Novel Anti-metastatic Agents that Reverse Epithelial-mesenchymal Transition in Cancer.

Innovations
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Category

Therapeutic: Novel chemical entity

Problem

Significant unmet need for metastatic cancer

Technology Overview

Novel small molecule drug that can inhibit metastasis

IP Status

- Patent Pending
- Available for Exclusive or Non-Exclusive Licensing

Value Proposition

- Revolutionize the treatment of metastatic cancer
- No DNA damage like other TOP2A therapies.

Market Attractions

- The market potential for CRC is 9 billion (2020) and still increasing.
- EMT drugs may have the potential for treating other prominent diseases

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Problem: Nine million people will die from cancer this year and 90% of those deaths result from metastatic disease. Colorectal cancer is one of the most prevalent cancers with a stage 4 5-year survival of 11%. Epithelial-mesenchymal transition (EMT) is a driving force in tumor progression that transforms relatively benign epithelial tumor cells into mesenchymal cells with cancer stem cell properties, promoting drug resistance, invasion and increased metastasis. There are currently no effective therapies for most late stage metastatic cancers. Thus, there is a significant unmet need and market demand for safer more effective drugs.

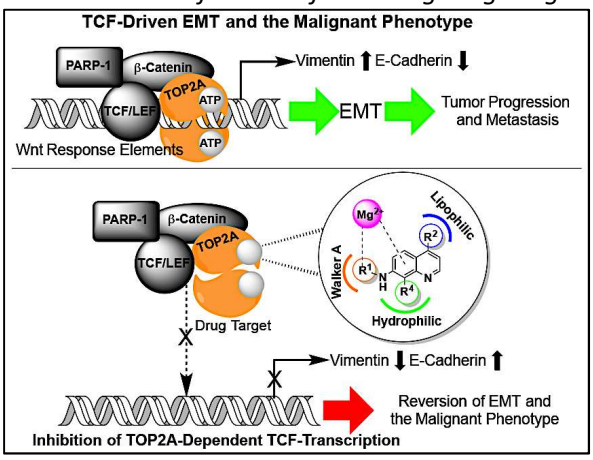
Solution: A University of Colorado research group led by Dr. Dan LaBarbera is developing small molecule drugs that reverse EMT, making malignant mesenchymal cells become more benign epithelial cells. Reversing EMT will inhibit metastasis and sensitize tumors and metastatic lesions to other clinical drugs and therapies. The inventors have determined that Wnt/TCF transcription is a master regulator of EMT in CRC.[1] The Wnt signaling pathway regulates T-cell factor (TCF) / lymphoid enhancer factor (LEF) transcription and is the root cause of >90% of all colorectal cancer and 100% of familial adenomatous polyposis. Mutations in the Wnt pathway cause aberrant TCF transcription and this is the major driving force for CRC initiation, tumor progression, and malignant transformation.

The investigator's lead drugs are ATP-competitive inhibitors of topoisomerase IIα (TOP2A), and TOP2A is a required DNA binding factor recruited by the TCF-transcription complex. Likewise, TOP2A may be recruited by other factors that regulate EMT and other metastatic genes. This project has the potential to revolutionize the treatment of metastatic cancer, which currently has no sustainable options. If successful, EMT drugs could be used to treat a variety of human cancers with multi-billions in market potential.

Advantages:

- EMT targeting drugs may slow primary tumor growth but will inhibit metastasis.
- There are no effective therapies for most late stage metastatic cancers, thus, EMT targeting drugs may help extend patient survival rate beyond 5 years.
- When used in combination with other drugs EMT drugs can sensitize primary tumors and metastatic lesions.

Mechanism of Action of EMT targeting drugs:



Additional Documents and Sources:

(1) Zhou, Q.; Abraham, A. D.; Li, L.; Babalmorad, A.; Bagby, S.; Arcaroli, J. J.; Hansen, R. J.; Valeriote, F. A.; Gustafson, D. L.; Schaack, J.; Messersmith, W. A.; LaBarbera, D. V. Topoisomerase IIα mediates TCF-dependent epithelial-mesenchymal transition in colon cancer. *Oncogene* **2016,** 35, 4990-4999.
(2) Topoisomerase IIα inhibitors and methods of treating cancer and using the same" Provisional patent application No. 62/827,818 filed April 1, 2019; available under NDA.
(3) Pending publication in the *Journal of Medicinal Chemistry* before 2020. Drug Design Targeting TCF-Driven EMT as a Therapeutic Strategy for Colorectal Cancer.

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