

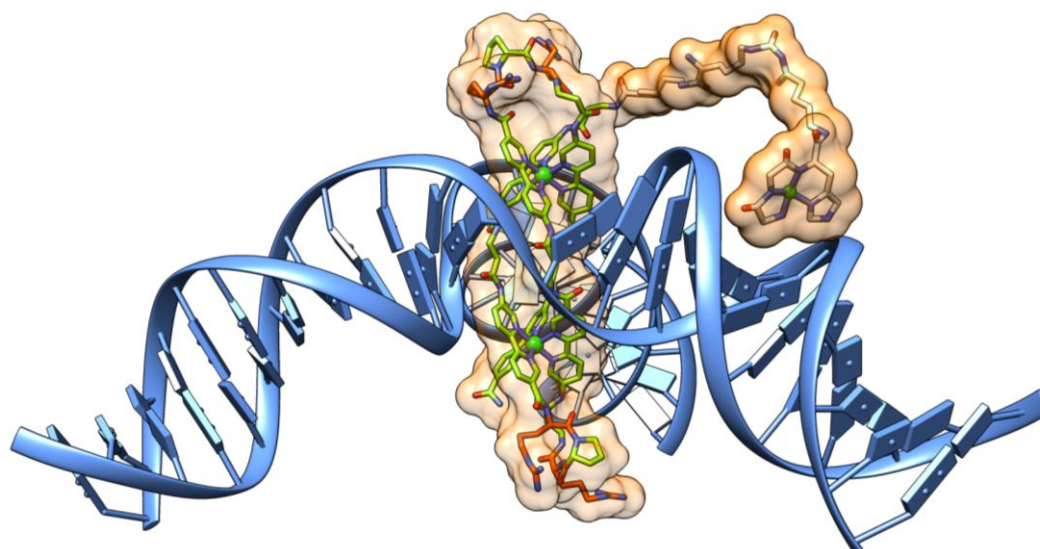
Selective Cleavage of DNA Replication Foci in Cell Nuclei by Peptide Helicates

M. Vázquez López,^{a*} J. Gómez-Gonzalez,^a B. McGormann,^b A. Alcalde,^a N. Barreiro,^a F. Rivadulla,^a J. Martínez-Costas,^a A. Kellett,^b M. E. Vázquez^a

^a Center for Research in Chemical Biology and Molecular Materials (CIQUS), University of Santiago de Compostela, Spain.

^b School of Chemical Sciences, National Institute for Cellular Biotechnology, Dublin City University, Ireland.
miguel.vazquez.lopez@usc.es

Recently, we reported the synthesis of oligocationic peptide ligands containing artificial bipyridine amino acid residues, which fold predictably into self-assembled helicates in the presence of Fe^{II} ions. These peptide helicates show a high affinity and selectivity towards DNA Three Way Junctions (DNA-3WJ) over B-DNA both in vitro and in vivo, being able to selectively label DNA replication foci in cell nuclei.¹ As a continuation of this work, here we report the design and synthesis of a series of peptide helicates that exhibit high and extremely selective nuclease activity towards DNA-3WJ in vitro. We also show that these helical peptides selectively cleave DNA replication foci in functional nuclei, therefore acting as selective metallonucleases for DNA-3WJ in vivo. To our knowledge, this is the first example of a nuclease agent selective for DNA-3WJ, both in vitro and in vivo. Considering that DNA replication is deregulated in cancer cells, these novel artificial metallonucleases should be, in principle, much more active in cancer cells than in healthy ones. We believe that we may be on the verge of discovering a new family of anticancer drugs with extraordinary cancer cell selectivity.



¹ J. Gómez-González, Y. Pérez, G. Sciortino, L. Roldan-Martín, J. Martínez-Costas, J.-D. Maréchal, I. Alfonso, M. Vázquez López, M. E. Vázquez, *Angew. Chem. Int. Ed.*, **2021**, *60*, 8859–8866 (VIP).