

An interview with Atul Dhir, MBBS, DPhil, President, Cancer Information and Research Group, US Oncology

Community oncology and cutting-edge research

By Peter Tarr, PhD

Atul Dhir is a man of diverse accomplishments. Having been trained as a physician, he also holds a Doctor of Philosophy degree from Oxford University, where he was a Rhodes scholar. In his doctoral research, he sought to uncover the molecular basis for infectious meningitis. In his professional life, he has been a McKinsey healthcare consultant, a vice president at Monsanto, and an entrepreneur, having founded and served as president of a company that provided consulting services to hospitals and physicians.

Seven years ago, Dr. Dhir joined US Oncology and now serves as president of its Cancer Information and Research Group, which oversees the company's clinical research and bone marrow transplant services. About half of the almost 1,000 physicians in US Oncology's nationwide network of community-based oncologists take part in the clinical research portion of the network that Dr. Dhir oversees.

The group's clinical research network is the central component in a major new initiative the company has launched with the Molecular Profiling Institute of Phoenix, Arizona: creating a repository for the storage and genomic analysis of cancer tissue specimens. Called TBAC (Tissue Banking Analysis Center), the facility utilizes many of the same technologies employed by the Biospecimen Core Resource facility, recently established by the National Cancer Institute (NCI) and the National Human

Genome Research Institute, which are now compiling a comprehensive genomic atlas of human cancers.

US Oncology brings its network of clinicians and their patients to the private TBAC partnership; Florida-based Ameripath, Inc., brings a large network of pathologists; and the Molecular Profiling Institute provides a state-of-the-art facility and technologies for tissue storage and analysis. A recently concluded pilot program resulted in the successful "banking" of 2,000 specimens. More than 100 of US Oncology's clinician-researchers are now collecting samples from patients enrolled in five clinical trials. As they are trained in collection procedures, over time, physicians throughout the group's research network will be able to participate.

The tissue bank is a powerful concept, both in terms of its potential impact on patient care and the opportunity it provides for community-based oncologists with an interest in research, as Dr. Dhir explained in a recent interview.

Community Oncology: How did US Oncology's tissue bank project come about?

For a number of years, we've been looking into the question of how the 500 physicians in our research network can participate in more innovative clinical trials. This is where drug development in oncology is headed—trials in which you can ask thoughtful scientific questions based on the target a candidate drug is designed to address or the genomic profile of the

patient's tumor. But the single biggest barrier to doing this has been a lack of tissue samples.

So having a patient's sample and subjecting it to various genomic technologies and diagnostics will enable the physician to select a targeted therapy?

That's the ultimate objective. But specifically, in the case of our tissue bank, having the sample will help our clinicians-researchers determine, in a clinical trial setting, why drug X worked or did not work in a particu-



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lar patient. In many types of cancer, more than 50% of the patients fail to respond to the first line of treatment. Why did it fail? Should they even have gotten the therapy they were given? The therapy failed them because we really didn't understand the tumor, and if we knew the tumor in a more precise fashion, maybe these patients would have received different

therapies. To this end, we will be applying several techniques to analyze the samples—immunohistochemistry, DNA microarrays, and proteomic analysis, although they will vary according to trial type.

You said that not having tissue samples has been ‘a barrier.’ Please explain.

When I say “samples,” I mean high-quality tissue, collected in an ethically appropriate fashion and correlated with the patient’s clinical information. This is the critical element. If, in the context of analyzing clinical trial results, we have a tissue sample and see a certain genomic profile of interest, but we don’t know if the patient responded to treatment or not, we don’t know what to make of that information.

You’re saying that such samples are not readily available.

Science in this instance is far ahead of the logistics. The problem is that the patient and the patient’s tissue sample are often in completely different institutions. For example, the patient goes to a surgeon in a hospital, and a tissue biopsy is taken to help make the diagnosis. That tissue stays in the hospital, in the pathology department. However, after diagnosis the patient goes to an oncologist—more often than not a community-based oncologist—who takes over the patient’s care. But the tissue sample remains under the jurisdiction of the pathology department. The community oncologist’s practice has limited ability to obtain that tissue from the pathology department at the hospital, and the pathology department doesn’t have any access, at that point, to the patient or the clinical information regarding that patient.

The two are disconnected.

That is one aspect of the problem. In part because of this disconnect, there are important unresolved ethical issues surrounding the process of tissue

collection. How do we do it in a scientifically disciplined, IRB [Institutional Review Board]-reviewed, and patient-consented fashion? The fact is, even if you have a tissue bank, samples will not be usable unless they are collected and “banked” in a manner that is standardized and ethically appropriate.

What are some of the ethical issues involved in tissue collection? What kind of consent is called for and who owns the tissue once it has been collected?

In complete candor, these are issues that are still being worked through. Collectively, we will have to wrestle with issues of ownership and the like. But we are clear about the process: to be able to create a tissue bank that can provide answers to some of our questions means that collection has to be done in a clinical trial setting. You’re getting tissue from the patient that may not be of immediate medical benefit, but may help provide benefit in the future. We cannot promise the patient that the tissue they’re giving, versus tissue given for normal diagnosis of the tumor, is going to directly affect their treatment decision-making or outcome. That’s why it has to be handled with the same ethical sensitivity as when you are testing an investigational drug.

How does a tissue bank such as the one you have established differ from the biorepository just organized by the government in connection with the NCI’s Cancer Genome Atlas project?

The government has just created a core repository for cancer tissue in connection with its intention to create a database for understanding the genetic sequences of different tumor types at different stages of tumor development. It is hoped that genetic changes characteristic of different cancers can be catalogued, codified, and published for research purposes. Our tissue bank has a specific pur-

pose. It’s a translational effort focused on collecting tissue for clinical trials funded by pharmaceutical and biotech companies. The goal is to speed clinical development of targeted treatments.

Although ours is a private tissue bank, we are leveraging similar technologies and the same location as the Biospecimen Core Resource facility, which is the repository for the government’s Cancer Genome Atlas project. In fact, our pilot project predated the government effort and involved non-profit partners—TGen [Translational Genomics Research Institute] and IGC [International

“There are great opportunities for community oncologists to do an even higher level of clinical research.”

Genomics Consortium]—who have since been chosen to manage the government repository. And while our private tissue bank benefits the pharmaceutical and biotech companies that are interested in making trials more efficient and effective, to the extent we are successful, we are also benefiting cancer patients.

You’ve noted that good tissue samples are essential for sophisticated analysis of patients and tumors. Can you say a bit more about how this will work in practice?

Tissue samples will help in trials that involve targeted therapy. We’re already designing trials that require the presence of a certain genomic profile in selecting patients who will be candidates for the therapy being tested. Ideally, you want to be able to give targeted therapy only to those patients who are most likely to respond. By trying to ask the most precise science questions, you will need fewer patients in a trial than you would if

you were randomly testing unprofiled, untargeted patients.

So by selecting only those patients who are good candidates for targeted therapies, you are more likely to shorten the time it takes to get the therapy through the approval process.

That's one aspect. The second pertains to trials in which the therapy is not targeted. In analyzing trial results in those cases, we don't know why some patients responded and others did not. To be able to refine the questions for subsequent trials—again, to accelerate the pace of drug development, so you're not asking the same question over and over and making the same mistakes—you can refer to tissue that has been collected from patients who were enrolled in the initial trial and is already in the tissue bank. You can go back and see, retrospectively, if there are any correlative genomic data that

help you get a deeper understanding of why a given patient's tumor responded or did not respond. This step enables you to refine the question and identify more precisely the future population for trials, limiting it to patients who are likely to respond.

What, then, is the bottom line for community oncologists about tissue banking? Is there an opportunity for them?

There are three great opportunities. First, because community oncologists see 85% of cancer patients, they are uniquely positioned to make a huge contribution to future progress. They'll be the ones who have the greatest ability to access the tissue and the clinical information that is vitally needed.

Second, they can offer to their patients the trials and therapies that will help target the tumor in a more precise fashion than has been possible previously. So they are helping accelerate

the development of those therapies and bringing those choices to their patients sooner.

Third, because of this program, community oncologists who have an interest and capability will have the chance to do an even higher level of clinical research than they have been able to do historically. Until now, questions that require collection of tissue specimens could only be answered in an academic setting. Because of the disconnect between tissue samples and clinical information about patient care, for the most part, patients were excluded from the trials that asked the most advanced questions. Our program provides a great opportunity for community oncologists to design and participate in the leading edge of clinical trials.

Dr. Dhir can be reached at atul.dhir@usoncology.com.