Chemistry and Biochemistry of Nucleic Acids Components

HEAD:

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GROUP MEMBERS:

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RESEARCH PROFILE:

- Synthesis of 5' end mRNA (cap) analogues and their usage in biochemical and biophysical studies on translation initiation, splicing, intracelullar transport and stability of mRNA in eukaryotic cells;
- Synthesis and biochemical investigation of translation inhibitors with potential therapeutical application as anti-cancer drugs;
- Synthesis of nucleotides conjugates capable to penetratrate cell membrane;
- Design and synthesis of tools for examinations of gene expression in parasitic nematodes;
- Chemistry and biochemistry of nucleosides and nucleotides.

CURRENT RESEARCH ACTIVITIES:

(A) Design and synthesis of new cap analogs as translation inhibitors with potential therapeutic application. To date numerous modified cap analogues have been synthesized in our laboratory and tested as translation inhibitors of cap-dependent translation *in vitro* that compete with mRNA for the binding site of eIF4E (eukaryotic initiation factor 4E). One of the most interesting and promising group of compounds, which synthesis have been developed in our group, contains N2-modified 7-methylguanosine (the best of them is shown in the figure). Currently, we are working on an introduction of different types of aromatic groups (such as oxazole, thiazole) into this position and on the synthesis of cap analogues possessing double modifications (e.g. in N2 and N7 positions).

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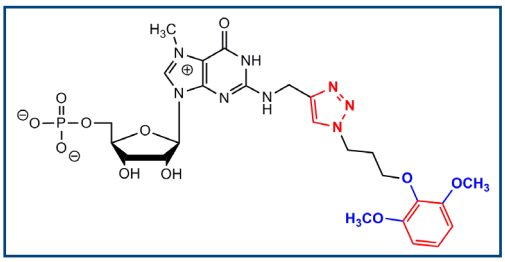
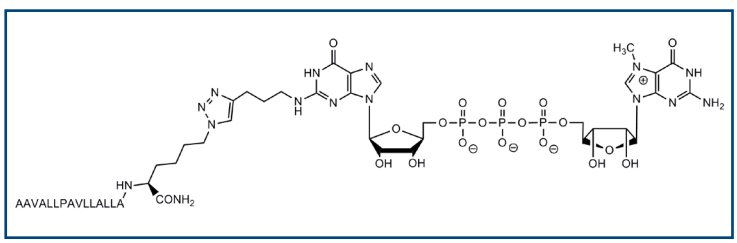
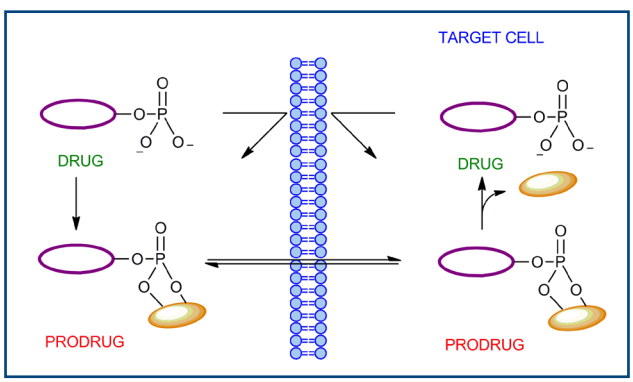


(B) Synthesis, biological and biophysical evaluation of mRNA cap-peptide conjugates for targeted delivery of cap analogues to cancer cells. All cap analogues obtained so far, unfortunately, have not been used in in vivo studies because they are unable to pass through the cell membrane due to the presence of electrical charge. The development of a system for the delivery of analogues to cancer cells would open the possibility of practical use of such cap analogs with excellent inhibitory properties. Currently we are testing two ways for such a delivery: conjugation of analogs with cell-penetrating peptides (CPP) and masking the charge of nucleotides. The first idea is based on the exceptional property of CPP to carry into cells a wide variety of cargoes. Our project comprise of the design and synthesis of conjugates consisting of a cap analog and a cell-penetrating peptide (such as MPS shown in the figure, TAT) and/or a cell-targeting peptide (such as iRGD) that are connected through enzyme degradable various types of bonds. The resulting constructs are subjected to *in vitro* and *in vivo* biological and biophysical studies.

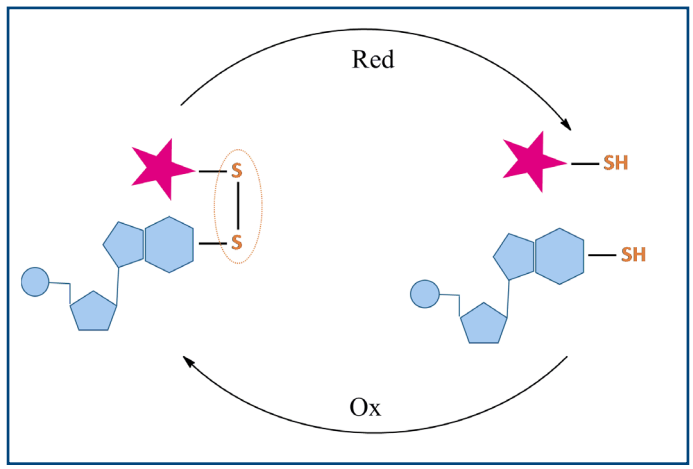


(C) Pro-nucleotides based on mRNA cap structures – synthesis, biological and biophysical evaluation. Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active drug. We'd like to implement this idea to 5'-monophosphate cap analogs and convert them to prodrug forms by derivatization of the phosphorus-coupled oxygen(s) to form neutral phospho di- or triester(s) or amidophospho mono-, di- or tiesters.



(D) Synthesis of dinucleotide cap analogs for RNA-based biopharmaceuticals.
RNA-based biopharmaceuticals, which include therapeutics and vaccines, are a relatively new way of treatment for a number of chronic and rare diseases. Application of 5'-capped RNA requires synthesis of RNA terminated with cap that most often are accomplish by the use of a cap dinucleotide such as m7GpppG. Our group is focused on the synthesis of new dinucleotide cap analogs that allow proper incorporation of dinucleotide cap analog during *in vitro* transcription and improve an effectiveness of translation and stability of transcripts.

(E) Synthesis of mono- and dinucleotide disulfide derivatives.
Compounds containing a thiol group in their structure (thiols) play a fundamental role in many biochemical and pharmacological processes due to the redox properties of function group (-SH). In our group, we develop methods for the synthesis of disulfide bridge between nucleotides and compounds performing a specific function i.e. fluorescent marker, cell penetrating peptides, compounds increasing solubility or affinity for a particular protein.



SELECTED PUBLICATIONS:

1. K. Piecyk, P. Pietrow, T. Arnold, R. Worch, N.L. Korneeva, M. Jankowska-Anyszka, Effect of HIV-1 TAT Peptide Fusion on 5′ mRNA Cap Analogs Cell Membrane Permeability and Translation Inhibition, Bioconjugate Chem. 31 (2020) 1156-1166.
2. K. Piecyk, M. Łukaszewicz, K. Kamel, M. Janowska, P. Pietrow, S. Kmiecik, M. Jankowska-Anyszka, Isoxazole-containing 5′ mRNA cap analogues as inhibitors of the translation initiation proces, Bioorganic Chemistry. 96 (2020) 103583.
3. I. Koćmik, K. Piecyk, M. Rudzińska, A. Niedźwiecka, E. Darżynkiewicz, R. Grzela, M. Jankowska-Anyszka, Modified ARCA analogs providing enhanced translational properties of capped mRNAs, Cell Cycle. 17 (2018) 1624-1636.
4. K. Piecyk, P. Kryńska, J. Kałużna, M. Jankowska-Anyszka, Synthesis of the first double-functionalized dinucleotide mRNA cap analogue for its specific labeling, Tetrahedron Letters. 58 (2017) 3037-3040.
5. R. Worch, K. Piecyk, A.B. Kolasa, M. Jankowska-Anyszka, Translocation of 5′ mRNA cap analogue — peptide conjugates across the membranes of giant unilamellar vesicles, Biochimica et Biophysica Acta (BBA) – Biomembranes. 1858 (2016) 311-317.
6. K. Piecyk, A. Niedźwiecka, A. Ferenc-Mrozek, M. Łukaszewicz, E. Darżynkiewicz, M. Jankowska-Anyszka, How to find the optimal partner—studies of snurportin 1 interactions with U snRNA 5' TMG-cap analogues containing modified 2-amino group of 7-methylguanosine, Bioorganic & Medicinal Chemistry. 23 (2015) 4660-4668.
7. K. Piecyk, M. Łukaszewicz, E. Darżynkiewicz, M. Jankowska-Anyszka, Triazole-containing monophosphate mRNA cap analogs as effective translation inhibitors, RNA. 20 (2014) 1539-1547.
8. K. Piecyk, M. Jankowska-Anyszka, Chemical conjugation of an mRNA cap analogue with a cell-penetrating peptide as a potential membrane permeable translation inhibitor, Tetrahedron Letters. 55 (2014) 606–609.
9. K. Piecyk, R.E. Davis, M. Jankowska-Anyszka, Synthesis of N2-modified 7-methylguanosine 5'-monophosphates as nematode translation inhibitors, Bioorganic and Medicinal Chemistry. 20 (2012) 4781-4789.
10. W.Z. Liu, M. Jankowska-Anyszka, K. Piecyk, L. Dickson, A. Wallace, A. Niedźwiecka, J. Stępiński, R. Stolarski, E. Darżynkiewicz, J. Kieft, R. Zhao, D.N.M. Jones, R.E. Davis, Structural basis for nematode eIF4E binding an m(2,2,7)G-Cap and its implications for translation initiation, Nucleic Acids Research. 39 (2011) 8820-8832.