pension injection models. Regional lymph node metastases occurred in all MetaMice, and liver metastases appeared in 18 of 26 animals. Among the 15 cell suspension models, just one metastasis took place — to regional lymph nodes.

Genetronics, a San Diego biotechnology company, reports similar experience with cell suspension models. "Sometimes the tumors don't grow at all, sometimes they grow in ways which are different from [the way tumors grow] in man, and usually they don't metastasize in the same way," said senior vice president Martin Nash.

Cell-to-Cell

"Tumors need cell-to-cell contact to grow," explained Tetsuro Kubota, M.D., of Keio University, a co-author of the Cancer Research article. The enzymes that break up the tumors to make the suspension destroy the cell surface receptors that mediate this contact.

The cell suspension cancers might have metastasized had the researchers allowed enough time, said Nicolson. "They stopped their assay too early to tell." Perhaps 9 to 10 weeks was too soon, said Hoffman, but had they waited long enough, "the animals would probably have died of the primary [tumor] before then."

"We use MetaMouse because it's the only way we can get patient-like metastatic events," said Nash. "We've worked with five or six different cancers, including pancreatic and liver cancer, and we've not had a failure [to metastasize]."

Relevant Model

Human cancers that progress in MetaMouse as they do in Homo sapiens include liver, pancreas, head and neck, bladder, stomach, ovarian, colon, and all types of lung cancer. MetaMouse is also the only relevant model of mesothelioma, said Hoffman. Breast and prostate cancers metastasize very slowly in this model, if at all, perhaps because human breast cancer is fueled by estradiol, of which rodents produce very little.

Besides testing new drugs, MetaMouse can be used to test new routes and new doses, as well as new indications for old drugs, said Hoffman.

MetaMouse could also serve as a surrogate cancer patient. "We can do prognosis of the patient using this model," said Kubota. "This is an important problem in the clinical field."

Similarly, clinicians think they will be able to make better choices for chemotherapy by first testing the drugs on the patient's tumor grown in MetaMice. In such a case, five drugs might be tested, each in two mice, said Perry. Since such studies would take at least several months, initial treatment would have to proceed using more conventional guidelines.

— David Holzman

Hyaluronan Seeps Into Cancer Treatment Trials

Hyaluronan, one of the most water-loving molecules in nature, is reputed to help skin hold its moisture, making it a popular ingredient in cosmetics. But this naturally occurring polysaccharide has many biological roles, and research is revealing it plays an intimate part in cancer development and progression.

Hyaluronan, or hyaluronic acid, is involved in both cell transformation and cancer cell metastasis. Paradoxically, in large quantities it can also retard cancer development. According to some researchers, it also has a sort of homing instinct for injured and tumor tissues, which sprout many more receptors for hyaluronan than do normal tissues.

While several institutions in the United States, Canada, and elsewhere are investigating hyaluronan's biochemical properties, a small biotechnology company is using the substance as a drug delivery vehicle for cancer treatment.

Dynamic Molecule

Hyaluronan is naturally present in synovial fluid, the vitreous humor of the eye, and connective tissues. Possessed of a giant reservoir-like capacity, it can mix with and hold in place several hundred times its weight in liquid.

"It's an extremely dynamic molecule," said Vincent Hascall, Ph.D., a research biochemist at the Cleveland Clinic in Ohio.

But it was not these qualities that led, initially, to a Canadian investigation of hyaluronan as a cancer treatment delivery system. It was the pungent, gar-
The Falk Oncology Center in Toronto was using to aid penetration of chemotherapy drugs into the advanced, refractory tumors suffered by patients there.

Despite the building’s closed ventilation system, “on a warm summer’s day you could smell the clinic on the street,” said Samuel Asculai, Ph.D., president of Hyal Pharmaceuticals, the biotechnology company in Toronto working on hyaluronan.

Worse, the staff in the government offices on the first floor of the building were also complaining of the smell, said Rudolf Falk, M.D., founder of the clinic.

In their quest for an odorless substitute, Falk and his staff began experimenting with hyaluronan. The substance already had a history of two decades of safe use in ophthalmological surgery, and its properties intrigued them. While the uproar over DMSO spurred those efforts on, the choice of hyaluronan was largely serendipitous. Admitted Falk, “We did it on a blind shot.” Nevertheless, they mixed the substance with anticancer drugs and administered it intravenously to treatment-refractory patients with various types of tumors on an experimental, case-by-case basis.

Increased Kill

The researchers said they saw increased tumor kill in the infused patients compared to what they had been seeing with standard chemotherapies. But they also said that unexpected side effects were similar to those observed in patients receiving tumor necrosis factor. Some of the patients died not of spreading disease, but because of an accumulation of the by-products of tumor breakdown, an effect known as tumor lysis syndrome.

Degenerating tumor tissue — and the macrophages called in to mop it up — produce prostaglandins, which inhibit the immune system. Nonsteroidal anti-inflammatory drugs have been investigated to block the prostaglandins and mitigate the effects of tumor breakdown.

Pain Relief

Hyal began experimenting with this concept in 1991, and found that hyaluronan combined with NSAIDS could be administered for up to 21 days without NSAIDs’ usual gastrointestinal and kidney toxicity, and with fewer people dying of the breakdown products of tumors. The clinic also found that NSAIDs, when combined with hyaluronan, were adequate for pain relief, so that many patients could be taken off narcotics.

The pain relief experienced by cancer patients — and hyaluronan’s use as a moisturizer — led the company to devise a topical gel, based on hyaluronan and containing the NSAID diclofenac, for arthritis treatment. (Ciba-Geigy Corp. markets a similar product in Europe.) But Hyal Pharmaceuticals made another interesting discovery: While using the gel for tennis elbow, a man participating in Hyal’s trials found it cleared up a basal cell skin carcinoma. Further study revealed the treatment also worked on actinic keratoses, precancerous lesions resulting from sun exposure.

A topical gel containing hyaluronan and diclofenac is in phase III trials in Canada and the United States for treatment of AK. At least one phase III trial for treatment of basal cell carcinoma is finished, and an injectable version of the therapy containing mitomycin-C will undergo trials for the treatment of breast cancer in Australia starting this year.

Hyal’s work, however, has raised skepticism for a number of reasons: The idea of using hyaluronan clinically in cancer treatment is new, and hyaluronan itself is seemingly innocuous. And although Falk has given at least two presentations before scientific societies, no peer-reviewed papers have been published either by Hyal Pharmaceuticals or by other scientists in support of the firm’s clinical work.

Emerging Instead

What is emerging instead is an independent body of literature at the basic science level that explains hyaluronic acid’s interaction with normal and cancer cells, and exploring the pathways by which it may inhibit tumorogenesis. This work has been slow to gain acceptance.

“It’s not a mainstream thing,” said Bryan Toole, Ph.D., a professor of anatomy and cell biology at Tufts University School of Medicine in Boston, who is studying the molecular actions...
of hyaluronan. "I've been through several periods where it's been very difficult to convince people of what we're doing. It's the usual skepticism."

Like many other molecules, hyaluronon has contradictory effects. Produced naturally by the body in nanograms or picograms, it works as a signaling entity and can promote cancer. When hyaluronan is introduced in large quantities, it destroys the cells' hyaluron-based signaling mechanism and halts its cancer-promoting action.

Looking for a way to control metastasis, researchers at the University of Manitoba have been studying a gene called RHAMM, or receptor for hyaluronic acid-mediated motility, which produces a protein that helps cells move through the body.

It is known that hyaluronan facilitates the migration of melanoma cells, and that hyaluronan and its receptor are present in large amounts in highly metastatic tumor cells. Further, when RHAMM loses its ability to bind hyaluronan, it also is unable to transform normal cells into cancer cells. Thus, hyaluronic acid itself is involved in the transformation process, said Eva Turley, Ph.D., a cell biologist and professor in the university's Department of Pediatrics and Physiology.

Transforms by Itself

The research team found that when RHAMM is overexpressed, it can transform cells by itself; it can also initiate and maintain transformation in concert with the nearby ras gene, and send the transformed cells migrating through other tissues. Similarly, when RHAMM signaling is disrupted, tumor cells return to normal, or nearly so. That is, they no longer form tumors and are poorly proliferative — and oddly enough, too much hyaluronan can disrupt the signal.

In Turley's experiments, hyaluronic acid-treated mice injected with RHAMM-transformed cells developed no tumors over 6 months. Untreated mice given the same tumor cells developed large cancers on their legs within 3 months; in half the animals, the cells spontaneously metastasized to the lung.

Blocking Action

While Hyal Pharmaceuticals and the University of Manitoba investigated RHAMM, researchers at Tufts studied the other main cell surface receptor for hyaluronon, CD44. Toole, Ivan Stamenkovic, M.D., an immunologist at Massachusetts General Hospital, Boston, and others have reported that fragments of hyaluronon can slow tumor growth and prevent implantation of tumor cells in laboratory animals by attaching to CD44 and blocking action of the full molecule. Using local administration of hyaluronan oligosaccharides, the researchers have achieved regression of melanoma in animals, and they are now tackling ovarian cancer.

Researchers are just beginning to understand how CD44, RHAMM, and hyaluronan interact with cancer cells. But together, said Stamenkovic, they "represent an area that is currently full of promise because it offers the possibility to control tumor migration, implantation, growth, and metastasis."

— Jan Ziegler

Immunotoxins Show Some Promise In Human Studies

After 12 years of research, scientists at the National Cancer Institute have demonstrated that a genetically engineered immunotoxin can home in on and destroy solid tumor cells in patients with refractory cancers. The immunotoxin, known as LMB-1, shows potential as a treatment to eradicate epithelial solid tumors, as may its more refined analogue LMB-7, which is being evaluated in a recently launched phase I trial.

LMB-1 was engineered in 1991 by Ira Pastan, M.D., and his team of researchers in NCI's Laboratory of Molecular Biology. The immunotoxin has been in a phase I clinical trial for the past 2 years where, for the first time, antitumor activity was shown in patients with colon or breast cancer (see Nature Medicine, March 1, 1996).

According to Arthur Frankel, M.D., associate professor of medicine at the Medical University of South Carolina, "solid tumors have been a brick wall therapeutically, and now Dr. Pastan and his team are breaking through that brick wall and taking a pioneering step where others have been unwilling to go."

The phase I trial, conducted by Lee Pai, M.D., involved 38 patients with large solid tumors, usually widespread,