Job title: Research assistant professor (post-doc) in mol. biology, biochemistry

Project: Small molecule modulators of the tumor necrosis factor alpha signaling pathway for the inhibition of inflammatory processes and the enhancement of cancer immunotherapy

Name of the unit/place of work: Department of Biomedical Chemistry, Faculty of Chemistry, University of Gdansk - Gdansk, Poland

https://chemia.ug.edu.pl/wydzial/katedry/katedra-chemii-biomedycznej

Number of positions: 1

Requirements:
- PhD degree in molecular biology or biochemistry,
- Proven experience in protein expression and purification, PCR, DNA cloning,
- Proficiency in spoken and written English.

Job description:
The post-doc will be responsible for:
- Expression and purification of proteins,
- Activity assays of TNF modulating molecules (compounds and their peptide conjugates) in cell lines,
- In vitro affinity of small molecules and their conjugates to TNF, internalization and degradation of TNF in cells.

NCN competition type: OPUS 27

Deadline for submission of proposals: April 21, 2025, at 00:00

Form of submission: e-mail

Employment conditions:
- Full-time employment contract for 33 months,
- Annual leave: 36 working days,
- Salary: PLN 11 666 gross/gross per month.

Additional information:
Applications with the required documents (in pdf format only) should be sent by e-mail to: tadholak@hotmail.com or s.rodziewicz-motowidlo@ug.edu.pl writing in the subject line of the message: “post-doc_bio_OPUS_27”.

Required documents:
- Application, cover letter,
- CV including information on completed studies, previous academic achievements (list of publications, participation in conferences, participation in research projects, awards and prizes, etc.),
- A copy of the diploma or other document indicating the awarding of a doctoral degree; it is also acceptable for the Candidate to provide a statement indicating the provision of a document confirming the awarding of a doctoral degree at the time of signing the employment contract,
- A scan of documents confirming skills (e.g.: language certificate, etc.),

- Opinion of the dissertation supervisor and possibly letters of recommendation,
- Signed statement of consent regarding the processing of personal data
- The rules of the competition are set out in the regulations for the awarding of NCN research grants in research projects (Appendix to the NCN Council Resolution No. 25/2019, dated 14.03.2019),
- The competition will be resolved by April 21, 2025.

Abstract

The research objective of our project is to characterize the mechanism of degradation of the tumor necrosis factor alpha (TNF) by lysosome-targeting chimeras (LYTACs). In particular, we are interested in studying how these TNF-LYTACs modulate the tumor immune microenvironment and whether they could synergize with the immune checkpoint blockade (ICB)-induced responses in cancer.

LYTACs are bifunctional conjugates that bind to both the extracellular domain of the target protein and the cell surface lysosome-targeting receptor. The target protein is then degraded in the lysosome. Elimination of the target protein by protein degradation, using LYTAC molecules, has many advantages. Compared to traditional direct inhibitors that rely on occupancy-driven pharmacology, LYTACs exhibit sub-stoichiometric activity where one LYTACs molecule is capable of inducing multiple rounds of degradation. Deactivation, i.e. removal, of an oncoprotein occurs at lower concentrations compared to traditional small-molecule inhibitors. As a result, LYTACs generally exhibit less toxicity than conventional direct inhibitors.

Our TNF-LYTAC conjugates will be used in immuno-oncology, both alone and in combination with antibodies against immune checkpoint receptors such as PD-L1 and PD-1. Blockade of immune checkpoint receptors (for example, PD-1, PD-L1 or CTLA-4) has revolutionized cancer therapy and have fundamentally changed the treatment regimen and prognosis for many cancers, providing long-term clinical responses and even cures in a subset of cancer patients (Sharma et al. (2021) The Next Decade of Immune Checkpoint Therapy. Cancer Discov. 11, 838–857). It is now used in clinics around the world and was recognized with the 2018 Nobel Prize in Physiology or Medicine to James P. Allison and Tasuku Honjo. Immune checkpoint blockers (ICBs) based on antibodies against the PD-1/PD-L1 pathway are currently the cornerstone of this cancer immunotherapy. Despite the success of immune checkpoint inhibitors, resistance limits the number of patients who can achieve durable responses, and most patients develop immune-related adverse events (irAEs). These include colitis, an inflammatory bowel disease that can be treated with anti-TNF antibodies such as infliximab. The mechanism of irAEs is unclear, but in the case of TNF, it is thought that TNF contributes to resistance to anti-PD-1 therapy. TNF blockers have been shown to enhance the antitumor therapeutic activity of ICBs in mouse models. Reducing TNF expression is considered a promising strategy and has become an area of intense research.

TNF alone is of enormous therapeutic importance. It is a pleiotropic cytokine with both proinflammatory and immunoregulatory functions. TNF is dysregulated in autoimmune diseases such as psoriasis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease. In fact, TNF-neutralizing biologics have been in clinical use for decades for the treatment of many inflammatory conditions. There is also increasing evidence that the TNF system plays an important role in the immune aspects of cancer (Chen, A.Y., Wolchok J.D., Bass, A.R. (2021). TNF in the era of immune checkpoint inhibitors: friend or foe? Nat. Rev. Rheumatol. 17, 213–223). Thus, the clinical promise of TNF LYTAC degraders also motivated our studies of their mechanism of action and the role of TNF in cancer.

We have been working for some time on the properties of PD-L1 and PD-1 (e.g., Zak et al., (2017) Structure, 25, 1163; Magiera-Mularz et al. (2017) Angew. Chem. Int. Ed. 56, 13732; Mikitiuk et al., (2023) Molecules 28, 7519). We plan to use our chemical PD-1/PD-L1 probes and TNF modulators to study the interdependence of TNF and checkpoint proteins in immune aspects of tumorigenesis.