

BCHM 421/422 – 2020/2021

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Project Title: Developing novel actin-targeting antibody drug conjugates for metastatic cancers

Keywords (3-5): cancer, cell invasion, actin toxins, antibody drug conjugates

Project Outline:

Metastasis involves the dissemination of cancer from the primary tumor to secondary sites, and is the leading cause of cancer-related deaths. To address this, new therapies are needed that target major drivers of metastasis. Early events in metastasis require rapid extension of specialized cell protrusions that depend on polymerization of filamentous actin (F-actin) to breach basement membranes, invade tissues, and blood vessels or lymphatics. Targeting dynamic F-actin in tumor cells may provide additional forms of therapy to limit progression to metastatic disease. We recently showed that the F-actin severing and capping toxin Mycalolide B induced rapid loss of leading edge protrusions and suppressed motility and invasion of HER2+ breast and ovarian cancer cell lines at low nanomolar doses. In HER2+ tumor xenograft models, Mycalolide B treatment suppressed both tumor growth and metastasis. Our next objective is to achieve delivery of simplified analogs of this toxin to HER2+ cancer cells as HER2 antibody-drug conjugates or nanoparticles.

Project Goals:

1. Test synthetic analogs of Mycalolide B on filamentous actin (F-actin) polymerization in vitro
2. Test lead actin toxin analogs for effects on F-actin dynamics in cancer cells
3. Test the activity and cell specificity of actin toxin analogs conjugated to HER2 antibodies

Experimental Approaches:

1. Pyrene actin polymerization assays
2. Cell culture, transfection, treatments, and staining of F-actin
3. Fluorescence microscopy and image analysis
4. Live cell imaging using Life-Act-GFP reporter expressed in cancer cells
5. Kinetic studies of actin toxin analog treatments on cytotoxicity, cell migration and cell invasion

References:

1. Tanaka J, Blain JC, Allingham JS. (2008) Actin-binding toxin "tail" wags the dog. *Chem Biol.* 2008 Mar;15(3):205-7.
2. Harish Chander, Peter Truesdell, Jalna Meens and Andrew W.B. Craig (2013) Transducer of Cdc42-dependent Actin Assembly Promotes Breast Cancer Invasion and Metastasis, *Oncogene* 32:3080-90
3. Sarah Nersesian, Rodette Williams, Daniel Newsted, Kavan Shah, Stephanie Young, P. Andrew Evans, John S. Allingham and Andrew W. Craig. (2018). Effects of Modulating Actin Dynamics on HER2 Cancer Cell Motility and Metastasis. *Scientific Reports*, Nov 22;8(1):17243.