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The Rockefeller University 1901

news&notes

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Prospective students visit RU campus

Prospective graduate students arrived on campus last night for two days of the RU experience. This week's Open House, and another one next week, give potential students the chance to learn more about the university—both its research and its ambiance.

President Levine welcomed the students at a pre-dinner reception yesterday and spoke to them about the groundbreaking research being done at Rockefeller. Today applicants will have one-on-one meetings with scientists they have expressed interest in, and they will attend a poster session describing RU research. Later, applicants will be treated to an evening of Broadway theater—one of the cultural perks of studying in New York City.

According to Dean George Cross, applications to RU are up 30 percent this year, and the applicant pool is particularly strong. "Hopefully as the applicants are meeting with RU scientists, they will truly connect with them," says Cross. "That's how we attract our best students."

Around campus:

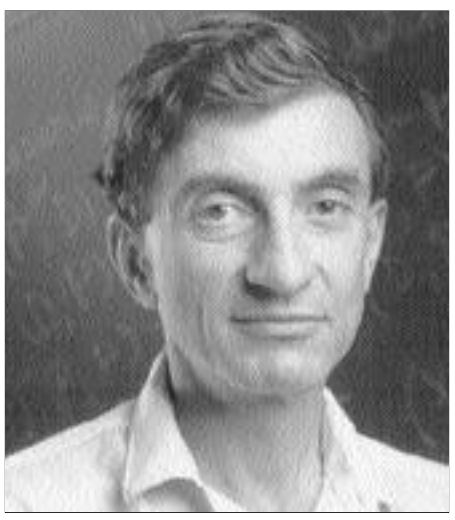
Laboratory safety at Rockefeller

Amy Wilkerson is the director of RU's Laboratory Safety and Environmental Health program.

The American Museum of Natural History's new exhibition "Epidemic!" describes various microbes responsible for infectious disease. Notably, the exhibition includes information about the scientific laboratory itself as a place where infectious disease microbes are deliberately cultivated. The exhibition features a model of a "high containment" laboratory.

"'High containment' implies to me a BSL3 [biological safety level 3] laboratory," says Amy Wilkerson, director of The Rockefeller University's Laboratory Safety and Environmental Health program. BSL3 labs are used for work with "an unacceptably high risk of morbidity or mortality associated with the biological hazard, if we don't have a treatment method for the infection or if the work involves any airborne infectious materials." Precautions for this level of research

Cohen awarded the 1999 Tyler Prize



Abby Rockefeller Mauzé Professor Joel Cohen is the co-recipient of this year's Tyler Prize Prize for Environmental Achievement.

For his work in advancing the environmental understanding of human population dynamics, Abby Rockefeller Mauzé Professor Joel E. Cohen is the co-recipient of this year's Tyler Prize Prize for Environmental Achievement. He shares the $200,000 prize with Te-Tzu (T.T.) Chang of Taiwan, a rice geneticist whose research on the evolution and variation of rice has led to major advances in plant breeding, productivity and disease resistance with a profound impact on agricultural productivity throughout much of Asia, Africa and South America.

"Their work spans basic science and practical application, and has greatly influenced both," said Robert P. Sullivan, chair of the 11-member Tyler Prize Executive Committee, which annually selects the Tyler Prize recipients.

Cohen's studies of human population dynamics began in the 1970s. He observed that neither birth rates nor death rates were constant over time, and he developed an important mathematical model representing these random fluctuations. This work laid the foundation for more realistic assessments of the uncertainty of future human population size and age composition. His 1995 book *How Many People Can the Earth Support?* has raised the level of sophistication of public discussions on population.

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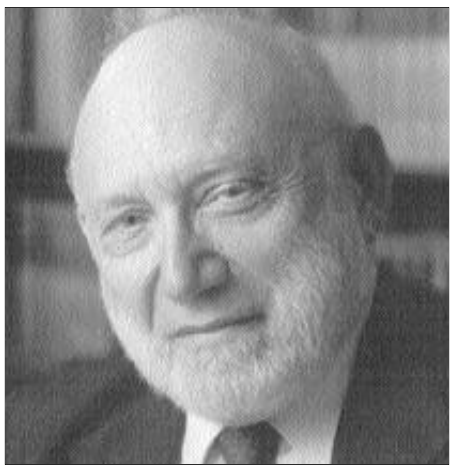
RU scientists behind the scenes at the American Museum of Natural History's new "Epidemic!" exhibit

Rockefeller scientists have often made scientific history, but recently two of them turned their efforts to helping tell the history of infectious diseases in the American Museum of Natural History's new exhibit "Epidemic!" Sackler Foundation Scholar Joshua Lederberg and Professor David Ho (scientific director of the Aaron Diamond AIDS Research Center), along with RU alumnus and public health expert Barry Bloom, served on the advisory committee for the exhibit, which opened Sat., Feb. 27.

This exhibit explores the biological and ecological factors that influence the causes, spread and control of infectious diseases and investigates the way different cultures meet and fight devastating diseases. In addition to the exhibit itself, the museum is publishing a book featuring selections written by members of the "Epidemic!" advisory board. Several members of the committee, including Lederberg, also took part in an "Epidemic!" Fred Friendly Seminar to be televised later this spring.

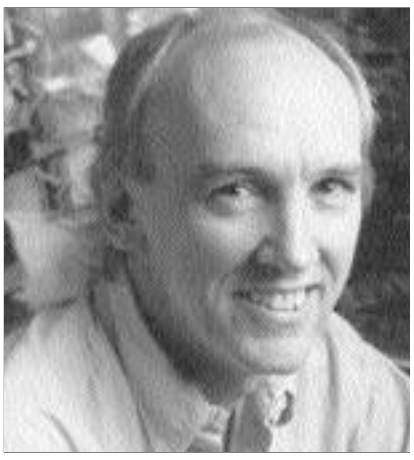
Lederberg was awarded the Nobel prize for his work on bacterial genetics. Ho is an AIDS researcher whose HIV studies led to the design of multiple drug treatment strategies that have, in recent studies, reduced the virus to undetectable levels in certain patients.



Sakler Foundation Scholar Joshua Lederberg (left) and RU Professor David Ho, scientific director of the Aaron Diamond AIDS Research Center, were on the advisory board for the new "Epidemic!" exhibition.

Friday Lectur e

Gadsby to discus cystic fibrosis ior channel today



RU Professor David Gadsby will discuss the cys fibrosis ion channel at the Friday lecture today (Mar. 5).

What's the most common let genetic disease? For people Caucasian descent, it's cyst fibrosis. About one in 25 Caucasians c ries the altered gene that causes it. In last decade, scientists have learned a great deal about how this disease wor at the molecular level. In 1989, researchers discovered that the cystic fibrosis gene encodes a membrane pro tein called CFTR, which is now know to be a chloride ion channel subject to exquisite regulation. At the Friday lec ture today (Mar. 5), RU Professor Dav Gadsby will present a talk entitled "Th Cystic Fibrosis Ion Channel: Not a Simple Open-and-Shut Case."

"Patients who inherit two altered copies of CFTR genes," Gadsby explai "are unable to move sufficient numbe of chloride ions across their cell mem branes, and if chloride ions won't mo then you can't move salt, and that me you can't move water across the mem brane." As a result, cystic fibrosis patients are unable to hydrate the sur faces of their epithelial cells, causing a build-up of thick, dry mucus in the lungs, which makes them vulnerable t potentially fatal bacterial infections.

Using a patch-clamp technique tha allows observation of just one ion cha nel at a time, Gadsby's lab is striving t understand how a cystic fibrosis ion channel works. All ion channels are characterized by two properties: their ability to select and conduct particula ions across a membrane, and their requirement for a gate that opens and closes to regulate the ion flow, since th

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with biological agents include wearing lab coats, gloves and respirators, using high-efficiency particulate air filters installed in work cabinets and exhaust systems, as well as double-door entry and negative air pressure differentials in the facilities. These precautions preserve the safety of both the research and researcher, as well as the general public, by rigorous containment of potentially dangerous microbes.

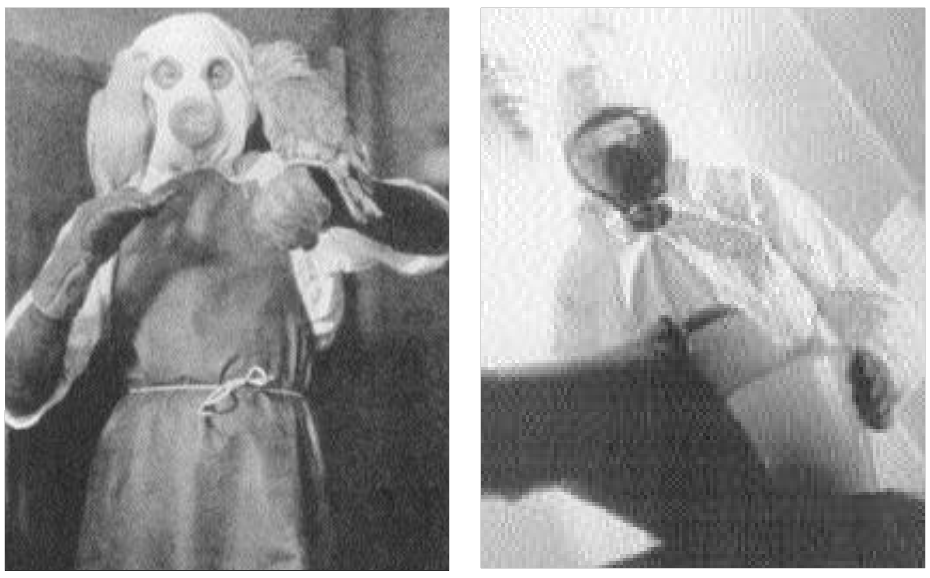
High containment might also mean a BSL4. At this level a scientist wears a containment suit with its own oxygen supply. There are no such facilities in New York City, and they are rare among non-military institutions nationwide. Most labs at RU perform work at BSL1 or BSL2 conditions.

The Laboratory Safety and Environmental Health program at Rockefeller was established in 1981 by then-President Joshua Lederberg, with infection control as a vital component. Wilkerson credits Lederberg with recognizing the potential for public health problems and increased research needs associated with the reemergence of infectious diseases such as tuberculosis. She also credits him with the wisdom of creating an integrated safety program: "In the modern laboratory, the same person works with chemicals, radioisotopes and biologicals. They work with a biological agent, tag it with radioactive isotopes, and fix their slides with chemicals. Many institutions do not have a fully integrated program," explains Wilkerson.

If you look back through the ages of infection control (the term that predates "containment"), ways of establishing safety varied widely. Rockefeller has been very thorough. "We have a long history of biocontainment," says Wilkerson. "A lot of guidelines established by Rockefeller researchers earlier in the century are now part of the Centers for Disease Control's recommendations for laboratory safety. In addition, we're still ahead of the curve with policies such as an annual inventory of biological hazards and observing a plus rating system."

If a researcher is conducting work that presents slightly higher risks than a given containment level, additional protective practices and engineering controls are required. And in certain cases, the entire protocol is upgraded to the next higher containment level. While inspections and questions might sometimes seem like intrusions, Wilkerson emphasizes that the safety program is intended to serve and support the entire Rockefeller community. "We're all in this together," she observes.

COURTESY OF THE ROCKEFELLER UNIVERSITY ARCHIVES



Then and now: Virologist George Berry (left) had the right idea at a time when biological hazards were unregulated; in the 1930s, he used an apron, respirator and gloves to study parrot disease, but they didn't provide the protection of contemporary BSL3 attire (right).

Portrait of RU immunologist is unveiled in Weiss

The late Henry Kunkel, a world-renowned immunologist and Th Rockefeller University's first Ab Rockefeller Mauzé Professor, was hon· ored with a new portrait that will be d played in the RU Hospital. The painti was unveiled on the 17th floor of the Weiss Research Building last Tues., Fe 23, in a ceremony attended by Kunke family and a large RU crowd. Kunkel worked at the university from 1945 u his death in 1983.

In the mid-1980s, Kunkel's colleag and students established the Henry Kunkel Society to perpetuate his ideal through annual meetings and by enco aging future generations of investigato to strive for the high standards set du ing his distinguished career.

The new portrait of the late immunologist Henry Kunkel was unveiled by Kunkel's widow, Betty Kunkel-Fisher, and Jacob Natvig, president of th Henry Kunkel Society.

Potpourri

Discount theater tickets

Human Resources has a new benefit for all theater enthusiasts at RU. The office will purchase tickets to Broadway and Off-Broadway shows, through the Theatre Development Fund, and reduced price tickets to the New York City Opera. These tickets will be made available at cost to members of the RU community (faculty, staff and students). The office is presently offering reduced price tickets to the following productions of Lincoln Center's New York City Opera:

La Boheme,Sat., March 20 at 8 p.m.
3rd Ring: ordinarily $58 is now $45
4th Balcony: ordinarily $20 is now $14

Don Giovanni,Fri., April 23 at 8 p.m.
3rd Ring: ordinarily $58 is now $45
4th Balcony: ordinarily $20 is now $14

Please call Human Resources, x8303, if you would like tickets to these operas. *News&Notes*will provide regular updates of what tickets are available.

Lottery for cottages

Spring isn't far away, so the Housing Office is making plans to open the university's two cottages in upstate New York. The cottages, located 53 miles from campus, are near Bear Mountain and West Point. They offer a rustic retreat on 10 wooded acres sloping toward the Hudson River. The MacInnes Cottage sleeps six in three bedrooms, and Hostage Cottage accomodates four in two bedrooms. The deadline for entering the annual lottery for reservatrions is Fri., March 19, at 3 p.m. Reservation request forms are stocked in the Founder's Hall kiosk bin, just right of the main entrance. The daily rate for the cottages is $40, with a two-night minimum stay, for weekdays (Sun. through Thurs.); the weekend rate is $85 for the weekend (Fri. and Sat.). Amenities include stone fireplaces, screened porches, modern kitchens and bathrooms with showers. Blankets, utensils and phone service are provided. The living rooms contain materials on nearby hiking and other activities in the area, as well as guest books for visitors to sign. Guests are asked to leave the cottages clean for the next guests. Complete information on the use of the cottages is posted in Founder's Hall. The Housing Office will draw requests and issue confirmations after Thurs., April 1.

Hurricane Relief

Donations to help the Colombian earthquake victims are now being accepted in two locations on campus. Marjorie Goldsmith, director of the Rockefeller Child and Family Center, has a drop-off location at the CFC, and Research Associate Scott Kellogg has a drop-off location in the lobby of Weiss. Donations of food, diapers, toys, medicines, bandages, aspirin and other items are now being accepted. Please bring your donations as soon as possible so that they may go to the earthquake victims as soon as possible.

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 327-7007.

Purchasing corner

1) Stock Num. 11510
Renaissance Western Blot Reagent Plus 1000cm2
NEN # NEL 103
2) Stock Num. 11520
Renaissance Western Blot Reagent Plus 5000cm2
NEN # NEL 105

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Cohen's work on food webs was the first to call attention to regularities in the feeding relationships in ecological communities and to develop quantitative models to explain these regularities. This work laid the foundation for the development of food-web ecology over the last 20 years.

His work on the infectious diseases of humans has focused on some neglected killers (malaria, schistosomiasis and Chagas disease) of disadvantaged people in tropical countries and on the interactions of diseases with demography, economics and the environment. For example, his studies on the household ecology of Chagas disease in Argentina have generated knowledge that could make it possible for families to prevent this incurable disease, which currently affl up to 20 million people in Latin America.

As director of the Board of the Societal Institute of the Mathematical Sciences, a non-profit organization devoted to bringing mathematical me ods to bear on social problems, Cohe helped improve monitoring of air and water quality, less-polluting energy pr duction and more effective AIDS surv lance, modeling and prevention.

The Tyler Prize, administered by t University of Southern California, is a international award honoring achieve· ments in environmental science, envi· ronmental protection and environmen aspects of public health. This year's awards ceremony on April 16 is in Lo Angeles.

FRIDAY, continued from page 1

cannot remain permanently open. In the case of the cystic fibrosis chloride channel, the mechanism that regulates the gate is unique and extraordinarily complex ("byzantine," says Gadsby).

At his lecture today, he will explain the gating process step by step and will present a simple model that describes it. He will also present new work with CFTR mutants that reveals how cystic fibrosis chloride channels are constructed, and he will discuss what they might look like in light of recent crystal structures of related bacterial proteins. Gadsby's lecture begins at 3:45 p.m. in Caspary Auditorium and is preceded by a tea in Abby Aldrich Lounge at 3:15 p.m. All are welcome.

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RU's Laboratory of Cellular Biophysics

Examining Multidrug Resistance in Cancer Treatment

BY PAUL C. FOCAZIO

Tumors are the culmination of a series of hits taken by healthy cells.

"There are hundreds if not thousands of different mutations that cause different cancers," says RU Associate Professor Sandy Simon, head of the Laboratory of Cellular Biophysics. Yet, all malignant tumors share certain fundamental properties. For example, they are more sensitive to chemotherapeutic drugs than most normal cells. Also, they ignore certain societal rules that govern cells in an organism: they continue to grow, even after contacting other cells, and they invade the space of their neighbors. This invasion is the result of both a reduced adhesion to the surrounding cells and an active attack on the space around them. "The tumor per se," Simon notes, "is not as dangerous as the damage it causes when it invades and presses on healthy tissue.

"Our understanding of cancer has recently undergone a major revolution: Studies of viral oncogenes by RU's Hidesaburo Hanafusa and colleagues and the identification of genetic mutations in human cancers such as the p53 gene by President Levine and colleagues have converged with the recent advances in molecular genetics to identify a common set in tumor cell biology."

Since each tumor is the consequence of a series of mutations, and each tumor has a different combination of mutations, then all cancers might be expected to be quite different. Simon's laboratory is trying to characterize how it is that they all have some common cell biological properties. One potential key to these cellular changes has been the sensitivity of tumor cells to chemotherapy.

During the last 20 years, researchers in the field have identified genetic differences between two tumor cell types: drug-sensitive (which distribute chemotherapeutic drugs in both the nucleus and the cytoplasm) and drug-resistant (in which drugs are excluded from the nucleus). Multidrug resistance, a generic term for the variety of strategies that tumor cells develop to evade the toxic effects of anticancer drugs, is characterized by decreased cellular sensitivity, not only to drugs employed in chemotherapy but also to a broad spectrum of drugs with neither obvious targets nor structural similarity. Citing this resistance as a major obstacle to the successful treatment of tumors, Simon says, "It offers investigators an insight into some of cellular changes that occur within a tumor cell."

Simon's lab has homed in on determining the causes for changes in the internal distribution of chemotherapeutics as Adriamycin. Adriamycin belongs to a class of compounds known as anthracyclines. These are weak bases that should freely cross the membrane boundaries of a cell. However, upon entering any cellular compartment that is acidified, these chemotherapeutics will be protonated, and thus trapped. Simon notes differences in the distribution of chemotherapeutics between drug-sensitive and drug-resistant cells may reflect differences in the dispersion of pH throughout a cell.

> If each tumor is involved in a series of mutations, and if every tumor has a different combination of mutations, how is it that they all have these common cell biological properties?

In a May 1998 *Journal of Experimental Medicine* paper, Simon's lab showed a quantitative map of the pH distribution in cancer cells that were either sensitive or resistant to chemotherapeutic drugs. These results confirmed that weak base chemotherapeutics accumulate in any membrane-bound compartment that has a low pH. Further, eliminating this lower pH sensitized the tumors to chemotherapeutics. Simon suggests that acidification of organelles is causally related to drug resistance and is consistent with the hypothesis that the deposits of drugs in acidic organelles and subsequent extrusion from the cell through the secretory pathways contribute to chemotherapeutic resistance.

"If there is a shift in a cell's internal pH," Simon surmises, "one would expect this to affect the physiology of these cells in ways that would affect both the growth of cancer cells and their adhesion to the surrounding environment. Therefore, the research is proceeding in two directions: First, examining what happens to normal cells when acidification of organelles is disrupted, and second, testing whether the cellular changes we observe in tumor cell lines are observed in cancers in living animals."

Recently the Simon lab has looked specifically at the anti-cancer drug tamoxifen, which is similar in structure to the hormone estrogen. Scientists know that this drug clearly blocks the growth of breast tumors which have receptors for estrogen, but it also induces many other effects that scientists have not been able to explain.

"Many of the physiological consequences of tamoxifen treatment that are independent of the estrogen-receptor may be the result of just a few specific mechanisms," Simon says. "We have found that tamoxifen blocks acidification in tumor cells, normal cells, yeast and even bacterial cells." Many of the side effects of tamoxifen can be mimicked solely by inhibiting this acidification of cellular organelles. Thus, the effects of tamoxifen on acidification are sufficien to account for many of these effects. "What is encouraging about the work that by characterizing a specific biochemical mechanism for the side-effec we can screen for other drugs without tamoxifen's adverse side-effects but sti preserve the positive therapeutic attrib utes of blocking estrogen-receptor pos tive breast tumors."

"This is an exhilarating time to be studying biology – with recent technic advances we are able to finally use inta living cells for studying biochemistry. I have been very fortunate to have an incredible group of students whose stu ies range from how proteins are integr ed into membranes to how phages esc from bacteria. In their intellectual pursuits each of them has been fusing bio physics, cell biology, genetics and phys ology. They represent the interdisciplinary structure of Rockefeller at its best

Simon is the Walter Annenberg Res Professor at The Rockefeller University above research is supported by the American Cancer Society, the Nationa Institutes of Health, the Keck Founda the Wolfensohn Foundation, the Willi and Helen Mazer Foundation, the Irvi Hansen Memorial Foundation and Hamamatsu Photonics.

Associate Professor Sanford Simon is looking m drug resistance in cancer cells

Structural biologist sheds light on how cells commit suicide

A team of researchers led by Associate Professor David Cowburn has determined the three-dimensional structure of a molecule that regulates programmed cell death, a critical process important for many diseases, including cancer, heart disease and autoimmunity. The structure, reported in today's issue of the journal *Cell*, provides a model for developing compounds to switch cell suicide on or off to treat these diseases. An accompanying paper by Gerhard Wagner of Harvard Medical School describes a similar structure.

"The three-dimensional structure of this molecule provides insight into how these proteins mediate specific cell death," says Cowburn, who heads the Laboratory of Physical Biochemistry.

Programmed cell death, or apoptosis, is an integral component of the well-being of an organism because it controls the number of cells and eliminates genetically or environmentally damaged cells. Many diseases can be seen as a result of cellular imbalance. Cancer and autoimmune diseases result in part from the survival of too many cells, while immunological diseases, neurodegenerative disorders and infertility occur when there is an excess of cell death.

Cowburn collaborated with Stanley Korsmeyer at Washington University School of Medicine. Korsmeyer, now at the Dana-Farber Cancer Institute at Harvard Medical School, has spent the last several years studying a family of proteins called Bcl-2, which he and others have shown to be involved in the cell death process. Some members of the protein family induce cell death and are known as proapoptotic agents, while others, called antiapoptotic agents, prevent it.

The structure solved, known as Bid (Bcl-2 interacting domain), is a proapoptotic member of the Bcl-2 protein family. Recently, Korsmeyer's group and others showed that Bid, which is normally inactive, becomes active when cleaved, or chopped up, by an enzyme called a caspase. The truncated form of Bid, designated tBid, travels to the cell's power house, the mitochondria, wreaking havoc with the cellular machinery and causing the cell to die.

Postdoctoral Fellow James McDonnell and Research Associate David Fushman worked with Cowburn using a technique called nuclear magnetic resonance (NMR) spectroscopy to study the Bcl2 proteins. NMR is a technique for observing molecules as they float in solution, much like their natural environment in the living cell, providing dynamic views of the molecules and their functions.

The structure is a complex packing of several helices against each other. The site of cutting by the enzyme surprisingly resides in a long unstructured loop. Modeling how the cut molecule looks suggests that the product is much more hydrophobic and less charged, possibl making it suitable to be a membrane pore former in the mitochondria. The solution NMR structure confirms an e lier observation Korsmeyer and his co leagues made using biochemical techniques and provides a framework for understanding the structures of other members of the Bcl-2 protein family a how some stimulate cell death and so suppress it.

"Our paper now permits a clear c sification, previously unavailable, of th sequential and structural alignments c the Bcl-2 family," says Cowburn. "Our work provides a model for the Bcl-2 family's cell-death inducing and inhib ing roles, as well as the modifications needed for activation." *-J.B.*

The research at Rockefeller was su ported in part by the National Institut General Medical Sciences, part of the al government's National Institutes of Health.