

Chemical Investigations of Poly(ADP-Ribose)

Michael J. Lambrecht, Dr. Matthew Brichacek and Prof. Paul J. Hergenrother

Poly(ADP-ribosylation) is a common post-translational modification of proteins implicated in processes such as cell death, DNA repair, and mitosis. Poly(ADP-ribose) (PAR) is known to bind both covalently and non-covalently to over 500 proteins through eight distinct binding motifs. In many cases, why and how PAR binds these proteins is unknown. A lack of structural biology data for PAR-binding proteins exists largely due to the difficulties in obtaining pure, homogeneous PAR from enzymatic synthesis and the lack of any significant progress towards a chemical synthesis of the polymer.

We have developed a chemical synthesis of PAR to provide polymers of homogeneous lengths. Chemically synthesized PAR will facilitate structural biology studies and begin to elucidate the role of PAR in diverse and essential cellular processes in ways that *in vitro* enzymatic synthesis and fractionation of the polymer cannot. Key to our synthesis has been the α -selective ribosylation of adenosine and development of efficient chemistry to iteratively form the pyrophosphate bond. Thus far we have successfully completed the synthesis of a PAR dimer and studies to make longer and branched oligomers are in progress.

