Researchers use mathematics to fight cancer

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Using mathematical models, researchers in the Integrated Mathematical Oncology (IMO) program at Moffitt Cancer Center are focusing their research on the interaction between the tumor and its microenvironment and the "selective forces" in that microenvironment that play a role in the growth and evolution of cancer.

According to Alexander R. A. Anderson, Ph.D., chair of the IMO, mathematical models can be useful tools for the study of cancer progression as related to understandings of tumor ecology.

"Cancer is a complex disease driven by interactions between tumor cells and the tumor's microenvironment," Anderson said. "By developing mathematical models that describe how tumors grow and respond to changes in their surroundings (such as treatment), we can better understand how an individual patient might respond to a whole suite of different therapies."

Robert Gillies, Ph.D., chair of imaging and metabolism at Moffitt, is working closely with Anderson and Robert Gatenby, M.D., chair of Diagnostic Imaging. They say it is important to pair tumor imaging with mathematical model building.

"Imaging is a key to validate mathematical modeling," Gillies said. "Because imaging can be conducted over time, it affords us a good look at the actively changing systems in tumors that are predicted by the models."

For Gatenby, because cancer is an evolving, always changing nonlinear system, it must be monitored over time and space.

"Imaging noninvasively captures tumor changes, and the mathematical models, which are much more rigorous than language, can then be used in cancer research," Gatenby said.

Clinical imaging and mathematical modeling combined will afford clinicians a valuable predictive tool. One tool will be familiar. Just as meteorologists develop "spaghetti models" from satellite images to predict the myriad possible paths of hurricanes, Anderson said, they will be able to generate similar models to inform clinicians about a patient's risk, which treatments may be best and whether recurrence is possible.

"By incorporating specific information about a patient, such as the size of their tumor, the treatments they have had, the organ that the cancer is growing in, we can predict forward in time how the tumor will grow, shrink, and respond to different combinations of therapies. By the results of imaging, biological experiments and mathematical models, we are leading the world in patient-specific medicine," Anderson said.

Mathematical models generated by IMO researchers are already finding clinical uses.

Fibroblasts contribute to melanoma tumor growth

"We used an integrated mathematical and experimental approach to investigate whether melanoma cells recruit, activate and stimulate fibroblasts to deposit certain proteins known to be pro-survival for melanoma cells," Anderson said.

Fibroblasts, the most common connective tissue functioning in the extra cellular matrix, were known to be activated by and drawn to cancer cells.

When they investigated the relationship between fibroblasts and tumors using mathematical models, Anderson and colleagues found that fibroblasts have direct effects on melanoma tumor behavior, including aiding tumor growth and tumor drug resistance. They published their findings in *Molecular Pharmaceutics*.

Deadly glioblastomas better understood through mathematical models

IMO researchers and colleagues also developed mathematical models for investigating the progression of glioma, an aggressive and fatal form of brain cancer. The mathematical models augment imaging and histologic grading of gliomas, graded on their blood vessel growth patterns (an angiogenic feature) and incorporating the tumor's cellular and microenvironmental changes.

When the researchers observed a disparity between grading schemes and tumor activity observed through imaging, they developed a mathematical model based on changes in cell appearance, proliferation and invasion rates. The new model improved predictive and prognostic ability.

"Being able to identify and predict patterns of dynamic changes in glioma histology as distinct from cellular changes in appearance and proliferation may provide a powerful clinical tool," Anderson said.

They published this study in a recent issue of Cancer *Research*.

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