New Approaches in the Treatment of Melanoma:

BETTER THERAPEUTICS BASED ON THE BIOLOGY OF THE DISEASE

A Discussion with

Gavin P. Robertson, Ph.D.

Director of Penn State Melanoma Center and Foreman Foundation Melanoma Research Laboratory in the Department of Pharmacology and Penn State Cancer Institute

ManagedCare Oncology recently sat down with Gavin P. Robertson, Ph.D., professor of pharmacology, pathology, dermatology and surgery at Penn State University, to gain his insights on the future of melanoma therapeutics that target multiple disease pathways. Dr. Robertson is also the director of the Penn State Melanoma Center and director of the Foreman Foundation Melanoma Research Laboratory in the Department of Pharmacology and Penn State Cancer Institute. Beyond his role in academia, Dr. Robertson serves as chief scientific officer for Melanovus Oncology, a late preclinical stage oncology company focused on developing new approaches to treating and even preventing melanoma and other skin cancers. Among his research interests and achievements are the targeting of AKT3 signaling in melanoma and the direct delivery of therapeutics into melanoma cells through nanoliposomes and ultrasound.

MCO: Can you give us a little background on melanoma and where there are unmet needs in the therapeutic armamentarium?

Dr. Robertson: Skin cancers are the most diagnosed kind of cancer in the U.S., and melanoma is the deadliest form of skin cancer, accounting for less than 5 percent of all skin cancer cases but 75 percent of skin cancer deaths. The incidence of melanoma has risen dramatically in recent years among young adults, and one person dies of the disease every hour. While the five-year relative survival rate of...
early detected melanoma is around 98 percent, it drops to 15 percent when the disease has spread to distant organs. So people are dying from the disease because you have these cancers developing in your skin, and what makes melanoma different, is that the melanoma cells disseminate through the blood or lymphatic system and end up in distant organs. These secondary tumors can grow to be large and eventually disrupt organ function.

For about 30 years, there hadn’t really been a lot of progress in the treatment of melanoma. Most of the agents looked to poison the cancer cells before the disease affected normal cells, and most of them had been relatively ineffective. Clinicians tried quite a number of agents for the treatment of melanoma, but nothing was ever truly effective. Dacarbazine, for example, is one of the original agents that is still approved by the U.S. Food and Drug Administration (FDA) for melanoma, but it is generally ineffective. In fact, most oncologists today won’t even administer it; for some time, clinicians have tried these agents and offered radiation, which is still used for brain metastases.

Following these early chemotherapeutic treatments, immune therapy came into use. Presently, that’s part of the problem: A huge amount of the resources being used to develop melanoma therapies have been devoted to the immune modulators or immune system regulators or vaccines; however, none of them has really ever panned out to be successful. Then, five years ago, a gene was identified and found to be the most mutated gene in melanoma: the BRAF mutation. This is a series of proteins that talk to one another through a cascade. One protein essentially puts a phosphate group on another and so on, relaying these signals from the surface of the cell all the way to the nucleus, and this process controls cell proliferation. Normally, this cascade of events is controlled, but the mutation turns on one of these upstream proteins and makes it act like it has been phosphorylated. So the upstream protein in patients with this mutation is on all the time and keeps phosphorylating the downstream proteins, leading to unchecked proliferation.

This discovery turned out to be very significant, as 50 percent of people with sporadic melanoma had the BRAF mutation. In other words, if two patients came into the clinic with melanoma, it was likely that one of them would have the mutation. This finding led to research focused on finding drugs that would bind to this mutant protein and shut it down. The first-step drug, vemurafenib (Zelboraf), binds to the site of the mutation and inhibits it. In a phase 1 clinical trial, vemurafenib demonstrated efficacy in 80 to 90 percent of patients. Subsequent phase 2 and 3 trials showed about 50 percent of patients had a sustained response to the drug. This is due to the fact that vemurafenib targets only a single protein and the cancer finds a way around it. As cancer cells develop resistance to the drug, they reactivate proteins downstream of the protein encoded by the mutant gene, and the disease recurs. It’s analogous to using an alternative route on a smaller side street to bypass a traffic jam on a main road. Although you’ve blocked the BRAF pathway, the cancer eventually finds a way around this original route. This persistence of the disease has led to confusion among the oncology community as to how to effectively treat melanoma. What most of the industry and clinicians are doing now is combining vemurafenib with other agents that they think will target other major pathways in melanoma. The idea is that we will be able to reduce disease resistance and prolong the therapeutic effect of treatment through various combinations of agents.

**MCO:** What is Melanovus Oncology’s approach to the treatment of melanoma? How does this approach differ from current treatments?
**Dr. Robertson:** Melanovus Oncology’s philosophy is that the current single-target drugs aren’t working because the disease will likely develop resistance. Furthermore, if you combine drugs, you’re going to have problems because each drug has its own toxicity profile. Sometimes drugs will cancel out one another’s effects, and sometimes they can lead to a whole series of adverse events that you don’t want. As an alternative approach, Melanovus is investigating a first-in-class single agent that targets multiple key disease pathways in melanoma. Since it’s a single agent, the severe toxicity and drug interaction issues associated with multidrug regimens can conceivably be avoided.

Building upon that principle, the company has licensed a patent portfolio from the Penn State Research Foundation and is developing a number of these first-in-class multitarget inhibitor-type drugs. Melanovus has a number of agents like this, but the lead compound is a nanodrug that serves as a base platform to which components targeting different pathways can be added. We believe this is where the field of melanoma treatment is going. A patient comes into the clinic and a blood sample is taken. In that blood sample, there are some of these circulating melanoma cells from the tumors in the patient. The melanoma cells are then profiled. The resulting profile reveals which of the various genes are aberrant in the patient’s disease. What the company is betting on is that we’ll be able to load drugs into the nanoparticle that are essentially able to shut down those particular pathways.

**MCO:** Can you talk a little more about the lead compound in the company’s R&D pipeline and describe how it works?

**Dr. Robertson:** The lead compound in development is Nanolipolee-007. The active ingredient in this nanoparticle — leelamine — is an agent isolated from the bark of pine trees. What’s unique about this agent is that it simultaneously targets the BRAF pathway, the AKT3 pathway, which is active in about 70 percent of melanomas, and the STAT3 pathway, which is equally important in melanoma. So far, it seems to be quite effective, even in cancer cells with the BRAF mutation that are resistant to an agent like vemurafenib. It also appears to be effective in cancer cells with wild-type BRAF; an aggressive form of metastatic melanoma that has fewer treatment options. This is in stark contrast to vemurafenib, which is effective in only half of melanoma patients: those who have the BRAF mutation. In patients with wild-type BRAF, vemurafenib actually promotes disease progression. For this reason, patients with wild-type BRAF typically receive treatment with ipilimumab or interleukin-2, but treatment resistance is developing with these agents as well. Those patients with wild-type BRAF who are resistant to ipilimumab don’t really have another viable treatment option. However, Nanolipolee-007 may elicit a response in these patients because leelamine also targets AKT3 and STAT3 in addition to BRAF. Using the traffic jam analogy I mentioned earlier, in addition to blocking the main road, the agent also eliminates the side streets as alternative routes, thereby reducing the cancer’s ability to bypass and resist treatment. The company has also identified a number of other agents that synergize with leelamine, so in the future, there may be potential to provide complete tumor shutdown if resistance to the base formulation of Nanolipolee-007 develops.

**MCO:** Can you provide us with further detail on the nanoformulation and how this technology facilitates drug delivery?

**Dr. Robertson:** Because of what the company wants to do — that is, have a
platform that you can add components to — you need to have a base that has hydrophobic and hydrophilic domains to adapt to different agents. In other words, agents that can dissolve in water and agents that can dissolve in fat can both be loaded into the nanoparticle. The nanoliposomal membrane that has been developed has a lipid membrane and an aqueous core, so it accommodates both types of agents and is customizable for the delivery of different agents with different chemical characteristics (Figure 1).

What nano means essentially is that it’s less than 100 nanometers in size. In addition, the outside surface of the nanoparticle can be pegylated, preventing it from being recognized by the liver or removed by the immune system and thus increasing circulation time and the chances that it will be taken up by the cancer cells. Furthermore, the nanoparticles allow for increased uptake into tumor cells because of an enhanced permeability and retention effect. What this means is that in tumor tissue you have vessels, but the vessels are very poorly formed. These poorly formed vessels tend to be very porous, so the nanoparticles tend to leak out of the vessels — due to their small size — and preferentially accumulate in the tumor tissue. Cumulatively, these characteristics of the nanoliposomal formulation allow for increased bioavailability, thereby maximizing the therapeutic effect of the drugs delivered.

**MCO**: Where is this product in terms of development and what are the next steps and timing?

**Dr. Robertson**: Investigational new drug (IND) enabling studies will be conducted to establish a method for measuring levels of leelamine contained in Nanolipoole-007 in the serum or tissues of animals over time, following intravenous administration. This will form the basis for dosing in terms of therapeutic efficacy, toxicokinetics and pharmacokinetics. Escalating dose and 10-day repeated intravenous dosing studies in animals will also be conducted, followed by measurement of leelamine levels present in the serum and tissues. Results from these studies will form the basis for IND status for systemic Nanolipoole-007 treatment from the FDA and enable evaluation of the agent in a phase 1 clinical trial. This will be a multicenter trial, with the Melanoma Center at Penn State likely serving as the coordinating site. We anticipate the trial to begin in the second half of 2013.

**MCO**: What do advances in the field of multitarget inhibitors mean for the future of melanoma treatment?

**Dr. Robertson**: For many decades, stage III or IV melanoma meant the patient had six to nine months to live. Now, for the first time in this field, we are seeing some light at the end of the tunnel. Targeted inhibitors hitting single pathways were the first step. And now, similar to the strides made with the introduction of biologic therapy, these developmental compounds represent the next step. So in the future, the treatment of melanoma will likely be centered on combination therapy or multitarget inhibitors such as those being developed by Melanovus. It may turn out that a researcher will stumble across a combination of agents that achieves a persistent treatment response, but I think these first-in-class multitarget inhibitors may be the way that we not just incrementally move the therapeutic field forward but make a giant progressive leap. Agents of this type don’t currently exist for melanoma, meaning we have the potential here to satisfy a real clinical need. It’s exciting stuff.