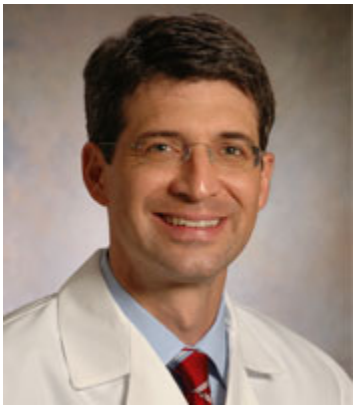
Combination Peptide Amphiphiles



James LaBelle, MD, PhD
Assistant Professor of Pediatrics

The Hoogland Lymphoma Biobank is a fundamental necessity to making palpable headway into advances in lymphoma treatment. Without a repository of human samples, cures for the most aggressive forms of lymphoma will undoubtedly remain out of reach. The combination of the Hoogland Lymphoma Biobank, cutting-edge translational research, physician leadership, and patients makes the University of Chicago uniquely poised to make great strides against this disease.

My work with the biobank and interest in lymphoma are inspired by my work with children, adolescents, and young adults with forms of the disease. Despite great success over the last 30 years, cancer remains the No. 1 cause of disease-related death in children. Pediatric cancers behave differently than adult cancers, and many times, the exact causes remain largely unknown. Because of this, treatment of refractory disease in children is often difficult. Lymphomas are the most common form of blood cancer and the third most common cancer of childhood. As a pediatric oncologist, I am inspired by the children I treat who, by no fault of their own, battle each and every day. We must do better for these children and extend what we learn to all patients with diseases that remain resistant to conventional treatments.

A major part of my laboratory focuses on using portions of the actual proteins, or peptides, as drugs and biological tools to uncover specific molecular pathways in diseased and normal cells. Peptide-based therapeutics have enormous potential for immune modulation and direct cancer treatment but have traditionally lacked efficient stabilization and delivery within patients and, thereby, have had limited clinical applications. To overcome these barriers, we are developing, within the lab and through collaboration, peptide amphiphiles (PAs). PAs chemically stabilize the alpha-helical secondary structure of helical peptides, protect them from proteolytic degradation, and allow for facile cellular internalization. PAs spontaneously self-assemble into micelles, structures akin to those made by the detergents in your kitchen sink or washing

machine, which are nanometer-sized particles that can concentrate therapeutic peptides and efficiently deliver their cargo into targeted cell populations.

Existing drug platforms severely limit the ability to treat many diseases despite identification of the cellular pathways responsible for them. In fact, currently available drugs are only able to target an estimated 10%–20% of proteins known to be responsible for a wide variety of disease states. However, peptide therapeutics are now able to drug protein interactions that were once thought to be undruggable. Biochemical modulation of natural amino acids and the use of new chemical techniques now allow the development and testing of a new class of therapeutics with the potential to target entirely new intracellular processes.

Our objective is to therapeutically target cell death pathways in the most resistant forms for diffuse large B-cell lymphoma (DLBCL) using peptides that simultaneously target the BCL-2 family of proteins and p53, two major regulators of DLBCL resistance to conventional chemotherapy.

The BCL-2 family comprises an essential network of proteins that govern the cell's decision to live or die. Pro-apoptotic BH3-only proteins of the BCL-2 family are master regulators of B-cell homeostasis and their functional suppression is believed to be a key pathogenic factor in B-cell lymphoma.

We hypothesize that the potency of BH3 proteins in triggering cell death reflects their capacity to engage a diversity of key protein targets and death pathways, and that pharmacologic replacement of multiple BH3 "death domains" using peptide therapeutics will restore cell death for therapeutic benefit in B cell lymphoma. However, it has become clear that despite single agent small molecule and peptide therapeutic success in targeting apoptotically sensitive, or "primed" lymphomas, there exists cell death pathway dependence heterogeneity in refractory malignancies that correlates to poor conventional chemotherapeutic responses and increased patient mortality. Therefore, our ultimate goal is to combine various peptides targeting divergent cell death pathways into one targeted therapeutic.

Our lab applies a multidisciplinary approach and chemical collaboration to (1) test the capacity of stabilized peptides fashioned after BCL-2 proteins' BH3 helix and p53 to reactivate the death program in B-cell lymphomas driven by distinct mechanisms of apoptotic blockade, and (2) identify the explicit protein targets of these chemical tools to link cellular activity to in situ mechanism of action.

By intertwining patient samples from the Hoogland Lymphoma Biobank, chemistry, lymphoma biology, and developmental therapeutics, we aim to generate fresh mechanistic insight into the pro-apoptotic potency of combination therapeutic peptides in diverse B-cell lymphomas driven by distinct and clinically relevant chemo-resistance mechanisms.