# 8th Indian Peptide Symposium,

# 24-26th Mar, 2021

**Virtual Symposium Hosted by**

## Indian Institute of Science

### Bangalore, Karnataka, India

# Awardees at the 8th Indian Peptide Symposium

**Virtual Symposium Hosted by IISc, Bangalore, 24-26th Mar 2021**

## Lifetime Achievement Awardee
## Virander S Chauhan

Arturo Falaschi Emeritus Scientist
International Centre for Genetic Engineering and Biotechnology, New Delhi, India

## Young Scientist Awardee
## Dibyendu Das

Department of Chemical Sciences
Indian Institute of Science Education and Research (IISER), Kolkata, India

# Schedule of 8th Indian Peptide Symposium (virtual symposium)

March 24-26th 2021, Indian Institute of Science, Bangalore, Karnataka, India 560012

## Day 1: 24th Mar 2021 (2:45 pm – 8:35 pm IST)

**24/S1 – 1st Session 2:45-3:50 pm** (65 min)

| S1 | Time (IST) | Program |
|---|---|---|
| 1 | 2:45 – 2:49 pm | Welcome address to 8th IPS 2021 and invitation of IPS President, T K Chakraborty by Conveners (E N Prabhakaran / Jayanta Chatterjee, IISc) |
| 2 | 2:49 – 2:50 pm | Invitation of **P Balaram** by IPS President, **T K Chakraborty**, to introduce the Lifetime Achievement Awardee, **V S Chauhan** |
| | | Chairperson: **T K Chakraborty** |
| 3 | 2:50 – 3:00 pm | **P Balaram's** Introduction of Lifetime Achievement Awardee **V S Chauhan** |
| 4 | 3:00 – 3:30 pm | **Virander S Chauhan** Lifetime Achievement Award Lecture |
| 5 | 3:30 – 3:50 pm | *"Multimeric Alpha Helical Amphipathic Peptides with Nanomolar Cell Permeability and Selectivity"*<br>**Yan Lee**, Dept of Chemistry, Seoul National University, Seoul 08826, Republic of Korea |
| | | **Short Break – 3:50-4.00 pm** (10 min) |

**24/S2 – 2nd Session 4:00-5:00 pm** (60 min)

Chairperson: **V V Suresh Babu**

| S2 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 4:00 – 4:20 pm | *"Computer-aided Peptide Therapeutics"*<br>**Gajendra P. S. Raghava**, Dept of Computational Biology, IIIT, Delhi, India |
| 2 | 4:20 – 4:40 pm | *"Principal Component Analysis to understand peptide dynamics and its correlation with sequence"*<br>**Durba Roy**, Dept of Chemistry, BITS-Pilani, Hyderabad, Telangana, India |
| 3 | 4:40 – 5:00 pm | *"Peptidomimetics inhibitors to tackle multifaceted toxicity in Alzheimer's disease"*<br>**T. Govindaraju**, New Chemistry Unit, JNCASR, Bengaluru, India |

**24/P – Virtual Poster Session 5:00-6:15 pm** (75 min)

All participants Go to: https://8th-ips.iisc.ac.in/posters.php → Login (using your registered email ID) (no password) → Click "Posters" → Click "All Posters" → Browse titles, view Videos, Posters and Discuss with poster presenters virtually through "link"

**24/S3 – 3rd Session 6:15-7:15 pm** (60 min)

Chairperson: **Ishu Saraogi**

| S3 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 6:15 – 6:35 pm | *"Synthetic glycopeptide vaccine for cancer immunotherapy"*<br>**Yanmei Li**, Dept of Chemistry, Tsinghua University, Beijing, P.R. China |
| 2 | 6:35 – 6:55 pm | *"Mirror-image proteins to block RBC invasion by malaria parasites"*<br>**Kalyaneswar Mandal**, TIFR, Hyderabad, Telangana, India |
| 3 | 6:55 – 7:15 pm | *"COVID-19 immunogen design"*<br>**Raghavan Varadarajan**, Molecular Biophysics Unit, IISc, Bangalore, India |
| | | **Short Break – 7:15-7.30 pm** (15 min) |

**24/S4 – 4th Session 7:30-8:35 pm** (65 min)

Chairperson: **Jayanta Chatterjee**

| S4 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 7:30 – 7:50 pm | *"Spatial Position Regulates Power of Tryptophan: Discovery of Nuclear Localizing Cell Penetrating Peptide"*<br>**Surajit Ghosh**, Dept of Bioscience and Bioengineering, IIT Jodhpur, Rajasthan, India |
| 2 | 7:50 – 8:10 pm | *"Peptide based Nanoconjugates as New Age Scaffolds for Cell Internalization and Bio-sensing Agents"*<br>**Rohit Kumar Sharma**, *Dept of Chemistry, Panjab Univ, Chandigarh, India-160014* |
| 3 | 8:10 – 8:30 pm | *"Hydrocarbon shake flask logD and LPE: in search of bRo5 passive permeability"*<br>**Matthew R. Naylor**, UCB Pharmaceuticals, Boston, USA |
| 4 | 8:30 – 8:35 pm | Closing remarks of the day – Conveners 8th IPS 2021 – **ENP / JC** |

## Day 2: 25th Mar 2021 (2:55 pm – 8:35 pm IST)

**25/S1 – 1st Session 2:55-3:50 pm** (55 min)

Chairperson: **Gautam Basu**

| S1 | Time (IST) | **Program** |
|---|---|---|
| 1 | 2:55 – 3:00 pm | Gautam Basu's Introduction of Young Scientist Awardee, Dibyendu Das |
| 2 | 3:00 – 3:30 pm | *"Systems Chemistry: How complexity emerges from chemistry?"*<br>**Dibyendu Das**, Chemical Sciences, IISER Kolkata, Kolkata, India |
| 3 | 3:30 – 3:50 pm | *"Precision chemistry of native proteins enabling biology and medicine"*<br>**Vishal Rai**, Dept of Chemistry, IISER Bhopal, India |
| | | **Short Break – 3:50-4.00 pm** (10 min) |

**25/S2 – 2nd Session 4:00-5:00 pm** (60 min)

Chairperson: **E N Prabhakaran**

| S2 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 4:00 – 4:20 pm | *"Foldamers for mimicking and engineering the backbone of biologically active peptides"*<br>**Gilles Guichard**, Univ. Bordeaux, CNRS, CBMN, UMR 5248, Institut Européen de Chimie et Biologie, Pessac, France |
| 2 | 4:20 – 4:40 pm | *"Revisiting old peptide chemistry: ring-closing metathesis in water and preparation of peptide with C-terminal Cys"*<br>**Taku Yoshiya**, Peptide Institute, Inc., Osaka, Japan |
| 3 | 4:40 – 5:00 pm | *"Understanding the conformational properties of aza-peptidomimetics"*<br>**Bani Kanta Sarma**, JNCASR, Bangalore, India |

**25/P – Virtual Poster Session 5:00-6:15 pm** (75 min)

All participants Go to: https://8th-ips.iisc.ac.in/posters.php → Login (using your registered email ID) (no password) → Click "Posters" → Click "All Posters" → Browse titles, view Videos, Posters and Discuss with poster presenters virtually through "link"

**25/S3 – 3rd Session 6:15-7:15 pm** (60 min)

Chairperson: **T. Govindaraju**

| S3 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 6:15 – 6:35 pm | *"Self-assembling peptide based soft materials in health care and environmental remediation"*<br>**Arindam Banerjee**, School of Biological Sciences, IACS, Jadavpur, Kolkata, India |
| 2 | 6:35 – 6:55 pm | *"Single amino acid enzymes shining light on the prebiotic catalyst"*<br>**Pandeeswar Makam**, IIT BHU, India |
| 3 | 6:55 – 7:15 pm | *"Peptides from the nature to the laboratory"*<br>**Fernando Albericio**, School of Chemistry, University of KwaZulu-Natal, Durban, South Africa |
| | | **Short Break – 7:15-7.30 pm** (15 min) |

**25/S4 – 4th Session 7:30-8:35 pm** (65 min)

Chairperson: **A A Natu**

| S4 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 7:30 – 7:50 pm | *"Peptide-based strategies for delaying labor and improving neonatal outcomes"*<br>**William D. Lubell**, Dept of Chemistry, Univ de Montréal, Montréal, QC, Canada |
| 2 | 7:50 – 8:10 pm | *"Chemical Strategies for the Development of Novel Therapeutic Agents*"<br>**Ishu Saraogi**, Dept of Chemistry & Dept of Biological Sciences, IISER Bhopal, India |
| 3 | 8:10 – 8:30 pm | *"Elevation of serum SIRT2 in Parkinson's disease: Plausible diagnostic protein biomarker and therapeutic target"*<br>**Sharmistha Dey**, Department of Biophysics and Geriatric Medicine, AIIMS, New Delhi, India |
| 4 | 8:30 – 8:35 pm | Closing remarks of the day – Conveners 8th IPS 2021 – **ENP / JC** |

**25/S5 – 5th Special Session – 8:35 – 9.35 pm – General Body Meeting (60 min)**

## Day 3: 26th Mar 2021 (3:00 pm – 8:20 pm IST)

**26/S1 – 1st Session 2:55-4:00 pm** (65 min)

Chairperson: **Nandita Madhavan**

| S1 | Time (IST) | **Program** |
|---|---|---|
| 1 | 3:00 – 3:20 pm | "***Peptide-based strategies in Antibiotic Action and Structural Colors***"<br>**Sandeep Verma**, IIT Kanpur, India |
| 2 | 3:20 – 3:40 pm | *"Biophysical studies on latarcins: antimicrobial peptides from venom of Lachesana tarabaevi"*<br>**Parvesh Wadhwani**, Karlsruhe Institute of Technology, Institute of Biological Interfaces, Karlsruhe, Germany |
| 3 | 3:40 – 4:00 pm | **"***Generic Peptides – opportunities and challenges***"**<br>**Dinesh Bothra**, Indo Bioactive Labs, Pune, India |
| | | **Short Break – 4:00-4.10 pm** (10 min) |

**26/S2 – 2nd Session 4:10-5:00 pm** (50 min)

Chairperson: **Durba Roy**

| S2 | Time (IST) | **Program** (10 min Presentations) |
|---|---|---|
| 1 | 4:10 – 4:20 pm | *"Alternative Approaches to Overcome the Bottlenecks in the Peptide Synthesis Workflow"*<br>**Amit *Mehrortra***, Biotage, Sweden |
| 2 | 4:20 – 4:30 pm | *"Purification of Liraglutide by peptide easy clean technology"*<br>**Manoj Kumar Muthyala**, Belyntic GmbH, Germany |
| 3 | 4:30 – 4:40 pm | *"Optimize your workflow and speedup your research- Solutions for peptide synthesis through automation"*<br>**Parshad Hirapara**, CS Bio, India |
| 4 | 4:40 – 4:50 pm | *"Activotec Peptide Synthesizers"*<br>**Chris Littlewood**, Activotec, UK |
| 5 | 4:50 – 5:00 pm | *"Fmoc-Cys(Msbh)-OH – A sophisticated Building Block for Cysteine-rich Peptides. A Journey from Discovery through to Large Scale Production"*<br>**Markus Weishaupt**, Iris Biotech GmbH, Germany |

**26/P – Virtual Poster Session 5:00-6:15 pm** (75 min)

All participants Go to: https://8th-ips.iisc.ac.in/posters.php → Login (using your registered email ID) (no password) → Click "Posters" → Click "All Posters" → Browse titles, view Videos, Posters and Discuss with poster presenters virtually through "link"

**26/S3 – 3rd Session 6:15-7:15 pm** (60 min)

**Poster Award Winning Lectures**

Chairperson: **K. Muruga Poopathi Raja**

| S3 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 6:15 – 6:25 pm | **Best Poster award presentation 1** |
| 2 | 6:25 – 6:35 pm | **Best Poster award presentation 2** |
| 3 | 6:35 – 6:45 pm | **Best Poster award presentation 3** |
| 4 | 6:45 – 6:55 pm | **Best Poster award presentation 4** |
| 5 | 6:55 – 7:05 pm | **Best Poster award presentation 5** |
| 6 | 7:05 – 7:15 pm | **Best Poster award presentation 6** |
| | | **Short Break – 7:15-7.30 pm** (15 min) |

**26/S4 – 4th Session 7:30-8:20 pm** (50 min)

Chairperson: **Arindam Banerjee**

| S4 | Time (IST) | **Program** (17 min Presentation + 3 min Q&A) |
|---|---|---|
| 1 | 7:30 – 7:50 pm | *"Ribosomal Formation of Thioamide Bond in Polypeptide Synthesis"*<br>**Rumit Maini**, Merck, New Jersey, USA |
| 2 | 7:50 – 8:10 pm | *"Extrapolating from Proteins"*<br>**Samuel H. Gellman**, Dept of Chemistry, Univ of Wisconsin, Madison, WI, USA |
| 3 | 8:10 – 8:20 pm | *Vote of Thanks*<br>**T Govindaraju**, JNCASR, Bangalore, Karnataka, India |

# Platinum Sponsors

**of 8th Indian Peptide Symposium** (virtual symposium)

March 24-26th 2021, Indian Institute of Science, Bangalore, Karnataka, India 560012

# Abstracts

# of

# Invited Lectures

**A journey with synthetic peptides, big and small**

Virander S Chauhan

*International Centre for Genetic Engineering and Biotechnology, New Delhi, India*

We have been working on the rational design and preclinical development of recombinant poly-peptides based on a few key vaccine target antigens from the blood stage P. Falciparum malaria. While the research and laboratory production of these polypeptides has been an exciting scientific challenge, the preclinical development of these experimental vaccines turned out to be complex scientific and management problem. However, we were able to conduct the very first Phase-I clinical trials in India. Another major area of interest in our laboratory has been the design, synthesis, characterization and possible applications of conformationally restricted peptides containing α,β-dehydrophenylalanine (ΔPhe). We have shown that introduction of ΔPhe induces stabilization of β-turns in short and helical structure in longer peptides and conferred stability to enzymatic degradation. We have used this design principle for synthesizing peptides for diverse biological applications. Design and synthesis of cationic helical peptides has led to peptides with potent antimicrobial activity against a broad spectrum of microbes. Recently we have found that ultrashort peptides containing ΔPhe at the C-terminal readily selfassemble into different, well defined nanostructures, depending on the nature of the N-terminal residue. We have explored bimolecular delivery potential of these nanostructures taking cancer as a model for the proof of principle. Some of these peptides also readily form hydrogels and we have explored their potential for 3D cellular growth, and in bone healing as a proof of principle.

**Multimeric Alpha Helical Amphipathic Peptides with Nanomolar Cell Permeability and Selectivity**

Yan Lee

*Department of Chemistry, Seoul National University, Seoul 08826, Republic of Korea*

Cell penetrating peptides (CPPs) are attractive candidates as intracellular delivery vehicles. However, some intrinsic properties of CPPs are still limiting their clinical applications. Most CPPs can show the penetrating activity only above micromolar concentrations, which are difficultly achieved for in vivo administration of peptides. Another important limit is the target selectivity. In order to overcome these limitations, we developed a platform of CPPs which can show cell penetration at nanomolar concentrations in cell- or tissue-specific manners.

First, we discovered that CPPs based on multimeric alpha-helical leucine (L) and lysine (K)-rich amphipathic peptides can effectively penetrate cells at 10 nM, a 1,000-fold lower concentration than the penetrable concentrations of previous reported cell penetrating peptides (CPPs), Tat or oligo arginine. The antiparallel conformation of the LK multimer was critical for the effective penetration of the CPPs at low nanomolar concentrations. The heparan sulfate proteoglycan (HSPG) receptors are highly involved in the rapid internalization of multimeric LK-CPPs. As proof of concepts in biomedical applications, various biomolecules were delivered into cells with bioactivities at nanomolar concentrations.

Then, we further intended to introduce selectivity to the LK multimeric structures. pH-activatable moieties was introduced to the structure for selective penetrating in weakly acidic conditions. A histidine-based dimer, $LH_2$ can penetrate cells specifically in weak acidic conditions, even at few tens of nanomolar concentrations. The peptide effectively delivered paclitaxel into triple-negative breast cancer cells, MDA-MB-231, via formation of non-covalent complexes (PTX-$LH_2$(M)) or covalent conjugates (PTX-$LH_2$(C)). Moreover, $LH_2$ showed prolonged circulation in the body and enhanced accumulation in tumors. Both PTX-$LH_2$(M) and PTX-$LH_2$(C) showed strong antitumor effects in a triple-negative breast cancer grafted mouse model at an extremely low dosage.

The multimeric alpha helical amphipathic CPP can be a useful platform for the intracellular delivery of biomacromolecular reagents that have difficulty with penetration in order to control biological reactions in cells at feasible concentrations for biomedical purposes.

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2. S. Hyun, S. Lee, S. Kjm, S. Jang, J. Yu and Y. Lee, *Biomacromolecules*, 2014, 15, 3746 -3752.
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7. S. H. Nam, J. Jang, D. H. Cheon, S.-E. Chong, J. H. Ahn, S. Hyun, J. Yu, Y. Lee, *J. Control. Release* (in press) DOI: 10.1016/j.jconrel.2020.10.063
8. S. -E. Chong, J. H. Oh, K. Min, S. Choi, J. H. Ahn, D. Chun, H. H. Lee, J. Yu, Y. Lee, *J. Control. Release*, 2021, 330, 161.

**Computer-aided Peptide Therapeutics**

Gajendra P. S. Raghava

*Department of Computational Biology, IIIT, Delhi, India*

In last few decades, peptides-based therapeutics has emerged as major player in the field medicines. As per recent survey, protein/peptide drugs is estimated around 10% of the entire pharmaceutical market and will make up an even larger proportion of the market in the future. In this talk, I will focus on peptide-based therapeuticst that will include; i) peptide based inhibitors, ii) peptide-based subunit vaccines, iii) peptide-based drug delivery, iv) designing of anti-microbial peptides. There are number of challenges in designing peptide-based therapeutics that includes, i) toxicity of peptides, ii) half-life in biofluids, iii) immunogenecity and antigenecity of peptides, iv) hemotoxicity of peptides. I will also focus on aspects associated with human health especially, the role of bioinformatics in development of biological databases and web-servers that can be used for solving real life problems. Furthermore, how these approaches can guide effective decoding of biological processes for disease biomarkers, epitope-based vaccines and personalized medicine in general.

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**Principal Component Analysis to understand peptide dynamics and its correlation with sequence**

Durba Roy

*Department of Chemistry, Birla Institute of Technology and Science-Pilani, Hyderabad Campus, Telangana 500078, India*

Inherent flexibility in small peptides often obscures the prevailing relationship between their structure and complex dynamics. It is pertinent to understand how the amino acid sequence of a peptide in a specific solvent environment controls its litheness. This sequence-solvent control could lead to preferential outcomes from post-translational modifications, such as disulfide bond formation between a certain pair of cysteine residues in multiple cysteine containing peptides. Dimensionality reduction of the complex dynamical modes in such peptides through principal component analysis (PCA) could thus prove very useful in delineating the structure-dynamics link. Two conopeptides, AuIB and GI are studied as test cases in water and aqueous ionic liquid solvent environments to bring out the diversity in their structure and dynamical freedom.

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2. F. Sittel, A. Jain, G. Stock, *J. Chem. Phys.*, **2014**, 141, 014111.
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**Peptidomimetics inhibitors to tackle multifaceted toxicity in Alzheimer's disease**

T. Govindaraju

*Bioorganic Chemistry Laboratory, New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Jakkur P.O., Bengaluru-560064, India*

Alzheimer's disease (AD) is chronic multifactorial neurological disorder and common form of dementia. Current treatments are only symptomatic and temporary, do not directly target the mechanisms underlying the disease pathogenesis. The production, accumulation and aggregation of proteins in the human brain are considered as one of the hallmarks of the disease. Reactive oxygen species (ROS) are the major sources of biomolecular and mitochondria damage, and oxidative stress in neuronal cells, which damage DNA, proteins, and lipids, contributing to additional trait of toxicity in AD. Oxidative stress, neuroinflammation, mitochondrial dysfunction and microglia contribute significantly to the disease pathogenesis. In this context, we have adopted multipronged strategies to develop therapeutic agents to modulate multifaceted toxicity. I shall present our recent results on the development of multifunctional peptidomimetic inhibitors to ameliorate multifaceted toxicity in AD.

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**Synthetic glycopeptide vaccine for cancer immunotherapy**

Yanmei Li

*Department of Chemistry, Key Lab of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Tsinghua University, Beijing, 100084, P.R. China.*

Cancer immunotherapy endows inspiring opportunities for tumor treatment. Different from other immunotherapies (e.g., checkpoint blockade and adoptive T cell transfer), a cancer vaccine is designed to fully activate both innate and adaptive immune systems with safety and efficacy.[1] In the recent year, different chemical strategies targeting MUC1 glycopeptide were developed in our group. Two-component glycopeptide vaccines were firstly built. To amplify the antigenicity, MUC1 glycopeptide was conjugated with protein or T cell epitope.[2,3] Then small molecule agonist was introduced to construct a three-component vaccine. Typically, the built-in agonists of Toll-like receptor 2 and STING show well compatibility and applicability in antibody evocation and therapeutic efficacy.[4] To enhance immune response, cluster and size effects were achieved using peptide fibril fabrication and nanomaterial display.[5,6] Considering in vivo codelivery of glycopeptide antigen and agonist, nanovaccines and hydrogel vaccine were both studied which elicited high titer of tumor-specific antibody for tumor killing.[7]

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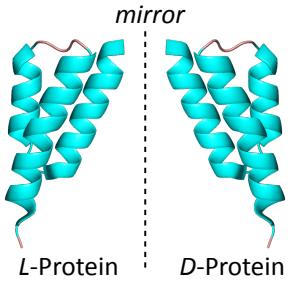
**Mirror-image proteins to block RBC invasion by malaria parasites**

Kalyaneswar Mandal

*Tata Institute of Fundamental Research, Hyderabad, Telangana-500046, India*

Interactions between two key parasite proteins, apical membrane antigen 1 (AMA1) and rhoptry neck protein 2 (RON2), are crucial for moving junction formation which triggers malaria parasite entry into erythrocytes. Identifying a suitable small protein to inhibit the interaction between AMA1 and the extracellular domain of RON2 would be an ideal strategy to turn off the junction formation, which, in turn, will shut down the invasion process. We are using a unique combination of 'chemical protein synthesis' and 'mirror-image phage display' to systematically identify mirror-image protein molecules that will have potential to interfere with the AMA1-RON2 interactions. Mirror-image proteins are resistant to proteolysis and less immunogenic. Therefore, a suitably engineered D-protein molecule (consisting of all D-amino acids and glycine) would be superior to a conventional natural peptide/protein as a candidate antimalarial therapeutic.



**COVID-19 immunogen design**

Raghavan Varadarajan

*Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India*

An affordable, efficacious vaccine against SARS-CoV-2, the causative agent of the ongoing COVID-19 pandemic is essential to curb infections and minimize disease spread. A number of vaccines are currently being deployed worldwide, including two in India. An overview of the various types of vaccines will be presented. Current COVID-19 vaccines have shown varying degrees of efficacy in different geographic locations and there are concerns about how recent viral mutations might impact vaccine efficacy. Neutralizing antibodies that prevent viral entry into host cells are currently the clearest correlate of protection and are largely directed against the Receptor Binding Domain of the viral Spike protein. Most current vaccine formulations require low temperature storage, a major impediment to widespread deployment. We have developed highly expressed, thermotolerant Receptor Binding Protein derivatives that induce titers of neutralizing antibodies that are considerably higher than several vaccine candidates currently in clinical trials. Such subunit vaccine formulations hold great potential to combat COVID-19 [1]

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**Spatial Position Regulates Power of Tryptophan: Discovery of Nuclear Localizing Cell Penetrating Peptide**

Surajit Ghosh

*Department of Bioscience and Bioengineering, IIT Jodhpur, Rajasthan-342037, INDIA*

Identification of key amino acids is required for development of efficient cell penetrating peptides (CPPs) and has tremendous implications in medicine. Extensive research work enlightened us about the importance of two amino acids, arginine and tryptophan in the cell penetration. This presentation will focus on a top-down approach to show how spatial positions of two tryptophans regulate the cellular entry and nuclear localization. This enables us to develop short nontoxic tetrapeptides with excellent potential of cell penetration and nuclear localization. Among them Glu-Thr-Trp-Trp (ETWW) emerges as most promising one. Result suggests that it enters into the cancer cell following endocytic pathway and binds at major groove of nuclear DNA, where successive tryptophan plays major role. Subsequently, we showed that it is not a P-gp substrate and nontoxic to PC12 derived neurons, suggesting its excellent potential as CPP. Furthermore, its potential as CPP has been validated in multi-cellular 3D cell culture (spheroid) and in in vivo mice model. This study provides major fundamental insights about the positional importance of tryptophan and opens new avenues towards the development of next generation CPP and major groove specific anticancer drugs.

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**Peptide based Nanoconjugates as New Age Scaffolds for Cell Internalization and Bio-sensing Agents**

Rohit Kumar Sharma

*Department of Chemistry, Panjab University, Chandigarh, India-160014*

Peptide-nanoconjugate systems provide novel hybrid materials having combination of the unique optical, electronic, or catalytic properties of the nanoparticles with the recognition or biocatalytic functions of biomolecules. Such bioconjugate systems have applications in various fields such as biosensing, bio imaging, cell internalization etc. In this regard, we have been exploring our research mainly in two categories: (a) How does the peptide nanoconjugate system act as a platform for biosensing? (b) How is this hybrid system capable for cell internalization?

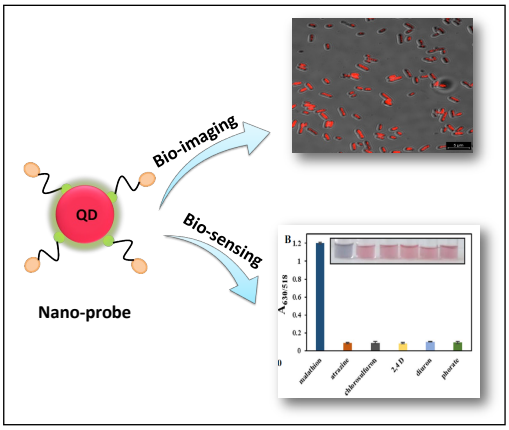


**Fig. 1**. Schematic illustration of the multifunctional biomolecule/peptide nanoconjugate systems for bioimaging and biosensing

The first step of the research comprises of development of peptide nanoparticle conjugate systems which would be efficient for biosensing as well as for cell internalization. The main challenge in this work is the specificity and selectivity of developed bioconjugate systems towards specific analytes. In this regard, we have developed various peptides, aptamer and polymer based hybrid systems using nanoparticles (gold nanoparticles and silver nanoparticles) as well as quantum dots. These developed biomolecule-nanoconjugate systems provide an array for specific and selective detection of various analytes such as organophosphorous pesticides, metal ions etc. In other context, as we know that internalization of therapeutic agents is one of the most important requirements for treatment of any type of infection and generally most of the drugs used are not able to penetrate into microbial cell membrane on their own, therefore, efforts have been done for the cell internalization studies using these biomolecule nanoconjugate systems. Alongwith these applications, I would also like to discuss the implications of these systems towards the sensing of toxic metal ions as well as their internalization studies using various methods.

**Hydrocarbon shake flask logD and LPE: in search of bRo5 passive permeability**

Matthew R. Naylor

*UCB Pharmaceuticals, USA*

Considerable interest has risen in the development of medicines capable of targeting protein-protein interfaces not druggable by conventional small molecules. Yet the achievement of passive permeability in beyond-Rule of 5 chemical space requires a careful balance of electronic exposure against numerous lipophilic liabilities. Hydrocarbon-based lipophilicity measurements have received renewed interest for their ability to directly measure membrane-relevant lipophilicity. Hydrocarbon shake flask logD measurements for cyclic peptides and bRo5 drugs will be presented, along with a simple metric (Lipophilic Permeability Efficiency) capable of generalizing the permeability performance of bRo5 chemical scaffolds.

**Systems Chemistry: How complexity emerges from chemistry?**

Dibyendu Das

*Dept of Chemical Sciences, IISER Kolkata*

There remain critical gaps in our understanding of the emergence of functional biopolymers in the origins of Earth's biosphere. For instance, extant proteins, evolved over millions of years, carry out an impressive array of responsibilities, from catalysis and molecular recognition to motility and compartmentalization. One of the major goals of our lab is to investigate the possible origins of advanced enzymatic functions from folds of short peptide based paracrystalline phases.[1,2] Further, we are excited in understanding the non-equilibrium structures of living systems.[3-6] I will show our recent discoveries of simple chemical systems that can be substrate-driven to access higher energy self-assembled states, just as seen in Natural microtubules. Entwined with negative feedback networks, I will attempt to sketch our aims of developing self-assembled autonomous materials that can show temporal control of functions.[3,5-8]

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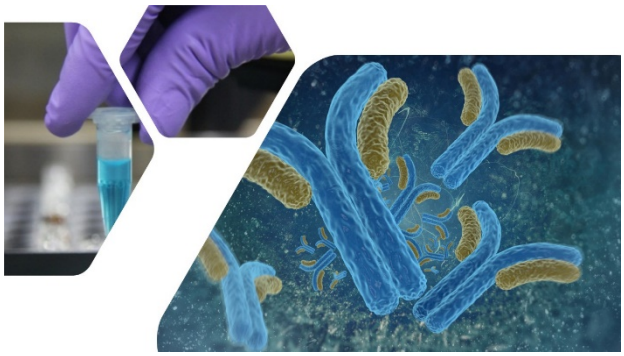
**Precision chemistry of native proteins enabling biology and medicine**

Vishal Rai

*Department of Chemistry, Indian Institute of Science Education and Research Bhopal, India*

The chemical toolbox for investigating biological systems or enabling therapeutics requires the precise covalent attachment of tags to the proteins. In this perspective, we have been investing efforts to develop chemical technologies that can empower precise control over the site of bioconjugation.
The critical barrier involves the simultaneous deconvolution of multiple challenges associated with reactivity and selectivity. In this perspective, we have developed a DisINtegrate or DIN theory that allows us to create new reactivity landscapes on a protein's surface. Overall, it enabled the development of methods for (a) utilization of N-terminus as a reactivity hotspot,[1] (b) single-site tagging of Lys or His,[2] (c) N-Gly residue-specific labelling (Gly-Tag®),[3] and (d) modular linchpin directed modification (LDM®) for labelling single His or Lys residue.[4] The LDM platform delivers single-site installation of various probes in native proteins. The user-friendly protocols result in analytically pure labelled proteins. The structure, enzymatic activity, binding to receptors, and downstream signalling pathways are typically unaffected. Importantly, these technologies allow access to homogeneous antibody-drug conjugates (ADCs) for directed cancer chemotherapeutics.[4,5] The talk would highlight our journey and specific milestones that led to the development of a comprehensive platform for precision engineering of proteins.



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**Foldamers for mimicking and engineering the backbone of biologically active peptides**

Gilles Guichard

*Univ. Bordeaux, CNRS, CBMN, UMR 5248, Institut Européen de Chimie et Biologie, 33607 Pessac, France*

Peptides are key molecules in modern drug discovery owing to some specific advantages (e.g. high molecular and structural diversity, effective synthesis methods, and relative ease of generating sequences with high affinity and selectivity for difficult biological targets). However, there is commonly a need for further optimizing standard peptides consisting of proteinogenic amino acids to alleviate some of their limitations such as poorly defined conformation, short in vivo half-life and/or poor membrane permeability. This incited chemists to develop innovative approaches to address these challenges, among which constrained peptides have gained momentum with several drug candidates at different stages of clinical trials.[1] In my group, we have a general interest in foldamer chemistry and in the development of α-helical peptide mimics such as oligourea foldamers.[2] Recently, we have shown that we can insert short foldamer segments into peptides to generate inhibitors of protein-protein interactions[3,4] or receptor ligands with a reduced peptide character.[5] By selecting ubiquitin ligase MDM2, vitamin D receptor and histone chaperon ASF1 as targets, we have designed peptide-oligourea chimeras that both retain affinity for their protein target and show increased resistance to proteolysis. X-ray structure analysis of several of these peptide–oligourea hybrids bound to their respective protein targets confirms the high degree of α-helix mimicry that can be achieved with oligoureas and reveals some general principles that should enable the design of more potent peptide-based inhibitors of protein–protein interactions.

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**Revisiting old peptide chemistry: ring-closing metathesis in water and preparation of peptide with C-terminal Cys**

Taku Yoshiya

*Peptide Institute, Inc., Osaka 567-0085, Japan*

Solid-phase peptide synthesis (SPPS) introduced in 1963 made peptide preparation easier. Peptide preparation was further facilitated by the emergence of 9-fluorenylmethyloxycarbonyl (Fmoc) SPPS. Additionally, chemical modifications of peptides thus obtained enable wider application. Among known modifications, replacing disulfide bonds with olefin bonds using ring-closing metathesis (RCM) firstly reported in 1980 is widely applied. However, there are still subtle problems. Here, we would like to report our two attempts to improve old peptide chemistry. The first one is about aqueous RCM, and the second one is about epimerization-free preparation of C-terminal Cys peptide.

RCM has been mainly applied for fully or partially protected peptides in organic solvents. However, solubility of such protected peptides in organic solvent is sometimes limited. As can be seen from the fact that native chemical ligation in water flourishes for the preparation of peptides/proteins, the combination of unprotected peptides and water should be superior to the combination of protected peptides/proteins and organic solvents from the viewpoint of solubility and applicability. Thus, to expand applicability of RCM in peptide science, we attempted to optimize aqueous RCM reaction using unprotected peptides and a water-soluble Ru catalyst 'AquaMet' recently reported by Grela et al.[1] Different RCM conditions in water were evaluated. Eventually, the addition of $MgCl_2$ and/or use of acidic conditions was confirmed to achieve the efficient RCM reaction of unprotected model peptides in water.[2] Our method would become a cornerstone of artificial bioactive peptide mimetic development in future.

Preparation of C-terminal Cys peptide acid (not peptide amide) is still a notorious problem of Fmoc SPPS. Two side reactions at the C-terminal Cys caused by the base treatment are recognized: (i) the conversion of Cys to D/L-β-piperidinoalanine via dehydroalanine (Dha) and (ii) the epimerization to D-Cys. Many studies have been conducted to solve these problems.[3] Although many peptides were prepared based on such studies so far, some amounts of the undesirable side reactions are still observed. Under this circumstances, we recently discovered that C-terminal Cys peptide acids can be synthesized without epimerization using a Cys-pseudoproline 'Cys($\Psi^{Dmp,H}$pro)' and Trt(2-Cl) resin. This is probably because the ring structure at Cys prevents the unfavorable keto-enol tautomerization. As a result, epimerization during basic treatment was not detected even under accelerated basic conditions. This combination would become a standard method to prepare C-terminal Cys peptide acids.[4]

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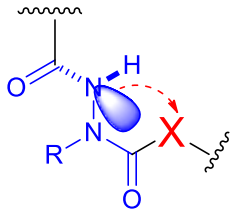
**Understanding the conformational properties of aza-peptidomimetics**

Bani Kanta Sarma

*Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bangalore 560064, India*

Peptides possess a wide range of biological activities. However, they have serious limitations as drug candidates due to their low cell-permeability and high protease sensitivity. Azapeptidomimetics[1], especially the azapeptides, have emerged as attractive alternates. Azapeptides are generated by isosterically substituting the α-carbon of one or more amino acid residues of a peptide with nitrogen atoms.[2] This substitution endows azapeptides with favourable drug-like properties including higher conformational rigidity and enhanced proteolytic stability compared to α-peptides.[3] Although a lot of progress has been made towards developing protocols to synthesize azapeptides in solution and the solid-phase, their conformational properties are still not clearly understood. Azapeptides are composed of aza-amino acid monomers, which leads to incorporation of diacylhydrazine units in their sequence. The repulsion between the hydrazide amide nitrogen lone pairs ($N_{lp}$-$N_{lp}$ repulsion) is often used to describe the conformational properties of azapeptides. Our recent investigations with acyl- and diacylhydrazines have led to the discovery some unusual noncovalent interactions mediated by their hydrazide amide nitrogen lone pair.[4] In this talk, I will discuss how these noncovalent interactions play crucial roles in the conformational properties of azapeptides. I will also discuss about the conformational properties of azapeptoids, an oligomeric peptoid scaffold derived from acylhydrazide submonomers.



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**Self-assembling peptide based soft materials in health care and environmental remediation**

Arindam Banerjee

*School of Biological Sciences, Indian Association for the Cultivation of Science, Jadavpur, Kolkata-700032, India*

Molecular self-assembly plays a pivotal role in chemical, biological and material sciences. Peptides with suitable functionalities are endowed with a unique property to form supramolecular soft materials by the assembly using various non-covalent interactions such as hydrogen bonding, pi-pi stacking, electrostatic, hydrophobic and others. Under suitable conditions, a peptide can be self-assembled to form a soft material called gel with a micro/nano-fibrillar network structure with a huge amount of entrapped solvent molecules (water/organic solvent). It is interesting to tune the assembly of designer synthetic peptides to create functional gels and also to explore fascinating applications of these gels as new biomaterials.

These peptide-based hydrogels have been utilized for various functions including encapsulation and sustained release of drugs[1] and biologically important molecules[2], potent antibacterial agents for Gram-positive and Gram-negative bacteria[3] as well as for three dimensional cell culture[4]. An interesting study includes the discovery of an amphiphilic peptide-based non-cytotoxic, proteolytically resistant hydrogels with potential anti-bacterial activity against Gram-positive and Gram-negative bacteria. Moreover, these antibacterial peptide gels do not show any significant hemolytic activity at the minimum inhibitory concentration of the tested bacteria.[3b] A very recent study vividly demonstrates that two-component hydrogel consisting of peptide and succinic acid is successfully used for two and three-dimensional cell culture using mouse fibroblast cell line (NIH-3T3). This result indicates a future promise for the usefulness of such peptide-based gels as tuneable biomaterials in 3D cell culture and regenerative medicine. A recent study includes the successful demonstration of a peptide based gel in environmental remediation for the removal of toxic organic dyes and harmful metal ions ($Pd^{2+}$ and $Cd^{2+}$) from waste water and the gel has also been used in oil spill recovery[5].

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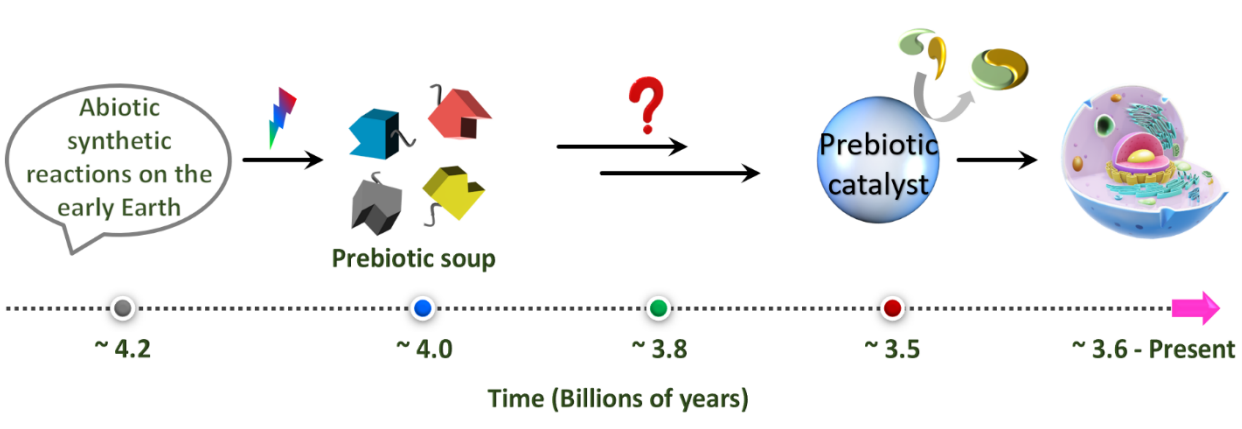
**Single Amino Acid Enzymes Shining Light on The Prebiotic Catalyst**

Pandeeswar Makam

*Department of Chemistry, Indian Institute of Technology (BHU) –Varanasi, Uttar Pradesh-221005, India*

Darwinian evolution began on Earth approximately 3.5 billion years ago. However, the molecular basis for the origin of life is one of the most mysterious quests in modern science.[1–3] To solve this enigma, scientists have focused on the possible potential chemical precursors of life. Nevertheless, in the 1950s, pioneering work is known as the Miller–Urey experiments has shown that amino acids, serving as prebiotic components of life on early Earth, could be synthesized under simulated laboratory conditions.[4] Since then, several laboratory experiments have shown that, in addition to amino acids, lipids and nucleotides can emerge from model prebiotic reactions. However, the mechanism by which life has emerged from this non-living prebiotic soup is still a mystery. In this talk, I will briefly explain our recent research findings on the potential of amino acid, metal ions, which most likely existed in prebiotic Earth, to self-assemble into potent and stable enzyme mimetic catalytic superstructures.[5,6] Such assemblies might have served as the primary means to allow the acceleration of chemical reactions prior to the evolution of contemporary enzymes. Our results may provide a new paradigm for the emergence of primordial catalysts and the origin of life.

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**Peptides from the Nature to the Laboratory**

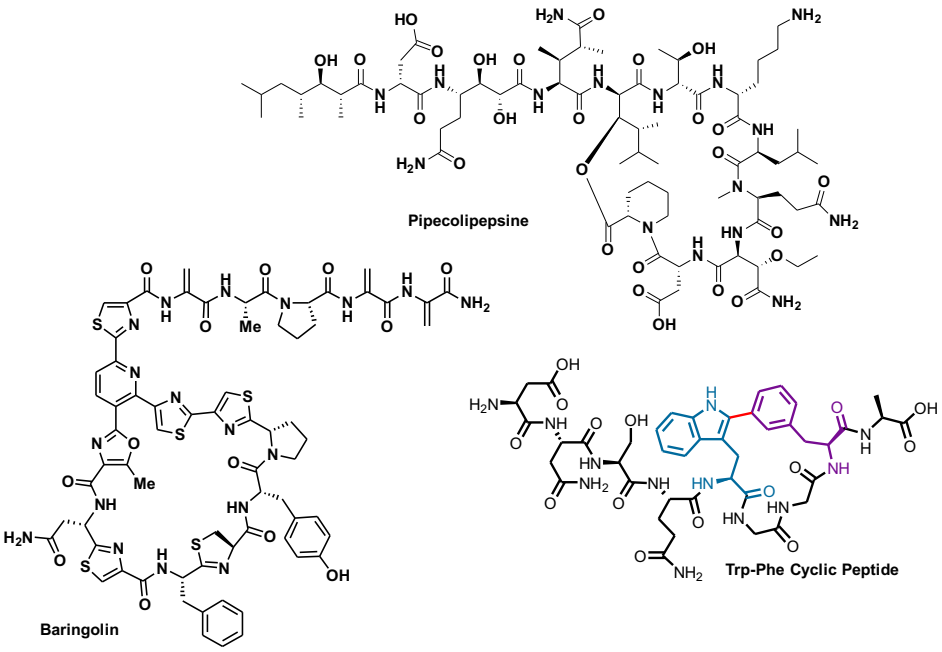
Fernando Albericio

*School of Chemistry, University of KwaZulu-Natal, Durban, South Africa; Departments of Chemistry, University of Barcelona, Barcelona, Spain*

Peptides have experienced a remarkable renaissance as therapeutic agents in recent years. They are situated between small molecules (<1000 Da) and proteins, two of the most extensive classes of well-established therapeutic agents.

Peptides provide both the specificity and potency of larger protein biologics but with zero or low immunogenicity. Furthermore, they are smaller, more accessible and cheaper to manufacture using chemical methods, thus presumably combining the advantages of the two therapeutic approaches. While nature has been fine-tuning the bioactive chemical structure of these structures for thousands of years, peptide chemists and protein engineers have the exciting challenge of improving the intrinsically unfavorable pharmacokinetic properties of the majority of native peptides. The drawbacks of peptides as therapeutic agents are associated with their generally high conformational instability.

In this presentation, we will review our current research devoted to the synthesis of natural cyclic peptides (pipecolidepsin, baringolin, teixobactin) as well as the design and synthesis of cyclic peptides with improved properties. In this regard, we will discuss the strategies carried out in our laboratory for improving the potency and the stability of peptides. In addition to homodetic cyclizations, we will show as common techniques used in conventional organic chemistry can be applied to peptides for that purposes. Thus, Pd catalyzed coupling reactions allows the efficient preparation of linked, constrained and stapled peptides through C-H Pd activation processes.



**Peptide-based strategies for delaying labor and improving neonatal outcomes**

William D. Lubell

*Department of Chemistry, Université de Montréal, Montréal, QC, Canada*

In 2010, India accounted for about one quarter of the global total of premature births [1], which may lead to long-term health problems for the newborn. Exploring different therapeutic points of intervention to delay birth as well as the potentially harmful inflammatory component of premature parturition, our team has focused on the central cytokine, interleukin-1β (IL-1β) and its receptor (IL-1R), which play key roles in the induction of labor and immune vigilance against invading pathogens. Our presentation describes a peptidomimetic strategy for inhibiting IL-1R mediated signaling without effect on immune vigilance through the use of lactam analogs of the IL-1 modulating peptide **101.10** (H-D-Arg-D-Tyr-D-Thr-D-Val-D-Glu-D-Leu-D-Ala-$NH_2$) [2,3].

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**Chemical Strategies for the Development of Novel Therapeutic Agents**

Ishu Saraogi

*Department of Chemistry & Department of Biological Sciences, IISER Bhopal, Bhopal, 462066, India*

Our research is at the interface of chemistry and biology, and currently focuses on the use of structure-based design strategies for the development of novel anti-amyloidogenic and antibacterial agents. In my talk, I will summarize our work in these two areas.

Bacterial resistance to antibiotics poses an unprecedented challenge to global health. In search of novel antibacterial strategies capable of evading existing resistance mechanisms, we identified the bacterial signal recognition particle (SRP), an essential protein transport machinery, as a potential target.[1] Functional SRP is composed of a protein (Ffh) and a 4.5S RNA component, so we envisioned that antisense peptide nucleic acid (PNA) molecules targeting 4.5S RNA might inhibit the RNA-Ffh interaction, thus compromising bacterial viability. Designed PNA molecules indeed bound specifically to 4.5S RNA, and inhibited the 4.5S RNA-Ffh interaction in a dose dependent manner, leading to inhibition of SRP mediated GTP hydrolysis. The most potent PNA molecule, when tagged with a cell penetrating peptide, was able to effectively inhibit *E. coli* cell growth. The PNA-mediated inhibition was relieved by overexpression of 4.5S RNA, suggesting that the PNA specifically blocks 4.5S RNA function. Our work validates SRP as an antibacterial target for the first time, and invites research into small molecule inhibitors of bacterial SRP as potential antibacterial agents.

Amyloidosis is a well-known, but poorly understood phenomenon caused by the aggregation of proteins, often leading to pathological conditions. The aggregation of insulin, for example, poses significant challenges during the preparation of pharmaceutical insulin formulations commonly used to treat diabetic patients. We have identified a small molecule, which causes a dose dependent reduction in insulin fibril formation. Biophysical analyses and docking results suggested that the inhibitor likely bound to partially unfolded insulin intermediates. Further, molecule-treated insulin had lower cytotoxicity, and remained functionally active in regulating cell proliferation in cultured *Drosophila* wing epithelium.[2] Thus, our inhibitor is a promising lead for regulating insulin fibrillogenesis. Our second-generation molecules are able to completely shut down insulin aggregation at the time-scale tested. We are currently testing several commercial insulin analogs (like Lispro, Glargine, Aspart etc) for aggregation inhibition using our small molecules.

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**Elevation of serum SIRT2 in Parkinson's disease: Plausible diagnostic protein biomarker and therapeutic target**

Sharmistha Dey

*Department of Biophysics and [2]Geriatric Medicine, All India Institute of Medical Sciences, New Delhi, India*

Parkinson's disease (PD) is the age-related neurodegenerative disorder due to the loss of dopaminergic neurons from substantia nigra in the brain. Atypical Parkinson Syndromes (APSs) often have symptoms that overlap with those of Parkinson's disease (PD), especially in early in disease, making these disorders difficult to diagnose. Previous studies have demonstrated association of oligomeric α-synuclein (α-Syn), a key element in the pathogenesis of PD, with Sirtuin (SIRT)2 proteins for modulating PD. Inhibition of SIRT2 protein rescues the α-synuclein toxicity in vitro and in vivo models of PD. Thio-acetyl group can structurally mimic the acetyl group and restrain the de-acetylating p53 reaction by SIRT2. We aimed to evaluate SIRT proteins expression in serum of PD patients and compare it with APSs and normal elderly control (GC); correlate with α-Syn and evaluated the biological activity of designed pentapeptides inhibitor containing N-thioacetyl-lysine against SIRT2. SIRT proteins expression was evaluated in sera of 68 PD; 34 APS and 68 GC without any neuro-psychiatric illness as controls by Surface Plasmon Resonance and correlated with α-Syn. Pentapeptide by introducing thioacetyl-lysine as an inhibitor of SIRT2 was screened by molecular docking and synthesized by solid phase method. The inhibition of pure recombinant SIRT2 as well as SIRT2 in serum of PD patients by peptide was done by Fluorescent Activity Assay. The inhibition of SIRT2 was assessed in PC12 cell line by measuring acetylated □□tubulin level.
Significant ($p<0.0001$) differences were observed between serum SIRT2 concentration in PD and APS and GC; and between APS and GC. ROC analysis revealed the strong cut off value to differentiate PD from APS and GC and also APS from GC. Significant correlation was observed among SIRT2 levels in early PD patients with UPDRS, H and Y and increase duration of disease. In addition, a strong positive correlation of SIRT2 with α-Syn ($p<0.0001$) was observed. However, no such difference was detected for serum SIRT1 in cases of PD and APS; and GC. The peptide YKK(ε-thioAc)AM and HRK(ε-thioAc)AM were found to be SIRT2 inhibitors by molecular docking. However, YKK(ε-thioAc)AM was more specific towards SIRT2 than SIRT1. It inhibited recombinant SIRT2 by $IC_{50}$ value of 0.15μM and KD values $9.92x10^{-8}$M. It also inhibited serum SIRT2 of PD. It increased the acetylation of □□tubulin in PC12 neuroblastoma cells which is essential for maintaining the microtubular cell functions of brain.
The present study is the first to report elevated serum SIRT2 in PD. The study also provided a simple test to distinguish PD from APS which may have translational utility as a blood based biomarker for diagnosis. A novel peptide YKK(ε-thioAc)AM may be a platform for therapeutic agent for Parkinson's Disease targeting SIRT2

**Peptide-based strategies in Antibiotic Action and Structural Colors**

Sandeep Verma

*Department of Chemistry and Center for Nanoscience, IIT Kanpur, Kanpur, India*

Our laboratory has recently described peptide-based systems for optimal delivery of nitric oxide for neuritogenesis and modulation of protein expression necessary for neuronal regeneration,1a-c release of H2S in a transgenic C. elegans model system to ameliorate dopaminergic neuronal degeneration,1d targeted antibiotic delivery through H2S-responsive structures,1e and a new molecular design exhibiting excellent antibiotic activity against multidrug-resistant S. aureus and resensitization of fluoroquinolones (FQ) towards FQ-resistant, methicillin-resistant S. aureus strains.1f In this lecture, I will briefly present two disparate aspects of peptide-based design: (i) two tripeptides having the ability to promote proliferation of human mesenchymal stem cells and wound healing, via modulation of mechanical properties of stem cells;2a (ii) bottom-up fabrication of short self-assembling peptides as surface covering films, resulting in a multilevel morphology of foamlike hydrophobic enclosures producing brilliant structural colors.2b

1. (a) Chem. Sci., 2017, 8, 6171-6175; (b) ChemBioChem 2018, 19, 1127-1131; (c) Chem. Asian J., 2019, 14, 4673-4680; (d) Chem. Commun., 2019, 55, 10142-10145; (e) ACS Infect. Dis., 2020, 6, 2441-2450; (f) Chem. Commun., 2019, 55, 8599-8602.
2. (a) Chem. Commun., 2020, 56, 3043-3046; (b) J. Colloid Interfac. Sci., 2021 (https://doi.org/10.1016/j.jcis.2021.02.122).

**Biophysical studies on latarcins: antimicrobial peptides from venom of *Lachesana tarabaevi***

Parvesh Wadhwani

*Karlsruhe Institute of Technology (KIT), Institute of Biological Interfaces (IBG-2), POB 3640, 76021 Karlsruhe, Germany*

*Lachesena tarabaevi* produces one of the most potent venom that is largely composed of membrane active peptides.[1] Latarcins are one group of linear cytolytic peptides isolated from this venom.[2] They are short (20-35 residues), highly charged, and display membrane activity against bacterial and mammalian membrane[3] but only a few members of this group have been biophysically well-characterized. In this work, we investigated seven latarcins under identical experimental conditions for their ability to fold into α-helix in presence of membrane, and determined their orientation in the membrane using oriented circular dichroism (OCD) and solid state $^{15}$N-NMR. Furthermore, their ability to induce membrane damage was studied by monitoring vesicle leakage. The antimicrobial and hemolytic activities of the peptides were also determined. N-terminus truncation of latarcins resulted in shorter latarcins with reduced hemolytic side effects. Membrane bound shorter latarcins were also characterized using OCD, solid state $^{15}$N-NMR as above. Their antimicrobial and cell penetrating properties were also evaluated. These results will be presented.

1. P.V. Dubovskii, A.A. Vassilevski, S.A. Kozlov, A.V. Feofanov, E.V.; Grishin, R.G. Efremov, *Cell Mol Life Sci* 2015, 72, 4501-4522.
2. S.A. Kozlov, A.A. Vassilevski, A. V. Feofanov, A.Y. Surovoy, D.V. Karpunin, E.V. Grishin, *J Biol Chem* 2006, 281, 20983-20992.
3. P.V. Dubovskii, A.A. Ignatova, P.E. Volynsky, I.A. Ivanov, M.N. Zhmak, A.V. Feofanov, R.G. Efremov, *Future Med Chem* 2018, 10, 2309-2322.

**Generic Peptides – Opportunities and Challenges**

Dinesh Bothra

*Indo Bioactive Labs (P) Ltd., Pune 411019, India*

Indo Bioactive Labs (P) Ltd. mainly focusses on the large-scale synthesis of many generic peptide drugs. These generic therapeutic peptides offer significant opportunities. The structural complexities of these peptides pose significant manufacturing challenges including unnatural amino acids, multiple disulfide bridges, long chains leading to solubility issues etc. My talk will be focusing on the challenges in large scale synthesis of peptides at Indo Bioactive Labs (P) Ltd.

**Alternative Approaches to Overcome the Bottlenecks in the Peptide Synthesis Workflow**

Amit Mehrotra Global Product Manager – Organic & Peptide Synthesis

*Biotage, Sweden*

The typical peptide synthesis workflow is a multi-step process which essentially involves synthesis, purification and evaporation. This requires the steps from the starting amino acid building blocks to the final purified peptide product proceed as efficiently and smoothly as possible. Solid phase peptide synthesis is becoming more routine and now even more complex and difficult sequences can be made easily. Although the synthesis step is the most important part of the workflow, downstream processing issues can dramatically impact the efficiency of the workflow and are the cause of many bottlenecks.

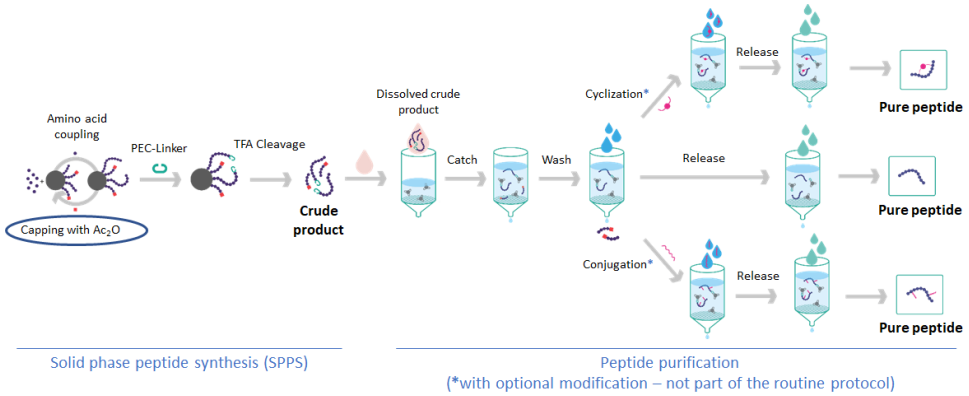
I will present strategies to improve the entire peptide synthesis workflow and demonstrate alternative approaches to facilitate the downstream processing including a rapid purification and evaporation technique that results in a simpler, faster and greener way to obtain a pure peptide product.

**Purification of Liraglutide by Peptide Easy Clean Technology (PEC)**

Manoj Kumar Muthyala, Oliver Reimann, Dominik Sarma, Nadja Berger and Robert Zitterbart

*Belyntic GmbH, Richard-Willstaetter-Str 11, 12489 Berlin, Germany*

Purification of peptides via preparative HPLC is a bottleneck and costly endeavor. Furthermore, purification of long hydrophobic peptides – some even featuring fatty acid side chains – by preparative HPLC is a cumbersome challenge due to its low solubility and tendency to aggregate. Truncations often co-elute with the full-length peptide. We present the Peptide Easy Clean technology (PEC),[1] a side-reaction-free, catch and release process. The process engages the coupling of a reductively cleavable linker to the peptide's N-terminus during the solid phase peptide synthesis (SPPS). The linker coupled peptides chemo-selectively immobilizes through oxime ligation onto the aldehyde functionalized resin, enabling wash-out of unwanted truncations. The covalent capture on the aldehyde resin allows functionalizing the peptides with desired modifications, such as lipids or bridging scaffolds on a solid support using an excess of reagents. Reducing the linker's arylazide core to aniline by reducing agents (DTT or $Ph_3P$) initiates the modified peptide release.[2] The product liberates via a 1,6-elimination reaction in a pure form upon treating the activated linker by an acid. Herein, we report two independent approaches to purify Liraglutide by applying the PEC technology. The first approach involves synthesizing Liraglutide (with palmitoyl group) on SPPS and using the PEC technology to remove unwanted truncations. In a second approach, we obtain Liraglutide via SPPS without sidechain functionalization and subsequent introduction of the palmitoyl glutamic acid group during the PEC process.




1 O. Reimann, O. Seitz, D. Sarma, R. Zitterbart, *Journal of Peptide Science* 2019, *25*, 3136 -3144.
2 R. Zitterbart, N. Berger, O. Reimann, G. T. Noble, S. Lüdtke, D. Sarma, O. Seitz, *Chemical Science* 2021, *12*, 2389-2396.

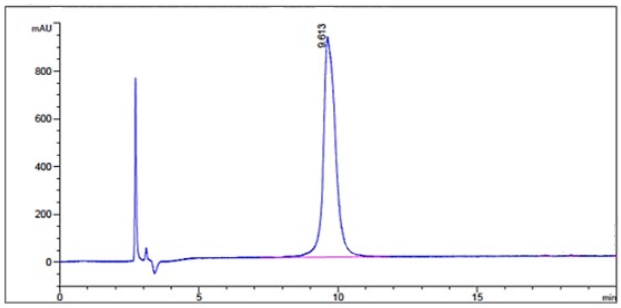
**Synthesizing a 132-mer peptide with high purity through automation**

Parshad Hirapara and Hanson Chang

*CSBio Instrumentation Co. 20 Kelly Court, Menlo Park, CA, 94025*

Synthesis of peptides at any length requires extreme attention to detail for accuracy and purity of the desired compound. Correctly synthesizing peptides of 50 mer length is difficult; over 100 mer length is a remarkable feat. CSBio's fully automated instruments are purposefully designed to maximize resin and solvent interaction while maintaining a clean system throughout the synthesis protocol, making it possible to consistently synthesize peptides containing over 130 amino acids at very high purities.

The chemists in CSBio's in-house cGMP peptide manufacturing facility were tasked with making a cyclic peptide 132 amino acids in length containing a Cysteine to Cysteine disulfide bond linking the 39th and 79th amino acids. Using a research scale CSBio peptide synthesizer, Fmoc protected amino acids were attached one by one in a stepwise fashion. Engineering decisions such as 180° inversion mixing as well as dedicated lines to separate the delivery of amino acids and piperidine ensure more resin to solvent interaction than nitrogen bubbling, vortex or oscillation mixing, while also maximizing coupling with no risk of chemical cross contamination.




| Peak # | RT [min] | Area | Height | Area % |
|---|---|---|---|---|
| 1 | 7.950 | 53.56 | 3.13 | 0.19 |
| 2 | 9.613 | 28109.37 | 921.11 | 98.69 |
| 3 | 10.683 | 219.14 | 12.22 | 0.77 |
| 4 | 17.454 | 41.79 | 4.76 | 0.15 |
| 5 | 18.359 | 38.68 | 4.56 | 0.14 |
| 6 | 19.989 | 19.57 | 2.52 | 0.07 |

Upon peptide synthesis completion the resin was cleaved giving the chemist's 620mg of crude at 75% purity. A portion of the crude (220mg) was loaded into a 1" C18 HPLC column, cyclization of the fractions was performed using iodine. Post purification the chemists were able to extract 18mg of the re-purified disulfide peptide which tested at 98.7% purity. Resulting in an 8.2% yield from crude for a compound whose molecular weight was >15000g/mol.

CSBio synthesizers are designed to deliver the user with the highest crude quality for any possible peptide. As the only automated synthesizer manufacturer that produces cGMP peptides, constant collaboration of in-house chemists and engineers during the design process enables CSBio to improve synthesis results compared to industry competitors; making CSBio synthesizers the most robust and reliable instruments on the market for synthesis of any peptide.

**Activotec Peptide Synthesizers**

Chris Littlewood

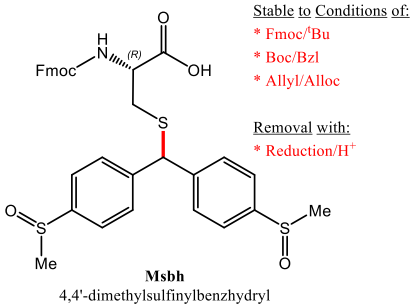
*Activotec UK*

A presentation of Activotec's range of peptide synthesis tools covering semi and fully automated synthesizers available now in India with local technical support.

**Fmoc-Cys(Msbh)-OH – A sophisticated Building Block for Cysteine-rich Peptides. A Journey from Discovery through to Large Scale Production.**

Markus Weishaupt[1*], Thomas Bruckdorfer[1,2], Haixiang Zhang[2]

*[1] Iris Biotech GmbH, Adalbert-Zoellner-Str. 1, 95615 Marktredwitz, Germany [2] Iris Biotech Laboratories GmbH, Adalbert-Zoellner-Str. 1, 95615 Marktredwitz, Germany*




A safety-catch cysteine protecting group, 4,4'-dimethylsulfinylbenzhydryl (Msbh), has increasingly been gaining interest. It allows researchers to expand their synthetic toolbox for the regioselective formation of disulfide bonds in cysteine-rich peptides. Examples where Msbh has been used in the past include sequences with up to four disulfide bonds, or peptides containing both disulfide bonds and unpaired cysteines that tend to suffer from disulfide bond shuffling. The orthogonality of Msbh towards Fmoc, Boc and Alloc deprotection conditions promoted this complex cysteine derivative to become a broadly used building block for challenging peptide sequences in bulk scale peptide synthesis. We describe how route of synthesis and conditions changed from discovery and use in research applications to industrial scale with a focus on production efficiency, economics, and sustainability.

1. Total Synthesis of Human Hepcidin through Regioselective Disulfide-Bond Formation by using the Safety-Catch Cysteine Protecting Group 4,4'-Dimethylsulfinylbenzhydryl; Zoltan Dekan, Mehdi Mobli, Michael W. Pennington, Eileen Fung, Elizabeta Nemeth, and Paul F. Alewood; *Angew. Chem. Int. Ed.* 2014; **53:** 2931-2934. DOI: 10.1002/anie.201310103.
2. A new safety-catch protecting group and linker for solid-phase synthesis; S. Thennarasu and C.-F. Liu; *Tetrahedron letters* 2010; **51**: 3218-3220. doi:http://dx.doi.org/10.1016/j.tetlet.2010.04.047
3. A Reductive Acidolysis Final Deprotection Strategy in Solid Phase Peptide Synthesis Based on Safety-Catch Protection; T. Kimura, T. Fukui, S. Tanaka, K. Akaji and Y. Kiso; *CHEMICAL & PHARMACEUTICAL BULLETIN* 1997; **45**: 18-26. doi:10.1248/cpb.45.18
4. A safety-catch type of amide protecting group; M. Pátek and M. Lebl; *Tetrahedron Letters* 1990; **31**: 5209-5212. doi:10.1016/s0040-4039(00)97844-4
5. The p-(methylsulfinyl)benzyl group: a trifluoroacetic acid (TFA)-stable carboxyl-protecting group readily convertible to a TFA-labile group; J. M. Samanen and E. Brandeis; *The Journal of Organic Chemistry* 1988; **53**: 561-569. doi:10.1021/jo00238a016

**Ribosomal Formation of Thioamide Bond in Polypeptide Synthesis**

Rumit Maini

*Merck, USA*

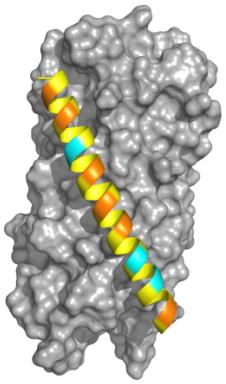
It has been well established that the ribosome can accept various nucleophiles on the X-acyl-tRNA in A site during elongation, where X can be amino, N-alkyl-amino, hydroxy, and thiol groups. However, it remains elusive that the ribosome is able to accept electrophile in P site other than the carboxyl group during elongation. Here we report ribosomal formation of thioamide bond in the mRNA-dependent polypeptide synthesis. In this study, amino(carbothio)acyl-tRNA was prepared by flexizyme and used for the expression of peptides containing a thioamide bond in the nascent peptide chain. We have given solid evidence that the thioamide-peptide was formed but accompanied by the oxoamide counterpart due to rapid carbo(S-to-O) exchange during the synthesis of amino(carbothio)acyl-tRNA. We also demonstrated the ribosomal formation of thioamide and N-methyl-thio-amide bond in linear as well as macrocyclic peptide scaffolds in the mRNA-dependent manner, showing its potential for applications such as ribosomal synthesis of thioamide-peptide and proteins.

**Extrapolating from Proteins**

Samuel H. Gellman

*Department of Chemistry, University of Wisconsin, Madison, WI 53706, USA*

Folded biopolymers perform diverse functions in biological systems. Most of these operations require the biopolymer chain to adopt a specific conformation. Over the past two decades there has been growing interest in the prospect that biopolymer functions might be recapitulated and perhaps even improved upon with unnatural oligomers that manifest discrete folding preferences. Such systems are referred to generically as "foldamers". This lecture will provide an overview of the goals of this field, and progress toward those goals we have achieved with peptidic oligomers that contain β-amino acid residues, exclusively or in combination with α-amino acid residues. Recent developments in development of foldamers that catalyze organic reactions or that disrupt protein-protein interactions associated with viral infections.



An antiviral α/β-peptide engaged with its target (crystal structure; PDB 3O43)

# Abstracts of
# Poster Presentations

**Radically simplified total chemical synthesis of proteins using 'Fmoc' group as a mask of *N*-terminal cysteine in peptide thioester segment**

Abhisek Kar,[a] Jamsad Mannuthodikayil,[a] Sameer Singh,[a] Anamika Biswas,[a] Puneet Dubey,[a] Amit Das[b] and Kalyaneswar Mandal[a]*

[a] *TIFR Centre for Interdisciplinary Sciences, Tata Institute of Fundamental Research Hyderabad, Telangana, India – 500 046;* [b] *Protein Crystallography Section, Bhabha Atomic Research Centre, Trombay, Mumbai – 400 085*

**BACKGROUND** Multi-segment native chemical ligation (NCL) in one-pot greatly simplifies chemical protein synthesis in terms of time, efforts and yield by obviating intermediate purification steps. Temporary protection or masking of the *N*-terminal cysteine residue of middle peptide segment(s) is a necessary criterion to avoid peptide self-cyclization or polymerization in *C*-to-*N* one-pot ligation. Several cysteine protecting groups or *N*-masking groups have been reported, which are either incompatible with the reaction conditions frequently used for thioester generation, or require complicated reaction sequences for the protection or deprotection of cysteine. We show that the Fluorenylmethyloxycarbonyl (Fmoc) can be used as a mask of the *N*-terminal reactive cysteine residue of peptide thioester segment(s) during multi-segment NCL.

**RESULTS** We found that the Fmoc group is stable to harsh oxidative conditions frequently used for the generation of peptide thioester from hydrazide or *o*-aminoanilide synthesized by the Fmoc chemistry solid phase peptide synthesis (SPPS). The Fmoc-Cys(Trt)-OH, a protected amino acid routinely used in Fmoc chemistry SPPS, minimizes additional steps required for the temporary protection of the *N*-terminal cysteinyl peptides. This protecting group can be removed quantitatively after ligation reaction by short exposure (<7 min) to 20% piperidine at pH 11.0 in aqueous condition at room temperature. Moreover, the presence of piperidine in the ligation buffer does not interfere with the subsequent ligation reaction at neutral pH, enabling multi-segment peptide ligations in one-pot. We have demonstrated the synthetic applicability of our method by synthesizing functional EETI-II micro-protein (28 amino acid residue) via *three-segment* one-pot ligation and human lysozyme protein (130 amino acid residue) via *four-segment* one-pot ligation. Clean conversion in every synthetic step gives high purity full-length polypeptide in excellent overall yields.

**CONCLUSION** We have established an operationally very simple method to achieve one-pot C–to–N native chemical ligations utilizing the Fmoc moiety as an *N*-masking group of the reactive cysteine of the middle peptide thioester segment(s). Our methodology provides an alternative and highly efficient method that would be very useful for high yielding chemical protein synthesis.

A. Kar, J. Mannuthodikayil, S. Singh, A. Biswas, P. Dubey, A. Das, K. Mandal, *Angew. Chemie. Int. Ed.* 2020, *59*, 14796–14801.

**Unraveling novel binding sites of *Pf*Rh5 to inhibit RBC invasion by malaria parasites**

Akash Narayan[a], Abhisek Kar[a], Mahita J[a], Purna Chandra Mashurabad[b], Mrinal Kanti Bhattacharya[b], Kalyaneswar Mandal[a*]

*[a]TIFR Centre for Interdisciplinary Sciences, Tata Institute of Fundamental Research Hyderabad, Hyderabad 500046, India;[b]Department of Biochemistry, School of Life Sciences, University of Hyderabad, Hyderabad 500046, India.*

**BACKGROUND** Rh5-CyRPA-Ripr ternary complex of *Plasmodium falciparum* binds with basigin at the surface of red blood cells (RBC), which constitutes an essential step prior to parasite invasion into RBCs.[1] X-ray crystallographic studies established the interactions between *Plasmodium falciparum* Rh5 (*Pf*Rh5) and basigin involved in the primary invasion process. Peptide which interferes with the binding of *Pf*Rh5 with its receptor can potentially inhibit RBC invasion by malaria parasites. We have undertaken protein fragment-based analysis of *Pf*Rh5 to explore its other possible binding regions that may inhibit invasion process. As a prelude to this study, we present synthetic strategies to first systematically fragment *Pf*Rh5 and then identify the active ones using biophysical experiments and invasion-inhibition assays.

**RESULTS** Peptide segments, designed based on the three-dimensional structure of *Pf*Rh5 protein, have been chemically synthesized by solid phase peptide synthesis. The secondary structure and the inhibitory activity of each purified peptide segment have been assessed by circular dichroism followed by growth inhibition assay on 3D7 parasite culture. This fragment-based approach led us to identify new regions of *Pf*Rh5 that have potential to reduce or inhibit malaria parasite invasion inside red blood cells.

**CONCLUSION** We have used protein fragment-based approach to identify natural peptide ligands that have potential to inhibit parasite invasion into red blood cells and thus prevent malaria. The peptide segments that showed inhibitory activity can be further stabilized by chemical modification to achieve augmented inhibitory activity.

1. W. Wong et al. *Nature* 2019, *565*, 118. [2.] K. E. Wright et al. *Nature* 2014, *515*, 427.

**Design and synthesis of peptide functionalized silver nanoparticles for Anti-microbial applications**

Alisha Lalhall [a,b] and Nishima Wangoo [b]

[a] *Centre for Nanoscience and Nanotechnology, Panjab University, Sector-25, Chandigrah, India*
[b] *Applied Sciences, U.I.E.T, Panjab University, Sector-25, Chandigrah, India*

**BACKGROUND** Silver nanoparticles are one of the most vital and fascinating nanoparticles that have attracted increasing attention in recent years for their wide range of applications such as in biomedicine, sensing, antimicrobial agents due to their biocompatibility, ease of synthesis, reliability and cost effectiveness [1]. Various synthetic methodologies have been used ranging from green synthesis to electrochemical synthesis of nanoparticles. Herein, we have synthesized biocompatible and functionalized silver nanoparticles at room temperature by sodium borohydride-mediated reduction of silver nitrate with various di-peptides, cell penetrating peptides and organic compounds[2].

**RESULTS** The resulting metal nanoparticles displayed a narrow size distribution comparable to or better than those achieved with other synthetic methods. UV-visible spectroscopy was used to monitor the formation of silver nanoparticles. Functionalized silver nanoparticles were further characterized using UV-Vis spectroscopy, FE-SEM and FTIR. Further optimizations will be carried out to investigate their potential as antimicrobial agents.

**CONCLUSION** The synthesized nanoparticles can be a step forward towards overcoming the multi drug resistance (MDR) in microbes.

1. E. Oh, J.B. et al., ACS Nano 5,2011, 6434–6448
2. Munish Kumar et al., Biophysical Chemistry 237,2018,38–46

**A synthetic approach towards developing peptide inhibitors to disrupt malaria parasite invasion into red blood cells**

Anamika Biswas[1], Suman Sinha[1], Mrinmoy Jana[1], Sreejith Rarankurussi[1], Purna Chandra Mashurabad[2], Mrinal Kanti Bhattacharyya[2], Maruti Uppalapati[3] and Kalyaneswar Mandal[1*]

*[1]TIFR Centre for Interdisciplinary Sciences, Tata Institute of Fundamental Research Hyderabad, Hyderabad 500 046, India; [2]Department of Biochemistry, School of Life Sciences, University of Hyderabad, Hyderabad 500046, India; [3]Department of Pathology and Laboratory Medicine, University of Saskatchewan, Saskatoon, S7N 5C9, Canada*

**BACKGROUND** Malaria is a mosquito-borne disease caused by *Plasmodium* species, the deadliest of which is *Plasmodium falciparum*. There is no effective vaccine reported yet to tackle malaria. Moreover, the widespread resistance of the frontline medicine 'artemisinin combination therapy' is also responsible for the delayed control of malaria. Therefore, there is an urgent need to develop an alternative and effective anti-malarial therapeutic. In all Apicomplexan parasites a unique invasion mechanism exists that involves moving junction (MJ) formation between the host cell and the parasite[1]. Interactions between two malaria parasite proteins, named Apical Membrane Antigen 1 (AMA1) and Rhoptry Neck Protein 2 (RON2), participate in the MJ formation. Our aim here is to understand and disrupt the AMA1-RON2 protein-protein interaction by natural or non-natural peptides or proteins, resulting the inhibition of *Plasmodium falciparum* merozoite invasion into red blood cell (RBC). Studies have shown that a small RON2 peptide (RON2ed) which binds with the hydrophobic pocket of the AMA1 is sufficient to compete with native RON2 protein leading to the inhibition of invasion[2]. We aim to develop peptide/protein-based binders of RON2 extracellular domain using 'chemical protein synthesis' and 'phage display'.

**RESULTS** We have designed and chemically synthesized the target molecules for phage display based on the sequence of the 39-mer RON2ed and validated their activity against refolded AMA1 expressed in *E. coli*. After phage screening against these targets, we obtained several binder proteins that specifically bound to RON2ed. Further, the activity of binder proteins was examined by growth inhibition assay to verify if the selected binders can block the active site of RON2 leading to the disruption of AMA1-RON2 interactions, hence inhibiting the merozoite invasion. One of the selected binders successfully inhibited the merozoite invasion with an $IC_{50}$ value of ~ 10 μM.

**CONCLUSION** We have successfully designed a potential binder protein to stop the merozoite invasion into the RBC. Further optimization of the initial binder sequence by rational design followed by computational validation as well as affinity maturation by phage display will lead to a superior binder sequence.

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2 A. Biswas, S. Raran-kurussi, A. Narayan, A. Kar, P.C. Mashurabad, M.K. Bhattacharyya, K. Mandal, *Biochem. Biophys. Reports.* 2021, *26,* 100950.

**Design, Synthesis and Confirmational Analysis of HBS-constrained β-turns in tripeptide and pentapeptide sequences**

Ankur Kumar and Erode N Prabhakaran*

*Department of Organic Chemistry, Indian Institute of Science, Bangalore, Karnataka, India – 560012*

As we know that, $3_{10}$-Helix is the second most abundant helical structure (10%), next to the α-helix (90%) that prevalently occurs in globular protein (especially membrane proteins) contain the i+3 → i hydrogen bond register along the peptide backbone. These are shorter in length (usually 1-2 turns) than the α-helix and are often found at the termini of the α-helix contain the i+4 → i hydrogen bond register along the peptide backbone. β-Turns are also an important Secondary structural component in proteins, playing a crucial role in peptide chain reversal and also play an important role in the formation of β-hairpin structures and α-hairpin structures. β-turn are also help in the protein-protein folding in the proteins. The b-turn also known as b-bend, b-loop or reverse turn. β-turns have been extracted from 58 non-identical protein (resolution greater or equal to 2 Å) using the standard criteria that the distance $C^{\alpha}_{i}$ and $C^{\alpha}_{i+3}$ is greater than 7 Å and that the central residues are not helical[1]. The H-bond surrogate (HBS) method has used successful to mimic the α-helical and $3_{10}$-helical conformations[2], but β-turns molecules did not synthesized yet by using HBS model. We are incorporating HBS at i+3 → i hydrogen bond register along the peptide backbone by using covalent surrogate (propyl linker). Our target molecules for tripeptide and pentapeptide are for GS, SST cyclic analogues for the β-turns. Our goals are with these molecules HBS constraint β-turns peptide backbones into different β-turn conformations for applications in molecular recognition. examples- The sequence RGD has been found to be the consensus of matrix proteins for binding cell surface receptors (integrins)[3], Gramicidin-S is a cyclodecapeptide antibiotic effective against some Gram-positive and Gram-negative bacteria as well as some pathogenic fungi and Somatostatins (SST) are hormones implicated in the regulation of growth hormone stimulation and glycogen release. There are 5 natural analogues of somatostatin (SST-I to V), all of which have the same tetrapeptide sequence – -Phe-Trp-Lys-Thr- – at the β-turn recognition domain. But they have different conformations at the turn motif[4].

1 C. Wilmot, J. Thornton, *Protein Eng. Des. Sel.* 1990, *3*, 479-493.
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**A peptidomimetic ADH-31 inhibits $A\beta_{42}$ monomer aggregation and destabilize protofibril structure: Insights from molecular dynamics simulations**

Anupamjeet Kaur,[a] Deepti Goyal*[a] and Bhupesh Goyal*[b]

*[a]Sri Guru Granth Sahib World University, Fatehgarh Sahib, Punjab, India –140406 [b]Thapar Institute of Engineering & Technology, Patiala, Punjab, India –147004*

**BACKGROUND:** Alzheimer's disease (AD) is a neurological disorder, a growing epidemic worldwide due to no effective medical aid available in the market.[1] AD is known to be directly associated with the toxicity of amyloid–β (Aβ) aggregates. In search of potent inhibitors of Aβ aggregation, Hamilton and co–workers reported an α–helix mimetic ADH–31, which act as a powerful antagonist of $A\beta_{42}$ aggregation.[2] To identify the key interactions between protein–ligand complex and to get insight into the inhibitory mechanism of ADH–31 against $A\beta_{42}$ aggregation, molecular dynamics (MD) simulations[3] have been performed in the present study.[4]

**RESULTS:** The MD simulations highlighted that ADH–31 showed distinct binding capabilities with residues spanning from N–terminal to the central hydrophobic core (CHC) region of $A\beta_{42}$ and restricts the conformational transition of helix–rich structure of $A\beta_{42}$ into another form of secondary structures (coil/turn/β–sheet).[4] Hydrophobic contacts, hydrogen bonding and π–π interaction contributes to strong binding between ADH–31 and $A\beta_{42}$ monomer. The Dictionary of Secondary Structure of Proteins (DSSP) analysis highlighted that the probability of helical content increases from 38.5% to 50.2%, turn content reduces from 14.7% to 6.2% with almost complete loss of β–sheet structure (4.5% to 0%) in the $A\beta_{42}$ monomer + ADH–31 complex. The per–residue binding free energy analysis demonstrated that Arg5, Tyr10, His14, Gln15, Lys16, Val18, Phe19 and Lys28 residues of $A\beta_{42}$ are responsible for favourable binding free energy in $A\beta_{42}$ monomer + ADH–31 complex, which is consistent with the 2D HSQC NMR of $A\beta_{42}$ monomer that depicted a change in the chemical shifts of residues spanning from Glu11 to Phe20 in the presence of ADH–31. The MD simulations highlighted the prevention of sampling of amyloidogenic β–strand conformations in $A\beta_{42}$ trimer in the presence of ADH–31 as well as the ability of ADH–31 to destabilize $A\beta_{42}$ trimer and protofibril structures. The lower binding affinity between $A\beta_{42}$ trimer chains in the presence of ADH–31 highlight the destabilization of $A\beta_{42}$ trimer structure.

**CONCLUSION:** Overall, MD results highlighted that ADH–31 inhibited $A\beta_{42}$ aggregation by constraining Aβ peptide into helical conformation and destabilized $A\beta_{42}$ trimer as well as protofibril structures. The present study provides a theoretical insight into the atomic–level details of the inhibitory mechanism of ADH–31 against $A\beta_{42}$ aggregation as well as protofibril destabilization and could be implemented in the structure–based drug design of potent therapeutic agents for AD.

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**Sonication-Induced, Solvent-Selective Gelation of a 1,8-Napthalimide-Conjugated Amide: Structural Insights and Pollutant Removal Applications**

Apurba Pramanik and Mindy Levine*

*Department of Chemical Sciences, Ariel University, 65 Ramat HaGolan Street, Ariel 40700*

Ultrasonication is a highly useful technique to impart sufficient energy to a system in order to facilitate molecular reorganization based on non-covalent interactions, which can result in the formation of stimuli-responsive functional materials. One application of ultrasonication is in the formation of low molecular weight supramolecular gels, semi-solid materials that can encapsulate a significant amount of organic solvent. These gels are generally composed of entangled fiber-like networks, obtained by self-assembly of building blocks through various non-covalent interactions such as hydrogen bonding, π-π stacking, dipole-dipole interactions, and Van der Waals interactions. These gels are responsive to various external stimuli like solvent polarity, temperature, light, pH and ultrasound. These anticipate supramolecular gels suitable for various applications such as in the field of sensing, actuating, charge transport, pharmaceutics, catalysis, reaction media, oil spill recovery and dye absorption. Moreover, although there are many reports of low molecular weight organogelators, but there are no reports of solvent-specific gelation, nor are there reports of using such gels to remove materials from aqueous solutions. One class of materials that are found in aqueous solutions are organic dyes, which are used widely in the textile, plastics, and cosmetic industries. Waste from these industries has been shown to leak into water and contaminate surrounding ecosystems. There are various methods such as sedimentation, carbon black adsorption, chemicoagulation, advanced oxidation procedure to remove dyes from wastewater. However, these processes have some disadvantages, including the high costs of the removal and disposal procedures, and the difficulties associated with regeneration and reuse of the functional materials. Thus, removal of dyes from wastewater is highly demanding in the current research. Herein, we have design and synthesized a series of dipeptides which conjugated with 1,8-Napthalimide and investigated the self-assembly of structurally small different of peptides are sufficient to cause significant differences in the organogel formation. The peptide are highly solvents specific and effectively performed as a dye removal agent from wastewater.

We have designed and synthesized two amides, which have small structural differences, and are highly solvent-specific in their formation of organogels. From these two peptides, the more flexible peptide **1** forms organogel only in the presence of alkylated benzene solvents by sonication. Ultrasonication in this procedure provides the necessary energy to reset the normal self-assembly pattern and modify the morphology of the peptides from polydisperse microspheres to an entangled fiber network. The sonication induces instant fibril formation and concomitant organogelation in toluene, xylene, mesitylene, ethyl benzene. In other solvents, by contrast, microspheres form, and gelation is not observed. Scanning electron microscopy (SEM) of the peptide **1** xerogel reveals the sonication-induced microfibrillar morphology. As the peptide **1** has an electron rich phenyl ring, the corresponding gel interacted with the cationic dyes and selectively removes cationic dyes from wastewater. More interestingly, the peptide **1** performs strongly to remove Rhodamine B from wastewater, and the high-performance dye removal reported herein has significant potential in the development of practical water purifier agents.

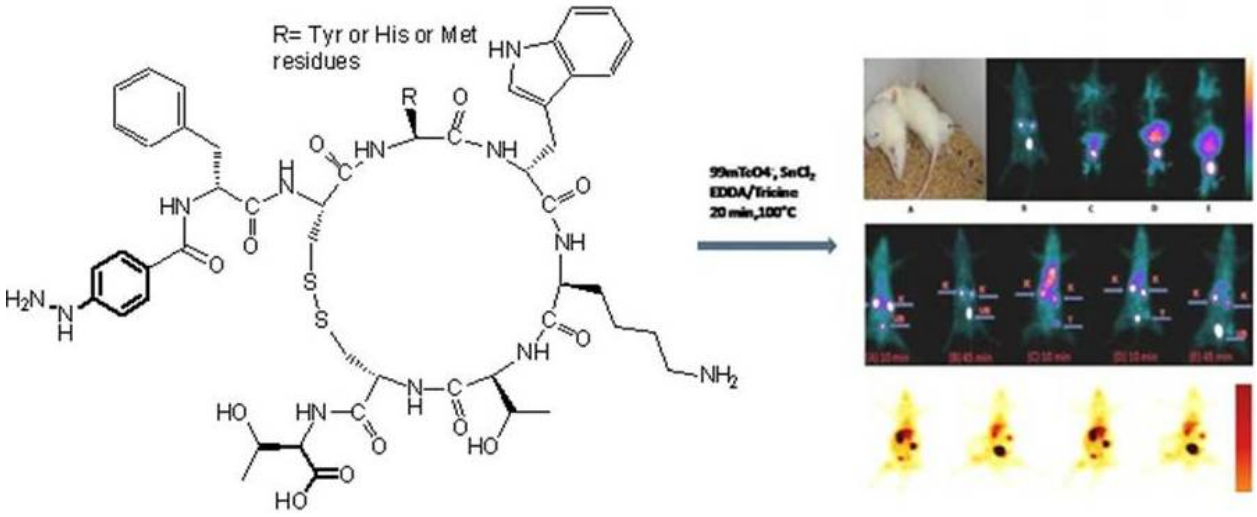
We have designed and synthesized a new class of peptide based gelators which are highly solvent selective and that can separate dyes by phase-selective gelation of the dye from water-dye mixtures at room temperature. As the peptides have electron rich phenyl groups, the corresponding gels also exhibit interactions with cationic dyes and can remove those cationic dyes selectively from the wastewater and good reusability of the gel in such dye's removal application was observed. In view of all these findings, it may be concluded that the development of our gelator is very useful, as it forms a low cost, non-toxic, easy-to-handle material for the successful removal of cationic organic dyes from contaminated aqueous environments.

**Design, synthesis, radiolabelling and biological evaluation of cyclic peptides as tumor imaging agent**

Ashok Behera [1, 3*], Sankha Chattopadhayay [2], Mridula Misra[3]

*[1]DIT Universiy, Pharmacy Department, Dehradun, Uttarakhand, India. [2]Radiopharmaceuticals Laboratory, Regional Centre, Board of Radiation and Isotope Technology, Variable Energy Cyclotron Centre, 1/AF, Bidhan Nagar, Kolkata 700 064, India. [3] Dept.Nuclear Medicine, CSIR-Indian Institute of Chemical Biology, 4, Raja S.C. Mullick Road, Kolkata-700032, India.*

Cancer has become one of the most devastating diseases worldwide. Therefore, diagnosis of cancer in the primary stage is important for proper treatment and therapy. Somatostatin receptors (SSTRs) are over expressed in homogenous and heterogeneous manners in the majority of tumors like neuroendocrine tumors (NETs), small cell lung cancer, breast cancer, gliomas and lymphoma. Five distinct subtypes of SSTRs have been identified (SSTR1-SSTR5) and cloned till yet. The native hormone is, however, susceptible to rapid enzymatic degradation ($t_{1/2}$ = 2-3 min in blood) and is, therefore, unsuitable for in vivo applications. For this purpose, long-lived synthetic octapeptide analogs have been synthesized indigenously, purified by HPLC and characterized by NMR, Mass and IR spectroscopy and different biophysical studies has been performed and biologically evaluated as SSTR Positive Tumor Imaging Agent.

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**Direct validation supporting the two-site binding paradigm in C5a-C5aR1 system**

Aurosikha Das[1] , Lalita Mohan Behera[1] , Manaswini Ghosh[1] and Soumendra Rana[*1]

[1]*Chemical Biology Laboratory, School of Basic Sciences, Indian Institute of Technology Bhubaneswar, Odisha 752050, India.*

**Background:** G-protein coupled receptors (GPCRs) are the largest class of pharmacologically relevant transmembrane proteins, classically known for their ability to modulate myriad of physiological functions in humans. The GPCRs can sense several class of ligands and thus, can demonstrate functional versatility. Out of the all known GPCRs in human genome, it is evidenced that ~120 GPCRs recognize endogenous peptide or proteins as ligands. Interestingly, complement component fragment 5a receptor (C5aR1) is one such GPCR that recognizes C5a, the most potent proinflammatory glycoprotein produced during the activation of the complement system. The C5a-C5aR1 system is an attractive target for drug discovery, due to its association with several chronic inflammations induced diseases, such as asthma, lung injury, multi organ failure and sepsis. It is noteworthy that structural biology has not been successful so far in capturing the C5a in complexation with C5aR1 in its native state. However, bio molecular signaling (1) and computational biology (2) studies have hypothesized that the complexation of C5a with C5aR1 involve a "two-site" binding interaction: precisely through, (i) recognition of the bulk of C5a by the N-terminus (NT) of C5aR1 ("site1"), and (ii) recognition of C-terminus (CT) of C5a by the extra cellular surface (ECS) of the C5aR1 ("site2"). Nevertheless, the biophysical understanding of this biomolecular recognition involving C5a and C5aR1 is still not clear in the literature.

**Result:** The current study has attempted to provide a clear understanding of the "two-site" binding paradigm in C5aR1 at the biophysical level, by recruiting the native (SR3) and mutant variants of NT peptides (SR4 and SR5), including the extracellular loop 2 peptide (SR1) of the C5aR1 against C5a. The data obtained from the molecular dynamics studies, binding free energy calculation, including the circular dichroism and fluorescence titration studies appreciably validate the highly refined "two-site" binding model structural complex of C5a-C5aR1, postulated earlier (2).

**Conclusion:** The structural complex of C5a with C5aR1 strongly support a two-site binding interaction experimentally.The NT peptide of C5aR1 (site 1) interacts with the core of C5a that demonstrates an appreciable conformation change in its loop. Additionally a significant conformation change was observed in C5a-NT system post binding to the ECl2 peptide (site 2). Thus, it is proved experimentally that C5a C5aR1 interaction demonstrates a two-site binding. Furthermore from the cationic nature of C5a, it can clearly be concluded from the above results that the binding at the plausible "site1" is strongly driven by the interaction with a set of anionic residues of the NT peptides of C5aR1, such as D10, D15, D16, D18, D21 and D27. In addition, Y11 and Y14 of NT of C5aR1 also contribute significantly toward the binding affinity at the "site1".

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**Soluble polynorbornene support bearing rink amide linker for peptide drugs conotoxins with minimum reagents**

Babita Bisht and Nandita Madhavan

*Indian Institute of Technology, Bombay, Maharashtra, India – 400076*

**BACKGROUND** Peptides and peptidomimetics are becoming highly important for the development of therapeutics and materials. A majority of the biologically active peptides have amide groups at the C-terminus. These peptides have been synthesized on insoluble resins such that the growing peptide can be easily separated from the reaction mixture by filtration.[1] Scaling up reactions in the solid phase has been challenging and has been addressed to a large extent using automated flow based peptide synthesis.[2] However, to overcome the reduced reactivity of the amino acids/peptides on the insoluble support, large excess of amino acids (3-20 equiv.) are used.

**RESULTS** Our efforts are directed towards synthesizing peptides using minimal reagents.[3] We have developed a polynorbornene support with a rink-amide attachment site that enables synthesis of peptide drugs, difficult peptide sequences, conotoxins, and larger peptides using only 1.2-2 equivalents of amino acids, which is significantly lower than reported procedures. The support is highly soluble in DCM and DMF and insoluble in diethyl ether. A variety of acidic, basic, and neutral amino acids could be loaded onto the polymer support with 0.3-0.7 mmol/g loading capacity. At room tempearture octapeptide synthesis took ca. 22 h, which includes coupling, deprotection, precipitation and centrifugation. To reduce the coupling reaction time and deprotection time, peptide synthesis was carried out at elevated temperature. The optimized protocol afforded octapeptides in 4h 56 minutes using only 1.2 equivalents of amino acid.

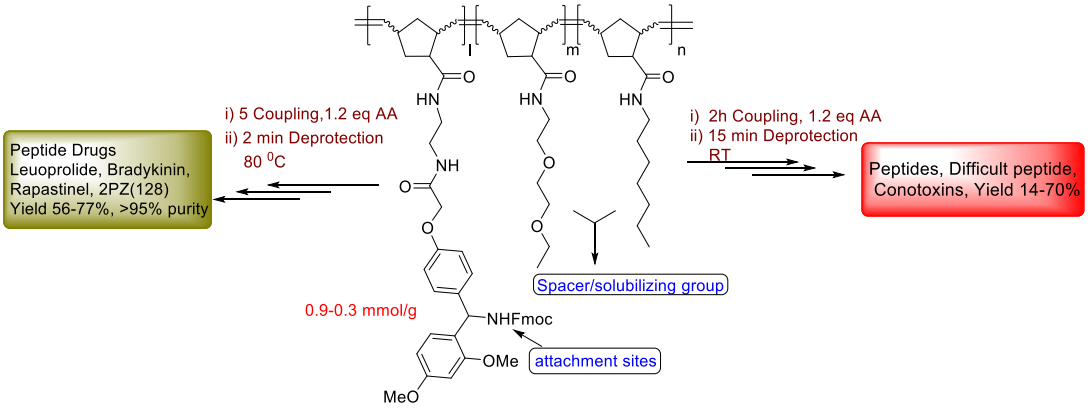


**Fig 1.** Polynorbornene support used for peptide synthesis

**CONCLUSION**. A highly soluble non-crosslinked polynorbornene support bearing rink amide attachment site with tunable loading capacities (0.93-0.7mmol/g) has been developed. The support provided quick access to drugs and conotoxins in high purity using significantly lower equivalents (1.2 equiv) of amino acids and coupling reagents as compared to SPPS (4-5 equivalents of amino acids).

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**Antioxidant Silk Fibroin-Melanin Hydrogel Composition for Wound Healing in Diabetic Rats**

Biswanath Maity, Shadab Alam, Sourav Samanta, R G Prakash, Thimmaiah Govindaraju*

*Bioorganic Chemistry Laboratory, New Chemistry Unit, and the School of Advanced Materials (SAMat), Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Jakkur P.O., Bengaluru 560064, Karnataka, India.*

Wound healing is a complex biological process requiring multiple biological pathways and chemical responses to be activated and synchronized to recover tissue integrity and homeostasis. In normal physiological circumstances, the damage restoration process of the epidermal barrier through new tissue formation is highly efficient. However, increased production of reactive oxygen species, attack of pathogenic microorganisms, and high glucose level at the wound site delay the normal healing process in diabetic patients. In this study, exploiting the hypolipidemic properties of biocompatible silk fibroin protein and the antioxidant property of melanin, the antioxidant hybrid hydrogel (SFCH) was formulated by the physical mixing of these two biomaterials for rapid wound healing in diabetes condition. The microscopy analysis revealed the highly cross-linked mesoporous morphology inside the SFCH matrix, suitable for cellular infiltration and proliferation. SFCH exhibits storage modulus of 4.5 kPa, which is comparable to the stiffness of human dermis tissue, appropriate to support the cell adhesion. DPPH radical scavenging assay indicates the efficient antioxidant property. The SFCH formulation is non-toxic and supports excellent cell migration under in vitro conditions. The efficacy of hydrogel in wound repair was evaluated in streptozotocin-induced diabetic Wistar rats. A full-thickness excision wound was created on diabetic male rats and SFCH was applied to the wound and scab formation, dryness, and wound closer behavior in treated rats was monitored. The SFCH treated wounds displayed very less leaching pathological fluid on the wound site, good scab formation, and faster wound healing compared to the control diabetic groups. Therefore, the biocompatible antioxidant silk fibroin hydrogel system can be used as a potential wound healing dressing in diabetes.

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**Role of Peptidomimetics Architectures in the Differential Stabilization and Reactivity of Copper in Tandem Reactions**

Debasis Ghosh, Mouli Konar, Tanmay Mandal and Thimmaiah Govindaraju*

*Bioorganic Chemistry Laboratory, New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Jakkur P.O., Bengaluru 560064, Karnataka, India*

The scheme molecular architectonics facilitate custom design and engineering of molecular assemblies by manipulating the subtle noncovalent interactions to generate nature-inspired architectures. In this poster, we exemplify this customized strategy to modulate the assembly behavior of pyrene conjugated peptidomimetics ($Akd^{NMC}Py$) incorporated with cyclic dipeptide units. $Akd^{NMC}Py$ spontaneously self-assembled into fibrils, which gradually transformed to nanosheets in the presence of Cu(II). Notably, the slow and stepwise addition of Cu(II) to $Akd^{NMC}Py$ resulted in micelle-like hollow architectures that subsequently transformed into nanosheets over a period of 7 days. In contrast, addition of Cu(II) at once to $Akd^{NMC}Py$ formed nanosheets without the intermediate micelle-like hollow architectures. Our further studies revealed that micelle-like hollow architecture stabilized Cu(II) state, while the nanosheets contained Cu(I) state. Interestingly, the micelle-like hollow intermediates were found to catalyze the tandem-like oxidation of 2',7'-dichlorofluorescin diacetate (DCFH-DA) into fluorescent DCF, while the nanosheets were ineffective for the same reaction. Further, the micellar-like architectures of $Akd^{NMC}Py$-Cu(II) that induced the DCFHDA oxidation was rearranged to form oxidatively inactive nanosheets due to reduction of Cu(II) to Cu(I). This molecular architectonics-guided differential architectures and reactivity of redox-metal-peptidomimetics complexation is anticipated to provide insights into the complex redox behaviors of biological metalloproteins.

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**Regulating peptide self-assembly towards precision and compartmentalization**

Deepika Gupta,[a] Ashmeet Singh,[a] Ranjan Sasmal,[b] Jojo P. Joseph,[a] Sarit Agasti,[b] Asish Pal[a]*

[a]*Chemical Biology Unit, Institute of Nano Science & Technology (INST), Mohali, Punjab* [b]*Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Jakkur, Bangalore*

**BACKGROUND:** Nature has an excellent ability to design multifunctional materials that require organization of complex multicomponent systems in a set of subsystems mediated by the orthogonal relationships among the structural components. In this regard, self-sorting- an ability to distinguish between the self and non-self, plays an important role to the formation of specific self-assembled structures rather than all possible ensembles of unspecific architectures.

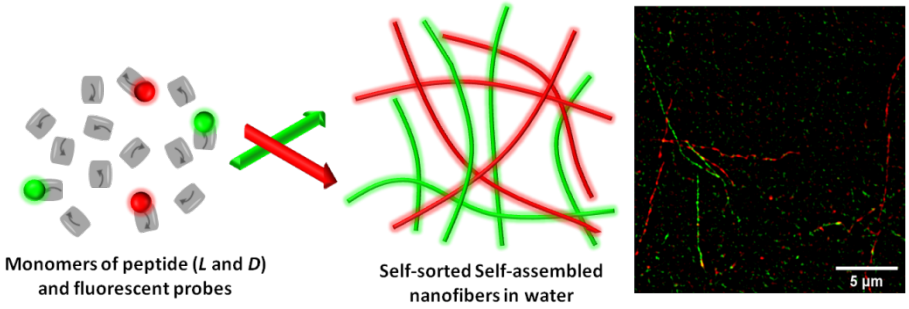


**Figure:** Visualization of chirality driven self-sorted self-assembled nanofibers.

**RESULTS:** We designed enantiomeric peptide amphiphiles with the sequence, $^{N}$VFFA$^{C}$ inspired by Aβ42 amyloid nucleating core. The competitive formation of self-sorted fibers over coassembled fibers is investigated in details using peptide fluorophores having donor and acceptor FRET pairs. We postulate chiral-recognition-driven efficient FRET in the homochiral peptide co-assembly and quantified the chiral self-sorting in the self-assembled nanofibers. The nucleation-mediated growth for the peptide amphiphiles is evident from the seeding and cross-seeding experiments, as obtained from AFM image analysis and time dependent thioflavin-T (ThT) binding assays indicating the chirality driven orthogonal growth of nanofibers. Chirality driven self-sorted peptide fibers were directly visualized using super resolution structured illumination microscopy (SR-SIM) for the first time. Lastly, the orthogonal nature of the assembly was established with the enantioselective enzymatic degradation of the *L*-peptide fibers and consequential weakening of the mechanical strength of hydrogels.

**CONCLUSION:** We have demonstrated the fidelity of the self-sorted system by utilizing structurally similar chiral FRET pairs that was further validated with the seeding and cross-seeding methodology and SR-SIM. Finally, we have shown enantioselective hydrolysis of the *L*-fibers over *D*-fibers for the first time through super resolution microscopy. This results in enantioselective weakening of the hydrogel's strength, that may potentially be used in desiging stimuliresponsive hydrogel mediated drug delivery applications in future. We postulate that the present study elucidates a deeper understanding of self-sorting events and may have implication in the design of mutually orthogonal functional biomimetic supramolecular systems.

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**Protein directed synthesis of bimetallic gold-silver (Au-Ag) nanoclusters for the effective pico-molar level detection of ethyl parathion**

Deepika Sharma and Rohit K. Sharma

*Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160014*

Nanoclusters (NCs) are new era materials with size less than 2 nm that have witnessed wide attention owing to their unique optoelectronics and chemical properties including strong photoluminescence, large stork shift and excellent photostability along with good biocompatibility. Proteins are among the extensively used template for the green synthesis of NCs mainly due to presence of distinct functional groups offering a number of binding sites, synthesis at ambient conditions, and also eliminates the use of toxic reducing agent by acting as both reducing and capping agent.

In the present abstract, bovine serum albumin (BSA) has been reported as template for the effective and one pot synthesis of bimetallic Au-Ag NCs (BSA@AuAg NCs). The synthesized BSA@AuAg NCs has been utilized to fabricate an ultrasensitive sensing scheme based upon enzymatic strategy for the pico-molar level detection of ethyl parathion; an organophosphorus pesticide (OPs). The toxicity of ethyl parathion derives its origin from being an effective inhibitor to plasma, red blood cells and brain acetylcholinesterase (AChE). This inhibition leads to imbalance of acetylthiocholine (ATCh) amount, a neurotransmitter in central nervous system (CNS), giving rise to sensory and behavioral disturbances. The synthesized biosensor is appropriate for the ultrasensitive sensing of ethyl parathion in pM range, exhibiting 2.40 pM as lowest limit of detection (LOD). Further, the developed sensing scheme has shown excellent reproducibility and robustness in real sample analysis, along with specificity towards OPs in general and ethyl parathion in particular when employed with other commonly used non-OPs pesticides.

In summary, a rapid and highly sensitive fluorometric biosensor for detection of ethyl parathion has been reported by utilizing BSA@AuAg NCs as an effective probe. The overall high sensitivity of the developed sensing strategy owing to the involvement of fluorescence-based methodology, synergic effect of both atoms (Au and Ag) exhibiting better performance in terms of electronic, catalytic and optical properties along with inhibition of catalytic activity of acetylcholinesterase (AChE) enzyme even in the trace concentration of ethyl parathion.

D.Sharma, N. Wangoo, R.K. Sharma, *Talanta***,** 2021, 221, 121267.

**Cationic peptide mediated ultrasensitive colorimetric aptasensor for rapid and naked eye detection of $Pb^{2+}$ ions**

Gurpreet Kaur and Rohit Kumar Sharma

*Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160014*

**BACKGROUND** Lead ($Pb^{2+}$) is a naturally occurring toxic metal found in the Earth's crust and its widespread usage has resulted in extensive exposure that is mainly responsible for deterioration of human health such as cancer, brain disease, cardiovascular disorders, failure of kidney and nervous system when the permissible limit (72 nM) is exceeded along with environmental contamination. Therefore considering the serious complications arising worldwide due to the presence of $Pb^{2+}$ ions, it is needful to fabricate a highly sensitive and selective device for on-site detection. Among all the biological molecules, peptides offer better opportunity for developing a reliable and cheap sensor because of their easy synthesis, self-assembly, biocompatibility, structural diversity and specific targeting ability. Herein, we developed a cost effective, rapid, highly selective and sensitive method for the detection of $Pb^{2+}$ ions using cationic peptide, AuNPs and $Pb^{2+}$ specific aptamer.

**RESULTS** In the present work, we propose a simple, cost effective, rapid, sensitive and label free colorimetric biosensor for detection of lead ions using a novel strategy which employs cationic peptide (KRKRKR-amide) AuNPs and aptamer. The proposed assay for lead detection has limit of detection(LOD) in pico-molar range, which is the best reported so far as per latest literature survey. In the absence of $Pb^{2+}$ ions, the cationic peptide interact electrostatically with $Pb^{2+}$ specific aptamer as a result the AuNPs retain their dispersity and red color. The $Pb^{2+}$ ions addition "turns on" the aptasensor and its color change from wine red to blue owing to presence of free peptide which aggregates the AuNPs. Moreover, the SPR peak depicts the red shift from 520 nm to 650 nm which further validates the $Pb^{2+}$ ions detection. The $Pb^{2+}$ ions could be quantitively detected in the range of 0.01 nM to 1 µM with high determination coefficient. The sensor array was demonstrated to be highly selective to $Pb^{2+}$ ions as compared to other metal ions and shows excellent reproducibility and robustness in real sample analysis.

**CONCLUSION** In summary, herein a novel AuNPs based colorimetric aptasensor has been designed and tested which allows selective, sensitive and reliable detection of $Pb^{2+}$ ions. The LOD of the proposed biosensor was observed to be 98.7pM for $Pb^{2+}$ ions, which is the best reported so far using colorimetric method. The principle of present sensing system is based on aggregation of AuNPs which induces color change in the solution from wine red to blue with subsequent change in the absorption spectra. Further the presently designed methodology was observed to be highly selective when tested in the presence of other metal ions as well as in real samples. Thus, the proposed aptasensor allows the rapid detection of trace amount of $Pb^{2+}$ ions with use of inexpensive portable devices in simple and highly specific way.

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**Synthesis and optimization of Fmoc-Phenylalanine hydrogels at physiological conditions**

Jagannath J, Virender Singh, Ashwani K.Thakur

*Institute of Affiliation – Indian Institute of Technology Kanpur, UP-208016, India.*

**BACKGROUND** Hydrogels are hydrophilic 3-dimensional assemblies that can remarkably integrate a high volume of water molecules into their structure. The rheological properties of the hydrogels make them ideal scaffolds for many biological applications such as tissue engineering and drug encapsulation.[1] Hydrogel can be synthesized from peptides, amino acids, and their derivatives. These molecules self-assemble to form fibril-like structures, which then entrap water molecules resulting in hydrogels. Fmoc-Phenylalanine (FMOC-F) is one such amino acid derivative with potency to form stable hydrogel at certain conditions owing to the anti-parallel stacking and π-π interactions of FMOC molecules to form β-sheet rich fibrils.[2] However, most of these processes involve the dissolution of FMOC-F in organic solvents, making them biologically incompatible.[3] In this study, we have reported the mechanism of FMOC-F gel formation and the possible factors governing the gelation process.[4]

**RESULTS** For FMOC-F hydrogel synthesis at physiologically relevant conditions, a method was developed. For this purpose, FMOC-F (99%, Sigma) powder was added to sodium phosphate buffer (50 mM, pH 7.4). The suspensions were vortexed and then sonicated for 10 minutes to increase the homogeneity and then heated at 80˚C for 10 minutes to aid the dissolution. The vials were kept undisturbed overnight at 25˚C, resulting in the formation of a stable hydrogel. The gel formation was dependent on multiple factors like pH, buffer ionic concentration, and sonication time. FMOC-F hydrogelation occurred in sodium phosphate buffer and potassium phosphate buffer but not in TRIS buffer. This behaviour might be because of specific ions contributing to the increase in solubility of Fmoc-F and cation-pi/anion-pi interactions. No gelation was observed up to pH 5.5, whereas at pH 7.4, Fmoc-F formed a stable, transparent hydrogel. From FTIR studies, it was confirmed that there were no changes in the molecular structure of Fmoc-F, post sonication. However, as analyzed by DLS, the particle size and polydispersity index dropped significantly, indicating that the Fmoc-F dispersion was comparatively more homogeneous. Analysis of pyrene fluorescence assay indicates the critical gelation concentration as 6mM. The hydrogel so formed shows sustained release as observed in time-dependent studies, making it fit for potential biological applications. FTIR analysis of Fmoc-F powder, gel state, and lyophilized gel showed a significant drop in the peak intensity at 1720$cm^{-1}$ of lyophilized gel compared to powder form. However, the features were retained during the transition of gel state to a lyophilized gel state, signifying these structures' stability.

**CONCLUSION** : In this study, we have developed a novel method of FMOC-F hydrogel synthesis at physiological conditions and elucidated the factors governing the hydrogel formation. The synthesized gel shows optimum stability after lyophilization and exhibits sustained release of FMOC-F at physiologically relevant conditions. According to FDA guidelines, the synthesis process must be optimized and scaled-up for industrial use. As a part of this approach, the method would be optimized to enable the translation of this gel for potential biomedical applications.

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**Stimuli-responsive supramolecular peptide-polymer conjugates: structural to functional control**

Jojo P. Joseph, Chirag Miglani, Nidhi Gupta, Ashmeet Singh, Deepika Gupta, Asish Pal*

*Institute of Nano Science and Technology (INST), Knowledge City, Sector – 81, Mohali, Punjab-140306*

**BACKGROUND** Nature has unprecedented handle over the conformation and dynamics of its macromolecular morphologies. In order to mimick engineering of nature to design greatly precise supramolecular materials with higher order morphology from nano to macro, it demands perfect control over dimensions using bottom-up self-assembly. While most of the self-assembly processes in nature are controlled by out-of-equilibrium phenomena, chemists have been able to develop very few kinetically controlled supramolecular polymers in the laboratory.

**RESULTS** In a bid to design precise supramolecular materials with higher order morphology, we took cue from amyloid beta sheet assembly and developed coumarin tethered short peptide fragments to perform stimuli-responsive self-assembly processes out-of-equilibrium to yield kinetically controlled 1D fibers and 2D nanosheets. Control over length and area distribution was realized by living supramolecular polymerization on fiber and sheet seeds which later played important role in determining the mechanical stiffness of the resulting hydrogels. The peptide nanostructures were also envisioned as excellent exfoliating agents for inorganic hybrid materials *e.g*. $MoS_2$. Further the dynamic amide crosslinking of a semi-flexible fibrous network of peptide with thermo-responsive polymer resulting in peptide polymer conjugate network is demonstrated that exhibited inner stress generation by onset of a coil-to globule transition upon heating above the lower critical solution temperature. This renders mechanical heat-stiffening response that extended to higher orders of magnitude in modulus. Furthermore, conjugate network intensely stiffen in response to applied shear stress and large amplitude oscillator strain in rheology with power law exponents that match with biopolymer networks

**CONCLUSION** Thus a new approach to show unprecedented topological control over dimensions is demonstrated in a synthetic supramolecular material by interplay of orthogonal interactions that led to self-assembly in multiple pathways. This study pave the way for a prototype to apply design and functional properties of nanocomposites in adaptive materials and devices. Further, the strain-stiffening phenomenon, a ubiquitous characteristics of soft biological materials *e.g.* fibrin gels in blood clotting and actin filaments in cellular cytoskeletons that manifests on deformation in its microenvironment is shown in the synthetic peptide fiber network.

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**Development of lipopeptide based antimicrobial hydrogel**

Monikha Chetia, Sunanda Chatterjee*

*Department of Chemistry, IIT Guwahati, Guwahati, Assam 781039.*

Growing antimicrobial resistance against the widely used antibiotics has stimulated the research for alternate therapeutic molecules. Antimicrobial peptides, AMPs present in several classes of plants and animals are an exciting group of compounds that are being studied and an alternative class of antimicrobial therapeutics. Some AMPs have an intrinsic property to self-assemble and give rise to a new class of materials which are known as antimicrobial hydrogels. Lipopeptides are known to have enhanced antimicrobial properties and abilities of self-assembly. In the present study we have focussed on the development of lipopeptide based antimicrobial hydrogels for the treatment of localized infections. We have developed the material, studied their antimicrobial properties and their self-assembling ability. We intend to further load these antimicrobial hydrogels with standard antibiotics and administer them on the resistant microbial strains.

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**Antibacterial activity and therapeutic implications of a self-assembled hydrogel of FMOC-Phenylalanine**

Nabodita Sinha, Avinash Y.Gahane and Ashwani K.Thakur

*Institute of Affiliation – Indian Institute of Technology Kanpur, UP-208016, India.*

**BACKGROUND** Fluorenylmethyloxycarbonyl (FMOC) protected amino acids or peptides self-assemble to form fibrous structures using non-covalent interactions and entrap water molecules to form a hydrogel.[1] Emergence of bacterial resistance and the need for new antibiotic therapeutics have led to prominence of hydrogels as antimicrobial agents due to their biological compatibility, biomimetic mechanical properties, and sustained drug release ability. Based on cues of earlier works displaying antibacterial activity of FMOC-protected peptides,[2] in this study, we have shown significant antibacterial activity of FMOC-Phenylalanine (FMOC-F) hydrogel prepared in physiologically relevant conditions against multiple Gram-positive bacteria when used alone and synergistic activity against Gram-negative bacteria with antibiotics aztreonam.[3-4]

**RESULTS** Antibacterial activity of FMOC-F hydrogel alone and with aztreonam against Gram-positive and Gram-negative bacteria **-** FMOC-F solution at a concentration above 0.4 mM and hydrogel formed at a concentration >10mM exhibited an 80% reduction in *S.aureus* and other Gram positive bacteria cell survival. The effective concentration ($EC_{50}$) and minimum inhibitory concentration (MIC) were found to be 0.35 mM and 0.46 mM respectively, against *S.aureus*. Mechanistic studies with bacterial cells and oleic acid liposomes suggest that the FMOC-F molecules disrupt the cell membrane and induce oxidative stress. FMOC-F alone did not show any significant antibacterial effect on Gram-negative bacteria. Therefore, we loaded FMOC-F hydrogels with aztreonam (AZT), an FDA-approved antibiotic, specific for Gram-negative bacteria. The drug release was observed to be a diffusion-controlled process and decreased 90% bacterial cell survival against a co-culture of *S.aureus* and *P.aeruginosa*. AZT loaded hydrogels exhibited a significant bacterial load decrease in mouse superficial skin wounds, aiding in healing wounds loaded with a co-culture of *S.aureus* and *P.aeruginosa*. Mechanistic investigation suggests that AZT increases bacterial membrane permeability, thereby facilitating FMOC-F entry into the bacterial cell.

**CONCLUSION** FMOC-F in hydrogel and solution phase shows significant antibacterial activity against Gram-positive bacteria. For Gram-negative bacteria, membrane permeabilizers such as AZT need to be loaded into the gel for synergistic activity. The biological compatibility of these hydrogels, both *in-vitro* and *in-vivo,* exhibits their potential for biomedical applications. Toxicological data regarding the polymorphic structures of the molecule in hydrogel and solution phases at different conditions might further explain the mechanistic details and lead the way to translation.

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**Pathway driven self-assembled peptide nanostructures templated bioglass hydrogel composite as self-healable matrix**

Nidhi Gupta,[a] Ashmeet Singh,[a] Namit Dey,[b] Sabyasachi Chattopadhyay, [b] Jojo P. Joseph,[a] Munia Ganguli [b] and Asish Pal [a]

*a. Institute of Nano Science and Technology, Sector 64, Mohali, Punjab - 160062 (India) b. CSIR-Institute of Genomics and Integrative Biology, Sukhdev Vihar, Mathura Road, New Delhi – 110025 (India)*

**BACKGROUND** Regenerative medicine demands design of smart scaffolds that mimic the structural and functional characteristics of natural tissue for inducing healing. Bioactive glass (BG) has shown interesting applications as bone cementing materials in drug delivery and prosthetic medical implants due to its biomineralization properties. Interestingly, peptide amphiphile templated biomineralization shows structural analogy with collagen template mineralization in tendon and ligaments. Herein, we demonstrate pathway controlled self-assembly of peptide amphiphile **1** to furnish kinetically controlled nanofibers (**1NF**) and thermodynamically stable twisted helical bundles, which directly regulate the properties of resulting bioglass composite matrices and eventually influence the bone regeneration.

**RESULTS** Peptide supramolecular nanostructures have varied persistence lengths and promote *in sit*mineralization to form templated bioactive glass composites, **1NFBG** and **1TBBG**. The resulting hydrogel composites are resorbable, mesoporous and degradable biomaterials to serve as bone scaffolds. Upon extensively investigating the structural features with microscopic characterization, EDX, Raman, XPS **1TBBG** exhibit superior material characteristics. From rheological studies excellent dynamic and self-healing behaviour was observed, with the elastic modulus of **1TBBG** being almost comparable to natural bone. Upon incubation in simulated body fluid, the bioglass composites illustrate tuneable bioactive response mediated by the structural and topological control to induce the deposition of multiphasic calcium phosphate along with octacalcium phosphate and carbonate hydroxyapatite. Lastly, such spatiotemporal composites assist stiffness- controlled osteoblast cellular interactions to support U2OS subsistence in the hydrogel matrix highlighting their potential as substrate in 3D bone tissue modelling and for osteoblast growth for prolonged culture periods.

**CONCLUSIONS** In summary, we have exploited pathway driven peptide self-assembly for developing supramolecular inorganic-organic hybrid hydrogel composites with variation in mechanical stiffness of the scaffold in context of matrix microenvironment cues. Such hybrids can be further explored as an implant coating for bone tissue engineering applications.

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**Establishment of NONAMER-core Length of T-cell Epitopes by Kullback–Leibler divergence with Uniform Residue Composition: A Genetic Coding Context**

Praharshit Sharma*

**Indian Institute of Information Technology, Allahabad, Uttar Pradesh – 211015 *BioClues Organization, Vivekananda Nagar, Kukatpally, Hyderabad, Telangana – 500072*

**BACKGROUND** T-cell epitopes that function as key antigenic determinants are typically Nona-peptides. In the realm of immunological applications such as Vaccine development, their Shannon entropy measure [1] is calculated on basis of overlapping 9-mer peptides (1–9, 2–10...n–(n+8)...9–17) [2] as per a specific methodology [3]. At any given nonamer position, we have to take into account both the incidence and number of distinct nonamer peptides which are part of the T-cell epitope protein primary structure. Actually, the nonapeptide entropy is computed with respect to the median ($5^{th}$) position amongst the nine residue-sites of overlapping 9-mer peptide sequences, theoretical maximum being 38.897352854

**RESULTS** The Relative Entropy measure (KL-divergence) which essentially results upon a positive addendum to maximal nonamer entropy, corresponding to Optimized Genetic Coding characterized by near-nepit neighborhood-dependent mutation framework, computed assuming "uniform" distribution of amino-acid residues that have unary representation each in averaged-20-length PROSITE motif accounts exactly for Establishment of the Nonamer core-length of T-cell epitopes. As per following Equation [4] :

$$\log_2(20^x) + \log_2(20) = \log_4(20^{20})$$

Solving for x in above KL-divergence Computational equivalence yields, x=9 , core-9-mer T-cell epitope.

**CONCLUSION** In-silico Computational T-cell epitope mapping and prediction is an important problem, especially the aspect of achieving high accuracy, so as to phenotype T-cells. Herein, a mathematical paradigm shift has been initiated, in agreement with Big Data Genetic Coding concept [5].

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**Translating host-microbe interaction into antimicrobial therapy via peptides as the connecting bridge**

Prajosh P, Shabeer Ali H and Sreejith K

*Dr.Janaki Ammal Campus,Kannur University, Kerala-670661*

**BACKGROUND** Sudden outbreaks of multidrug resistant pathogens increase the demand of novel classes of antimicrobial agents with extreme resistance to drug resistant mechanisms ((Khem Raj *et al*., 2016). In the present scenario, peptides produced by microorganisms that are in close contact with higher organisms are considered as the molecule of future antimicrobial therapy ((Laxminarayan *et a*l., 2013). This study deals with the identification of peptide class of antibiotics produced by the microflora associated with the gills of fish.

**RESULTS** A novel strain *Bacillus tequilensis* PP1 (accession number MK648314) isolated from the gills of an estuarine water fish Chelon parsia was found to exhibit broad spectrum antibacterial activity against different bacterial pathogens. A molecule with m/z 1018.54 produced by the isolate was found to contribute the antimicrobial property. The partially elucidated LC-MSMS spectrum of the molecule showed fragmentation pattern corresponding to peptides conjugated with a non-peptide moieties. The purified peptide was found to be highly potent against clinically relevant bacterial pathogens with minimum inhibitory concentration range (MIC) of 3 to 6 □g/ml. The amphiphilic nature of the peptide was determined by emulsification index (32.21 %) and oil spreading test. As a result of its surfactant property, the molecule is efficient enough to remove the *Pseudomonas aeruginosa* biofilm formed on silicone catheters.

**CONCLUSION** This study bring forward an antibacterial peptide (m/z 1018.54) derived from the fish-gill commensal bacterium *Bacillus tequilensis* PP1. The peptide was found to exhibit strong antibacterial activity with MIC range 3 to 6 □g/ml. The amphiphilic nature of the peptide contributes to biofilm removal from abiotic surfaces. This is an ongoing research and the detailed structural identity of the peptide is under investigation.

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**Tau derived short peptides based anti-aggregation inhibitors against Tau aggregation in Alzheimer's disease**

Pravin Hivare, Krittika Ralhan and Sharad Gupta

*Indian Institute of Technology Gandhinagar, Gujarat, India – 382355*

**BACKGROUND** Tau is an intrinsically disordered protein and helps maintain the structure and stability of axonal microtubules. In Alzheimer's disease and related disorders, tau may undergo biochemical and structural changes to form intraneuronal tangles of paired helical filaments, which progressively result in neuronal death.

**RESULTS** In the present study, we have demonstrated the length dependency effect of the tau-derived peptides on the tau fibrilization. All peptides were synthesized by using the Fmoc-SPPS method as described by Ralhan *et al.*and characterization done by using MALDI TOF/TOF and Ion Trap MS. The full-length recombinant tau protein expressed by using *Escherichia coli* BL21DE3 (RP) strain and further purified tau used to study the tau aggregation and the inhibitory effect of these peptides using ThS fluorescence assay and turbidity assay. The real-time aggregation monitored by using ThS fluorescence assay and turbidity assay showed the concentration-dependent effect of the peptides on tau fibrillization and was further confirmed by using Fluorescence Microscopy and Atomic Force Microscopy. The AFM data showed the nano-scale insights of the fibrils morphology of the aggregates when compared to control tau fibrils; we did not observe tau fibrils formation in the case of the aggregation prone peptide region which further confirmed the inhibition of tau fibrillization in the aggregation reaction. The aggregation prone peptide region showed the complete inhibition of tau fibrillation, and no toxicity was observed in SH-SY5Y human neuroblastoma cells.

**CONCLUSION** In the present study, we have successfully express tau 2N4R isoform by using a heterologous recombination system with *Escherichia coli* BL21 DE3 (RP) Strain. The amyloid formation reduced in the presence of tau-derived peptides in the concentration manner, which indicated the tau fibril formation inhibition, while no significant decrease was observed for the control peptides. The tau-derived peptides of the aggregation prone region can inhibit tau fibrillization.

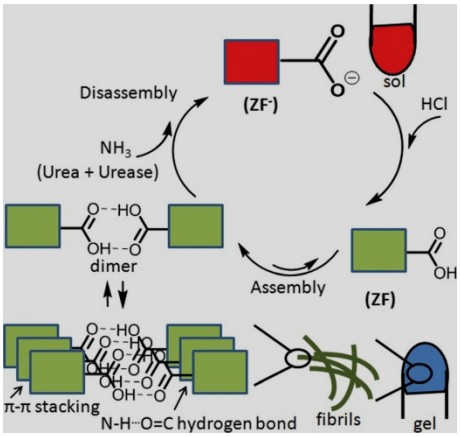
**Acid-responsive fibrillation and urease-assisted defibrillation of phenylalanine: a transient supramolecular hydrogel**

Sahabaj Mondal and Debasish Haldar *

*Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur-741246, India*

**BACKGROUND** The aggregation of proteins and peptides into fibrils is associated with many neurodegenerative diseases in humans, including Alzheimer's disease, Parkinson's disease and non-neurological type-II diabetes. To date, amyloidogenesis is an incompletely understood process. A better understanding of the fibril formation process and defibrillation using biochemical tools is highly important for therapeutics. Under physiological conditions, acidic pH promotes the formation of toxic fibrils.

**RESULTS** Here, a mimic of living systems has been achieved by the acid-responsive assembly of benzyloxycarbonyl-L-phenylalanine to fibrils, as well as the urease-assisted disassembly of the said fibrils. The simultaneous incorporation of the two triggers helped to prepare a transient supramolecular hydrogel from benzyloxycarbonyl-L-phenylalanine-entangled fibrils with a high degree of control over the self-assembly lifetime and mechanical properties. Further, under acidic pH, the compound formed the O–H---O=C hydrogen-bonded dimer. The dimers were further self-assembled by intermolecular N–H---O=C hydrogen bonds and π-π stacking interactions to form fibrils with high mechanical properties, from this simple molecule. However, the self-assembly process is dynamic. Hence, the in situ generated $NH_3$ uniformly increased the pH and led to the homogeneous disassembly of the fibrils. Thus, this report provides a valuable approach to defibrillation.
The cartoon showing acid-responsive fibril formation and $NH_3$-responsive defibrillation. HCl was responsible for decreasing the pH while the counter trigger $NH_3$ reverted the pH causing the gel to sol transition.




**CONCLUSION** In conclusion, we successfully created a supramolecular transient hydrogel from benzyloxycarbonyl-L-phenylalanine. The hydrogel is highly responsive to temperature and pH. We developed the pH-responsive transient gel system by the simultaneous incorporation of two triggers. Acidic pH promotes fibril formation and gelation. The controlled and uniform pH increase caused by $NH_3$ generated from the autocatalytic reaction between urease and urea leads to defibrillation and dehydrogelation. The gel fibrils exhibited positive results in the Congo red assay but the sol showed negative results. The results presented here provide a valuable approach to defibrillation and may foster new studies.

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**Protein directed synthesis of bimetallic gold-silver (Au-Ag) nanoclusters for the effective pico-molar level detection of ethyl parathion**

Saima, Munish Kumar and Rohit K Sharma

*Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160014*

Quantum dots (QDs) are semiconductor particles a few nanometres in size, having optical and electronic properties that differ from larger particles due to quantum mechanics. They are a central topic in nanotechnology. When the quantum dots are illuminated by UV light, an electron in the quantum dot can be excited to a state of higher energy.

This report illustrates a strategy for designing a nanoconjugate derived vector that efficiently delivers antimicrobial drug directly into bacterial cells. The nanoconjugate comprises of negatively charged CDTe@CdS quantum dots (QDs) with its surface functionalized using cationic BP-100 (KKLFKKILKYL-amide), a known cell-penetrating peptide (CPP), via electrostatic approach. The interactions between QD and CPP in QD-functionalized CPPs (QD–CPP) have been well analyzed using fluorescence spectroscopy, gel electrophoresis, and ζ-potential analysis. The QD–CPP conjugate was internalized into Gram negative (Escherichia coli) as well as Gram positive (Staphylococcus aureus) bacterial strains with confocal studies exhibiting a strong signal in tested microorganisms. Further, to check the applicability of QD–CPP conjugate as a delivery vector for generating an effective therapeutics, ampicillin molecules were conjugated on QD–CPP surface to generate QD–CPP–Amp conjugate. The CPP and drug molecules on the surface of QDs were well quantified using high-performance liquid chromatography (HPLC) data. It was observed that the internalization and bacterial debilitation of the QD–CPP–Amp conjugate is 2- to 4-fold effective as compared to that of bare ampicillin. The morphological changes to the bacterial cells upon the treatment with QD–CPP–Amp conjugates were noted with no cytotoxic effect on tested mammalian cell lines. The results inferred that the proposed QD–CPP vector provides a targeted and proficient approach for cellular internalization of cargo (drug) in bacterial cells with effective tracking through florescent QDs.

Munish Kumar, Satish Pandey,Anuradha Swami,Nishima Wangoo**,** Saima, Rahul Jain, Rohit K. Sharma, R.K. Sharma , *ACS Appl. Bio Mater.* 2020, 3, 4, 1913–1923

**The effect of amide bond orientation and symmetry on the self-assembly and gelation of discotic tripeptides**

Santosh Kumar, Santu Bera, Sujay Kumar Nandi, and Debasish Haldar*

*Department of Chemical Sciences, Indian Institute of Science Education and Research-Kolkata, Mohanpur, Nadia, 741246, West Bengal, India.*

The discotic compound contains a C3-symmetric aromatic core functionalized with three amide groups. Depending on the orientation of the amide groups, there are two distinct types of discotic tricarboxamides, namely, N-centered and C=O-centered. Both types of discotic compounds self-aggregate resulting in well-defined supramolecular architectures.[1, 2] A series of discotic tripeptides containing a rigid aromatic core and L-phenylalanine have been developed.[3] The orientation of the amide bonds yielded variations of the structure and self-assembly properties of the compounds. The aggregation behaviour of the discotic tripeptides was studied by various spectroscopic techniques. The morphology of the resulting aggregates was studied by field emission electron microscopy and atomic force microscopy. These studies showed that the orientation of the amide bonds has a strong influence on the intermolecular interactions, resulting in huge differences in the aggregation properties, and morphology of the discotic tripeptides. Only the C3-symmetric discotic tripeptides formed organogels. The supramolecular aggregation mechanism of N-centered and C=O-centered discotic tripeptides for forming 3-fold intermolecular H-bonded helical column were the same, there was only a smaller enthalpy change due to the occurrence of longer distances for the N–H...O=C bonds of the N-centered discotic tripeptide. Whereas, the C2-symmetric discotic tripeptides **2** and **3** adopted a 6-fold intermolecular H-bonded dimer structure. Thus, this report presents a valuable approach for the fine-tuning of the discotic tripeptide based functional material.

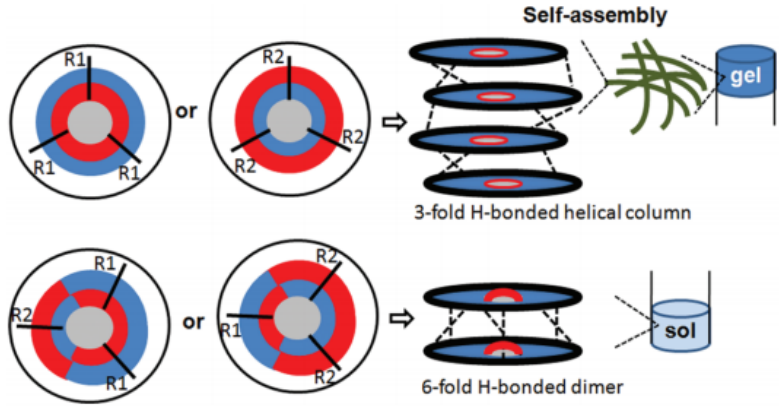


**Figure 1:** Proposed molecular assembly pattern of the discotic tripeptides.

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**Peptide-based allosteric activators of human glucokinase**

Siddharth Yadav, Swati Rana and Puniti Mathur

*Centre for Computational Biology and Bioinformatics, Amity Institute of Biotechnology – Amity University, Sector-125, Noida, Uttar Pradesh – 201313*

**BACKGROUND** Diabetes and related complications are a global phenomenon with rising incidences over the past 30 years. Glucokinase (GK), an isoform of hexokinase, is a key component of the glucose sensing mechanism of the Islet cells in the pancreas and hence is an important factor in blood glucose management. Glucokinase Activators (GKAs) have emerged as viable candidates for the management of type-II diabetes as proven by various in-vitro studies, animal models and phase-II clinical trials[1]. However, GKAs have not been granted public approval due to concerns over hepatic toxicity and development of resistance over time[2]. Peptide-based GKAs constitute a much less investigated family of GKA with potential to alleviate the mentioned shortcoming of traditional GKAs. This study utilizes ligand- and structure-based computational approaches along with solid-phase peptide synthesis for the identification of novel peptides as potential GKAs for the management of type-II diabetes.

**RESULTS** We were able to develop quality pharmacophores and validated them against a decoy set comprising of 1000-drug like ligands. These pharmacophores along with extensive molecular docking analysis led to the identification of peptides with comparable in-silico performance to that of known GKAs. Following lead optimization, the most promising leads were synthesized using Solid-phase peptide synthesis with Fmoc chemistry on Wang resin. Incorporation of α,β-dehydrophenylalanine was performed in solution phase via azlactonization. Subsequent characterization was done via ESI-MS and NMR.

**CONCLUSION** We believe to have identified promising peptides containing non-standard residues with the potential to allosterically activate glucokinase. Such peptides can aid the development of GKAs for the management of type-II diabetes.

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**Naphthalene Monoimide Derivative Ameliorates Amyloid Burden and Cognitive Decline in a Transgenic Mouse Model of Alzheimer's Disease**

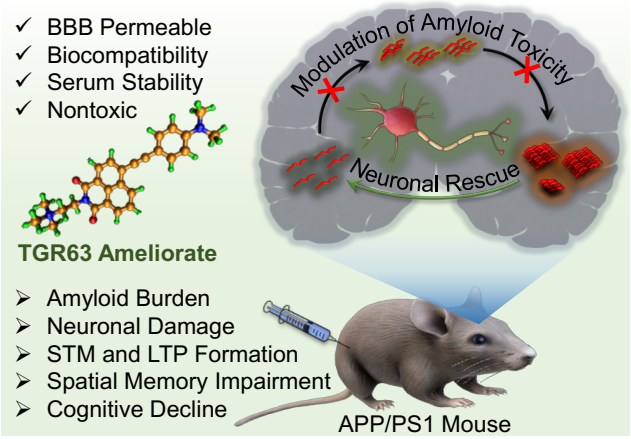
Sourav Samanta, Kolla Rajasekhar, Madhu Ramesh, Natarajan Arul Murugan, Shadab Alam, Devanshi Shah, James Premdas Clement, and Thimmaiah Govindaraju*

*Bioorganic Chemistry Laboratory, New Chemistry Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Jakkur P.O., Bengaluru 560064, India*

**BACKGROUND:** Alzheimer's disease (AD) is a major neurodegenerative disorder and the leading cause of dementia worldwide. Predominantly, misfolding and aggregation of amyloid-β (Aβ) peptides associated with multifaceted toxicity is the neuropathological hallmark of AD pathogenesis and, thus the primary therapeutic target to ameliorate neuronal toxicity and cognitive deficits. Herein, the design, synthesis, and evaluation of small molecule inhibitors with naphthalene monoimide scaffold to ameliorate in vitro and in vivo amyloid induced neurotoxicity are reported.

**RESULTS:** The detailed studies establish TGR63 as the lead candidate to rescue neuronal cells from amyloid toxicity. The in silico studies show the disruption of salt bridges and intermolecular hydrogen bonding interactions within Aβ42 fibrils by the interaction of TGR63, causing destabilization of Aβ42 assembly. Remarkably, TGR63 treatment shows a significant reduction in cortical and hippocampal amyloid burden in the progressive stages of APP/PS1 AD mice brain. Various behavioral tests demonstrate rescued cognitive deficits.

**CONCLUSION:** The excellent biocompatibility, blood-brain barrier permeability, and therapeutic efficacy to reduce the amyloid burden make TGR63 a promising candidate for the treatment of AD.

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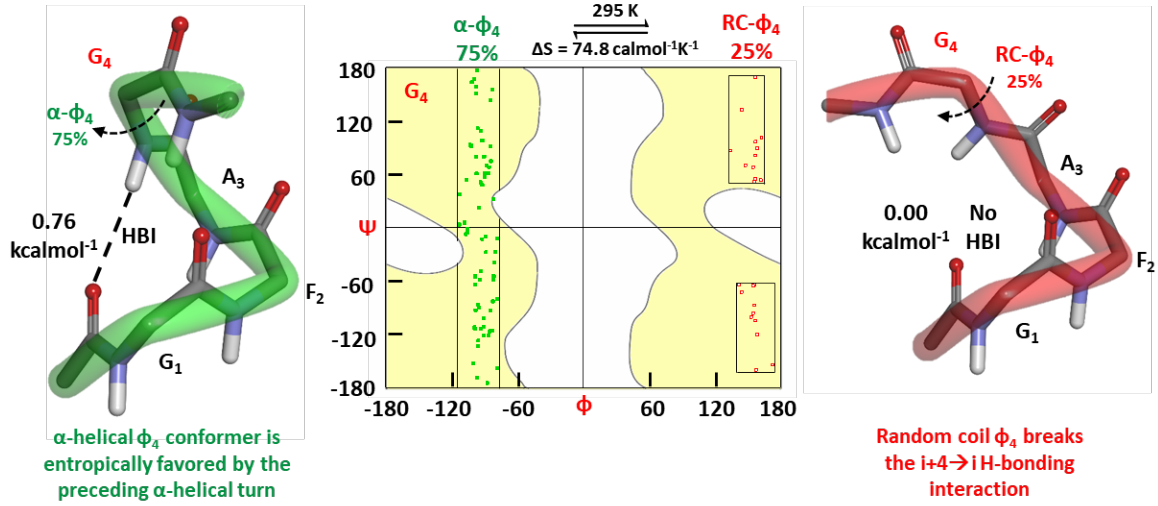
**Helix-Coil Transition at a Glycine Following a Nascent α-Helix: A Synergetic Guidance Mechanism for Helix Growth**

Sunit Pal, Shreya Banerjee and Erode N. Prabhakaran*

*Department of Organic Chemistry, Indian Institute of Science, Bangalore, Karnataka, India – 560 012.*

Studies on the helix folding kinetics so far have established a transition primarily between time-averaged bulk states of a long-lived helix and several transiently populated random coils, along the whole helix model sequence. However, the two-state helix-coil transition theory that fits this kinetics is proposed to originate at the residue level by the two long-standing models of Zimm & Bragg[1] and Lifson & Roig[2]. Additionally, the conformational space of the random coil state, as well as the predominant thermodynamic forces driving either this two-state transition, or the faster helix-growth following helix-nucleation, are not well-defined. Here we investigate the restrictions placed on the conformational space of a Gly residue backbone, as a result of it immediately succeeding a nascent α-helical turn that is artificially rigidified by our recently developed covalent hydrogen bond surrogate (HBS)[3]. Analyses of the temperature-dependent 1D-, 2D-NMR, FT-IR, CD spectra and GROMACS MD simulation trajectory of our model reveal that: i) the α-helical turn guides the ϕ torsion of the Gly exclusively into either a predominantly populated entropically favored α-helical (α-ϕ) state or a scarcely populated random coil (RC-ϕ) state; ii) the α-ϕ state of Gly in turn favors the stability of preceding α-helical turn, while the RC-ϕ state disrupts it, revealing an entropy driven synergetic guidance for helix growth in the residue following helix-nucleation[4].

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**Deciphering the aggregation and dissociation kinetics of a yeast prion derived amyloidogenic peptide**

Shreya Ghosh, Nabodita Sinha and Ashwani Kumar Thakur

*Institute of Affiliation –Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh-208016, India.*

**BACKGROUND** Amyloids are proteinaceous deposits of misfolded proteins, enriched in cross β-sheet structures.[1] More than 30 proteins of human origin have been reported to be associated with amyloid diseases till date.[2] Amyloid formation is linked to several neurodegenerative disorders like Alzheimer's, Huntington's, Parkinson and Prions disease.[2] Till date, for most of these diseases, symptomatic treatment is the only therapeutic option available. Decoding the mechanisms underlying amyloid formation in these disorders has been a daunting challenge to the scientific community since ages. This might account for one of the major failures in developing therapeutic strategies for amyloid disorders. Aggregation and dissociation kinetics of amyloidogenic peptides and proteins is one such study that plays a role in understanding the kinetic control on different molecular events underlying amyloid formation. In this study we have portrayed the aggregation and dissociation kinetics of an amyloid prone peptide, derived from a yeast prion Sup 35 protein. Both the amyloidogenic peptide and full-length Sup35 forms amyloid like fibrils enriched in steric zipper structure.[3] It serves as a potential candidate to understand the aggregation and dissociation process because of its small size and ability to form diverse fibrous structures.

**RESULTS** The peptide was solubilized in water, pH 2.0. The size exclusion chromatography (SEC) confirmed homogeneity of the peptide solution. It was aggregated at a concentration of 1700 μM and the kinetics was monitored by the drop in monomer concentration at different time intervals using RP-HPLC method. The peptide aggregated via nucleation dependent mechanism to attain equilibrium state in 5 days. The final fibrils formed exhibited intense green fluorescence and apple green birefringence in presence of thioflavin T (ThT) and Congo red dye respectively confirming their amyloid structures. Water was added to the fibrils to start the dissociation process. The kinetics was monitored in a similar manner as association. The dissociation kinetics also reached equilibrium in around 4-5 days. The decrease in the number of ThT positive fibrils as the dissociation progresses further confirms the dissociation process.

**CONCLUSION** We have elucidated the aggregation and dissociation kinetics of the heptapeptide, GNNQQNY at pH 2. Understanding the aggregation kinetics (association and dissociation) of these small peptide fragments might enable us to successfully interpret the amyloidogenic behavior of the corresponding full-length proteins. Besides, it will pave new ways in future to identify the dynamic structural features underlying the events associated with amyloid formation and disassembly of these intrinsically disordered proteins. Moreover, it will help in developing several mechanistic based therapeutic strategies to target the amyloid formation associated with neurodegenerative disorders.

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**Palladium nanoparticles embaded peptide based organogel for environment-friendly Suzuki and Negeshi C-C cross-coupling reactions**

Srayoshi Roy Chowdhury,[a] Debasish Haldar*[a]

[a]*Department of Chemical Sciences, Indian Institute of Science Education and Research-Kolkata, Mohanpur, Nadia, 741246, West Bengal, India.*

The development of hybrid systems by encapsulating nanoparticles in low molecular weight supramolecular gel scaffolds are highly crucial for the catalysis and organic synthesis.[1] We have developed smart materials for diverse applications.[2] Recently we have developed a fenamic acid containing phase selective organogel which is highly sensible to $H_2SO_4$.[3] Herein, a series of peptides containing a m-aminobenzoic acid at the N-terminal and Gly/ Phe/ Leu at the middle and dimethy amine(dma) at C-terminal were synthesized and studied. Among them, only the peptide 1 (Boc-maba-gly-dma) can form organogel in different solvent by heating-cooling and sonication. The organogel is further proved by inverted vial method. From rheology, the gel has shown storage modulus (G') greater than loss modulus (G") and did not cross each other over the entire range of angular frequency, which indicates that the gel is elastic in nature. Further, The Palladium acetate was embedded in peptide 1 organogel in dichlorobenzene. The TEM images of the hybrid gel have confirmed the formation of Pd nanoparticles which incorporated in the gel fibres. This hybrid gel was used for catalysis of different Pd catalyzed C-C cross coupling reaction. The Suzuki and Negeshi cross-coupling reaction was successfully carried out in water medium by slight vibration using the hybrid gel as a catalyst. The Pd doped gel was easily recovered from the reaction mixture and can be reused as a catalyst for multiple cycles.

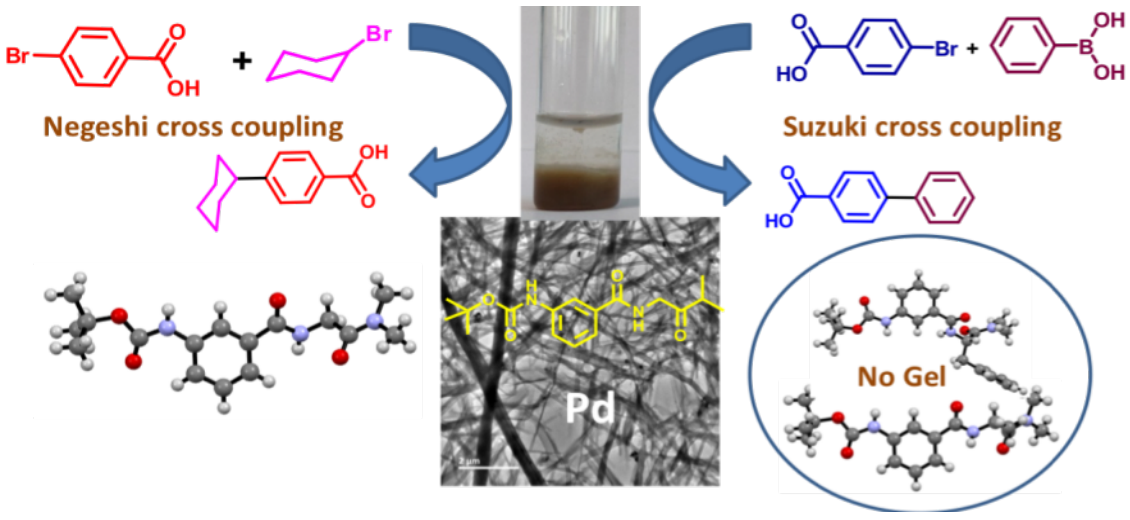


Fig: Schematic representation of the catalysis of cross coupling reaction.

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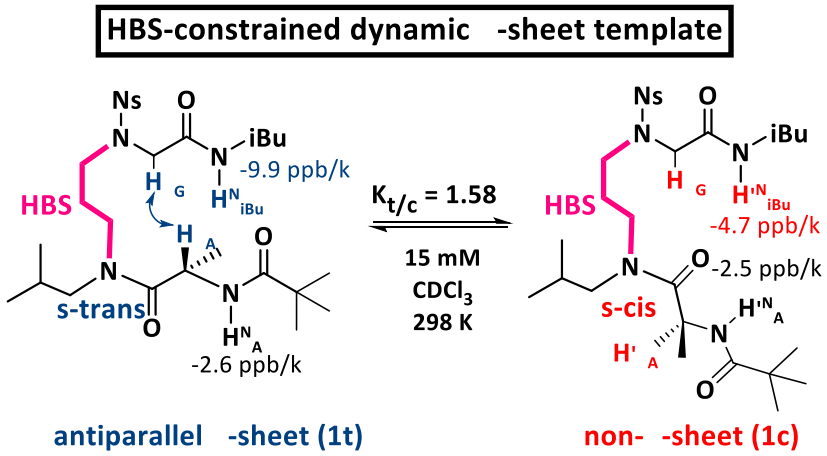
**Dynamic Templates for Studying Antiparallel β-Sheet ↔ non-β-Sheet Equilibrium: HBS-constrained Shortest Antiparallel β-Sheets**

Sravanthi S. Reddy, Sunit Pal, Sudip Ghosh and Erode N. Prabhakaran*

*Department of Organic Chemistry, Indian Institute of Science, Bangalore, Karnataka, India – 560 012.*

β-sheets are dynamic, non-static structures that rapidly equilibrate with non-β-sheet conformations[1]. Conventional static β-sheet models have revealed details of the β-sheet structure [2]. But an understanding of factors influencing the β-sheet ↔ non-β-sheet equilibrium in proteins and amyloids requires models that can mimic such dynamism. So, the dynamic β-sheet template is very important in this regard in which the template is restricted with the shortest (Gly/Ala) residue pair in dynamic equilibrium between a compact, antiparallel, 14-membered ring H-bonded β-sheet conformer (**1t**) and a disordered random coil ensemble (**1c**) [3].




The β-sheet fold in **1t** is compacted by a hydrogen-bond surrogate (HBS), Thorpe-Ingold effect from a tertiary (3°) amide and a nosyl group, inter-strand interactions and a H-bond. **1c** is largely favoured by entropy. The s-trans/s-cis rotational energy barrier ($E_a$ = 16.7±0.1 kcal/mol) at the 3° amide slows the **1t↔1c** equilibrium so that structural and energetic details of even rapid β-sheet ↔ non-β-sheet transitions between single residue strands are easily elucidated from simple 1D, 2D NMR data. These are ideal features to understand the dynamism in longer biologically important β-sheets containing this template.

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**Design, synthesis, *in–vitro* and *in–silico* investigation of multifunctional peptidomimetics against Alzheimer's disease**

Sukhmani Mann, Anupamjeet Kaur, Amandeep Kaur, Nitesh Priyadarshi, Bhupesh Goyal, Nitin Kumar Singhal and Deepti Goyal

*Sri Guru Granth Sahib World University, Fatehgarh Sahib, Punjab, India – 140406*

**BACKGROUND** The abnormal self–assembly of amyloid beta peptide plays a key role in pathogenesis of Alzheimer's disease (AD). Along with this, the presence of redox active metals like $Cu^{2+}$, $Fe^{2+}$, $Zn^{2+}$ further induce Aβ aggregation, oxidative stress and cellular toxicity. Due to the complex pathomechanism and lack of clear understanding of the molecular mechanism of AD, there is no such potential drug until a date that can completely cure or halt the progression of disease. During last years, numerous multifunctional small molecules[1], peptides and peptidomimetics[2] have been synthesized against self–induced $A\beta_{42}$ aggregation, metal–induced $A\beta_{42}$ aggregation, β–secretase (BACE1), acetylcholinesterase (AChE) as well as possessing metal chelating and antioxidant activities.

**RESULTS** Herein, we presented a library of multifunctional peptidomimetics based on the conjugation of a metal chelator (di–triazole moiety) and $A\beta_{42}$ aggregation inhibitor (hydrophobic core sequence). Among the synthesized peptidomimetics **S2** was identified as the most potent inhibitor of amyloid aggregation. The results of the studies highlighted that **S2** interacts with $A\beta_{42}$ and prevents the formation of $A\beta_{42}$ aggregates as well as disassembles the preformed $A\beta_{42}$ aggregates. Moreover, **S2** inhibited metal induced $A\beta_{42}$ aggregation and disassembled preformed metal induced $A\beta_{42}$ aggregates. Further, **S2** successfully reduces oxidative stress by sequestering $Cu^{2+}$ from copper redox cycle and thus halt the generation of reactive oxygen species (ROS). In addition, **S2** rescued SH–SY5Y cells from toxicity generated by $A\beta_{42}$ aggregates and itself did not show any cytotoxicity. In addition, molecular docking was performed to find the preferred binding modes and key interactions of **S2** with $A\beta_{42}$ monomer and $A\beta_{42}$ fibrilar structure. All these attributes make **S2** a potential therapeutic candidate for the treatment of multifaceted AD.

**CONCLUSION** From the designed and synthesized series of peptidomimetics (**S1**, **S2**, **S3** and **S4**), **S2** exhibited as most potent inhibitor of $A\beta_{42}$ aggregation and all the above mentioned results make **S2** a potential candidate for the treatment of multifaceted AD.

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**Effect of differential geminal substitution of gamma amino acid residues at the (i+2) position of αγ turn segments on the conformation of template β hairpin peptides**

Swapna Debnath, Subhankar Ghosh, Gopal Pandit, Priyadarshi Satpati* and Sunanda Chatterjee*

*Department of Chemistry, IIT Guwahati, 781039, India.*

In this report, we have investigated the effect of insertion of three geminally di-methyl substituted gamma amino acid residues [$\gamma^{2,2}$ (4-amino-2,2-dimethylbutanoic acid), $\gamma^{3,3}$ (4-amino-3,3-dimethylbutanoic acid) and $\gamma^{4,4}$ (4-amino-4,4-dimethylbutanoic acid)] at the (i+2) position of a two residue αγ $C_{12}$ turn segment, in a model octapeptide sequence Leu-Phe-Val-Aib-Xxx-Leu-Phe-Val (where Xxx = gamma amino acid residues). The conformation of the peptides in solution was confirmed by NMR, CD, IR and ab initio structure calculations. Peptides, with $\gamma^{3,3}$ and $\gamma^{4,4}$ residues were well accommodated into the αγ $C_{12}$ turn, adopts well-defined β-hairpin conformation, in contrast to $\gamma^{2,2}$ which was unable to form a tight $C_{12}$ β-hairpin nucleating turn and promote a well registered β-hairpin. Geminal disubstitution at the $C^{\alpha}$ carbon in $\gamma^{2,2}$ led to unfavorable steric clashes, limiting its accommodation in αγ $C_{12}$ hairpin nucleating turn. Germinal substitutions of gamma amino acid residue at different carbon atoms generates diverse effect on their conformation. This fundamental idea can further be explored for the designing of unique foldamers in future.

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**Oligo-lysine-based peptide amphiphiles for various cell-culture applications.**

Tamalika Paul, Joshna Gadhavi, and Sharad Gupta*

*Indian Institute of Technology Gandhinagar, Palaj, India-382355*

**Background** Self-assembling peptide amphiphiles are structures that have a hydrophobic lipid tail and hydrophilic peptide sequences. They can self-assemble and form bilayers, micelles, and nanostructures like nanofibers. The hydrophobic interactions between the alkyl tails, the attractive force caused among the peptides play significant roles in the self-assembly of such amphiphiles. Therefore, the hydrophobic alkyl tail can be varied, and on such variation, it disrupts the β sheet formed by the hydrogen bonds and reduces their ability to develop the nanostructures.[1] They can behave as surfactants. Positively charged peptides like lysine, histidine, arginine can form cationic surfactant like peptide amphiphiles with the peptide as the hydrophilic head. Nanorods, nanospheres are also created.
These peptide amphiphiles have been studied and used to analyze the membrane proteins as they can improve the order of the assemblies formed by the supramolecules [2]. Another set of structures named “bola amphiphiles” are compounds with two hydrophilic heads, and they can be developed into nanowires, nanotubes, nanotubes, and membrane-mimetic films [3].

**Results** Lysine is a positively charged amino acid and, when dissolved in water, tends to self-assemble into amyloid-like structures upon adding a large number of lysine residues. In our studies, we synthesized various length-dependent lysine peptides starting from 3K to 8K. After synthesizing different peptides’ lengths, we modified its N-terminal side chains with various alkyl chains ranging from acetyl to nonanoyl. We observed that these different lengths of peptides with varying alkyl chains form amyloid-like structures and peptide amphiphiles upon varying carbamylation conditions of lysine side chain residues. Further, the systems were characterized by ThT assay, ANS assay, Fluorescence Microscopy, congo red birefringence, and SEM. We confirmed that varying conditions could tune different kinds of nanostructures.

**Conclusion** The above results confirmed the length of the peptide sequences and alkyl chain length and observed the differences in the structure and width of the nanofibers formed. After following the differences, the characterization techniques further confirmed the formation of the nanostructures. These self-assembling peptide amphiphiles have potential applications in tissue regeneration and regenerative medicine. They are biodegradable and biocompatible. The future prospects of peptide amphiphiles include employing their excellent thixotropic properties for prolonged drug delivery release applications. They can be prepared into scaffolds and utilized for various cell culture studies.

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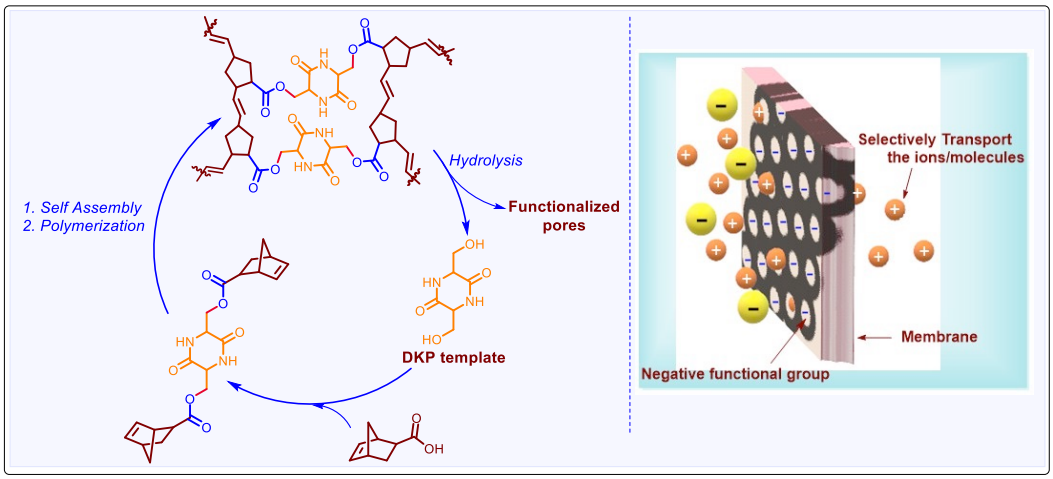
**Diketopiperazine (DKP) as Template for Functionalized porous polymer membrane**

Umatai A. Hale and Nandita Madhavan

*Indian Institute of Technology, Bombay, Maharashtra, India – 400076*




Functionalized porous polymers find significant application in drug delivery, ion transport, ion-encapsulation, catalysis, and gas/liquid separation.[1] They are traditionally synthesized using supramolecular approaches which are often challenging and suffer from poor selectivity.[2] An elegant alternative using peptide templates for accessing functionalized porous polymer membranes was reported by Perrier and Jolliffe. They developed multi-shell soft nanotubes with an internal pore having aldehyde group, using an cyclic octapeptide template.[3] Inspired by this our group reported the use of a similar cyclic octapeptide template to synthesize robust carboxylated polymeric pores.[4] In spite of these, no other reports exist on the synthesis of functionalized pores using peptide templates. On the other hand diketopiperazines (DKPs) are well known to undergo self-assembly to furnish nanotubes and nanospheres and are relatively easy to synthesize as compared to the cyclic octapeptides.[5] However the use of DKP as a template to prepare functionalized pores is yet elusive. So working in the regard serine derived DKPs were conjugated with norbornene acid, using an easily cleavable ester linkage. These conjugates were then self-assembled in DCM and polymerized using a ring opening metathesis reaction using Grubbs II$^{nd}$ generation catalyst. The resulting nanospheres were then subjected to base mediated hydrolysis to remove the DKP template to furnish porous nanospheres bearing carboxylate groups. In conclusion carboxylate functionalized porous nanospheres were synthesized using a serine derived DKP template and further explorations towards their application and functional group modification are currently underway in our laboratory.

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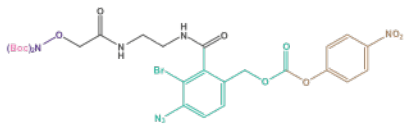
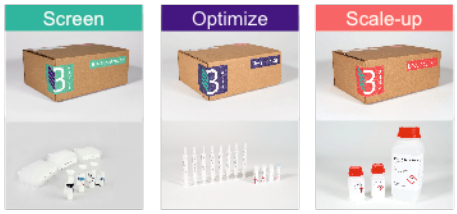


R. Zitterbart *et al.*, Traceless parallel peptide purification by a first-in-class reductively cleavable linker system featuring a safety-release, *Chemical Science*, **2021**

## Our kit products

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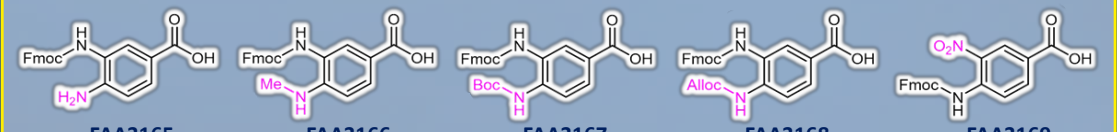
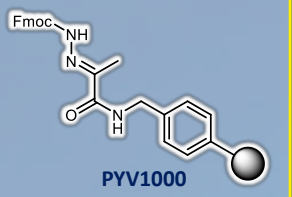



**FAA3165** **FAA3166** **FAA3167** **FAA3168** **FAA3169**

→ Peptide hydrazides can easily be synthesized using Hydrazone Resins, which are polystyrene resins functionalized with the hydrazone linker. The hydrazone linker is completely stable in the course of standard Fmoc-SPPS. Synthesized peptide hydrazides can either be used as building blocks for **hydrazone ligation** or be converted into peptide azides as precursors for the formation of appropriate **peptide thioesters** used in native chemical ligation (NCL). Find **many more** hydrazone resins in our Webshop!




**PYV1000**

values: sustainability & responsibility
state-of-the-art equipment & latest technologies
high-quality standards, qualified suppliers & audits

High Standards

Transparency & Documentation

talk to our specialists – customer care
certificates of analysis + impurity profiling
analytical and process reports

Trust, Honesty & Confidentiality

Know-How

family-run business valuing partnerships
meeting the customer's expectations
integrity towards our customers

one-step reactions & complex multi-step synthesis
scalability from mg to kg quantities
route scouting

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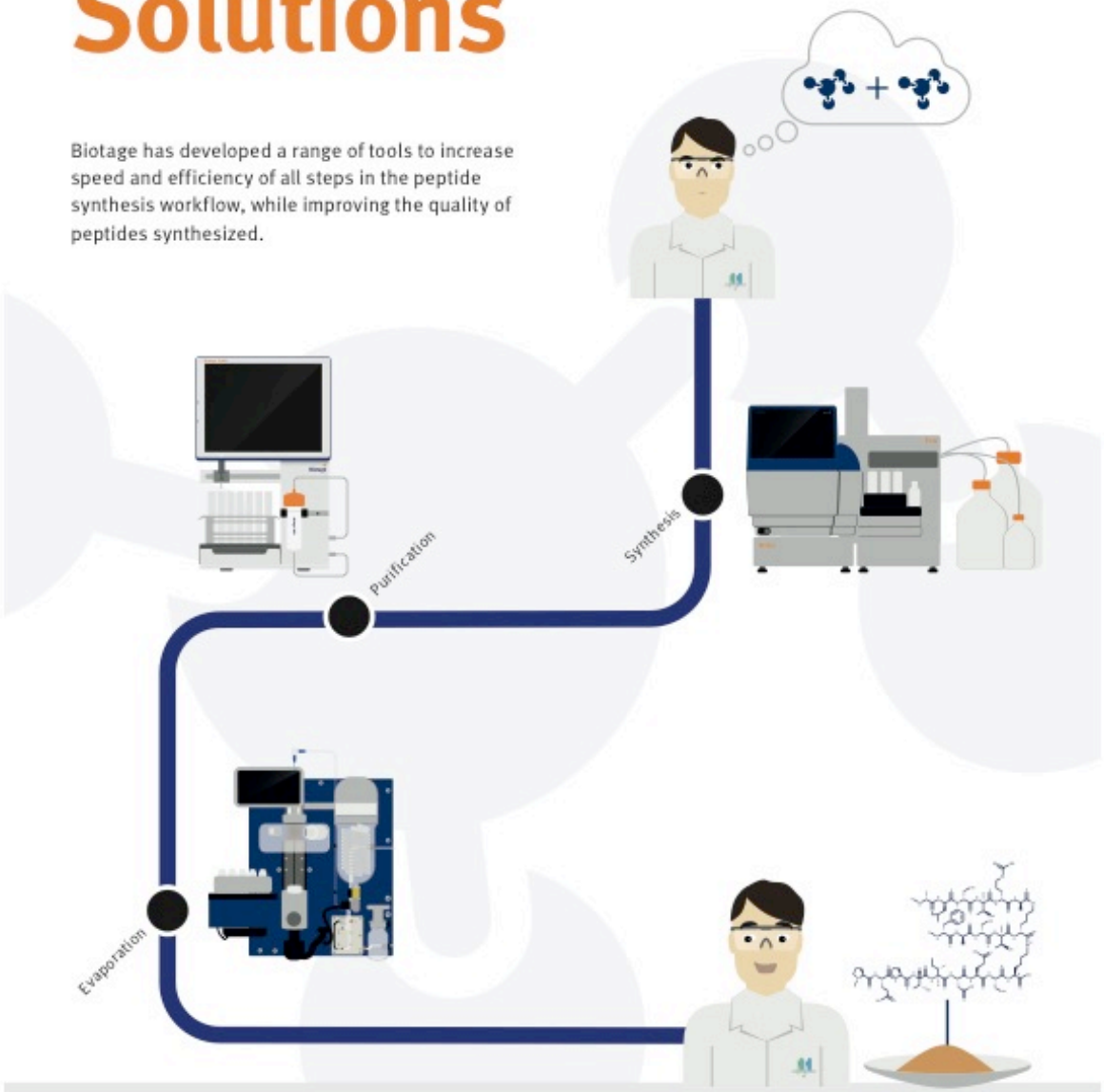
Fax: +49 (0) 9231 97121-99
Email: info@iris-biotech.de
www.iris-biotech.de

# Peptide Workflow Solutions

Biotage has developed a range of tools to increase speed and efficiency of all steps in the peptide synthesis workflow, while improving the quality of peptides synthesized.




Scan and learn more about peptide synthesis workflow

Biotage®

# Brief Intro about us and our Principals.

| | |
|---|---|
| Anarghya InnoTech | Established in Jan 2007 – Anarghya Innovations and Tech Pvt Ltd., became an important player in design, manufacturing, producing marketing sales and service of scientific research equipment to customers doorsteps in India and across globe with its daughter companies in Singapore, Germany and USA.<br><br>We provide Peptide synthesizers, Oligosaccharides synthesizer, Oligo/DNA/RNA/LNA and modified oligo synthesizers. |

| | | |
|---|---|---|
| Anarghya InnoTech | Activotec | K&A |

**ACTIVOTEC UK:** www.activotec.com

| | |
|---|---|
|  | **Activotec is a customer focussed peptide synthesis company.**<br>■ Activotec provides a complete range of peptide and organic synthesizers, chemicals and custom peptide synthesis services.<br>■ Activo-P11 is a fully automated peptide synthesizer with reactor heating and UV monitoring, the best instrument for synthesizing long difficult sequences.<br>■ Activo-P14 is a semi-automated peptide synthesizer. The lowest cost synthesizer on the market, ideal if you have limited lab space or budget.<br>■ Activo-PLS is a very flexible tool for parallel peptide synthesis and organic synthesis. Heating and cooling allow for many different types of reaction. |

**K&A Laborgeraete GbR**: www.ka-lab.de

| | |
|---|---|
|  | K&A Laborgeraete is the leading producer of column synthesizers which allows you to make highest quality oligos, modifications, wobbles, probes, RNA, S-Oligos, universal CPG and any other possible variations. The powerful online trityl monitor in our synthesizers allows you very efficient quality check already during the synthesis. Single syntheses can be started and stopped individually and independently from the state of process. Furthermore, the online trityl monitor indicates quality of the running synthesis at all times. |

## Enabling Therapeutic Development and Commercialization

PEOPLE WHO LOVE PEPTIDES
CS
PEOPLE WHO KNOW PEPTIDES

INTUITIVE
RELIABLE
TRUSTED

### Providing automated peptide synthesizers in addition to high-quality R&D and cGMP peptides to the global biotech community

#### Instrumentation

- Automated peptide synthesizers to fulfill any lab's needs; from small scale product development to commercial scale manufacturing
- Research scale systems perfect for labs new automated synthesis or experienced peptide chemists who need flexible chemistry
- Custom built to order systems to meet your specific needs

#### cGMP Manufacturing Services

- Agile manufacturing scale and timelines to meet your project needs. State of the art cGMP manufacturing facility

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