Proposed Project for First Year Undergraduate – A. Morris Group, Department of Chemistry

In the United States today, there is a 1 in 8 chance a woman will develop breast cancer at some stage of her life.[1] In recent years, routine screenings have been paramount in the early detection of breast cancer.[1] The 5-year survival rate for early detection breast cancer patients is around 98%, but this number drops drastically to 27% for patients whose cancer has metastasized to other sites in the body.[2] A common treatment option for such patients is chemotherapy. Chemotherapy regimens can be used to shrink tumors preempting surgery, to reduce the risk of tumors returning after surgery, and to treat patients with advanced stage breast cancer. However, a 2018 study found that 70% of patients with early stage breast cancer saw no benefit from chemotherapy treatment, largely in part due to the toxic side effects associated with the dosage.[3] Indeed, the clinical efficacy of most chemotherapeutic drugs for breast cancer treatment is crippled by unwanted side effects, off-target accumulation, and poor pharmacokinetics. This leads many patients to forego treatments, which limits their care options and leaves invasive surgery as the next best choice of treatment. Therefore, there is a critical need to develop materials to control the localization and delivery of such therapeutics. Although the development of drug delivery vehicles (DDVs) has been a research interest for several decades, the clinical applicability of many systems is largely limited due to a variety of issues, including low drug loading capacity, uncontrolled release of cargo, lack of tumor targeting mechanisms, and toxicity. In order to realize the clinical potential of these materials, it is critical to consider these aspects collectively in order to develop a successful DDV.

In response, we have developed a one-of-a-kind, metal-organic framework (MOF) DDV for the photo-controlled release of therapeutics with simultaneous breakdown of the carrier into small molecules. The design involves a photo-responsive MOF loaded with chemotherapeutic drug cargo and coated with a functionalized polymer that facilitates preferential delivery to breast cancer cells over healthy cells. Such a design will not only eliminate off-target drug side effects but will also provide a user-controlled platform for modulating drug release over a certain treatment period through the use of light. This research has the potential to improve the safety of chemotherapy agents by delivering the drugs selectively to tumors, which will redefine the patient experience and make chemotherapy a much more reasonable option of care for the treatment of breast cancer. When light is implicated in the mechanism of therapeutic action or drug delivery, the first and most important consideration must be the optical properties of biological tissues. The competitive absorption by endogenous chromophores or water plays a critical role in determining the efficacy of the photo-induced treatments. For maximum penetration depth and light-induced process efficiency, our MOF should have a light response between 650–850 nm. The proof-of-concept, MOF we have developed exhibits a maximum light absorption in the UV (λ_{max} ~340 nm). Therefore, the light response of the material is well outside of the therapeutic window and need to be further optimized. A tremendous amount of literature knowledge exists in regard to strategies to manipulate the absorption spectrum of azobenzene photo-switches. Of the demonstrated strategies the one well-suited for MOF incorporation is the derivatization of the benzene ring to impart push-pull character to the azobenzene. This is typically accomplished using heteroleptic azobenzenes, with electron donating groups on one of the benzene rings and electron withdrawing groups on the other. For the proposed project, the student will explore photophysical properties of a library of azobenzene-like compounds computationally. The goal is to identify promising candidates for further experimental study.

(1) How Common Is Breast Cancer? | Breast Cancer Statistics https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html (accessed Mar 25, 2019).
(2) Female Breast Cancer - Cancer Stat Facts https://seer.cancer.gov/statfacts/html/breast.html (accessed Mar 25, 2019).
(3) Sparano, J. A.; Gray, R. J.; Makower, D. F.; Pritchard, K. I.; Albain, K. S.; Hayes, D. F.; Geyer, C. E.; Dees, E. C.; Goetz, M. P.; Olson, J. A.; et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *New England Journal of Medicine* **2018**, *379* (2), 111–121.

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