

Designing Novel Protein Mimetics to Target Metastatic Melanoma



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Dr. McInnes and his company, PPI Pharmaceuticals, were recently awarded a \$225,000 small business technology transfer award to develop technology that can target cancer cells without harming healthy cells.

The National Institutes of Health (NIH) Small Business Technology Transfer (STTR) award will be used to advance REPLACE, a drug discovery technology developed at the University of South Carolina, and further apply it to molecular targets in cancer.

Every year in the United States more than 76,000 new melanoma cases are diagnosed - one every eight minutes - while more than 9,000 of these cases will be fatal. An insidious trait of melanoma is its ability to widely spread to other parts of the body. Melanoma is the deadliest of all skin cancers. It accounts for only four percent of skin cancers, but 80 percent of skin cancer-related deaths.

“Melanoma is the most dangerous form of skin cancer and occurs when skin cells acquire DNA damage mostly as a result of ultraviolet radiation from the sun or tanning beds,” explains **Dr. Campbell McInnes**. “Mutations that result from damage to the melanocytes allow the malignant cells that arise in the skin to multiply uncontrollably.”

While the overall five-year survival rate is high, that rate decreases dramatically once melanoma spreads to other parts of the body. “If diagnosis occurs at an early stage and treatment is rapidly initiated, melanoma is almost always curable. Unfortunately this disease may not be recognized in time, allowing it to metastasize to other parts of the body. At this stage it is very difficult to manage and becomes resistant to treatment,” according to Dr. McInnes.

Despite tremendous advancements in medicine and cancer

treatment as a whole, the melanoma death rate has remained static over the past 30 years. More effective options for prevention, diagnosis, and treatment are urgently needed to transform the outlook for patients.

The recent FDA approval of the drug vemurafenib is a breakthrough. “This drug was initially shown to be highly effective in melanoma patients who overexpress a mutant form of the BRAF gene, a frequent occurrence in those with metastatic disease,” said McInnes. Despite initial dramatic responses in a significant proportion of treated patients, including what appeared to be almost complete



remission, many individuals quickly relapse and progress even more rapidly than before due to a paradoxical activation.

McInnes said that sometimes these breakthrough drugs lose their effectiveness and can instead activate and stimulate the tumor growth. McInnes and his team are now trying to

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Education

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develop and synthesize a library of “protein mimetics” – mimics of nature – that can be developed as novel, targeted, anti-cancer therapeutics effective against tumor cells that have become resistant to certain drugs.

“Our approach is to develop BRAF inhibitors that block protein-protein interactions of the enzyme rather than interfere with the catalytic activity,” said McInnes. “These interactions are critical to paradoxical activation and we can circumvent the major resistance mechanism to vemurafenib in this way. To do this, we are making use of a unique strategy called REPLACE. This technology has been specifically developed for targeting protein-protein interfaces and in general makes drug design and development

more feasible for these types of interactions. Through the design of protein mimetics, it therefore opens up many new potential drug targets which are not amenable to conventional drug discovery.”

Using computer screening, design, and chemical synthesis, McInnes and his team are also applying REPLACE to develop novel, anti-cancer drugs based on inhibition of protein kinases involved in regulation of the cell cycle in cancer cells. “Cancers are dependent on a number of altered molecular pathways typically involving bypassing of normal checkpoints in the cell cycle. Cell cycle inhibitors can potentially help treat tumors that develop resistance to single agent therapy, thus combinations of therapeutic approaches including

targeted agents will be necessary to provide durable control and cure for patients,” adds McInnes. Dr. McInnes’ laboratory is planning to demonstrate the potential of these protein mimetic compounds as novel chemical biology tools that can better target cancer cells by overcoming resistance that has been clinically observed with current oncology therapeutics. McInnes, who also owns PPI Pharmaceuticals, was recently awarded an NIH Small Business Technology Transfer (STTR) award to advance REPLACE technology. This technology allows for pharmaceutical development against targets previously inaccessible through conventional methods and therefore facilitates next generation cancer therapeutics.