

2023
4-6
September

LMU Campus Großhadern

Munich
**8th Symposium
on Foldamers**



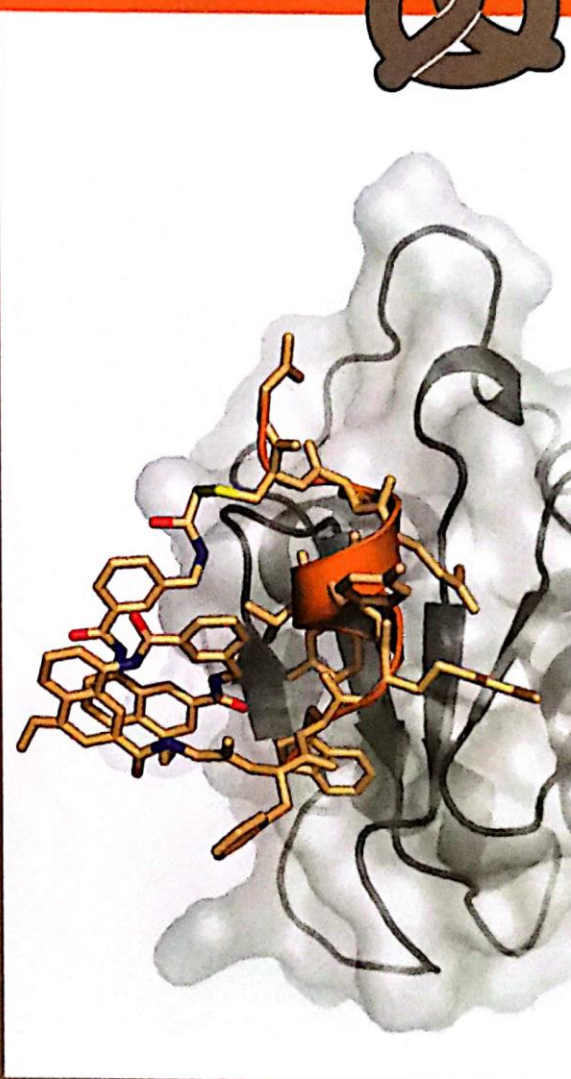
Plenary Speakers

William De Grado
Claudia Höbartner
Kyu-Sung Jeong
James Nowick
Helma Wennemers

Invited Speakers

Jianfeng Cai
John Chaput
Andre Cobb
Hosahudya Gopi
Galia Maayan
Finn Hansen
Françoise Ochsenbein
Sandrine Onger
Tomohisa Sawada
Aya Tanatani

Contact us: foldamer@cup.lmu.de



**Program and
Abstract Book**

Inhibition of Rad6 protein-protein interactions using foldamers and selective covalent inhibitors

Bence Nagymihály,^a Edit Wéber,^{a,d} Attila Tököli,^a Éva Bartus,^{a,d} Gabriel Fenteany,^{a,d} Gaurav Sharma,^b Lajos Haracska,^b György M. Keserü,^c Tamás A. Martinek,^{a,d}

^a Department of Medical Chemistry, University of Szeged, Hungary, ^b Institute of Genetics, Biological Research Centre Szeged, Hungary, ^c Medicinal Chemistry Research Group, ELKH Research Centre for Natural Sciences, Budapest, Hungary, ^d ELKH-SZTE Biomimetic Systems Research Group, University of Szeged, Hungary
martinek.tamas@med.u-szeged.hu

Protein-protein interactions (PPIs) play a role in several pathophysiological processes; however, only twenty percent of these interactions can be attacked with small molecules. We previously showed that H14 helical β -peptidic foldamers with two proteinogenic side chains can recognize protein surfaces^[1]. We hypothesize that these foldamers can be used as building blocks, and following a fragment-based approach, high-affinity PPI inhibitors can be constructed.

Our target protein, the ubiquitin-conjugating enzyme Rad6 is involved in the ubiquitination of PCNA (Proliferating cell nuclear antigen), which initiates translesion synthesis (TLS). TLS is a DNA error tolerance mechanism that enables the replication of damaged DNA, thus helping tumor cells to survive. Our goal is to prevent TLS and develop a potential antitumor agent by inhibiting the functions of Rad6 using foldamers linked with covalent inhibitors (warheads).

A 100-membered foldamer library was screened against Rad6. The foldamers were equipped with a UV-reactive photo-tag, which can form covalent bonds with the protein. Based on the results of the photo-foldamer experiments, the binding sites of the 13 best-binding molecules were determined by HPLC-MS analysis and by ¹⁵N HSQC-NMR titration. We identified three main binding regions on the surface of Rad6, and selected foldamers were implemented in a protein-templated dynamic covalent library experiment. After the affinity maturation, we obtained a foldamer dimer that inhibited the formation of the Rad6-ubiquitin thioester. As Rad6 contains a cysteine in its active center, selective blocking of this amino acid may be promising. Therefore, a 24-membered cysteine-selective covalent inhibitor library was tested. Molecules containing isothiocyanate, maleimide, and thiol groups proved to be effective warheads against Rad6 and can be applied as covalent anchoring functions.

In view of the determined binding sites, we are designing a foldamer-warhead construct (Figure 1) using 3D modeling to develop a highly effective and selective inhibitor against Rad6.



Figure 1. Blocking Rad6 with a combined foldamer-warhead strategy: foldamers (red helices) can bind to the surface of the protein, while warheads can block the active site cysteine (yellow star).

References

- [1] Tököli *et al.*, *Chem. Sci.* **2020**, *11*, 10390–10398.