The Mathematics of Cancer Metastases

By Mike Fillon

Ja
cob Scott, M.D., began his career studying physics and engineering but entered medical school when he discovered his true calling: to treat, and hope-

fully cure, cancer patients.

Although Scott knew beforehand that strides had been made in understanding the disease’s many complexities and vari-
ants, he became frustrated that knowledge about metastases lagged far behind. He found that that although biologists had researched many aspects related to metas-
tases, for the most part no one had tried to unify these aspects into a coherent theory.

He believes that helps explain why the cure rate for metastatic disease had barely budged over the years, and he hoped to help change that. After meeting Alexander R.A. Anderson, Ph.D., chair of integrated mathematical oncology at H. Lee Moffitt Cancer Center in Tampa, Fla., he was on his way.

Scott is now a research associate in the department of radiation oncology at Moffitt and, along with Anderson, has begun to develop a unifying theory on the causes of cancer metastases. Their the-

ory appeared online May 24, 2012, in Nature Reviews Cancer.

The article describes the researchers’ focus: circulating tumor cells (CTCs), which exist throughout the vas-
cular system in advanced cancer patients. Although theories abound about when and where CTCs form, their role in metastases is not well known.

Beyond Seed–Soil

In their article, Scott, Anderson, and Peter Kuhn, Ph.D., associate professor in the department of cell biology at the Scripps Research Institute Physical Sciences–Oncology Center in La Jolla, Calif., wrote that although Paget’s seed–soil hypothesis suggests that both the site of a metastasis (the soil) and the metastatic cells (the seed) are necessary for metastasis to occur, how seeds are disseminated to specific soil remains a puzzle. “We think that it is during this poorly understood phase of metastasis that we can answer some important questions,” said Scott.

In theory, until the evolution of a suitable seed, any number of CTCs could flow through the circulation and arrest at end organs without forming metastases, Scott continued. Because tumor heterogeneity is thought to expand with tumor progression, at some point a seed suited to a specific soil within that patient’s body will develop. The seed must find its soil.

“We think this process is governed by solvable physical rules that relate to the dynamics of the circulatory flow between different organs and how these organs filter,” said Scott. “Although these biological mechanisms are not yet known, we might be able to infer their existence by finding out which measurements do not fit a model that is defined only by physical flow and filtration.”

Understanding Cancer With Physics and Mathematics

That’s where mathematical modeling comes in, which though not new in cancer research has perhaps been under-

represented, according to some experts. Larry Norton, M.D., medical director of the Evelyn H. Lauder Breast Center at Memorial Sloan–Kettering Cancer Center in New York, has long believed that more mathematics is needed to better understand and develop better cancer ther-

apies. Specifically, Norton has said that oncologists should spend more time devising equations that explain how fast tumors grow, how quickly cancer cells develop resistance to therapy, and how often they metastasize.

Larry A. Nagahara, Ph.D., director of the Office of Physical Sciences–Oncology at the National Cancer Institute, said that mathematicians, physicists, and engi-

neers can bring new perspectives to understand cancer. “I think by having a diverse group of disciplines, we can get some fresh views and contribute to our understanding.”

Earlier this year, Nagahara served as scientific adviser on the Physics and Mathematics of Cancer workshops held at the Kavli Institute for Theoretical Physics in Santa Barbara, Calif. The workshops focused on physical and mathematical models of tumor initiation, progression, and metas-
tases, as well as developing new physical probes of cancers.

Quantifying Biological Processes

Scott, who is working on a Ph.D. in math-

ematics at the University of Oxford Centre, and colleagues propose four key biological processes that could be quantified:

1. The rate at which the tumor sheds CTCs into the vasculature
2. The CTC phenotypic heterogeneity, defined as the distribution of CTC phenotypes present in the circulation
3. The filtration fraction (the proportion and type of CTCs “arrested” in a given organ)
4. How quickly CTCs are cleared from the blood or organ after arrest
Looking Treatment Complications in the Mouth

By Norra MacReady

Complications of the mouth occur in many cancer patients—often without warning—leaving a particularly sour taste in patients’ mouths.

Perhaps the disconnect exists because mountains of information are pushed on individuals who often are still reeling from the diagnosis, said radiation oncologist Mohan Suntha, M.D., professor of radiation oncology at the University of Maryland in Baltimore. “They’re told about the aggressive, multidisciplinary approach to their disease, and they’re told about the side effects, some of which can be dramatic. My best guess is that the dental issues are raised at that time, but when you add them to that laundry list, it’s easy to see how they drop to the bottom, given everything else the patient has to think about. So when they start to experience the dental complications, they say, ‘I was never told about this.’ That’s one reason why dental evaluation is so important: It’s hard to ignore the issue when you’re actually being referred to the dentist.”

Oral side effects occur in virtually all patients receiving radiation for head and neck malignancies, in approximately 80% of hematopoietic stem cell transplant recipients, and in nearly 40% of chemotherapy patients. Effects range from mild and transient to severe and persistent, sometimes even permanent. “Almost every cancer therapy has associated oral complications, even if the cancer is distant from the mouth,” said Timothy Meiller, D.D.S., Ph.D., professor of oncology and diagnostic sciences at the University of Maryland and the Marlene and Stuart Greenebaum Cancer Center.

Effects to Watch For

Radiation brings the most substantial complications. A standard dose of head-and-neck radiation is 70 gray (Gy), but salivary glands may be damaged at doses as low as 26 Gy, Suntha explained. Saliva protects against oral infection and tooth decay, so the dry mouth (xerostomia) resulting from salivary gland damage increases risk of cavities and infection, including fungal infections such as candidiasis.

One of the most serious complications of head-and-neck radiation is osteoradionecrosis of the jaw, in which the bone loses its mucosal covering and deteriorates, said Cherry Estilo, D.M.D., of the Memorial Sloan–Kettering Cancer Center in New York. Symptoms include pain, swelling of the oral tissues, exposure of the bone, tooth