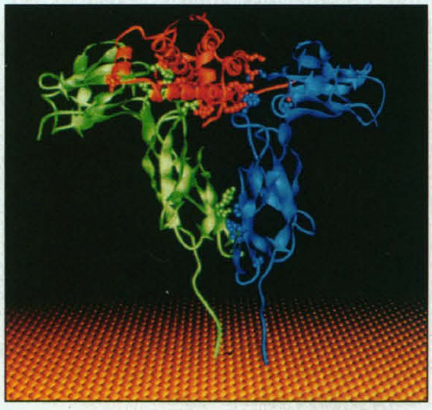
small molecule would have enough contact points," says James Ihle, who studies cytokine receptors at St. Jude Children's Research Hospital in Memphis, Tennessee.

But on page 257, researchers at Ligand Pharmaceuticals in San Diego and SmithKline Beecham Pharmaceuticals in Collegeville and King of Prussia, Pennsylvania, prove the skeptics wrong. They report their discovery of a small molecule that activates the receptor for granulocyte–colony-stimulating factor (G-CSF), a cytokine that triggers the growth of white blood cells. G-CSF is commonly used to boost patients' immune systems after chemotherapy, which kills off immune cells. Although the new compound works in mice but not humans, it is being heralded as evidence that the right small molecule can indeed fill a protein hormone's shoes.



A. M. DE VOS, M. ULTSCH, A. A. KOSSIAKOFF, *SCIENCE*

Togetherness. Two receptors for the cytokine growth hormone (blue and green) are held together by the growth hormone protein (red). Small molecules may produce the same effect.

"A lot of people have been trying to do this," says Alan D'Andrea, who studies cytokine receptors at the Dana-Farber Cancer Institute in Boston, "and this is proof that it really can happen. It has generated a lot of excitement." The discovery will also spur the pharmaceutical industry's search for protein-mimicking drugs, says Mark Goldsmith, who studies cytokine receptors at the University of California, San Francisco. It suggests, he adds, that with small molecules, "we can mimic many interactions that just a few years ago would have been expected to be much more difficult."

The Ligand–SmithKline Beecham team had some grounds for optimism when they began their search for a G-CSF mimic. When cytokines bind to their receptors, they drag the receptors together into pairs called dimers. That aggregation seems to be what turns on a receptor, as researchers have shown by using antibodies to bind receptors together or mutating the receptors so that they stick together of their own accord. And linking receptors was a job that a small molecule might be able to do.

In the past 2 years, moreover, two research teams showed that peptides—small fragments of proteins—can activate the receptors for the blood cell cytokines thrombopoietin and erythropoietin. Peptides can't be given orally, but they are considerably smaller than proteins. That peptide finding was "encouraging," says Ligand researcher Peter Lamb, who with his teammates was already at work to find a small molecule that could link G-CSF receptors.

To speed the search, the team had engineered a line of mouse cells as a biological test for G-CSF–like activity. When G-CSF activates its receptor, a cascade of cellular events begins that ultimately activates proteins called STATs, which turn genes on and off to stimulate growth or cause other changes in the cell. To monitor STAT activity in their test cells, the team added a gene for the light-generating protein luciferase, engineered to be turned on by STATs. They then treated the cells with thousands of compounds and picked out the ones that made the cells literally light up.

After further tests to make sure that the candidate compounds really were activating STATs and that the G-CSF receptor was playing some role, the group was left with a small organic compound called SB 247464. This compound actually stimulated the growth of mouse white blood cells in culture and in living mice. "As far as we know, this is the first example of a [nonpeptide] cytokine mimic," says Lamb. The data suggest that the compound binds and dimerizes the G-CSF receptor, but more tests are needed to prove that is actually how it works.

The researchers admit that they were disappointed to find that the compound works in mouse but not human cells. It remains to be seen whether chemical alterations will make the compound capable of acting on the human receptor. "That is a lesson about the importance of using human [receptor] molecules for screening for human compounds," says Goldsmith. But despite that weakness, he says, the paper has taken the field "a quantum leap" along the path toward developing oral substitutes for protein drugs.

Ligand plans to use luciferase-gene assays to search for substitutes for other cytokines that work through STATs, Lamb says. And the drug industry as a whole is likely to mount a broader search. "The insulin receptor is fundamentally no different" from the G-CSF receptor, Goldsmith notes, pointing out that it too is activated by dimerization. "Why not consider [searching for] a synthetic compound that can be taken as a pill and will activate your insulin receptors?" If drug companies aren't looking already, it certainly won't be long before they start.

–MARCIA BARINAGA

ScienceScope

COW DONE DOLLY-STYLE?

Japanese scientists say they have replicated in cattle the technique used to produce Dolly, the sheep that was the first mammal cloned from adult somatic cells. Twin calves were born on 5 July; their mother reportedly died unexpectedly the next day. The research group won't release further details until it completes a DNA analysis to confirm the calves' origin.

A team at the Ishikawa Prefectural Livestock Research Center and the Kinki University School of Agriculture in Nara put cells from a cow's uterine tube into eggs stripped of their nuclei and implanted the resulting embryos into surrogate mothers. Team leader Yukio Tsunoda says a second birth is expected in the next few weeks. The news was released prematurely, he says, in accord with new government guidelines requiring prompt disclosure of cloning research.

It was the second report of Dolly-style cloning in 2 weeks. On 26 June, Ryuzo Yanagimachi of the University of Hawaii, Manoa, claimed his group had cloned mice using adult somatic cells.

BAIKAL JAM SESSION

Hoping to save the world's largest freshwater lake from the depredations of industrial pollution, tourists, and exotic species, U.S. and Russian researchers and policy experts plan to meet next month in Irkutsk, Russia, to plot joint studies and to draft legislative initiatives geared toward protecting Lake Baikal.

Sponsored by the nonprofit Tahoe Baikal Institute, the forum aims to learn from alterations wrought by 40 years of development around California's Lake Tahoe, including a dimming of its stunning water clarity. "Baikal is now at the stage that Tahoe was in the 1950s, just before development really got under way," says UC Davis limnologist Charles Goldman, a forum participant.

Lake Baikal

Goldman and Valentin Brovchak, chair of the Baikal Commission, hope the forum will lead to the establishment of a government agency to defend Baikal's interests, along the lines of the Tahoe Regional Planning Agency. Future forums will be hosted at UC Davis's planned Lake Tahoe Center for Environmental Research, slated to open by summer 2000.

belt. If it really is cometary debris, the number of comets orbiting the star must be 1000 times larger than in our solar system.

The inner region of the disk, comparable in size to our own planetary system, contains little material, perhaps because it has been swept clean by planets forming from the dust. A bright spot in the ring is probably "either dust trapped around a planet or dust perturbed by a planet orbiting just inside the ring," says Greaves.

It is "good evidence but not convincing proof" of a planet, agrees theorist Jack Lissauer of the NASA Ames Research Center.

Any planets around Epsilon Eridani are likely to be either relatively small or far from the star, says Geoff Marcy of San Francisco State University. Marcy has observed Epsilon Eridani for the past 11 years, looking for the wobbles that might betray the presence of a massive planet. The absence of detectable wobbles implies, he says, that "no companion having a mass greater than three Jupiter masses is likely to exist" within five times the Earth-sun distance. That, of course, leaves a comfortable margin for planets like our own. **–GOVERT SCHILLING**

Govert Schilling is an astronomy writer in Utrecht, the Netherlands.

PNAS 95, 9274 (1998)

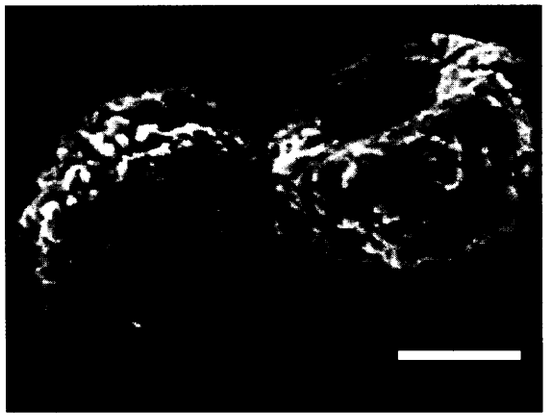
MICROBIOLOGY

Bacteria to Blame for Kidney Stones?

Tiny bacteria have been fingered as possible culprits behind kidney stones and abnormal calcium deposits in other tissues. The bacteria, described in the 7 July *Proceedings of the National Academy of Sciences*, are among the smallest ever found, barely bigger than some viruses.

Physician Olavi Kajander of the University of Kuopio in Finland first noticed the bacteria more than 10 years ago as a white film in his mammalian cell cultures. From the film, he was able to culture the slow-growing bugs, which he dubbed nanobacteria. At 200 to 500 nanometers wide, they are one-tenth the diameter of a typical *Escherichia coli*. So far, Kajander and his colleagues have found the nanobacteria in cattle blood, in 80% of samples of commercial cow serum in which mammalian cells are grown in the lab, and in the blood of nearly 6% of more than 1000 Finnish adults tested. The organisms had not been implicated in any diseases, however—until now. Kajander and clinical microbiologist Neva Çiftçioglu report that they have cultured nanobacteria from all 30 human kidney stones they examined.

Kajander and his colleagues suspected that the bacteria may play a role in the formation of kidney stones because, under certain growing conditions, they build calcium-rich spherical shells around themselves. Now the team has found that the structures are made of apatite, a primary component of kidney stones and other calcified deposits in tissue but different from the calcium compound in teeth and bones. Blood contains several proteins that inhibit the formation of apatite crystals, but Kajander speculates that the bacteria might be free to form shells if they leave the bloodstream and take up residence in tissues. The small spheres, he says, may be seeds for larger calcium deposits, such as kidney stones or the abnormal calcifications found in patients with scleroderma or some cancers.



Seeds of kidney stones? Tiny bacteria form calcium shells that may trigger larger deposits. (Scale bar is 1 μm.)

The hard shelters protect the bacteria from most assaults, including high heat and many antibiotics. However, says rheumatologist Dennis Carson of the University of California, San Diego, tetracycline is known to accumulate on apatite crystals and so might be a promising candidate for attacking nanobacterial infections.

The link between bacteria and kidney stone disease is far from proven, however. "They may have something here," says microbiologist Mitchell Cohen of the Centers for Disease Control and Prevention in Atlanta. "But I'd like to see broader studies looking at different types of stones in different parts of the world." Nevertheless, the find is "one of the most intriguing and fascinating additions to this area of research that I can imagine," says nephrologist and kidney stone specialist Fredric Coe of the University of Chicago. Coe notes that at least four teams have reported tiny spherical deposits in or near the calcified plaques often found in the kidneys of patients who suffer from kidney stones. "I don't know that it's their bacteria," he says, "but it sure looks suspicious." **–GRETCHEN VOGEL**

ScienceScope

NO ESCAPE FROM RED TAPE

Stanford biologist Paul Berg's idea for cutting through onerous legal paperwork in the lab has taken off somewhat like a lead balloon. His proposal—to abolish material transfer agreements (MTAs) signed when research tools are shared between nonprofit labs—has won plenty of verbal support but only one formal endorsement.

This spring Berg and Stanford's licensing chief Kathy Ku proposed eliminating as many as 50% of MTAs—routine agreements designed to protect an inventor's rights. Berg says that when he phoned scientific leaders at a half-dozen other institutions, they responded enthusiastically. But only one actually signed up—the Carnegie Institution of Washington, D.C. "It's a fine idea, but it cannot bring back the good old days" before universities became enmeshed in a commercial environment, says Karen Hersey, intellectual property counsel for MIT.

Berg, meanwhile, says he is dropping his scheme and hoping for a measure of relief as a result of guidelines on legal aspects of scientific collaborations now being drafted by the National Institutes of Health (*Science*, 12 June, p. 1687).

NEW ERA AT RIKEN

Physicist Shun-ichi Kobayashi will be stepping into some pretty big shoes next month as president of Japan's Institute of Physical and Chemical Research (RIKEN), Japan's leading research center, outside Tokyo. He succeeds physicist Akito Arima, widely regarded as the most powerful scientific figure in Japan. A veteran dispenser of science advice to the government, Arima resigned in May to run for the Diet (*Science*, 22 May, p. 1181).

Kobayashi

Kobayashi, little known outside the University of Tokyo where he is vice president, is by comparison "an unknown quantity," according to one RIKEN staffer. Kobayashi admits "I've got some studying to do," joking that he took the job because Arima, a former mentor, "ordered me to." His immediate challenge will be looking out for RIKEN's interests in the coming merger of its funding body, the Science and Technology Agency, with Monbusho, the Ministry of Education, Science, Sports, and Culture.

Contributors: Dennis Normile, Richard Stone, Eliot Marshall