

CANCER THERAPEUTIC STRATEGIES

an Interview with John Marshall, M.D.



By Frank Reider

John Marshall, M.D., is the director of developmental therapeutics and gastrointestinal oncology at the Lombardi Comprehensive Cancer Center at Georgetown University. He also serves Lombardi as the associate director for clinical research and director for extramural research. Marshall is focused on early-phase clinical research for cancer patients. He has established an enduring, productive record of innovative phase I and II clinical trials. In the past six years, he has completed more than 40 phase I trials, 22 of which were first trials in human studies. These trials have centered on the testing of novel agents targeting PKC, angiogenic factors, bcl-2, retinoid receptors, and matrix metalloproteinases, among others. His current efforts are centered on the development of novel CEA-based vaccines to be used as therapeutics for cancer patients.

Marshall likes to tell the story of his visit to the National Zoo—he had been invited on rounds to observe an orangutan with colon cancer and animals with other ailments. He asked the head veterinarian what was the biggest problem they had. The answer was the exotic bug collection—evidently, it had been invaded by local bugs, and there was no way to get rid of the invaders without harming the exotics.

Marshall: I mean, you couldn't just go in there with a can of Raid. You'd kill the collection along with the bugs you were trying to get rid of. And that's the same problem I have as an oncologist. I'm trying to kill cancer cells, human cells inside of a human, and the trick there is to find some secret difference that the cancer requires to live, whereas the normal cells do not. It's very different than trying to treat a virus or bacterium. Those are foreign invaders, and there are very important differences that we can take advantage of—that's how antibiotics work; we take advantage of the fundamental differences in the cell types between a bacterium and human.

Georgetown Medicine: *So what do we do to go after cancer?*

Marshall: For decades really, the only toehold we have had in cancer medicine is to attack DNA—the principle that cancer cells need to grow and divide in order for them to move forward. But the problem

with that approach is that normal cells have to do that, too, and there's significant collateral damage. Also, cancer cells become really resistant to that approach very quickly, so it only works in a few select cells. The reason we've made progress is that molecular biology teaches us some fundamental distinctions—some fundamental genes and proteins that are different in cancer—that allow us to target those things with less collateral damage.

GM: *But the cancer cell is a moving target.*

Marshall: That is correct. But it's moving in the sense that it evolves. One of the fundamental problems with cancer cells is that there are mutations, errors in the repair of the cell, so mutations build up. The cancer evolves out from underneath this. If you have a billion cancer cells in a ball, which by the way isn't very big, what are the odds that one of those cells has an error in one of the genes that

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makes it so the drug won’t work? The odds are very high. So as you apply the Darwinian selective pressure of the chemotherapy, well, of course you’re going to select out the cells that are resistant to that drug, and those then become the dominant members of the pack.

GM: So it’s important to understand precisely how cancer evolves?

Marshall: Oh, sure, those are where we get some of our clues as to what we ought to be targeting, those fundamental genetic changes. But we’re only now just having the tools that enable us to test large tumor banks, to say, “Okay, what genes are different now that weren’t there before?” And as an example of that, there’s a new test that was just shown in breast cancer where we can actually look at 18 genes. And those 18 genes predict who should get chemotherapy and who shouldn’t. We’re really learning quickly about being able to profile an individual patient, both to predict outcome and to predict who should get what treatment.

GM: What therapeutic strategies are we focusing on at Lombardi?

Marshall: We have a bunch of different angles. Probably our most famous angle is using the immune system, employing vaccines to rev up the immune system to attack the cancer. We’ve had a recent CNN piece; we’re all over the press with that kind of stuff, so that’s fairly nationally recognized, the work we do in that. We also are targeting a whole host of different fundamental oncogene targets. Each one in its own right has a distinctive profile. Probably the two that are most tightly linked are vaccine and the concept of targeting P53.

GM: P53 is the gene that’s widely implicated in cancer. Is that correct?

Marshall: It’s pretty widely expressed, yes. And it controls a process called apoptosis. The apoptosis analogy is the insurance adjuster. If your car gets wrecked badly, the insurance adjuster comes and decides whether to junk it or whether to pay the money and fix it. Well, that’s exactly what these genes do when deciding on apoptosis. If your cell has been damaged—genetic errors, whatever—then along comes this gene program that assesses the cellular damage and decides, “Should I spend the energy and fix it or should I trash the cell and start over?” Well, in cancer, the insurance adjuster is broken, so the repairs aren’t made and these busted cells accumulate.

GM: What are we doing when we target P53?

Marshall: The therapy—the gene therapy that we are trying to incorporate—is to repair the P53 pathway by replacing the genes in those broken cells. And that should have, essentially, no collateral damage because normal cells already have normal P53. So [the therapy] should only fix the broken cells.

GM: How is that done?

Marshall: That’s the novel part that we helped develop—it’s a nanotechnology that basically encapsulates the gene in a very small envelope that is attracted to the cancer cells and gets taken into the cancer cells. Pretty cool, actually.

GM: You’ve mentioned immunological and gene therapy strategies. What others are being pursued?

Marshall: Well, broadly speaking, I think there are three main areas of research. One is harnessing the immune system. Two is repairing broken genes, if you will, or control cell functions, restoring normal cell function. And the third would be to shut down growth pathways. If you think of the normal cell function as the brake in a car, the other side is an accelerator. Sometimes the accelerator gets stuck in the “on” position. And we now know many of those genes. The famous drugs of course are the ImClone drug, Erbitux, made famous by Martha Stewart; the Iressa drug in lung cancer; the Gleevec drug in chronic myelogenous leukemia (CML). Those are all brakes that basically take the foot off the accelerator and prevent the cell from being under continuous stimulation to grow.

GM: What is your current take on how cancer begins and progresses—are there different theories that suggest different strategies?

Marshall: There are theoretically an infinite number of possibilities—not truly infinite but close to infinite—for the way these things happen. Once you have a few key errors, the odds increase that random events will occur. In other words, the further along the pathway you are—the more evolved a cell is—then the greater the likelihood that a random event will occur. Now, our cells are getting bombarded all the time. There are errors occurring in our cells all the time. And most of those don’t matter a lick, or they matter so much that the cell insurance adjuster comes along and says, “Forget it; let’s get rid of you and start over.” A bad sunburn that

causes your skin to peel versus causing a skin cancer, that's the insurance adjuster saying, "Forget it, we ain't fixing this." But if the error occurs randomly in the insurance adjuster, then these cells accumulate and become cancer. They don't repair. They don't make a decision one way or the other, so they build up. There are important genes that can be randomly hit.

Now you can also inherit a busted gene. The classic is a syndrome called familial adenomatous polyposis, where the insurance adjuster gene is broken in every cell. With these patients, essentially a hundred percent of them will get colon cancer. There is another colon gene that's busted, which is the spell-checker—where the repair gene, the "body shop" if you will, is busted, and can't fix it even if it wanted to. So the

GM: And there are causative factors beyond defects in the gene itself—epigenetic phenomena?

Marshall: That means once a gene gets translated into a protein, it has to then be modified—methylated genes and all sorts of things happen—not just in the raw sequence of the gene but after the messenger RNA is made and after proteins are made, and so those are things that can be broken as well.

GM: So, if there was some difference in the amount of the protein that was being expressed, then we have a problem?

Marshall: Exactly. And what makes that interesting and why it's further complicating is that if you did a gene analysis on that patient, it would be normal. But that

Marshall: We have the only phase I clinical trial development program in the Washington region. We've taken these vaccines from their beginnings just a few short years ago now to a phase III trial in pancreas cancer, which if positive, will get the vaccines approved. I think we've really done a nice job in moving the bar on that. We are the providers of this within this part of the country for our patients. And if you combine the very active clinical program with the basic scientists who are actively involved in the development of these drugs, then it becomes pretty straightforward as to how we distinguish ourselves. We have sort of our own pipeline, if you will, of drugs that we're developing and moving forward into clinic. And we have Dr. Richard Pestell, the Lombardi director,

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errors pile up, and people almost always get cancer. You can inherit these things, and we're sure that there are many other inherited genes that we don't understand yet. We know that common cancers, such as breast and colon and ovarian, have genetic family links, but we don't understand all the genes that go along with that.

But you could also say the hope—and this is true—the hope is that ultimately we will uncover some fundamental differences that enable us to say, "Okay, this is common to cancer. Is there some fundamental switch that we can identify and turn off or turn on that treats a broad range of cancers?" We may uncover some fundamental thing like that.

doesn't mean the gene is functioning properly. That's the concept of using proteomics. So the real answer is in what proteins are out there, not what genes. Because that's the fundamental common pathway, that's what's really doing the business. And, so there's a push—although it's unclear whether it'll come to fruition or not—to use protein analysis instead of genetic analysis in a concept called proteomics.

GM: Is that mainly diagnostic or is it actually therapeutic?

Marshall: Diagnostic. But ultimately you would think it could be therapeutic.

GM: What distinguishes the work we're doing here at Lombardi?

whose focus and goals are on moving away from empirically treating patients—by that I mean, just trying a drug and seeing if it works—to selecting out those patients and determining who should be treated with what. The emphasis is on using our expertise in genetics, using our knowledge to define the population that should receive specific treatments. We're studying our patients—not just looking at their CAT scans. We're looking at molecular changes within them, we're looking at their changed immune responses and trying to correlate all of those things as best we can. There are only a few centers that really do that well, and I think we're one of them. ■