

## BCHM 421/422 (2024-25) – Jia Lab Projects #1 and #2

**Project Background and Outline:** Inorganic polyphosphate (polyP) is a polymer composed of three to over 1,000 phosphate residues linked together via high-energy phosphoanhydride bonds. PolyP has been implicated in an astonishing array of biological functions—ranging from phosphorus storage to molecular chaperone activity to blood coagulation. Our lab has recently discovered a new type of protein modification in which polyP can robustly and specifically interact with protein containing histidine-repeat sequences in many human and bacterial proteins. Similar to post-translational modification (PTM), His-repeat polyP modification has been termed (HPM). More recently, we also discovered Lysine-repeat can similarly interact with polyP (KPM) with high affinity and specificity. A highly unique and yet-to-be-understood feature of the non-covalent HPM/KPM is their ability to survive denaturing conditions (a hallmark of PTM).

Our lab has shown that HPM/KPM can modulate protein's function in preliminary *in vitro* and cellular experiments. Our plan is to investigate HPM/KPM's effect on several key human proteins which are involved in various cellular pathways and disease conditions (for example, in blood coagulation and cancer, pathogenicity etc.). Two protein examples include the clinically relevant human histidine repeat proteins dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and transcription factor MafB, suggesting HPM/KPM as a novel protein modification with potentially widespread regulatory implications.

**Supervisor:** Dr. Zongchao Jia

**Project Title:** His- and Lys-repeat protein modification by polyphosphate and regulation of protein function

**Project Goals:**

- Analysis of the interaction in HPM/KPM using biochemical and biophysical approaches
- Investigate function regulation of HPM/KPM *in vitro*
- Investigate physiological relevance of HPM/KPM using cell biology approaches

**Experimental Approaches:**

- Cloning and site-directed mutagenesis
- Protein expression and purification
- *In vitro* protein activity assay with and without HPM/KPM
- Cellular experiments to assess HPM/KPM's role
- Fluorescence microscopy

**References:**

- N. Neville, K. Lehotsky, Z. Yang, K.A. Klupt, A. Denoncourt, M. Downey and Z. Jia. (2023) Modification of histidine repeat proteins by inorganic polyphosphate. *Cell Rep.* **42**:113082.
- C. Azevedo, T. Livermore and A. Saiardi. (2015) Protein polyphosphorylation of lysine residues by inorganic polyphosphate. *Mol. Cell.* **58**, 71–82