts, with emphasis on the effects of

growth factors. In collaboration with Tom Doetschman at the University of Cincinnati and Robert Florkiewicz at Prizm Pharmaceuticals in San Diego, he has developed transgenic mice that overexpress FGF2 and provide a model for human chondrodysplasias with premature closure of the long bones. Together with eminent heart surgeon Carlos Duran of the International Heart Institute in Missoula, Montana, he also is evaluating the effects of growth factors in enhancing the beneficial effects of transmural laser revascularization in severe coronary artery disease. Dr. Coffin also supervises the Institute's transgenic mouse facility, and has added Leroy Hood of the University of Washington to the list of outside users.

Developmental biologist William R. Crain joined the Institute as a Senior Scientist in 1993, following a long and productive career at the Worcester Foundation for Experimental Biology in Massachusetts. Switching from sea urchins to mice, his research focuses on sex determination early in development. By applying differential display to identify genes that are expressed exclusively in males or females, Dr. Crain is dissecting the pathways involved in determining whether genital ridge cells develop into ovaries

or testes. The Y<sup>pos</sup> sex-reversed model developed by Eva Eicher at the Jackson Laboratory provides a genetic approach to this complex process.

My research applies the power of mouse genetics towards dissecting complex diseases. A concentration on neurodegenerative disorders evolved from a long-standing collaboration on the genetics of prion susceptibility with Stanley Prusiner at the University of California, San Francisco. In addition to scrapie research, my laboratory is using amyloid precursor protein transgenic mice to identify novel genes that might be involved in Alzheimer's disease; these studies are in collaboration with Karen Hsiao at the University of Minnesota, Brad Hyman at Massachusetts General Hospital, Paul Chapman in Wales, and Steven Younkin at the Mayo Clinic, Jacksonville. Similar work using presenilin transgenic animals produced at the Institute is underway in collaboration with Peter St George-Hyslop and David Westaway at the University of Toronto. A mouse mutagenesis screen designed to identify genes specific to prion disorders and Alzheimer's disease is a recent new direction.

#### *Small Science*

In a lecture at the Institute two years ago, Ernst Eichwald speculated on whether the time for "small science" had passed, but he argued that establishments like the McLaughlin Research Institute may well be an ideal setting in which curiosity, flexibility, and the fun of doing science can be maintained. Ensuring the survival of such

an environment is difficult, but it is made easier by the dedication of the Institute's supporters, particularly the members of our Scientific Advisory Committee. Each year the Committee convenes in Great Falls to discuss each investigator's program, help foster collaborative studies, and provide advice on research directions and recruiting. In conjunction with the Advisory Committee meeting, scientists, students, physicians, and educators are invited to a day-long workshop; usually more than 100 people participate. The lineup of speakers is impressive, and in 1997 included Advisory Committee members Jeff Frelinger, Irving Weissman, Neal Copeland, Nancy Jenkins, Leroy Hood, and David Baltimore, along with guest speakers George Bloom from the University of Texas Southwestern Medical Center in Dallas and Kim Hasenkrug from the Rocky Mountain Laboratory of the National Institute of Allergy and Infectious Disease.

At this writing, the Institute is engaged in a search for two additional scientists to join us in Great Falls. The response to our advertisements has been gratifying. It is clear that working in a very small, geographically isolated institution is not for everyone. However, it is equally clear that there are many outstanding investigators whose work can flourish in a collegial environment with minimal administrative impediments to research. We hope that McLaughlin Research Institute can continue to provide a place for the spiritual successors of Ernst Eichwald and Jack Stimpfling, working on the frontiers of science.