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Adrenal Cancer: Locks and Keys

Orphan diseases, such as adrenal cancer, often are overlooked in medical research in favor of diseases that afflict far greater numbers of people. Gary D. Hammer, M.D., Ph.D., the Millie Schembechler Professor of Adrenal Cancer, directs the Endocrine Oncology Program in the U-M Comprehensive Cancer Center — recognized as an international center of excellence for the treatment of adrenal cancer. Research in Hammer's laboratory and those of U-M colleagues has led to new national and international therapeutic trials with biological-based therapies that target molecular defects. →

Q: How rare is adrenal cancer?
A: The Orphan Drug Act of 1983 defined rare as 200,000 or fewer cases a year. With only 500 cases a year in the U.S., adrenal cancer can perhaps be considered an ultra-rare disease. The challenge with a rare disease is threefold. Most doctors who see a case have never seen a case before and might never see one again; there are too few physicians and scientists researching the disease; and there is no funding because the return on investment from the point of view of government or industry is too incremental. Having a dedicated center and research group at the U-M is so important and can provide real leverage to make a difference. Because most patient advocacy groups link themselves to our patient-oriented web sites and the U-M community in general, we see a high percentage of the patients across the country, as well as from Hong Kong, South Africa, Europe and Australia.

Q: What do we know about adrenal cancer? How can we offer more effective diagnosis and treatment?
A: Adrenal cancer is very aggressive. The only approved drug for the treatment of patients with this disease is mitotane, a derivative of the pesticide DDT. It's effective in a small subset of patients but has significant toxicity and isn't well tolerated. We aim to understand the genetics of the disease in hope of finding new targets for therapy. We have a hunch that we first must identify the common denominator across patients and the mutations that occur that are important for initiating the disease. Then we can dive into what's unique about each cancer and each patient. Most cancer is sporadic: one mutation in one cell. There are also cancers that we refer to as familial cancer syndromes, where every cell in your body has the mutation and you pass it on to your children and they pass it on to their children. We figured out that some genes involved in familial adrenal cancer are the same genes that are mutated in sporadic adrenal cancer. They are the WNT and IGF pathways — which are both signaling pathways in the cell — and the tumor suppressor gene, P53. The challenge has been that cancer is tough, and when we've tried to inhibit the IGF pathway, it's been effective in only a very small proportion of patients, despite the fact that over 80 percent of adrenal cancers have mutations that cause over-activation of the pathway.

Cancer cells find other mutations to get themselves around the block. That means most patients with adrenal cancer have handfuls of mutations, not just one or two, so it ends up being a very difficult cancer to treat. We hope that studies that dive deep into the mechanisms by which the normal adrenal gland grows will give us clues. As such, a big portion of our work focuses on adrenal stem cells. Moreover, many of these projects involve our colleagues around the world because research in a rare disease demands collaboration to make progress.

Q: What will that take?
A: Having resources to expand and do research has been critical. The other kind of leverage that's been important at Michigan is that we've grown the international team. In 2003, we held a meeting where we brought together the handful of people around the world who were seeing patients with adrenal cancer. We realized there was no consensus about how to treat, and none of us knew what the others were doing. We vowed to work together on research, education and clinical care, and came up with guidelines.

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This consortium is important because to learn anything about a rare disease requires collaboration and large data banks. The consortium also has enabled us to leverage research to garner funds from big pharma, which paid for one of the first large trials for adrenal cancer, last year. That trial was possible only because of the research done here at Michigan on the role of the IGF pathway in adrenal cancer. And when the National Cancer Institute took on a bold initiative to sequence the entire genome of 20 of the most common cancers, they later chose adrenal cancer as the first rare cancer to go after because of our consortium and our collaborative nature.

Q: What strengths does the U-M bring to the study and treatment of adrenal cancer?

A: Michigan has a history of adrenal research that goes back 50 years, and with great support from many grateful patients, we've been able to assemble a world-class team that will lead the field for years to come and be able to make significant strides through coordinating international efforts. What sets Michigan apart is the fact that we have strengths in the basic science of the adrenal gland, in translational science, and in the clinical arena. No one else has what Michigan has in terms of incredibly strong basic science and some of the best clinical folks in the world.

Q: How do shrinking funds affect the work?

A: We've developed a world-class database and repository for adrenal disease and adrenal cancer. It's essential that it have continuing updating and maintenance. A significant investment would provide critical infrastructure for this effort. We've also developed a robust clinical research team here. Most of our trials are investigator-initiated; meaning that while they come from our home-grown research efforts, we often get no money from industry to run such a trial. These trials sometimes cost over $20,000 per patient. It's critical that we try to fund these trials, which are often the most creative and rationally-based out there for adrenal cancer.

Q: How will our alliance with Brazil benefit our adrenal cancer research?

A: Adrenal cancer in Brazil is 15 times more prevalent than anywhere else in the world, mostly due to one mutation in one gene. For that reason, Michigan has been collaborating with the adrenal cancer group in Sao Paulo for a number of years. This collaboration was instrumental in forming our international network.

Q: What can studying one of its very rare forms teach us about other forms of cancer?

A: One might argue that since all cancer is about uncontrolled cell growth, what we learn about any one cancer will inform us about the others. Rare cancers can be examples of those cancers where it's easier to tease out the mechanism, since there are often only a few genes that are critical linchpins for the disease. Adrenal cancer is a component in a small handful of familial cancer syndromes. We've learned a lot about the role of those genes in many cancers by studying those cancer syndromes, because we know they're involved in the etiology of those cancers. It's easier to study how one or perhaps a few locks and keys work together than how 50 work.

Interview by Jeff Mortimer