Faculty Member Contact Information

Name	Dr. Maria Kontoyianni
Contact Info	
SIUE Email	mkontoy@siue.edu
Campus Box	2000
Department	Pharmaceutical Sciences

1 Funded, 2 Unfunded URCA Assistants

	This position is **ONLY** open to students who have declared a major in this discipline.	
	This project deals with social justice issues.	
	This project deals with sustainability (green) issues.	
	This project deals with human health and wellness issues.	
	This project deals with community outreach.	
X	This mentor's project is interdisciplinary in nature.	

Are you willing to work with students from outside of your discipline? If yes, which other disciplines?

- Yes, Computer Science, Chemistry, Biology, Math.

How many hours per week will your student(s) be required to work in this position? (Minimum is 6 hours per week; typical is 9)

- 10 hours

Will it be possible for your student(s) to earn course credit?

- No

Location of research/creative activities:

- Science East, Suite 3280

Brief description of the nature of the research/creative activity?

The Toll-like receptor (TLR) family are a subset of the larger Pathogen Recognition Receptors (PRRs), which recognize Pathogen-Associated Molecular Patterns (PAMPs). PRRs are proteins of the innate immune system. Lipopolysaccharide (LPS) is a glycolipid conjugate on the outer surface of Gram-negative bacteria acting as a PAMP. LPS consists of an O-antigen tetrasaccharide, an oligosaccharide core, and a terminal bioactive lipid A moiety. In vivo hydrolysis of LPS frees lipid A which then binds to PRRs such as toll-like receptor 4 (TLR4), myeloid-differentiation factor 2 (MD2), and cluster of differentiation 14 (CD14). TLRs provide the defense against pathogen-derived ligands leading to production of pro-inflammatory cytokines and type 1 interferon. Overexpression of TLRs results in disruption of immune homeostasis, increasing the risk for inflammatory diseases, autoimmune disorders and certain cancers. We are mostly interested in sepsis and breast cancer, with the former being a leading cause of death, while the latter is affecting over 200K women annually in the US alone.

Our interdisciplinary team (SIUE,UMSL, SLU), involving three Universities, has discovered amino acid-monosaccharide conjugates (AMs) which inhibit TLR4 activation with low nanomolar potency, antagonizing LPS. In an effort to improve these ligands, we need to first decipher the chemical features that render them active and selective towards one TLR over another. Towards that end, the URCA students will (1) calculate physicochemical properties and fingerprints of all TLR ligands reported in the literature, (2) perform clustering to categorize them based on the discriminatory descriptors from step 1, and (3) generate predictive classification models to be able to predict TLR activity and possibly prioritize future synthetic targets for TLRs 2, 3, 4, 5, 7, 8 and 9.

TLR4 utilizes accessory proteins including CD14 and MD-2 forming protein-protein interfaces (PPI). Another direction of this project focuses on exploring which amino acids of the TLR4/MD2 PPI (protein databank ID: 3FXI) contribute the most to the binding free energy. This will be accomplished with computational mutagenesis and free energy perturbation simulations of the wild type and mutant 3FXI. The mutations will target the amino acids calculated to cause a change in binding free energy greater than -2 kcal/mol, which are the so-called hot spots.

Brief description of student responsibilities?

1. Calculate physicochemical properties of small molecules.

2. Calculate molecular fingerprints of the same molecules as in 1.

3. Cluster the molecules based on their properties and fingerprints.

4. Generate classification models for activity and selectivity towards TLR receptors using machine learning.

5. Perform computational mutagenesis of a protein-protein interface (TLR4/MD2).

6. Run free energy perturbation (FEP) simulations of the wild type TLR4/MD2 protein-protein interface and mutants based on 6.

7. Identify the hot spots, ie amino acids causing a change in binding free energy, based on FEP results from 6.

URCA Assistant positions are designed to provide students with *research or creative activities* experience. As such, there should be measurable, appropriate outcome goals. What exactly should your student(s) have learned by the end of this experience?

The student would be able to: (1) understand chemical features, especially as they relate to activity towards a therapeutic; (2) use state-of-the-art computational methods toward tangible outcomes; (3) develop critical thinking and analytical skills; (4) run computational mutagenesis, FEP simulations and classification methods; (5) use Unix-operated workstations; (6) identify patterns and extract information from the computational experiments.

Requirements of Students

If the position(s) require students to be available at certain times each week (as opposed to them being able to set their own hours) please indicate all required days and times:

- It is on campus

If the location of the research/creative activities involves off campus work, must students provide their own transportation?

- N/A

Must students have taken any prerequisite classes? Please list classes and preferred grades:

- NA

Other requirements or notes to applicants:

- N/A