The Pursell Lab: Beyond Basic DNA Biochemistry

Faithful replication of the human genome is vital to preventing genetic diseases, most notably cancer. The DNA polymerase enzymes that are responsible for DNA synthesis can introduce mutations into the genome if they themselves become mutated. The lab of Zachary Pursell studies how a specific set of mutations in the exonuclease domain (the domain responsible for proof-reading newly-synthesized DNA) can lead to mutations, with an eye toward how this can affect human health and diseases like cancer.

DNA Polymerase ε: Defects in DNA Proofreading Lead to Ultramutated Tumors

The lab is unusual among polymerase labs in several ways. Specifically, 1) it studies the human as opposed to the bacterial or yeast polymerase, and 2) it is not strictly a biochemistry lab. Instead, they synthesize techniques from biochemistry and cell biology to build a picture of how the mutated polymerase can affect human health. Mutations in this polymerase are well-documented in a variety of human cancers, including colon and brain. These tumors are unusual in that they display an ultramutated profile.

While all cancers display numerous mutations, tumors with mutations in this polymerase can display on the order of two orders of magnitude more mutations (500 mutations per 1 million DNA bases vs. 1-12 mutations per 1 million bases). Additionally, families with these mutations develop cancers at an accelerated rate. For example, individuals with these mutations can develop colon cancer in their teens or 20s, as opposed to the more typically observed 50’s or 60’s. This makes the study of these mutations especially relevant to cancer biology.

The focus is on the study of mutations in this polymerase found recurrently in real patients, grounding even the labs most basic biochemical analysis in real human disease. Biochemical analysis can reveal information about specific types of mutations caused by the errant polymerase as well as relative speed of replication. In addition to biochemical analysis, the mutant polymerase is also studied in a cellular context.
A Pipeline: Biochemical Analysis to *in vivo* Modeling

The lab studies these mutations not only biochemically, but also in tissue culture and using animal models. Using CRISPR/Cas9 technology, a number of cell lines has been generated, each able to induce & express the different mutant polymerases. The CRISPR/Cas9 technology has also been employed to develop a mouse model using the most commonly found mutant variant of this polymerase, which enables the study of carcinogenesis and disease progression. This can happen both independently or in conjunction with other commonly mutated pathways found in patients with polymerase ε mutations.

When paired with second generation sequencing analysis of patient samples, this allows the lab to uniquely position itself to twist a traditionally more biochemically-oriented question -- and instead study it in a way that has more direct relevance to human health and disease, and the potential for an accelerated impact on oncology research and treatments.

Contact & Further Info:

James R Zanewicz, RTTP  
Chief Business Officer  
zanewicz@tulane.edu  
504.919.3800 (m)

Claiborne M Christian, PhD  
Business Development Assoc.  
christian@tulane.edu  
504.909.3905 (m)

engage.tulane.edu  
t: @engagetulane