More than Magnolias

By Sylvia Wrobel

"Magnolia grandiflora. Fifty million years ago, they ruled the earth. Now they are back from the swamp."

So reads the framed museum poster of a rather lurid magnolia, more plant demon than Georgia O'Keefe, in Jack Arbiser's crowded office.

"Ah, the magnolia," says Arbiser, with the exuberance he expresses when speaking of almost any natural product. "Nothing wants to eat it. It's resistant to insects, fungi, virtually everything. Only God knows what it is about. But we've found out a little!"

He's being modest. Magnolia tea has a long tradition in Eastern medicine, primarily as a treatment for anxiety, but in 2003 the Emory researcher received international attention when he discovered that honokiol, the active ingredient in such preparations and the same substance that allows the magnolia to resist invasion, slows the progression of several human tumors.

One of the mechanisms through which it does this is by inhibiting the growth of the new blood vessels that supply tumors the oxygen and nutrients they need to grow. Arbiser found that honokiol encourages the endothelial cells that make up the walls of these abnormal, rapidly developing blood vessels to self-destruct (a naturally occurring process called apoptosis) while sparing normal cells. When he inoculated immune-deficient mice with human tumor cells, the mice given honokiol showed fewer new microvessels and had only half the tumor growth found in similar mice not given the magnolia extract.

Arbiser's first honokiol study focused on sarcomas, tumors arising out of connective tissue. The laboratory then progressed, accompanied by rapid-fire publications, to honokiol's anti-angiogenesis effects on growth and metastasis of breast and prostate cancers, chronic lymphocytic leukemia and myeloma, and melanoma. (Both a basic scientist and practicing dermatologist, Arbiser often tests compounds against melanoma cells, figuring, he says, that if you can stop the progression of melanoma you can stop almost any kind of cancer.)

Native magnolia trees are only one item in Arbiser's ever-widening search for compounds. When the brilliant yellow of a turmeric root caught his eye in the farmers market, for example, he carried the unusual plant back to the lab to create an extract. Recipe: chop, infuse in alcohol, grind, filter, and evaporate. He then tested the extract in mouse endothelial cells to see if it inhibited their growth. Curcumin, the component of turmeric responsible for its color, does. Better yet, it works in a different way from honokial. Other compounds his team is testing include mate tea extracts, ant venom, and gentium violet (used for a century to treat fungus and thrush seen in babies).

If Arbiser finds some of his research samples almost by chance, his approach is anything but random. It is built on a continually expanding armamentarium of research tools, a powerful hypothesis, and a high-energy commitment to moving rapidly from theory to practical applications.

Ahead of the times

Arbiser developed an interest in anti-angiogenesis while he was a Howard Hughes Fellow and on the faculty at Harvard, where he worked with Judah Folkman, who first proposed that cancer tumors were dependent on angiogenesis for growth. Although few initially believed Folkman, anti-angiogenesis is one of the most promising fields of cancer research 30 years later.

Arbiser already had investigated signal transduction pathways, including how tumor cells signal for new blood vessels to be built and how chemotherapy affects the process. He began to hypothesize that oncogenes (genes that increase the chance that a normal cell will develop into a cancerous one) work in part by disrupting the balance between factors that stimulate angiogenesis and those that inhibit it. Watching the disappointing failure of the first clinical trial of a protein that had worked to inhibit blood vessel formation in mice with tumors, Arbiser realized that no one compound or drug was likely to succeed in halting tumors through angiogenesis inhibition. Instead, compounds would have to be identified and drugs developed that hit multiple targets.

Jack Arbiser is looking for new cures in old places

Ten years ago, he returned to the Druid Hills neighborhood where he had grown up and to the university where he had studied organic chemistry. Here at Emory, Arbiser created new tumor cell lines and mouse models and began to use them to test extracts for angiogenesis in endothelial cells.

When he finds such an extract, he identifies the active ingredient and then tests to see if it will reduce blood vessel growth and tumor size in tumor-prone mice. The next step is to find the mechanism through which the compounds work, identify the precise target, and synthesize new compounds to see if they are even more potent against that target. His goal is to develop compounds that can attack different targets in the cancer sequence.

"Look how easily cancers adapt and become resistant to chemotherapy drugs, just as infections become resistant to specific antibiotics," Arbiser says. "Merging two or more molecules makes resistance harder."

And, of course, the ultimate target: making the "theoretical practical," in Arbiser's words, by getting discoveries to patients. He has licensed his research on curcumin, and another of his compound discoveries is in the process of being licensed. That means a pharmaceutical company believes in the drug potential of the compounds sufficiently to pay Emory for the right to take them into the drug development process. Arbiser envisions that the drugs to come from these natural products will be able to hit targets along the tumor growth spectrum and will be used together with more traditional cancer treatments, potentially reducing dosage regimens and toxicity of chemotherapy.

In the meantime, Arbiser is continuing to take his angiogenesis research in new directions, most recently discovering its role in leprosy. He and collaborators at Emory have found that different stages of leprosy vary widely in the number of blood vessels contained in the skin lesions, a finding published online in the *Archives of Dermatology*. A treatment approach using an angiogenesis inhibitor could substantially shorten the length of therapy, he says. ●