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Dr. sc. Ruža Frkanec, University of Zagreb
Dr. sc. Andreja Jakas, Ruđer Bošković Institute
Dr. sc. Adela Štimac, University of Zagreb
Prof. dr. sc. Leo Frkanec, Ruđer Bošković Institute
Arijana Mihalić, University of Zagreb
FOREWORD

It is our great pleasure and honour to welcome you at the symposium „Peptide Chemistry Day„ organized for the first time in Croatia.

Research in the field of peptide chemistry in Croatian science has a tradition lasting for almost half a century. Investigations of the structure of the insulin derivative where scientists from academia and those from PLIVA pharmaceutical company worked together marks the beginning of peptide chemistry in Croatia. Numerous domestic and foreign patents of PLIVA's researchers bear witness to it. Up to this time investigations in the field of synthetic chemistry, biochemistry as well as biology of peptides are very intensive and scientifically significant.

Furthermore, the scientists who worked in the field of peptide science in Croatia have continuously participated at international scientific meetings and Croatia has had a representative in the Council of the European Peptide Society since the Society was establish.

The aim of this symposium is to bring together all the research scientists who work on different aspects of the field of peptide science and present a part of the research of peptides which is carried out in our scientific community. Besides presentations of research results, we would like to stimulate all forms of collaboration and networking, especially for younger colleagues and students.

This symposium is organized by the University of Zagreb. The symposium is a scientific part of the celebration of the 350th academic year of the University of Zagreb and also celebrates 45 years of systematic scientific research of peptides in Croatia.

The symposium is sponsored by Croatian Science Foundation, European Peptide Society, Croatian Chemical Society, Institute Ruđer Bošković and PLIVA.

We thank the University of Zagreb and all the sponsors whose support is invaluable to the success of the Symposium.

We would like to express our sincere thanks to all of the speakers and participants for sharing their research achievements, therefore contributing to the excellence of our meeting.

Finally, we sincerely hope that you will enjoy the socializing and the friendly atmosphere of the symposium. We are also already looking forward to the next peptide symposium!

Ruža Frkanec
President of the Organizing Committee
# PROGRAMME

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CRYSTALLIZATION AND X-RAY CRYSTALLOGRAPHIC STUDIES ON INSULIN DERIVATIVES

Biserka Prugovečki* and Dubravka Matković-Čalogović

Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, 10000 Zagreb, Croatia
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Insulin is a hormone protein which is produced in the β-cells in the Islets of Langerhans, located in the pancreas. Owing to its crucial metabolic role and its pharmaceutical importance many structural studies on chemically and genetically modified insulins have been done.

In this talk, crystallization and single crystal X-ray crystallographic studies of modified insulin hexamers will be presented. Replacement of zinc ions with selected essential elements: copper, nickel, manganese and cobalt has been done and the prepared insulin derivatives were structurally characterized. All of the investigated insulin derivatives belong to the $T_6$ form (Figure 1a).[1−3] Crystallization of insulin in the presence of chloride anions resulted in new crystal forms of the cobalt and nickel $T_6$ insulin derivatives.[4] Derivatives of the insulin hexamers that were crystallized in the presence of bromide (Figure 1b), $T_3R_3^1$ form, and iodide ions, $T_6$ form (Figure 1c) have also been prepared and structurally characterized.[5] Coordination of zinc ions and conformation of the insulin molecule in all investigated insulin hexamers will be discussed.

Figure 1. Hexamer of: a) the nickel derivative of insulin, $T_6$; b) the zinc-bromo insulin derivative, $T_3R_3^1$; c) the zinc-iodo insulin derivative, $T_6$.

REFERENCES
BIOLOGICALLY ACTIVE PEPTIDES AND GLYCOPEPTIDES AS A RESULT OF CHEMICAL MODIFICATION OF NATURAL COMPOUNDS

Andreja Jakas,* Kristina Vlahoviček-Kahlina, Ljiljana Mrkus, Jelena Batinić, Nina Bjeliš

Division of organic chemistry and biochemistry, Ruđer Bošković Institute, Bijenička c. 54, Zagreb, Croatia
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Quercetin and resveratrol are polyphenolic compounds, members of the flavonoid and the stilbene family, respectively, both medicinally important as dietary anticancer and antioxidant agents. They are present in a variety of foods—including fruits, vegetables, tea, wine, as well as other dietary supplements—and are responsible for various health benefits. Different quercetin and resveratrol esters of Leu/Met-enkephalin and tetrapeptide Leu-Ser-Lys-Leu (LSKL) were synthesized (Figure 1a).[1]

New potential antimicrobial peptide (AMP) library was prepared using sugar amino acid [SAA, muramic acid (Mur)][2] and tetrapeptide LSKL as building units. One of the prepared peptide exhibit antimicrobial activity against Staphylococcus aureus (Figure 1b).

Figure 1. 1a) Resveratrol and quercetin peptidomimetics, 1b) Antimicrobial peptide with SAA

ACKNOWLEDGMENTS

This work was supported by Ministry of science and education of Croatia and NATO SfP 983154.

REFERENCES

MACROCYCLE-INSPIRED PEPTIDOMIMETICS FOR CHALLENGING TARGETS

Goran Kragol

Fidelta d.o.o., Prilaz baruna Filipovića 29, Zagreb
goran.kragol@glpg.com

Macrocycles belong to the middle chemical space with properties between small molecules and biologicals. Although they do not fit into the Lipinski “Rule of 5”, they do have druggable PhysChem properties.[1,2] FideltaMacro™ technology[3] affords, apart from diversifying and enriching chemical space with different ring sizes, novel macrocycles specifically designed and constructed for the particular purpose. Valuable examples of purpose-built macrocycles are novel peptidomimetics designed to interact with specific targets.

FideltaMacro™ has been successfully used to design and prepare a library of novel macrocyclic peptidomimetics as inhibitors of IL17A/IL-17R and p53/MDM2 protein-protein interactions. IL-17A is a pro-inflammatory cytokine that has been implicated in autoimmune and inflammatory diseases.[4] Inhibition of p53/MDM2 interaction and reactivation of p53, which is powerful tumor suppressor, is validated therapeutic strategy in oncology.[5]

REFERENCES
DISCOVERY OF POTENT DESMURAMYLPEPTIDE AGONISTS OF THE INNATE IMMUNE RECEPTOR NOD2 AS NOVEL ADJUVANTS

Martina Gobec,a Tihomir Tomašič,a Adela Štimac,b Ruža Frkanec,b Jurij Trontelj,a Marko Anderluh,a Irena Mlinarič-Raščan,a and Žiga Jakopin,a,*

a Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, SI-1000 Ljubljana, Slovenia.
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Muramyl dipeptide (MDP), a fragment of bacterial peptidoglycan, has long been known as the smallest fragment possessing adjuvant activity, on the basis of its agonistic action on the nucleotide-binding oligomerization domain-containing protein 2 (NOD2). There is a pressing need for novel adjuvants and NOD2 agonists provide an untapped source of potential candidates. Here, we present the design, synthesis and characterization of a series of novel acyl tripeptides. A pivotal structural element for molecular recognition by NOD2 has been identified, culminating in the discovery of compound 9 (Fig. 1), the most potent desmuramylpeptide NOD2 agonist to date. Compound 9 augmented pro-inflammatory cytokine release from human peripheral blood mononuclear cells in synergy with lipopolysaccharide. Furthermore, it was able to induce ovalbumin-specific IgG titers in a mouse model of adjuvancy. Our findings provided deeper insights into the structural requirements of desmuramylpeptides for NOD2-activation and highlight the potential use of NOD2 agonists as adjuvants for vaccines [1].

![Figure 1. Structure of desmuramylpeptide 9.](image)

ACKNOWLEDGMENTS
This work was supported by the Slovenian Research Agency grant (No. 0787-P208) and the Croatian Science Foundation (HrZZ) (Project No. 7387).

REFERENCES
The peptidomimetics are peptide or non-peptide molecules with a potential for enhanced conformational stability and activity compared with natural peptides. One of the numerous design approaches utilizes a small molecular scaffold aimed to induce the formation of turn structures upon insertion into the peptide backbone. Owing to the distance between cyclopentadiene rings, 1,1′-disubstituted ferrocene scaffolds exhibit a great potential to nucleate turns and β-sheet-like structures in the derived peptides. The recent results obtained on conjugates of Ala‒Pro sequences and −NH‒Fn‒NH− scaffold (Fn = ferrocenylenylene) revealed a different conformational properties of homo- and heterochiral peptides. Also, the bulkiness and basicity of the N-terminal Boc and Ac groups were founded to influence their conformational behaviour.\(^\text{[1]}\) Novel ferrocene peptides 1–4 are synthesized to explore not only the impact of the backbone chirality and N-terminal groups, but also the influence of a ferrocene scaffold −NH−Fn−CO− on their conformational patterning. Furthermore, the ability of the prepared conjugates to inhibit the growth of estrogen receptor-responsive MCF-7 mammary carcinoma cells and HeLa cervical carcinoma cells is tested.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Homo- (1 and 2) and heterochiral (3 and 4) ferrocene peptides.}
\end{figure}

\section*{ACKNOWLEDGMENTS}
This work is supported by Croatian Science Foundation (IP-2014-09-7899).

\section*{REFERENCES}

\url{https://doi.org/10.1002/chem.201701602}
SYNTHESIS, CHARACTERIZATION AND SELF-ASSEMBLY OF SMALL PEPTIDIC GELATORS BASED ON AMYLOID β-PROTEIN

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Alzheimer's disease is characterized by the extracellular fibrillar deposits of the 39-42 amino acid amyloid-β proteins (Aβ).[1] It was shown that the KLVFF fragment of Aβ-peptide is responsible for the formation of amyloid fibrils. The self-assembly phenomena of the low molecular weight peptides into supramolecular gels show resemblance to amyloid-β protein aggregation and hence may serve as a simple model for Aβ-aggregation.[2,3] The series of tripeptide gelators incorporating amino acids sequence present in the Aβ-protein denoted responsible for the protein aggregation have been synthesized and characterized. Tripeptide derivative Ac-FFA-NH₂ (Figure 1) was capable to self-assemble into hydrogel network at physiological pH.

Figure 1. Capped stick model of the Ac-FFA-NH₂ molecule.

The obtained hydrogel successfully mimics the extracellular matrix and was proved to serve as stable and biocompatible physical support in improving HEK293T cells biological outcome in vitro.[4]

ACKNOWLEDGMENTS
This work is supported by Croatian Science Foundation (IP-2018-01-6910).

REFERENCES
INTERACTION OF POSITIVELY CHARGED PEPTIDES IN WATER AND PHOSPHOLIPID BILAYERS

Mario Vazdar

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It is a textbook knowledge that charges of the same polarity repel each other. However, in aqueous solutions this Coulomb repulsion is strongly attenuated by a factor equal to the dielectric constant of the medium. The residual repulsion, which now amounts only to units of kJ/mol, can be offset by attractive interactions. Probably the smallest like-charge pair, where a combination of dispersion and cavitation forces overwhelms the Coulomb repulsion, consists of two guanidinium cations in water.

The importance of pairing of guanidinium cations in aqueous solutions has significant biochemical implications. For example, arginine-arginine pairing has been frequently found in structural protein databases. In particular, when strengthened by a presence of negatively charged carboxylic groups, this binding motif helps to stabilize peptide or protein dimers as suggested by molecular dynamics simulations, SAXS and NMR experiments.

The like-charge pairing of the guanidinium side chain groups may also hold the key to the understanding of the arginine “magic”, i.e., the extraordinary ability of arginine-rich polypeptides to passively penetrate across cellular membranes in contrast to polylysines, which are also highly cationic but lack the ease in crossing membranes. This unusual behavior of arginine-rich cell penetrating peptides can be exploited in controlled delivery of molecular cargos into the cell.

ACKNOWLEDGMENTS

This work is supported by Croatian Science Foundation (UIP-2014–09–6090).

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ASSEMBLY OF PEPTIDOMIMETICS BY MULTICOMPONENT REACTIONS

Ivanka Jerić

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Approximately 5.000-10.000 potential drug targets are encoded within the human genome of which nearly two-thirds could be favorable to small- and medium-size molecule drugs, while one-third to proteins, nucleic acids and. However, small-molecule drugs currently present on market are directed against only 500 different targets. Screening of small-molecule libraries is the most available and easy-to-use tool in searching for biologically active molecules, and multicomponent reactions (MCRs) are powerful tool for introducing chemical diversity and the rapid generation of small-molecule libraries.

Based on the constant need for novel molecular architectures, biological tools, and lead compounds for total synthesis of natural products, chemical biology, and drug discovery, our main goal is to expand the chemical space of natural product-like compounds by using multicomponent reactions. This goal is achieved by developing novel non-natural amino acid-, carbohydrate- and enediyne-based building blocks; performing multicomponent reactions to obtain structurally diverse compounds and studying the stereochemistry of multicomponent reactions. Some representative examples are presented at Figure 1.[1,2]

Figure 1. Some representative examples of MCRs products.

ACKNOWLEDGMENTS
This work is supported by Croatian Science Foundation (IP-2014-09-3102).

REFERENCES
IUPAC – RECOMMENDATIONS FOR NOMENCLATURE AND GRAPHICAL REPRESENTATION IN PEPTIDE CHEMISTRY

Lidija Varga-Defterdarović

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Nomenclature as well as the drawings of two-dimensional chemical structure diagrams of peptides and its derivatives should be designed in ways that avoid ambiguity and can be understood correctly by all interested.

International Union of Pure and Applied Chemistry (IUPAC) was established in 1919 by chemists from industry and academia. Today, one hundred years since its founding, it is recognized as the world authority on chemical nomenclature and terminology. Their activities also include maintaining and developing standard systems for designating chemical structures, as well as computer-based systems.[1]

This presentation will give the major IUPAC nomenclature and graphical representation rules and recommendations important for the peptide chemistry.[2–4]

ACKNOWLEDGMENT

IUPAC rules and recommendations are translating and adopting in Croatian under the joint Section of Organic Chemistry Nomenclature of the Croatian Chemical Society and the Croatian Society of Chemical Engineers.

REFERENCES

BIOMOLECULAR INTERACTIONS OF PLANT LECTIN AND SELF-ASSEMBLED HYBRID BILAYERS MODIFIED WITH BACTERIAL PEPTIDOGLYCAN

Adela Štimac,a Ruža Frkanec,a,*

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Peptidoglycan (PGN) is the major component of bacterial cell walls which is recognized by the innate immune system through a series of pattern recognition receptors (PRR), which play a key role in first-line defense of the body.[1] Lectins, naturally occurring carbohydrate-binding proteins, are involved in numerous biological processes and some of them act as PRR and bind significantly to PGN.[2] Therefore, lectins are subject to extensive studies in the fields of infectious diseases and cancer research as potential drug targets or therapeutic agents.

In this study we were primarily interested in testing the interaction of peptidoglycan monomer (PGM),[3] disaccharide pentapeptide isolated from B. divaricatum with model plant lectins by quartz crystal microbalance (QCM) method. In order to study interactions of PGM with lectins, lipophilic derivative, PGM-oleyl was synthesized and used for preparation of the self-assembled hybrid bilayer membrane (HBM). It was demonstrated that PGM was effectively recognized by wheat germ agglutinin (WGA) and that the strength of interactions depends on the amount of PGM-oleyl used for HBM preparation. Since the peptidoglycan recognition by PRRs involves moderate- to high-affinity interactions with the carbohydrate moiety as well as the peptide moiety of peptidoglycan, the established method could be successfully employed in analyses of lectin-carbohydrate interactions, such as specificity, affinity and kinetics.

ACKNOWLEDGMENTS
This work is supported by Croatian Science Foundation (IP-2018-01-6910).

REFERENCES
DESIGN, SYNTHESIS AND IMMUNOSTIMULATING ACTIVITY OF MANNOSYLATED DESMURAMYL PEPTIDES

Rosana Ribić, a, * Srđanka Tomić b

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Muramyl dipeptide (MDP), N-acetylmuramyl-L-alanyl-D-isoglutamine, is the smallest structural unit of bacterial peptidoglycan responsible for eliciting of immune response. It acts as a pathogen-associated molecular pattern and activates nucleotide-binding oligomerization domain-containing protein 2 (NOD2).[1] Desmuramyl peptides possess L-Ala-D-isoGln pharmacophore which is essential for the immunostimulatory properties. We have designed mannosylated desmuramly peptides (Figure 1) using multiple pathogen recognition receptor activation approach.[2] Mannose receptors are C-type lectin receptors expressed on immunocompetent cells and represent additional pattern recognition target for affecting immune system.[3]

![Figure 1. The most active mannosylated desmuramyl peptide](image)

Adamantane was introduced in order to increase the lipophilicity of L-Ala-D-isoGln peptide and to facilitate the anchoring of the compound to the lipid bilayer.

ACKNOWLEDGMENTS

This work is supported by Croatian Science Foundation (IP-2014-09-7899).

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PEPTIDE BASED SYNTHETIC VACCINES: FROM EPITOPE TO ADJUVANTS

Ruža Frkanec

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Peptide vaccines represent an alternative to conventional vaccines which are trying to address issues of possible vaccine side effects related to vaccination with a heterogeneous multicomponent preparation of classical vaccines.[1] Synthetic peptide vaccines are usually composed of 20–30 amino acids comprising the specific epitope of an antigen related to infectious and/or chronic diseases including cancers. Their advantages over other types of vaccines such as conventional vaccines and newly developed DNA vaccines include easy synthesis at a low cost, increased stability, and relative safety generally demonstrated in numerous preclinical and clinical studies. In addition, peptide vaccines have no limitation in target diseases, from virus infection to Alzheimer disease, cancer and even allergy. Despite high expectations, the peptide-based vaccines that have been explored in the clinic have so far had limited therapeutic activity. Some of limitations include epitope identification and selection of most relevant epitopes, lack of immunogenicity, immune evasion and clinical evaluation.[2]

The lecture attempts to summarize the most significant challenges in peptide vaccine development focusing on the innovative approach overcoming those limitations, in particular in vaccine formulations with appropriate adjuvants.

ACKNOWLEDGMENTS

This work is supported by Croatian Science Foundation (IP-2018-01-6910).

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LIST OF PARTICIPANTS

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Ban, Željka
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Prskalo, Katarina
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Vuletić, Srećko