Leroy Hood: Thinking Big in Seattle

In his pioneering new department at the University of Washington, biologist Hood and his colleagues want to develop the next century's molecular biology tools

SEATTLE—Nobody could accuse Leroy Hood of thinking small. In the early 1980s at the California Institute of Technology, Hood set out to transform genome research. His goal: to develop the first automatic machines to handle the tedious jobs of sequencing and synthesizing DNA. These tools, commercialized by Applied Biosystems Inc., are now standard fare in molecular biology labs around the country. Once he had accomplished that task—a feat that ushered in much of the large-scale genetic analysis of the past decade—Hood started thinking even bigger. He wanted to build a new breed of academic department in which physicists, engineers, chemists, and computer scientists would work side-by-side with biologists to develop the technology that Hood believes will revolutionize biology in the 21st century.

An impossible task? The kind of interdisciplinary venture universities often talk about but seldom have the resources to bring off? That's the way it seemed even to Hood's supporters until a couple of years ago when Hood hooked up with software king William Gates—another man not known for thinking small. Now, bankrolled in part by a $12 million gift from Gates, a new department of molecular biotechnology is taking shape at the University of Washington (UW) in Seattle that is being watched by biologists around the world.

It's like no other academic biology department, say its inhabitants. Instead of focusing on traditional biological sub-disciplines, Hood and his hand-picked colleagues—most notably Maynard Olson, formerly of Washington University in St. Louis—are trying to forge a venture that combines technology development with cutting-edge biology; provides interdisciplinary graduate training; transfers its inventions to industry and academics; and even tries to turn on the next generation of high school students to the excitement of genome research (see box). One guiding principle, as Lee Huntsman, head of UW's department of bioengineering, puts it, is that "new technology drives science just as much as the converse." Or, in Hood's words: "Instruments have incredible power to decipher biological information. They will revolutionize our lives."

Hood and his 10-faculty-member department are taking on the next generation of advanced biological instrumentation: ultrasensitive protein sequencers, ever faster and cheaper DNA sequencers, and exquisitely sensitive mass spectrometers for protein analysis. It is this heavy concentration on tools rather than biological problems that sets the venture apart. "In my experience, technology development is looked at somewhat askance by 'pure biologists,'" says Gerald Seltzer of the National Science Foundation, who oversees Hood's Science and Technology Center (STC) and funds part of Hood's ambitious experiment. "It has tended to be the stepchild in biology; people bootleg it off their regular grants. It is unusual to see, at least in biology, a group of people focused on technology development."

JON A. REMBOLD

Diverse crew. Maynard Olson (front), Leroy Hood (in plaid shirt), Barbara Trask (to Hood's right), and their multidisciplinary colleagues.

Not everyone is so enthusiastic about this approach. As Hood himself points out, he left Caltech, his research home for 22 years, because he could not persuade his colleagues of his vision of the future or convince them to carve out a brand-new department. "One of the places where I failed at Caltech was to get most of my colleagues interested in all these technologies. There was a feeling that 'they don't have much to do with our biology'," concedes Hood. He disagrees. "The future of biology is all wrapped up in the analysis of complex systems and networks," he says, and if biologists ever hope to understand such systems, they need access to "really sophisticated tools"—tools he and his colleagues intend to create in Seattle. His new department will be the test bed of these ideas.

Finding a benefactor

It was Huntsman of UW's bioengineering department who first got the idea of teaming up Hood's vision with Gates' money. Huntsman, who considers Hood a "legitimate visionary," had been trying to recruit Hood ever since they met in 1988 but was stymied by lack of money, space, and positions. Enter Gates, the Seattle icon known not only for his vast wealth and computational expertise but also for his keen interest in biotech. After finagling an introduction to Gates at a football game brunch in 1990, Huntsman regaled him with tales of Hood's pioneering work at the interface of engineering and biology and asked for Gates' help in bringing Hood to Seattle. When Gates showed interest, the dean of the medical school invited Hood, whom his colleagues consider the "consummate salesman," to give three lectures on campus. Gates attended all three. After the last lecture in April 1991, Gates and Hood went out to dinner, where they spent 4 hours talking about the interdisciplinary science of the future. Gates was sold. In September, UW announced its coup: a $12 million, no-strings-attached gift from Gates to create a new department of molecular biotechnology, with Hood filling the $3-million William Gates III Endowed Chair.

Hood immediately pulled off a coup of his own by persuading Olson to join him. Olson, like Hood, has emerged as one of the leading lights of the Human Genome Project. Co-inventor of a key technology for cloning large pieces of DNA, Olson "is always looking for clever ways to do things," says UW colleague Deborah Nickerson. And like Hood, Olson had been increasingly frustrated by what they both see as biology's "undervaluation" of technology. "Lee has been an absolute pioneer in orchestrating the effective interaction between the world of high technology and experimental biology,"

says Olson. "The chance to be part of an effort [from scratch] was irresistible." Olson gave up his generous support from the Howard Hughes Medical Institute and relocated to Seattle in fall 1992, where he has had a major role in shaping the department.

Specifically, Hood and Olson agreed to build a department based on certain "fundamental values"—interdisciplinary training, technology transfer, and public education—that Hood says were largely shaped by his experience in running the STC at Caltech. Hood's center, part of which he moved to Seattle, is one of 25 established by the National Science Foundation in the past few years that combine basic and applied research in diverse fields and that interact with both industry and local schools. While all the STCs have outreach efforts, says NSF's Seltzer, Hood "really got into it," establishing a notably ambitious program and seeking additional funds to support it.

Growing pains

For their department to work, Hood and Olson realized it had to have the right mix of people who were willing to gamble on an untried experiment. Hood brought five faculty members with him from Caltech and then recruited five more from such fields as applied mathematics, chemistry, and applied physics, ending up with "the very broad and diverse set of skills that could handle almost any problem we run into." Recruiting was no problem, says Hood: "We got everyone we wanted." Molecular biologist Nickerson, who moved with Hood from Caltech, attributes this success to Hood's "natural leadership and tremendous enthusiasm," which, she says "infects us all." But it's not just Hood's broad vision of integrating technology into biology that attracts people to him, she adds. "Things happen around Lee. Things do change."

It hasn't been entirely smooth sailing, however. "The chaos factor is high," concedes Hood. "The quest for identity is being played out," especially, he says, because many of the faculty are junior and are understandably preoccupied with securing grants and establishing their own scientific careers. Problems range from minor inconveniences, such as cramped offices until the new building is completed in late 1994, to major ones, such as having to learn new scientific languages and define the department's specific mission.

"We were all housed in the same place but didn't know what the hell the other was doing and didn't talk the same language," recalls Barbara Trask, a cytogeneticist who moved from Lawrence Livermore Laboratory to Seattle in large part because she "buys into Hood's vision of getting weird disciplines together." Frequent bull sessions, including a journal club and informal weekly seminars, "have brought us around," she says.

The trick was to find "commonalities" in their diverse approaches, agrees Nickerson. "Talking as a group we came to some fundamental interests among ourselves, such as identifying and eliminating the bottlenecks in DNA sequencing. To put effort into working as a group is not something you usually do in an academic department. This is a whole lot different than being in a biology department," says Nickerson.

That said, working with Hood does present its own challenges. Hood's interests are broad, ranging from immunology to genome analysis to protein folding, and his strong suit is the big picture, not the details, say Olson and others. "Lee is good at creating opportunities," says Olson. "He created a great one here. But he doesn't map out any detailed path for how to take advantage of that opportunity. That is a blanker slate than some members of the department find easy to deal with."

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Not surprisingly, much of the first year and a half has been spent trying to figure out what, exactly, the department should do: how much emphasis to place on biology versus technology in the curriculum, for instance, or which research projects to undertake. Now, after much brainstorming, the group is finding its feet and carving out its distinctive niche. The department has applied for a Ph.D. program and is offering its first graduate course on the analysis of complex genomes, which, to the group's delight, has attracted students from diverse fields including computational science, bioengineering, molecular biology, and chemistry. To ensure that the next generation of scientists is more adept than the current one at spanning disciplines, Hood and Olson plan to implement a "dual mentor" approach, in which graduate students may work with faculty in, say, both biology and physics.

At the same time the diverse faculty are beginning to forge the collaborations that will be the department's bread and butter. The projects fall out into two broad but overlapping areas: "pushing the frontiers" of analysis for both nucleic acids and proteins, a process Hood began at Caltech; and a nearer term effort, spearheaded by Olson, to integrate existing technologies for genome analysis.

Unlike Hood, Olson's efforts are focused squarely on genome analysis—a problem he has been butting his head against for the past 15 years. And since moving to Seattle, he has undergone a transformation in his views. "I actually feel for the first time that we have a complete set of tools," says Olson. "A formal solution to the problem of analyzing genomes is in hand." And that newfound optimism is a major shift for Olson, a born skeptic whose unofficial role in the Human Genome Project until now had been pointing out that the project's goal—mapping and sequencing the entire human genome—is more difficult than anyone had been letting on.

What prompted this change was Olson's realization that genome researchers don't need ever fancier tools to finish mapping and sequencing the human genome. And that's just as well, he notes, since these "blue-sky" technologies everyone is waiting for have yet to materialize. Instead, Olson believes he can get the job done by picking and choosing carefully among the tools that exist and integrating them into an overall system for genome analysis, which will be automated as much as possible. He thinks that his team, including Deborah Nickerson, Roger Bumgarner, and Ger van den Engh, can have the rudiments of an integrated system for genome analysis up and running in three years.

Deciphering complex systems

But for what Hood wants to do—understand complicated networks—new tools are definitely de rigueur, he says. Genes and proteins are the fundamental elements of the networks Hood hopes to decipher, which explains the department's intensive focus on ever more sensitive instruments to isolate, handle, and sequence them. For instance, Bumgarner, a physical chemist who did his postdoc in geology and planetary sciences, is creating what Hood calls the "second generation" DNA sequencing machine. Hood, Rob Kaiser, and Allen Blanchard are experimenting with tiny computer chips, the size of a fingernail, containing thousands of gene fragments. When unknown DNA is hybridized to these chips, a computer reads off "words" rather than single letters in the DNA language, providing a shortcut for both mapping and sequencing. This technology, Hood believes, should allow researchers to do away with the tedious process of sequencing stretches of DNA several times to ensure accuracy: Just sequence once and use the DNA chips to verify the results. "My guess is if we use this quick and dirty approach, we will get the sequence 10 times faster" without sacrificing accuracy, says Hood.

Proteins pose a more daunting challenge, however. One problem is that the most interesting proteins, such as the transcription

UW Team Reaches Out to Grade- and High-School Students

If you think that human genome research can only be done with state-of the-art equipment in a major biology lab, take a look at what is happening in some Seattle-area high schools. Kids are learning to synthesize DNA, using thermal cycling, modified for use in frying pans, and gel electrophoresis; others are actually sequencing DNA. And that's not all. University of Washington (UW) biologist Maynard Olson even has plans to enlist high school students in the Human Genome Project. "I hope to have students sequence new human DNA never sequenced before and be sure it gets into the database," he says.

Welcome to one of the more unusual projects of UW's new department of molecular biotechnology: an outreach program in which researchers from department chair Leroy Hood on down work with local teachers to expose kids to cutting-edge science. Hood asks faculty members to devote 5% to 10% of their time to outreach, as he does himself. So far, about a third are actively involved—a gratifying response, says outreach manager Valerie Logan, considering the other pressures facing junior faculty.

DAN LAMONT

Outreach. Students at Shorewood High School near Seattle sequencing human DNA.

The program is modeled partly on an effort that Hood and his colleagues launched at Caltech a few years ago. With the help of two local teachers, Susan Grethan and David Bowlus, and a grant from the Keck Foundation, Hood established a summer institute on the Caltech campus to provide high school teachers hands-on experience in molecular biology techniques such as polymerase chain reaction, restriction mapping, and chromatography. Their assumption is that if overburdened teachers can get excited about science, their enthusiasm will rub off on the students and perhaps on parents and administrators as well.

Molecular biologist Deborah Nickerson and several department colleagues are now designing a similar summer institute at UW, this time focusing on seventh-and eighth-grade teachers. Two Seattle teachers—Caroline Kiehle and Kimberly Klinke—convinced them to concentrate on these middle school years, in which molecular biology is rarely if ever taught. It's a critical period when many kids are lost to science, says Roger Bumgarner, who heads the department's elementary effort: "If you look at many of the bad things in science, like the disparate representation of minorities and women, you find it happens between fifth and eighth grade. Kids get turned off to science."

To keep kids involved, Kiehle and Klinke have been working for the past year with Nickerson, Rob Kaiser, and John Yates to develop training "modules," each covering a particular area of science, that teachers can learn at the summer institute and then take back to the classroom along with free kits and materials. Kiehle and Klinke are already testing the first module, which is called Molecular Machines and focuses on enzymes and proteins and their role in industry and medicine, in their classrooms. If funding comes through in June, as expected, the department will launch the program this summer, bringing in eight local teachers for a one-week training session.

Reaching elementary-age kids is a tougher challenge, says Bumgarner, because their teachers rarely have any training in science. He hopes to remedy that by holding Saturday workshops for elementary-school teachers and parents, funded with a grant from the Seaver Foundation, where teachers get to try a variety of experiments themselves before introducing them in the classroom. Bumgarner also wants to attack the problem at its source: He and Carole Kubota of the UW education department are developing a new course that will expose future teachers to hands-on science.

Olson is working at the other end of the scale. His efforts to bring sequencing into the high schools were inspired by Pat Ehrman, a high school teacher from nearby Yakima. Ehrman wanted to teach sequencing to his high school students, but he had a problem: He didn't know how to do it himself. So last summer he worked in a lab at Immunex, a Seattle biotech firm, to learn the technique. When Olson heard about Ehrman's initiative, he quickly became convinced that this somewhat esoteric skill was an appropriate topic for high school.

Olson now has a grant from the Department of Energy to provide support for teachers like Ehrman to learn their way around a sequencing lab. He's also working with Ehrman, Maureen Munn—a Ph.D. biologist whose experience raising three small children drew her into science education—and five other high school teachers to develop user-friendly experiments on DNA synthesis and sequencing. These are now being tested in three classrooms.

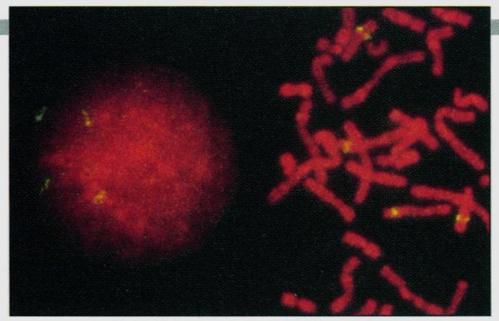
The kids are also exploring the ethical, legal, and social issues the genome project raises, such as "who has the right to genetic information, how do you decide who is aborted, and should you genetically engineer humans," says Hood, who is adamant that these issues be examined at the same time as the science. By the time they are finished, the kids should be ready to start cranking out sequences for the Genome Project—and, Hood hopes, to pursue a science career.

–L.R.

factors that regulate gene expression, are present in cells in tiny amounts—for example, a few hundred to a few thousand copies per cell—and there is no way to amplify them as there is with DNA. That puts a premium on the development of ultrasensitive tools, able to work with minute amounts of protein. Hood and Seattle colleagues Reudi Abersol and John Yates, and also Caltech's Mark Stolowitz, are taking several different approaches to building these tools. Stolowitz is developing a highly miniaturized microsequencing instrument that uses a new kind of chemistry known as thiobenzylation, says Hood. "The current state of the art is you need about 5 picomoles of peptide to determine a sequence. We would like to be able to determine a sequence on 5 femtomoles, which is 1000 times more sensitive."

Cracking the regulatory code

A major testing ground for this new technology is a collaborative project headed by Hood and developmental biologist Eric Davidson at Caltech. The goal is to decipher the regulatory code that governs the first 24 hours of a sea urchin's development. During this time, the sea urchin embryo expands from one cell to 500 and differentiates into five distinct territories. This early territorial specification is accomplished by transcription factors that turn on specific sets of genes within each territory, which then create a gut or a skeleton, for example. The immediate task for Davidson and colleagues is to isolate and characterize these transcription factors.



B. TRASK IN COLLABORATION WITH E. GREEN & G. SCHELLENBERG

Going FISHing. Fluorescent in situ hybridization is among the many techniques the Hood group is using for genome analyis.

Fishing them out is no mean feat, however, since transcription factors are present in such small amounts in the cell. Former Davidson postdoc Frank Calzone, now at Amgen in Thousand Oaks, California, took a big step toward that goal by devising biochemical procedures to isolate those factors. He was aided in the task by a particularly felicitous characteristic of the sea urchin: its prodigious production of eggs. Davidson calls the sea urchin "an enormous gonad surround by a spiny life-support system." He and his colleagues grow eggs by the billions in 20-gallon garbage cans filled with seawater. When the embryos reach the 500-cell stage, the investigators harvest them and purify the cell nuclei, which contain the transcription factors, ending up with a preparation in which the factors are enriched, on average, 400-fold. "So here is the whole gene regulatory system sitting in a test tube. And it is stable for years in the freezer," says Davidson.

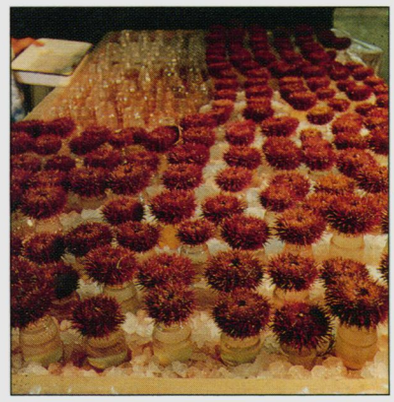
But even in those enriched preparations, the transcription factors are too scarce to separate from other proteins by conventional means. And that's where the collaboration with Hood group's has proved invaluable, says Davidson. It's "a terrific scientific partnership," Davidson says. "We each can contribute something the other cannot. Together we are using wonderful technology to elucidate a wonderful set of problems."

Aided by an automated affinity chromatography device for separating proteins—built collaboratively by the Davidson and Hood groups—James Coffman and colleagues have so far isolated dozens of transcription factors out of the 100 or so they think may be involved in regulating the first 24 hours of sea urchin development. Davidson's group has been rapidly sequencing these factors, using a commercially available microsequencing instrument first designed by Hood in the 1980s. Now, the two groups are trying to determine how the transcription factors are modified during the early stages of development and how their modification, in turn, affects gene expression—again, with the help of a new tool, this one an automated 2D gel electrophoresis system Mike Harrington is developing.

Breaking down barriers

Hood's collaboration with Davidson is the department's longest running; it started in the 1980s when Hood was at Caltech. In Seattle, the UW group is just beginning to forge similar collaborations with its new colleagues, starting with other biologists, to whom Hood feels a "special obligation." Says Hood: "I want to encourage biologists to start projects that might otherwise be beyond their means." And he has had no shortage of takers. For instance, Hood is setting up a collaboration with King Holmes of the UW AIDS Center to sequence numerous genomes of the AIDS virus to study such problems as drug resistance and epidemiology. Olson, Trask, Nickerson, and others are working with Dan Geraghty of the Fred Hutchinson Cancer Center in sequencing the class I region of the major histocompatibility locus, which contains genes needed for mounting immune responses. The same genes also trigger rejection of transplanted organs—an outcome the team would eventually like to help to circumvent. Olson and John Yates have teamed up with yeast geneticist Lee Hartwell of UW; using an ultrasensitive mass spectrometry method devised by Yates, they hope to understand what makes a yeast cell decide to divide.

What is proving tougher by comparison is reaching across disciplines to, say, physicists and chemists. Says Hood: "It is a totally different problem of communication. I would like to find people who want to make a 5-year commitment to help me find out how to do certain complex technologies, and the only way you can get that kind of commitment is if they really understand and get excited by the biology." Involving industry can be even more difficult when the prospects for near term payoffs are slim.



Egg farm. Sea urchins provide billions of eggs for the Davidson-Hood group's work on isolating proteins needed for early sea-urchin development.

Even so, the department is off to an encouraging start, say Hood and Olson, in a new collaboration involving Deidre Meldrum of the electrical engineering department and researchers at a Seattle engineering company. While doing a postdoc at Stanford on space robotics, Meldrum found herself increasingly intrigued by the challenge of the Human Genome Project. When she arrived at UW as an assistant professor, she asked Hood if there were some way she could apply her robotics expertise to problems of genome analysis. The answer was an enthusiastic 'yes.'

Since then, Meldrum has been working with the department to try to devise an automated system for DNA sample handling, the myriad steps in which reagents are picked up, mixed, dispensed, and so on. Most are now done by hand or by a workstation that is slower, if more accurate, than a trained technician—a major roadblock in genome analysis.

But first Meldrum had to learn biology, which she did with the help of biweekly tutorials from Olson and Nickerson and by serving a stint with several investigators in the department. Says Nickerson: "This is the concept Lee is talking about. Tell people our problems and let them think of new ways to handle them." The collaboration widened last summer when Olson persuaded Applied Precision Instruments (API), which specializes in precision motion control, to lend its talents as well. Much to Olson's delight, API engineers threw themselves into the process of "cross education," learning the basics of DNA and how to sequence it and map it.

The collaborators are now testing a prototype sample-handling device. The ultimate goal is a mechanized system, working under computer control, that will not only extract DNA from cells but analyze it with techniques such as polymerase chain reaction and electrophoresis. "This is a model of the kind of thing that will have to happen for this department to be successful," says Hood of the collaboration, who adds that it is too soon to tell whether his new department will end up being an anomaly or a harbinger of things to come.

"This department is clearly a frontier experiment," agrees Olson. "Not every university wants to run out and start one." To Olson, the true test of success is whether the department comes up with technology that makes a decisive difference—in other words, that doesn't just speed up something biologists can already do but enables them to tackle problems too complicated to approach now by technological means. A case in point is natural genetic variation, or why, and by how much, DNA varies from one person to another. Epidemiologic studies offer a perfect way to collect such data, but epidemiologists rarely do them because most are not conversant with molecular tools. "Ten years from now it will be routine to do some type of genotyping of individuals from which [epidemiologic] information is taken," predicts Olson. "I would like to learn how to do that. I would like technology to co-evolve with theory and study design." That's a tall order, admittedly, but Olson, like Hood, has never been accused of thinking small.

–Leslie Roberts