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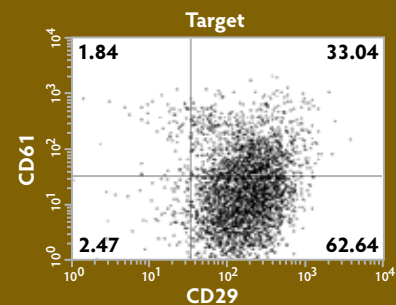
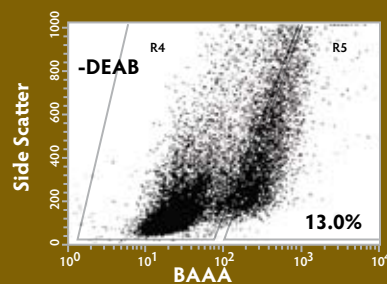
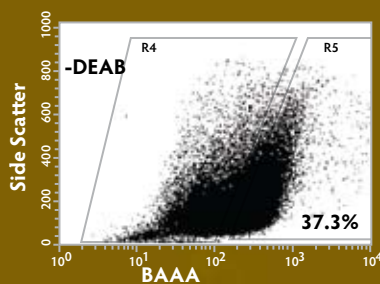
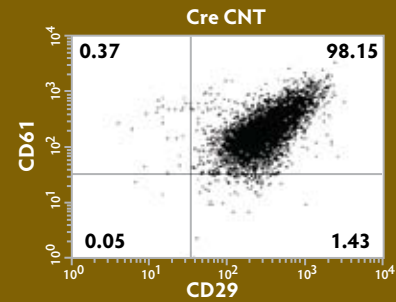
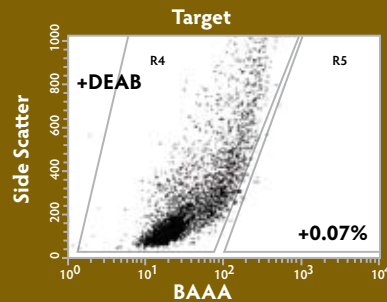
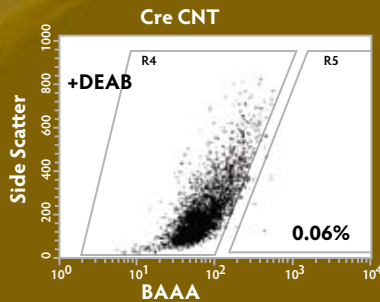
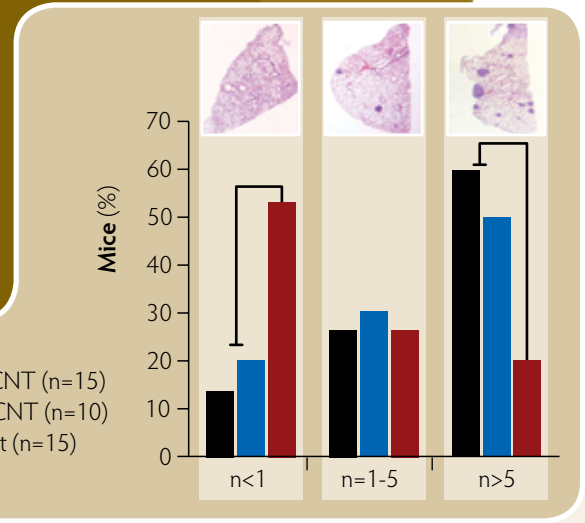
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# Cell Signaling

*RIGHT: Examples of lung metastatic nodules (micrographs) and quantification showing suppression of metastasis in FAK conditional knockout mouse model of breast cancer.*

*BELOW: Analyses of mammary cancer stem cells in various genetically modified mouse strains by flow cytometry.*



### Deciphering Cellular Signals to Target Disease

Complex communication networks exist among the cells of an organism. These signaling pathways not only regulate cell growth, division and differentiation; they trigger immune responses to infection, help maintain homeostasis and, in short, play a pivotal role in basic cellular functioning. When the pathways are disrupted, however, whether by genetic mutation or environmental assault, disease can ensue.

Professor **Jun-Lin Guan, PhD** (*below*), has made important discoveries about how alterations and defects in cell signaling pathways lead to illnesses such as cancer. Much of his recent work has focused on an enzyme called focal adhesion kinase, or FAK, a type of tyrosine kinase. This family of enzymes is found in cellular cytoplasm and acts as a crossing guard of sorts for cellular communications. Dr. Guan uses mouse models to study the role of FAK in breast cancer—how the enzyme may help initiate tumor growth, regulate the creation of new tumor blood vessels and lead to cancer metastasis.

Research has suggested that breast cancer, like other cancers, is driven by a small fraction of cells within tumors, termed mammary cancer stem cells (MaCSCs). “Conventional therapies remove the bulk of the tumor mass, but if you don’t remove or destroy every cancer stem cell, the patient suffers a relapse and the tumors grow back,” explains Dr. Guan. “In order to cure cancers like these, we need to design ways to target cancer stem cells specifically. To do that we need to understand the signal transduction pathways that regulate these cells.”

Dr. Guan and the researchers in his laboratory developed a mouse model that lacks FAK, specifically in mammary epithelial cells. The team induced breast cancer in mice—in both those with FAK and in the mice without FAK expressed in normal mammary cells. The investigators found that those without FAK, had significantly decreased tumorigenesis and metastasis as well as reduced numbers of cancer stem cells in their tumors.

Secondly, the group demonstrated that mammary cancer stem cells deficient in FAK showed a reduced ability to self renew and to develop tumors. The findings of this work support a critical role of FAK in the maintenance and renewal of breast cancer stem cells. The research was published this year in the journal *Cancer Research*.

But although deleting FAK substantially inhibited the regeneration potential of the cancer stem cells it did not completely eliminate them. While important, FAK is likely not the only player regulating breast cancer causing stem cells.

In fact, new research from Dr. Guan’s lab is finding that Pyk2, another tyrosine kinase related to FAK, may partially compensate for the role of FAK when FAK is knocked-out in mice and that FAK has both kinase-dependent and -independent functions in cellular signaling. He and his group are creating additional mouse models and conducting further investigations into these mechanisms. It may turn out that some recently-developed tyrosine kinase inhibitors used to treat

breast cancer are not setting up roadblocks along all of the pathways involved. Dr. Guan is hoping that further studies will yield insights into comprehensive and effective ways to specifically target mammary cancer stem cells, to block all implicated pathways.

Several years ago Dr. Guan’s lab identified a protein, FIP200, which can bind to FAK and inhibit its activity. He has generated mouse models wherein this protein is inactivated, and studies have shown that the protein indeed regulates cellular growth, spreading and migration, processes that run amok in cancer but are also critical to embryonic development, wound healing, blood vessel growth and immune responses. “This protein is highly conserved in different species and widely expressed,” adds Dr. Guan. Studies of FIP200’s role as a breast tumor suppressor are ongoing in his lab.

“We also suspect that FIP200 may play important roles in other diseases besides breast cancer,” Dr. Guan explains. In a brain-specific FIP200 knockout mouse model, for example, he found that the animals showed neurodegenerative decline, supporting the role of the protein in maintaining neuronal health.

His lab is continuing its investigations into how the protein may lead to neurological disease. Early work indicates FIP200 may interact with the genes that regulate basal autophagy, the process by which a cell consumes some of its contents for nutrition or as a defense mechanism. Autophagy is especially important in neurons, whose function can be disrupted if waste products accumulate. Without FIP200, neuronal cells appear unable to carry out the process.

Dr. Guan joined the U-M faculty in 2006 from Cornell University, where he served on the faculty for 15 years. Much of his work has involved collaboration with others at the U-M as well as beyond. “This is a really positive aspect for me, this culture of collaboration,” he says. “Coupled with the strong clinical research being done here, the potential to develop this basic research into treatments for cancers and other diseases is very real.”

