

Immunity in action

Rockefeller scientists capture the first-ever live images of immune system dendritic cells at work

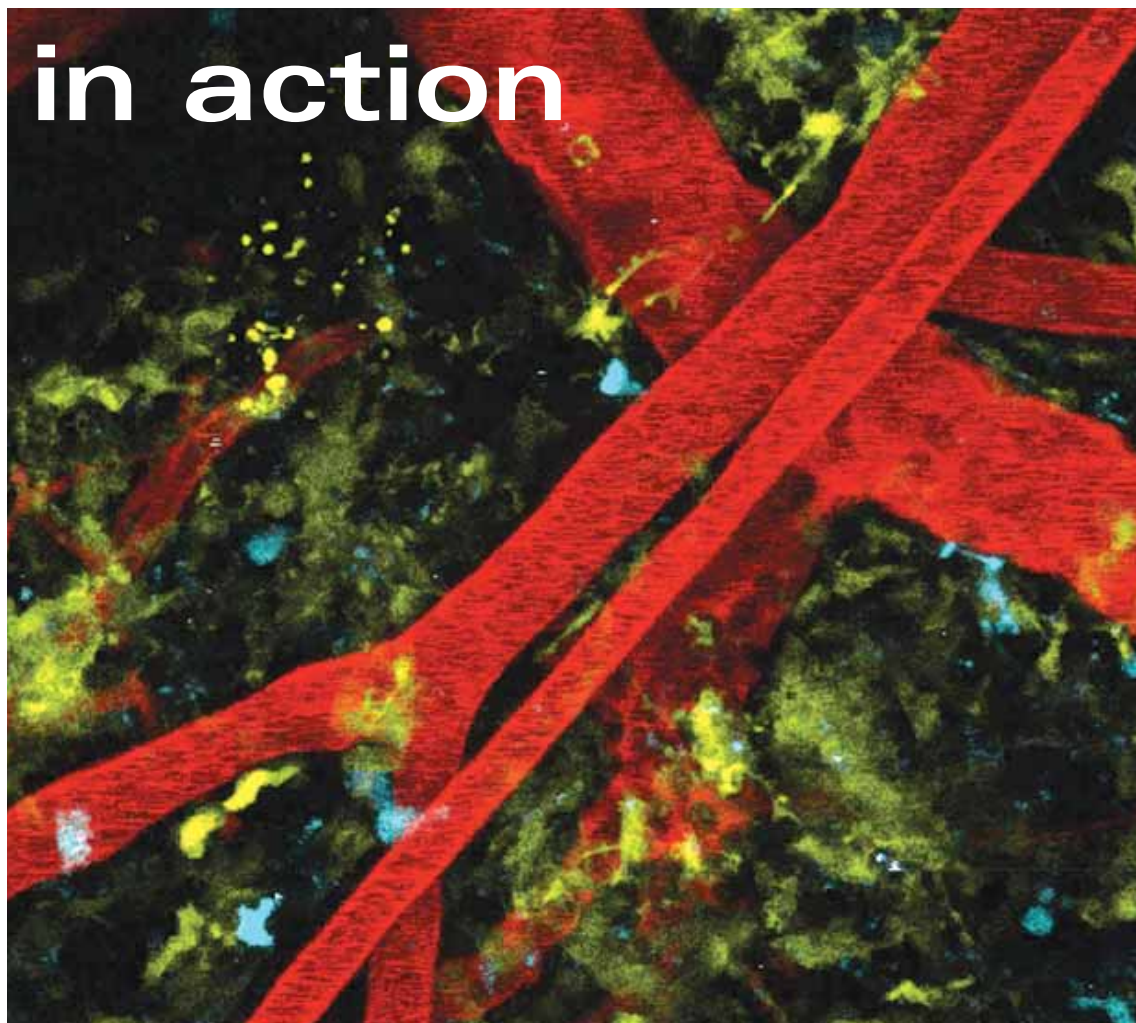
BY LYNN LOVE

If the immune system is an army, the lymph nodes are its field command centers. Located at pivotal traffic points throughout the body, they coordinate information sent back from immune system cells that circulate along the body's periphery.

Now, in a series of experiments that has caused scientists to rethink some of their basic beliefs about how the cells of the immune system communicate with one another, Rockefeller's **Michel Nussenzweig**, along with Michael Dustin of NYU Medical School, and colleagues have used genetic techniques and fluorescent microscopy to penetrate deep inside lymph nodes and visualize the activities of specialized components of the immune system called dendritic cells.

The work, which was published in the December issue of *Nature Immunology*, provides the research community's first view, in real time, of the live actions of a network of dendritic cells that spend their entire lifespan inside the body's lymph nodes.

Dendritic cells were discovered by Rockefeller scientists Ralph Steinman and Zanvil Cohn in 1973, and they play a special role in protecting the body from microbes and other potential threats, such as cancerous tumors. The dendritic cells' long, spindly arms extend and retract in order to detect antigens. Once foreign material, or antigens, are detected, dendritic cells migrating throughout the body typically travel to the lymph nodes to use those same spindly arms, called



Control room. A combination of stationary and migratory dendritic cells (yellow) form a vast, seemingly coordinated system and likely vary their behavior depending on their location, based on recent studies in mouse lymph nodes.

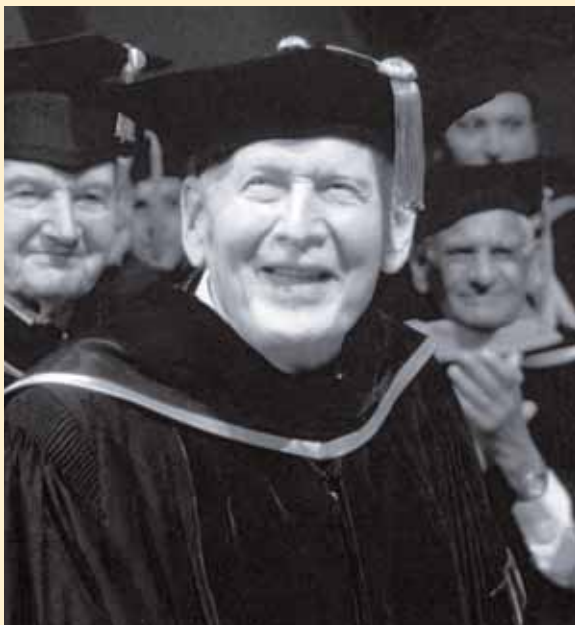
processes, to inform other immune cells, the white blood cells called T and B cells, to take action.

But in addition to migratory dendritic cells, scientists now say there's a network of dendritic cells that never leave the lymph nodes, and serve primarily to teach T and B cells what the body's own tissues look like so that they will be safe in the event of an immune system emergency.

To visualize these stationary dendritic cells, the research team created laboratory mice genetically modified so that their dendritic cells produce a yellow fluorescent

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Remembering Mac McCarty



Maclyn McCarty, who died this month at 93, was one of three Rockefeller scientists who discovered in the 1940s that DNA is responsible for carrying genetic information, a finding that has been called "the pivotal discovery of twentieth century biology." For more on McCarty, visit www.rockefeller.edu/scientist.

The alcoholic brain

Rockefeller scientists find that a familiar protein, tPA, plays a role in both alcohol dependence and symptoms of withdrawal

BY BETSY HANSON

For alcoholics, quitting drinking sometimes comes with fatal consequences.

About five percent of alcoholics experience delirium tremens during withdrawal — a disorder characterized by tremors, seizures and hallucinations. Actor Ray Milland made the DTs famous in his gritty, Academy Award-winning 1945 performance in *The Lost Weekend*.

But what Milland didn't know was that the seizures occur because heavy consumption of alcohol — or ethanol, the addictive component of beer, wine and liquor — changes the brain. These changes allow an alcoholic to develop tolerance to ethanol, but they also trigger the DTs when he abruptly stops drinking.

Now Rockefeller University scientists, in experiments with mice, have discovered a protein that

regulates the seizures induced by ethanol withdrawal. The protein, called tissue plasminogen activator, or tPA, is the same factor that dissolves the blood clots that can trigger heart attacks and strokes.

"We have found that tPA's interactions with certain brain receptors contribute to the development of physical dependence on ethanol," says **Sidney Strickland**, who directs Rockefeller's Laboratory of Neurobiology and Genetics. "Our new findings imply that interfering with these interactions, with a drug for example, might protect against alcohol-withdrawal pathologies in the brain." The study appears in the January 4 issue of *Proceedings of the National Academy of Sciences*.

Consuming alcohol slows down the transmission of chemical messages in the brain. Ethanol molecules sit in a receptor known as the NMDA

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The Rockefeller University
1230 York Avenue
New York, NY 10021

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To learn to sing, choose a strategy

Baby songbirds and human infants learn sounds in similar ways

BY BETSY HANSON

As a young bird learns to sing, soft burbling gradually gives way to a crisp, distinct song. It's a process that takes weeks of study and practice.

Wan-Chun Liu, a postdoc in **Fernando Nottebohm's** Rockefeller lab, wants to know just how songbirds learn to chirp, whistle and trill. The birds, he says, may teach us a thing or two about how human infants learn, as well.

"Until now, no one has thought a lot about birds' learning strategies," says Nottebohm. "How, starting from their earliest food-begging calls, do they piece together a perfect song?"

The answer, according to new research from Nottebohm's laboratory, may depend on the birds' siblings. In the first study to analyze song-learning with birds kept in family groups, rather than isolation chambers, Liu and Nottebohm have found that zebra finch brothers take different approaches to learning the same song. Some finches focus on perfecting individual song "syllables," while others practice longer patterns called motifs. "The siblings try to avoid each other's style of song learning," says Liu.

Of all the world's animals, only humans, some kinds of birds and perhaps some porpoises and whales learn the sounds they use to communicate with each other through a process of listening, imitation and practice. Other animals, including nonhuman primates, develop vocalizations instinctually, without imitating a model.

Zebra finches are native to Australia, and are highly social birds that breed in colonies of up to several hundred pairs. Adult male zebra finches sing a single song, a roughly one-second mixture of scratchy and nasal sounds clustered into several distinct syllables. "It's very brief and unassuming and not particularly musical, but practical to quantify," says Nottebohm. A young bird learns its song by imitating his father or other adult males, often copying different parts of the song from different adults.

To understand how the learning process works, Liu and Nottebohm studied 37 young male zebra finches from 15 clutches. The birds were kept in cages that they shared with their parents and siblings.

Liu observed the birds and recorded them on tape for as much as seven hours a day. The recorded songs were then analyzed with a computer program that produces a sound spectrogram, a visual representation of the sound that plots frequency over time. This allowed the

researchers to quickly see similarities and differences among the songs.

By the time the birds were 42 days old, two clear strategies of imitation were apparent. About half the birds tended to repeat one song syllable many times; from these repetitions all of the syllables in the adult song eventually emerged. The researchers dubbed this the repetition strategy. The others attempted to sing the entire song motif, with all its different syllables, like their adult model, and did so in a way that was noisy and imprecise. This was the motif strategy. Of the latter birds some included the silent intervals between the different syllables and others joined all the sounds together without interruptions.

The researchers found that finches within each family were likely to choose different strategies. In one group of three siblings, for example, each of three approached the learning process differently even though they all were imitating the same adult song, that of their father.

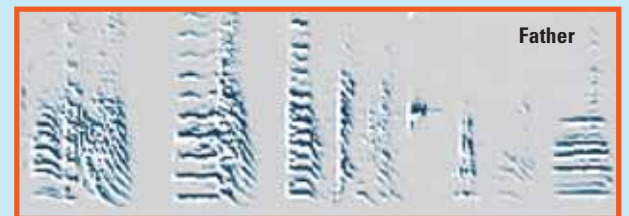
The researchers propose that in a family setting, a young zebra finch chooses a strategy different from that of his siblings, perhaps to better track his own vocal development as he learns the song.

The findings, published in the December 28 issue of *Proceedings of the National Academy of Sciences*, point to a remarkable parallel in vocal learning in infants and some songbirds, according to Nottebohm, who is Dorothea L. Leonhardt Professor and head of the Laboratory of Animal Behavior at Rockefeller.

"In both cases vocal learning seems to be approached as a challenge in problem solving," Nottebohm says. A problem-solving approach may apply to other kinds of sensory motor learning beyond vocal learning, he adds, suggesting that zebra finches may offer further insights into human learning.

Human infants also follow different routes toward mastering the sounds of language, for reasons that remain unknown. Some infants focus at first on repeating individual words and others go through a stage of short, jumbled phrases, mostly unintelligible, with the cadence and inflection of adult speech. Eventually the individual words become clear.

"In both infants and zebra finches vocal learning does not unfold in a pre-set manner, but rather emerges as an



Carrying a tune. Computer-generated spectrograms of the sounds made by two 42-day old zebra finches show the differences between their learning strategies. One sibling repeats the same syllable over and over while the other attempts to tackle the entire five-part motif at once.

exercise in problem solving that leaves much room for external influences and individual learning styles," Nottebohm says. "We're not teaching our zebra finches how to learn their song — how to get there is totally up to the birds."

"I find it amazing that something that infants, with brains weighing approximately 1,000 grams, do over a period of years can be accomplished, perhaps in a similar way, by young songbirds over a period of weeks, with brains weighing just 1 gram," says Nottebohm.

SCIENCE BRIEFS BY BETSY HANSON & KRISTINE KELLY



Dying wishes. Too much of the ced-13 protein leads cells (the enlarged discs in this curled-up roundworm) to self-destruct in greater numbers than normal.

in the development of better tumor-fighting agents. Shaham is head of the Laboratory of Developmental Genetics.

Cell Death and Differentiation, January 12, 2005

Molecular pinch-hitter. Before potassium ions can enter a cell through a channel in the cell's membrane, they must be separated from other ions. The cell achieves this by queuing up the potassium ions in a molecular tube formed from four amino acids. This tube, which acts as a filter, has puzzled scientists because it seems to defy nature: its shape

How cancer cells survive. In mice, the well-studied p53 tumor suppressor gene interacts with two other genes — called PUMA and Noxa — to trigger cell death in response to DNA damage. Researchers in **Shai Shaham's** laboratory have now identified the roundworm equivalent of the mouse Noxa gene, which they've named ced-13. Their experiments in *C. elegans* indicate that ced-13 gene expression or activity depends on p53, and that over-expression of ced-13 increases the number of cells that die, providing additional evidence that the p53 pathway is evolutionarily conserved. The finding has implications for understanding how cancer cells survive attempts to destroy them and may aid

in the development of better tumor-fighting agents. Shaham is head of the Laboratory of Developmental Genetics.

Cell Death and Differentiation, January 12, 2005

Molecular pinch-hitter. Before potassium ions can enter a cell through a channel in the cell's membrane, they must be separated from other ions. The cell achieves this by queuing up the potassium ions in a molecular tube formed from four amino acids. This tube, which acts as a filter, has puzzled scientists because it seems to defy nature: its shape

requires amino acids that are essentially mirror images of each other — left- and right-handed — but the cell only makes "left-handed" amino acids from which to assemble it. Now **Tom Muir** and **Roderick MacKinnon** have shown that the filter works because glycine, one of its amino acids, is ambidextrous. That is, glycine is a surrogate "right-handed" amino acid in the potassium filter. Glycine's being the only natural amino acid that can play this role helps explain why the potassium ion filters of all organisms are identical. Muir is head of the Selma and Lawrence Ruben Laboratory of Synthetic Protein Chemistry; MacKinnon is head of the Laboratory of Molecular Neurobiology and Biophysics.

Proceedings of the National Academy of Sciences, December 7, 2004

Insulin insight. MicroRNAs, which contain just 21 to 23 segments, jam the cell's translation of RNA to protein and, in doing so, regulate biological processes. **Markus Stoffel**, **Thomas Tuschl** and colleagues at three other institutions recently identified a new microRNA that helps control the secretion of insulin. In studies with mouse cells, they showed that the microRNA called miR-375 is found only in the insulin-producing pancreatic "islet cells" and not in other tissues or organs. When they overexposed the cells to miR-375, insulin secretion was suppressed by about 40 percent; too little miR-375, on the other hand, enhanced secretion. The researchers also discovered the gene miR-375 interferes with — the Myotrophin (Mtpn) gene — and

determined that miR-375 acts independently of other factors that affect insulin secretion, such as changes in glucose metabolism. This makes miR-375 a potential target for drugs to treat diabetes. Stoffel is head of the Robert and Harriet Heilbrunn Laboratory of Metabolic Diseases; Tuschl is head of the Laboratory of RNA Molecular Biology.

Nature, November 11, 2004

Drug-defying bugs. New strains of *Staphylococcus aureus* that are resistant to vancomycin, the antibiotic of last resort in bacterial infections that withstand all other drugs, have raised the spectre of untreatable staphylococcal disease. Research led by **Alexander Tomasz** sheds new light on the mechanism of vancomycin resistance in staph as a first step toward finding new ways of controlling these dangerous multi-drug resistant pathogens. Vancomycin kills bacteria by trapping the building blocks of the bacterial cell wall and preventing them from reaching sites where these blocks are linked together to surround the bacterium. Resistant bacteria produce wall building blocks of novel chemical structure, which are not recognized and cannot be trapped by the antibiotic. The Rockefeller scientists identified the bacterial protein, penicillin binding protein (PBP) 2, that is primarily responsible for rerouting these new building blocks in resistant cells for the production of a protective cell wall. The study suggests that selective inhibitors of PBP2 should block vancomycin resistance in staphylococci. Tomasz is head of the Laboratory of Microbiology.

Antimicrobial Agents and Chemotherapy, December 2004

Immunity in action *continued*

protein. The protein, coupled with a microscopic imaging technique that excites the fluorescent molecules with infrared light, creates perfect conditions for studying molecular activity in living systems.

“This imaging study has never been done before,” says co-first author Randall Lindquist, a Rockefeller University graduate student in Nussenzweig’s Laboratory of Molecular Immunology. “All of the other live microscopy experiments looking at dendritic cells in lymph nodes used cells that came from other sources and that were labeled with fluorescent dye.” Lindquist and his colleagues’ imaging technique preserves the immune system’s natural conditions to the fullest extent possible, and most closely represents how the immune system really works.

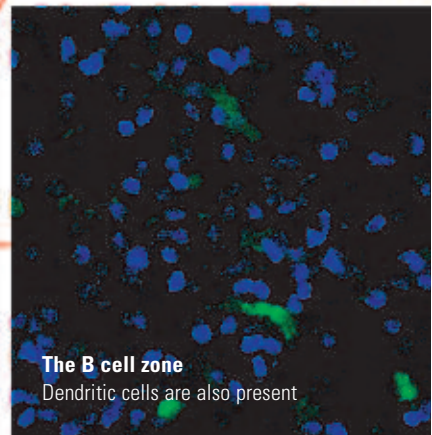
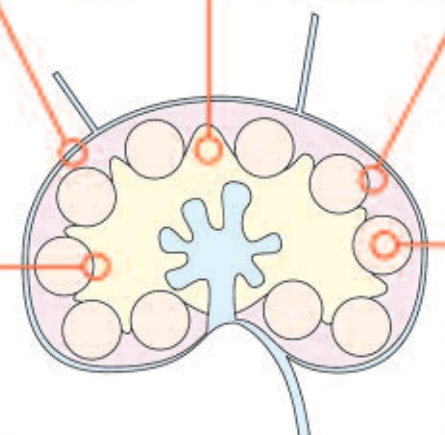
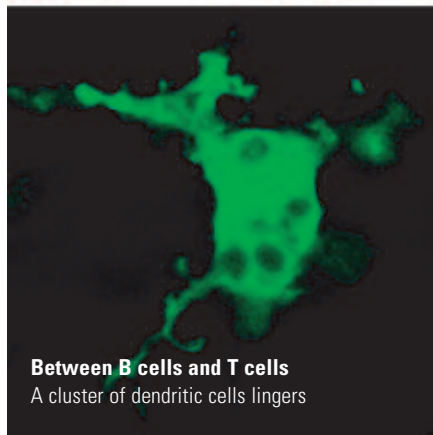
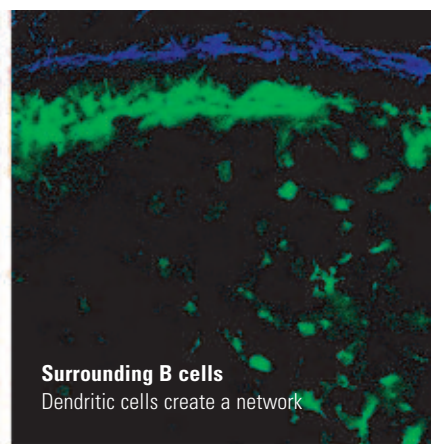
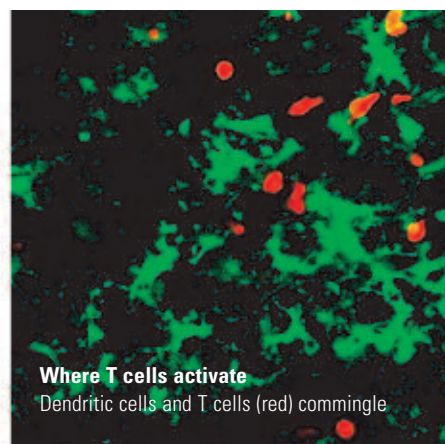
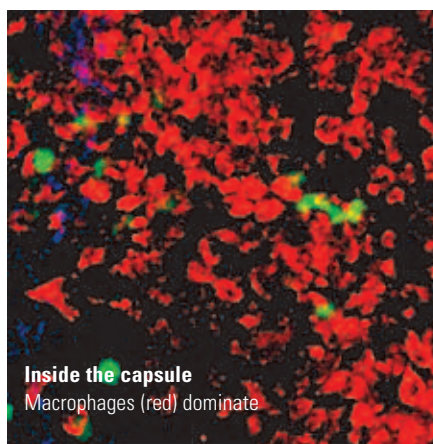
“It surprised us to see that this entirely different population of dendritic cells inside lymph nodes form what looks like a stationary network,” says Lindquist. “The network dendritic cells are just sitting there waving their processes. They’re not migrating.”

The much-studied mobile population of dendritic cells seems to interact with the stationary population, says Lindquist. In a related set of experiments, the researchers showed that transiting, mature dendritic cells can and do join the network, and they likely share their information across the network.

“Being able to watch dendritic cells in their natural state is valuable,” says Lindquist. If this network is teaching other immune cells to recognize, or tolerate, the body’s own tissues significant medical advances in the treatment of cancer and autoimmune diseases such as lupus may follow.

Already other research teams around the country are following in the Rockefeller-NYU team’s footsteps, and Nussenzweig, the university’s Sherman Fairchild Professor, predicts many new dendritic cell insights will emerge from noninvasive live-imaging techniques, such as the system he and his colleagues have developed.

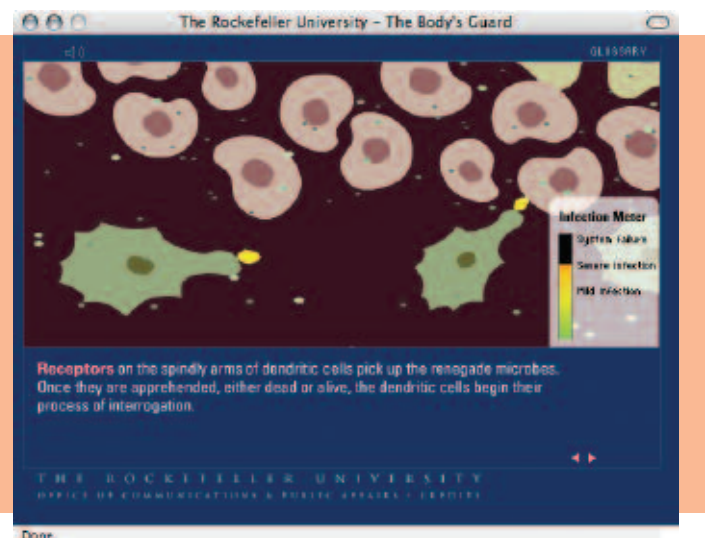
Lindquist, Nussenzweig and their colleagues, too, are pursuing many new experiments based on what they’ve already learned. “The next thing we’d like to determine,” says Lindquist, “is how the network dendritic cells interact with T cells under conditions that induce tolerance or active immunity.”



Lymph nodes, zone by zone. Dendritic cells (*all in green, above*) are detected in nearly every hub of activity inside the lymph node. New visualization techniques developed at Rockefeller have prompted questions about the range of dendritic cells’ contributions to immunity.

Dendritic cells, online

Dendritic cells are known to play multiple roles in the immune system, even as scientists continue to learn more about them. But how can the importance of the dendritic cell be explained to the lay public and to young students with a taste for science? A new animation, “The Body’s Guard,” produced by the Office of Communications and Public Affairs, introduces the dendritic cell as an immune system sentinel that mobilizes adaptive immune response to microbial infection. The interactive media project, and others at www.rockefeller.edu/interactive, explain some of the basic research happening at The Rockefeller University in terms accessible to non-scientists.



The alcoholic brain *continued*

receptor that would normally be occupied by a stimulant — a neurotransmitter called glutamate — thus preventing glutamate from delivering its message. When a person drinks large amounts of ethanol over a long period of time, the brain compensates by making more NMDA receptors on cells.

“The increase in NMDA receptors allows the brain to function even under the depressive effect of ethanol,” says Strickland. “But when alcohol consumption stops, the brain is essentially too active. The person in ethanol withdrawal feels anxious and agitated.”

Strickland and his colleagues knew from earlier research that tPA interacts with NMDA receptors, in particular a form of NMDA receptor with a binding site called NR2B. “tPA is better known as a clot-buster,” explains Strickland. “But it also functions in the central nervous system. tPA is involved in making synapses work better, to facilitate learning and memory.”

To investigate further the connection between tPA and NMDA receptors in alcohol dependence, Strickland and his colleagues studied two groups of mice that were genetically identical except for the tPA gene: one group had the gene and made the protein normally; the other did not have the gene for tPA, and thus did not produce the tPA protein.

For 14 days the researchers put the mice on a well-established regimen for mimicking the development of alcohol addiction in humans. They fed all the mice a liquid diet that included vitamins and a quantity of ethanol that increased from 2.3 to 10 percent of the diet volume over the course of the study. Then, on the 15th day, they switched the mice to an alcohol-free diet.

The normal mice suffered from seizures and other symptoms of ethanol withdrawal that peaked six hours after they stopped drinking the alcohol-containing diet. The mice that lacked tPA also suffered the effects of ethanol withdrawal, but far less severely.

“The action of ethanol in the brain is complex,” says Robert Pawlak, the post-doctoral associate in the Strickland laboratory who spearheaded the study. “It’s important to stress that tPA-NMDA interactions are not solely responsible for the development of physical dependence to ethanol. Changes to other neurotransmitters and receptors could explain why the mice in our experiments that lacked tPA

still developed moderate signs of ethanol withdrawal.”

Strickland and colleagues also found that tPA levels in certain brain structures — the hippocampus and the amygdala — increased during the period when the mice were ingesting increasing amounts of alcohol. This confirmed the scientists’ suspicion that tPA plays a role in ethanol dependence.

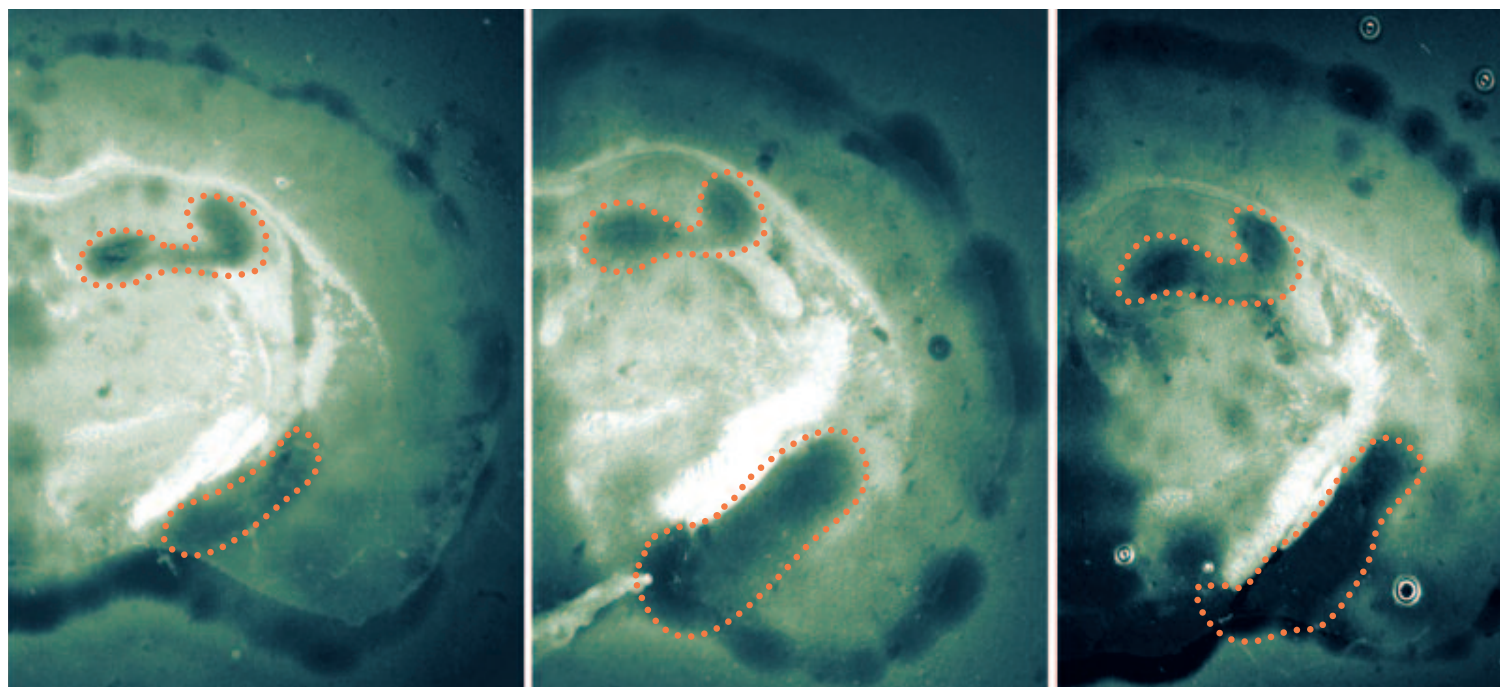
Next, after the mice stopped the alcohol diet, the researchers injected tPA into the brains of mice that lacked tPA. This led to an increase in seizures, confirming the link between tPA and symptoms of ethanol withdrawal.

Finally, the researchers injected ifen-

prodil, a drug that prevents tPA from binding specifically to the NR2B subunit of NMDA receptors, into mice undergoing ethanol withdrawal. The seizures and other symptoms abated.

“tPA sensitizes the nervous system,” concludes Strickland. “That’s good while ethanol is there, but bad once the ethanol is gone. Too much tPA has pathological effects.”

The findings suggest that tPA pathways may be potential drug targets and could lead to medicines that would help alcoholics get through the critical first 72 hours after withdrawal. “The next step will be to figure out in more detail tPA’s mechanism of action,” says Strickland.

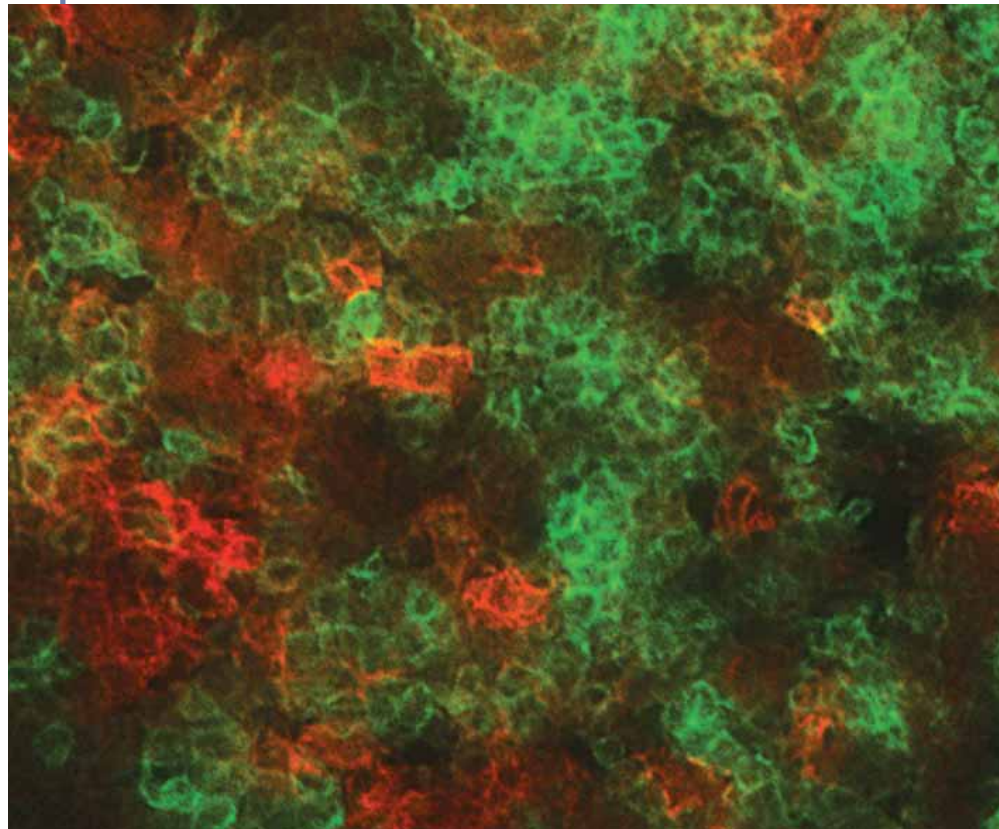


Drinking and excess. Compared to a mouse that has not ingested alcohol (left), levels of the tPA protein have increased in the hippocampus and central and medial amygdala (outlined) of the brain of a mouse on an alcoholic diet (center). During alcohol withdrawal tPA levels are even higher (right).

Great science often moves incrementally, with each new discovery building on and expanding upon the last. From time to time, we'll use this new feature to bring you short updates on the new progress that's been made in some of Rockefeller's most exciting and promising ongoing projects. —Editor

Training for hired killers

Last February, **Christian Münz** reported that natural killer cells — the assassins of the body's immune system — go through a period of “training” in the tonsils, lymph nodes and spleen



Teacher-student relations. Dendritic cells (red) and natural killer cells (green), together in a human lymph node. Scientists say that dendritic cells send signals to the natural killers that help them grow and mature.

before they are released into the bloodstream. It's during this period that immune system cells called dendritic cells activate the natural killers in one of two modes. Either the cells become full-fledged executioners or they become dispatchers, secreting cytokines, a type of chemical messenger protein that influences the strategies the body uses to fight infection.

“We saw that dendritic cells were able to make the natural killer cells proliferate, secrete cytokines, and increase their killing ability,” Münz says. “We then got curious about where this interaction takes place.”

In the November 23 issue of *Proceedings of the National Academy of Sciences*, Münz and colleagues show that dendritic cells and natural killer cells are found together in a specific area of human lymph nodes. Two proteins that the dendritic cells secrete ensure the survival and proliferation of the natural killer cells and increase natural killer cell production of the protein interferon-gamma.

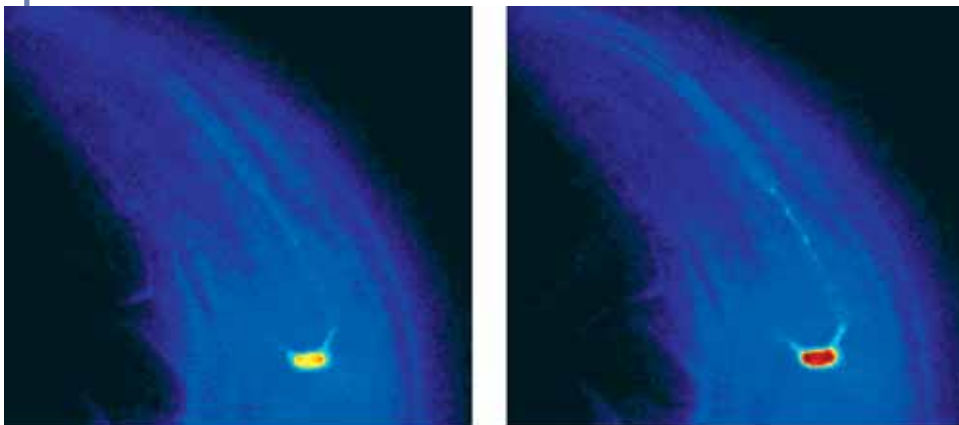
It's the interferon-gamma that's the key. Natural killer cells are part of the innate immune response, broadly battling all types of infection. But interferon-gamma signaling can sway the adaptive immune response, which tailors its attack to a specific type of intruder. When they interact with dendritic cells in the lymph nodes, the natural killer cells become a bridge to the adaptive immune system, helping direct its response.

“Our new findings change the view of natural killer cells,” says Münz. “Initially it was thought that as part of the innate immune response, they only limit viral infection or tumor cell mass until the adaptive immune response kicks in. Now we can see that natural killer cells aren't just effectors, but helper cells for the adaptive immune response.”

Channeling healthy fats

In a study published in 2003, **Cori Bargmann** — then at the University of California at San Francisco — and Rockefeller's Jeffrey M. Friedman demonstrated that a protein called TRPV4 is essential to an organism's sense of touch. Now research from Bargmann's newly established Rockefeller lab indicates that this protein, and the molecules that control it, may have implications for cardiovascular health.

Bargmann and Friedman identified the protein TRPV4 in mice, and *osm-9* in *C. ele-*



A stimulated worm. A cluster of sensory neurons in a *C. elegans* roundworm glows red (right) when TRPV ion channels in the worm's nerve cells are triggered in response to touch or taste stimuli. This reaction is diminished when critical fatty acids are missing.

gans roundworm, as a component of a specific set of openings or channels in a cell's membrane that are key to transmitting impulses between nerve cells and are involved in an organism's ability to sense fluids. In one experiment, the scientists showed that worms that were lacking the protein were unable to avoid noxious chemicals placed in their path.

“We have a pretty clear sense of what these channels are doing in the sensory system,” Bargmann says. “But we knew that we didn't have the complete story. There was something the cell was providing to help them sense the environment.”

There were hints from other research that polyunsaturated fats were important for controlling TRPV ion channels. With the help of Jennifer Watts at Washington State University, Bargmann and colleagues used worm mutants to manipulate the pathways involved in fatty acid synthesis. Examination of the mutants showed that certain fats — specifically omega-3 and -6, the same healthful dietary fatty acids that are found in fish — are involved in TRPV channel function.

“We know that polyunsaturated fatty acids are associated with cardiovascular health, but we don't really understand what they are doing,” says Bargmann. “Our research shows that these fatty acids may act as regulators of TRPV channels, helping them carry out their sensory functions. It is possible that the health benefits of fatty acids may be explained through the actions of these channels.”

The artificial cell, evolving

“It's like putting a drop of vinegar in oil,” says physicist **Albert Libchaber**, about the process of creating a self-contained artificial bioreactor the size of a single cell.

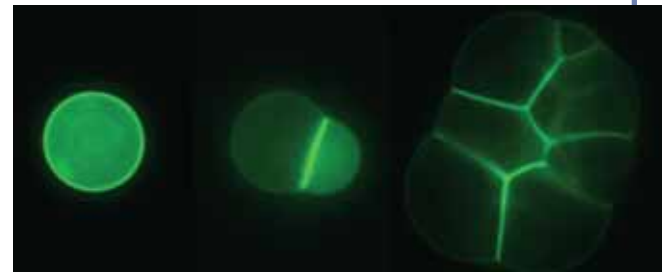
Libchaber, the university's Detlev W. Bronk Professor and head of the Laboratory of Experimental Condensed Matter Physics, and Vincent Noireaux, a postdoc in his lab, began the process of building their own “minimal cell” about a year ago, when they successfully expressed proteins in synthetic vesicles.

Now they've taken a commonly used compound known as a phospholipid to make an emulsion oil-extract (the cellular extract being the vinegar). Synthetic vesicles with a cell-free expression system inside are created when the emulsion droplets are centrifuged into an aqueous background solution.

The background solution is the energy source for gene expression of a small genetic network borrowed from the *Escherichia coli* bacterium, and the lipid layer they created serves as a membrane to contain extract. The scientists used a toxin derived from the *Staphylococcus aureus* bacterium to poke holes in the membrane, creating artificial pores through which small molecules can pass.

Under these conditions, the vesicle's genetic apparatus produced protein products for up to four days, the scientists report in the December 21 issue of *Proceedings of the National Academy of Sciences*. They even made their vesicle membrane more “intelligent” by binding proteins to the membrane with short peptides.

Applications for the project include biosensors and cellular delivery. “Eventually we might be able to send a vesicle to a cancer cell, where, if recognized, it could produce a drug that would destroy the cell,” Libchaber explains.



Biotech bubble. Synthetic vesicles created from droplets of an oil-based emulsion serve as artificial cell membranes, capable of sustaining genetic reactions for up to four days at a time.

A 'death patch' that dooms cells

Shortly after moving to Rockefeller in May 2003, **David Allis** and his colleagues at the University of Virginia published findings in the journal *Cell* suggesting that specific chemical “flags” on the protein tails of histones — the spools around which DNA helixes are wound — could induce programmed cell death in mammalian cells.

It was an exciting find, but mammalian cells have thousands of histones, and Allis wanted to determine which specific chemical flags are involved in triggering cell death. So he turned to a simpler organism with just one histone: yeast.

Sung Hee Ahn, a graduate student in Allis's Laboratory of Chromatin Biology and Epigenetics, took yeast cells from which specific histone tails had been removed, and treated them with hydrogen peroxide, a chemical that triggers the cell death pathway. She found that only the cells lacking the H2B tail survived — indicating the culprit was somewhere on H2B.

Ahn then showed that chemical changes to a specific component of H2B, called serine 10, was implicated: hydrogen peroxide had no effect on the cell when serine 10 was substituted with a different amino acid that does not bind to a phosphate chemical group in the way that serine 10 does (a process called phosphorylation). Ahn also replaced serine 10 with glutamic acid, a molecule that mimics phosphorylated serine 10. According to Allis, the cells looked like they wished they were dead.

“The cells with glutamic acid looked bad before they were exposed to hydrogen peroxide, and looked worse after the treatment,” says Allis, the university's Joy and Jack Fishman Professor.

When Ahn and Allis looked closely at the amino acid sequence of H2B, they identified a stretch of amino acids on either side of serine 10 that Allis nicknamed the “death patch.” When this 12-amino acid long peptide was transferred to other histones, those cells also underwent apoptosis, confirming that this section of H2B is critical to the cell death pathway. The results were published in *Cell* on January 14.

Although more research is needed, Allis believes that these findings may lead the way to new strategies for “de-silencing” genes that are inappropriately shut down in diseases such as cancer, when cells do not die at the time they are supposed to.



Paul Nurse, President
Joseph Bonner, Director of Communications

Editor: Zach Veilleux
Art Director: John Haubrich
New Media and Design
Contributors: Joseph Bonner, Betsy Hanson,
Kristine Kelly, Lynn Love

Address correspondence to:
Editor, RU Scientist, Box 68
1230 York Ave. | New York NY 10021