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## **MetaMouse Models Colon Cancer Metastasis With Clinical Potential**

**By David N. Leff**  
Science Editor

People owe a debt of gratitude to a mouse born into the world totally bald. The nude mouse's nakedness comes about because of genetic mutations, which also leave the beast devoid of a thymus, thus lacking immune defenses. This weakness is its strength as an animal model for mimicking human diseases.

Research oncologists inject suspensions of human tumor cells under the skin of a nude mouse, knowing that it can't reject the foreign tissue. They then observe the cancer's growth, and test it for response to potential anti-cancer drugs and other therapies.

This is all very well, but only up to a point. That point is where a typical solid tumor, after growing bigger and bigger in place, begins to send out malignant cells to colonize distance organs. Such tumor metastases travel to their

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## MetaMouse

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remote target tissues by way of the bloodstream and lymphatic network, neither of which is very handy to a subcutaneously implanted cancer.

That's why AntiCancer Inc. (ACI), of San Diego, Calif., invented and patented its MetaMouse, as an animal model closer to the human cancer condition. The U.S. Patent Office, ACI's president, Robert Hoffman, told *BioWorld Today*, has just notified it of allowance on its pending application.

"This mouse model and the patent for it," Hoffman said, "involve tumor transplant technology developed at AntiCancer, such that a human or xenograft cancer can be transplanted orthotopically — literally, to the correct place — from a patient to the animal's corresponding organ. These models are the first in which animal-implanted human tissues closely replicate the complex behavior of the original tumor while still in its human host. It allows the tumor to grow and spread, and then metastasize, as it does in patients." (See *BioWorld Today*, March 11, 1993, p. 3.)

Hoffman pointed out that "this contrasts with the usual nude-mouse subcutaneous mode, which very rarely metastasizes, and even more rarely to the proper target organ."

In human colon cancer, this metastatic target is almost invariably the liver, Hoffman observed. "In this country, 150,000 people a year get colon cancer, and at least half are fatal over five years or so. Surely the vast majority of these die from liver metastases."

ACI's president, who also is a professor of surgery at the University of California's San Diego (UCSD) campus, is senior author of a paper in last month's *Proceedings of the National Academy of Sciences (PNAS)* dated Dec. 19, 1995. Its title: "Liver colonization competence governs colon cancer metastasis."

That paper tests *in vivo* its co-authors' concept that some colon cancer strains are predestined to metastasize, and others not. At Tokyo's University of Keio, Hoffman joined Japanese cancer surgeons intermittently over the past two years in orthotopically implanting a series of eight human colon cancer strains into "maybe 100 nude MetaMice, as a ballpark figure," he said.

As these malignancies, stitched to the surface of the animal's own guts, rather than under their skins, duly increased in size, the investigators transplanted aliquots of the tumors to their livers. Some of the samples "took;" oth-

ers did not.

"The colonization step is what distinguishes metastatic from non-metastatic cancer," Hoffman said.

To show that only orthotopic tumors, conditioned by growing on colon tissue, could strike out for the liver, the team tried planting one strain on stomach and colon surfaces alike. "There was a vast difference," Hoffman said, "On the stomach it grew rather extensively, but only on colon could it progress and metastasize to the liver. This showed how important the originating, or primary, organ is."

For the past year at UCSD, Hoffman, wearing his academic hat as a cancer surgeon, has been "transplanting all the colon cancers into MetaMice. We're going to correlate metastasis with the patients and mice, and see if the direct liver assay will correlate with the patients' tumors. If that's the case," he continued, "then we have at least the liver tumor assay to determine if they are going to be metastatic."

He said that "Liver metastases, as the main cause of death in colon cancer, are a great target to attack. And that is what this is all about with regard to reduction to clinical practice."

He and his colleagues "are now setting up the orthotopic transplant assay" to demonstrate if it is practical in patient prognosis. At the same time, he added, "We're busily at work comparing the non-liver colonizers — that is, the non-metastasizers — with the colonizers, trying to see what the basic physiological and molecular differences are."

### Moving Up From Mice To Molecules

Hoffman speculated that "If we can from our mouse studies identify a molecule, a receptor or growth factor, we would do it. But I'm not sure it's so simple."

He regards molecular oncologist Lance Liotta at the National Cancer Institute (NCI) as "the maven in this field." Liotta heads the NCI's tumor invasion and metastasis section. Having read the *PNAS* paper, he told *BioWorld Today*: "If they follow that up, and find a cytokine and a receptor that cause the difference, then I would say that that cytokine receptor could be such a marker."

Liotta added that, "One potential cytokine and receptor, which fulfill all the criteria from their model, is hepatocyte growth factor and its metastatic oncogene receptor. I don't know if that's the right one, but it would fit with everything they have reported in their study." ■