

Genome

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Issue 12

November/December 04

DUKE Institute For Genome Sciences & Policy

Oh, the Humanities

Genomics, Narrative, Art & Popular Culture

A legal wrangle over who owns a spleen and its DNA content. Werewolf movies. Bestselling novels. The English Romantic poet William Wordsworth. Tim Burton's film *Planet of the Apes*. A fluorescent rabbit popularized by an artist.

What does any of this have to do with the genome?

Plenty, according to a growing cadre of Duke faculty members and their collaborators. Associate Professor of English Priscilla Wald, who recently organized a conference on "Genomics, the Arts & Popular Culture" at Duke, says that narratives of various sorts—books, movies, the news media, works of art, legal and historical documents—incorporate genomics and its implications into the stories they tell and the images they project. The consequences of that are not intrinsically good or bad, she says. But, she thinks it would behoove us to be aware of such narratives because they ultimately help to shape our ideas of what it means to be human in the age of the Genome Revolution.

Only Human

Wald and others at Duke, such as Assistant Professor of English Rob Mitchell and William Neal Professor of Law James Boyle, have written extensively about a court case from the 1980s which previewed issues now finding their way into popular novels. The court case involved a doctor who received a patent on a cell line derived from his patient's cancerous spleen without the patient's consent. The Supreme Court of California ultimately ruled that the man—John Moore—retained no property-interest rights to his own spleen, while the doctor



went on to accrue significant financial gains from his patent on the cell line.

Even though the Moore case pre-dates the Human Genome Project, Wald says the reverberations from the case still have everything to do with the genome sciences. "On the surface," she says, "the Moore case is about body parts. But at a deeper level, it's about the information contained in our DNA. The genomic information in this man's cells was useful to the pharmaceutical industry. Because of that, we start to ask who has control over the information contained in our DNA."

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Message from the Director



We've come a long way since Quincy.

Remember that show? From 1976 to 1983, Jack Klugman yelled and screamed his way into our living rooms as medical examiner Dr. R. Quincy. As I recall, he even had what he called, futuristically and almost reverently, a "DNA Sequencer." In its

time, Quincy's willingness to venture into a DNA-laden storyline was an anomaly. But turn on your TV today and you'll find it's now a given. Increasingly, the public is exposed to regular doses of genomics and related biotechnology. It's even become a respectable profession: this season, *CSI: Miami* pushes the entertainment envelope by expanding the role of Ryan Wolfe, a cop who is pursuing a Master's degree in genetics, something that never would have occurred to anyone toiling in Quincy's lab in 1977.

Perhaps it's not surprising that ten years after the OJ Simpson case invaded our collective consciousness, forensic DNA's dramatic potential is being explored so relentlessly by purveyors of pop culture. And it's not just forensics: DNA figures heavily in *Alias*, much as it did in *The X-Files*. An animated version of the late evolutionary biologist Stephen J. Gould performed DNA tests on *The Simpsons* in 1997. Richard Preston, best-selling author of *The Cobra Event*, described the use of genome sequencing and database searching to identify an unknown virus so vividly that it was sure to inspire future genome scientists (hopefully even more than future terrorists). And NBC's Brian Williams,

reporting on the Bush-Kerry election, spoke breathlessly of candidates who have "politics etched in their DNA." That's the genome, folks, right on primetime TV.

I'm not complaining; primetime works, and, if anything, I'd like to see even more "Genome TV." Same goes for "Genome Art" and "Genome Music." Far from putting the scientific enterprise at risk, such exposure can only help us engage and attract those capable of advancing genome sciences and policy. While a growing number of students continue to pursue graduate and professional work in genome-related fields, I have a sense that—at least at most institutions—they often do so despite their college coursework. Pre-med and pre-grad studies are still used to weed out prospective scientists—to discourage them rather than encourage them. One colleague has lamented that the whole process has become like a fraternity hazing ritual.

Changing the way science is taught is an obvious and necessary approach to this problem, and many prominent scientists have taken up this challenge. But I would argue that, well beyond science, pop culture will always be more potent and reach a broader audience than classroom pedagogy, whatever forms the latter may take. How many kids applied to law school after seeing *The Paper Chase*? How many would-be reporters were inspired to pursue journalism by *All the President's Men*? If science were portrayed as something more directly relevant to real life, might we not engage a broader cross-section of the next generation? Somewhere out there is a budding writer aspiring to write the first great "Genome Novel." Might we see normal people on stage or on screen occasionally be portrayed as genome scientists? Or the reverse: genome scientists occasionally portrayed as normal people?

As we've discussed before in *GenomeLIFE*, the impact of the Human Genome Project on health is just beginning to take form, and it will no doubt take time before it's felt on a broad scale. Meanwhile, for evidence of just how pervasive the Genome Revolution is, take a look at the marketplace. Entrepreneurs of various stripes are now selling genetically engineered fish as pets, DNA chips to test food products, skin creams designed according to customers' DNA profiles, and bobblehead dolls modeled on Nobel Prize-winner James Watson.

Of course, by itself, this sort of commerce is unlikely to inspire a wave of new biology or public policy majors. All the more reason, then, to put plausible dramatizations of genome science on television or on the big screen. PBS is fine, but its talking-head science shows and aura of "This is supposed to be good for you" are things kids can sniff out a mile away. In all likelihood they are more impressed by David Caruso comparing suspects' DNA sequences on *CSI* or by Jennifer Garner doing, well, almost anything, but certainly talking about genome databases.

Those of us trying to offer the future of genome science to students should keep that in mind. Because how the Genome Revolution is portrayed on the tube or in the theatre or in a studio isn't just academic. It's life. ▶

Huntington F. Willard, Director

Oh, the Humanities (continued)

The anxieties surrounding ownership of genomic information are also manifested in other types of narratives, such as popular books and movies. Wald sees some of the same dilemmas apparent in the Moore case reappear in Robin Cook's novel *Chromosome 6*. In it, a scientist transposes human chromosomal material into chimpanzees in order to create immunological doubles of humans to be used for organ transplants. The metaphor invoked by the novel, says Wald, is one of "bioslavery." "It brings out the idea of bioslavery and invokes the 13th Amendment of the Constitution prohibiting slavery. The public gets this sense if we start down this line of research, we're going to run the risk of enslaving transgenic creatures with human features, and then we'll be headed down a slippery slope toward justifying the enslavement of human beings again."

Wald rejects the bioslavery argument as "an old narrative used to explain new phenomena," but she says the Moore case, books like *Chromosome 6* and movies like *Planet of the Apes* are all concerned with how the genome sciences are "...making us see once again how fundamentally unstable the definition of 'human being' is and always will be."

Rob Mitchell uses science fiction in teaching and scholarship to explore similar ethical and policy themes. In his class on Cultural Narratives of Genomics, Mitchell considers *Beggars in Spain* by Nancy Kress. The novel begins in 2008 and chronicles the rise of a class of genetically modified individuals who are brighter, more attractive and can do without sleep and so are therefore more productive. The "Sleepers" soon begin to discriminate against the "Sleepless." The book is a useful jumping off point for discussion, says Mitchell, because it touches on issues of genetic discrimination and current controversies in forensic DNA, evidence gathering and gene banks. "These types of texts are valuable representations of some of the narrative strategies by which we try to make sense of what's happening in terms of these new developments in genomics."

History Lessons

Mitchell and his graduate student Andrew Burkett also look backward for insights into how the genome continues to make its way into our consciousness. In his Cultural Narratives class, Mitchell examines the development of information technologies at the turn of the 20th century and their symbiotic relationship with the then-nascent field of genetics. He notes that industrialists created distribution and filing systems that were later applied to genetic research and more practical pursuits: Leland Stanford—railroad magnate, politician and founder of Stanford University—used these systems in horse breeding, for example. "This is a case where genetics and information technologies came together long before molecular biology."

Burkett is studying the ways in which the ideologies of the British Romantic poets influenced the thinking of the forefather of genomics, Charles Darwin. William Wordsworth's (1770-1850) longest poem, "The Excursion," was a philosophical work published in 1814 and meant to counter popular despair over the failure of the French Revolution. Burkett explains that Darwin read and reread "The Excursion" as he was preparing to embark on his fateful voyage on the *HMS Beagle* that led to the theory of evolution by natural selection. He observes that in both Wordsworth and Darwin, the death of the individual is less important than the survival of the species. Asked how his own work is relevant not just to the French Revolution but to the Genome Revolution as well, Burkett says, "To better understand the way current cultural narratives are impacting the expression of genomics and the way it's practiced, we need to look back at other moments in time where this was happening. In the 19th century, [Romantic] narratives and ideologies were creating this zeitgeist and impacting how science was expressed."

Flora versus Fauna: Getting it Wrong

Genetically modified (GM) organisms such as corn and soybeans have provoked their share of anxiety among consumers and environmentalists. But

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Kac, Eduardo. "The Book of Mutations", giclee prints 20 X 20" (50 X 50cm) each, 2001. The first and last images evoke the switching between white light and ultraviolet light that takes place

in the Genesis installation, which is responsible for the bacterial mutation. The three prints in the center show mutations of the original biblical sentence employed in Genesis, displayed in

spiral form against a black background. The color palette of these three prints matches the hues in the photographs, creating a visual transition between them (see text, p. 4).

Oh, the Humanities (continued)

Susan McHugh, Assistant Professor of English at the University of New England, argues that, to date, we've actually been more fixated on GM animals than we have on GM plants. She says that animals are more "charismatic" but notes that since almost all of us eat transgenic soybeans and corn, GM plants are actually much more a part of our everyday lives than GM animals and therefore deserve more thoughtful consideration than they've gotten thus far.

For her part, Heather Schell of George Washington University says animal metaphors reveal the general public's incomplete understanding of genetics and genomics. She sees perceived patterns of modern behavior such as aggression in the workplace prompting the media to declare that the causes of such behavior lie in our genes. Popular portrayals of wolves—and werewolf movies in particular—have propagated the idea that contemporary men are "...naturally, insistently and enticingly predatory," she says. "Werewolf movies, with their fuzzy heroes and fuzzy biological details, are a perfect example of the popular understanding of genetics."

That fuzziness is par for the course, according to UCLA medical geneticist Wayne Grody, who moonlights as a consultant to the film and television industry. Producers have sought his advice on projects ranging from *The Nutty Professor* movies to TV dramas such as *CSI* and *Chicago Hope*. Grody says that he still finds Hollywood portrayals of genomics to be cringe-inducing—even some of those on shows he's worked on—but that he's grown numb to it. "I've come to accept that this is drama, or it's comedy—it's not real life. As long as the audience can suspend its disbelief, I'm fairly happy. As one producer told me, the proportion of the Nielsen ratings audience that's made up of geneticists is pretty miniscule."

The Art of the Genome

Popular expressions of genomics are not limited to books and movies. Visual art, too, has engaged with the Genome Revolution. Eduardo Kac, one of the keynote speakers at the conference, has probably made the biggest public splash among artists incorporating the genome sciences into their work. Kac (pronounced "Katz") has explored the cultural impact of genomics and other biotechnologies through "transgenic art." "Genesis," (1999) for example, included an "artist's gene"—a synthetic gene that was created by Kac by translating a sentence from the biblical book of Genesis into Morse Code, and converting that into DNA sequence according to Kac's own conversion principle.

Kac also achieved notoriety for the "creation" of "GFP Bunny." The GFP (green fluorescent protein) Bunny was in fact a rabbit named Alba who was genetically modified to glow when illuminated with blue light. Kac views the entire work to encompass not only the creation of the rabbit, but the public dialogue generated by the project and his own failed attempts to adopt Alba. He has continued to make art from the controversy surrounding Alba's creation, including an exhibit of photos and drawings entitled "Free Alba!"



Kac, Eduardo. "Transgenic Art – GFP Bunny". Alba, the fluorescent bunny.

Assistant Professor of English and Media Studies at the Catholic University of America Lisa Lynch notes that "GFP Bunny" has had a provocative and sometimes polarizing effect. She says that in the "Alba Guestbook," a message board that Kac created on the Internet, one can find extreme responses to the GFP Bunny project, with some calling Kac "a monster" and others supporting his efforts to "free" Alba. The irony, says Lynch, is that according to the French research institute where Alba was created, the rabbit is long since dead. Thus, she says, Kac's ongoing efforts to secure Alba's release are essentially a "performance" that's part of the work's larger mission to bring the public into contact with a transgenic animal. Whether Alba exists or not, says Lynch, "Kac wants to show the public that this kind of thing is inevitable. He is saying that [transgenic animals] are already here on the ground among us and we need to confront that idea."

Life Stories

Kac's work, says Wald, is provocative and interesting because it challenges existing narratives of genomics. "His art asks us to speculate about these issues and confront our own desire to make meaning of genomics and what the consequences of that desire can be."

Wald sees the impulse to question and challenge as integral to her work and those of her colleagues exploring narrative and pop culture vis-à-vis genomics. She says her motto is, "Change the story, change the world." By that she means we owe it to ourselves to examine and question our assumptions about genomics and the narrative prism through which we view genome sciences and policy. "The words we choose and the narratives we construct will define what genomics is. Once we start giving it a definition and accruing language about it and telling stories about it, it starts becoming something. Those things create it, and everything follows from there." ▶

integrate

School Days

IGSP Begins Integrating Genome Curriculum

When asked about the IGSP's recent steps to forge an integrated curriculum in genome sciences and policy at Duke, Provost Peter Lange says that it was all part of the plan. From his perspective, when the Board of Trustees approved its strategic plan in 2001, curriculum development was a primary objective.

"It's extremely important to be able to take the fruits of what we're doing on the research side," he says, "especially in interdisciplinary areas like genomics, and make them show up in curricula."

Integration by Parts

That was the impetus behind IGSP Director Hunt Willard's application to the National Institutes of Health for a Roadmap grant (the Roadmap is the NIH's strategic plan to identify gaps and opportunities in biomedical research). The grant was awarded in September and is designed to integrate teaching, learning and research in genome sciences and policy across the Duke campus.

Recently, Willard surveyed the landscape at Duke for existing genomics and related ethics, law and policy courses. "It's impressive," he says. "In the past two years alone, there have been more than fifty courses offered that fall under the rubric of genome sciences and policy. And every School on campus is represented."

Trinity College Dean Bob Thompson says that the breadth of course offerings is no accident, noting that genomics is a "transformative" field not only in Medicine, but in Arts & Sciences and the Nicholas School of the Environment & Earth Sciences, too. "When we received a grant from the Howard Hughes Medical Institute for our undergraduate Making Meaning of Genomic Information Program a couple of years ago, we tried to embed genomic content in as many courses as possible."

Despite so many choices covering various aspects of genome sciences and policy in the classroom and laboratory, Willard says that what's lacking is a sense of integration. "It's a

long list of courses," he says, "but as a menu it's strictly 'a la carte.' If I were a student, I would have to be extremely entrepreneurial to assemble my own interdisciplinary program in genome sciences and policy."

Starting Early

Making the transition from the "a la carte" model to an integrated menu of genome courses at Duke will be a major part of Julianne O'Daniel's job. O'Daniel, a trained genetic counselor, is the IGSP's new Assistant Director for Educational and Training Programs.

Her first task will be to assess what genome education and training initiatives are already available at other institutions. Whatever shape Duke's genome sciences and policy training program ultimately takes, O'Daniel recognizes that some part of it must be available to incoming freshmen. "Genomic literacy is going to have to involve incoming undergrads—to get them interested, whether it's through medicine, policy or even their own personal health."

Thompson hopes that undergraduate involvement in genome sciences and policy will eventually have three components. The first is the existing Making Meaning Program and its coursework and experiential opportunities in genome science laboratories. The second is the FOCUS (First-Year Opportunity for Comprehensive, Unified Study) program on "The Genome Revolution and its Impact on Science, Health and Society," which was offered for the first time this fall and directed by Willard. The third would be a program of concentrated study in genome sciences and policy leading to a certificate, just as Duke undergraduates can earn now certificates in fields such as Health Policy and Neuroscience. "That would be the ultimate level of

engagement," says Thompson.

In addition to integrated coursework, Willard envisions less formal education and training mechanisms in genome sciences and policy, ranging from seminars to happy hours. He and Lange share the view that the less-structured teaching that goes on outside of the classroom is just as integral to the Duke educational experience as formal coursework. Lange says that those experiences build community. "You need a vast number of opportunities for people to intellectually bump into each other."

Genome: The Next Generation

The funding of the Roadmap grant is a sign that dissemination of the science and policy aspects of genomics across campus can be commensurate with the investment the university has made, says Willard. "It's essential that our curriculum reflect Duke's broad commitment to exploring the genome and its implications for the way we conduct research, treat patients and live our lives. We need to get the next generation to buy into what we're doing." ▶



Julianne O'Daniel, with pipe cleaner DNA model at Club Boulevard Elementary's Science Day.

Genomes and Global Health

Computational Biology of Infectious Diseases

Too often, scientific meetings are the equivalent of “lost weekends.” Participants assemble, listen to a succession of didactic lectures, and after a few days return to whence they came.

In organizing the 2004-2005 Program on Genomes to Global Health: Computational Biology of Infectious Diseases, Tom Kepler was determined that this meeting would be different. Kepler, from the IGSP Center for Bioinformatics & Computational Biology, saw the program as an opportunity to get the attention of mathematicians, through his work with program sponsor the Statistical and Applied Mathematical Sciences Institute (SAMSI) in Research Triangle Park.

Group Think

More importantly, he wanted to extract a commitment from SAMSI to attack significant problems in infectious disease, especially those diseases afflicting the developing world. To do that, the program was organized to include

September’s opening workshop, semester-length didactic coursework, and the piece Kepler is most excited about, three working groups that will meet for a year. The working groups include Mathematical Genomics for Vaccine Design, Cell Communication, and Mathematical Epidemiology.

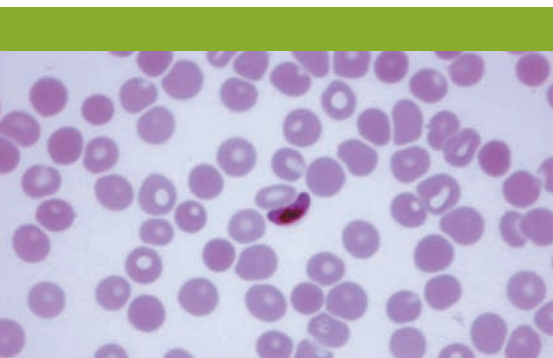
Kepler is facilitating the Vaccine Design group and says the group’s initial meeting in September made it clear to him exactly how ambitious the idea really was. “We’re going to learn as much as we can about the genome of *Plasmodium falciparum* (the parasite that causes malaria and is transmitted by mosquitoes), learn about the difficulties in designing a vaccine for malaria, do some comparative genomics, and try to come up with new quantitative techniques,” he says. “We have this strange blend of people, some of whom aren’t quite sure what DNA is. But somehow we think by putting our heads together and working as a team we’ll be able to make real progress in the course of a year.”

WHO in the World

Kepler and his colleagues are also working with the World Health Organization’s Ayoade Oduola, who manages the Committee on Pathogenesis and Applied Genomics in WHO’s Special Program

for Research and Training in Tropical Diseases. “I met him in Geneva in August and was so struck by him that I invited him to SAMSI,” Kepler says. “WHO is setting up a program to ‘train the trainers’ for bioinformatics in the developing world, which [Assistant Professor of Biostatistics & Bioinformatics] Lindsay Cowell and I have agreed to participate in.” WHO believes that the only way to conquer parasitic and infectious diseases is by empowering the developing world itself to do that task. Kepler shares that view and says that researchers and clinicians in those nations can play a significant role just by learning the statistics and bioinformatics—efforts that require no more than a desktop computer and a connection to the Internet.

Kepler expects that the initial measure of success will come at the program’s transitional workshop in May, where participants will review what they’ve accomplished and how they will go about disseminating their findings. “We will gather all of the folks who’ve participated and see what we’ve learned. Is it worthwhile to continue and if so how are we going to do it? SAMSI has done its work—they’ve provided the opportunity, the funding and the space. The rest is up to us.” ▶



Opaque, bean-shaped Plasmodium falciparum, the malaria-causing parasite, visible in a blood smear.

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faculty

New Faculty Profile:

Jen-Tsan Ashley Chi, PhD

Assistant Professor of Molecular Genetics & Microbiology Jen-Tsan Ashley Chi joins the IGSP from his position as a Postdoctoral Fellow in the laboratory of microarray pioneer Patrick O. Brown at Stanford University. While there, Chi carried out gene expression profiling of endothelial and smooth muscle cells in order to explore their diversity and ways in which they differentiate. He also examined the molecular basis of cellular responses to environmental stress and performed genomic analysis of RNA-mediated gene silencing.

At Duke, Chi's initial work will involve further studies of endothelial and smooth muscle cell differentiation, using a variety of genomic, biochemical and computational techniques. "I believe these analyses will help us to elicit the regulatory circuitry that controls the regional specialization of endothelial cells and smooth muscle cells in different anatomic locations," he says. He hopes to continue to use microarrays and other genomic tools to elucidate further the molecular basis of human diseases and disease-related biological questions.

Chi is looking forward to collaborating with a range of both clinical and basic scientists. "Duke offers me unique opportunities to realize my research goals with its assembly of scientists and doctors of different disciplines. By accelerating the formation of partnerships between biologists, clinicians and statisticians, I think the IGSP will create fertile ground for discovery, invention and education." ▶



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New Faculty Profile:

Terry Furey, PhD



Terry Furey, PhD

Assistant Research Professor and IGSP Scholar Terry Furey joined the IGSP and the Department of Biostatistics and Bioinformatics this fall.

Furey comes to Duke from the University of California at Santa Cruz, where he worked with David Haussler as a

Postdoctoral Researcher in

the Center for Biomolecular Science and Engineering. Most recently, Furey co-coordinated the effort to ensure the completeness and correctness of the essentially finished human genome sequence unveiled last year.

Looking ahead, Furey sees part of his work at Duke focusing on chromosome and genome structure. "The whole field of chromatin and chromosome structure is wide open," he says. "I think that the more structural features can be related to the genome sequence, the better our understanding of how chromosomes work will be." Another major interest is on genomic variation and its relationship to cellular function and disease.

Furey says Duke offers new vistas for him not available elsewhere. "I like the fact that we have computational people in the same building as the wet lab people. You can have casual interactions that often lead to exciting things. I was never going to get that at a strictly computational place. And for me, having access to the Medical Center and a focus on applied biology is great." ▶

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Artist rendering of the new CIEMAS building.

Engineering a Partnership

Genomics-Engineering Interface Signals New Opportunities

A genome scientist, a physician and an engineer are having coffee.

No, that's not the setup for a bad joke or the premise for an ill-advised sitcom, but a matter-of-fact description of a ritual that will probably be repeated on a regular basis now that the ground-floor cafe is open for business in the new Center for Interdisciplinary Engineering, Medicine and Applied Sciences (CIEMAS) building. CIEMAS opened in September and its lab, office and classroom space is currently being occupied by the IGSP along with groups from the Pratt School of Engineering and the School of Medicine.

IGSP Director Hunt Willard says that while he's happy to see people chatting over coffee downstairs, the real fruits of CIEMAS will come from the interdisciplinary activities that are explicit in the building's name. "The scientific literature is devoting more and more space to 'systems biology,'" Willard says. "Genomics and engineering are critical to that type of global effort to understand how life works at the systemic level. At Duke, we're really fortunate to be among the first to have both disciplines under one roof."

Completing the Circuit

Biomedical Engineering (BME) Chair George Truskey notes that even prior to CIEMAS opening its doors, "systems biology talk" had picked up on campus. "There are now large-scale efforts looking at the organization of signaling and genetic pathways, for example."

Among those trying to decipher such pathways is new recruit Lingchong You. You, having completed a postdoc at Caltech, recently arrived on campus and will assume a junior faculty position in BME to continue his current studies of gene circuits. The idea behind his work is to see if genetic pathways can be manipulated to perform specific tasks, such as killing cancer cells. To test the principle, You programmed a population of bacteria to maintain a low cell density (cancers are characterized by uncontrolled cell division and thus, high cell densities). Using a protein from another bacterium as a sensor, You was able to construct a system in which, at high cell densities, the sensor protein binds and activates a transcriptional regulator, which in turn activates a "killer" gene, leading to cell death. Thus, You was able to create a population control circuit, a significant achievement, he says, in light of all of the "noise" present in an active cell whose constituents are undergoing thousands of chemical reactions at any one time. "With the circuit," he says, "we were able to show that cell-cell communication is an effective tool to coordinate the behavior of individual cells across a population and to achieve robust circuit dynamics."

Truskey says the interest in gene circuits is just one of many ways in which his field is embracing the genome sciences. "A lot of our research is becoming more and more molecular—biosensors, tissue engineering, drug delivery and the like. In my lab, for example, we're starting to use microarrays in a tissue engineering system to look at genomic responses to physical forces."

Location, Location, Location

Another new CIEMAS occupant, Joseph Nevins, Director of the IGSP Center for Applied Genomics & Technology, says he looks forward to working alongside scientists able to invent, develop and/or tweak the genome technology integral to the work of his Center. "You could imagine there might be someone developing new methods for sequencing or microarray analysis," he says. "Or new methods in some area we don't even anticipate. Those are the opportunities for synergy."

When asked about his own perceptions of life alongside Engineering faculty, IGSP Center for Genomic Medicine Director Geoff Ginsburg likens it to real estate. "Location, location, location. For what I do as a physician-scientist, to be strategically placed right between Duke North, Duke South and the Pratt School is just phenomenal."

Ginsburg observes that in the two months he's been in the building, he's already bumped into several potential collaborators in the hall. One was Professor of Electrical and Computer Engineering Jeffrey Krolik. "He told me he was interested in digital signal processing," says Ginsburg. "I told him about microarrays and how we're trying to measure signals from 30,000 points simultaneously. We agreed we need to get together." Another was Professor of Biomedical Engineering Roger Barr, who works on electrophysiology of the heart and cardiac arrhythmias, which happens to be a clinical interest of Ginsburg's.

Hiring investigators with preexisting ties to both camps should also foster interdisciplinary collaborations, says BME Professor Monty Reichert. He is enthused about You and looks forward to the hiring of a second, as-yet-unnamed recruit. "The other person we're looking for is someone who's technology-based; someone interested in designing and developing new assay approaches."

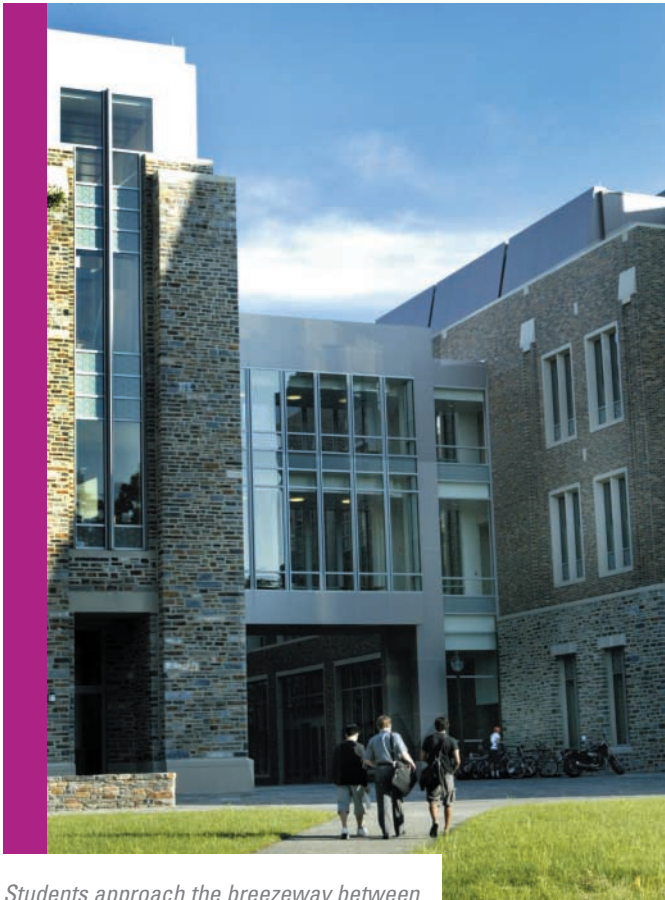
For his part, You appears to have already absorbed Duke's interdisciplinary ethos. "Besides the reputation of Duke, the exciting initiatives in bioengineering, genomics and systems biology are certainly at the top of my list of reasons for coming," he says. "These efforts, plus the tradition of extensive research collaboration across Duke's campus, present a unique opportunity to integrate expertise from multiple disciplines to improve our understanding of biological systems."

Stairmasters

From Willard's perspective, the IGSP and its affiliated faculty are already knee-deep in systems biology. He cites the program of Nevins and Mike West in cancer cell signaling pathways and Biology Chair Philip Benfey's ongoing interdisciplinary group devoted to studying networks in biological systems (to be highlighted in the January *GenomeLIFE*). "By getting input from engineers, we only stand to gain," points out Willard. He references a recent article in *Nature Biotechnology* by Roger Brent of the Molecular Sciences Institute on the potential for partnership between biology and engineering. "Brent talks about how engineering increases 'the complexity of the cultural collision' when added to the more common existing mixes of biologists, chemists, and mathematicians. I think the more collisions we can orchestrate, the better."

Truskey is impressed by the rapidity with which the genomics and engineering interface is coalescing. "Two years ago there was not much of a presence in this area at Duke, but I think it's really starting to change. I think the IGSP being where it is in CIEMAS and the faculty involved will only move that forward. I hope to see a lot of movement up and down those stairs."

And not just at coffee breaks. ▶



Students approach the breezeway between the East wing of CIEMAS (on the right) and the West wing.



Genome Innovations: Joseph Heitman, MD, PhD

Fungal diseases can be difficult to treat with high specificity, since fungi and

humans share certain basic biochemical pathways. Recently, James B. Duke Professor of Molecular Genetics and Microbiology Joe Heitman's lab has found a potential new target for specific antifungal therapy by studying yeast (the simplest fungus). Their work appears in the October issue of *Eukaryotic Cell*.

The yeast enzyme FKBP12 is best known for its ability to act as a receptor for the common immunosuppressive drug FK506, which is frequently used in organ transplant patients. Heitman's lab was able to learn more about the cellular functions of FKBP12 by identifying mutations in other genes that are lethal to yeast already harboring mutations in the gene that codes for FKBP12. Specifically, Heitman's group found that a mutation in the gene coding for FKBP12 was lethal when combined with a mutation in the gene encoding the enzyme homoserine dehydrogenase.

In theory, a combination of FK506 or its derivatives could be combined with a homoserine dehydrogenase-specific inhibitor to reproduce the lethal effect of the double mutant. Because such a therapy would be targeting a biosynthetic pathway that is present in fungi but not in mammals, it would presumably exhibit minimal toxicity in humans. ▶

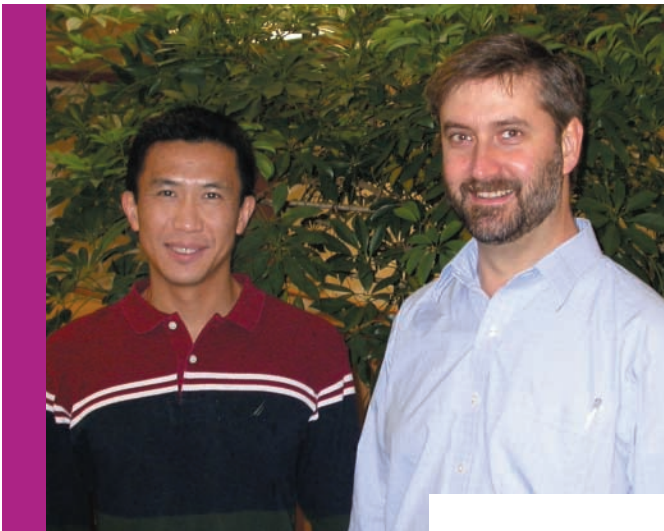
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Vive la Difference

How Genetic Variants Affect Evolution and Disease

Hai Yan and Greg Wray don't have anything against proteins or the DNA sequences that code for them. But both are quick to point out that 98 percent of our DNA does not code for protein. Thus, they contend there's a lot to be gained by studying genetic variation in that 98 percent. Variants lying outside of the protein-coding regions of DNA may not change the *structure* of proteins, but they can affect *how much* protein is made. That's because the non-coding portions of our genome regulate to what extent a gene is switched on or off.

Yan, an Assistant Professor of Pathology, sees genetic variation in the non-coding portions of the genome as key to understanding disease. Wray, Associate Professor of Biology, says such variants can teach us about our own evolutionary history.



Hai Yan, MD, PhD and Greg Wray, PhD

Regulation: A Revelation

Given that gene expression is regulated by DNA sequences that lie “upstream” from the regions that code for protein, the idea that variants in those upstream regions can affect whether a gene is turned on or off is not surprising. A variant in a regulatory sequence may attenuate or boost the expression of the gene it regulates. Yan, who recently published a review on the subject, says if enough such variants accumulate in the same genome, they may make the difference between sickness and health.

In 2001, he identified a putative non-coding variant rendering certain families more susceptible to familial adenomatous polyposis (FAP), a single-gene disorder associated with multiple benign tumors in the colon. He is now working to identify variants associated with human behavior and other characteristics.

A Rapidly Evolving Story

Greg Wray is interested in the way upstream variants influence natural selection—the way in which those organisms best adapted to their environments tend to survive and transmit their genes to succeeding generations. Such genes and their corresponding traits are said to be “selected for.” Recently, Wray's lab examined the evolutionary history of a variant in a gene called *MMP3*, which has been associated with heart disease.

Graduate student Matt Rockman, Wray and their co-authors observed that one of the two human *MMP3* versions (“alleles”) with variants in the noncoding region of the gene had been selected for—but only in Europe. Some 23,000 years ago, the frequency of the rarer allele shot up on the European continent, which was then in the middle of the Ice Age.

Selection, the conventional wisdom goes, implies importance: if evolution has kept a version of a gene around over a long period of time and favored it over other versions, it must be doing something important. Might the favored European *MMP3* allele be protective against heart disease? Wray admits that the possibility is intriguing, especially given Europeans' heart-unhealthy carnivorous diets at the time, but he cautions that it's only speculation.

“It's true that people in Europe at that time were eating large mammals. But this gene does many other things in the body, so we can't make a convincing case that heart disease was the driving factor in one *MMP3* allele being selected for.”

Wray sees the *MMP3* story as an important example of the power of rapid evolutionary change. Traditionally, important alleles are thought to change very slowly. However, Wray points out that when the environment changes rapidly, organisms with genes that can also evolve rapidly may have an advantage. The rapid rise of the European *MMP3* allele suggests that that may have been the case 20,000 years ago.

The other lesson, Wray says, is that alleles should not be viewed in absolute terms. “There might be an allele that works better in one circumstance—say, a cold climate—and another that works better in another circumstance. It really depends on the local environment.”

Upstream without a Protein

Yan and Wray have helped to establish the importance of genetic variation outside of regions of DNA that code for proteins. Both lament how little attention the subject has received in the literature. Wray attributes that to inertia.

“As scientists, we get used to thinking about how to approach a gene in a lab,” he says. “It establishes a workflow for us. I've read many papers where the investigators scoured a gene for a mutation or variant and only looked at upstream non-coding sequence out of desperation. And then when they did find something [in a non-coding region], they didn't know what to do with it. But I think it's starting to resonate in the community that we need to look explicitly at these things. They are a part of the [evolutionary and medical] picture and we can't ignore them.”



Victor Dzau, MD The Chancellor Talks Shop

On July 1, Victor Dzau assumed the mantle of Duke's "top doc." Dzau, the new Chancellor for Health Affairs and President and CEO of Duke University Health System, now runs an enterprise with \$1.3 billion in annual revenues and oversees some 25,000 employees. But this has not prevented the physician-scientist from continuing his research activities.

In addition to basic work on the molecular mechanisms of cardiovascular disease, Dzau has a number of therapeutic irons in the fire: in August, his group published a rat study on a so-called "smart gene therapy" designed to detect oxygen deficiency and thereby protect organs and tissues from damage in heart attack patients. His group is also leading Phase III trials on another gene therapy designed to prevent the failure of vein grafts in heart bypass patients. And in October, he was awarded the Max Delbrück Medal by the Max Delbrück Center for Molecular Medicine in Berlin.

Dzau spoke to *GenomeLIFE* at length about his own involvement in genomics (he was the founding editor of *Physiological Genomics*), current projects, the prospects for genomic medicine in general, and where he thinks Duke can have a lasting impact.

What made you realize that understanding genes was going to be critical to treating heart disease?

The observation goes back a long time that there's

a genetic component to cardiovascular diseases. But it wasn't until the technology became available that people could study these things.

I would say that most of my work in genetics is really dabbling. It doesn't have the same power as some people who do it full-time. But as a physician-scientist I think it's very cool and important to do it. My job is to bring a different perspective, which is mainly the phenotype side—the physiology. My roles are to appreciate the importance [of genes] and try to find the right collaborations.

What have you been working on lately?

We have some very interesting things coming out. For example, we're looking at genetic correlates of heart valve surgery. Why don't people get their valves fixed much earlier? It's because if you do it too early you get all these potential surgical complications. But if you do it too late, the ventricle undergoes cardiomyopathy and the procedure fails. Up until now, we have used very crude ways to look at whether the ventricle is strong enough or if the surgeon has waited too long. Using gene expression ratios, we can pretty much look at a piece of heart tissue and predict, even blinded, whether a ventricle is right on the cusp of being ready for surgery or not.

We're also examining gene profiles associated with specific diseases. For example, hypertrophic cardiomyopathy is associated with a set of unique genes, as is dilated cardiomyopathy. We've also looked at Chagas' disease, an infectious disease which is a common cause of heart failure in Latin America due to *Trypanosoma cruzi*, a parasite transmitted by insects. The infection turns on certain cytokine genes.

You're also looking at genetically modified stem cells as therapeutic agents to repair injured tissue following heart failure. What can you tell us about that?

Genetically modified stem cells turn out to be really fascinating—just looking at what these cells may do. If you place any kind of hematopoietic stem cells into the myocardium early enough, they will actively influence the myocardium [in a posi-

tive way]. We don't know exactly how it works—it's not repair, it's not fusion, it's not regeneration. There are probably mediators protecting the myocardium and inducing [restorative factors] around it. Whatever it may be, I think stem cell therapy is clearly in our future.

Where do you envision Duke making the most substantive contributions to genomic medicine?

I think science has to drive the questions. They have to be what individual investigators think are important, not what I think is important. But as far as what we want to facilitate as an institution, I'd say that it's clearly translational. We are sitting in the middle of a world-class medical center with unmet needs in patient care. Fortunately, the technology is now at a place where we can begin to see new applications.

We have the patients, the scientists and the infrastructure. I expect the IGSP to be hugely successful in terms of science and medicine. [IGSP's Center for Genomic Medicine Director] Geoff Ginsburg's major effort in genomic medicine and the overall push towards personalized health care combined with some of the concepts of prospective health that [former Chancellor] Ralph Snyderman put forward before me represent the big picture. And then of course you have Bob Cook-Deegan and the Genome Ethics, Law & Policy people addressing those aspects. It's everybody's dream. It's all there for us to screw it up, so we'd better not *(laughs)*. ▀

Further Reading:

Liew CC, Dzau VJ. Molecular genetics and genomics of heart failure. *Nat Rev Genet*. 2004 5:811-25.

Gibbons GH, Liew CC, Goodarzi MO, Rotter JI, Hsueh WA, Siragy HM, Pratt R, Dzau VJ. Genetic markers: progress and potential for cardiovascular disease. *Circulation*. 2004 109:IV47-58.

Melo LG, Pachori AS, Kong D, Gnechchi M, Wang K, Pratt RE, Dzau VJ. Gene and cell-based therapies for heart disease. *FASEB J*. 2004 18:648-63.

The Tuesday Series

A seminar series sponsored by the University

Program in Genetics and Genomics (UPGG)

and the Institute for Genome Sciences &

Policy. All seminars take place at 12:30 p.m.

in Room 147 of the Nanaline Duke building.

November

16 John Moran, PhD, *Human Genetics and International Medicine, University of Michigan*; Studies of a Human Retrotransposon

30 Louise Glass, PhD, *Plant & Microbial Biology, University of California, Berkeley*; Fatal Attraction: Nonself Recognition and Programmed Cell Death in *Neurospora*

December

7 Maynard Olson, PhD, *Genome Sciences, Medicine, Computer Science & Engineering, University of Washington*; Human Genetic Variation – What is the Big Picture?

14 Jonathan Hodgkin, PhD, *Genetics, Oxford University*; Bacterial Infection, Innate Immunity and MAP Kinase signaling in the Nematode *C. elegans*



GenomeLIFE, the newsletter of the Duke Institute for Genome Sciences & Policy, is published monthly and edited by Misha Angrist and Denise Haviland. We welcome your input! Please direct all inquiries, suggestions, and ideas to genomelife@genome.duke.edu

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