

# Irreversible Inhibitors of Type II Transglutaminase

#### **Summary**

Cancer stem cells (CSC) comprise a subpopulation of tumor cells that are slow-cycling, express stem cell markers, display enhanced

#### **Key Investigator**

Abdullah Akbar Gail Johnson Jeffrey Keillor Matthew Fisher Richard Eckert

## **Field**

Therapeutic Cancer

#### Technology

Small molecule type II transglutaminase inhibitors

#### **Advantages**

Lead TG2 inhibitors provide a potential therapeutic for aggressive cancer phenotypes.

Utility extends to other conditions with altered TG2 function

#### **Status**

Available for licensing Available for sponsored research

Patent Status Pending

## UMB Docket Reference

RE-2016-066

## **External Reference**

Eckert RL et al. (2015) *Mol Carcinog.* 54(10):947-958.

Kerr C et al (2016) Oncogene. DOI:10.1038/ onc.2016.452. population of tumor cells that are slow-cycling, express stem cell markers, display enhanced migratory potential, undergo epithelial-mesenchymal transition (EMT), and form rapidly growing and highly vascularized and aggressive tumors. CSC often survive conventional cancer therapy and proceed to form rapidly growing and highly aggressive and invasive tumors. Studies suggest that type II transglutaminase (TG2) is overexpressed in cancer and associated with aggressive cancer phenotypes, drug resistance, and survival. TG2 expression has been studied extensively in pancreatic, breast, ovarian, epidermal squamous cell carcinoma, prostate, glioma, melanoma, lung, and colon cancer. In these cancers, TG2 levels are markedly elevated and have been shown to affect CSC survival, migration, and invasion. In collaboration with the University of Ottawa, UMB researchers have developed and validated a range of small molecule inhibitors of TG2 and demonstrated their anti-cancer efficacy in epidermal squamous cell carcinoma cell lines.

#### Market

Commercially-available TG2 inhibitors are not as well-characterized or clinically-relevant as NC9, the lead research compound identified at UMB. Naturally occurring inhibitors do not inhibit human TG2, and most synthetic inhibitors are also potent Factor XIII inhibitors, affecting coagulation. The novel TG2 inhibitors described here show superior in vitro selectivity toward human TG2. There is currently one TG2 inhibitor undergoing clinical development, being evaluated for the treatment of Celiac disease. Targeting TG in cancer represents a novel treatment strategy. In addition to their application in cancer, these TG2 inhibitors may be used to study other biological functions and pathology where TG2 is involved, such as autoimmune, inflammatory, and neurological diseases.

## Technology

NC9 is a TG2-selective targeted,

covalent inhibitor. NC9 inhibits TG2 by binding to its transamidase site, locking it in a conformation in which the GTP binding site is disrupted and inactivated, thereby abolishing the activity that is required for the pro-cancer and CSC survival activity of TG2. TG2 is highly elevated in epidermal cancer cells (ECS) and TG2 knockdown, as well as treatment with NC9, have been shown to reduce ECS cell survival, spheroid formation and Matrigel invasion and migration, as well as enhanced apoptosis and impaired EMT.

## **Technology Status**

This technology has been tested in vitro in squamous cell carcinoma cell lines.



(A) TG2 inhibitors suppress cancer stem cell survival. SCC-13 cells were permitted to form spheroids for eight days before being treated for 48 h with 0 or 20  $\mu$ M of the indicated inhibitor, and surviving spheroids were counted.

B) TG2 inhibitors reduce SCC-13 cell matrigel invasion. SCC-13 cells were plated on a Matrigel-coated membrane in the presence of 0 or 20  $\mu$ M of the indicated inhibitor, and after 24 h the cells migrating to the internal side of the membrane were counted.

\*The values are mean ± SEM, n=6 (P<0.001)

Contact: Mark Wozniak Mark.Wozniak@umaryland.edu 410-706-7293 University of Maryland, Baltimore 620 W. Lexington St., 4<sup>th</sup> Floor Baltimore, MD 21201