No Gene Is an Island

Genes do what they do in conjunction with other genes and proteins. The study of their interaction -- systems biology -- is one of the hot spots in life sciences and a strength of the Richmond, Va., biotech sector.

By Peter Galuszka

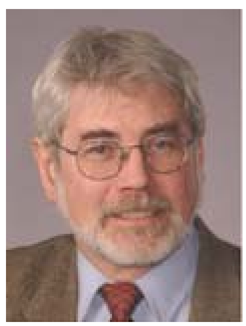
Dr. Gregory A. Buck, a convert to "systems biology," a holistic approach to studying how living organisms work at a chemical level, uses a metaphor to convey the thinking behind the discipline.

Take the Bible, cut up the words on every page and drop them in a bag. Shake them up, and then dump out the words. Shorn of context, would the text make any sense? Could you learn what happened to Jonah in the whale or to Christ on the cross?

Of course not. But if you somehow managed to restring the words in sequential sentences, you would have the Bible again, both in its physical form and as an understandable, readable entity, if not the Word of God. The meaning of the words, explains Buck, is an "emergent property," dependent upon the way they are strung together in sentences, paragraphs and chapters.

The challenge of systems biology is similar, says Buck, who is director of the Center for the Study of Biological Complexity and a professor of Microbiology and Immunology at Virginia Commonwealth University in Richmond. For the Bible, substitute the human genome. For words, substitute genes. Then toss in proteins and enzymes, which help decide how the genes work together.

Systems biology considers an organism as a living whole rather than a mere sum of its parts. If the genomes are chopped up piecemeal, they can be understood in only a limited way, Buck says. Once the pieces fit together, scientists can examine how the subunits of a living organism such as a human being work together as a beneficial whole. Life is the emergent property of the interactions of the genes and proteins of a cell.



Gregory A. Buck

With such an omniscient template, an entirely new day for pharmaceuticals, medical treatments or biotechnology could be at hand. Getting to that day faster is the goal of researchers at VCU, the Virginia Biotechnology Research Park and several Richmond-area companies, small and large, including Philip Morris USA. The Greater Richmond area moved the clock forward in late March when VCU and the Research Park sponsored a three-day "Summit on Systems Biology" that brought some of the leading names in the field.

Speakers on a range of topics -- from using genomics to dissect the genetics of a drug response to exploring the proliferation and differentiation of embryonic stem cells -- hailed from Harvard, the University of Georgia and Notre Dame. They came as well from leading biotechnology and pharmaceutical companies such as Amgen Inc., GlaxoSmithKline and Merck Research Labs. Experts also attended from the University of Washington, which has been an incubator in the new field.

The conference provided a forum for leaders in systems biology to exchange insights. And it threw the spotlight on Richmond, an up-and-coming player in biotech, on the academic map of one of the most important new fields in life sciences today. As Robert T. Skunda, president and CEO of the research park, acknowledges: "It heightens our stature to get these kinds of folks."

Several of the 55 enterprises in the Research Park use a systems-biology approach to develop breakthrough drugs and medical procedures. Living Microsystems, for instance, uses a holistic approach to spotting rare cells, with the goal of detecting diseases in a very early stage – even in the fetus.

Another firm, Vital Sensors, is experimenting with wireless monitors that can be inserted in a human body in a minimally invasive way to monitor cardiac data real time. That firm, which recently bought a German firm with the same name, has just raised $1 million in seed financing from venture capital firms in Chicago, Pittsburgh, Washington and Hamburg, Germany.

A third company, Obetech, uses systems biology in its research on the causes of obesity. Richard Atkinson focuses his research primarily on one particular virus be believes to be responsible, but he considers many factors that may explain why people become morbidly overweight. A Petersburg native and retired professor from the University of Wisconsin Medical School, Atkinson started his lab in the Research Park about 18 months ago.

By infecting test animals with the obesity virus, Atkinson explains, he is investigating how the virus can be fought. “Sixty to 100 percent of the animals infected with the virus become obese,” he says. “If you’re a nice skinny guy and you get tested and you are found to have the virus, what do you do? Could you take medicine to stop from becoming obese?”

Thanks to systems biology, however, Atkinson recognizes that the virus is only one possible cause of obesity. Deficiencies of a protein hormone called leptin could be responsible. So could a biochemical malfunction that sends the brain wrong signals about when to eat. There’s even evidence that if a pregnant woman is malnourished, the odds increase that her child will be obese. Says Atkinson: “Systems biology helps you understand all of these things.”

Another Research Park resident applying systems biology is tobacco giant Philip Morris USA, which is investing $300 million in new lab facilities. Although Philip Morris has revealed little of its research agenda, news accounts claim it will test aerosols as mechanisms to disperse gaseous forms of drugs -- insulin, painkillers and asthma medicine -- efficiently and inexpensively into the lungs. Systems-wide strategies are a key to bringing safe and effective products to market rapidly and cost effectively.

If the Research Park is one prong of Greater Richmond’s new attention to systems biology, the other is VCU, which jumped into systems biology with both feet. Buck, who has been researching and teaching at VCU and its medical school for more than 20 years, says that VCU professors and administrators were watching closely when the concept of systems biology started showing up on the academic radar screens some years ago.

The term “systems biology” can be traced to "systems theory," which developed as a discipline in the 1950s. The Santa Fe Institute, founded by Nobel Prize Winner Dr. Murray Gel-Mann in 1984, was an early strong proponent of applying systems approaches to all fields of science, including biology. Work in "systems biology" accelerated in the late 1990s with the advent of genomics, proteomics and bioinformatics as strategies to dissect life holistically at a molecular level. Individuals like Dr. Leroy Hood, who left the University of Washington to found the Institute for Systems Biology in Seattle in 2000, and Dr. Hiroaki Kitano, who founded the Systems Biology Institute in Tokyo the same year, popularized the new field and demonstrated its power. More recently, centers in Massachusetts, California, Michigan and other states "caught the systems bug," Buck says.

VCU, Buck says, got a major boost in the spring of 2000 when Eugene Trani established VCU Life Sciences with a systems biology focus. Trani set up the program at the vice provost level, which made sure the center got funding and attention. Only a handful of other universities, such as Cornell and Michigan, have life sciences programs headed by a vice provost, says Buck.

The Center for the Study of Biological Complexity, directed by Buck, is leading VCU Life Sciences efforts in the field. Besides recruiting new systems oriented faculty and enhancing VCU's systems-oriented research infrastructure, the center has expanded its computer base to be able to handle the complex computations needed to trace and interpret new genomic and proteomic data sets. Says Buck: “The idea was to make sure that VCU was prepared and able to compete in 21st-century life sciences research."

At his Center for the Study of Biological Complexity, which focuses on infectious diseases, Buck counts over 100 faculty members from six different VCU schools. Buck estimates that about 70 graduate student and a similar number of post-doctoral trainees are involved in systems biology research at VCU. New systems biology training programs include a bachelor's and master's, and a combined five-year accelerated bachelor’s/ master’s degree in bioinformatics, and a Ph.D. in integrated life sciences, which is really a doctoral degree in systems biology.

VCU, Buck says, scored a recent coup when it recruited Dr. Yuan

Gao, a globally respected geneticist now at Harvard Medical School. Widely published, Gao will come to VCU this July to teach and beef up its research faculty in genetics, systems biology and informatics.

Although VCU doesn't have supercomputer capacity as some large universities do, it does have adequate computing power to process the many calculations needed to track genomes and build models of how the molecules interact. "We build it (computing power) as we need it and we now have a highly efficient facility for high-performance computing," he says.

"We're all over systems biology," Buck says. "We put it on the map in Virginia five or six years ago." The recent conference on the topic was so well-received that plans are afoot for a follow-up conference in 2007. If that goes as well as this year's conference did, Greater Richmond will be more of a destination for systems-biology research and understanding.

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