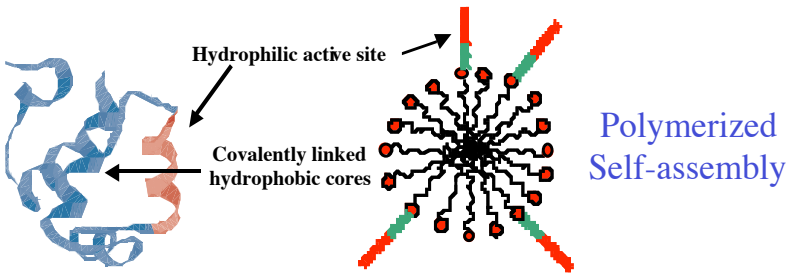
NIRT Highlight (Novel Structures and Phenomena)

Creating Functional Nano-Environments by Controlled Self-Assembly

Our group has developed a versatile synthetic route to making peptide lipid conjugates with wide variations in structure and properties. Solid-phase Fmoc synthesis of peptides is followed linkage to a variety of possible synthetic lipid tails. Recently, through a combination of cryo-transmission electron microscopy and neutron scattering, we have shown that molecules such as these usually form spherical micelles. These micelles have cores composed of the hydrophobic lipid tails and coronas displaying the peptide functional group. In this kind of assembly, we have discovered that peptides derived from triple helical regions of collagen, or □□helical regions of DNA-binding molecules such as the GCN4 repressor protein, form ordered peptide secondary structures that the un-conjugated peptides alone do not form. These micellar objects are very much like protein molecules in overall architecture, as illustrated below.

These protein-analogous micelles may be useful for a variety of protein-like functions that are being studied in our NIRT team: raising antibodies, DNA packaging, gene regulation, particularly those where the relevant activity is found in a relatively short, linear peptide sequence.
As a recent specific example of peptide amphiphile micellization, a member of our team has recently found that the iron-sequestering siderophore compounds produced by certain marine bacteria are peptide amphiphiles. In the absence of iron, the marinobactin and aquachelin peptide amphiphiles form micelles, however upon Fe(III) coordination a phase change to vesicles occurs [1]. The tantalizing discovery of relevance to our NIRT grant is that the ferric complex of these siderophores is photoreactive [2]. In the dark the iron vesicles are stable for months, however in the presence of UV light (*ca*. 300 nm, □ ~0.02), the head group is oxidized and in the process the fatty acid tail dissociates. Thus we envision developing nano-scale molecular containers that can selectively release encapsulated compounds upon photolysis.

Amphiphilic peptides are emerging as a common structural theme of marine siderophores, which surprisingly are rare in terrestrial bacteria. In very recent work we have partially characterized a new suite of ten peptide-amphiphile siderophores produced by another marine bacterium. The new siderophore family contains yet a third distinct head group that coordinates Fe(III) and one of a series of fatty acid tails. We are still in the process of identifying the fatty acid tail groups. Moreover two other marine bacteria that we have in our group have also been found to produce cell-associated siderophores, which we believe will turn out to be a suite of siderophores differing in the identity of the fatty acid tail. Elucidating the structural strategy that marine bacteria have evolved to acquire iron based on amphiphilic peptides is a central goal of our team's research efforts, as well as harnessing potential applications based on the attendant self-assembling properties of these peptide amphiphiles.



• Protein Protein Analogous Micelles

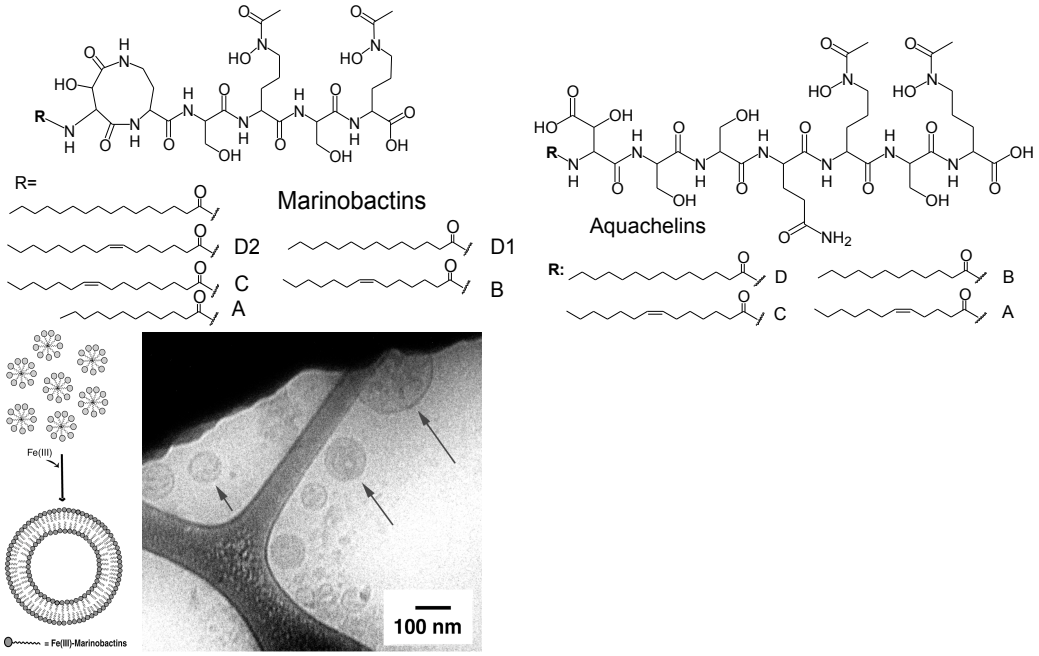


Figure Caption: Structures of the Marinobactin and Aquachelin siderophores; depiction of the micelle to vesicle transition; cryo-transmission electron microscopy of the iron(III)-marinobactin vesicles.

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References:

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[1] Self-assembling amphiphilic siderophores from marine bacteria, J.S. Martinez, G.P. Zhang, P.D. Holt, H.-T. Jung, C.J. Carrano, M.G. Haygood and Alison Butler, *Science,* 2000, *287*, 1245-1247.

[2] Photochemical cycling of iron in the surface ocean mediated by microbial iron(III)-binding ligands, K. Barbeau, E.L. Rue, K.W. Bruland and Alison Butler, *Nature*, 2001, *413*, 409-413.