News News News

Of Mice and Metastasis: A New For-Profit Model Emerges

The first commercial mouse model of metastasis received U.S. Patent # 5491284 on Feb. 13. But these carefully engineered creatures had already been a hot item for savvy researchers for several years.

In ordinary mouse models, metastasis, a hallmark of malignancy, is a rare event. But cancer in the new model, dubbed MetaMouse (the Meta stands for metastasis), is designed to spread from the primary organ, just as in humans.

"The limitations in [the conventional] model contribute to the failure of so many agents which are active in such systems to become licensed anticancer drugs," said Edward Sausville, M.D., Ph.D., associate director of developmental therapeutics at the National Cancer Institute, who hastens to add that he is not condemning conventional mouse xenografts.

The conventional models are made by injecting suspensions of single cells from tumor cell lines beneath the skin of nude mice. Nude mice lack thymus glands, and so do not reject the transplanted material. The mice wear their cancers like little backpacks — large, but relatively inert bumps.

In MetaMouse, pieces of tumor — not suspensions of cells — often from human patients, are transplanted into the organ of primary growth in the mouse.

Besides metastasizing like normal tumors, cancers in MetaMouse cause other symptoms, such as weight loss, normally associated with the disease in humans.

Currently, 19 companies, including one of the top five independent U.S. biotechnology companies, and universities are conducting studies using MetaMouse, said Robert M. Hoffman, Ph.D., professor of surgery at the University of California, San Diego, and president of AntiCancer, Inc., the company that created MetaMouse. Ten other companies have completed studies, and AntiCancer is negotiating with about 50 more.

At $200 apiece for a typical bulk order of 20 or 30 mice, a MetaMouse costs about twice as much as conventional models, and the price rises to $500 for a single unit. Each mouse is individually prepared, but "once the surgeon is set up and we have the tumors, he can produce the MetaMice quite fast," said Andrew Perry, Ph.D., president of consumer products at AntiCancer. Although some cancers are slightly harder to install than others, the difference is not enough to warrant price sensitivity, he said.

MetaMouse, looking to the future of cancer research.

To turn a nude mouse into a MetaMouse with lung cancer, a microsurgeon extracts the left lung, appends tumor tissue with sutures finer than a hair shaft, and replaces the lung inside the chest wall. He then closes the chest and reinflates the lung. Now the mouse is ready to serve medical science. Elapsed time: 2 to 3 minutes. But developing these surgical techniques took nearly a decade, said Hoffman.

Another Step Closer

Conceptually, some observers see MetaMouse as a refinement of an idea that Isaiah J. Fidler, D.V.M., Ph.D., of the Department of Cell Biology, University of Texas M. D. Anderson Cancer Center, Houston, has been promoting since the mid-1980s: that cancer models should be seeded "orthotopically," that is, in the appropriate organ.

"I don't consider it a breakthrough," said Garth L. Nicolson, Ph.D., professor and chairman of tumor biology at M. D. Anderson. "But practically, it could be very useful."

"The model does take us another step closer to an in vivo environment that more accurately reflects the clinical situation," said Robert Kerbel, Ph.D., director of cancer biology research at Sunnybrook Health Science Center in Toronto.

Even when injected into the correct organ, cell suspensions in the conventional mouse model metastasize either much more slowly than pieces of tumor, or not at all. In a paper published in *Cancer Research* in 1993, Toshiharu Furukawa, M.D., of Keio University in Tokyo, Hoffman, and others compared gastric cancer cell line MetaMice with correct-organ cell sus-

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.


Dr. Robert M. Hoffman

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.


Dr. Tetsuro Kubota

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*