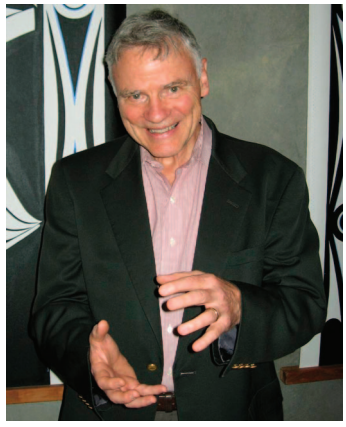
A Conversation with Dr. Leroy Hood: Visionary Biologist and Biotechnologist



Dr. Leroy Hood describing a molecular machine at the Novelty Hill Winery in Woodinville, WA.

I met with Dr. Leroy Hood at his office in the Institute for Systems Biology in Seattle, WA, and at the Novelty Hill Winery in Woodinville, WA, where he gave a talk to the Institute's Board and invited others. As a pioneer in biotechnology, including the development of many of the instruments now used in molecular biology and genomics, Dr. Hood is an example of how integrative science and interdisciplinary approaches can dramatically advance our understanding of the world around us. Both our conversation and the talk focused on the future of medicine—*P4 medicine*, as Dr. Hood describes it. We discussed the impact that it will have on our future and the roles of nanoscience, nanotechnology, and other interdisciplinary efforts in its development.

PSW: How do you define P4 medicine?

Leroy Hood: P4 medicine is what I think is going to happen over the next 20 years. Medicine will move from its current largely reactive state to one that is *predictive*, that is *personalized*, that is eventually *preventive* and *participatory*. I'll say a word about each of those.

The heart of *predictive* and *personal* medicine will emerge over the next five years, maybe a little bit longer. Everyone will have their genome sequenced, and from that data we will increasingly be able to make predictions about probabilistic future health histories. You [might] have an 80% chance of prostate cancer by the time you are 60 or a 30% chance of ovarian cancer by the time you are 50. A second aspect of predictive medicine comes from the realization that each of the 50 or so human organs secrete into the blood proteins specifically made by those organs. These proteins in their relative concentrations constitute a molecular fingerprint that makes the blood a window into health and disease. There will be one set of concentrations for a healthy organ, and distinct sets of concentrations for each of the different diseases that might be present in the organ.

The idea would be that nanotech and microfluidic measurements will make it possible to have a device in the home that could prick the thumb, take a fraction of a droplet of blood, make 2500 measurements, maybe 50 for each of the 50 or so organs in the human body, and send the information via wireless to a server. It'll do an analysis and then send you and your physician an email that says, "you're fine; do it again in six months", or "see your oncologist". The personalized part of the medicine comes from the fact that each of us differs one from another by on average 6,000,000 letters of the DNA language, nucleotides, and most of those make no difference. They predispose you to unique combinations of different diseases. Hence, when we do your future health history prediction from your genome, we are creating a unique signature for each different individual. And when you follow those predictions, you bias yourself about things you should be worried

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To hear Dr. Hood's welcome to nanoscientists, please visit us at the podcast page of http://www.acsnano.org/.

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about. When you follow your current health status with the blood molecular fingerprints, then again you are looking in a uniquely individualistic way at each individual. One important aspect of personalized medicine is, in this future where we've made a whole series of dynamical measurements across the lifetime of the individual, the individual will become their own control. So, we will not be so much interested in absolute concentrations; we will be interested in how things change. It is those changes that will indicate the onset and the progression of disease.

The *preventive* aspect of medicine deals with the fact that, in the future, we will be able to redesign with drugs, or re-engineer with drugs, disease-perturbed networks so as to make them behave in a more normal fashion or at the very least to abrogate some of their more deleterious functions. And so, we will approach drug target discovery in the future by asking, how can we effectively re-engineer the major casual biological networks of the disease? And, of course, what we have the potential of doing in the future, once we've read out the probabilistic future health history, is designing drugs that actually *prevent* your networks from ever becoming disease-perturbed. So, we can say that you *had* an 80% chance of prostate cancer by the time you are 60, but if you start taking these pills when you are 40 that chance reduces to 2%. That is the essence of what a predictive drug will mean. What we will also say about drugs in the future is that you do not re-engineer networks with individual drug compounds. Almost all re-engineering will be done by a multiplicity of drug compounds acting in concert with one another.

The final "P" is *participatory*, and that creates interesting social problems. The point is, with this enormous amount of information, [you are] increasingly going to understand more deeply the nature of your likely future health history and where you stand at any point in time. And, if you can be appropriately educated, you can *participate* in making choices about your future health directions that are just utterly impossible now. Of course, this ability to make those choices depends on two really important conditionals: (1) how are we going to educate physicians, many of whom have already been trained about this new P4 medicine, and (2) how are we going to educate society about the possibilities of P4 medicine?

I think, in the future, the educational process will be a critical function of a revolutionary change in information technology for health care. I think a lot of the education is going to be on the Internet, is going to be web-based, is going to be fascinatingly exploratory. Making healthcare companies realize that there is much more to the so-called "digitalization of health care" than digitalizing medical records is going to be one of the challenges of the future.

I'll say two final things. All of these new technologies and these computational approaches and indeed the systems view of disease is inextricably going to lead to what I call the digitalization of medicine. That is, we *will* in the future be able to extract relevant information from single molecules, from single cells, and even from single individuals. I think this digitalization is going to have an impact that will far exceed that of the digitalization of information technology and communication, and it will do so because one of its most profound consequences will be that there will be a point in the future when we will turn around the ever-escalating increasing healthcare costs in a really dramatic way. And, turn them around and bring them down to the point where we will be exporting P4 medicine to the developing world. That means P4 medicine in the future is going to become the heart and soul of global medicine. This has enormously interesting implications for where foundations, like the Gates Foundation with its interest in global medicine, should be going. The final point that I would make is that if we really believe this vision for P4 medicine, then, I would argue, it means that virtually every sector of the healthcare industry will have to rewrite their business plans in a major way. Their whole *modus operandi* will be changed in fundamental ways that for some are even hard to predict at this point.

My own experience in catalyzing and dealing with paradigm changes is almost never [about whether] old organizations have the ability to adapt to really transformational change. Almost always, that change is mediated by the creation of new organizations that have been set up to execute these new opportunities. So, it will be very interesting to see how the healthcare industry, in a global sense, adapts to these transforming and disruptive types of change. I would also say, anytime there is such disruptive change, there are enormous industrial opportunities, business opportunities for creating structures that are going to be effective in this very new and very different context.

PSW: Is there a particular set of challenges for nanoscience and nanotechnology?

Leroy Hood: I think there are a whole series of technical challenges that microfluidics and nanotechnology are going to have to address. I think a beautiful example is, "how can we make DNA sequencing efficient, rapid, inexpensive, and accurate?" In the end, the big winner among the alternatives we see out there for DNA sequencing is going to be something that has two properties: (1) it can sequence single molecules, and (2) it can sequence them in a massively parallel format. That is the

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My real interest in this is not so much pushing the state-of-the-art technology, because that gets to be more and more an engineering/surface-chemistry problem. My interest is to interact with people having those skills so we can direct the technology development in ways that are most expeditious for its application to human populations.

My real interests in sequencing human genomes, the thing that I find most fascinating, are the associated computational problems. In the future, we're going to have billions of genomes sequenced, so the computational problem, if we do an all-by-all comparison to extract differences, is one of such enormous magnitude we cannot even think about how to do it. So, are there biological ways we can use this vision of biology being an informational science to reduce the dimensionality of that problem and to focus it in on places that are critical for making these predictions? I think the answer is yes.

The problem in systems biology and in the generation of measurements from many, many different types of biological data, global measurements of the data, is always signal-to-noise. You get an enormous amount of noise, and how do you differentiate out uniquely that very small amount of signal? And again, I think another whole area is the measurement technologies that have to be employed to look at many of the different levels of biological information. So, can we measure in a digital manner RNA molecules, identify them and quantify them? Can we analyze those molecules in a sense qualitatively for the modifications, the processing, that the environment has superimposed on the digital information? And, the same is true of proteins. Can we quantitate them? Can we look at modifications? Can we look at processing? Can we look at localization? Can we look at turnover rates? Those all center on problems that become much simpler when you can analyze at a single-molecule level rather than looking at the average of millions of molecules. Those are all measurements that fall in the realm of nanotechnology. The same would be true for metabolites. The same is going to be true of interactions: How do we measure which proteins interact with one another? How do we measure how they mediate these interactions? I think they're fascinating problems. Are there new ways we approach understanding three-dimensional structures, again of individual molecules? And, once having these structures, how do we connect those to function?

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In a broad sense, systems biology, if you look at it from an informational point of view, has two areas of enormous fascination.[1] One is the area of molecular machines and how they execute their function. What are the elements? How do they come together? How do they execute their chemistry, their biology, whatever it is? What are the dynamics of how the machine operates and so forth? And, the second area is, you can ask all the same questions of biological networks, because it is biological networks that capture information and transmit information and integrate and modulate information and, finally, hand it off to the molecular machines for execution. How is all of that done? How does information flow down a network?

Many people use the common vernacular of "pathways"; there are *no* pathways in biology. There are only *networks* in biology. When people use the term "pathways", they confine the dimensionality of their thinking in ways that really confuse many deep and fundamental kinds of issues. It seems to me that all of these things that we're talking about here ultimately come down to issues of measurement and/or issues of visualization that very naturally can fall in the realm of nanotechnology.

PSW: You mentioned different industries and educational institutions being receptive or not. What responses have you gotten when you put forward these ideas to instrumentation companies, pharmaceutical companies, medical schools, insurance companies?

Leroy Hood: I think that I can say generically that if we look at the different sectors of the healthcare industry, it is totally safe to say that the majority in any particular sector—be it pharma, be it medical instrumentation, be it biotech, or IT healthcare—the majority in any given sector would not be interested in this because they do not understand it and they do not realize how quickly it is going to be coming. One of the real keys to making predictions (and I've spent my entire career making predictions)...there's only really one major key, and that is (A) to understand that what drives biology to change is technology, and (B) to understand there are many periods in the evolution of technology when the change is exponential.

I remember pushing the genome project. After the first meeting on the genome project in 1985, one of my friends said, "If it's going to take a day to sequence the genome, it'll take 100 years", and you know, he was absolutely right. With the technology we had in 1985, [it] easily would have taken 100 years to sequence it. What he did not understand and what he was incapable

of understanding was the exponential envelope of transformation that the sequencing technologies were undergoing. And it was 12 or 13 years later where we had instruments that could seriously take on sequencing the whole genome.[2–4]

I think for P4 medicine, exactly the same is true. What are the major technologies that are really going to drive it? Measurement technologies, visualization technologies, and the development of mathematical and computational tools. Those are the transformational thrusts, and I would say that nanotechnology will certainly play a very central role in two out of three of those drivers. And they're *all* changing in this incredibly exponential fashion. If I really thought about it, I would guess my 5-to-10-to-15-to-20-year time scale might be way too long. But, the one constraint is that exponential changes in technology make assumptions about funding levels. I think it is *really* difficult to make assumptions about funding levels at this point in time, both because of what the war has done to discretionary money and what tax cuts have done to discretionary money. So, given reasonable funding levels, I think the predictions are absolutely safe, but we will wait and see what actually happens.

PSW: How do you decide where to take your science, and what technology to push?

Leroy Hood: In all of my years in science, what has struck me about most scientists is how conservative they are and how modestly incrementally they think about their science and where it is going. I remember [entrepreneur and philanthropist] Norton Simon giving me a really fascinating quote about careers and career trajectories. He said, "You know most people, their career is exactly like a bell-shaped curve: they go up to a certain maximum, and they kind of decay and go down." He said, "The one way you can get around that is to go up to that maximum and then completely change what you do." You go through the uncertainty and the insecurity of starting all over and not knowing what you are doing. But, what you do is you think about the new thing you take on from a completely different perspective than all of the other people.[5] So, if you can do that every 10 or 15 years, you have a chance of really transforming areas because you come at it with a different context of experience and with the insecurity of knowing, "Gee, I better think of something really interesting if I am going to move the field forward." I think this whole idea of being able to think outside the box, however you do it, is absolutely critical to making changes.[6]

[In a career change] you go through the uncertainty and the insecurity of starting all over and not knowing what you are doing. But, you think about the new thing you take on from a completely different perspective. So, if you can do that every 10 or 15 years, you have a chance of really transforming areas.

I remember when I went to Caltech in 1970, I told the chair, "I want to spend half my time doing technology development." After three years he came into me and said, "I advise you in the strongest possible terms to give this up." Twenty years later, he told me that was because his senior faculty felt it was inappropriate to have engineering in a biology department. But, I went on and did it and it worked very well.[7]

Developing the DNA sequencer was interesting. I spent three years with a really good biologist, and he got nowhere because he did not have all the requisite skills to be able to think about DNA sequencing in a global way. And, within about six weeks of when I got together a computer scientist, an engineer, a chemist (Lloyd Smith was a chemist, he was really critical), and a molecular biologist (myself), we had formulated the four-color strategy for sequencing, and in three years we had a proof-of-principle.[2] But it took, I realized, getting these different kinds of scientists together and free association.

I went to the president of Caltech in about '88 or '89 and said, "Look, I want to start a new kind of biology department, I want to make it cross-disciplinary." Again, the chemists and engineers thought it was a great idea. The biologists vetoed it. I went to the University of Washington with Bill Gates's help and started a cross-disciplinary department. And you know, it was really spectacular. Two of our faculty basically invented the fundamental first procedures in proteomics.[8,9] One developed a really high-speed cell sorting device.[10] We developed the inkjet technology for generating arrays,[11] which Agilent has commercialized. And, we had a couple of human genome centers.

What was really clear is, when I attempted to superimpose systems biology on top of that wonderful cross-disciplinary framework, the bureaucratic organization of the university could not deal with all of the deep and fundamental changes that systems biology brought. It was then that we had to go and start the Institute for Systems Biology.[12] Now, we're at this really interesting juncture systems biology has brought us to, this so-called P4 medicine. And, a really fascinating question is, "how is that going to emerge and be driven and be made a reality?" Is it going to need to be one or a whole series of new organizations, or are old organizations going to be able to do it? If I had to bet, I'd bet on a lot of new organizations.

PSW: Do you keep that 50/50 balance between biology and technology now?

Leroy Hood: I would say if you include in the strategic partners that we're collaborating and interacting with, it is easily 50/50. Yeah, absolutely.

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Let me just say something about that. I think one thing that is very important for engineers and applied physicists to understand, at least in the context of biology, is that the driver of new technologies really should be the biology. Because, what you want to do when you create new technologies is explore new dimensions of data space. The reality is that data space is infinite. So, if you want to explore new dimensions, you better figure out from the biology where you are going to go to explore those dimensions. Hence, I've always advocated this close coupling, and that is really the essence of our institute—a cross-disciplinary environment where biology is constantly the driver of the new technologies, and equally, it is the driver of the nature and type and content of the computational and mathematical tools. Those things all come back and transform the biology, so it is this marvelous, circular, ever-reinforcing, powerful way of doing science.

What I find fascinating is how, when you go around the world and look at many institutions that claim to be doing systems biology, they are really doing one or, in some cases, two dimensions of systems biology. I would argue, if you want to really achieve the full potential, you have to have the biology, the technology, the computation, and the mathematics all intimately integrated one to another.

That gets to one of the fundamental aspects of what I believe good institutes are all about. You have got to remain small, and cohesive, and interactive. I'm always amazed when I go to either academic institutions or research institutes [to see] how growth seems to be checked only by the level of funding, rather than by the rationality of "how big can you get before you lose coherence?"

PSW: While it is clear what the rewards are for people in biology with common goals, how do you bring in top people from other fields that you want and need? How do you get the people that you would want when this would probably not be the proper home for them?

Leroy Hood: The whole question of how you assemble the right kind of talent is a deep one I've thought a lot about. It really breaks down into two issues: (1) What kind of talent do we need here in the immediate vicinity of ISB [Institute for Systems Biology], and (2) how do we supplement what we have here with strategic partners?

The supplementation with strategic partners is no problem whatsoever. We can reach out and, if we can capture the right individuals with the vision, the potential, the possibility, it is no problem at all setting up the collaborations.

So, we come down to the question of who makes sense *here*. I would say there are a number of different dimensions to that. One dimension is, we've tried to recruit some people here who came and said, "But, you don't have tenure, and I don't know if I feel comfortable with that." My answer is, "Don't come. You should go back to the university. Good people don't need tenure, and if you're so insecure that you need tenure to feel comfortable, you don't belong here at all." The second thing that is really interesting is the question of the vision, and the question of the company, and the question of what you really want to do. Some people who have spent most of their life in an academic context, in a department with undergraduates and graduate students, actually find it a delight to come here and focus on getting the science done and not to have lots of distractions. But, more than that, to do it in a manner that has an intensity that I think is rarely, if ever, matched in most academic institutions.

I, in my own mind, have a pretty clear picture of the minimal hierarchy of skills that we'd like to get here. What I've been doing is kind of methodologically exploring with different people whether they would find this the right kind of environment. Some people do and some people do not. The really key question is, and I always tell them to ask this, "If you're going to come here, extrapolate ahead five years and ask yourself, is this where you want to be? Is this the right place?'" If you have questions about the answer to that, then you probably should not come.

[Literature citations were added after our conversation to direct the reader to relevant publications.]

— Paul S. Weiss, Editor-in-Chief

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