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news&notes

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Library of Medicine Web site profiles Rockefeller DNA pioneer Avery

The National Library of Medicine (NLM) recently launched a new Web site called Profiles in Science that allows Internet users access to the articles, unpublished writings, letters and lab notes of great scientists. The first scientist to be featured on the new site is Oswald Avery (1877-1955), who, along with Professor Emeritus Maclyn McCarty and Colin MacLeod first identified DNA as the substance of genes in 1944. NLM Director Don Lindberg calls this research, which was performed at the Rockefeller Institute, "the single most critical discovery in the history of modern genetics."

Professor Emeritus and former RU President Joshua Lederberg gathered and edited Avery's previously dispersed writings for the new "electronic museum." He had been collecting material about the scientist since the early 1970s, so when Lindberg called him to discuss the idea of the new NLM Web site, Lederberg suggested that Avery be the prototype. Although the discovery of

COURTESY OF THE ROCKEFELLER UNIVERSITY ARCHIVES

Oswald Avery, above, spent most of his career at Rockefeller, where he, McCarty and MacLeod identified DNA as the genetic material in 1944.

DNA is the basis of molecular biology, Avery's research has been overshadowed by that of later scientists, such as Francis Crick, James Watson and Maurice Wilkins, who won the Nobel Prize for discovering the structure of DNA.

According to Lederberg, many of today's leading scientists credit Avery with influencing their work, "but not so many people have actually read the astute discussions about how such a weird idea that DNA is the genetic material could be corroborated." Lederberg and the NLM want this new Web site to make the Avery lab's contribution better known. The site is for everybody, from historians to high-school students. Lederberg also hopes that graduate students and postdocs will take time from their daily experiments to look into the origins of their work.

"Avery was such an important figure in the history of the institution," he says, "and his work with McCarty represents the best in how science is done. They represent the spirit of this institution so well. I think it's a great thing for RU that the library made this the centerpiece of the new electronic museum."

The Profiles in Science Web address is http://www.profiles.nlm.nih.gov.

Computational Biology

Theresa Gaasterland joins RU as head of lab

Theresa Gaasterland, a new assistant professor and head of lab at RU, has a Ph.D. in computer science, but a decidedly biological bent.

"I'm a hybrid," she says. "Since finishing my Ph.D., I have undergone a metamorphosis from computer scientist to someone focusing first on biological problems and then on how to design computational approaches to address those problems."

Gaasterland's research focuses on designing and developing computational methods to handle the huge amount of data being generated by genome sequencing projects. In collaboration with sequencing groups in the United States, Canada and Europe, she created and spent several years refining a system called MAGPIE (Multipurpose Automated Genome Project Investigation Environment) to analyze data in real time and beyond the lifetime of a sequencing project. In her laboratory here at RU, she hopes to combine artificial intelligence and database search engines to make this data accessible to scientists and to drive the construction of logical models of organisms. Her goal is to create models that will, in turn,

New RU Assistant Professor Theresa Gaasterland applies computer science to biological problems.

lead to better drug targets for pathogenic organisms, improved understanding of genomic regions associated with human disease and deeper insight into the evolution of biochemical pathways.

Getting computers to make sense to people has long been Gaasterland's goal. She first became interested in artificial intelligence during her senior year at Duke University, where she received her B.A. in 1984. As a graduate student at the University of Maryland, she focused on how to make computers emulate human reasoning.

"A computer can put together an answer, and it's encoded in logic," she explains, "but non-computer scientists shouldn't have to learn the logic. People seek a natural language, so I really wanted to get that answer as close as I could to what a person would think of as an answer. My particular focus was to get the computer to explain why a question fails to have an answer." The problem was interesting, but Gaasterland became restless writing test programs to answer questions about travel and gardening databases. "These examples were so limited, and I wanted to make what I was doing in computer science have an impact on the world beyond just my logic-programming and database colleagues."

Her desire to "make a difference" led her to turn down five tenure-track computer science positions after she received her Ph.D. in 1992. Gaasterland had always been interested in medicine and biological systems, so when she heard about a Department of Energy postdoctoral program for computer scientists, she applied to the program through the Argonne National Laboratory. Although the fellowship paid less and was less secure, it was a chance to apply her work to a field "in a way that actually helped people in that field do something they couldn't do before."

At Argonne, Gaasterland had complete freedom to look for biological problems that could use the help of computer science, and she saw the genome project as "this huge, unsolved computational challenge looming on the horizon." She already knew how to deal with large databases, heterogenous data and human-computer interfaces, so genome interpretation seemed like the meaningful application she had been seeking.

For two years she talked to biologists and tried to translate their thinking into logic the computer could under-

see **MAGPIE**, page 3

FRIDAY LECTURE

Neuroscientist to discuss cerebral cortex development

Chris A. Walsh, associate professor of neurology at Beth Israel Deaconess Medical Center, will discuss "Genes That are Essential for Normal Cerebral Cortical Architecture in Mice and Humans" at the Friday lecture today (Oct. 2).

Walsh's research focuses on the cellular and genetic mechanisms of development of the cerebral cortex, the largest structure of the mammalian brain and the structure that is responsible for all of our uniquely human cognitive activities. The cortex represents a folded sheet of neurons that forms a wrapping around the outside of the brain. The cortex is a good system for studying neuronal development, because there are known mutations that systematically disrupt its development. In humans, abnormal development of the cortex is associated with mental retardation and other cognitive problems and seizures.

Previous and ongoing work in Walsh's lab uses libraries of retroviral vectors to define the lineage of cerebral cortical cells, i.e., the sequence and patterns of mitoses leading from undifferentiated progenitors to post-mitotic cells. Cortical lineage patterns form the framework in which the functions of cloned genes are being analyzed using molecular biological techniques and gene expression vectors. Walsh and his colleagues recently genetically mapped and cloned the gene for a mouse disorder in which the cortex is turned upside down. They also cloned the gene responsible for a human disorder, called double cortex, in which the normal cortex is divided into two structures, as well as another human disorder associated with mental retardation.

Walsh received a doctoral degree in 1983 and a medical degree in 1985, both from the University of Chicago. From 1985 to 1989, he was an intern in medicine and a resident in neurology at Massachusetts General Hospital (MGH), and from 1989 to 1992 he was a clinical and research fellow at MGH and Harvard

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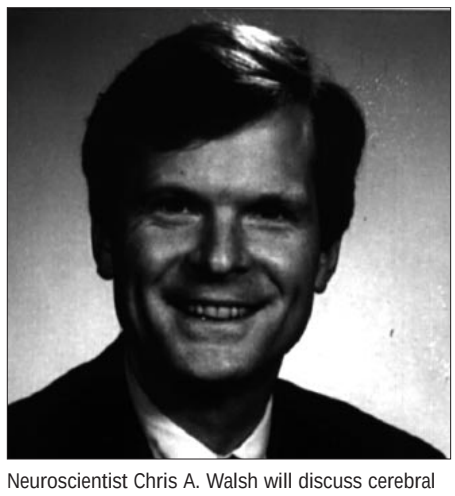

COURTESY OF CHRIS A. WALSH

Neuroscientist Chris A. Walsh will discuss cerebral cortex development at the Friday lecture today.

Diamond Center AIDS researchers receive grant

RU Professor David Ho is the scientific director of the Aaron Diamond AIDS Research Center.

The Aaron Diamond AIDS Research Center at RU and Columbia University jointly received a $1.3 million Centers for AIDS Research (CFAR) Award this year from the National Institute of Allergy and Infectious Diseases. The 1998 CFAR grants, which distributed more than $13 million to twelve recipients, also provide three to five years of continued support for AIDS research centers. The Columbia-Aaron Diamond Center grant will total $7.2 million between now and 2003.

The project director is David D. Ho, a professor at RU and the scientific director of its affiliated Aaron Diamond AIDS Research Center. According to Ho, the CFAR grant "is an incredible resource that will provide solid infrastructure support for the AIDS research and core facilities. In addition, CFAR will aid the development of our younger scientists and help fund an impressive AIDS seminar series. We are very happy to have forged this collaboration with Columbia."

The dozen institutions receiving the CFAR grants will become part of a network that encourages collaboration and enables the different centers to pool equipment and expertise. The centers are also committed to addressing the concerns of minority communities, where AIDS is of particular concern; they explore ways to increase the number of minority scientists in AIDS research and to deal with the problems of enrolling and retaining women and minorities in clinical trials.

The Diamond Center, the world's largest private HIV/AIDS research center, signed a cooperative agreement with Rockefeller University in 1996. Since 1995, scientists from the center have conducted inpatient and outpatient studies of HIV/AIDS at the RU Hospital. Ho's HIV research led to the design of multiple-drug treatment strategies that have, in recent studies, reduced the virus to undetectable levels in certain patients.

Potpourri

Are you…

Musical?

The Choral Symphony Society is looking for new members to perform J.S. Bach's *Christmas Oratio*. This small chamber choir rehearses on campus on Tuesday nights and performs in New York City. For more information about joining the group, call David Labowitz at 864-7541.

The music room on the first floor of Caspary Hall is available for use. The room, equipped with a Steinway grand piano, music stands and chairs, may be reserved for time slots of one hour during the day or evening. A sign-up sheet is available on the door outside the music room.

Artistic?

The eighth Medical Complex Art Show is looking for entries. All members of the RU community are eligible to submit six slides or photographs of their paintings, sculpture, ceramics, computer-generated art, photograph, or handicrafts. Send your entries by Fri., Oct. 9 to Helen-Ann Brown, C-115, Cornell Medical Library, 1300 York Avenue. Call 746-6092 for more information.

Literary?

If you have recently published a book, *News&Notes* would like to know about it. Please send your publication particulars, along with a brief summary of the book, to Lisa Stillman at Box 68 or fax x7876.

Cancer screening

The Employee Health Office is offering all men in the RU community a free screening for prostate cancer, the most common type of cancer in American men and one that rarely has any symptoms in the early stages. The screening program, which runs until Tues., Nov. 17, consists of a blood test to determine levels of prostate specific antigen (PSA); a follow-up physical examination will also be offered on Wed., Nov. 18.

Who is at risk? The American Cancer Society recommends annual PSA screening for all men over age 50; in addition, African American men and men with two or more first-degree relatives (father, brother or son) with prostate cancer should be tested annually after age 45. Please call the Employee Health Office at x8414 for more information.

New RU events hotline

Trying to find information about an upcoming event at RU? The university has a new phone number with information about RU events, including the Peggy Rockefeller Concerts, Tri-institutional Noon Recitals, public lectures and symposia, along with directions to the campus. Call x7007.

Visa lottery

The Department of State will award immigrant visas to 50,000 winners of a visa lottery. The filing period runs from noon Thurs., Oct. 1 through noon Sat., Oct. 31. For detailed information about the lottery, please visit the Office of Human Resources, Founder's Hall 103.

Around Campus

Sharisse Brown: Rockefeller Housing's "welcome wagon"

The Scholar's Residence, above, is one of RU's high-rise housing options. Sharisse Brown, leasing coordinator of the Housing Management Office, helps university newcomers find and settle into their new homes.

One of the foremost concerns among new postdoctoral fellows and faculty members is choosing a place to live within the university's off-campus housing. Sharisse Brown heads the Housing Management Office's leasing process and may be the first person many newcomers get to know besides their lab head. She orients them to the community and matches their needs with the available apartments within the eight off-campus buildings the university offers, stretching from East 62nd Street to East 84th Street.

Faculty members and postdocs come from all over the world, so Brown's job often begins with a long-distance exchange of information. Even people from other parts of the United States may be visiting New York City for the first time. Regardless of where newcomers are from, though, the majority of them have never had the experience of "high-rise living" before.

From her desk in the Housing Management Office, Brown guides newcomers through their options among buildings ranging from Faculty House, the Scholar's Residence and Sutton Terrace to the northern residences located at 220 East 70th Street, 325 East 84th Street, and 238 East 81st Street. Her job, though, extends well beyond assigning apartments.

Brown, who has a B.A. in communication from Hunter College, says the key to her success as the university's official "welcome wagon" is that she is a patient listener for new arrivals who often find their first few days on campus an anxious time. "After their first three weeks, I know that they will become immersed in their research and go on to their own life in New York City," Brown says. "But before they settle in, I sometimes function as a temporary best friend."

In addition, Brown and her colleagues in the Housing Office realize the importance of interacting not only with the Rockefeller affiliate but also with his or her family. "I keep toys for kids of all ages close at hand, since I never know just who will come along for a meeting," she says.

To further assist prospective university affiliates, the Housing Office is developing an interactive Web site that will provide information about Rockefeller's residential resources and will also enable applicants to submit their requests at their own convenience, which is especially helpful for those many time zones away. "There are so many people coming from overseas who cannot make trips to tour their future apartment," Brown says, "so the Web site will really help increase their comfort with the housing aspect of their new careers at The Rockefeller University."

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Medical School. He began his academic career at Harvard Medical School in 1992 as an instructor in neurology, rising through the ranks to become associate professor of neurology in 1997. Walsh is also chief of the Division of Neurogenetics at Beth Israel Deaconess Medical Center.

Walsh has received many honors, including the William Randolph Hearst Award and the Clinical Investigator Award from the National Institutes of Health. He was a Klingenstein Foundation Fellow, a Rita Allen Foundation Scholar, a Dana Foundation Fellow in Neuroscience and a Howard Hughes Medical Institute Fellow in Genetics.

The lecture will be held at 3:45 P.M. in Caspary Auditorium and preceded by tea at 3:15 P.M. in Abby Aldrich Rockefeller Lounge. All are welcome.

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Marching in Double-time: Rockefeller geneticist reveals more clues to circadian rhythm

BY JOSEPH BONNER

The body's circadian rhythms control a number of internal functions, including the sleep/wake cycle, stress hormone levels and immune system function. The fruit fly *Drosophila,* long a tool for molecular geneticists, has provided many clues to the regulatory mechanisms that govern circadian rhythms. RU Professor Michael Young, head of the Laboratory of Genetics, has contributed to much of the knowledge of molecular control of circadian rhythms in *Drosophila*. In a pair of papers that were the cover story of the July 10 issue of the journal *Cell,* Young and his colleagues identified a new gene in the fruit fly called *double-time* (*dbt*), which provides more details about the workings of the molecular clock.

Scientists began to answer some of the questions about circadian regulation in the early 1970s, when Ron Konopka and Seymour Benzer, at the California Institute of Technology, discovered a gene in the fruit fly called *period* (*per*), the first of several genes that would eventually be linked to the regulation of biological clocks. Both fruit flies and humans have activity rhythms that adapt perfectly to a 24-hour cycle of night and day, but the researchers showed that *per* mutants changed the fly's 24-hour body clock in one of three ways: by increasing the circadian cycle to 30 hours, decreasing it to 19 hours or abolishing it altogether. In 1984, Young and his co-workers, Rob Jackson and Thaddeus Bargiello, cloned the *per* gene, and soon showed that the 19 and 30 hour mutations altered the structure of a protein, PER. Rhythmless mutants had lost the ability to make PER. Recently several laboratories have found human versions of the *period* gene that are active in clock cells of the brain.

In 1994, Young's laboratory identified a new circadian rhythm gene called *timeless (tim)*. Mutations of *tim* also produced fast or slow clocks, or arrhythmia. By 1995, Young and his colleagues were able to show that the fly circadian rhythm requires both genes because of an essential pairing of the PER and TIM proteins. All cells of the fly have *per* and *tim* genes, but the brain cells set the body clock. PER and TIM proteins accumulate in the nuclei of light-sensitive eye cells, called photoreceptors, as well as pacemaker cells of the central brain.

Professor Michael Young, with members of his laboratory, identified a new gene called *double-time,* which delays the formation of the protein complexes that drive circadian rhythms in the fruit fly.

Brother, can you spare a dimer?

The fly circadian cycle begins around noon, when the *per* and *tim* genes become active, making RNA (molecules needed to create the PER and TIM proteins), but only after sunset does the accumulated RNA prompt the cell to stockpile the PER and TIM proteins.

At night, the proteins pair in the cytoplasm, forming a molecular partnership called a dimer, and then migrate into the nucleus, home to the cells' genetic material. This movement to the nucleus is what signals the *per* and *tim* genes to stop making RNA and, hence, new PER and TIM proteins. Near dawn, the old PER/TIM protein pairs disintegrate. With the proteins depleted, the *per* and *tim* genes begin to make RNA again by midday. The pace of the clock is set by a time lag: while the *per* and *tim* genes are freed to make RNA early in the day, PER and TIM protein pairs form at night.

Previous work by Young's laboratory hinted that this delay was caused by the late arrival of one of the two protein partners, PER. During the investigation of *tim,* Young noticed that if a fly had a mutation in *per* that destroyed its ability to make PER protein, TIM protein would accumulate to high levels and remain in the cytoplasm because it did not have a partner to enter the nucleus.

When the experiment was performed the other way round—with a mutation in *tim* that makes it impossible to make TIM protein — PER proteins did not accumulate even though *per* RNA levels increased.

Leslie Vosshall, a former graduate fellow in Young's lab, did experiments in which much of the PER protein was removed and replaced with an unrelated marker protein. Now when TIM protein was removed, the RNA levels increased, and the modified PER protein began to accumulate to high levels.

"This suggested that the per RNA was translatable in the absence of TIM, but the protein being made does not stick around," says Young. "We postulated that there was some activity that was killing PER protein, even as the RNAs for PER and TIM were rising."

What makes a clock a clock?

Young says that these results were mirrored in experiments that investigated the light responsiveness of *per* and *tim*. The researchers found that light degrades TIM protein, causing the flies' clocks to reset. In addition, once TIM disappeared, PER rapidly went away also, suggesting that TIM was acting as a protector of the PER proteins that are gathering in the cytoplasm.

"It seems that an important element in this system—one that creates a long delay and really makes this a clock—is an activity that is holding PER protein down while RNA levels for both PER and TIM go up," says Young, "until there is so much TIM protein in the system that TIM proteins can grab onto newly translated PER proteins before they are destroyed by that activity."

"We've always realized," he continues, "that there had to be some kind of a delay between the time *per* and *tim* RNAs are made and the time the proteins they encode finally get back into the nucleus in order to have an oscillation within this molecular mechanism."

So Young and his co-workers had made two key observations: First, it takes time to get these two proteins together, and pairing is needed to get them back into the nucleus. Second, an activity is delaying the ability to make these dimers by eliminating one of the two partners as it is made until the stable partner is so overwhelmingly abundant in the cell that it can form that partnership rapidly after the unstable partner is made.

That activity, says Young, is the *dbt* gene.

Regulating the hands of time

Young and co-workers named the new gene *double-time* because their first mutation produced an 18 hour clock, among the fastest to be uncovered in a mutant fly. They later found more *dbt* mutants. A second mutation slows down the fly's clock, to about 28 hours. The third mutant blocks the circadian cycle altogether. This last mutant, which lacks the protein product of the *dbt* gene, provided the clues to deciphering the mechanism behind the circadian oscillations.

The researchers found that, in the mutants lacking DBT protein, very high levels of PER protein accumulate in the cytoplasm; these PER proteins no longer disintegrate when not paired with TIM, meaning that both PER and TIM proteins are produced at the same time. Without the usual time lag, PER and TIM can pair and move into the nucleus prematurely.

"In other words, the *double-time* gene regulates the buildup of PER protein in the cell. This determines the time it takes to complete the cycle, or whether there is any cycle at all," says Young. "Without *double-time,* you won't get a clock," he continues. "In the presence of *double-time,* you have a mechanism that produces about a 10 hour delay in the formation of the TIM/PER complexes."

Young and his co-workers cloned the *dbt* gene and found that it produced a kinase, a protein that phosphorylates, or places phosphate molecules on, other proteins. Scientists have known for some time that PER proteins are phosphorylated with a rhythm. In the *dbt* mutants, however, PER proteins are overproduced and there is little or no phosphorylation.

The scientists then asked, "Do these two proteins — PER and DBT — ever get together?" The answer is yes. They found that PER and DBT proteins physically make contact with one another in *Drosophila* cells.

"We think that the way *double-time* regulates this cycle is to hold down the rate of accumulation of PER protein by phosphorylating it as soon as it is made," says Young. "Phosphorylation is often a mark put on a protein that labels it for degradation. Because the *double-time* (DBT) protein is made constantly, unlike TIM and PER, the only way for PER to survive is for TIM to come in and rescue it by attaching to it."

Young thinks that the partnership between PER and TIM either prevents a phosphorylation event that causes the instability of PER, or prevents destruction of PER even if it is phosphorylated. Future work will attempt to determine the role of the PER/TIM partnership. Either way, says Young, TIM becomes a protector of PER under these conditions.

"If this is the case, an enormous amount of TIM must be present to finally capture PER before it is destroyed by this regulatory scheme that *double-time* imposes," he says.

Young directs the National Science Foundation (NSF) Science and Technology Center for Biological Timing at Rockefeller. The work was supported by NSF and by the National Institute of General Medical Sciences and the National Institute of Mental Health, both part of the federal government's National Institutes of Health.

MAGPIE, continued from page 1

stand. But the early sequencing data she was getting were so riddled with errors that she considered just walking away from the project after her two-year fellowship ended in 1994. Then she met Christoph Sensen, of the Canadian National Research Council, who was sequencing *Sulfolobus solfataricus* at a rate of one error in 10,000 base pairs. Gaasterland realized that if he could give her data of that quality, she could test her software. So again, she turned down a safe, tenure-track position in computer science and started collaborating with Sensen in Canada. For the next two years, from 1995 to 1997, the pair worked to define what it meant to take an emerging genome as input, annotate the sequence data and create a picture of the organism based on the genomic data. During this time, Gaasterland held a joint appointment at Argonne and the University of Chicago, where she designed two courses that combined database design, advanced data architectures and genomic analysis.

Once MAGPIE was stable, Gaasterland started trying to enter and compare multiple genomes. "The general idea is to take the genomes of certain organisms and use them to have a deeper understanding of other organisms."

When a biologist explains a problem to her, the two of them can work together to create a query that the computer can understand; then Gaasterland can use her expertise to make the computer give a comprehensible answer. One of her main motivations in coming to RU was the university's commitment to computational biology as a serious research endeavor (she notes that Andrej Šali's research here "was a major plus"). After one of her interviews at RU, she left with 10 different problems people had given her, so she knew that the lab heads "were genuinely interested in how computation could be integrated into what they are doing."

As someone persuing interdisciplinary research, Gaasterland also likes the idea of being in an academic setting without formal departments. In her laboratory here, she hopes to mix computer scientists with biological interests and biology students with computational interests. Her goal is to make them "masters of both genres."