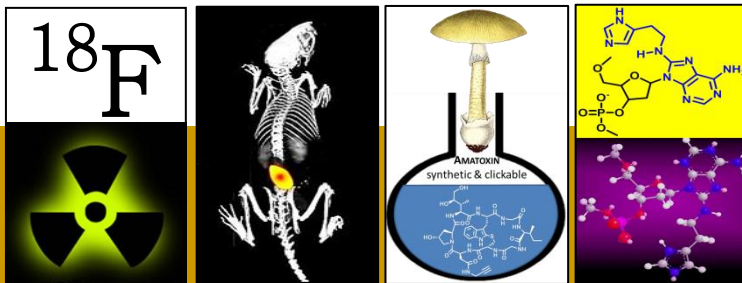


THE PERRIN LAB



Where Chemistry Solves Problems in Biology and Beyond

Highlights

- Using Synthetic Organic and Bioinorganic Chemistry to Create New Biologic Probes, Imaging Agents, and Catalytic Drugs
- Key Words: PET Imaging Agents, Aptamers, DNazymes, Biomimicry, Synthetic Peptides and Nucleosides, Heterocycles, Synthetic/Mechanistic Chemistry, Molecular Recognition
- Over 60 Peer-reviewed publications in 15 years, h-index 21, over 1400 citations
- 2 patents issued, 1 patent entering national phase and 3 provisional patents filed
- Placed five Ph.D. students and two postdoctoral fellows in academic positions, two Ph.D. students and two postdocs in industrial jobs, several undergraduates and M.Sc. students in medical schools
- Winner of a Michael Smith Senior Scholar Award and the 2015 TEVA Award for Biological Chemistry (CSC)
- Competitively awarded funding from NSERC, CIHR, CCSRI, and Genome-BC



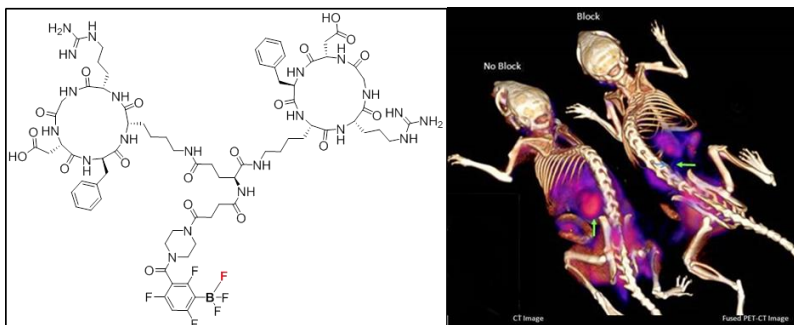
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Bioorganic Chemistry, the Chemistry/Biology Interface, and Medicine

Bioorganic chemistry offers exciting opportunities to apply synthetic organic chemistry to questions in biology, biotechnology, the origin-of-life, and personalized medicine. We are pursuing 4 global themes and are always interested in new student-driven ideas:

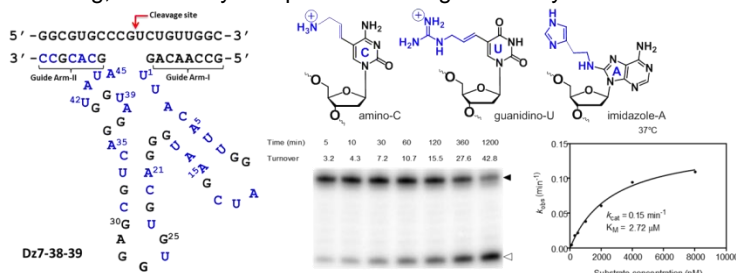
The Next Generation of PET Imaging agents

At the “bleeding edge” of personalized medicine is molecular imaging where a physician uses PET imaging to make a personalized diagnosis. As biologic drugs (e.g. peptides, antibodies, aptamers) continue to gain traction in clinical trials, molecular imaging is key to target validation and drug development. Currently, ^{18}F -fluorine is the radioisotope of choice for PET imaging, yet its odd chemical properties challenge clinical use. We have pioneered a breakthrough approach that uses boron to provide an ^{18}F -labeled organotrifluoroborate in a single aqueous step. In collaboration with colleagues at B.C. Cancer, we have imaged peptides for cancer imaging and are preparing for a first-in-man trial.

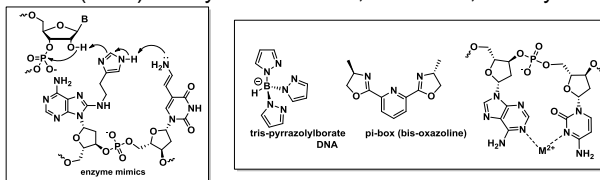


DNazymes as Catalysts for Health and Chemical Transformations

For decades, the pharmaceutical and biotech industries have sought catalysts to cleave messenger RNA to treat viral infections and cancer. Through a merger of synthetic organic chemistry and combinatorial molecular biology, we have discovered a unique class of DNA-based catalysts that cleave viral and oncogenic targets. Protein-mimicking DNazymes afford exciting new antiviral agents, which we study by combining synthetic chemistry, biophysics, and molecular biology, and mechanistic enzymology. Other applications involve metal-ion and metabolite sensing, biomimicry and potential for organo-catalysis.



We are looking for organic and inorganic chemists who want to exploit an intriguing analogy between classic metal ligands (e.g. tris-pyrazolyl-borate and py-box) and DNA, which enables combinatorial sampling of 10^{15} potential ligands. Activity screens will lead to new DNA catalysts for M^{X+} (DNA)-catalyzed oxidation, reduction, and hydroamination reactions.



Highlighted Publications

A Broadly Applicable One-step Method for ^{18}F -labelling, Z. Liu, *et al.* *Angew andte Chemie* **2014** 53: 11876–11880.

Preclinical evaluation of a high affinity ^{18}F -trifluoroborate octoate derivative for somatostatin receptor imaging, Z. Liu *et al.*, *J. Nucl. Med.* **2014** 55: 1499-1505.

Base-promoted Protodeboronation of 2,6-Disubstituted Arylboronic Acids, J. Lozada, *et al.* *J. Org. Chem.* **2014** 79: 5365-8.

^{18}F -Trifluoroborate Derivatives of [Des-Arg $_{10}$]-Kallidin for Imaging Bradykinin B1 Receptor Expression with Positron Emission Tomography, Z. Liu *et al.* *Molecular Pharmaceutics* **2015** 12: 974-82.

One-Step ^{18}F -Labeling of Dimeric CycloRGD at High Specific Activity for Functional PET Imaging of Tumors in Mice, Y. Li *et al.*, *Nucl. Med. and Biol.* **2013** 40: 959-966.

Towards the Combinatorial Selection of Sequence Specific RNaseA Mimics, M. Hollenstein, *et al.* *ACS Combinatorial Science* **2013** 15:174-182.

A divalent metal-dependent self-cleaving DNAzyme with a tyrosine-like side chain C.H. Lam *et al.* *Org. Biomol. Chem.* **2011** 9: 6949-54.

Investigation of the Catalytic Mechanism of a Synthetic DNAzyme with Protein-like Functionality: An RNaseA Mimic? J. M. Thomas *et al.*, *J. Am. Chem. Soc.* **2009** 131: 5648–5658.

Synthesis of a cytotoxic amanitin for bioorthogonal conjugation, L. Zhao, *et al.* *ChemBioChem* **2015** 16:1420-1425.

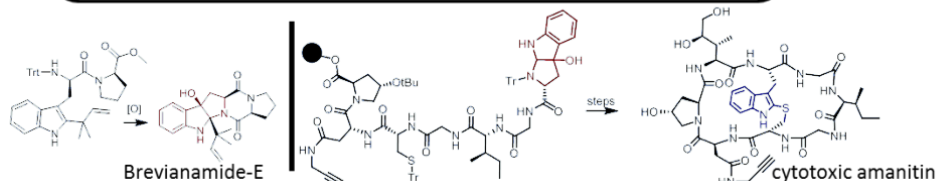
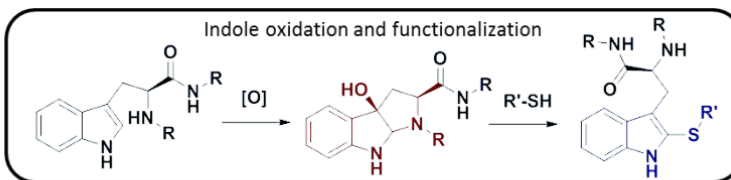
Stereoselective synthesis of Brevianamide E, L. Zhao *et al.*, *Org. Lett.* **2012** 14: 90-93.

A Pyrimidopyrimidine Janus-AT Nucleoside with Improved Base-Pairing Properties to both A and T with a DNA Duplex: The Stabilizing Effect of a Second Endocyclic Ring Nitrogen, E. Largy *et al.*, *Chem. – Eur. J.* **2014** 20: 1495-99.

Base-Pairing Behavior of a Carbacyclic Janus-AT Nucleoside Analogue Capable of Recognizing A and T within a DNA Duplex, E. Largy *et al.*, *ChemBioChem* **2013** 14: 2199-2208.

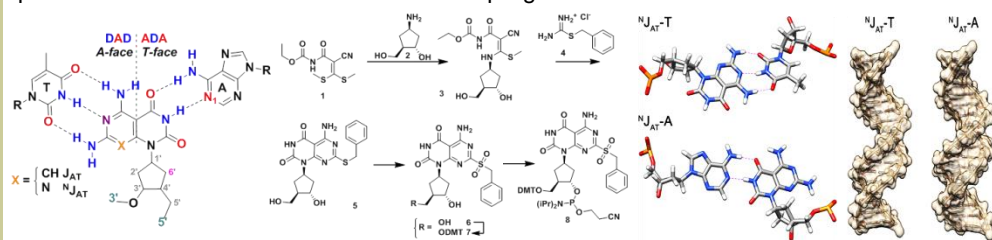
Peptides for Chemical Biology, Imaging and Health

Tryptophan derived natural products offer unique substrates for probing biology. Amanitin, a bicyclic octapeptide which is an exquisitely potent and highly selective inhibitor of RNA Polymerase II capable of inducing apoptotic cell death, may hold clues to understanding cell death and providing new targeted therapeutics against cancer. We have developed a robust synthesis of a clickable-amanitin and have explored aspects of indole functionalization that afforded a slick route to brevianamide E. Our publications lay the groundwork for understanding the structural basis of transcriptional inhibition and probing apoptotic cell death. Having mastered these syntheses, we are uniquely qualified to screen libraries of peptide-natural products for targeting cancer-specific targets and creating new imaging agents.



Heterocycles for DNA/RNA Recognition

We are working towards the long-term goal of sequence-specific DNA recognition by synthetic molecules for controlling gene expression in cells thereby driving therapeutic applications. We published the first synthesis of Janus-heterocycles that simultaneously complement the Watson-Crick faces of an AT base pair and performed critical biophysical measurements to establish these interactions. We were the first to synthesize these challenging “two faced” heterocycles to recognize DNA. At higher concentrations they self-associate into interesting noncovalent nanostructured polymers, ribbons, and rosettes to provide new nanoscale structures based on programmable H-bonded interactions.



Job Market

Over the past decade, the pharmaceutical industry has shed 300,000 jobs in synthetic chemistry leaving students wondering about future job prospects. Luckily, biologic drugs are on the rise: >30 antibody drugs are on the market and over 20 peptide drugs will enter clinical trials. As medicinal chemistry is changing, the application of chemistry to biology will increase to provide bio-sensors, diagnostics, clinical imaging agents, and “smart drugs” that “catalyze” cures. In my lab, synthetic chemistry is integrated in characterization that uses biochemistry, cell biology, and whole animal work. Much like a start-up company, we value nimble students who want to learn many techniques to see the fruits of synthetic endeavors through to characterization and hypothesis validation. If past students’ success is any indication, the work you do in my lab and your publication record will likely get you a job at the exciting interface chemistry and biology in industry or academia.

Publications / Thesis

Your first-author publications will be your “ticket” to a job; while 3-4 publications is the minimum for a Ph.D. at UBC, typically students in my lab publish 5-6 papers.

About the Lab

My lab is a culturally diverse group of undergraduate, graduate and postdoctoral students. We’re always looking for highly motivated students who want to make a difference in their lives. We work hard and have fun. Most members will attend at least one national or international conference e.g. CSC, ACS, American Peptide Symposium, Pacificchem, Soc. Nuclear Medicine, International Nucleic Acids Roundtable and others. We also participate in a yearly student-run conference at Pac-Forest in the shadow of Mount Rainier along with 8 universities in the Pacific Northwest. Fun times include a department holiday dinner dance, snow-shoeing/skate skiing at Cypress, and a summer beach BBQ.



Perrin lab BBQ – July 2015
Spanish Banks – Jericho Beach