New methods for chemical glycosylation

Alexei V. Demchenko

Department of Chemistry, School of Science and Engineering, Saint Louis University

3501 Laclede Avenue, St. Louis, Missouri 63103, USA

Author E-mail: alexei.demchenko@slu.edu

ABSTRACT

From the building blocks of nature to disease-battling pharmaceuticals, glycans have had a profound impact on evolution, society, economy, and human health. Numerous applications of these essential biomolecules in many areas of science and technology exist, most of which can be found at the forefront of therapeutic agent and diagnostic platform development. Although glycans are desirable for the pharmaceutical and biomedical communities, these molecules are very challenging targets for chemists because of the need for functionalization, protecting and leaving group manipulations, controlling anomeric stereoselectivity, separation, and analysis.

At the core of this presentation is the development of new methods and strategies for the chemical synthesis of glycans. These tools will be discussed in light of recent results related to the development of new rmethods including regenerative glycosylation[1-3] and the 4K reaction[4, 5] as well as automated technologies for glycan assembly on polymer supports[6] and carbohydrate synthesis in solution.[7, 8] This work has been generously supported by the National Institutes of Health and the National Science Foundation.

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Biosketch of the Speaker

Alexei V. Demchenko
Department of Chemistry, School of Science and Engineering, Saint Louis University
3501 Laclede Avenue, St. Louis, MO 63103, USA
Email alexei.demchenko@slu.edu

Alexei Demchenko was born (1965), raised, and educated in Moscow, Russia. He graduated from the Mendeleev University of Chemical Technology of Russia with a Diploma (M.S.) in Chemical Engineering (1988) before joining the laboratory of the late Professor Kochetkov at the Zelinsky Institute of Organic Chemistry in Moscow. In 1993, he was awarded a Ph.D. in organic chemistry by the Russian Academy of Sciences for his work on the development of thiocyanate methodology for glycosylation. After two post-doctoral years under Kochetkov, he joined Professor Boons' group at the University of Birmingham (UK) as a BBSRC post-doctoral research fellow. In 1998, he moved to the Complex Carbohydrate Research Center, University of Georgia (USA) as a research associate. In 2001, he joined the faculty at the University of Missouri - St. Louis (UMSL) as an Assistant Professor where he was promoted to the rank of Associate Professor with tenure (2007) and Professor (2011). In 2014, Demchenko was appointed Curators' Distinguished Professor of Chemistry and Biochemistry. In 2021, Demchenko joined the faculty at Saint Louis University as Professor and Department Chair.

With participation of 177 trainees, Professor Demchenko has co-authored around 240 articles (Scopus *H*-index 51, Scholar *H*-index 55) and has given around 200 lectures and seminars. His research interests are in the area of synthetic carbohydrate chemistry and research program has been funded by grants from a variety of sources totaling $13.3M. Professor Demchenko has served in many editorial roles and organized several international conferences including the 2015 Gordon Research Conference on Carbohydrates. From 2019, he has served as President of the U.S. Advisory Committee for the International Carbohydrate Symposia. Professor Demchenko was the 2020-2021 Chair of the Division of Carbohydrate Chemistry and Chemical Glycobiology of the ACS. Demchenko is the National Representative of the USA for the International Carbohydrate Organization.

Leveraging Non-classical σ-hole based Noncovalent Interactions and Asymmetric Catalysis: Emerging Frontiers in Stereoselective Carbohydrate Synthesis

Charles C. J. Loh*

UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland.

Author E-mail: charles.loh@ucd.ie

There is a recent renaissance amongst organic chemists in appreciating the value of stereoselective carbohydrate synthesis as an excellent platform for discovery of chemical phenomena.[1] In my talk, I will describe two emerging directions pursued by my research group. In the first direction, I will narrate our seminal efforts in developing mild and robust *σ*-hole based noncovalent catalyzed methods for selective carbohydrate synthesis – an approach we now define as the "*σ-hole based catalytic glycosylation strategy*".[2-3]

I will offer an overview of our early efforts in the development of exclusively halogen bonding (XB) catalyzed strain-release glycosylation and 2-deoxyglycosylation. These strategies contain unique advantages, such as the elevation of anomeric selectivity. Next, I will introduce our pioneering approach in chalcogen bonding (ChB) catalyzed glycosylations and glycomimetic synthesis. We recently demonstrated that the ChB catalysis performed exceptionally well on glycosyl substrates. We further developed versatile strategies that enabled access into biologically relevant 7-membered ring sugars known as septanosides,[4] β-indolyl glycosides[5] as well as in underexplored iminoglycosides.[6]

A second research axis is the harnessing of metal catalyzed asymmetric catalysis to surmount multiple enantio-, diastereo- and site-selectivity challenges within a single bond forming step.[2] Besides sharing novel asymmetric rhodium[7] and radical copper catalyzed[8] platforms we developed, I will touch on recent efforts to exploit NCIs for carbohydrate stereocontrol in the context of asymmetric palladium catalyzed site-selective functionalizations.[9]

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Bio-sketch of the Speaker

Charles C. J. Loh UCD School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland. *charles.loh@ucd.ie*	**Photo** 

Charles C. J. Loh commenced his doctoral research under the supervision of Prof. Dieter Enders at the RWTH Aachen University (Germany) in the area of merging organocatalysis and transition metal catalysis, and organocatalytic domino reactions. He successfully defended his doctoral thesis (*Summa Cum Laude*) and was decorated with the Borschers Plakette for outstanding performance in his doctoral studies in 2014. In the same year, he was awarded the Deutscheforschungsgemeinschaft (DFG or German Research Society) Postdoctoral Fellowship for postdoctoral research under the supervision of Prof. Mark Lautens at the University of Toronto (Canada), in the field of rhodium catalyzed asymmetric ring opening reactions between 2014-2016.

Between 2016 to 2024, Charles was a research group leader at the Max Planck Institute of Molecular Physiology. Since fall 2024, Charles moved to Ireland and joined the School of Chemistry at University College Dublin as an assistant professor. Charles is a pioneer in using "non-classical" σ-hole interactions such as halogen and chalcogen bonding to tackle major challenges in carbohydrate synthesis. His team is also developing innovative asymmetric catalytic strategies to solve long-standing problems of selectivity in carbohydrate chemistry. By combining noncovalent catalysis, asymmetric catalysis, mechanistic studies and computations, his group is breaking new ground in this emerging domain.

This year, Prof. Loh has been named a winner of the **2025 Advanced Science Young Innovator Award**, an international prize supported by *Wiley (Advanced Science)*. The award recognises outstanding young researchers worldwide who are driving breakthroughs across disciplines. He was also a recipient of the Liebig Fellowship from the Fonds der Chemischen Industrie and the prestigious Plus 3 Perspectives Programme from the Boehringer Ingelheim Foundation.

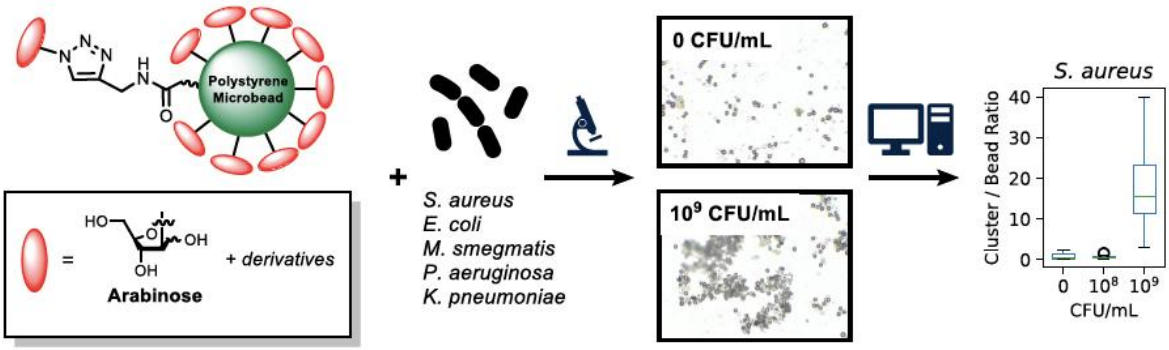
Synthetic glyco-tools for exploring and exploiting the glycome.

M. Carmen Galan

School of Chemistry, Cantock's Close, University of Bristol, Bristol BS8 1TS. United Kingdom.

E-mail: m.c.galan@bris.ac.uk.

O-Glycosylation is a ubiquitous post-translational modification that is highly dynamic and responsive to cellular stimuli through the action of the cycling enzymes. Expression of specific O-glycans is linked to changes in gene expression in, for example, inflammatory bowel disease, cystic fibrosis and several types of cancer.[1]
Glycan multivalent probes constitute a good bio-mimetic model of carbohydrate presentation at the cell surface and provide a powerful tool to screen for protein carbohydrate interactions and consequently for the identification of carbohydrate receptors or ligands associated with many inter- and intracellular recognition processes associated to disease including microbial infections.[2]
Antimicrobial resistance (AMR) is a rapidly growing issue and poses a significant threat to our ability to treat common infections. In the next 25 years, if current trends continue, the global death toll from AMR infections will exceed that of cancer.[2] Development of rapid and selective diagnostic strategies to identify or target bacterial infections at the point of care is of vital importance to avoid prescription of broad-spectrum antibiotic agents and reduce the risk of contributing to AMR.[2]
In recent years, our group has developed fluorescent multivalent O-glycan probes for the study of O-glycosylation-linked interactions in live cells and more recently in bacteria.[3] In this lecture, we will discussed the development of a rapid bacteria screening strategy based on carbohydrate-functionalized polystyrene microspheres.[4] Using this assay, we identified selective binding of C-2 linked arabinose moieties immobilized on a microbead surface to *Staphylococcus aureus*, a Gram-positive pathogenic bacterium of which antimicrobial-resistant strains are widespread and problematic.[5] We could quantify this effect using image processing software (Abacus), allowing selective detection of *S. aureus* over other bacteria species.



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Bio-Sketch of the Speaker

Prof. M. Carmen Galan
Affiliation:
School of Chemistry
Cantock's Close
University of Bristol
Bristol BS8 1TS
United Kingdom
Telephone: +44 (0)1174553093
Email: m.c.galan@bristol.ac.uk

M. Carmen Galan received her B.S. degree in chemistry from Universidad de Alicante, Spain and an MPhil in Chemistry from the University of Strathclyde (Scotland). She then moved to the USA where she received her Ph.D. in Organic Chemistry from the Complex Carbohydrate Research Center at The University of Georgia, USA, under the supervision of Prof. Geert-Jan Boons, where she carried out research in the field of carbohydrates. She then moved to California to pursue post-doctoral research with Prof. Chi-Huey Wong at The Scripps Research Institute. After that, she continued her post-doctoral training at Massachussetts Institute of Technology with Prof. Sarah O'Connor. Carmen returned to the UK in October 2006 on a lecturership in the School of Chemistry.

She is currently a Professor of Organic and Biological Chemistry in the Chemistry Department at the University of Bristol. Prior to that, she was awarded a series of prestigious fellowships e.g. ERC consolidator grant (2015-2020) and she held an EPSRC Career Acceleration Fellowship (2012-2017) and a Royal Society Dorothy Hodgkin Fellowship (2008-2012).

Her internationally recognized research spans from medicinal chemistry, carbohydrate synthesis, catalysis, functional nanomaterials to biological applications in the areas of cancer, antimicrobials and plant nanobionics. In 2017, she was awarded the RSC Dextra Carbohydrate Chemistry award in recognition of her research into new synthetic methodologies for oligosaccharide synthesis and the development of novel glycoconjugate probes. In 2021 she received the RSC Jeremy Knowles award for the development of bioinspired synthetic probes for the targeting and regulation of cellular processes and in 2022 she was awarded the Spanish Researchers UK (SRUK) Merit award for her contributions to science and the impact of her work to the wider community. In 2025 she received the ACS Melvile L. Wolfrom award for her scientific contributions in oligosaccharide chemistry and service to the community and the 2025 Emil Fisher Carbohydrate award.
In addition to her academic duties, She is the Secretary of the International Carbohydrate Committee and Editor-in-Chief of Carbohydrate Research. She is also the co-founder and co-Director of CDotBio Ltd a university of Bristol spin out.

Chemical Tools for Glycobiology

Valentin Wittmann

Department of Chemistry, University of Konstanz, 78457 Konstanz, Germany

Author E-mail: Valentin.Wittmann@uni-konstanz.de

The elucidation of the numerous biological functions of carbohydrates benefits enormously from the development of chemical tools designed to achieve tight binding of carbohydrates to proteins and RNA, to synthesize glycoconjugates, and to trace carbohydrates within cells. This lecture will give an overview of some of our achievements in these fields.

We synthesized numerous high-affinity **multivalent lectin ligands** including a photoswitchable one[1] and developed a new design of multivalent lectin ligands, termed inline lectin ligands (iLecs).[2] iLecs lead to exceptionally high binding affinities without concurrent precipitation of proteins due to crosslinking. **RNA-binding carbohydrates** derived from glucosamine-6-phosphate (GlcN6P) can function as activators of the *glmS* riboswitch and are promising lead structures for the development of future antibiotics with a potentially novel mode of action.[3]

Conjugation of unprotected (reducing) carbohydrates to surfaces or probes by **chemoselective ligation reactions** is indispensable for the elucidation of their biological functions. We studied the kinetics of the oxyamine ligation by real-time NMR spectroscopy and could show that the reaction rate is significantly increased (up to 500-fold) without the need for a catalyst when starting with glycosyl amines.[4]

Metabolic glycoengineering (MGE) is now a well-established approach to study the biological roles of carbohydrates.[5] We applied the inverse-electron-demand Diels-Alder (IEDDA) reaction in MGE to achieve the visualization of protein-specific glycosylation within living cells using confocal FLIM-FRET microscopy. To study protein-O-GlcNAcylation, we developed dienophile-modified glucosamine-1-phosphate derivatives that do not lead to non-specific labeling by the recently reported *S*-glyco modification.[6]

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Bio-sketch of the Speaker

Prof. Dr. Valentin Wittmann
University of Konstanz
Department of Chemistry
78457 Konstanz, Germany
Email Valentin.Wittmann@uni-konstanz.de

Valentin Wittmann studied Chemistry at the Goethe-University of Frankfurt (Germany). In 1994 he obtained a PhD from the Technical University of Munich (Germany) for his work on *C*-glycopeptides under the supervision of Prof. Horst Kessler. Subsequently, he carried out postdoctoral research with Prof. Christian Griesinger at the Goethe-University of Frankfurt (Germany) in the field of stable-isotope-labeled oligonucleotides and with Prof. Chi-Huey Wong at The Scripps Research Institute in La Jolla, California (USA) working on the chemoenzymatic synthesis of oligosaccharides. In 1997 he returned to Frankfurt to start independent research. Since 2003 he is professor of organic/bioorganic chemistry at the University of Konstanz (Germany). From 2006 until 2011 he was Dean of Studies, from 2016 until 2020 and from 2024 until 2025 head of the Department of Chemistry, and from 2016 until 2023 vice coordinator of the Collaborative Research Center SFB 969. His main research area is the chemical biology of carbohydrates including metabolic glycoengineering, investigation of multivalent carbohydrate-protein interactions, and RNA-targeting antibiotics.

Lectins in host-pathogen interactions: structure, function, and their analytical potential

Michaela Wimmerova

National Centre for Biomolecular Research, Faculty of Science & Central European Institute of Technology, Masaryk University, Brno, Czech Republic

michaw@chemi.muni.cz

Lectins are carbohydrate-binding proteins of non-immune origin. Although some participate in immune-related processes, they are not direct products of the immune response and lack enzymatic activity toward their ligands. Microbial lectins specifically recognize carbohydrates on host cell surfaces, such as glycoproteins or glycolipids, thereby mediating adhesion to host cells or mucosal surfaces and serving as key virulence factors.

Our long-term objective is to identify, isolate, and characterize lectins from bacteria and fungi, particularly those associated with human, plant, and insect pathogens. This contribution focuses on structure–function analyses of selected bacterial lectins involved in host–pathogen interactions, including those that may play a role in nematobacterial complexes exhibiting high pathogenicity toward diverse insect species.

Bio-sketch of the Speaker

Michaela Wimmerova
National Centre for Biomolecular Research & Central European Institute of Technology, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic
michaw@chemi.muni.cz

Michaela Wimmerova is a professor at Masaryk University (MU), Brno, Czech Republic, the head of the Glycobiochemistry Research group at Central European Institute of Technology of Masaryk University (CEITEC MU), and currently also serves as the Director of National Centre for Biomolecular Research (NCBR) at Faculty of Science MU since 2022. She received her PhD in Biochemistry from Masaryk University, Brno in 1996, and after one-year research stay at the Centre de Recherches sur les Macromolécules Végétales (CERMAV), CNRS, Grenoble, France she established the Glycobiochemistry Research Group primarily focusing on proteins involved in host-pathogen recognition. She established and led the Biomolecular Interactions and Crystallization Core Facility at CEITEC MU, equipping it with advanced instrumentation for state-of-the-art biophysical analyses (including SPR, microcalorimetry, MST, AUC, CD, DLS, and high-throughput crystallization). She is an active member of the scientific community at both the national and international levels. She serves on the national board of the Czech Society for Biochemistry and Molecular Biology and represents the Czech Republic in the International Glycoconjugate Organisation. She has been involved in several European infrastructures and projects, and has actively participated in organizing scientific conferences (FEBS Congress, CSBMB meetings, annual Meetings of Biochemists and Molecular Biologists). Over more than two decades, she has developed deep experience in protein biochemistry, molecular biology, biomolecular interactions, and bioinformatics with long-standing expertise in structural glycobiology, protein–carbohydrate interactions, and host–pathogen recognition. The group has identified and characterized several novel lectins and other carbohydrate-binding proteins with unique structural and functional properties.

Probing glycan receptor specificities of human flu viruses by chemoenzymatic synthesis, NMR, modelling, and cell biology

Author (Times new roman, font size 12)

[1] CICbioGUNE, Basque Research & Technology Alliance (BRTA), Bizkaia Technology Park, Building 800, 48160 Derio, Bizkaia, Spain. [2]Ikerbasque, Basque Foundation for Science, Euskadi Plaza 5, 48009 Bilbao, Bizkaia, Spain.

Author E-mail: lunione@cicbiogune.es

ABSTRACT (Times new roman, font size 11) (Max. 250 words, 1.5 spacing)

The dense layer of glycans decorating eukaryotic cell surfaces represents one of the front-line barrier that mediate interactions at the virus-host interface. These sugars are structurally diverse and expressed in tissue- and cell type–specific manners.[1] Numerous viruses display virally encoded lectins (glycan-binding proteins) on their surface, which act as molecular "keys" to engage glycan receptors on host cells and mediate viral attachment and entry.[2] The selectivity of these virolectins for specific glycan structures critically determines host range, tissue tropism, and pathogenesis.

A prototypical example is influenza A virus, whose hemagglutinin (HA) lectin binds to cell-surface glycans terminating in α2,6-linked sialic acid moieties (Neu5Ac(α2,6)Gal), which are predominant in the human upper respiratory tract. By contrast, certain coronaviruses, toroviruses, and influenza C and D viruses exhibit host-specific receptor recognition that depends on both the glycosidic linkage type and the O-acetylation pattern of sialic acids.

The rational design of new surveillance, prevention, and intervention strategies against viral infections requires detailed molecular and structural knowledge—ideally at atomic resolution—of viral receptor recognition mechanisms. Our research contributes to elucidating the molecular basis of viral lectin–host glycan interactions.[3,4] To achieve this, we employ a multidisciplinary approach that integrates chemical synthesis, recombinant protein expression, high-resolution biophysical binding studies, and cell-based assays. The insights gained from this work advance our understanding of glycan recognition in viral infections and hold potential for the rational design of vaccines, antiviral agents, and predictive models for the emergence of novel human virus variants.

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Bio-sketch of the Speaker

Luca Unione (Times new roman, font size 12) [1]CICbioGUNE, Basque Research & Technology Alliance (BRTA), Bizkaia Technology Park, Building 800, 48160 Derio, Bizkaia, Spain. [2]Ikerbasque, Basque Foundation for Science, Euskadi Plaza 5, 48009 Bilbao, Bizkaia, Spain. (Times new roman, font size 12) *lunione@cicbiogune.es (Italic, Times new roman, font size11)*	**Photo** 

Luca was trained as a chemist at the University of Naples (Italy) and obtained his PhD in Pharmacy within the international EU ITN Marie Curie project DYNANO, under the supervision of Jesús Jiménez-Barbero at the CIB Margarita Salas–CSIC in Madrid (Spain). His doctoral research focused on elucidating molecular recognition events between glycans and protein receptors in solution through an integrated approach combining NMR spectroscopy and molecular modeling.

During his first postdoctoral appointment, Luca was awarded the competitive national Torres Quevedo fellowship to pursue translational research at the pharmaceutical company Atlas Molecular Pharma, a spin-off of CIC bioGUNE (Derio, Spain), where he contributed to the identification of therapeutic candidates for rare diseases.

Returning to fundamental research with a continued interest in translational potential, Luca was next awarded the prestigious International Human Frontier Science Program (HFSP) Fellowship for his second postdoctoral position in the laboratory of Geert-Jan Boons at Utrecht University (The Netherlands). There, he developed chemo-enzymatic tools for the synthesis of complex human-derived glycans and investigated their roles in viral infection mechanisms.

After two years in Utrecht, Luca joined CIC bioGUNE as a Juan de la Cierva and Ikerbasque Research Fellow. In 2023, he received a highly competitive ERC Starting Grant to decipher the role of glycans in infectious diseases at atomic resolution. In 2025, Luca was awarded the Ramón y Cajal Fellowship. Since 2024, he has served as Associate Principal Investigator in the Chemical Glycobiology Laboratory, where he leads a research program focused on understanding glycan–receptor interactions in infectious diseases from both basic and applied perspectives, including the design and synthesis of broad-spectrum inhibitors of human influenza viruses.

Please submit the Bio-sketch of maximum of 350 words (Times new roman 11, Spacing 1.5) online by **November 10, 2025.**

Chemical Synthesis and Immune Functions of Bacterial Lipid A for Safe Vaccine Adjuvant Development

Atsushi Shimoyama

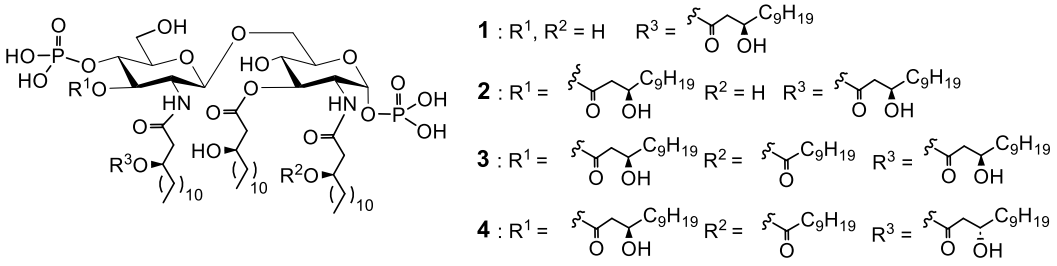
Graduate School of Science, The University of Osaka, 1-1 Machikaneyama, Toyonaka, Osaka, Japan

ashimo@chem.sci.osaka-u.ac.jp

Lipopolysaccharide (LPS) is a major glycoconjugate in outer membrane of Gram-negative bacteria and canonical Escherichia coli LPS activate innate immunity to induce lethal strong inflammation. The terminal glycolipid lipid A is the active principle of LPS. Low inflammatory lipid A have been expected as vaccine adjuvants.

We hypothesized that co-evolved parasitic and symbiotic bacterial components should modulate host immunity moderately with low toxicity. We synthesized parasitic [1] and symbiotic [2] bacterial lipid A and elucidated the molecular basis of immunoregulation, and developed safe and useful adjuvants. In this presentation, we introduce chemical synthesis and functions of lipid A from *Alcaligenes faecalis* inhabiting gut-associated lymphoid-tissue (GALT) that is responsible for the mucosal immunity regulation.

We synthesized *A. faecalis* lipids A **1**-**3** with diverse acyl group patterns and identified the active center as hexa-acylated **3** [2]. Lipid A **3** was confirmed to exhibit non-toxic but useful adjuvant function (enhancing antigen-specific IgA and IgG production) [3-5], and the vaccine model using **3** was found to be significantly protective against bacterial infection [4]. Since IgA is responsible for mucosal immune homeostasis, we found a promising adjuvant that can safely regulate mucosal immunity by focusing on GALT symbiotic bacteria. Furthermore, lipid A **4**, which reversed the stereochemistry of the acyl side chain hydroxy group, was found to be more active than **3**, and the molecular basis of the adjuvant function is also becoming clear.



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Bio-sketch of the Speaker

Atsushi SHIMOYAMA, Ph.D.
Graduate School of Science, The University of Osaka, 1-1 Machikaneyama, Toyonaka, Osaka, Japan
ashimo@chem.sci.osaka-u.ac.jp

Dr. Shimoyama received his Ph.D. in 2010 from Osaka University under the guidance of Prof. Koichi Fukase, supported by a Japan Society for the Promotion of Science (JSPS) research fellowship. In 2011, he received a permanent position at Tokyo Institute of Technology and was appointed as an Assistant Professor. He then returned to Osaka University in 2014 as an Assistant Professor and was promoted to Associate Professor in 2024.

His research focuses on the chemical biology study about glycoconjugates. In particular, he is currently investigating the relationship between bacterial lipid A and the host immune system based on the concept of 'bacterial-host chemical ecology', leading to the development of useful vaccine materials.

Education

2005	B.S.	School of Science, Osaka University
2007	M.Sc.	Graduate School of Science, Osaka University
2010	Ph.D.	Graduate School of Science, Osaka University, Supervisor: Prof. Koichi Fukase

Career

2008-2010	JSPS Research Fellowship for Young Scientist DC2
2010-2011	Project Researcher (Osaka University)
2011-2014	Assistant Professor (Tokyo Institute of Technology)
2014-2024	Assistant Professor (Osaka University)
2024-present	Associate Professor (Osaka University)

Developing potent inhibitors to resist resistance

Criss Dcosta, Amrita Suresh, Suvarn S. Kulkarni* and Ruchi Anand*

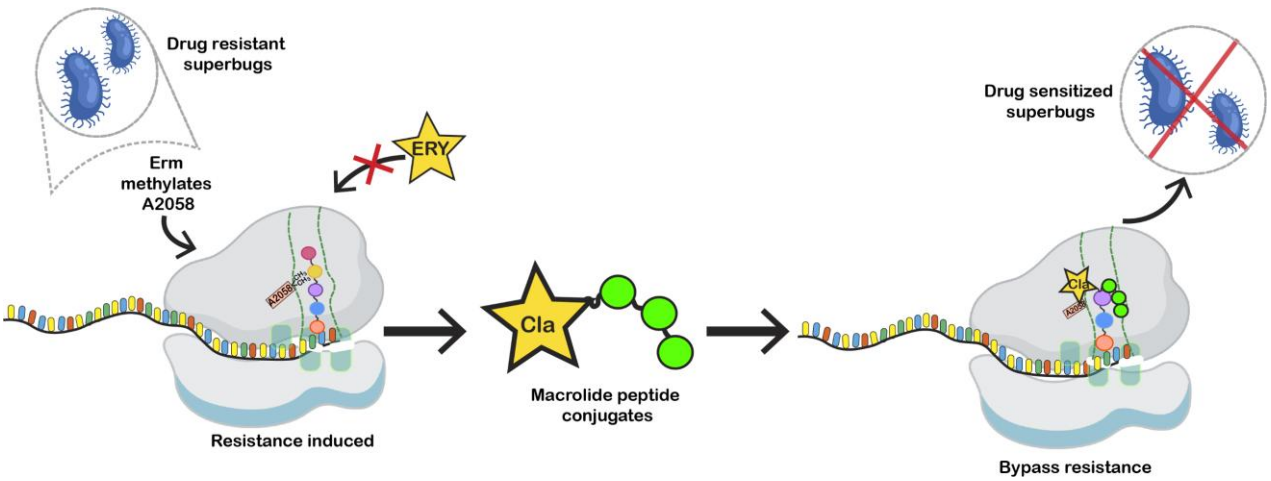
Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, Maharashtra, India

E-mail: suvarn@chem.iitb.ac.in , ruchi@chem.iitb.ac.in

The rapid rise of multidrug-resistant (MDR) pathogens threatens the efficacy of frontline antibiotics and poses a pressing global health crisis. Macrolides, such as erythromycin and tylosin, act by binding to the ribosomal nascent peptide exit tunnel (NPET) and blocking protein synthesis[1]. However, their clinical efficacy is compromised by Erm family methyltransferases, which modify a conserved adenine within the NPET to prevent drug binding. Expression of these enzymes is uniquely regulated through an antibiotic-induced ribosomal stalling mechanism, where a leader peptide sequence directs programmed translation arrest to trigger resistance[2].

To address this challenge, we employed a structure-guided design strategy to generate macrolide-peptide conjugates capable of interfering with Erm expression. By strategically modifying the macrolide scaffold with peptide-based extensions, we introduced conformational constraints within the NPET that disrupt programmed ribosomal stalling and suppress Erm activation, thereby bypassing resistance.

This work demonstrates how integrating structural biology and synthetic chemistry can directly target resistance-regulatory mechanisms. Our findings highlight a rational framework for the development of next-generation macrolides with the potential to restore clinical efficacy against MDR bacterial isolates



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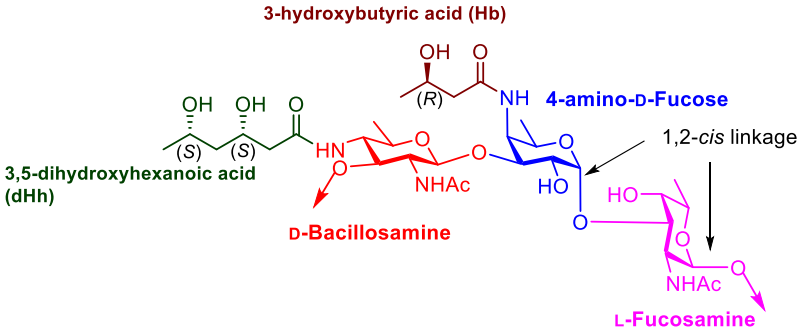
Orthogonal Amide Coupling Strategy for Conjugation-Ready Trisaccharide of *Vibrio cholerae* O100

Cell-surface bacterial carbohydrates consist of repeating units of rare deoxy amino glycans that, when conjugated with proteins, serve as promising vaccine candidates. Their limited natural availability necessitates efficient synthetic approaches, but the chemical synthesis of these structurally diverse glycans remains highly challenging. The emerging field of multicomponent carbohydrate-based synthetic vaccines involves the synthesis of bacterial glycans.[1] Herein, we describe the total synthesis of a structurally complex trisaccharide repeating unit of the O-antigen from *Vibrio cholerae* O100.[2] Our synthetic strategy involves the efficient construction of a conjugation-ready trisaccharide RU from *Vibrio cholerae* O100, utilizing orthogonally protected rare deoxy amino building blocks[3,4] and employing post-glycosylation orthogonal amide coupling at an advanced stage of amide coupling with Hb and dHh to achieve the desired target molecule.



Keywords: *Vibrio cholerae,* rare amino sugar, amide coupling

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Diastereoselective Gelation in ROMP Polymers from Sugar Cyclic Nitrones: Multifunctional Organogels for Adsorption and Insulation

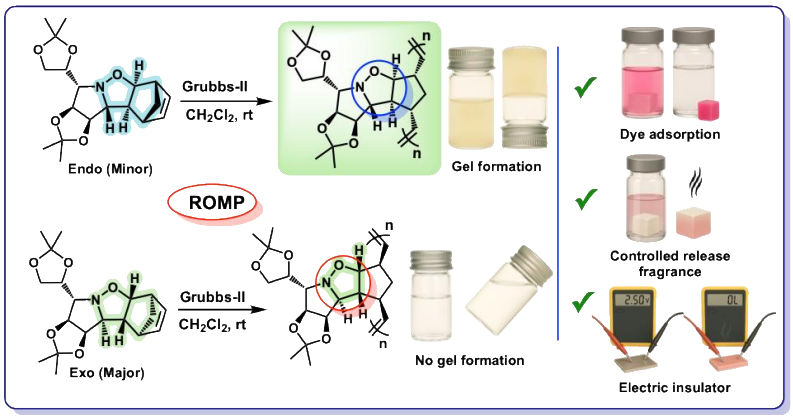
Anilkeerthi L.M, Krishna P. Kaliappan*

Department of Chemistry, Indian Institute of Bombay

Powai, Mumbai-*400076*, India

E-mail: *kpk@chem.iitb.ac.in*

Subtle stereochemical variations can decisively alter supramolecular assembly pathways, yet their impact on polymer gelation remains underexplored. In this work, carbohydrate-derived cyclic nitrones[1-3] were transformed into polymers *via* ring-opening metathesis polymerization (ROMP),[4] affording diastereomeric materials with contrasting outcomes in which *endo*-configured monomers yielded self-supporting organogels, that underwent spontaneous gelation in the ROMP reaction under ambient conditions, whereas the *exo* analogues produced only soluble polymers. The resulting gels displayed interconnected porous networks and thermal robustness. Beyond structural distinctiveness, they exhibited multifunctionality. Efficiently removing organic dyes with recyclability, enabling burst and sustained fragrance release, and functioning as electrical insulators in simple conductivity tests. These findings establish the first example of diastereomer-dependent gelation in ROMP-derived carbohydrate polymers, expanding the utility of renewable sugar scaffolds toward multifunctional soft materials.



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Unravelling viral haemagglutinin preferences to host glycans by chemoenzymatic synthesis and NMR

Cristina Fernández Pérez[1], María Moure Garcia[1], Diego Del Balzo[1], Iris Bermejo Ruíz[1], Alberto Marina[1], Jesús Jiménez-Barbero[1], Luca Unione[1]

[1]*Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), 48160 Derio, Bizkaia, Spain.*

E-mail: cfernandez@cicbiogune.es

The periodic emergence of global pandemics underscores the urgent need for effective strategies to combat viral diseases. Among these, human influenza A viruses (***h*IAVs**) remain a major public health concern, with the **A/H3N2** subtype responsible for most severe seasonal flu cases. While antiviral drugs provide an essential complement to vaccination, the rapid emergence of resistant strains demands innovative approaches for the development of next-generation therapies[1]. Central to *h*IAV infection is the haemagglutinin (**HA**) glycoprotein, which mediates viral entry by binding to host cell glycans terminating in α2,6-linked sialic acid residues (**Neu5Acα2,6Gal**). These receptors are usually located at the termini of extended oligosaccharides composed of LacNAc repeats, found in both N- and O-glycans[2]. Previous studies have shown that **antigenic drift**, driven by immune pressure, modulates HA receptor specificity and contributes to the diversification of glycan-binding profiles among different circulating viral clades. Our group has recently dissected these differences at the atomic level by means of chemoenzymatic glycan synthesis, state-of-the-art NMR spectroscopy, and computational modelling[3].

Here, we extend this integrative approach to investigate newly emerging A/H3N2 variants and elucidate the molecular basis of their evolving glycan recognition properties. The synthesis of a library of diverse glycans containing the minimal epitopes present in the human respiratory tract enables a comparative analysis of four A/SG/16-derived variants. Our results unveil epistasis among critical residues within the HA binding site, which synergistically reshapes receptor binding specificity while preserving immune escape. NMR-based experiments have been essential in providing comprehensive atomic-level insights into the evolutionary changes and receptor adaptations of contemporary A/H3N2 viruses, complementing and consistent with glycan array and molecular dynamics findings recently reported by Liang et al.[4].

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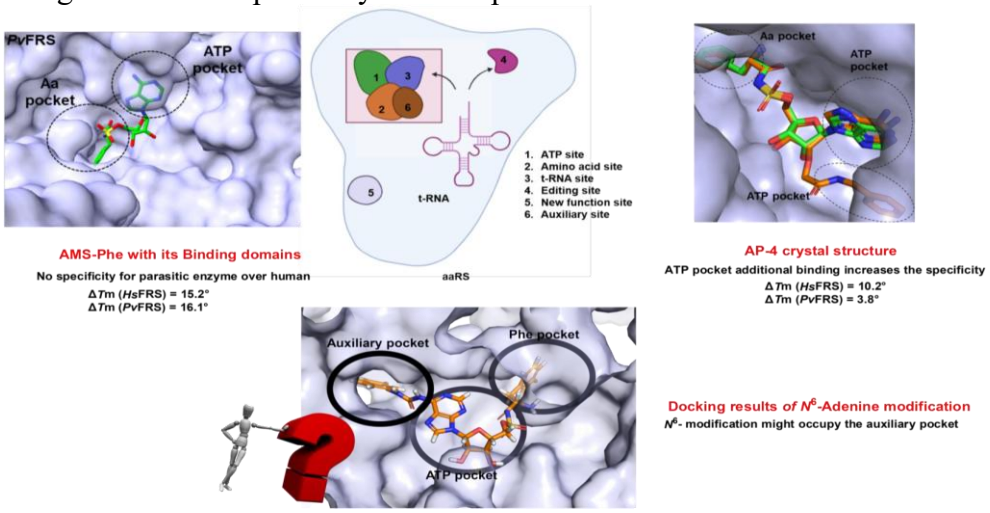
Targeting phenylalanine tRNA synthetase of the malarial parasite using nucleosideamino acid conjugates

Siddhesh Shewade[1], Siddharam Bagale[1], Manickam Yogavel[2], Mutharasappan Nachiappan[2], Amit Sharma[2], Pradeepkumar P. I.[1]

1. Department of Chemistry, Indian Institute of Technology Bombay, Mumbai, India
2. Department of Structural Parasitology, International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India

E-mail: 23d0191@iitb.ac.in, pradeepkumar@ iitb.ac.in

Malaria is a disease caused by *Plasmodium* parasites. Resistance to most antimalarial drugs, including Artemisinin, has emerged, which significantly reduces their efficacy[1]. This highlights the urgent need for novel drugs and therapeutic targets. Aminoacyl-tRNA synthetases (aaRS), enzymes responsible for the formation of aminoacylated tRNA, present promising druggable targets[2]. In recent years, several domainspecific inhibitors of aaRS have been reported[3]. Our group previously synthesised the AMS-Phe, which binds to the ATP and amino acid binding pocket of phenylalanyl-tRNA synthetase (PheRS) and acts as an inhibitor. However, AMS-Phe lacked specificity for parasitic enzymes. To address this, we employed a structure-based drug design approach by targeting the enzyme's auxiliary pocket[4]. Accordingly, we synthesised a derivative of AMS-Phe, modifying the 2′-OH group (AP-4) to facilitate binding in the auxiliary pocket. The newly synthesised compound demonstrated improved specificity for PhenylalanyltRNA synthetase of Plasmodium vivax (*Pv*FRS) ($\Delta T_m = 10.2°$ and $IC_{50} = 1.1$ µM), compared to the human analogue (*Hs*FRS) ($\Delta T_m = 3.8°$, $IC_{50} = 13.2$ µM. However, the crystal structure of this inhibitor with *Pv*FRS suggests that the 2′-modification actually occupies the ATP pocket and is involved in π-π stacking interactions with the adenine ring. These results indicate that although a new compound is a more specific inhibitor against the malarial parasite, its specificity can be further enhanced by increasing the rigidity of the 2′-extension for it to occupy an auxiliary pocket. Similarly, attempts were made to introduce modifications at different positions, including the Phenylalanine end of the molecule (4-chloro, 4-fluoro) and on the base part of AMS-Phe (N6-NHCONHPh), as well as the molecule with an N-linked sulfomyl linkage to increase specificity towards parasitic aaRS.



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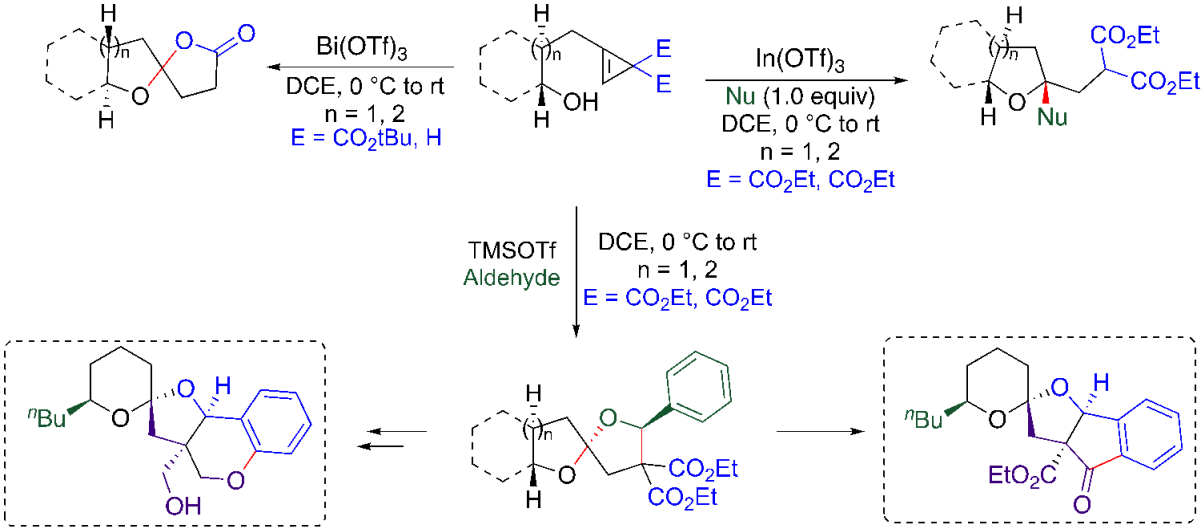
Lewis Acid-Promoted Hydroalkoxylation Reduction/Cycloaddition of Cyclopropenes: A Unified Route to Synthesize THF, THP, Oxaspirolactones and Spiroketals

Krishna S. Gupta, Rakhi Yadav, Santosh J. Gharpure,*

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai, 400076, India
e-mail: sjgharpure@chem.iitb.ac.in

Cyclic ethers like tetrahydrofurans (THFs), tetrahydropyrans (THPs), oxaspirocyclic lactones and spiroketals are fundamental structural core moieties present in many natural products and bioactive compounds.[1] Developing a method that enables the synthesis of these heterocycles is an important objective. Metal or acid-catalysed synthesis of these heterocycles *via* hydroalkoxylation reduction cascade of alkynes/olefins and spiroketalization of oxo diols are reported in the literature.[2] To the best of our knowledge, a unified approach towards the divergent synthesis of these heterocycles from cyclopropenes is unprecedented in literature. Herein, we report the utility of hydroxy cyclopropenes in the synthesis of these heterocycles through the generation of donor-acceptor cyclopropanes as a common reactive intermediate. In the presence of an external nucleophile under Lewis acidic condition reaction furnished the desired THF and THP derivatives, whereas in the absence of an external nucleophile, the diester functionality serves as an internal nucleophile to provide access to oxaspirolactones stereoselectively.[3] Similarly, the reactivity of donor-acceptor cyclopropanes in the cycloaddition reaction is exploited in the stereoselective synthesis of [5,5] and [6,5] spiroketals.[4] The developed methodology was found to be general with broad range of substrate scope with good functional group tolerance. Furthermore, these heterocycles were transformed to facilitate the access of intricate polycyclic heterocycles.



Scheme: Synthesis of THF, THP, Oxaspirolactone, Spiroketal from Hydroxy Cyclopropene.

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Smriti Subir Mukherjee

IIT Bombay

Palindromic Redox-Sensitive Peptidic Anion Transporter that Promotes Healthy Breast Cells over Breast Cancer Cells

The biocompatibility of peptides and the redox-responsiveness of cystines are harnessed to develop a library of palindromic acyclic scaffolds as anion transporters. The tryptophan-flanked cystine peptide selectively transports anions across lipid vesicles, with a preference towards nitrate and halide ion antiport. The disulfide backbone provides a covalent tether for the two anion-binding hydrophobic indole units, ensuring effective membrane insertion and anionic flux. The anion transport activity significantly drops when the cystine is reduced to cysteine in a GSH-rich environment. This attenuation arises not only from GSH-mediated reduction but also from altered peptide–membrane interactions and uptake, revealing distinct GSH-regulated ion-transport behaviour in the presence versus absence of a lipid bilayer.

Remarkably, this disulfide motif intrinsically demonstrates differential behaviour towards untransformed and transformed breast cells. When cultured separately, the triple-negative breast cancer line MDA-MB-231 shows lower viability upon treatment with the peptide compared to its untransformed counterpart, MCF10A. In co-cultures of these two cell lines over 4 days, exposure to the peptide favours the proliferation of MCF10A cells over MDA-MB-231 cells. Together, this study paves the way for using redox-sensitive disulfide scaffolds to mitigate off-target effects in cancer therapy, demonstrating their potential as selective modulators of healthy (non-cancerous) cells within the complex tumour microenvironment.

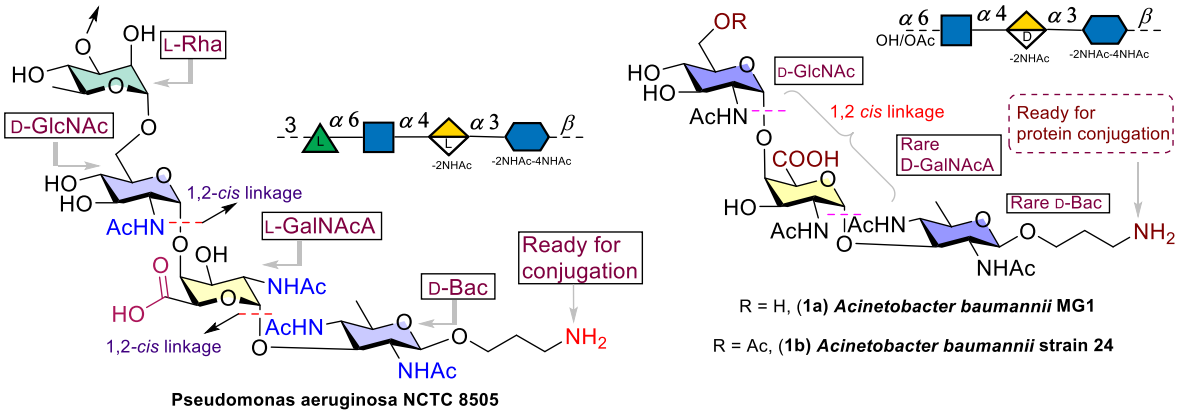
Total Synthesis of the Zwitterionic Trisaccharide Repeating Unit of *Pseudomonas aeruginosa* NCTC 8505 *Acinetobacter baumannii* MG1 and strain 24

Aishwarya A. Shelke, Kartikey Singh and Suvarn S. Kulkarni*

Indian Institute of Technology, Bombay, India

e-mail: suvarn@chem.iitb.ac.in

Cell-surface glycans are critically involved in a wide range of fundamental biological events, such as pathogen entry during viral and bacterial infections, intercellular recognition and signaling, and modulation of immune responses, thereby contributing to the pathology of many infectious diseases. Within the notorious ESKAPE group of pathogens, *Pseudomonas aeruginosa*, listed by the WHO as a high-priority multidrug-resistant bacterium, and *Acinetobacter baumannii*, ranked at the highest "critical" priority level, are responsible for life-threatening infections. These unique carbohydrate structures therefore serve as highly promising targets for the development of glycoconjugate vaccines and diagnostic reagents. Herein, we report the first total synthesis of the tetrasaccharide repeating unit of the capsular polysaccharide from *Pseudomonas aeruginosa* NCTC 8505 prepared in a conjugation-ready form suitable for vaccine construction. Also developed new methodology for synthesis of novel building block L-galactoronic acid. Further a systematic study was conducted for the notoriously difficult glycosylation of the most unreactive axial 4-OH of D-galactosamine with D-glucosamine unit. The successful outcome for this glycosylation was utilized to accomplish the total synthesis of linker-appended trisaccharide repeating units of *Acinetobacter baumannii* MG1 and strain 24, which is also a potential antigen for immunotherapy and vaccine development.



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