# New drug candidate may prevent metastasis

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A UCF College of Medicine researcher is developing a new treatment that could slow or even stop cancer cells from spreading.

Dr. Otto Phanstiel, a medicinal chemist, has created a compound that literally stops cells from moving and is working with the Mayo Clinic to optimize the design to make it more effective at keeping cells—particularly cancer cells—in place. Cancer that metastasizes—or spreads from the original tumor to other parts of the body—is the leading cause of death for most patients.

Dr. Phanstiel has centered much of his research on polyamines, organic compounds that are essential for normal cell growth, development, and the regulation of cell death. Scientists know that elevated levels of polyamines are associated with many cancers. Polyamines are also found in natural products harvested from nature.

In the 1990s, investigators at the University of British Columbia discovered a class of antimetastatic compounds in the extract of a sea sponge that was harvested off the coast of Motupore Island, New Guinea. They named these amine-containing compounds Motuporamines.

Dr. Phanstiel and his team synthesized derivatives of one of these isolated compounds, Motuporamine C. The compound has a polyamine tail—a section trailing off the main structure, improving its solubility in water. Scientists believe this tail may help Motuporamines bind to the active site of key enzymes in the body.

Dr. Phanstiel's Motuporamine C UCF derivative may help prevent metastasis in breast cancer patients.

In his latest project, Dr. Phanstiel has created a derivative of Motuporamine C that is more effective at keeping cancer cells in place so they cannot spread. He found that the UCF version (depicted above) was twice as effective as the natural compound at blocking cell migration.

"Who knows if Mother Nature made the perfect antimetastatic compound right out of the box? As medicinal chemists, we like to tinker with those molecular messages and see if we can make them better," said Dr. Phanstiel. "We wanted to figure out the secret code to what that amine tail could look like in an optimized design. By moving the polyamine chain away from the large ring by a single carbon spacer, we saw significant improvements in drug potency."

Dr. Phanstiel tested his new compound against a pancreatic cancer cell line called L3.6pl, which was acquired from MD Anderson Cancer Center at Orlando Health. This cell line is very aggressive and incredibly efficient in moving or metastasizing from the pancreas to the liver in mice models.

"L3.6pl is a very aggressive cell line that is hyper-metastatic. This mouse model is used to block the spread of tumor cells in vivo. We wanted to see if we could defeat this Frankenstein cell line of pancreatic cancer that is trained to run and spread and grow fast. The compound worked and blocked the spread of these cells to the liver. Thus, we really have something special," he said.

Dr. Debabrata Mukhopadhyay, a cancer researcher at the Mayo Clinic, verified Dr. Phanstiel's results in his lab and says this new research has incredibly high potential. The next step, he said, is to get funding to bring the UCF derivative through the preclinical steps and then clinical trials to see how it works on patients. Such drug development is a long and costly process.

"Finding this funding is a challenge for any drug, and particularly with novel drugs; we need to have patience," said Dr. Mukhopadhyay. "However, this drug has high potential, so it is worth trying to bring it through these steps because the potential is there."

A new anti-metastatic drug could be a game changer for cancer patients. Metastatic cancer accounts for 90% of cancer deaths, but anti-metastatic drugs are few and far between.

Due to current clinical trial designs, cancer drugs cannot advance to clinical trials unless they show cytotoxic or cell poisoning effects as endpoints. This means that many anti-metastatic drugs that stop cells from moving but do not harm or kill the cancer cells have been unable to advance, Dr. Phanstiel noted.

Dr. Phanstiel's UCF derivative of Motuporamine C is unique in that it blocks cell migration at low concentrations and is cytotoxic at higher concentrations, making it stand out against other anti-metastatic drug candidates. He hopes this distinction can help bring the drug candidate to clinical trials.

The next step in his research is demonstrating what Dr. Phanstiel calls the "mechanism of action," or how the drug candidate is actually producing these anti-metastatic effects.

"We are trying to understand how our drug is actually blocking metastasis. What are the targets? Is it selectively killing the metastatic cells? Is it disorganizing the cells' ability to move? There are drugs that have made it through the process just based on their effectiveness, so we are embracing the fact that we have something promising, but as scientists, we are excited to understand more."

Dr. Otto Phanstiel is a Professor of Medicine with over 30 years of

research and teaching experience, 28 of it at UCF. He received his Ph.D. in Organic Chemistry from the University of Florida in 1988 and has conducted research into polyamines, cancer treatment and immunoresistance. Early examples of his work on motuporamines were reported in the *Journal of Medicinal Chemistry.*

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