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PEPTIDE INHIBITORS OF HUMAN ISLET AMYLOID POLYPEPTIDE AGGREGATION: FROM MOLECULAR DESIGN TO THERAPEUTIC POTENTIAL

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ABSTRACT-

Huge amounts of human islet amyloid polypeptide (hIAPP) aggregate in patients with type 2 diabetes mellitus (T2DM) and this aggregation pathway is an important therapeutic target. In this review, peptide-based inhibitors of hIAPP aggregation are discussed about their molecular design, inhibitory mechanisms, translational potential. Structural and biophysical evidence suggests that hIAPP aggregation occurs through nucleation, formation of oligomers, secondary nucleation, fibril elongation and mature fibril assembly with membrane associated intermediates playing a role in the cytotoxicity. Regions of hIAPP are amyloidogenic, and can be disrupted by sequence complementarity, conformational restriction, stereochemical inversion, cyclization, glycosylation, and peptidomimetic modification. Methods reported are mimics of β-hairpin conformation, D-peptides, rationally designed hexapeptides, cyclic peptides, anti-cross amyloid compounds, and O-glycosylated peptides. Peptides inhibits primary nucleation, by interfering with oligomer formation, by capping fibril ends, by remodelling preformed aggregates, by protecting lipid membranes and by preserving the β-cell viability. Peptide inhibitors provide more options in designing sequences that recognize specific targets and in rational optimization as compared to small molecules, natural compounds, chaperones, and nanomaterials. The clinical translation is hampered by proteolysis, fast clearance, delivery issues, structural heterogeneity and lack of validation in physiologically relevant models. The future should involve integration of computational design, chemical stabilization, targeted delivery, kinetic and structural characterization, membrane assays, β-cell models and in vivo testing to identify peptide candidates to inhibit toxic aggregation whilst preserving pancreatic function. Standardized comparative assays will be important to distinguish reductions in fibril burden from reductions of toxic intermediates and improvements in biological outcomes.

Keywords: hIAPP; amyloid aggregation; peptide inhibitors; β-cell toxicity; type 2 diabetes

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1. Introduction

Islet amyloid polypeptide (IAPP), or amylin, is a 37-residue peptide hormone that is produced and co-secreted by pancreatic islet β-cells. The abnormal assembly of hIAPP is a highly related process to the islet amyloid deposition observed in type 2 diabetes mellitus (T2DM) where the accumulation of misfolded and aggregated species may lead to progressive β-cell dysfunction and loss (Milardi et al., 2021; Hassan et al., 2022).

Bhowmick et al. (2022) suggested that hIAPP turnover, misfolding, and toxicity are interlinked processes happening in the pancreatic environment, while Plesner et al. (2026) stated that aggregation kinetics create a certain time window of IAPP proteotoxicity. Soluble oligomeric and protofibrillar intermediates may interact with cell membranes, disrupt cell membrane organization and trigger downstream injury.

Protofibril-specific antibodies have been created to identify and intervene in the hIAPP pathology associated with T2DM (Bortoletto et al., 2022) and an antibody against pathological IAPP aggregates has been developed that prevents the death of β-cells in experimental diabetes models (Wirth et al., 2023). The use of anti-IAPP monoclonal antibody has also been shown to improve functionality in an experimental model of T2DM (Vogt et al., 2021). The combination of these results provides further support for the direct targeting of the aggregation pathway.

hIAPP assembly is a multistep process that consists of conformational change of the monomers, nucleation, oligomerization, fibril elongation, secondary nucleation, and the assembly of mature amyloid fibrils. Structural studies have revealed that hIAPP fibrils can assume polymorphic structures yet remain with the same fibril core features (Cao et al., 2021; Li et al., 2022). That this structural conservation is relevant for inhibitor design is due to the fact that it indicates that certain recognition surfaces can still be exploited for therapeutic purposes despite the polymorphism of the fibrils.

The two abundant components of pancreatic secretory granules, insulin and zinc, impact the ability of the hIAPP to aggregate and cause membrane injury (Khemtemourian et al., 2021). Copper can also control aggregation and toxicity in the presence of insulin, showing the complexity of the physiological environment in which the aggregation of amylos occurs (Roy et al., 2023). Therefore, inhibitors found under simplified experimental conditions may not work in the islet environment.

The surface of membranes is especially significant due to the fact that lipid interfaces may facilitate aggregation reactions. Elenbaas et al. (2022) showed that secondary nucleation significantly affects the membrane-catalyzed IAPP aggregation, and Rodriguez Camargo et al. (2021) found that surface-catalyzed secondary nucleation is a significant source of toxic IAPP aggregates. Elenbaas et al. (2023) also related fibril elongation to disruption of the membrane, suggesting that fibril aggregation and membrane toxicity are mechanistically connected.

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Peptides are very attractive inhibitors due to the specificity in structure of the process of amyloid formation. The short peptides can be developed to target specific regions of hIAPP, disrupt intermolecular interactions essential for nucleation, β-sheet organization or fibril extension, whereas the molecules have a broader activity. Short sequence motifs derived from the hIAPP amyloidogenic region can be modified to make sequences that are aggregation-prone into competitive inhibitors as the hIAPP amyloidogenic sequence itself serves as a molecular recognition template.

Lesma et al. (2021) showed that β-hairpin peptide mimics are able to inhibit the aggregation of hIAPP, and Roy and Paul (2022) demonstrated that an hIAPP amyloid-core-derived D-peptide can prevent aggregation and destabilize protofibrils. The peptides designed by Kaur and Goyal (2024) using in silico methods were aimed at inhibiting the aggregation of hIAPP, while Rani et al. (2025) employed molecular dynamics and experimental studies to explore rationally designed hexapeptides. Recently, Rani et al. (2026) showed that mutations that are synergistic in the amyloidogenic core can give rise to a strong inhibitor of human amylin fibrillation.

Peptides could also be modified with non-naturally occurring residues, glycosylated, cyclized, or otherwise modified to make them more resistant to degradation and more effective at target recognition.

In this review, the authors discuss the molecular mechanism and therapeutic value of peptide-mediated inhibition of hIAPP aggregation. Highlight is given to the structural features of hIAPP, mechanisms of amyloid formation, principles of peptide inhibitor design, and molecular mechanisms by which inhibitory peptides disrupt the nucleation, oligomerization, fibril elongation, and membrane associated toxicity. Innovative peptides, D-peptides, β-hairpin mimics, cyclic peptides, cross-amyloid inhibitors, and chemically modified peptide systems, which were recently developed, are incorporated in order to highlight the design principles that could be applicable to the translation to therapeutic agents against anti-hIAPP systems.

2. Structural and Biophysical Basis of hIAPP Amyloid Formation

2.1 Primary and Secondary Structure of hIAPP

The hIAPP is composed of 37 amino-acid residues, has a Cys2–Cys7 disulfide bond and an amidated C-terminus, and has a considerable conformational flexibility. It is important for its disordered to helical to oligomeric and to β-sheet rich states as this is essential for its amyloidogenic behavior. Structural analysis has revealed that the mature hIAPP fibrils have well-ordered β-sheet architectures with mutually stable intermolecular contacts between specific sequence regions. The cryo-electron microscopy studies have revealed fibril polymorphism, and also revealed conserved structural elements in the fibril core (Cao et al., 2021). Li et al. (2022)

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also reported another human amylin fibril polymorph with similar protofilament organization and shared structural core.

Because of the lack of morphological variability but the presence of the conserved structural elements, it is important to understand the implications of this for inhibitor design. Instead of identifying each conformational form of the peptide as a unique target, peptide inhibitors can be designed for residues that can repeatedly be a part of the amyloid core structure. This gives a structural foundation for peptides that can recognize the peptide self and peptides that disrupt the β-sheet structure of the protein, and peptides that are competitive with it.

Fibril architecture is not completely rigid. Brotzakis et al. (2023) studied the "fuzzy coat" of a conformational dynamics of an IAPP amyloid fibril, where ordered regions of the fibril co-exist with conformationally mobile external parts. This structural heterogeneity could impact the accessibility of inhibitor-binding sites and account for the preference of some inhibitors for binding to soluble oligomers or fibril ends instead of more mature fibril surfaces.

2.2 Stages of hIAPP Aggregation

The process of hIAPP Aggregation can be divided into the various stages (Figure 1). The process of aggregation starts with conformational changes between the monomeric hIAPP molecules. Nucleation and oligomerisation are observed as the result of subsequent self-association, which is followed by protofibrillar and fibrillar assemblies. It is not a linear pathway as existing fibrils can catalyse the initiation of further aggregates by secondary nucleation.

Rodriguez Camargo et al. (2021) showed that surface-catalyzed secondary nucleation makes a major contribution to the production of toxic IAPP aggregates. The aggregation kinetics can be additionally modified by changes in membrane surfaces. Elenbaas et al. (2022) concluded that secondary nucleation is the predominant mechanism in membrane-catalyzed aggregation, with the cellular membrane acting as a catalytic environment for amyloid formation in addition to being a target for toxicity.

Another important step is the elongation of fibrils. Elenbaas et al. (2023) correlated hIAPP fibril elongation with membrane damage, suggesting that elongation of fibrillar structures can directly lead to membrane perturbation. Therefore, a peptide inhibitor does not have to prevent all aggregation to be clinically beneficial; if a certain part of the process, e.g., secondary nucleation or elongation, is suppressed, then the amount of harmful species formed can be significantly decreased.

Timing of inhibition is also crucial. Plesner et al. (2026) found the relation between aggregation kinetics and a time window when IAPP has maximum proteotoxic effects. As a temporal

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component, peptide inhibitors should not be tested just on the final yield of fibril, but also on their effects on lag time, population of oligomers, growth rate, and toxicity of intermediate species.

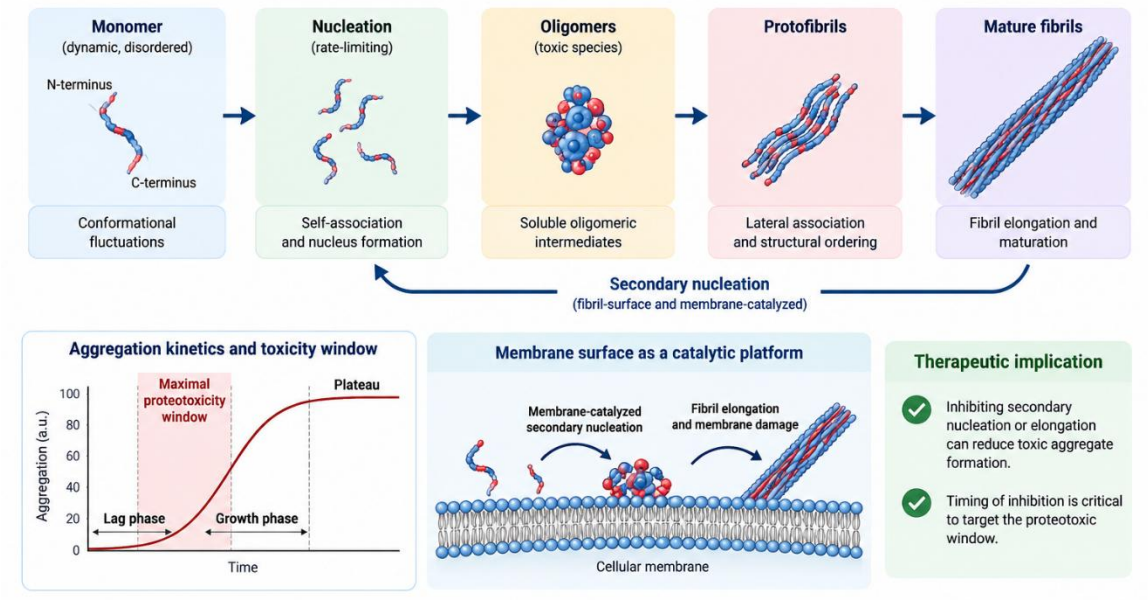


Figure 1. Schematic representation of hIAPP aggregation pathway

2.3 Amyloidogenic Core Regions

The region 20–29 (hIAPP) of the protein is a classical amyloidogenic region that has been abundantly exploited in the design of inhibitors and is one of the most important regions for self-association (Figure 2). Domains nucleated and stabilized by intermolecular β-sheet formation within aggregation prone sequences. Short peptide fragments containing the amyloid core can still bind to their parent hIAPP, either as template for aggregation or as a modified competitive inhibitor.

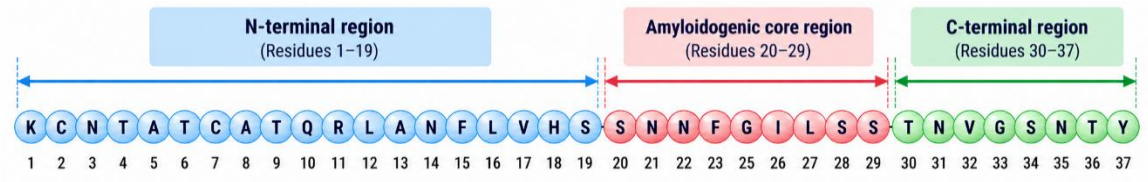


Figure 2. Primary sequence of hIAPP showing the N-terminal region (1–19), amyloidogenic core (20–29), and C-terminal region (30–37)

Roy and Paul (2022) took advantage of the principle to create a D-peptide, based on the hIAPP amyloid core. Their research showed that aggregation inhibitory and destabilizing self-recognition

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sequences can be obtained by modifying the stereochemistry of the sequences. Rani et al. (2025) also explored rationally designed hexapeptides, employing molecular dynamics and experimental studies to study the effects of sequence variations on the fibrillation of hIAPP.

This is further illustrated by Rani et al. (2026) who demonstrated that synergistic mutations in the human amylin core (12–25) could be used to generate a strong inhibitor of fibril formation. These kinds of findings imply that multiple residues do not function independently but rather as a team. Thus, the rational design of inhibitors should not be limited to the design of one-residue substitutions but should be based on patterns of intermolecular complementarity.

2.4 Factors Affecting hIAPP Aggregation

The aggregation of hIAPP is highly context dependent. The rate and pathway of assembly may be altered by peptide concentration, ionic environment, molecular crowding, membranes, metal ions and secretory-granule components. Khemtemourian et al. (2021) investigated how insulin and other physiological co-secreted molecules affect aggregation behavior and membrane damage of hIAPP, concluding that the co-secreted molecules can alter the aggregation behavior of hIAPP.

The same kind of effects can occur with metal ions. Roy et al. (2023) suggested that copper could act as a modulatory agent for hIAPP aggregation and toxicity, in the presence of insulin. This is especially relevant as an inhibitor that is optimized in an isolated buffer might not retain the same activity when hIAPP interacts with insulin, metals, and biological membranes simultaneously.

There is also a balance between the hydrophobic and hydrophilic interactions that influence assembly. Tang et al. (2022) showed that the hydrophobic-to-hydrophilic ratio of amphiphilic helix mimetics determines their effects on IAPP aggregation. Those are mimetics and not regular linear peptides; however, the idea is still quite relevant: too much hydrophobicity can lead to non-specific association, too little to a decrease in recognition of the amyloid interfaces.

Cross amylod interactions are an additional level. Co-aggregation was simulated between amyloid-β and fragments of IAPP (Kawecki et al., 2022) and both co-aggregation and cross-seeding between Aβ and hIAPP was investigated (Fan et al., 2024). These studies suggest that heterologous amyloid species could affect the aggregation of hIAPP, and that peptide inhibitors ultimately might have to be tested for cross-amyloid specificity.

2.5 Cytotoxic Mechanisms

The toxic property of hIAPP is linked to its misfolded and aggregated form. Soluble oligomers may interact with lipid bilayers, disrupt membrane organization, and induce permeability defects. Based on the results of Sepehri et al. (2021), oligomer toxicity seems to be structurally heterogeneous, with specific modes by which IAPP oligomers can interact with membranes.

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Membrane perturbation can also be further altered by chemical modification of hIAPP. The alkylation of the site was demonstrated to speed up self-assembly and improve the disruption of lipid membranes by Babych et al. (2021). This finding demonstrates that the aggregation rate and toxicity of the molecules can be modified at the same time, and the change of molecular structure is very small.

It is also possible that membrane damage does not occur only when the preformed oligomers are responsible for the damage but also during fibril growth. Elenbaas et al. (2023) showed the close relationship between fibril elongation and injury to the membrane. This observation broadens the therapeutic target to continuous aggregation reaction described by Table 1.

The hIAPP toxicity may eventually lead to a loss of β-cell homeostasis and lead to pancreatic dysfunction. Impaired clearance, misfolding and abnormal assembly, as well as cell stress, are highlighted as critical steps in the development of amyloid associated β-cell damage, which is reviewed (Bhowmick et al., 2022; Sevcuka et al., 2022). So the goal of therapy with peptide inhibitors should not merely be to remove visible fibrils, but rather to inhibit toxic pathways of assembly.

Table 1. Structural and Biophysical Determinants of hIAPP Aggregation and Toxicity

Determinant	**Role in hIAPP aggregation**	**Biological/structural consequence**	**Relevance to peptide inhibition**	**Key references**
Fibril polymorphism	hIAPP can assemble into structurally distinct fibril architectures	Produces heterogeneous amyloid assemblies while retaining conserved structural features	Conserved fibril regions may provide common recognition sites for peptide inhibitors	Cao et al. (2021); Li et al. (2022)
Primary nucleation	Initiates formation of aggregation-competent assemblies	Determines the early phase and lag period of amyloid formation	Peptides may bind monomeric hIAPP and suppress	Rodriguez Camargo et al. (2021)

	from soluble hIAPP		formation of initial nuclei	
Secondary nucleation	Existing fibrillar surfaces catalyze formation of additional aggregates	Amplifies production of potentially toxic intermediate species	Inhibiting fibril-surface interactions may reduce aggregate amplification	Rodriguez Camargo et al. (2021); Elenbaas et al. (2022)
Fibril elongation	Soluble hIAPP is incorporated at growing fibril ends	Promotes fibril growth and is associated with membrane perturbation	Fibril-end-binding peptides may act as molecular caps	Elenbaas et al. (2023)
Membrane interaction	Lipid interfaces facilitate hIAPP association and aggregation	Promotes membrane-active oligomers and membrane damage	Peptides may suppress membrane binding or membrane-catalyzed aggregation	Sepehri et al. (2021); Elenbaas et al. (2022)
Insulin and zinc	Modify hIAPP aggregation within the pancreatic environment	Influence amyloid formation and membrane damage	Candidate inhibitors should be tested under physiologically relevant conditions	Khemtemourian et al. (2021)
Metal-ion interactions	Metal ions can alter hIAPP	May modify aggregation and toxicity depending on	Metal-containing physiological	Roy et al. (2023)

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	aggregation pathways	the molecular environment	environments should be considered during inhibitor testing	
Aggregation kinetics	Toxicity varies across different stages of the aggregation process	Defines a temporal window of enhanced proteotoxicity	Inhibitors should be evaluated for effects on lag time, growth rate and intermediate populations	Plesner et al. (2026)

3. Principles of Peptide Inhibitor Design

3.1 Sequence-Based Rational Design

The design is based on sequence-based design, which makes use of the intrinsic molecular recognition property of hIAPP. The segments that tend to aggregate can be adopted as templates to initiate the search as they naturally interact with comparable parts of full-length hIAPP. But the use of unmodified self-recognition peptides directly is associated with the risk of co-aggregation. To achieve rational design, sequence modification must therefore occur that does not change the target recognition, but prevents productive β-sheet propagation.

Rani et al. (2025) is a recent example of this approach. Rationally designed hexapeptides were explored through molecular dynamics and other experimental methods, and the sequence variations were correlated with the modulation of hIAPP fibrillation. Rani et al. (2026) extended this idea by putting synergistic mutations at the amyloidogenic core and showing that simultaneous mutations of the residues in the core could yield a potent inhibitor.

Similarly, Kaur and Goyal (2024) applied computational screening and designing to discover new peptides which can reduce the hIAPP aggregation. The use of predicted binding, structure complementarity and aggregation propensity to prioritize sequences for experimental testing are illustrated with these approaches.

3.2 Structure-Based Peptide Design

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Structure-based design is based on 3D properties of the monomeric, oligomeric and fibrillar hIAPP. High resolution fibril structures have shed light on intermolecular interfaces that stabilize assemblies of amyloid structures. Conserved fibril-core features have also been observed in different polymorphs, making them potential structural targets for cryo-EM studies (Cao et al., 2021; Li et al., 2022).

A conformational change is likely to occur before mature fibrils are formed and an effective peptide can potentially bind to an exposed fibril edge, occupy an interface required for elongation, or interact with an oligomeric conformation. Another way to enhance selectivity is conformational restriction, which can minimize the energy cost of target recognition, as exemplified by β-hairpin peptide mimics that present residues at preorganized geometry for interfering with amyloid assembly (Lesma et al., 2021).

Another structure-guided approach is through the use of designed cross-amyloid inhibitors. Taş et al. (2022) identified supramolecular nanofiber co-assembling peptides which inhibit amyloids at the nanomolar scale. These systems do not stop an individual binding site, but instead force the amyloidogenic proteins into alternative assemblies, giving a different type of inhibition.

3.3 Physicochemical Parameters Governing Activity

The inhibitory activity of peptides is a balance of hydrophobic, electrostatic, hydrogen-bonding, steric and conformational effects. Hydrophobic contacts are crucial, as the hIAPP amyloid core has residues that contribute to nonpolar packing, but too much is bad for the tendency to aggregate. The hydrophobic/hydrophilic ratio of amphiphilic helix mimetics has been shown to strongly influence the effects on the aggregation of IAPPs by Tang et al. (2022), further supporting the importance of physicochemical balance.

Another design variable is charge. Incorporation of charged residues into amyloid-recognition sequences could interfere with the packing of β-sheets, enhance the solubility in water and induce electrostatic repulsions between peptide complexes (Kaur & Goyal, 2024; Rani et al., 2025). The placement of the charges, however, needs to retain a sufficient affinity towards the surface of the hIAPP.

Function is influenced by peptide length, too. Short peptides can have a good stability and be synthesized, but have a limited number of binding sites; long peptides have more binding sites but can be conformationally flexible or prone to self-aggregation. The results of rationally designed hexapeptides imply that relatively short peptide sequences can still possess enough recognition, provided that the composition of the residues is optimized. (Rani et al., 2025)

The stereochemistry is of special significance. Protease resistance and backbone structure of peptides containing D-amino acid sequences can be modified while the side-chain function

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remains unchanged. Roy and Paul (2022) have shown that chirality can be used as a structural and pharmacological design variable, as the D-peptide they described inhibited hIAPP aggregation and destabilized protofibrils.

3.4 Modification Strategies

It is possible to generate a more stable and functionally versatile inhibitor from a promising peptide by chemical modification (Table 2). The use of D-amino acid substitution is one of the most interesting options as it could enhance proteolysis resistance. Similarly, sequences that are retro-inverso or partially stereoinverted can maintain functional side-chain orientation, but make the sequence less susceptible to enzymatic attack.

Another way of achieving conformational restrictions is by cyclization. A rapid, continuous selection method was developed for generating cyclic peptide inhibitors of protein aggregation by Yang et al. (2025). All candidates resulting from such approaches may not be specific to hIAPP, but the methodology is an efficient way to screen large conformationally constrained peptide libraries.

Glycosylation is another promising modification that is now coming to the fore. The researchers in Zhang et al. (2025) found that the anti-aggregation and anti-toxicity effects of O-glycosylated peptides were observed. Glycosylation can influence the solubility, steric properties, intermolecular recognition, and aggregation propensity of peptides, which is a factor of interest for the development of hIAPP directed therapeutics.

Table 2. Modification strategies used to develop peptide-based inhibitors of hIAPP aggregation

Design strategy	**Molecular principle**	**Expected advantage**	**Major consideration**	**Representative reference**
Amyloid-core-derived peptides	Exploit sequence complementarity with aggregation-prone hIAPP regions	High target recognition and rational sequence design	Unmodified recognition sequences may themselves participate in aggregation	Roy & Paul (2022)

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Rationally designed short peptides	Introduce selected substitutions into short recognition sequences	Allows systematic optimization of interactions with hIAPP	Activity depends strongly on residue composition and position	Rani et al. (2025)
Synergistically mutated peptides	Combine multiple mutations within the amyloidogenic core	Cooperative modifications can enhance inhibition beyond isolated substitutions	Requires optimization of interacting residues rather than single-site changes	Rani et al. (2026)
β-Hairpin peptide mimics	Preorganize residues into conformationally constrained structures	Reduced conformational flexibility and improved interference with amyloid assembly	Structural geometry must remain compatible with the target	Lesma et al. (2021)
D-Peptides	Replace L-amino-acid stereochemistry with D-amino acids	Potentially improved proteolytic stability with anti-aggregation activity	Stereochemical alteration can modify target recognition	Roy & Paul (2022)
Cyclic peptides	Constrain the peptide backbone through cyclization	Increased conformational rigidity and potential metabolic stability	Appropriate ring geometry and target accessibility are required	Yang et al. (2025)

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Cross-amyloid inhibitory peptides	Redirect amyloidogenic interactions through controlled co-assembly	May interfere with multiple amyloid assembly processes	Cross-reactivity and biological specificity require evaluation	Taş et al. (2022)
Glycosylated peptides	Attach carbohydrate moieties to modify peptide properties	Can improve solubility and alter aggregation/toxicity	Modification position may influence molecular recognition	Zhang et al. (2025)
Peptidomimetics	Preserve peptide-like recognition while modifying the molecular scaffold	Expands chemical space and may improve metabolic stability	Biological compatibility and target specificity require validation	Maity (2023)

Further widened chemical space is provided by peptidomimetics. Selected peptidomimetics and their use against the mechanism of amyloid aggregation was reviewed by Maity (2023), who discussed the potential to preserve the peptide-like molecular recognition with enhancing metabolic stability. All these strategies suggest that the best inhibitors of the future might be engineered peptide-like molecules instead of straight, unmodified sequences. (Figure 3)

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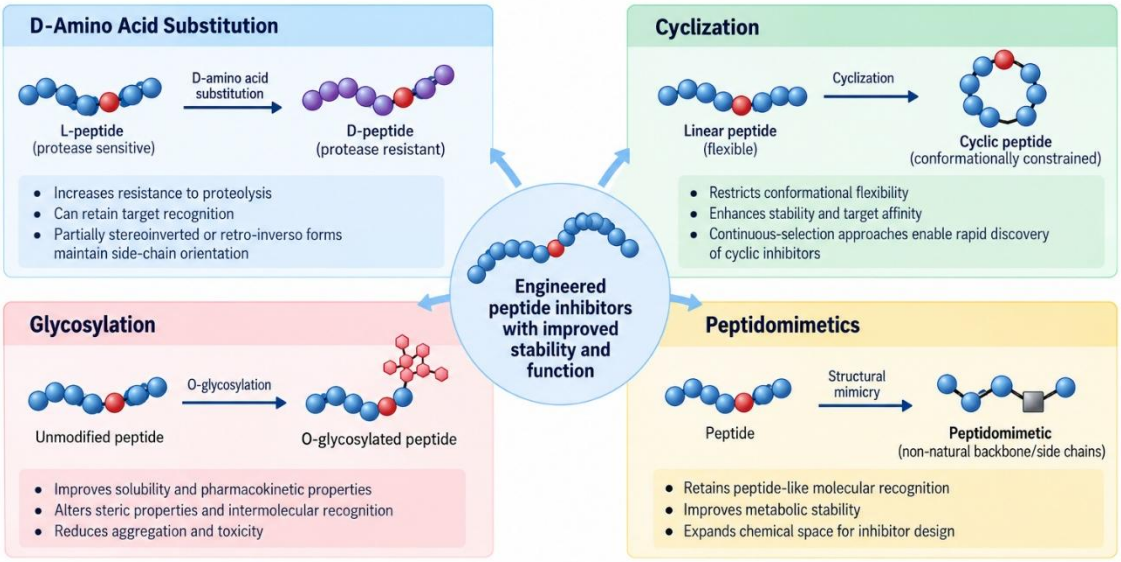


Figure 3. Chemical modification strategies of peptide-based inhibitors against hIAPP aggregation

4. Molecular Mechanisms of Peptide-Mediated Inhibition

4.1 Prevention of Primary Nucleation

Primary nucleation occurs when soluble hIAPP aggregates into initial nucleation sites. This stage can be inhibited by a peptide that binds to the monomeric hIAPP and prevents the exposure of the amyloidogenic residues, or the conformation of hIAPP becomes non-aggregation favorable.

Self-recognition sequences are of particular interest as they have the potential to interact with the same motifs that facilitate hIAPP–hIAPP interactions. These recognition elements can then be modified by rational mutations to become aggregation blockers. As shown in the studies of Kaur and Goyal (2024) and Rani et al. (2025), computational methods for sequence selection can be used to find short peptides that are predicted to disrupt the association of the hIAPPs.

An inhibitor which primarily inhibits primary nucleation should be expected to lengthen the lag phase of the aggregation. However, in later stages, primary nucleation inhibition may be less effective as hIAPP aggregation can be strongly influenced by secondary nucleation if it is possible to create fibrils.

4.2 Inhibition of Oligomer Formation

Soluble oligomers are particularly interesting therapeutic targets since the existence of intermediate species that are membrane active is related to hIAPP cytotoxicity. Peptides that are

able to interact with early oligomeric structures can inhibit the maturation, destabilize the interfaces between them, or steer them towards less toxic states.

The importance of oligomer targeting is further supported by the fact that IAPP oligomers have been shown to interact with membranes in different ways (Sepehri et al., 2021). Therefore, it is possible that the toxicity is not due to a single oligomeric structure. Ideally, peptide inhibitors should recognize general features or change the balance of oligomer populations.

This approach is indirectly supported by antibody evidence. Pathological hIAPP assemblies are recognized by prototibril-specific antibodies (Bortoletto et al., 2022), and in experimental models, aggregate-directed antibodies help the protection of β-cells (Wirth et al., 2023). These results showed that oligomer recognition of pathological conformations is possible and give a conceptual point of reference for the recognition of peptide-based oligomers.

4.3 Inhibition of Fibril Elongation

After the formation of nuclei and/or fibrils, elongation takes place by the attachment of soluble hIAPP molecules to the growing ends of the fibrils. A peptide attached to these terminal sites can be a molecular cap that blocks further extension.

This mechanism is particularly important as fibril elongation has been linked to membrane damage (Elenbaas et al., 2023). Thus, preventing elongation will also decrease both amyloid deposits and continued membrane damage.

This would be an appropriate approach if there is structural similarity between the fibril cores. Conserved features were found in patient-seeded hIAPP fibrils despite polymorphism by Cao et al. (2021) and by Li et al. (2022) in another fibril polymorph. Peptides targeted to similar terminal structural motifs might then retain their activity for several fibillar conformations.

4.4 Remodeling of Preformed Amyloid Fibrils

Ideal therapeutic agent: not only should it inhibit new aggregation, but should also modify existing pathological assemblies. Fibril remodeling by peptides can include destabilization, fibril fragmentation, disruption of intermolecular contacts or changes to fibril structure.

Roy and Paul (2022) found that their hIAPP-core derived D-peptide not only inhibited aggregation of hIAPP protofibrils, but also destabilized protofibrils. Likewise, Abioye et al. (2022) have studied the disaggregation of IAPP fibrils by TNGQ, and found that short peptide sequences can have an effect on preformed amyloid structures.

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However, fibril destabilisation needs to be done with great care. Mature fibrils may be broken down to produce more small and diffusible toxic species, theoretically. Remodelling should therefore be evaluated in conjunction with oligomer abundance, membrane damage, and cytotoxicity, rather than just based on a decrease in fibril mass.

4.5 Protection Against Membrane-Mediated Toxicity

One of the most significant effects of the misfolding of hIAPP is the disruption of the membrane. Lipid interfaces can promote aggregation, enhance nucleation, and produce membrane-interacting intermediates that promote peptide aggregation. Elenbaas et al. (2022) presented that secondary nucleation is a crucial process in hIAPP aggregation when using membranes as a catalyst, and Sepehri et al. (2021) revealed several mechanisms by which IAPP oligomers interact with membranes.

Peptide inhibitors can do this indirectly by decreasing the amount of toxic oligomers, or directly by binding to membrane binding interfaces. The ideal inhibitor should inhibit the formation of membrane active conformations without destabilizing the lipid bilayer itself.

A crucial study that emphasizes the evaluation of this property is the work of Babych et al. (2021) on the self-assembly and membrane perturbation of a hIAPP alkylated at the site. This shows that seemingly subtle changes in the structure of the peptide can have a dramatic impact on their toxicity to membranes.

4.6 Suppression of β-Cell Toxicity

Preservation of the viability and function of the β-cells is the ultimate goal of therapy aimed against anti-hIAPP. If toxic oligomers are not reduced or inflammatory pathways are not modified or membrane damage is not reduced then reduction of the amyloid signal is not sufficient (Table 3).

Studies with antibodies have shown the therapeutic significance of the use of aggregates. Bortoletto et al. (2022) explored the role of protofibril-specific antibodies in detection and treatment of hIAPP, and Wirth et al. (2023) demonstrated protective effects of an antibody against pathological IAPP aggregates in T2DM-models. Similarly, Vogt et al. (2021) found beneficial effects with an anti-IAPP mAb in an experimental model of diabetes.

The evaluation of peptide inhibitors should then go beyond aggregation kinetics to the integrity of the membranes, the viability of the β-cells, the oxidative damage, the stress caused to the cells, the insulin-secretory function, and recovery following amyloid challenge (Figure 4). The best candidates will be those that minimize biochemical aggregation and biological toxicity.

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Table 3. Mechanisms of Peptide-Mediated Inhibition Along the hIAPP Aggregation Pathway

Target stage	Pathological process	Proposed peptide action	Expected outcome	Supporting references
Primary nucleation	Soluble hIAPP forms aggregation-competent nuclei	Bind monomers, mask amyloidogenic regions or stabilize non-aggregating conformations	Delayed nucleation and prolonged lag phase	Kaur & Goyal (2024); Rani et al. (2025)
Oligomer formation	Early assemblies mature into potentially membrane-active oligomers	Bind or destabilize oligomeric interfaces and redirect assembly	Reduced accumulation of toxic oligomeric species	Sepehri et al. (2021); Bortoletto et al. (2022)
Secondary nucleation	Existing fibril surfaces catalyze generation of additional aggregates	Interfere with fibril-surface-mediated nucleation	Reduced amplification of toxic aggregates	Rodriguez Camargo et al. (2021); Elenbaas et al. (2022)
Fibril elongation	Monomers add to fibril termini	Bind fibril ends and function as molecular caps	Reduced fibril extension and amyloid accumulation	Elenbaas et al. (2023)
Preformed fibrils	Established protofibrils/fibrils persist after formation	Destabilize or remodel existing assemblies	Formation of altered or less fibrillar assemblies	Roy & Paul (2022); Abioye et al. (2022)

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Membrane-associated aggregation	hIAPP species interact with lipid interfaces	Reduce membrane-active species or compete with membrane interactions	Preservation of membrane integrity	Sepehri et al. (2021); Elenbaas et al. (2022)
β-Cell toxicity	Pathological hIAPP assemblies contribute to cellular dysfunction	Reduce toxic aggregate burden and downstream cellular injury	Improved β-cell viability and functional preservation	Bortoletto et al. (2022); Wirth et al. (2023)

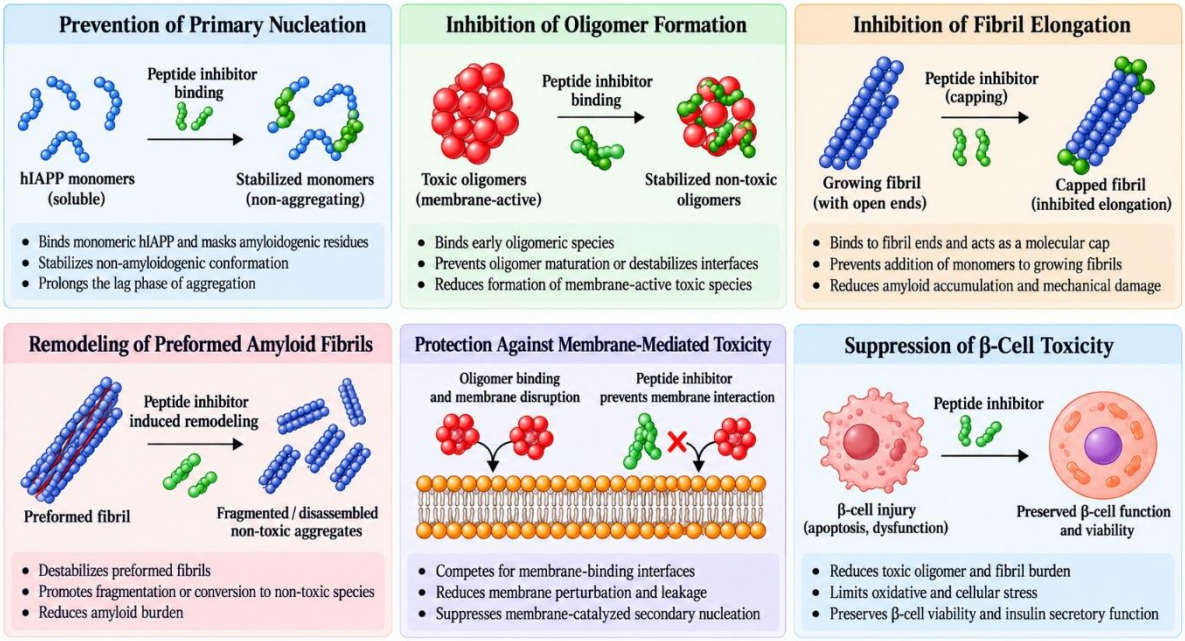


Figure 4. Major mechanisms through which peptide inhibitors interfere with hIAPP aggregation and toxicity

5. Comparative Evaluation of Reported Peptide Inhibitors

5.1 Reported Peptide Sequences and Their Target Regions

The literature on peptide-based hIAPP inhibitors can be divided into a number of conceptually different classes of molecules. These include self-recognition peptides derived from the amyloid core of hIAPP, β-hairpin mimics, D-peptides, rationally mutated short peptides, cross-amyloid

inhibitors, cyclic peptides, glycosylated peptides, and peptides found in nature that have anti-amyloid activity.

Lesma et al. (2021) showed that aggregation of hIAPP can be reduced by β-hairpin peptide mimics. They are conformationally constrained inhibitors, an architecture that is very different from the more flexible linear inhibitors, and provide an example of how preorganization can aid the inhibition of amyloid assembly.

Roy and Paul (2022) found an hIAPP amyloid-core derived D-peptide that was able to block aggregation and destabilize protofibrils. This design is a mix of both sequence recognition and stereochemical modification, which could be useful for both target specificity and proteolytic stability.

Rani et al. (2026) studied synergistic mutations in the amyloidogenic core of human amylin, while Rani et al. (2025) investigated rationally-designed hexapeptides. These studies collectively show the direction of research from empirical sequence modification to systematic engineering of interacting residues.

Another strategy was developed by Taş et al., (2022) that designed peptides can display nanomolar cross amyloïd inhibition by supramolecular nanofiber co-assembly. These inhibitors do not just prevent hIAPP binding sites, but they seem to divert aggregation in a controlled manner by co-assembling with hIAPP.

More modern techniques are cyclic and chemically modified peptides. Rapid discovery of cyclic peptide protein-aggregation inhibitors via continuous selection was described by Yang et al. (2025) and O-glycosylated peptides were demonstrated to be effective at inhibiting aggregation and toxicity of hIAPP by Zhang et al. (2025).

5.2 Comparative Inhibitory Performance

It is hard to directly rank the reported inhibitors as there are many differences between the conditions of the experiments. The apparent inhibitory potency can be affected by concentration of hIAPP, buffer composition, temperature, lipid content, agitation, peptide to hIAPP ratio, aggregation time, and readout method. Thus, it is not necessarily concluded that the stronger an inhibitor is in one ThT assay the better it will be in the other assayed under different conditions.

However, there are a number of mechanistic tendencies (Table 4). Amyloid-core-derived peptides are highly sequence specific, but must be modified to prevent self-aggregation. Molecular recognition can be maintained with D-peptides, which may be more stable, while β-Hairpin mimics allow for preorganization (Lesma et al., 2021), and rationally mutated short peptides enable precise control of individual residue contributions (Rani et al., 2025, 2026).

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Cross-amyloid peptides might have more widespread inhibitory effects, but should be thoroughly investigated with regard to specificity and biological interactions (Taş et al., 2022). Cyclic peptides offer conformational restriction and potential resistance to enzymatic degradation, along with glycosylated peptides, which offer steric and solubility changes that can also affect aggregation and toxicity (Yang et al., 2025; Zhang et al., 2025).

Table 4. Comparative Characteristics of Representative Peptide-Based Anti-hIAPP Strategies

Study	Peptide/inhibitor approach	Main design feature	Reported anti-hIAPP effect	Distinctive contribution
Lesma et al. (2021)	β-Hairpin peptide mimics	Conformationally constrained peptide architecture	Decreased hIAPP aggregation	Demonstrated the utility of β-hairpin-based conformational restriction
Roy & Paul (2022)	Amyloid-core-derived D-peptide	Core recognition combined with stereochemical inversion	Prevented aggregation and destabilized protofibrils	Combined preventive and remodeling activity
Abioye et al. (2022)	TNGQ tetrapeptide	Very short peptide sequence	Investigated disaggregation of IAPP fibrils	Demonstrated that short peptides can influence preformed fibrillar structures
Taş et al. (2022)	Designed cross-amyloid peptides	Supramolecular nanofiber co-assembly	Produced potent cross-amyloid inhibitory activity	Introduced co-assembly as an alternative inhibitory mechanism

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Kaur & Goyal (2024)	Computationally designed peptides	In silico sequence design and prioritization	Identified candidates for mitigation of hIAPP aggregation	Demonstrated computationally guided peptide discovery
Rani et al. (2025)	Rationally designed hexapeptides	Sequence-level optimization supported by molecular dynamics and experiments	Modulated hIAPP fibrillation	Integrated computational and experimental peptide evaluation
Yang et al. (2025)	Cyclic peptide inhibitors	Conformational restriction through cyclization	Identified aggregation-inhibitory cyclic peptides through continuous selection	Provided a rapid discovery platform for constrained peptides
Zhang et al. (2025)	O-glycosylated peptides	Glycosylation-based chemical modification	Reduced hIAPP aggregation and toxicity	Connected chemical modification with both anti-aggregation and anti-toxicity effects
Rani et al. (2026)	Mutated amyloid-core peptide	Synergistic mutations within the amyloidogenic core	Generated a potent inhibitor of human amylin fibrillation	Demonstrated cooperative effects of rational core mutations

5.3 Effects on Aggregation Kinetics

The aggregation kinetic and not the end point fibril measurements alone give more mechanistic information. Inhibitors can lengthen the lag phase, slow the apparent elongation rate, inhibit secondary nucleation, or decrease the quantity of fibrillar material.

This distinction is relevant because the toxicity of hIAPP is related to aggregation dynamics with a temporal characteristic. The aggregation kinetics have been used to establish a window of IAPP proteotoxicity by Plesner et al. (2026) and secondary nucleation has been proved as a critical pathway for the production of toxic aggregates by Rodriguez Camargo et al. (2021).

Therefore, it is preferable to compare peptide inhibitors through kinetic modeling instead of being compared through single point fluorescence value (Figure 5). Modest change in final fibril load and strong suppression of secondary nucleation may be of greater biological value than a greater decrease in mature fibril fluorescence.

5.4 Effects on Fibril Morphology

The results indicate that the peptide inhibitors do not simply disrupt dyes, but also affect the pathways of assembly. Electron microscopy, atomic force microscopy and other techniques can provide information on whether treatment shortens long fibrils, creates shorter structures, induces amorphous aggregates or destabilises the protofibrils.

The D-peptide in the Roy and Paul study (2022) destabilizes protofibrillar structures as well as preventing initial assembly, suggesting that the peptide action can be broader than just preventing initial assembly. Likewise, the disaggregation activity of TNGQ reported by Abioye, et al., 2022 shows the potential to affect the existing fibrillar material using short peptides (Figure 5).

The hIAPP polymorphism should be taken into account during the structural interpretation. Cao et al. (2021) and Li et al. (2022) demonstrated that several different fibril architecture can have common substructures. So, it is not always the case that a so-called altered morphology means that the amyloidogenic molecular organization is gone.

5.5 Cytoprotective Effects

Biological protection is not only a more meaningful endpoint than fibril suppression alone, but it is a more therapeutic endpoint to consider. An inhibitor that does not decrease ThT fluorescence would still allow for the possibility of forming soluble toxic oligomers, while another compound would allow for good β-cell function without stopping the formation of amyloid (Figure 5).

This is especially relevant with respect to toxicity mechanisms involving membranes. Fibril elongation has been associated with membrane damage (Elenbaas et al., 2023), and the IAPP oligomers can interact with membranes via two different pathways structurally (Sepehri et al., 2021).

Combination of biophysical and biological endpoints was shown by Zhang et al. (2025) to be valuable as O-glycosylated peptides were found to suppress both hIAPP aggregation and toxicity.

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Antibody studies against aggregates also show that molecular recognition of pathological hIAPP can also lead to β-cell protection (Bortoletto et al., 2022; Wirth et al., 2023).

5.6 Key Trends Across Published Studies

There are a number of uniform rules that appear throughout the literature on peptide inhibitors. Rational basis for target recognition: Sequence complementarity to amyloidogenic hIAPP regions. Second, unmodified self-recognition sequences typically need to be structurally modified for them not to participate in aggregation themselves. Third, control of peptide geometry can be enhanced by conformational restriction, either achieved by β-hairpin formation or by cyclisation. Fourthly, stereochemical inversion can be used to increase proteolytic resistance. Fifth, chemical modification like glycosylation may cause a simultaneous change in solubility, recognition and biological stability.

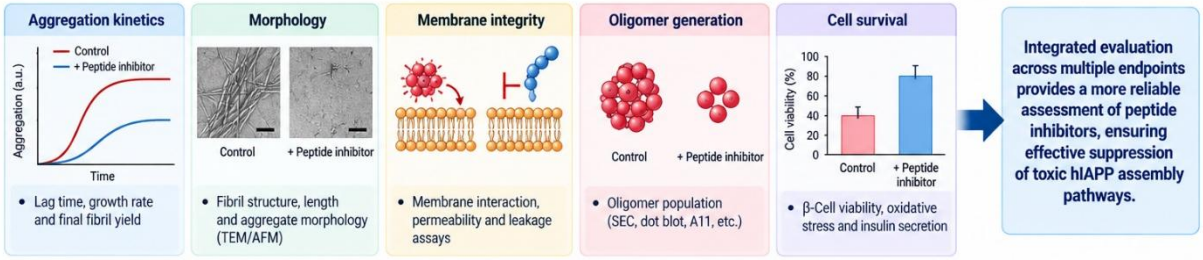


Figure 5. The multi-endpoint evaluation strategies for peptide inhibitors of hIAPP aggregation

Peptide inhibitors are distinct from small molecules, natural compounds, chaperones and nanomaterials primarily in their ability to recognize the regions of the amyloidogenic hIAPP by sequence. Small molecules typically interact with aggregation via noncovalent binding and kinetic effects (Tang et al., 2021; Taylor et al., 2025); natural compounds interact primarily through stereospecific, hydrophobic or hydrogen-bonding interactions (Garcia-Vinuales et al., 2022; Xu et al., 2021; Mahboob et al., 2023). In this case, non-amyloidogenic states are stabilized by chaperones such as prefoldin, while surface mediated interactions, curvature or chirality of nanomaterials are known to influence aggregation. Peptides, therefore, provide a more expansive room for rational optimization (of the sequence level) to inhibit hIAPP

6. Therapeutic Potential of Peptide Inhibitors

Peptide inhibitors offer multiple benefits for use as anti-hIAPP drugs. Their sequences can be optimized for specific recognition of amyloidogenic hIAPP regions and stereochemical and chemical modifications allow affinity, solubility, conformational stability, and resistance to degradation to be systematically optimized. The successful application of D-peptides, β-hairpin

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mimics, rationally designed hexapeptides, cross amyloids inhibitory peptides, and glycosylated derivatives has shown that the recognition of hIAPP can be achieved by different molecular architectures (Lesma et al., 2021; Roy & Paul, 2022; Rani et al., 2025; Zhang et al., 2025). The selection of cyclic peptides may be extended to enrich the chemical space for the discovery of constrained high-affinity scaffolds (Yang et al., 2025).

Translation is still an incomplete process due to pharmacokinetic barriers. Rapid proteolysis, renal clearance, and low absorption, as well as insufficient access to pancreatic islets and the extracellular or intracellular location of the pathological hIAPP assembly, may be present in linear peptides. Inversion, cyclization, glycosylation, conjugation or incorporation into nanostructured delivery systems could all help to enhance their stability and tissue exposure. Nanostructured approach: The use of a nanochaperone system to inhibit the aggregation of hIAPP is a broad example of how nanostructuring can be used. But any delivery method should maintain the recognition of peptides, not trigger unwanted immunogenicity and exhibit a meaningful protection of β-cells in physiologically relevant conditions.

7. Challenges and Current Limitations

One of the disadvantages of the existing literature is that there is no standard set of conditions for comparison of peptide inhibitors. hIAPP aggregation is highly sensitive to peptide concentration, buffer composition, pH, salts and metal ions, membranes, insulin and experimental handling. Different aggregation protocols can thus generate widely varying kinetic profiles. The behavior of hIAPP can change due to the presence of physiologically relevant components such as insulin, zinc, copper and lipid membranes, which can also influence the efficiency of hIAPP inhibitors (Khemtemourian et al., 2021; Roy et al., 2023). Moreover, fibril polymorphism and structural heterogeneity may make the assumption that a peptide that is optimized for one conformational state will be similarly effective in all pathological assemblies problematic.

Another constraint is the discrepancy between the biophysical inhibitory and therapeutic effect. The majority of candidate inhibitors are tested using fibril-sensitive assays, such as fluorescence or structural analysis, but the suppression of mature fibrils is not always correlated with the suppression of toxic oligomers. Mechanistic evaluation should not only include endpoint amyloid measurements, but also account for the importance of secondary nucleation, membrane-associated aggregation, fibril elongation and the importance of a temporally defined proteotoxicity (Rodriguez Camargo et al., 2021; Elenbaas et al., 2023; Plesner et al., 2026). The pharmacokinetics, delivery of the drug to the pancreas, immunogenicity, metabolic stability, and efficacy in clinically relevant models are relatively underdeveloped (Table 5).

Table 5. Translational Challenges and Future Directions for Peptide-Based hIAPP Inhibitors

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Current challenge	**Why it matters**	**Proposed strategy**	**Desired outcome**	**Relevant references**
Proteolytic degradation	Linear peptides may have limited biological stability	D-amino acids, cyclization and peptidomimetic design	Increased resistance to enzymatic degradation	Roy & Paul (2022); Maity (2023)
Conformational flexibility	Flexible peptides may lose favorable binding geometry	β-Hairpin or cyclic architectures	More stable target-recognition conformations	Lesma et al. (2021); Yang et al. (2025)
Limited solubility/stability	Physicochemical properties may restrict biological application	Glycosylation and other chemical modifications	Improved physicochemical and biological performance	Zhang et al. (2025)
Rapid clearance and delivery limitations	Adequate concentrations may not reach pancreatic islets	Nanocarriers, nanochaperones and targeted delivery systems	Improved exposure and pancreatic localization	Niu et al. (2021)
hIAPP structural heterogeneity	Multiple fibrillar conformations may limit single-structure targeting	Target conserved amyloid-core determinants	Activity across heterogeneous pathological assemblies	Cao et al. (2021); Li et al. (2022)
Complex physiological environment	Insulin, zinc, metals and membranes alter	Test inhibitors under increasingly	Greater predictive validity of	Khemtemourian et al. (2021);

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	aggregation behavior	physiological conditions	preclinical results	Roy et al. (2023)
Overreliance on fibril endpoints	Reduced fibril signal does not necessarily establish reduced toxicity	Integrate kinetic, oligomer, membrane and cell-based endpoints	Demonstration of genuine anti-proteotoxic activity	Elenbaas et al. (2023); Plesner et al. (2026)
Limited β-cell validation	Biophysical inhibition may not translate into cellular protection	Employ β-cell and disease-relevant experimental models	Demonstrated preservation of β-cell viability and function	Wirth et al. (2023)
Persistence of pathological hIAPP	Inhibition may not eliminate already accumulated pathological material	Combine aggregation inhibition with clearance approaches	Prevention plus removal of pathological species	Liu et al. (2023)
Limited translational evidence	Molecular efficacy alone is insufficient for therapeutic development	Pharmacokinetic, safety and in vivo validation	Progression toward preclinical therapeutic candidates	Bortoletto et al. (2022); Wirth et al. (2023)

8. Future Perspectives

The literature on hIAPP inhibition shows that it is shifting from screening to mechanism-driven molecular design. The transition is significant as it relates to a dynamic event which includes monomer rearrangement, nucleation, oligomer maturation, fibril elongation and membrane associated toxicity of hIAPP. Structural studies have revealed that there are common aggregation determinants among the different species, as well as common core features of the distinct fibril polymorphs, meaning that inhibitors with success must recognize common aggregation

determinants among structurally diverse species (Cao et al., 2021; Li et al., 2022). Toxic aggregate production is also shown to be influenced by surface-catalyzed secondary nucleation, as well as fibril elongation being related to membrane damage, from kinetic evidence (Rodriguez Camargo et al., 2021; Elenbaas et al., 2023). The design of future peptides should therefore aim at multiple stages, not just the mature fibril stage.

Rationally designed short peptides are promising due to their potential to be rationally designed to interact with the amyloidogenic core of hIAPP. Recent studies have shown that recognition motifs can be modified into inhibitors instead of aggregation partners. Rationally designed hexapeptides have been reported by Rani et al. (2025), which modulate hIAPP fibrillation by interacting with the protein via molecular interactions that are supported by experiments, and by Rani et al. (2026) who report on synergistic mutations in the amyloidogenic core that lead to potent inhibitors, validated both computationally and experimentally. Similarly, Kaur and Goyal (2024) employed in silico design to identify the peptide candidates that can reduce the aggregation of hIAPP. These studies together provide support for the optimization of the hydrophobic contact, steric complementarity, charge distribution and disruption of β-sheet all at once.

The second direction is that of development of conformationally constrained and protease-resistant peptide architectures. β-Hairpin mimics were developed to reduce the aggregation of hIAPP, and preorganized scaffolds have proven to be an efficient way to interfere with amyloid assembly (Lesma et al., 2021). Dpeptides are attractive due to the ability to enhance the proteolytic stability of peptides without compromising the recognition of amyloid surfaces by inverting the chirality. Roy and Paul (2022) reported an hIAPP amyloid-core derived D-peptide, which prevented aggregation and destabilized protofibrils, as examples of the potential for inhibitors that suppress assembly and remodel existing aggregates. Cyclic peptides can still further limit conformational flexibility and enhance the biological stability. Rapid Selection Strategy reported by Yang et al. 2025 may help to shorten the optimization process for cyclic peptide discovery platforms.

Multifunctionality should also be a key focus for future therapeutic development. Besides slowing down fibril formation, hIAPP pathology involves membrane perturbation, oxidative stress, proteostatic imbalance, and inflammatory injury, which make it clear that there is a lack of complete protection (Milardi et al., 2021; Bhowmick et al., 2022). The design of cross-amyloid inhibitors, based on supramolecular co-assembly, shows that peptide systems can also be potent anti-amyloid drugs (Taş et al., 2022). Other approaches involve the use of O-glycosylated peptides, which can be useful since glycosylation can alter the solubility, steric shielding, intermolecular interactions, aggregation and toxicity (Zhang et al., 2025). These changes could be combined with targeting motifs or delivery systems to enhance the pancreatic localization and pharmacokinetic properties.

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However, delivery and validation issues will need to be resolved for translation to take place. Peptides possess low enzymatic resistance, rapid clearance and low oral bioavailability. Nanostructured carriers and nanochaperone approaches could help prevent the therapeutic cargo from degradation and limit the local interactions between the aggregation-prone proteins (Niu et al., 2021). Additionally, extracellular clearance approaches indicate that clearance of aggregation-prone hIAPP may be used in conjunction with inhibition approaches (Liu et al., 2023). Antibodies against the β-cell targeting species generated by the same antibodies that have beneficial effects on β cells in disease models serve as a translational reference for peptide therapeutics (Bortoletto et al., 2022; Wirth et al., 2023).

Another goal is the employment of biologically realistic experimental models. The timing of aggregation and toxicity is important as interventions might be effective only in a certain proteotoxic window (Plesner et al., 2026). Future studies must include kinetic assays, structural characterization, membrane models, β-cell systems, and in vivo testing, in addition to the use of ThT fluorescence. In particular, comparisons under conditions where insulin, zinc, lipids, and metal ions were present in the condition are important, since these affect the behaviour of hIAPP in physiological conditions (Khemtemourian et al., 2021, Roy et al., 2023).

The most promising future approach will probably be a rational design, stabilization of the conformation, chemical modification, targeted delivery, and mechanism-based biological testing. While computational tools can help to generate candidates, experimental validation is important, as binding affinity does not directly translate to the suppression of toxic intermediates. Optimization of the next generation of anti-hIAPP peptides should not only be aimed at the ability to inhibit fibril formation, but at the ability to reduce the toxicity of the oligomers, preserve membrane integrity, and demonstrate β-cell protection, whilst also being resistant to proteolysis. With these properties, peptide inhibitors would be one step further to becoming viable drugs for type 2 diabetes.

9. Conclusion

The concept of peptide-based inhibitors of HIP aggregation has evolved from an anti-amyloid strategy to a mechanistically driven therapeutic strategy. The available evidence indicates that the toxicity of hIAPP is not solely contributed by mature fibrils but also by transient oligomers, secondary nucleation, fibril elongation, membrane interactions and the overall proteostatic environment. This complexity is why effective inhibitors need to have more than just a reduction on end-point fibril formation. Complementary approaches to interrupting different stages in the aggregation pathway exist for rationally designed short peptides, β-hairpin mimics, D-peptides, cross-amyloid inhibitors, cyclic peptides and chemically modified peptide scaffolds.

Recent studies have shown that targeted mutation in the amyloidogenic core to enhance inhibitory activity and stereochemical inversion, cyclization and glycosylation to increase structural stability and biological activity are possible. However, there are still significant translation hurdles to overcome such as proteolytic degradation, bioavailability, delivery to pancreatic islets, heterogeneous hIAPP conformers and proof of protection in physiologically relevant systems. Therefore, future research should involve kinetic analysis, structural characterization, models of the membrane, β-cell assays, and in vivo validation.

The combination of targeted delivery, mechanism-based peptide design, and stability-enhancing chemical modifications has the greatest potential to lead to therapeutic innovation. The most promising peptides for moving from experimental agents to clinically significant type 2 diabetes treatments are those that simultaneously inhibit the formation of toxic oligomers, preserve membrane integrity, resist degradation, and maintain functionality of β-cells.

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