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WHY QUEBEC IS A GIFT
TO GENETICISTS

ROBOTS AND RESEARCH
FROM A MAX PLANCK
INSTITUTE

LYNN COOLEY:
WITH ONE TOOL, A
CLONING REVOLUTION

PLUS:
HOW TO SURVIVE
COMMON LAB
MANAGEMENT
DISASTERS

is this
CHEATING?

WHAT WE CAN LEARN
FROM A SOCIAL AMOEBA



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Spor tower of the slime mold *Dictyostelium discoideum*. © David Scharf / Photo Researchers, Inc.

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Martin Vingron



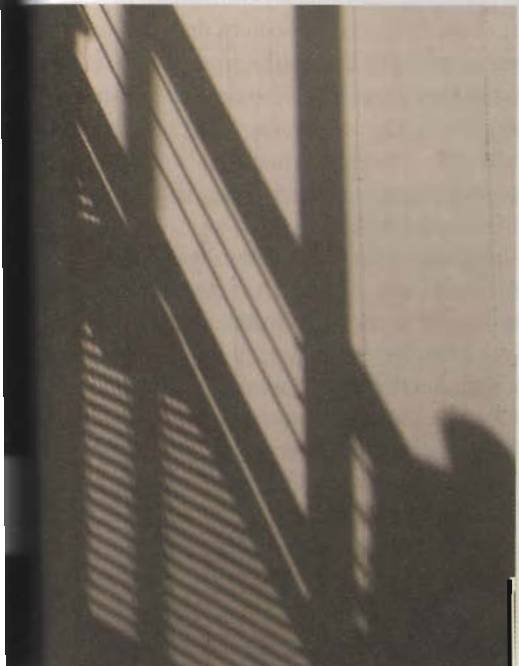
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PLANCK WALK

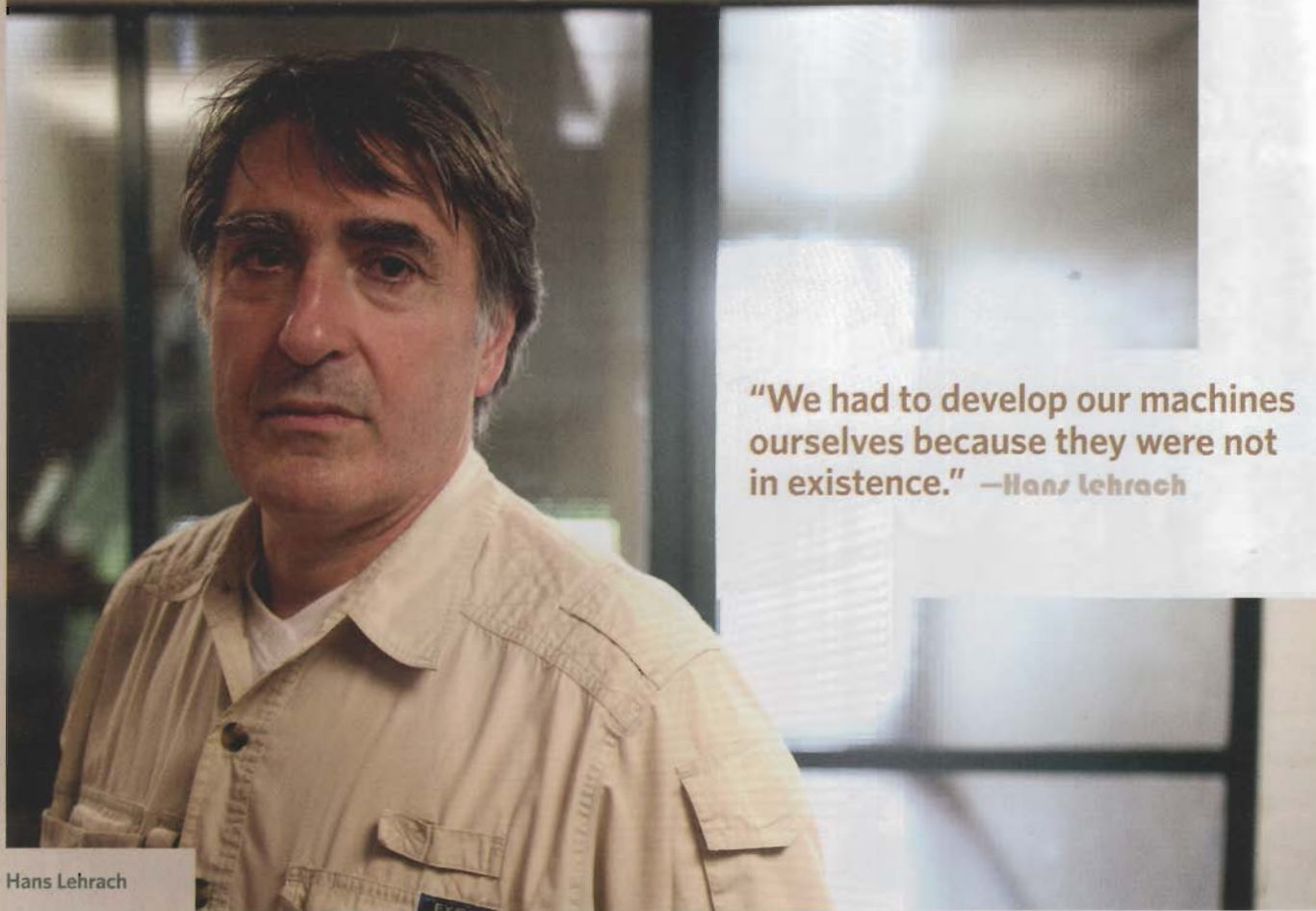
A shift in focus - and a couple of robots - have helped researchers at a Max Planck Institute pinpoint the genetics underlying entire systems.

By Stephen Pincock



In the basement of the Max Planck Institute for Molecular Genetics in Berlin, Hans Lehrach opens a door marked Robot Room. Aside from an electric hum and the whirr of tiny well-oiled parts constantly moving, the space is quiet. In the background, Patricia Zysik, a technical assistant, goes unobtrusively about her work as Lehrach introduces me to a pair of machines: One bears the label, Arranging Robot, and beside it, the Picking Robot.

Standing almost two meters tall and with a footprint of roughly six square meters, the two humming machines have a decidedly homemade feel to them. Which is unsurprising, given that Lehrach and his colleagues invented them 20 years ago. "These are the progenitors of all the cheap technologies around now," Lehrach says, ▶



Hans Lehrach

“We had to develop our machines ourselves because they were not in existence.” —Hans Lehrach

waving in the direction of another pair of instruments nearby – the considerably smaller, sleeker, and newer-looking 454 Life Sciences and Solexa sequencers.

“We had to develop our machines ourselves because they were not in existence.” Yet, the old machines still have their uses, he says. “For sequencing we use them less, but if you want to make a transgenic mouse using a BAC library, we still need them.”

For him and his colleagues at the institute, where he is director of vertebrate genomics, high-throughput technologies have long been fundamental tools that they have used to understand biology in terms of whole systems rather than individual components. These days, much of the technology needed for this work can be bought off the shelf. That wasn’t the case 10 or 15 years ago, says Zoltán Konthur, who works in Lehrach’s department. “He actually invented most of the equipment for array technology in the early 90’s,” Konthur says. Since then, the institute has continued to work on microarray fabrication and optics or detection systems for array technology, he adds.

“We’ve spent the last 10 years trying to develop systems biology in the sense of developing predictive models,” Lehrach says, as we leave the room and head back upstairs into the crisp light of a German summer day. In recent years, he has contributed to the field he helped develop 20 years ago by taking part in the sequencing of human chromosome X and chromosomes 21 and 22.¹⁻³

For some time, systems biology as a concept garnered less than the full support of the biological community, Lehrach notes. “There are a few people who really understand and push it, but

some who are opposed,” he says. “But I think it is naïve in the extreme to believe that we can’t understand a cell phone without modeling it, but that we can understand cancer without doing the same. Systems biology is an essential next step.”

Lehrach is one of four department heads who guide operations at the institute. Between them, these senior investigators oversee 481 group leaders, researchers, students, and administrative staff who work in its headquarters in a leafy Berlin suburb, not far from the sprawling US Embassy compound.

The institute is part of the Max Planck Society, an independent, nonprofit research community that gains around 80% of its €1.4 billion annual funding from the German federal and state governments (see sidebar). The society operates another 77 institutes and research facilities around Germany, in addition to several centers overseas. In the course of its 60-year history, the society has produced 17 Nobel laureates.

The Institute for Molecular Genetics was founded in 1964, and moved to its current home, a boxy modernist structure surrounded with manicured lawns, in 1970. Its initial focus was on the mechanisms of DNA replication and gene regulation, and on the structure, function, and evolution of ribosomes.

In the 1990s, however, the institute was transformed as the founding department heads – Heinz-Gunther Wittmann, Heinz Schuster, and Thomas Trautner – gradually retired and were replaced by Lehrach as head of the Department for Vertebrate Genomics, Hans-Hilger Ropers as head of the Department for Human Molecu-

lar Genetics, and a few years later by Martin Vingron as head of a new Department for Computational Molecular Biology.

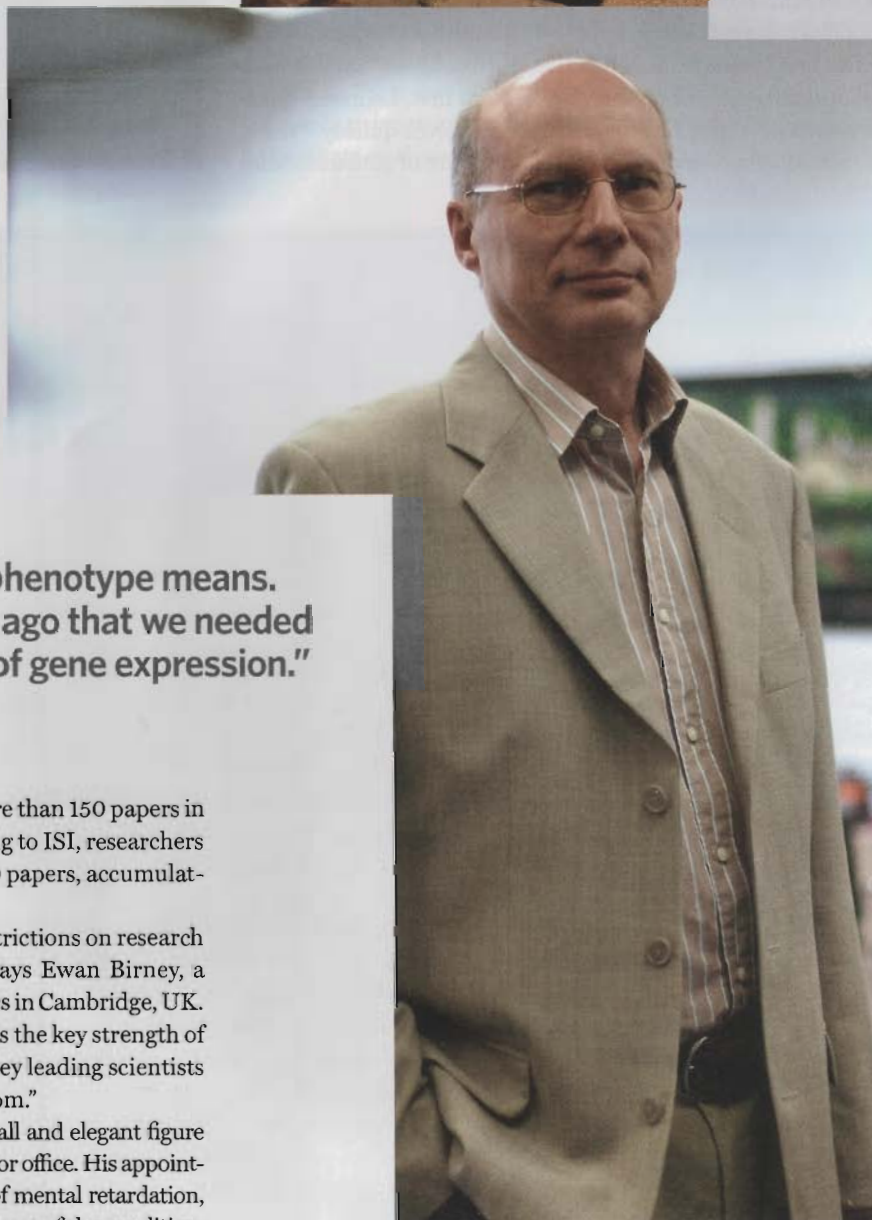
Taken together, these and other appointments, in the context of a changing scientific climate in the wake of the human genome project, pushed the research agenda away from just ribosomes and genetic regulation and replication, and firmly towards understanding the genetics of whole, complex systems. At the same time, the new appointees have overseen a dramatic expansion in the institute's operations; since 1994, the number of people working at the institute has doubled. "The increase in size correlated with the topic [of] genome analysis and systems biology," says Bernhard Herrmann, head of the department of Developmental Genetics, who brought early versions of his sequencing instruments with him when he arrived.

Since 2000, the total annual budget for the institute has been steady at around €25 million. "Almost all our money is in the form of grants," says Herrmann. Major sources of external funds include the European Union's Framework Program 7, he notes. Overall the institute gets roughly one-third of its funding from external sources.

In the past decade, the institute has obtained 97 patents and struck 37 licensing agreements with external companies. It also lists five spinoff companies including Scienion, which provides microarray technology and consumables, and Protagen, which provides protein analysis and



Mouse embryo slides



Bernhard Herrmann

"We want to explain what a phenotype means. I decided more than 10 years ago that we needed to do genome-wide analysis of gene expression."

—Bernhard Herrmann

protein biochips. The institute published more than 150 papers in each year between 2005 and 2007. (According to ISI, researchers at the institute have coauthored nearly 2,000 papers, accumulating more than 57,000 citations.)

The institute benefits from the lack of restrictions on research direction imposed on department heads, says Ewan Birney, a senior scientist at the European Bioinformatics in Cambridge, UK. "Each director runs their own area, and this is the key strength of the Max Planck Institutes: identification of key leading scientists and then giving them large degrees of freedom."

That's a sentiment seconded by Ropers, a tall and elegant figure who serves tea and biscuits in his airy second-floor office. His appointment offered the chance to study the genetics of mental retardation, including X-linked and autosomal recessive causes of the condition. "My impression," he says, "is that being appointed as a director of a Max Planck Institute is the best thing that can happen to [someone]."

MAX PLANCK

After leaving the Robot Room, Lehrach – who has dark brown eyes under a shaggy mop of dark hair, graying at the temples, and wears a gray sweater that gives him a faintly scruffy air – drops in on a Monday morning seminar on the ground floor of the building. Roughly 20 scientists from the Department of Vertebrate Genomics are gathered in the darkened room for the weekly catch-up.

Standing at the front, Konthur is bringing his colleagues up to speed on a couple of projects – his group's latest efforts to build a library of phage display-derived antibodies, and their related work identifying autoantigens in rheumatoid arthritis, celiac disease, and Graves disease. Konthur, a youthful looking 11-year veteran of the institute with a goatee and laughter lines around his eyes, finishes his talk with a casual reminder that anyone is welcome to make use of the antibodies he's generated so far, and opens the floor to questions.

The first comes from Lehrach in the front row. "Do you have any autoantibodies for tumors?" he asks. At first, Lehrach's question seems off-topic, but the discussion evolves quickly. "Yes ... well, actually there are reports in the literature of autoantibodies



The Robot Room

The making of Max Planck

In 1945, the Kaiser Wilhelm Society, Germany's premier science research institution, was in tatters. It was even at risk of being axed after the Second World War, but leading German scientists convinced the allies to rebuild and rebrand the renowned research organization. So an 86-year-old Max Planck once again assumed the presidency, after the Nazi regime forced him from the post in 1937. As part of the society's makeover, Planck, the founder of quantum theory, offered his own name. In 1946, he served as the first honorary president of the Max Planck Society (MPS) during its early development in postwar Germany's British zone.

Planck, however, passed away less than a year before the society's first official meeting in February 1948 in Göttingen. At that time, his eponymous society comprised only 25 small institutes with a combined budget of around \$5-6 million (about \$50 million in today's currency). Nowadays, the





from patients with cancer,” Konthur says. It’s a typical interchange in an institute where having a direct impact on human diseases such as cancer is considered central to the scientific mission.

Later, in his office, Konthur explains that his group’s work is almost all about antibodies and phage display. “We basically focus everything around the use of a single technology and apply it to as many problems as possible,” he says.

The group has pioneered the combination of selection techniques such as phage display and robotics to generate human recombinant single-chain antibody fragments.⁴ It’s work that his institute colleagues find useful, as demonstrated by the roughly half-dozen collaborations he has underway, including one with Sylvia Krobitch and her team, who are trying to decipher the molecular pathways involved in neurodegenerative disorders.

Meanwhile, Konthur says, he is part of the German national “Antibody Factory” initiative and a European collaboration known as ProteomeBinders, a consortium that aims to build a comprehensive resource of affinity reagents such as antibodies, to facilitate analysis of the human proteome.⁵

MPS encompasses 75 institutes in Germany, with a budget of more than \$2 billion, and around 4,000 permanent scientists, 8,000 support staff, and 9,000 students, postdocs, and guest scientists. Over those 60 years, MPS scientists have been awarded 17 Nobel Prizes, and the society has grown to become the top ranking nonuniversity institution in the world for science research, according to the 2006 *Times Higher Education Supplement*.

How did it get there? First, the MPS was instrumental in rebuilding postwar Germany at a time when much of the

beginning, the MPS safeguarded its autonomy to pursue questions of basic science.

Today, the German federal and state governments finance more than 80% of the society’s budget, but the founding statutes stipulate that the MPS “is an association of free research institutes, which belong neither to the state nor to industry.” Germany’s postindustrial, knowledge-based economy is now one of the largest in Europe, thanks in part to the MPS.

Some of the most notable discoveries to come out of the MPS’s model include: Feodor Lynen of the Institute for Biochemistry deduced the cholesterol and fatty acid metabolism pathway in the 1950’s; Georges Köhler of the Institute for Immunobiology invented monoclonal antibodies in 1974;

Christiane Nüsslein-Volhard at the Institute for Developmental Biology pioneered the study of mutagenesis in *Drosophila* embryos in 1980; and Erwin Neher and Bert Sakmann at the Institute of Biophysical Chemistry proved the existence of single-ion channels in 1974 (see p. 84 for related story).

But the MPS is not without its darker side as well. In 1999, then-president Hubert

Markl launched a six-year, \$5 million independent inquiry into the society’s support of the Nazi regime’s policies. The inquiry found that scientists at Kaiser Wilhelm institutes used samples and slave labor from concentration camp victims, helped develop Nazi weaponry, and plundered Soviet seed banks during the war. It also indicated that the Nobel-Prize winning biochemist Adolf Butenandt, who served as MPS president from 1960 to 1972, knew that scientists at his Institute for Biochemistry used blood samples from Auschwitz victims. Markl issued a formal apology to the victims of Nazi war atrocities in 2001.

Now, the MPS is looking forward. “Internationalization is a crucial principle today,” says Wirsing. The society already has three non-German institutes, one in Holland and two in Italy, and is looking to expand even farther. The first non-European institute in development is a bioimaging center planned for Florida, and Wirsing says the MPS is looking into options in India and China. But after 60 years of scientific excellence, getting old is on the mind, and the MPS’s newest institute is planned for closer to home. In September, the Max Planck Institute for the Biology of Aging will open in Cologne.

—Elie Dolgin

The MPS was instrumental in rebuilding postwar Germany at a time when much of the country’s infrastructure was destroyed.

country’s infrastructure was destroyed, says Bernd Wirsing, chief MPS spokesperson. “The universities at that point were not able to provide what government and business needed, which was technological and industrial progress,” he says. However, the MPS did not pander to industry and the government. The Nazi era highlighted the political threat to freedom of research, so from the

Downstairs from Konthur's first-floor office, the data being churned out by the successors of Lehrach's machines is being used by Herrmann and his group to understand the systems biology of development. "We want to explain what a phenotype means," says Herrmann, a serious man with a sparse corona of grey hair. "I decided more than 10 years ago that we needed to do genome-wide analysis of gene expression. We want to know how the wild-type organism is producing a [mammalian] trunk."

To this end, his group uses large-scale analysis platforms to probe the gene regulatory network that controls the development of the trunk, including segmentation and somite formation.

Among the genes already identified using these methods is *Axin2*, an inhibitor of the Wnt/beta-catenin signaling pathway.⁶

In a small microscopy room nearby, Lars Wittler, who leads a group in Herrmann's department, is beginning an experiment to try and understand the major players in the process of trunk development. Raising his eyes to the eyepiece, gloved hands carefully holding a tungsten wire needle in his hands, he begins dissecting parts of a mouse embryo that are important for organization of the organism.

"The idea is to find novel factors important for the different stem cell populations in the organizer region," he says, carefully manipulating the needle into position, "that is, for those stem cells that are located in the posterior organizer or anterior primitive streak and give rise to the paraxial mesoderm and therefore to the somite progenitor cells."

To do this, he needs to isolate the crucial parts responsible for organization in the mouse embryo, then sequence them using the institute's Solexa instrument, which will produce the whole transcriptome for that part of the organism. But the structures are tiny, and the dissection process is painstaking. "It's the first time I've done this sort of thing, and it's not as easy as I first thought," Wittler says resignedly.

The independent research group that Stefan Mundlos leads is working on related areas, focusing on the molecular mechanisms that regulate form and structure of the skeleton during vertebrate development. It's work that has led them to study congenital hand abnormalities, cystic renal disease⁷ and Marfan syndrome,⁸ and has impressed collaborators.

"This is an excellent group investigating the regulatory networks of genes in a very systematic way."

—Gudrun Rappold

Lars Wittler

"This is an excellent group investigating the regulatory networks of genes in a very systematic way," says Gudrun Rappold, from the Institute for Human Genetics at the University Clinic Heidelberg.

Researchers who come to Berlin, either from other parts of Germany or from overseas, find the city expensive, but stimulating, says Nathalie Veron, a PhD student originally from Freiburg, a city close to the French border. "Berlin is certainly a good place to work," she says, "because if there is a machine missing here, there is always another institute that surely has it."



Mouse embryos



"From my point of view, our institute is unique because of its interdisciplinary nature, with a bioinformatics department beside wet-lab departments."

—Silke Sperling

Silke Sperling
and daughter Lola

Tim Hucho, a native Berliner who studies the genetics of chronic pain, agrees. "Berlin is a good situation for collaboration, with the Free University and Charité [hospital] not far away."

Veron, like many of her colleagues, was drawn to the institute partly by the good reputation of the Max Planck Society, and partly by the caliber of the senior researchers. "There's lots of competition for places because it has well known names," she says.

Another benefit is the ability to do interdisciplinary work, says Silke Sperling, who is studying the genetics of cardiac development. "From my point of view, our institute is unique because of its interdisciplinary nature, with a bioinformatics department beside wet-lab departments," says Sperling, who arrived at the institute in 2000 after training as a cardiologist, bringing with her a collection of samples of cardiac tissue from children she had treated.

"I was always interested in cardiac development and spent 18 months working in pediatric cardiology in Berlin," she explains. After doing a PhD in cardiac physiology, she found herself struggling to explain the molecular basis of what she was observing. It seemed sensible to do molecular research," she says, so after stints at the Max Delbrück Center for Molecular Medicine and the Free University, both in Berlin, she made her way to Lehrach's vertebrate genetics group. "I thought Hans would give me the support and freedom to do what I wanted," she says. Using her cardiac samples, her multidisciplinary team employs expression-profiling microarrays and other techniques to study the mechanisms of normal and abnormal heart development.

In April, the Sperling team published the results of its integrative approach, analyzing the transcription levels of 42 genes from cardiac biopsies of 190 patients and healthy individuals, then correlating them with a detailed phenotypic description of the heart malformations. It's

work that is leading to a better understanding of the mechanisms underlying some of the most common birth defects in humans.⁹

Sitting in his office at the end of the day, Hans Lehrach suggests that the institute's researchers are united by a common focus on making a difference to human health. "There's a spirit [that] is very universal," he says. "There's a strong emphasis on diseases and real-world problems, and of development as a complex problem."

Any incremental improvement of a real-world problem is important, he says, leaning in for emphasis. "If we can develop predictive models that extend the lifespan for 10% of cancer patients, for example, then that is more important than any number of high-impact papers." ■

Have a comment? E-mail us at mail@the-scientist.com

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