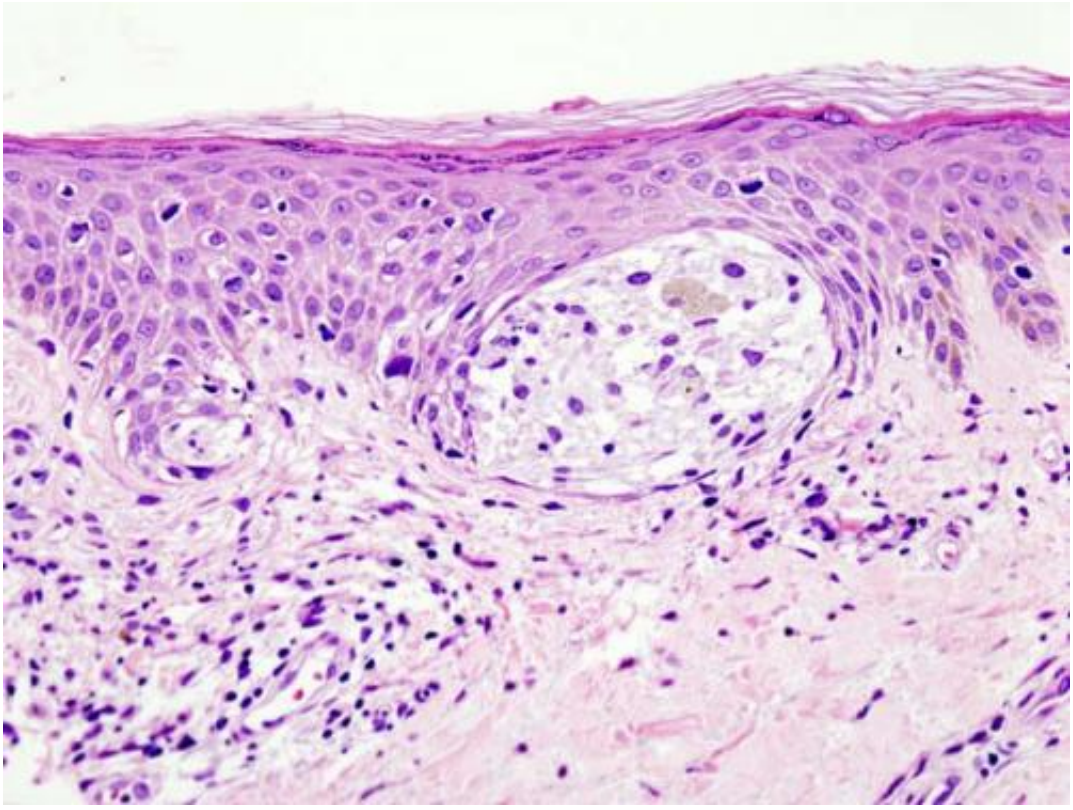
Researchers predict melanoma responses through mathematical modeling

November 10 2016



Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Scientists have significantly improved their understanding of cancer and have developed numerous therapies that have helped to reduce patient mortality; however, the majority of drugs that make it to the clinical trial phase of development fail, despite promising data in laboratory studies.

One reason for this high rate of failure is that preclinical studies cannot determine how effective a drug will be in the long term or accurately predict how effective it will be in different patients.

Preclinical studies are limited by time constraints and cell model systems that do not portray all of the genetic variability that is seen in different tumors and patients. Researchers from Moffitt Cancer Center's Integrated Mathematical Oncology (IMO) Department are overcoming the limitations of common preclinical experiments and clinical trials by studying cancer through mathematical modeling. A study led by Alexander "Sandy" Anderson, Ph.D., chair of IMO, and Eunjung Kim, Ph.D., an applied research scientist, shows how mathematical modeling can accurately predict patient responses to cancer drugs in a virtual clinical trial. This study was recently published in the November issue of the *European Journal of Cancer*.

Cancer is a complicated process based on evolutionary principals and develops as a result of changes in both tumor cells and the surrounding tumor environment. Similar to how animals can change and adapt to their surroundings, tumor cells can also change and adapt to their surroundings and to cancer treatments. Those tumor cells that adapt to their environment or treatment will survive, while tumor cells that are unable to adapt will die.

Preclinical studies with tumor cell models cannot accurately measure these changes and adaptations in a context that accurately reflects what occurs in patients. "Purely experimental approaches are unpractical given the complexity of interactions and timescales involved in cancer. Mathematical modeling can capture the fine mechanistic details of a process and integrate these components to extract fundamental behaviors of cells and between cells and their environment," said Anderson.

The research team wanted to demonstrate the power of mathematical

modeling by developing a model that predicts the responses of melanoma to different drug treatments: no treatment, chemotherapy alone, AKT inhibitors, and AKT inhibitors plus chemotherapy in sequence and in combination. They then tested the model predictions in laboratory experiments with Keiran Smalley, Ph.D., director of the Donald A. Adam Comprehensive Melanoma and Skin Cancer Research Center of Excellence at Moffitt, to confirm that their model was accurate.

To determine the long-term outcome of therapy in different patients, the researchers developed a virtual clinical trial that tested different combinations of AKT inhibitors and chemotherapy in virtual patients. The researchers show that this Phase i trial (i for in silico, and representing the imaginary number) or virtual clinical trial was able to reproduce patient responses to those observed in the published results of an actual clinical trial. Importantly, their approach was able to stratify patient responses and predict a better treatment schedule for AKT inhibitors in melanoma patients that improves patient outcomes and reduces toxicities.

"By using a range of mathematical modeling approaches targeted at specific types of cancer, Moffitt's IMO Department is aiding in the development and testing of new treatment strategies, as well as facilitating a deeper understanding of why they fail. This multi-model, multi-scale approach has led to a diverse and rich interdisciplinary environment within our institution, one that is creating many novel approaches for the treatment and understanding cancer," Anderson said.

More information: Eunjung Kim et al. Phase i trials in melanoma: A framework to translate preclinical findings to the clinic, *European Journal of Cancer* (2016). DOI: 10.1016/j.ejca.2016.07.024

Provided by H. Lee Moffitt Cancer Center & Research Institute