THE Stowers Report

NEWS AND INSIGHT FROM THE STOWERS INSTITUTE FOR MEDICAL RESEARCH

The Stowers Approach: Advanced Biotechnologies to Explore Basics of Life

The Stowers Institute for Medical Research was born of the union of dreams and visions held by two people with great wealth and by biological scientists looking to make a giant leap in our understanding of how life works.

After deciding to use their fortune to help remove the threat of dreaded diseases from people's lives, Jim and Virginia Stowers sought out Dr. Leroy Hood, a leading advocate of the use of technology to extend knowledge about the functioning of genes to larger areas of the body – a systems approach. He was joined by Dr. Eric Davidson, one of the country's most respected developmental biologists, in creating the scientific research focus of the Institute.

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A Research Environment for the Twenty-First Century

Seeking to create a major center for scientific investigation, the Stowers Institute for Medical Research is building what will be one of the nation's finest laboratory complexes on a 10-acre site in the cultural and intellectual heart of Kansas City, Mo. The facility, with its first phase to be ready for use in the year 2000, will eventually have the capacity for 50 to 60 principal investigators, each directing teams of about 10 researchers.

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Stowers Institute for Medical Research

Virginia and Jim Stowers- A Legacy of Hard Work, A Gift of Vision

As they approached ages that for most people mean retirement, Virginia and Jim Stowers faced the happy situation of being wealthier than they might ever have imagined. They shared a conviction that they wanted to use their money to help humanity, but they also wanted to make a difference, to get results. And they wanted to play an active role in launching the undertaking that would benefit from their largesse.

Their decision on how to use that great wealth led to the creation of the Stowers Institute for Medical Research in Kansas City, Mo., which operates with an endowment from the Stowerses currently worth about $336 million. In addition to donations to be sought from other contributors,

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Jim and Virginia Stowers

VOLUME 1
ISSUE 1

Brilliance and Knowledge o

A Marriage of High Tech and Biology

In Lee Hood's molecular biotechnology laboratory at the University of Washington, a jumble of people from many academic disciplines – engineering, computer science, physics, chemistry and several areas of biology – are looking for ways to understand each other and share their knowledge and skills. This undertaking, which he calls "ordered chaos," reflects Dr. Hood's conviction that biological science, to meet the challenges of the 21st century, must break out of its focus on single cells and study entire systems, which means processing immense amounts of information.

Dr. Leroy Hood

That, in turn, requires constantly improving technology, which calls for the collaboration of engineers, computer whizzes and others. Dr. Hood likes to say that the most significant thing to come out of the information revolution will be biological information, and he is setting the pace in the effort to amass it. In most cases, the Hood team seeks to design and build its own technology to meet research needs as they arise.

Though this is all done in pursuit of basic science, many people look to Dr. Hood — and his approach, combining technology with systems-level research — to make a major contribution to uncovering the kind of knowledge that will, eventually, enable medical science to correct the defective genes that underlie cancer and other diseases. Without making predictions about the time required for this to occur, he often points out that the transition time between fundamental science and its application to clinical research and treatment is now very brief.

"We have to deal with complex systems if we want to solve cancer or autoimmunity," he says. "And to develop the tools to study these things, we have to bring in chemists and physicists and computer scientists and applied mathematicians. It's the ability to decipher information that will allow us ultimately to understand complex systems. And the ability to manipulate information is what is going to lead us to designing new drugs and therapies and approaches to disease."

His vision captivated Virginia and Jim Stowers, founders of the Stowers Institute, who chose to incorporate many of Lee Hood's ideas into the research focus of the Institute. Since 1995 he has been chairman of the Scientific Advisory Board of the Institute, and his laboratory receives part of

"We have to deal with complex systems if we want to solve cancer or autoimmunity. And to develop the tools to study these things, we have to bring in chemists and physicists and computer scientists and applied mathematicians."

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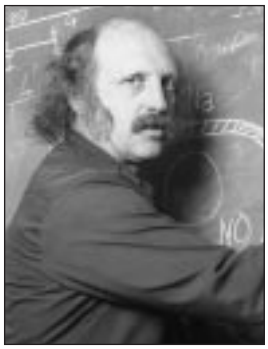
To Great Depths for the Perfect Embryo

To get a sense of the kind of scientist Eric Davidson is, it helps to know that when he and a colleague decided in 1971 to make the purple sea urchin an important embryonic system for studying how genes control development he first learned to scuba dive. He spent the summer diving into murky, choppy waters off Massachusetts under the direction of an ex-Navy Seal diver whose idea of a challenge was to throw his student's wet suit and gear into the water, make him dive in with just a snorkel, find everything and get dressed under water.



Dr. Eric Davidson

Certification in hand, Dr. Davidson returned to Pasadena, where he had been hired to teach embryology at Caltech, and put out the word among divers along the Southern California coast that he was looking for a supply of sea urchins. But he also had to find a way around the main drawback to using sea urchins as a genetic research animal: the fact that the females normally produce eggs only about half of the year.

The solution came from a diver in San Diego, who reported one day that he had been diving into deep water beneath a kelp forest and had seen yellow eggs coming out of sea urchins – in the middle of the summer, when they were not supposed to produce eggs. This seemed to prove Dr. Davidson's theory that by adjusting environmental conditions it would be possible to fool sea urchins into producing eggs year-around. So, Caltech built a sea urchin culture facility at Corona del Mar mimicking the conditions the diver had found

n Scientific Advisory Board

under the rocks in the dark, constantly cold water.

Even after all that, Dr. Davidson did not retreat fulltime to his classroom and laboratory and leave it to professional divers to bring up the sea urchins. During the next 15 years or so, he made regular deepwater scouting and collection trips to

> *"I'm the only person I know who has been rash enough or foolish enough to try to become professionally familiar with the natural history all the way to the molecular biology of the animal I work with."*

stock the marine station and study the environment from which the animals came. "I'm the only person I know who has been rash enough or foolish enough to try to become professionally familiar with the natural history all the way to the molecular biology of the animal I work with," he says.

This story reflects the determination, skill and depth of knowledge that Dr. Davidson, one of the most respected developmental biologists in the country, brings to the Stowers Institute as a member of its Scientific Advisory Board. Along with Dr. Leroy Hood, the Board chairman, he took a major part in shaping the research focus of

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Torturing Bugs Leads to Accomplishment and Honor

From a boy who liked to torture bugs, Michael Levine has progressed to the grown man who can't believe he gets paid for doing more or less the same thing he did as a child – under the mantle of academic respectability as a developmental biologist. He shares Einstein's view that the greatest thing about being a scientist is being able to remain a child.

Dr. Michael Levine

"My relatives still complain that they don't know what I do," he said as he leaned back in a tiny office in his laboratory at the University of California, Berkeley, and ran his fingers through a thick head of hair turning silver. "At family reunions they constantly ask what it is that I do for a living. Some of them think I'm some kind of doctor. They'll ask me what to do about a backache or something; I tell them to take aspirin and drink orange juice."

What a developmental biologist does, he says, is to study how a single cell with a fertilized egg cleaves, divides and makes lots of cells, all of which become different from each other and finally give rise to a very complex creature. That creature could be anything from the fruit fly, on which Dr. Levine focuses his research, to a human being. Simple though it may sound, such study can lead down limitless paths for someone who is paid to satisfy his curiosity.

"There is something spiritual in this," he says. "There is this process of discovery and figuring out how nature works. Being in awe of nature, the deeper you dig and the more intricacies you see you come to realize there's a certain beauty and logic there."

Unlike his relatives, Mike Levine's scientific peers have no confusion about what he does, or the importance of it. That became obvious with the telephone call he received from Washington at 6 a.m. one day in April 1998 bringing word that he had been elected to membership in the National Academy of Sciences at the relatively young age of 43. Many other awards and honors have also come his way, one of the latest being appointment to the Scientific Advisory Board of the Stowers Institute, where he has joined Dr. Leroy Hood and Dr. Eric Davidson to guide the research focus of the Institute.

Like Drs. Hood and Davidson, Dr.

> *"There is something spiritual in this. There is this process of discovery and figuring out how nature works."*

Levine believes that basic biological research today should focus on the regulatory DNA, which he calls "the real computational center of the gene." It determines when and where the gene is on and off and, therefore, is expected to become an important factor in efforts to find cures or treatments for cancer and some other diseases by changing or

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Stowers-Funded Research Consortia Take Cutting-Edge Approach

Ellen Rothenberg and her team of researchers at California Institute of Technology explore an area of science on the frontier where molecular biology, developmental biology and immunology intersect – and which could make long-term contributions to our understanding of various diseases, including leukemia. Government grant makers, however, tend to see the approach as too broad and too uncertain as to outcome, so they are reluctant to give financial support.

Or, as Dr. Rothenberg says: "You have to already know 90 percent of the punch line before they'll give you money."

But her work – focused on the development and function of T lymphocytes, the cells that act as controllers of the immune response — is the kind of cutting-edge scientific investigation that the Stowers Institute for Medical Research was created to support. Since 1995, the Rothenberg lab has been part of the first of two research consortia being underwritten by the Stowers Institute at universities and other sites across the country. The Institute launched the network of research efforts, at a current cost of about $5 million a year, because it wants to make a clear statement of its commitment to basic science even while the Kansas City campus is being designed and built.

"This is a very ambitious interest because there are so many moving parts," says Dr. Rothenberg of her work on T cells. "Stowers, with its emphasis on looking at things at the system level, is a fantastic opportunity to really address this in the way it needs to be looked at in terms of what regulators are expressed and how they duke it out, essentially, to turn on and off different target genes and how that changes the potential for what the cells can become."

Dr. Rothenberg, 46, reflects the high level of talent and academic excellence among the scientists whose work the Stowers Institute seeks to encourage and support through the consortia or at the future campus in Kansas City. After a carefully nurtured childhood as the daughter of two academicians – her father taught her algebra and formal logic in the fifth grade – she went to Harvard, from which she graduated summa cum laude with a degree in biochemical sciences.

Dr. Ellen Rothenberg

Starting graduate school at Massachusetts Institute of Technology, one of her first classes was David Baltimore's course in virology, and although she did not think she was particularly interested in viruses she found herself "enthralled by the clarity of thought" demonstrated by the future Nobel Laureate. When the time came for her to join a lab for her dissertation research, she chose his, an experience that she found to be "really fun, interesting, elegant, marvelous, beautiful, totally absorbing."

She did her dissertation on the replication of retroviruses and received her Ph.D. in cell biology in 1977. After doing post-doctoral research at Memorial Sloan-Kettering and then the Salk Institute for Biological Studies, she joined Caltech in 1982 as an assistant professor. In 1994, she was promoted to full professor.

In addition to the Rothenberg lab, Consortium I, of which it is a part, includes research teams working under Dr. Eric Davidson, also at Caltech; Dr. Leroy Hood at the University of Washington, and Dr. George Carlson at the McLaughlin Research Institute in Great Falls, Montana. Drs. Davidson and Hood, both members of the Stowers Institute Scientific Advisory Board, developed the consortium concept as a way to join the best scientists from throughout the United States for collaboration in research programs directed at fundamental challenges in biology and medicine.

Each unit of Consortium I works on different components, but shares a unified scientific focus directed toward study and analysis of the following:

- Overall gene expression patterns in both normal development tissues and in cancerous cells in which activity has been altered as a consequence of the disease state.
- Organization of large sets of genes that function in particular processes.
- Gene regulatory programming in the DNA to understand the underlying regulatory processes.
- Methods of altering gene expression in living cells and new ways to control the regulatory process.

Consortium II, which began research in mid-1997 at five laboratories, is mapping the DNA sequence of the genome of the sea urchin, a marine animal widely used as a model for developmental biologists. The genome is the home of all the system's genetic information and serves as a blueprint for the entire organism. Sea urchins are considered useful in this kind

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Financing of Stowers Institute Uses Lessons of a Lifetime in Investment

Don't spend the capital, Jim Stowers likes to say. That's the seed. Spend only from the income. And the assets of the Stowers Institute for Medical Research are being handled according to that philosophy, the advice he routinely gave as he was building American Century Companies into a mutual funds giant that today manages some $70 billion in assets.

Another tenet of the Stowers approach to financial management is that inflation is a greater menace to the value of capital than the risk posed by investment in common stocks. For that reason, whatever the ups and downs of the stock market, he puts his faith – and his money – in growing American companies, and that is where he intends to invest the assets of the Stowers Institute as well.

Today, the Stowers Institute is supported by an endowment created by Jim and Virginia Stowers, currently worth $336 million, but in the coming years the support for the Institute is expected to grow spectacularly by a combination of means, including:

- Investment of the assets in mutual funds that invest in companies with growing earnings.
- Contributions by other donors to the Stowers Institute for Resource Development, which serves as a supporting organization for the Stowers Institute for Medical Research.
- The gift of the estate of Virginia and Jim Stowers, which includes their remaining shares in American Century, currently worth $875 million, and other assets.

Recognized under the Internal Revenue Service code as a medical research organization, the Stowers Institute for Medical Research will spend 3.5 percent of its assets each year for scientific investigation and administration. Assuming that the invested assets earn substantially more than that – as has been the long-term history of the American Century mutual funds – the present assets alone will grow handsomely over the years.

> *"If we invested the money a conservative way, the Institute would probably run out of money."*

As the years go by, assuming successful investments, and with the addition of donations from other individuals and organizations, plus the value of the Stowers estate, the assets supporting the Stowers Institute could eventually reach $30 billion or more. That will enable the Institute to become one of the largest and best-funded scientific research centers in the United States.

Most endowments and foundations follow an investment approach that divides their assets between equities and bonds and are happy with annual growth of 10 percent, but the Stowerses hope to build the endowment quickly by staying almost fully invested in American Century funds holding shares in companies with accelerating earnings growth. They expect to achieve average annual growth in assets of at least 15 percent.

"If we invested the money a conservative way," Mr. Stowers says, "the Institute would probably run out of money. My belief is that the biggest long-term financial risk that the Institute faces is the lost in value of the dollar, not the risk of the market."

A separate entity, the Stowers Institute for Resource Development, was recently granted tax-exempt status by the IRS as a support structure for the Stowers Institute for Medical Research. It will raise funds from outside donors – individuals and foundations – under an innovative system that will keep donors always informed about how much their gift is worth. Individual accounts will be maintained for all contributions of $1,000 or more, and – almost like a mutual fund account – the donor will receive a regular statement telling him or her how much the gift has grown through investments, after deducting 3.5 percent each year for the Institute's work. Gifts of less than $1,000 will be pooled with others for record keeping. Contributions to the Institute for Resource Development from living donors are tax deductible to the maximum extent allowed by the IRS. Bequests from estates are exempt from federal estate taxes.

Borrowing from their mission statement, "Hope for Life," Jim and Virginia Stowers have designated the gifts from outside donors as "Hope Shares." They call them "living gifts that will continue to help humanity forever." These gifts will live far beyond the donor's lifetime and

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The Stowers Approach from page 1

Drs. Hood and Davidson believe that biologists have acquired a level of understanding of cells and genes that makes it feasible to break away from studying one thing at a time and undertake study of the complex systems that form human beings and other organisms. This daring approach — science for the 21st century — will be facilitated by the use of robotic devices, computers and other cutting-edge technology that enable researchers to process huge amounts of information in a fraction of the time required just a few years ago.

The Stowers Institute is a basic research facility that does not promise or seek to develop specific treatment or pharmaceutical options, but its creators believe that their scientific approach will someday enable science and medicine to make major improvements in today's primitive treatment methods for cancer and many other diseases.

To operate from a state of the art research campus now under construction in Kansas City, Mo., the Institute is currently creating its scientific infrastructure and preparing for the day in 2000 when the 594,000-square-foot center will open its doors. However, the Institute is already financing research in laboratories at five universities and one independent institute.

The development of the scientific focus of the Stowers Institute began with the desire of Mr. and Mrs. Stowers to help other people who, like themselves, have faced the terrible words: "You have cancer." Possessed of the fortune accumulated by their ownership of American Century Companies, the mutual fund giant created by Mr. Stowers in 1958, they initially considered endowing a new research facility to work specifically toward cures for breast and prostate cancer.

However, their nation-wide odyssey to existing research facilities and their lengthy conversations with scientists convinced them that more could be accomplished with a deeper and more basic approach that builds on the extensive research underway into how the genes in the DNA work to produce and maintain life. That is considered key to understanding the development of people and other living beings and the origin of most of the diseases that now confront society, including cancer, cardiovascular and auto-immune diseases.

> *"You can't study one gene or one protein or one cell anymore. In the future, we will try to understand the properties of cancer by looking at the systems as a whole."*

In 1994, their search led them to Dr. Hood, widely known as a co-inventor of the DNA sequencer, the device that identifies the sequences of the human DNA many times faster than manual methods. The sequencer is considered indispensable to the Human Genome Project, the international effort to decode all three billion letters of human DNA in the next five to seven years. Dr. Hood, who heads the Department of Molecular Biotechnology at the University of Washington and holds a chair endowed by Microsoft Chairman Bill Gates, accepted the invitation of Mr. and Mrs. Stowers to become chairman of the Scientific Advisory Board of the Stowers Institute.

"What underlies the future," Dr. Hood says, "is to look at biology and medicine as the study of complex systems. And to study complex systems you have to study lots of the parts so you can derive the fundamental

intrinsic properties of the system. You can't study one gene or one protein or one cell anymore. In the future, we will try to understand the properties of cancer by looking at the systems as a whole, rather than looking at a gene or a cell or a protein in isolation. That's the paradigm shift that we're really starting out with at the Stowers Institute."

Speaking of the impact that technology will have on biological research and medical treatment, he said, "My feeling is, if we look back in 100 years, everything else will be dwarfed by the kinds of things we're talking about today."

"What we want the Stowers Institute to have integrated into it," he continued, "is not only the ability to explore the new vistas but to create the technologies that will breach the subsequent barriers that we run into. It's this relationship between inter-disciplinary technologies and their application to biology and medicine that are at the heart of what is unique about the Stowers Institute.

Dr. Davidson, who holds the Norman Chandler Chair in Cell Biology at Caltech and was invited to join Dr. Hood in forming the Scientific Advisory Board during the Institute's early phase, explained why more can be accomplished through basic research than by working on drugs at this point. "Curing something like cancer isn't just a question of people banging away on cancer cells," he said. "We really need more basic understanding of how cells work before this becomes a tractable problem.…This problem is going to be solved by the acquisition of another kind of understanding of how genetic systems work, and that's what we're after here. A lot of good scientists will have to become oriented to a new approach if the problems of cancer and other diseases are going to be solved."

"The properties of living systems in which scientists are really interested cannot be described by looking at individual genes or individual elements or individual proteins," Dr. Davidson continued. "These are properties that derive from huge numbers of genes working together and it's necessary to understand genetic systems, to understand the control apparatus of the genes. This is the most exciting problem in the history of biology, and it takes thinking about this problem in a somewhat different way than has been classically used, or is being used today in most laboratories."

Specifically, the philosophy of the Institute states: "The scientific focus of basic research at the Institute is to obtain an understanding of how the genes in the DNA of all multi-cellular creatures work to produce and maintain life….The Institute

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Stowers Institute for Medical Research

Financing of Stowers Institute from page 5

express continuing love to children, grandchildren and others who come after us by giving them the opportunity for a longer, healthier life.

By keeping records for individual donations, and with regular statements about how much each gift has grown in value through investment, the Stowers Institute will avoid the criticism made of many charities that donors do not know how much of their gift actually supports the work of the organization. In the case of contributions to the Stowers Institute, donors will always know how much they are helping – and how much they are appreciated.

Lee Hood from page 2

its financial support from the Stowers Institute. He also enjoys financial backing from William Gates, chairman of Microsoft Corp., and the former junk-bond king, Michael Milken, plus the National Institutes of Health, the National Science Foundation and other federal entities that underwrite basic science.

National publications run glowing articles about Lee Hood, describing him in such terms as "superstar scientist" and builder of "revolutionary" machines. The Wall Street Journal, in a front-page article in 1995, called him "biotechnology's premier tool-and-die man." Even before setting up his forward-thinking department at the University of Washington in 1992, he was co-inventor of several machines used in sequencing and synthesizing proteins and DNA molecules. The DNA sequencer, which was developed commercially by a firm that Dr. Hood helped found, has become the workhorse of the mass DNA-sequencing effort of the Human Genome Project, automating the tedious process of sequencing nucleic acid bases.

Montana-born Leroy E. Hood, now 60, received his undergraduate degree in biology from Caltech, then set out for Johns Hopkins to get a medical degree, which he considered an important tool to round out his knowledge of human biology. After completing his M.D., he returned to Caltech and earned a Ph.D. in molecular immunology in 1968. After three years running a lab at the National Institutes of Health he joined the Caltech faculty, eventually becoming chairman of the Biology Department, a post he held until he left for Seattle in 1992.

> *"What has fundamentally changed in biology and medicine in the last 10 years or so is our capacity to decipher biological information."*

Dr. Hood is the co-author of six books, holds nine patents for biotechnology that he has developed, and is a member of the National Academy of Sciences and the American Association for the Advancement of Science. He has received dozens of professional awards and honors, including the Albert Lasker Basic Medical Research Award for studies of immune diversity and the Louis Pasteur Award for Medical Innovation, both in 1987.

Colleagues and admirers see him as an inspiring, charismatic, big-picture scientist with the demeanor and sincerity of a Boy Scout. He has the skill, rare among scientific researchers, to reach out to business people in order to make the connections that enable him to develop the technology he believes so important to science. He attributes that ability to two formative events that occurred while he was growing up in Shelby, Montana. First, he took debate in high school, where he learned to think on his feet and take complicated issues and make them understandable to anyone. Second, he was such a good biology student that, as a senior, he was asked by the teacher to co-teach the sophomore course. To get and hold the students' interest he used examples from Popular Mechanics magazine.

A man of undying optimism, he thinks scientific mysteries can be solved and health problems can be conquered, just like the mountain peaks he loves to climb. He is capable of framing the big questions for science and medicine, of thinking about what biologists will be working on for the next 200 years and where the physicians of the future will focus their efforts at patient care. He is a tireless speaker, teacher and campaigner for more and better science.

Even while dealing with some of the major scientific questions of our time, he takes time to try to improve the quality of science education available to the youngest Americans through the "Outreach" program developed by his wife, Valerie Logan. The program is in the third year of an effort to provide 100 hours of science education training to 1700 Seattle area teachers of kindergarten through fifth grade. In its developmental period, Dr. Hood himself often spoke to community groups and school boards to convince them of the importance of giving students early exposure to good science.

Maynard Olson, a respected researcher dedicated to genome analysis who gave up a Howard Hughes medical grant at Washington

Lee Hood

University in St. Louis to join Dr. Hood's team in Seattle, explained part of what attracted him: "I've been frustrated, much the same as Lee has, with the fact that biology is in an explosive phase of substantive advance, which is very exciting, but it's really behind the times technologically."

"That's cultural," he continued, "because most biologists are really enumerate. Lee was a pioneer. We've seen sort of two parallel revolutions in recent decades. One of them was the high technology revolution with lasers and computers and communications and so forth. The other has been a biological revolution with recombinant DNA and monoclonal antibodies and so forth. Lee actually accounts for a significant fraction of the overlap between these two worlds."

In Dr. Hood's words, "What has fundamentally changed in biology and medicine in the last 10 years or so is our capacity to decipher biological information. One kind of information is what's contained in your chromosomes; that's the information of the genome. A second kind of information is what's contained in your proteins. People have studied chromosomes and genes and proteins for a long time, but for the first time we can study them in large numbers and we can study how they act in a coordinated manner with one another and that's fundamentally different because of these developing new tools.

"But there's a third kind of biological information which is really at the heart of the future, and that information resides in complex biological systems and networks. Getting to that is how we will better explain disease. This approach can relate powerfully to any disease."

In the process, he says, "Biology is going to be fueled by miniature machines that will come out of computer science and engineering. My prediction is that in the next 10 years there will emerge an area of theoretical biology that will be manned by applied mathematicians and computer scientists who will analyze all this biological data – the genome."

Michael Levine from page 3

correcting the behavior of genes.

He believes that the National Academy extended membership to him on the basis of some 10 years of research related to the regulatory DNA, with the work of his lab essentially showing that the regulatory DNA can be modulated and that within a module there is great complexity in terms of the DNA responding to both positive and negative information.

But he says the research itself is just half of the story about why he was elected to the National Academy. The other half was coming into his own as a scientist at the time when the right technology was coming along. "Technology," he says, "had just become available to do this kind of analysis. To really understand how you make these precise patterns of gene activity in an embryo has depended on developing various kinds of technologies. I helped develop one of the technologies, but there were many of us who took part."

His experience provides justification for the longstanding argument of Dr. Hood, a co-inventor of the DNA sequencer, that technology is the key to carrying basic biological science to the next frontier, where knowledge about individual genes and cells will be expanded to the systems level. Constantly improving technology, he argues, will make possible the processing of huge amounts of biological information and tell us things we have not previously known about how nature works.

Speaking of the impact of this on the work of biologists, Dr. Levine said, "In the old days, you would have a guy with one big idea and this would be the idea that would sustain him throughout his career. Now, one idea is not enough. The turnaround time between figuring out the sequence to use to work through a problem and carrying it out experimentally is not so long anymore. That's because of technology. You can't just have this one great insight because you're going to do it faster than you think."

Growing up a science nerd in Los Angeles, Dr. Levine attended public schools, then went to the University of California, Berkeley, from which he graduated Phi Beta Kappa in 1976. Five years later, he received his Ph.D. from Yale, then held post-doctoral fellowships at the University of Basel in Switzerland and at Berkeley. Later, he taught at Columbia University and the University of California, San Diego, before returning to UC Berkeley as a full professor in 1996.

As a biologist, Dr. Levine often thinks he should demonstrate a fascination for the great outdoors in his off-hours, but the fact is that, except as a source for bugs, he doesn't feel much attraction to the outdoors. He takes his two sons on hiking trips and other outings only from a sense of parental duty and the last thing that interests him after a day walking around collecting rocks and fossils with them, he says, is pitching a tent and sleeping in it. He would rather have a shower and a drink in front of a color television set.

"In the old days, you would have a guy with one big idea and this would be the idea that would sustain him throughout his career."

What he likes to do in his off-hours is hole up somewhere with a good book of modern American fiction or something on Civil War or Revolutionary War history. He has also been inspired to delve into Southwest history by stories his grandmother told him about a great-grandfather who was a peddler on the U.S.-Mexican border and founded the town of Nogales, Arizona.

Eric Davidson from page 3

the Stowers Institute, and he has played an almost daily role in numerous decisions about the design and staffing of the Institute.

If there's a characteristic that seems to mark him it must be his determination to follow trails back to the genesis of whatever interests him. He delights in recounting tales of the lengths to which he has gone to satisfy the demands of a life in science. Listening to him, you get the feeling that if he were sitting on a barstool he would be telling the best stories in the place. That includes those about finding the Xenopus frogs on which he did research before switching to sea urchins. After an expert from the Smithsonian showed him how to tackle huge, chicken-eating frogs in the muck in the jungles of Panama, he did his own collecting.

He takes hobbies just as seriously. He doesn't merely play the banjo – as part of the Iron Mountain String Band, which performs at festivals and other events in Southern California – for years he also collected old-time music in the mountains of southwest Virginia. Drawn to the area while still a college student in the Fifties, he found places that had only recently benefited from rural electrification and the radios and record players that it brought. As a result, people were still playing and singing music formulated two centuries earlier. Dr. Davidson studied banjo players, ballad singers and fiddlers and made recordings to the Smithsonian, which issued the music under its Folkways Records label.

Despite being rejected for undergraduate admission to Harvard – on the grounds that he had not done well enough on the scientific aptitude test – the New York-born

> *"You have to be driven all the time by curiosity, by how something works. I'm not just interested in describing things; I want to know how they work."*

Dr. Davidson made his mark as a biologist from a very early age. He published his first paper at 16, in Biological Bulletin, after a summer working on a research project on sand dollars at the Marine Biological Laboratory on Cape Cod under the direction of L. V. Heilbrunn, a professor at the University of Pennsylvania. A year later, as a national winner in the Westinghouse Science competition, he began college studies under Dr. Heilbrunn at Penn.

After receiving his Ph.D. from Rockefeller University in 1963, he taught there until 1971, when he moved to Caltech, where he now holds the Norman Chandler Chair in Cell Biology and directs research projects funded by the Stowers Institute, the National Institutes of Health, and other entities. He has been a member of the National Academy of Sciences since 1985, is a fellow of the American Association for the Advancement of Science, and has been honored by the Alexander von Humboldt Foundation. His first book, Gene Activity in Early Development, published in 1968 when he was just past 30, had an almost revolutionary impact on the field of developmental biology, and his list of publications in scientific journals exceeds 25 pages.

Some four decades of distinguished research efforts have done nothing to diminish the thrill he feels for scientific discovery. He calls it the "the rarest form of thrill," and says it is one of two things a scientist has to feel. "The other is curiosity. You have to be driven all the time by curiosity, by how something works. What we're here for is to find out how things work. I'm not just interested in describing things; I want to know how they work."

To those who may be impatient with the speed of basic scientific research and wonder about its usefulness to human beings, he says: "The uses and results of their work can never be predicted by people who obtain basic knowledge. I am working on some of the most basic aspects of life, and there is no way of predicting how it will impact practical affairs. But there's no chance that there won't be an impact."

The Stowers Approach from page 7

research on genes and gene regulatory mechanisms will include explorations of both the normal output of genetic information in development and the abnormal output of genetic information, as in cancer. The basic goal is to obtain an understanding of the flow of genetic regulatory information during life and how this is translated into functioning proteins and systems."

To Drs. Hood and Davidson, the completion of the Human Genome Project will be just the beginning of functional investigation by scientists. In effect, it will produce a gene encyclopedia, which must then be studied for further understanding.

The Stowers Approach

"There are two levels of deciphering," Dr. Hood says. "One level is determining the order of the letters in the DNA alphabet all the way across our chromosomes. The second level is identifying what 3.7 billion years of evolution has embedded in those strings. The Human Genome project will give us an enormously powerful tool for going on to the second problem."

"It's very clear, it's inescapable," said Dr. Davidson, "that the things scientists really care about are programmed in that yard of DNA sitting in every cell. And it's the expression of the tens of thousands of genes in that DNA, the way they are regulated, that is going to give us the answers to all these great problems. These problems include how life works, how embryological development occurs, how evolution has worked, and also how many diseases work. This is the underlying kernel of all these problems."

One of the research efforts already being financed by the Stowers Institute, through one of its research networks, is a genome project. This one — underway at five research sites — is mapping the DNA sequence of the sea urchin, a marine animal that is a major research model for the systematic analysis of gene expression. Sea urchins are closely related developmentally to vertebrates, develop rapidly and have few cells — making them useful in research.

While creating a focus and connection among scientists doing research for the Stowers Institute, the Scientific Advisory Board is sensitive to the need not to order researchers to do one thing or another, thereby inhibiting the freewheeling exchange and intellectual freedom necessary to spur new ideas. "The kind of direction, for example, that we'll initially impose," according to Dr. Hood, "is that we'd like people with this very broad view of development, which entails the use of a systems analysis; there are 50 different ways you can do that, which are all terrific. But if they do wander off into something we think is non-fruitful, we're not going to spend our money on that kind of thing."

Research Consortia from page 4

of research because they are closely related developmentally to vertebrates, they develop rapidly and have few cells. Researchers hope that, eventually, information gleaned about the sea urchin can be transferred to other sytems, including humans.

Dr. Michele K. Anderson, a research associate in the Rothenberg Lab at Caltech

One of the features of Consortium II that particularly ties in with the Stowers Institute philosophy of putting the latest in technology to the service of biology is the use of a robot called the Q-Bot, which allows the Caltech team led by Dr. Davidson and Dr. Andy Cameron to array the cDNA and genomic cell libraries produced by all the Consortium II participants. Researchers use the Q-Bot, one of two purchased by the Stowers Institute at a cost of about $150,000 each, in two specific ways. The first is to arrange cloned libraries in a fixed order so researchers will know exactly where to find them when needed for study. It also allows researchers to study immense amounts of gene expression information, up to 50,000 to 100,000 genes, at one time.

Other universities where laboratories are participating in Consortium II, with a brief summary of their part of the undertaking, are:

- Carnegie Mellon University, where a team led by Dr. Chuck Ettensohn is generating a variety of cDNA libraries that represent the genes expressed in many specific cell types of the early sea urchin embryo.
- State University of New York at Stony Brook, where a team led by Dr. Greg Wray is studying the pencil sea urchin and will compare it to the purple sea urchin, the species being studied by the other Consortium II labs. These comparisons will help identify the genes responsible for the features specific to one species or the other.
- University of Missouri-Kansas City, where researchers led by Dr. Brian Livingston are constructing cDNA libraries representing the genes expressed both in the embryo at various stages of development and those expressed in adult tissues.
- University of Washington, where scientists led by Dr. Hood and Dr. Greg Mahairas are characterizing each of some 8,000 pieces of DNA so that they can be arranged with respect to each other. High-throughput DNA sequencing and enzymatic fragment analysis will be used to determine the relationship among these fragments of the sea urchin genome.

Virginia and Jim Stowers from page 1

the Institute will eventually receive most of Mr. and Mrs. Stowers' estate, now estimated at several times the present assets of the endowment.

When the Stowerses began planning for the Institute, many scientific and philanthropic experts around the country told them that a research undertaking of such magnitude would not succeed in Kansas City because great scientists would not come to an area not known for major scientific research. But the Stowerses dismissed that with their commitment to put their entire fortune behind the development of the Institute in the city that they love.

Hard work and unpretentiousness helped the Stowerses build successful lives. Now, whether entertaining brilliant scientists at their vacation home in La Jolla or sharing barbecue with construction workers in Kansas City, they are applying the same principles to their second careers as humanitarians and philanthropists. He is president and she is vice-president of the Stowers Institute, and they are so involved in every detail of its creation that, as she says, "Neither of us has time to think about a headache or a backache."

Virginia Stowers devotes much of her time today to assuring that the Stowers Institute will be a great place to work, with an environment that will encourage scientific investigation and freewheeling intellectual exchange. She makes, or takes part in, the decisions and discussions about many aspects of the interiors of the Institute as well as the landscaping. That ranges from selecting the woods for the cabinets and boardroom table and choosing floor and wall finishes to discussions about whether to create a giant double helix on the grounds.

One day, for example, she roamed the booths of the Plaza Art Fair in Kansas City with an interior designer selecting artists who may be invited to create art for the Institute. She has given special attention to the one- and two-bedroom residence units being created on one floor of the administration building to house scientists coming for temporary periods, a feature thought to be unique to the Stowers Institute. She has put her decorating skills to work in giving a warm and inviting ambiance to units that she says, with a smile, will be "above Motel 6 and below the Ritz."

Meanwhile, Jim Stowers has transferred the investment expertise that made him one of the most admired people in the mutual funds industry to the task of developing a financial structure that will assure the perpetual wealth and security of the Stowers Institute. Rejecting the more conservative approach of many foundations and endowments, Mr. Stowers intends investing the Stowers Institute assets in the same kinds of growing companies in which he put his faith as a funds manager. He is also creating an innovative supporting organization, the Stowers Institute for Resource Development, which will seek contributions from other donors and maintain their donations as individual accounts so that donors will always know how much their gift has grown through investment, while also supporting scientific research.

> *"Jim and I look at each other, and one of us will say, 'Can you believe we're doing this?'"*

People who have known Jim Stowers for many years inevitably describe him as the most determined, tenacious and visionary person they have ever known. The World War II fighter pilot trainee who could land his open-cockpit PT17 in a designated spot more often than any other cadet later became the entrepreneur who spent nights and weekends programming computers to analyze stocks. With the computers, he revolutionized the mutual funds business and turned a stake of a few thousand dollars into today's multi-billion-dollar American Century Companies.

In the words of one of her oldest friends, Virginia Stowers was the glue holding the Stowers family together while her husband followed the dream that took him from struggling young entrepreneur to the peak of the investment business. Before, between and after giving birth to their children, she pursued her career as a registered nurse, including many years working as a nurse-anesthetist at Research and Menorah Hospitals in Kansas City, Mo.

Born and reared in Kansas City, Jim Stowers was graduated from Kemper Military School and received a bachelor's degree from the University of Missouri, where he also completed a two-year degree in medicine. His father and grandfather were Kansas City physicians and Mr. Stowers initially planned to follow in their footsteps after completing his military service, but he found himself drawn to the business world and the limitless possibilities it offered.

The former Virginia Glascock was born in Rawlins, Wyoming, a town of about 5,000 people, to which her parents had moved from Iowa. She was drawn to nursing as a career because two favorite aunts were nurses. After beginning nursing training in Denver, she moved to Kansas

City at the urging of a family friend to complete her studies.

She was just out of nursing school at Research and beginning to work when Jim Stowers walked into a Christmas party at the hospital in 1952. He stirred her interest immediately, and he recalls feeling a natural attraction for her, even though she turned down the candy cane he offered in his first effort to break the ice. Nevertheless, they were soon dating, and in 1954 were married.

He sold mutual funds for another company and started a term life insurance company before making the big leap and launching Twentieth Century Investors in 1958 with himself and 10 other people as investors. Mrs. Stowers was concerned about the risk that this undertaking involved for their growing family, but she urged him to go ahead, convinced that she could make a living if necessary. Besides, she had confidence in a husband, who – as she says – never has any doubts once he sets out to do something.

One of the original investors in the startup firm was asked recently why he had enough confidence to invest in the venture of a young man he had only recently met and who did not even have a business plan. "Well," said the investor, "he's a sincere guy, he's a pretty good salesman, and he just seemed like the kind of fellow you could trust. He was smart, had good ideas and convinced you that he had the ability to actually go ahead and do these things."

Even Jim Stowers' own confidence and vision could not fully forecast his firm's success. That same investor recalls stopping by Mr. Stowers' small basement office one day when Twentieth Century Investors was young and chatting with him about how things were going. Mr. Stowers commented wistfully that if they could just attract $10 million worth of investments into their funds they would have it made. In 1998, the assets managed by the firm – renamed American Century Companies – surpassed $70 billion.

The Stowers Institute is an example of the loyalty the Stowerses have always shown to Kansas City and to the people who have become their friends and colleagues over decades. Jim Stowers' idea of a good meal is a hamburger from Winstead's, the pre-war drive-in restaurant a few blocks from the Stowers Institute. To buy a gift for his wife he heads for Tivol's in the elegant Country Club Plaza district and bargains with his old schoolmate, Harold Tivol, for fine jewelry. This combination of Winstead's, where the prices start at $1.65, and Tivol's, where prices seem to have no limit, says something not only about his loyalties but about the range of his taste as well because Jim Stowers manages to mix legendary frugality with an equally legendary demand for the very best.

Jim and Virginia Stowers

After Twentieth Century began to succeed, Virginia Stowers was often asked why she had not become part of it. She did help out when needed, particularly during Twentieth Century's time of explosive growth after Individual Retirement Accounts were created in the early 1980's, but she chose to stick to what she felt comfortable doing – nurturing a family and working in health care. While the children were growing up, Mr. Stowers was often traveling, trying to build his company, but because of his wife, says a friend, there was strength in the family, and structure, and a value system.

Sometimes, that required an incredible adaptability, such as during his motor home phase. Never wanting to miss an opportunity to do business, he bought the motor home in 1974 with the idea that the family could vacation in it while he took care of business matters around the country. His wife was never thrilled by the idea, and when she reached the point where she could not tolerate camping anymore, he said, "I will drive up to the front of a hotel and you can get out. I'll park it." That did not really happen, but when their youngest child finished college, Mrs. Stowers put her foot down. "Enough! Put a For Sale sign on this thing," she said.

She continued to work part-time at nursing until 1986, when the Stowers family was hit with the first of its battles with cancer. Mr. Stowers was diagnosed with prostate cancer and underwent surgery. In 1993, Mrs. Stowers went through surgery for breast cancer, followed by five years of treatment with tamoxifen. Their middle daughter, Kathleen, is struggling with cancer today.

The cancer experience taught Jim Stowers that he was not indestructible, but it also made him determined to do something about the disease. Cancer taught her, Mrs. Stowers says, not to waste time fretting about small things. She says you learn to focus on the most significant challenges. And the Stowers Institute is a challenge so big that it awes even them. "Sometimes," she said, "Jim and I look at each other, and one of us will say, 'Can you believe we're doing this?'"

A Research Environment from page 1

Architects and scientists who are part of the undertaking say it is highly unusual to develop a research facility of this magnitude from scratch. They express a growing excitement about creating a research environment with the best that present technology can offer. "The spare-no-object physical plant is completely different. There's not going to be any place like it in the world. It's going to be marvelous. It's going to be a fabulous place to do research," said Dr. Eric H. Davidson, who holds the Norman Chandler Chair in Cell Biology at the California Institute of Technology and is a member of the Stowers Institute's Scientific Advisory Board.

Virginia and Jim Stowers, who are dedicating their substantial fortune to the creation of the Stowers Institute, believe that bringing a large number of scientists together in a setting conducive to interaction, while also establishing a focus for their research, will speed breakthroughs in finding cures or improved treatments for cancer and other major diseases. Both have backgrounds in medical studies and have concerned themselves closely with every detail of the design and construction of the Institute that bears their name.

Jeff Johnson, who manages the construction project on behalf of the Stowers Institute, says that what is being created is "an incredible campus," adding that, "Within reason, there's nothing that can't be accommodated. If they want barrier animals, if they want marine animals, if they want lots of space with high ceilings, or if they need low ceilings for computer-type science, I can accommodate anything here."

One big challenge in the design and construction of the facility is how to provide for, and encourage, creative interaction among researchers. There is nothing scientific about how this occurs, but the designers and builders say they are creating a facility with interesting nooks and other great spaces that will invite researchers to pause for a while and exchange ideas. This will help eliminate the antiseptic feeling of a new laboratory and underscore that the purpose of the facility is to improve human existence.

For example, planners have tried to avoid creating flights of stairs so steep that people will take the elevator instead, thereby missing a chance for a chat in a stairwell. The fireplace at one end of the library is also expected to lure people to talk to each other. The gallery running the length of the wall of glass on the first level will be broken up with indoor gardens and planters.

Comfortable areas for quick snacks and drinks will be scattered around the laboratory floors, all with pleasing views to the campus outside. And since most of the researchers will not want food and drink in their labs, there will be a little shelf outside the lab to leave the coffee cup before returning to work.

In addition to promising to be a modern marvel as a place for research, the 594,000-square-foot Stowers Institute will add another architectural gem to the surrounding neighborhood. Situated across the street from the leafy campus of the University of Missouri at Kansas City, the Institute is a few blocks from the imposing neo-classic Nelson-Atkins Museum of Art and the widely admired Country Club Plaza, a shopping and dining district. A few blocks to the west is the Midwest Research Institute, which has performed contract research and development for government and private industry for more than 50 years. Slightly southeast of the Stowers site is the campus of Jesuit-run Rockhurst College.

The Institute's 10-acre site was formerly the home of Menorah Hospital, which moved to a new complex in the suburbs. Construction experts and architects said it would have been easier and cheaper to implode the old hospital and build everything anew. However, there were other considerations, as Rick Fortner, the project superintendent for J. E. Dunn Construction Company, the general contractor, explained.

"We researched this quite extensively, and we proved to Mr. Stowers that it would be cheaper to take it to the ground and come back," Mr. Fortner said. "But he made the decision that for historical reasons, and for Kansas City, he was going to leave part of Menorah Hospital, for sentimental value. You have to say something about somebody like that. Most businessmen don't think that way."

Michael A. Schaadt, vice-president of the Kansas City architectural firm Peckham Guyton Albers & Viets, with primary responsibility for the exterior and overall design, said he had approached the project as "a piece of sculpture." He said the completed campus will provide a "punctuation" to the intersection of Volker Boulevard and Rockhill Road, from which it will extend south to East 50th Street and east to Troost Avenue. A wall of water will shoot skyward from fountains along Volker, and there will be ponds and fountains elsewhere on the grounds.

Visitors will enter the six-story research complex off a circle drive and look through a wall of glass out to Brush Creek, a waterway with footpaths and fountains that winds through the neighborhood. The four-story administrative building facing the research facility will house a health club, offices and a floor of one- and two-bedroom apartments for visiting researchers.

The exterior walls of the Stowers Institute will be made of high quality, pre-cast concrete in the pale, cottonwood limestone color favored in the neighborhood. The landscaping will include natural stone, which will be installed to look like the limestone outcroppings that are common throughout the Kansas City area. One of the most dramatic aspects of the complex will be the roof of glass-bead blasted stainless steel. "When people hear stainless steel, they object, thinking it is very shiny," said Mr. Schaadt, "but the glass bead process actually knocks the reflectivity off the metal and gives you a beautiful matte finish. As the weather and the sky

change, the roof will take on the characteristics of the sky; it will change throughout the day." The architects hope to light the eaves from the underside so that at night the roof will glow softly and seem to be hovering above the walls.

Although working laboratories usually seem plain and utilitarian, they are much more complicated to design than their appearance suggests, according to Tully Shelley, senior vice president of MBT Architecture in San Francisco, one of a handful of architecture firms nationwide that specialize in laboratories. MBT, which is doing the interiors of the Stowers Institute, designed its first laboratory more than 40 years ago and now earns about half its commissions from laboratory work.

> *"There's a great debate that comes up in every job. It is whether better science is produced in an open laboratory. Or whether better science is done in a smaller laboratory."*

"There's a great debate that comes up in every job," Mr. Shelley said. "It is whether better science is produced in an open laboratory where there are lots of people, lots of activity, where you might look over someone's shoulder and see something that gives you an idea about something you're doing. Or whether better science is done in a smaller laboratory. There are proponents for both positions, so the architects, who can't make that call themselves, will produce a laboratory that strings a lot of these modules together so there can be one large laboratory or lots of little ones."

When the Stowers Institute opens, three floors in the main section will be dedicated to laboratories, and other laboratory space will be fitted out as needed. Each floor will have private offices for eight principal investigators and their key associates, plus eight laboratories of six to eight benches each. The lab modules will have gas, air, vacuum, power, communications, a bench that can be raised and lowered – and outside views. Support areas will occupy the center area, between the two rows of laboratories. Depending upon the needs of individual investigators, the support areas could include a radioisotope lab, a darkroom, a tissue culture lab or the cold room for marine animals used in research.

An auditorium for 225-250 people will occupy much of the first floor of the new wing, along with smaller conference rooms and space for teleconferencing and broadcasting symposia to and from points all over the world. There will also be a library and a wide, curving staircase leading down to a food area.

Mice are expected to be the primary research animal used by Stowers Institute investigators, and creating the space to house and care for them is one of the challenging aspects of the project. Also, ground-level space has been allotted for an aquarium in the event that any principal investigators using sea urchins in their research should join the Institute team. Sea urchins, which share a common ancestor with humans and have an immune system, are studied by a number of molecular biologists, including Dr. Davidson of the Institute advisory board.

About half of one basement level will be dedicated to the vivarium, the facility housing the mice. Its design and operation are largely based on a program written for the Institute by Dr. Joseph Spinelli, retired director of animal care at the University of California-San Francisco. Mr. Shelley said the vivarium will be divided into 15-by-15-foot rooms with racks to hold mouse cages. Each rack will hold 128 cages large enough for four or five mice in each. There will be as many as 2,000 mice in each room.

"These mice produce a lot of heat," Mr. Shelley said, "and a lot of them are second, third, fourth generations, specifically engineered for certain things. They become very valuable pieces of research and need to be protected, with the proper light levels, and cooled. There is an enormous amount of ventilating equipment that keeps the environmental conditions in this little room correct to support that mouse."

"A lot of these mice are designed to have no immune system," he continued, "so they're very susceptible to any kind of foreign organisms and have to be separated from each other. Even the racks they're on are designed to ventilate each of those 128 shoe boxes with specially filtered air that

continued on back

A Research Environment from page 15

isn't cross-contaminated with air from the next shoe box."

The mechanical systems provide for air that can be used only one time. Neil Krahn, facilities manager for the Stowers Institute, said that means, "It comes from outside, gets conditioned, blown into the room and gets exhausted outside. We don't recirculate any air except in certain areas. For safety in the labs, because of the chemicals and different things they might be working with, that air is just pumped in and pumped right out."

"That means you more than double the amount of conditioned air flow that you have to get through the building," Mr. Johnson said. "All it does is go out and go right up the roof. You don't get to reclaim anything. It's very expensive. You have to have huge air handlers because they're all designed for the coldest, dampest day and the hottest, dampest day."

In some cases, floors in the Institute are designed to have almost the equivalent of another floor of space between them in order to provide adequate space for the ventilation and other equipment, and to allow maintenance engineers space to monitor and service equipment. That is called "interstitial space."

The vivarium, for example, is designed with a 12-foot-tall interstitial space above it to allow workers to perform such tasks as changing light bulbs without going into the vivarium itself, where they would first have to shower, be blown for dust, and dress in "scrubs" to avoid contaminating the area. The interstitial space will have what Mr. Shelley called a "walk deck" a foot thick, with a hinged door through which workers will be able to reach the lighting and other equipment serving the vivarium.

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