GRADUATE SCHOOL OF BIOMEDICAL SCIENCES
BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

SPENCER ADAMS

MENTOR: Stephen Miller, PhD
Wednesday, January 29, 2020 12:00 p.m.
LRB 816

Deconstructing bioluminescence: from molecular detail to in vivo imaging

Bioluminescence is the chemical production of light that results when a luciferase enzyme catalyzes the luminogenic oxidation of a small-molecule luciferin substrate. The numerous luciferases and luciferins nature has evolved can be used to illuminate biological processes, from *in vitro* assays to imaging processes in live animals. However, we can improve the utility of bioluminescence through modification of these enzymes and substrates. My thesis work focuses on developing reporters that expand the bioluminescent toolkit and improving our understanding of how bioluminescence works on a molecular level.

The first part of my thesis focuses on characterizing luciferases and luciferins that improve bioluminescence imaging in vivo. Some of our luciferins can outperform the natural D-luciferin substrate in live mouse imaging, while others are selectively utilized by mutant luciferases in live mouse brain. We also engineered luciferins that can selectively report on endogenous enzymatic activity in live mice.

The second part of my thesis focuses on determining the molecular details of how enzymes related to firefly luciferase, long-chain fatty acyl-CoA synthetases (ACSLs), can function as latent luciferases. I have determined the structure for one of these enzymes and improved its bioluminescent activity with synthetic luciferins enough to image in live mouse brain. I also characterized the selectivity in chimerized enzymes that combine firefly luciferase and ACSLs. In summary, my work improves the utility of bioluminescence for *in vivo* use and informs us about how evolutionarily-related enzymes function as luciferases on a molecular level.

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