Visible Light Initiated Photorelease of Mitochondria Targeting Inorganic Polyphosphate

Sandra Moser, Jiahui Ma, Henning J. Jessen

Institute of Organic Chemistry, Albert-Ludwigs University of Freiburg,
Albertstrasse 21, 79104 Freiburg, Germany,
sandra.moser@ocbc.uni-freiburg.de

Inorganic polyphosphate (polyP), an ubiquitous molecule composed of multiple orthophosphates linked by high-energy phosphoanhydride bonds, is no longer regarded as a "forgotten polymer".[1] In recent years, many different regulatory functions of polyP have been discovered and very recently, the mammalian mitochondrial F_0F_1-ATP synthase was shown to be capable of synthesizing and degrading polyP.[2,3] However, most enzymes involved in mammalian polyP metabolism have not yet been identified[4], although the delivery of modified polyPs into mammalian cells promises significant advances in polyP research. Here we show the synthesis and photophysical properties of photocaged mitochondria targeting polyP10. The clickable DEACM-450 photocaged polyP10 precursor was accessed from polyP8 using a bisphosphorylation procedure with the corresponding P-amidite. This provides the first chemical synthesis of defined polyP10 and exceeds the previously possible maximum chain length by two phosphate units. A photolysis study with 490 nm light demonstrated that the photorelease of polyP10 competes with a [2+2] cycloaddition, thus slowing down the polyP10 release. After the addition, however, of the mitochondria targeting triphenylphosphonium residues by click chemistry, the photolysis finished in less than 25 min. The delivery of this new probe into mammalian cells with molecular transporters, and the organelle specific release of active polyP10 in the mitochondria, will help to rescue polyP depletion effects in the potential site of the polyP synthase in mammals.

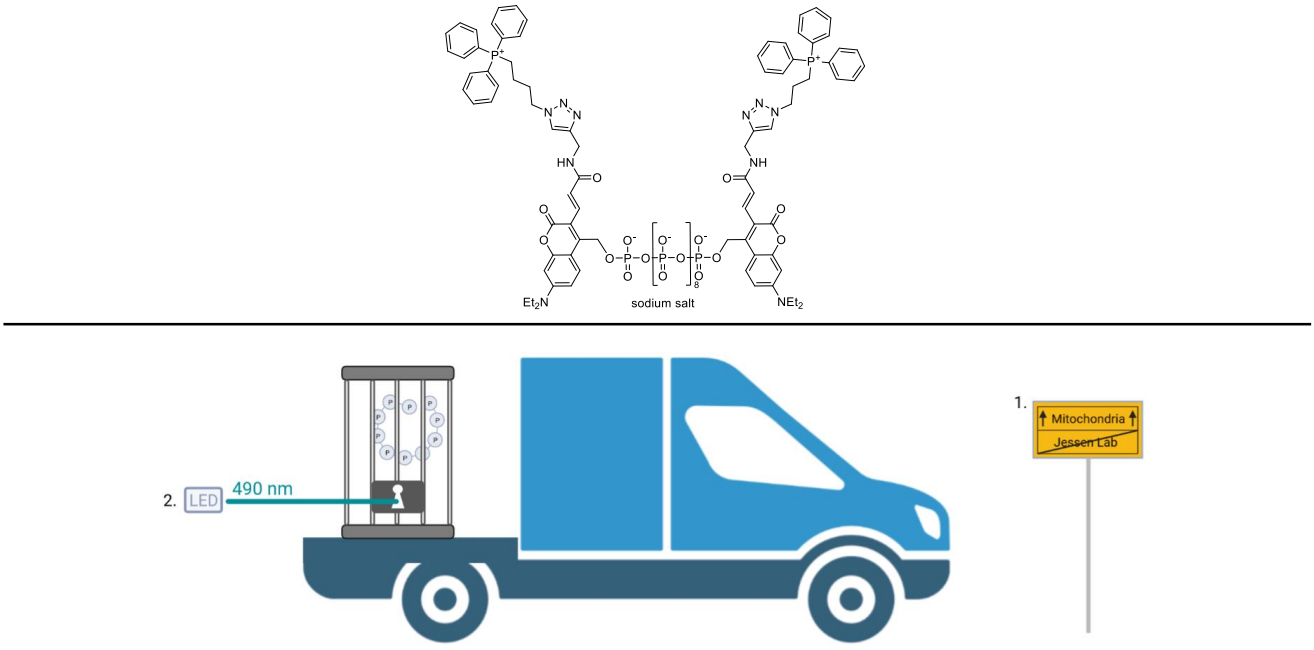

Figure 1: *Chemical structure of photocaged mitochondria targeting polyP10 and schematic representation of the concept created with BioRender.com*

[1] A. Kornberg, *J. Bacteriol.* **1995**, *177*, 491-496.
[2] Y. Desfougères, A. Saiardi, C. Azevedo, *Biochem. Soc. Trans.* **2020**, *48*, 95-101.
[3] A. Y. Baev, P. R. Angelova, A. Y. Abramov, *Biochem. J.* **2020**, *477*, 1515-1524.
[4] B. McIntyre, M. E. Solesio, *Neural Regener. Res*. **2021**, *16*, 2227-2228.