PURINE BIOSYNTHETIC INTERMEDIATE-CONTAINING RIBOSE-PHOSPHATE POLYMERS AS EVOLUTIONARY PRECURSORS TO RNA. Harold S Bernhardt[1] and Roger K Sandwick[2], [1]Department of Biochemistry, University of Otago, Dunedin, NZ (harold.bernhardt@otago.ac.nz), [2]Department of Chemistry and Biochemistry, Middlebury College, Middlebury, VT, USA (rsandwic@middlebury.edu)

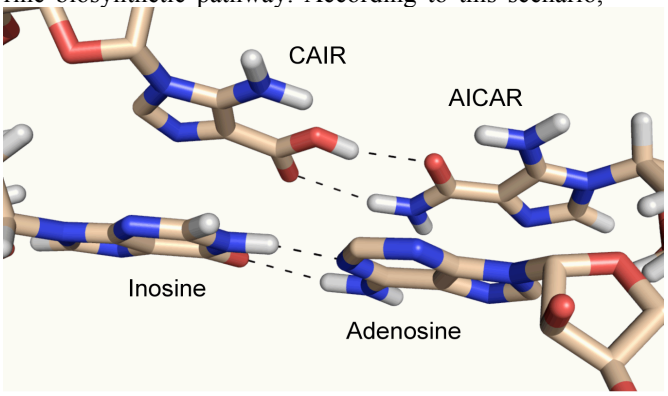
Introduction: The RNA world hypothesis proposes that RNA once functioned as both the principal biological catalyst and genetic material. However, RNA is a complex molecule made up of phosphate, ribose and nucleobase moieties, and its evolution is unclear. Yakhnin [1] has proposed a scenario in which there was a period of prebiotic chemical evolution prior to the advent of replication, in which macromolecules containing polyols joined by phosphodiester linkages underwent spontaneous transesterification reactions with selection for stability. Although he proposes that the nucleobases were obtained during this stage from less stable macromolecules, the ultimate source of the nucleobases is not addressed.

Hypothesis: We have proposed that the purine nucleobases arose *in situ* from simpler precursors attached to a ribose-phosphate backbone, and that the initially weaker and less specific intra- and inter-strand interactions between these precursors were the forerunners to the base pairing and base stacking interactions of the modern RNA nucleobases [2].

Further, in line with Granick's [3] hypothesis of biosynthetic pathways recapitulating evolution, we have proposed that these simpler precursors were the same or similar to the intermediates of the modern *de novo* purine biosynthetic pathway. According to this scenario, the pyrimidine nucleobases would have evolved at a later stage.

We have proposed that successive precursors formed progressively stronger interactions that stabilized the ribose-phosphate polymer, and that these increases in stability drove the selection and continued chemical evolution of the purine nucleobase precursors. Such stabilizing interactions may have included hydrogen bonding between ribose hydroxyl groups and between amide side groups, the coordination of metal cations, and the stacking of imidazole rings [2]. Interestingly, the imidazole ring-containing intermediates of the pathway, CAIR and AICAR, as well as inosine, adenosine and guanosine, are all potentially able to form purine-purine Watson-Crick-type base pair interactions with each other, similar to the inosine-adenosine base pairs found to occur in a synthetic oligonucleotide (see figure).

Five of the eleven steps of the purine biosynthetic pathway have previously been shown to have alternative nonenzymatic syntheses [4-6], while a sixth step has also been proposed to occur nonenzymatically [7], supporting a prebiotic origin for the pathway. We have proposed alternative nonenzymatic reactions for the entire pathway [2].



CAIR-AICAR potential hydrogen bonding interaction modeled on an adenosine-inosine (A-I) Watson-Crick-type base pair in a synthetic antiparallel RNA duplex incorporating tandem A-I/I-A base pairs (PDB 333D) [8]. Stacking interactions of the imidazole rings of CAIR and AICAR would presumably have provided additional stabilization.

References:

[1] Yakhnin A. V. (2013) *Orig. Life Evol. Biosph. 43:*39-47. [2] Bernhardt H. S. and Sandwick R. K. (2014) *J. Mol. Evol., 79,* 91-104. [3] Granick S. (1957) *Ann. N. Y. Acad. Sci., 69,* 292-308. [4] Cheng Y. S. et al. (1987) *Adv. Enzyme Regul., 26,* 319-333. [5] Mueller E. J. et al. (1994) *Biochemistry, 33,* 2269-2278. [6] Zubay G. and Mui T. (2001) *Orig. Life Evol. Biosph. 31,* 87-102. [7] Berg J. M. et al. (2012) *Biochemistry, 7th Edition, WH Freeman, NY.* [8] Carter R. J. et al. (1997) *Nucleic Acids Res., 25,* 4117-4122.