SVAR COMPLEMENT EXCELLENCE AWARD

Harnessing the Power of Cyclic Peptides: A Journey into Complement System Modulation

An interview with Svar Complement Excellence Award recipient 2023

Dr. Christina Lamers, a pharmacist with a passion for developing new therapeutics through medicinal chemistry, found her interest in the immune system while studying metabolic syndrome. Under the guidance of Dr. Daniel Ricklin in Basel, she delved into the complement field, aiming to use cyclic peptides to develop novel therapeutics.

Alongside her research, Dr. Lamers is dedicated to teaching and mentoring, aiming to cultivate a new generation of complement researchers. "Working with students and researchers allows me to challenge my own ideas and assumptions. They often bring fresh perspectives and ask thought-provoking questions. It is incredibly rewarding to develop novel project ideas that were sparked by their questions," says Dr. Lamers

In this article, Dr. Lamers discusses the advantages of cyclic peptides as therapeutic compounds and how structural insights will allow the development of novel complement inhibitors and research tools.

Novel complement therapeutics for a system beyond its traditional role

The complement system, once primarily associated with host defense, is now being recognized as a potential missing link in understanding and treating various diseases. The involvement of complement in diseases that lack effective treatments, such as neurodegenerative diseases, has sparked a growing interest in exploring its therapeutic potential. "This paradigm shift has attracted big industry players, expanding the scope of complement research beyond its traditional boundaries, and it is an exciting time to be in the field," comments Dr. Lamers.

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Structural insights and the future of complement inhibitors

Her research on compstatins, which are inhibitors of complement C3, has provided valuable insights into how clinical candidates selectively bind to their targets[1]. This understanding has improved our knowledge of how current compounds inhibit the complement system and is key to fine-tuning their mechanism and bringing relevant information for the development of new inhibitors.

According to Dr. Lamers, "Some of these compounds present species-related lack of binding or limitations in affinity which often hinders the possibility of extending these therapeutic options for other indications." Advancements in structure-based design are essential to develop pharmacological tools that exhibit high affinity and efficacy in animal models. Such tools will not only facilitate the potential use in a wide variety of diseases but also enhance our understanding of the molecular mechanism of complement activation.

> **"Receiving the Svar Excellence Award represents a significant milestone in my career in the complement field. It is a huge honor, especially coming from the medicinal chemistry side and being recognized by a renowned committee of people whose papers I have always cited. It feels amazing and serves as validation for the hard work and contributions made in the field."**

Dr. Christina Lamers
Junior Professor at the Institute for Drug Discovery
Faculty of Medicine, Leipzig University,
Principal Investigator at the Development of
Macrocyclic Peptide Therapeutics Laboratory

Phage display a powerful technique for peptide generation

Phage display is a technique that uses bacteriophages to present and select proteins or peptides with specific binding properties. It has been employed in the identification of the compstatin family of complement C3 inhibitors.

This technique can be used with purified targets to generate binders or in vivo phage display where the target is unknown, enabling the search based on the phenotype. This flexibility makes phage display a valuable tool for identifying potential complement inhibitors and exploring their therapeutic potential.

While phage display allows for the generation of binders, not all of them may exhibit functional properties, explains Dr. Lamers. Despite this challenge, having a starting structure through phage display is still valuable.

Optimizing compounds identified through phage display for affinity, stability, and pharmacokinetic behavior requires several crucial aspects to be considered. After the initial phage display selection, the binders typically have micromolar affinity. To improve their affinity, systematic optimization techniques like Alanine-scanning can be employed, where each amino acid is systematically replaced with Alanine to determine its impact on affinity. This allows for the identification and optimization of key amino acids to reach nanomolar affinity. “In terms of therapeutics, it is essential to achieve high affinity, particularly when targeting components of the complement system. This is because many components of the complement system are present in high concentrations, necessitating a higher affinity in order to effectively saturate the target and produce the desired therapeutic effect,” comments Dr. Lamers

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Beyond their therapeutic potential, these compounds also contribute to a deeper understanding of the complex biology of the complement system. By studying the interactions between ligands and complement components, researchers gain valuable insights into the underlying mechanisms and pathways. “This knowledge enhances our understanding of the complement system’s role in various biological processes and diseases.” It is worth noting that while phage display is useful for various applications, whether it can be translated into a therapeutic is a separate consideration.

Cyclic peptides: a stable and building blocks-like pharmaceutical tool

Stability in plasma is an important aspect of optimizing therapeutic compounds. In this context, cyclic peptides have an advantage over regular linear peptides due to their stable conformation. Further stability enhancement can be achieved by identifying specific cleavage sites using a mass spectrometry (MS) assay method and replacing vulnerable amino acids with modified D-amino acids or N-methylated amino acids mentions Dr. Lamers. This modification increases the stability of cyclic peptides, often without affecting their affinity. “What we are looking for is not to change the binding site but to make the backbone more stable.”

> **“One key aspect of cyclic peptides is the versatility of allowing the combination of active peptides with membrane-penetrating peptide parts, like building block pieces, and that is something my group is starting to work on and is really exciting.”**

With the increment of non-canonical complement roles and local production of complement components, the ability of compounds to penetrate membranes or barriers is gaining relevance. Cyclic peptides can exhibit conformational changes near membranes, which can aid in shielding hydrophilic regions and facilitating membrane penetration. This property makes cyclic peptides suitable for the development of membrane-penetrating therapeutics.

One notable area of interest lies in neurodegenerative diseases. There is a growing need to explore the complement system’s involvement in neurodegenerative diseases and identify potential therapeutic targets. Due to the unique characteristics of the brain, such as the blood-brain barrier, targeting the complement system in this context requires careful consideration and innovative strategies. “One key aspect of cyclic peptides is the versatility of allowing the combination of active peptides with membrane-penetrating peptide parts, like building block pieces, and that is something my group is starting to work on and is really exciting, “ comments Dr. Lamers

Advancing selective inhibitors of novel roles of complement cascade

The complement research landscape has evolved significantly since the early 2000s, with the increased focus on non-canonical functions and other novel areas of investigation, such as metabolic and neurodegenerative diseases, which pose interesting questions and challenges when it comes to inhibiting the complement cascade.

The exploration of cyclic peptides in the complement system has opened new avenues in the development of therapeutics. Dr. Lamers comments, “Compared to antibodies, cyclic peptides offer a more economically favorable option, as they are smaller in size and still exhibit similar affinities”. This size advantage makes them easier to produce and represents a promising format for achieving desired affinity levels.

The main challenge is carefully considering the target and indication for which the inhibitors are being developed. “It is crucial to find a way to selectively inhibit novel and relevant targets without inhibiting the entire complement system long-term, which could lead to problems with infections,” Dr. Lamers mentions. Structural insights and optimization techniques are crucial for the development of novel complement inhibitors.

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The potential impact of cyclic peptides in complement-targeted therapeutics is immense. “As our understanding of the complement system continues to deepen, we can anticipate the development of innovative therapies for a wide range of diseases, I am optimistic about the development of the field.” With continued research and innovation, cyclic peptides hold promise for really advancing the field of complement-targeted therapeutics.

ABOUT THE PRIZE

The Svar Complement Excellence Award is handed out annually to individuals that have made great contributions to the complement field.

The awards are intended as grants for two recipients, each worth €20.000. In 2023 the prize was handed out at the International Complement Workshop (ICW) in Newcastle in collaboration with the complement community.

To read more about Dr. Lamers’ work:

Selected Reference:

1 Lamers C, Xue X, Smieško M, van Son H, Wagner B, Berger N, Sfyroera G, Gros P, Lambris JD, Ricklin D. Insight into mode-of-action and structural determinants of the compstatin family of clinical complement inhibitors. Nat Commun. 2022 Sep 20;13(1):5519. doi: 10.1038/s41467-022-33003-7. PMID: 36127336; PMCID: PMC9488889.

ABOUT SVAR LIFE SCIENCE

We harness years of experience and deep specialist knowledge in innate immunity, the complement system, and its intricate connections. With synergetic platforms, Svar delivers tailored solutions spanning immunoassay development, cell engineering, and contract research services that address our customer’s assessment and testing needs.

The synergy created by our integrated suite of offerings provides customers with a comprehensive approach that not only enhances efficiency but also fosters innovation, enabling seamless transitions from discovery to clinical application.

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