



Synthetic peptide scaffolds as ion channels and molecular carriers

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Transmembrane ion exchange controls biological functions and is essential for life. Over the years, a great variety of nature-inspired artificial ion channels and carriers have been synthesized to control and promote ion exchange across biological membranes. In this context, peptides emerged as ideal scaffolds for synthetic ion channels due to their biocompatibility, accessibility and chemical versatility. Peptides have already shown their potential for the construction of a range of synthetic ion transporters either alone or in combination with other molecular scaffolds. Among the great diversity of peptide-based ion transporters, we can find key examples of single-molecule and supramolecular transmembrane ion channels and ionophores. Peptide scaffolds have also found great potential for the transmembrane delivery of biomolecular cargos such as nucleic acids and proteins. This review covers some of the most relevant advances in the peptide-based ion transport field from the last few years.

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Introduction

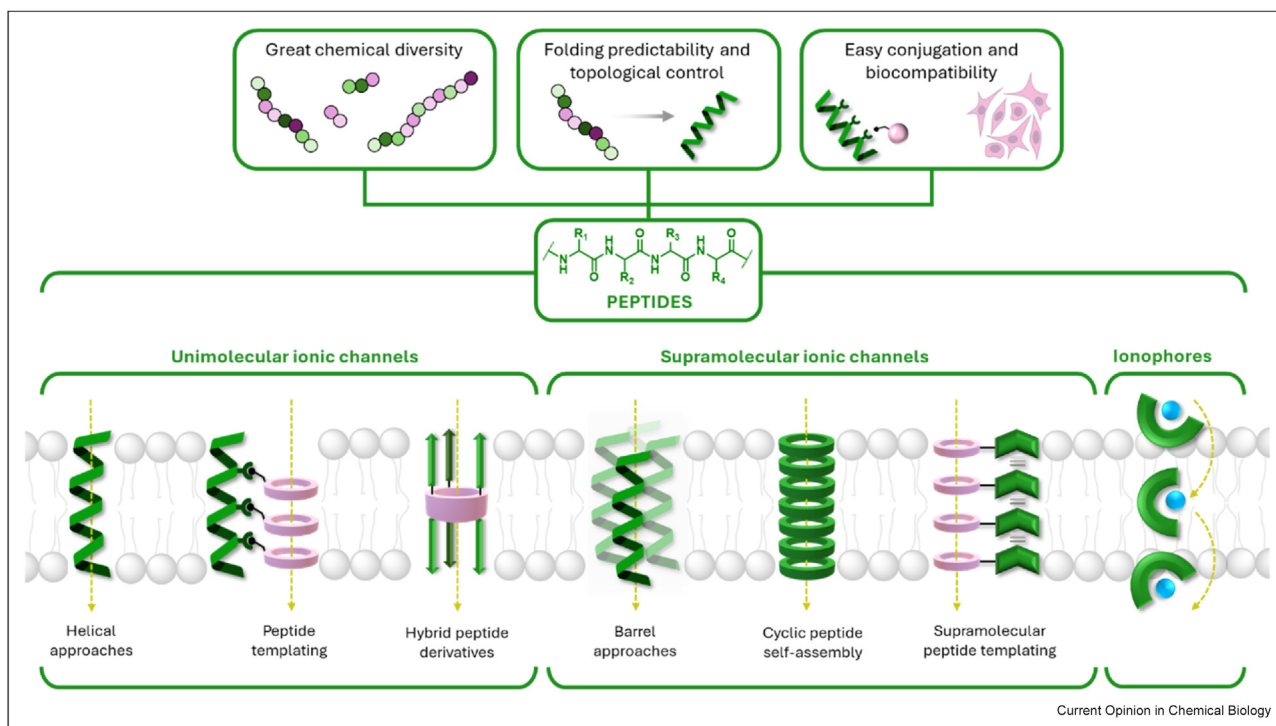
Transmembrane ion transport is a key function for sustaining life. The exchange of Na^+ , K^+ , Ca^{2+} and Cl^- among other ions controls biological functions such as metabolism, regulation of osmotic balance and pH, and signal transduction [1]. The malfunction of these ion transport processes can lead to cystic fibrosis, epilepsy or cardiovascular diseases [2,3]. In nature, a great variety of proteins are embedded in cell membranes to regulate

the selective ion transport across phospholipid bilayers. Most of these proteins are ion channels that facilitate the ion migration across membranes lowering the activation energy needed for ion desolvation [4]. Another family of ion transporters are ionophores, liposoluble molecules that bind and shuttle ions across the cell membrane by reducing the hydrophilicity of solvated ions [5]. Over the last few years, a great effort has been made to design and synthesize new artificial ion channels and carriers. Protein nanopores with the ability to conduct ions have been designed and exploited mainly as molecular sensors [6]. On the other hand, a wide diversity of synthetic ion transporters was designed over the last years by bottom-up approaches [7]. Simple and structurally robust molecules with tuneable transmembrane transport properties are emerging as attractive targets due to their potential applications in biomedicine [1]. Peptides show unique properties for this purpose: 1) synthetic accessibility with excellent chemical diversity; 2) folding predictability and topological control [8]; and 3) biocompatibility and easy conjugation to other complex molecules [9].

Since the early works from Besche's group with synthetic β -helical peptide ion channels [10], a range of peptide scaffolds have been described for peptide-based ion transporters (Figure 1). De Santis and collaborators introduced the use of polyproline peptides with alternating *L/D* chirality as ion channels [11,12]. DeGrado's group reported the synthesis of amphiphilic α -helical peptides that acted as proton channels [13]. Voyer and collaborators combined the versatility of α -helical peptides with the ion-binding ability of crown ethers to assemble aligned templates as synthetic ion channels that have also inspired multiple recent synthetic designs (Figure 3a) [9,14]. Matile's group pioneered supramolecular channels composed of a polybisphenol scaffold modified with short peptide chains as artificial beta-barrel ion channels [15,16]. Gokel and collaborators developed amphiphilic ion transporters based on heptapeptides linked to alkyl chains that self-assembled in pores for Cl^- -selective transport [17,18]. Granja's and Ghadiri's groups introduced self-assembled cyclic *D*, *L*-peptide nanotubes as selective ion transporters (Figure 4a) [19–21].

In recent years, the design of new peptide-based ion transport systems has continued to grow and diversify.

Figure 1



Advantages of peptide-based transmembrane transporters and general design approaches. Peptide moieties (in green) can promote the translocation of analytes on their own or in combination with other molecular entities (pink) by generating unimolecular or supramolecular ion channels or by carrying ions through membranes as ionophores.

Inspired by natural systems or through *de novo* designs, many groups have reported new ion channels or carriers that can efficiently transport ions across membranes. In this review, we cover a selection of recent peptide-based ion transporters, highlighting the role of the peptide scaffolds in the system. Not only fully peptide-based systems are included, but we also select examples of peptide backbones combined with other structural motifs, such as macrocycles. In some examples, peptides act as the transporting functional units, while in others they work as templating scaffolds for various ion transporter units or as "molecular glue" to promote higher-order supramolecular aggregates. In this short review, we have grouped transmembrane transporters according to their transport mechanism (e.g., peptide-based ion channels or ionophores). Ion channels are also divided into single-molecule channels and supramolecular channels. In the last section, we include a brief mention of peptide-based carriers to showcase the potential of these scaffolds to transport larger biomolecular cargos.

Peptide-based ion channels

Single-molecule systems for ion transport

The high structural diversity of natural nonribosomal peptides allows a wide range of biological activities. For

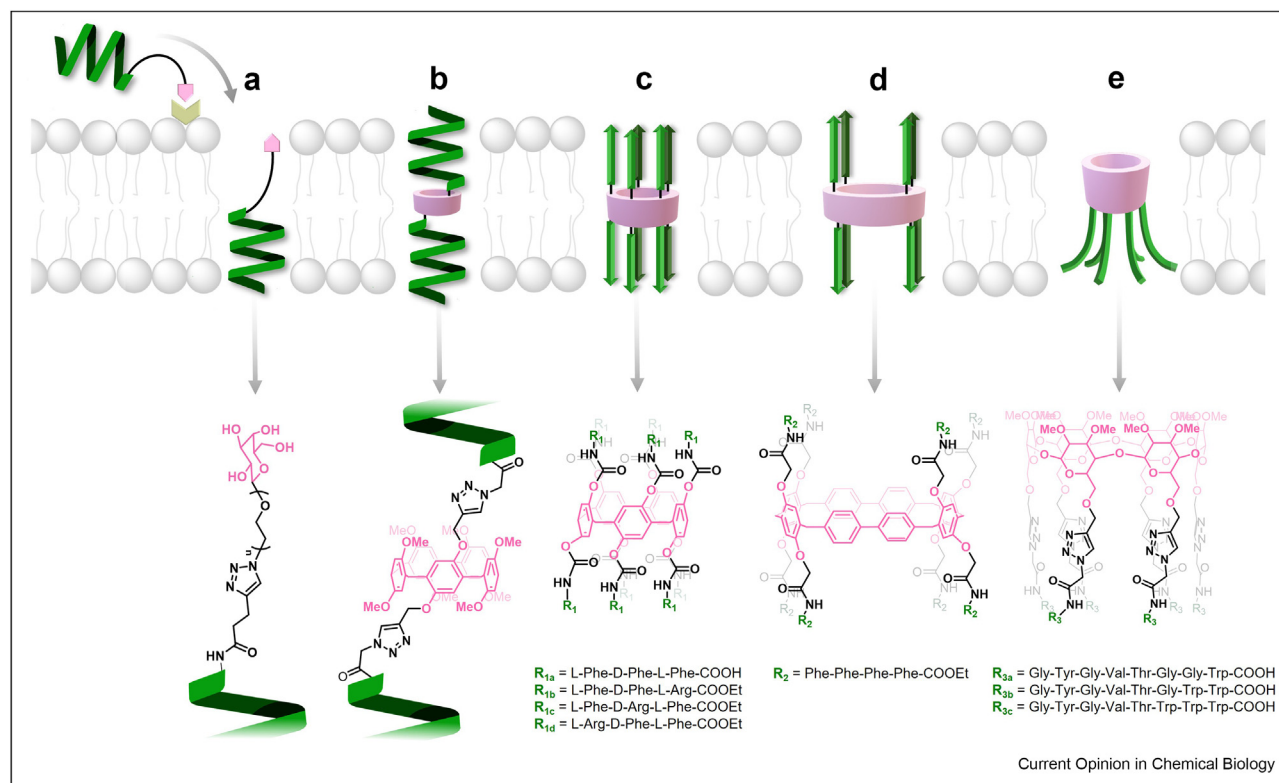
example, polytheonamide B and gramicidin A (gA) act as ion channels across phospholipid bilayers and thus they have inspired the design of simple peptide-based ion transporters [22,23]. Polytheonamide B folds in a β -helical conformation in lipid bilayers generating a single-molecule channel that can transport monovalent cations. Inoue and colleagues developed a polytheonamide artificial analogue with structural simplifications to facilitate its synthesis that emulated its biological functions [24]. The gA protein adopts a β -helical conformation that, once inserted in cell membranes, can form a head-to-head dimer to generate a transmembrane channel that allows the transport of monovalent cations (selectivity: $\text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+ > \text{Li}^+$) [25,26]. It should be noted that the dimer can also adopt a β -double helix without channel properties. gA disturbs ion homeostasis and exerts both antimicrobial and cytotoxic effects. Hou's group has recently engineered a gA surrogate by adding a galactose moiety, which is recognized by the asialoglycoprotein receptor to introduce targeting towards liver cancer cells (Figure 2a) [27]. Interestingly, the glycoside-gA conjugate was found to generate a unimolecular transmembrane channel in contrast to the dimer formed by the natural peptide. The channel was able to actuate on the H^+ , Na^+ and K^+ intracellular concentration leading to apoptosis.

The same group designed a gA sequence linked to a gA-analogue through an extra glycine linker to mimic active dimeric gA channel within a single molecule [28]. By modifying the amino acids in the N- and C-termini of the peptide, they observed that the conformation of the terminal COO^- group may enable K^+ dehydration, thus favouring cation selectivity (i.e., $\text{K}^+ > \text{Rb}^+ > \text{Cs}^+ > \text{Na}^+ > \text{Cl}^-$). This caused ions to flow from C to N terminus and, together with an asymmetric insertion into the lipid bilayer (the C-terminus shows an orientation bias towards the *cis* membrane leaflet), resulted in directional ion transport. In a more recent work, Xin and collaborators developed a new unimolecular ion channel by appending two gA-analogous peptides to a pillar[5]arene scaffold, generating a tubular structure similar to the natural gA dimer (Figure 2b) [29]. By modifying the charge status of the peptide domains they were able to modulate channel activity, demonstrating that anionic residues at the end of the peptides increased K^+ conductance.

Using an artificial design, Hou and colleagues decorated a pillar[5]arene scaffold with short Arg-containing tripeptides appended on both rims, yielding unimolecular K^+ channels with the ability to insert into

membranes in response to voltage (Figure 2c) [30]. Later on, they described the potential selectivity of a similar system towards gram-positive bacteria over mammalian cells by attaching Trp-containing peptides to the pillar[5]arene scaffold [31]. More recently, a side chain was also introduced to tune ion transport rate by controlling the length of the side chain [32]. In a similar *de novo* approach, Feng and collaborators proposed a unimolecular nanopore consisting of a pillararene derivative functionalized with eight phenylalanine peptides that stabilize the interaction with the lipid bilayer (Figure 2d). The resulting nanopores showed improved K^+/Na^+ selectivity at high ion concentration [33]. In 2023, Xin's group aimed to rebuild the core module of natural K^+ selective channels in a fully artificial unimolecular channel through rational design strategy (Figure 2e) [34]. The α -cyclodextrin was used as the pore scaffold, which was modified with "selectivity filter-like peptides" containing the TVGYG sequence to one of the rims. Tryptophan residues were shown to be key to ensure the membrane insertion ability. The resulting biomimetic channels exhibited high selectivity for K^+ over Na^+ and were able to insert into cell membranes, disrupting K^+ homeostasis and leading to apoptosis.

Figure 2



Selection of unimolecular peptide-based ion channels. **a**) Glycoside-modified gA targets tumour cells and generates a monomeric ion channel. **b**) gA subunits connected by a pillar[5]arene generating a unimolecular ion channel. **c**) Pillar[5]arene functionalized in both rims with tripeptides generating a single-molecule ion channel. **d**) Pillararene derivative functionalized in both rims with phenylalanine tetrapeptides generating a single-molecule ion channel. **e**) α -Cyclodextrin decorated with six peptides with the signature filter-like peptide sequences generating selective K^+ channels.

Supramolecular systems for ion transport

The cation transport ability of natural peptide gA relies on its precise dimerization in the lipid bilayer. Following this design principle, Inoue and collaborators engineered a gA analogue, bridging its structure through a lactam functionality to stabilize the corresponding β -helix [35]. In this approach, the gA dimer stays in the proper head-to-head configuration avoiding its transition to the inactive β -double helix. The lactam-bridged gA analogue exhibited higher H^+/Na^+ exchange than natural gA in model membranes and retained its antibiotic activity while lowering its toxicity to mammalian cells [36]. Photoresponsive gA-based dimeric channels were also engineered in the past by appending photosensitive moieties to gA or by introducing photosensitive amino acids allowing ion current modulation through light stimuli [37,38].

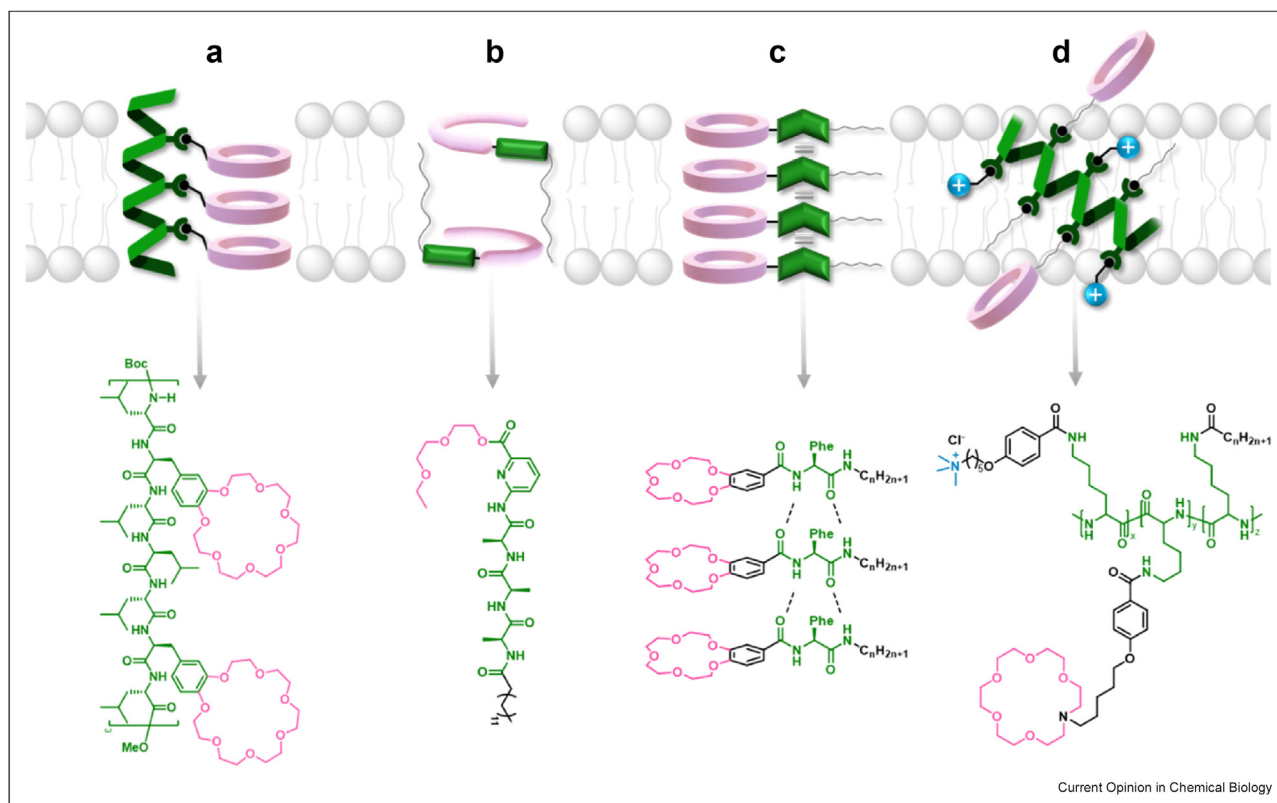
In addition to the synthetic engineering of natural peptides, several *de novo* design strategies have been devised as new peptide supramolecular ion channels. The Woolfson group has designed coiled-coil peptides that self-assemble in hexameric α -helical barrels with the ability to insert into lipid bilayers generating cation-selective channels [39]. The hydroxyl groups of serine and threonine residues in the lumen of the barrel provided cation selectivity leading to a permeability ratio of 5:1 for K^+ versus Cl^- and were also able to transport Na^+ and Cs^+ . Leucine residues favoured interaction with the hydrocarbon region of phospholipids while tryptophan matched their headgroups. In 2024, Dutta et al. developed amphiphilic peptide-oligourea chimeric helices as transmembrane ion channels [40]. The combination of peptidomimetic oligoureas with α -helical peptides led to the formation of new helical structures stabilized by a network of H-bonds. The designed molecules adopted well-defined helical structures that oligomerized into octameric transmembrane pores with anion transport activity by an antiport mechanism (X^-/OH^-) with the following selectivity: $Cl^- > NO_3^- > Br^- > SCN^- > I^- > AcO^- > F^-$. Due to their versatility and accessibility, peptides have also been applied as scaffolds for the arrangement of different molecular domains in supramolecular ion channels. To generate cation-selective channels, Madhavan's group proposed a tetrapeptide backbone containing alanine and aminopicolinic acid, linked to an oligoether chain at the C-terminus and an alkyl chain at the N-terminus (Figure 3b) [41]. This molecule was proposed to form dimeric cation-transporting pores in lipid bilayers with the oligoether moieties generating a pore at the membrane's surface while the alkyl chains anchor the pore in the phospholipid bilayer. The resulting pores showed selectivity for Na^+ over Li^+ and K^+ . In a subsequent study, they demonstrated that selectivity could be switched from Na^+ to K^+ by increasing the length of the oligoether chain to generate a bigger pore size [42].

The hydrogen bonding networks found in peptide-based assemblies can be also exploited in the development of versatile supramolecular ion transporters. The Zeng's group designed a self-assembled K^+ -selective channel via a peptide backbone to control the topological disposition of crown ethers (Figure 3c) [43]. The monomers are composed of an amino acid bound to a crown ether and to an alkyl chain. The hydrogen bonding network generated by the peptide backbone favours the stacking of the crown ethers, generating the ion channel. By tuning the different elements of the monomers, they identified a candidate with remarkable K^+ conductance and selectivity over other biologically relevant cations such as Na^+ , Ca^{2+} or Mg^{2+} . Conversely, in a work published by Li and collaborators, they changed the original electron-withdrawing group with an electron-donating group ($-CONH$ vs $-HNCO$) [44]. Increasing the electron density around the crown ether motif boosted K^+/Na^+ selectivity and resulted in enhanced transport activity. These results suggested that the limiting step in potassium transport for these artificial channels is related to crown ether-binding selectivity. More recently, Zeng's group improved the K^+/Na^+ selectivity of their supramolecular channels from 9.8 to 20.1 by simply tuning the length of the alkyl chain, which was the highest selectivity achieved up to date for an artificial potassium transporter [45]. The same group proposed a similar scaffold with the crown ether moieties substituted by tetrafluoriodobenzyl units that stack on top of each other driven by the peptide hydrogen bonding network [46]. These moieties have electron-deficient iodine atoms that create a transmembrane pathway able to facilitate anion transport through halogen-bonding. After combinatorial optimization of the monomers, a highly active and selective chloride channel that shows anticancer activity *in vitro* was identified.

Peptide-based ionophores

Synthetic ionophores are attractive transporters due to their structural robustness and simplicity [1]. Again, nature has served as inspiration for the development of synthetic carriers, such as in the case of natural depsipeptide cereulide, which is a well-known cytotoxin that acts as a K^+ ionophore mainly in pancreatic beta cells impairing insulin secretion. Barboiu and collaborators were able to mimic the activity of this natural toxin with a synthetic cyclic depsipeptide with high K^+/Na^+ selectivity, which worked as a monovalent M^+/H^+ antiporter and mimicked cereulide effect on beta cells [47]. Focusing on *de novo* designed ionophores, in 2019 Lee et al. developed helical poly-L-lysine peptides conjugated with trimethylammonium and crown ether moieties to achieve potassium transport and induce endoplasmic reticulum stress-mediated apoptosis (Figure 3d) [48]. The obtained molecules acted as selective K^+ ionophores and exhibited antitumoral activity. In 2020, Madhavan's group designed low molecular

Figure 3



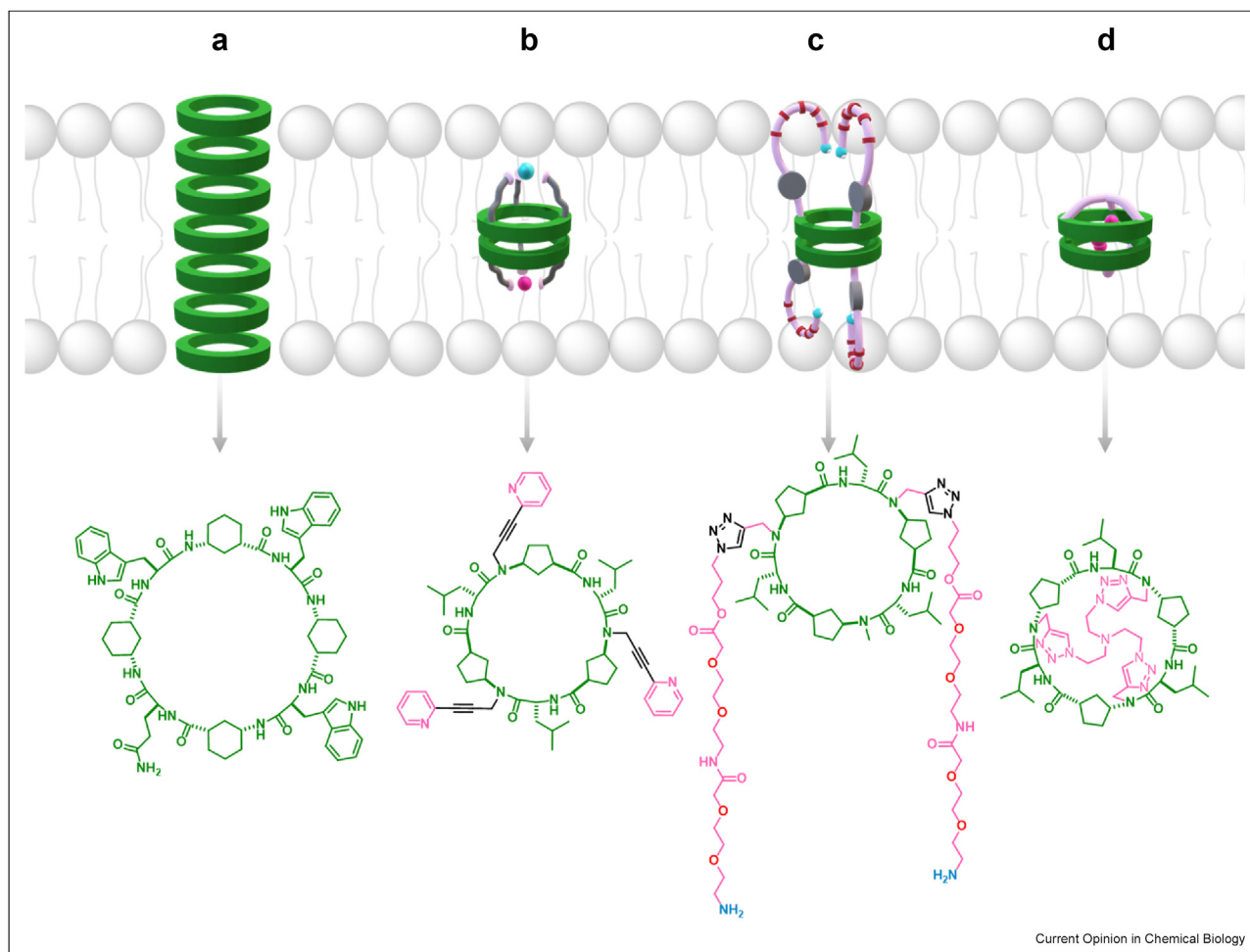
Peptide-based ion transporters with crown ether or related motifs. **a)** Crown ethers assembled by an α -helical peptide scaffold generating an ion channel. **b)** Dimeric ion channel formed by a tetrapeptide scaffold bound to an oligoether moiety and an alkyl chain. **c)** Supramolecular ion channel formed by peptides bound to crown ethers and alkyl chains that self-assemble through a hydrogen bonding network. **d)** Helical polylysine with alkyl chains, crown ether and trimethylammonium moieties that act as an ionophore across cell membranes.

weight cation selective carriers based on di- to tetrapeptides [49], equipped with aminobenzoic acid and *L/D* alanine, which were able to transport cations through an antiport M^+/H^+ or symport M^+/OH^- mechanism. Due to their tuneable yet simple structure, peptides can also be used as scaffolds for enhancing ion transport activity and selectivity. More recently, the same group designed a new lipidomimetic peptide for HCl transport [50], which comprises two aspartic acid residues bearing three carboxylate units, two of them to append long alkyl chains and a free one as a polar hydrophilic group. The anion binds to the NH groups of the peptide and the lipid-like structure facilitates the membrane integration and flipping. The resulting carriers exhibit $H^+ > Cl^- \gg M^+$ selectivity probably due to the protonation of the free carboxylate and the weak halide-binding ability of the NH group. In a different work, Madhavan and colleagues approached an ion pair co-transport system by using simple cyclic dipeptides with ester motifs pendants [51]. The designed molecules had the ability to co-transport M^+/X^- ions through a symport mechanism with potassium selectivity. The NH groups in the peptide scaffold favour the interaction

with Cl^- , while the carbonyl and ester linkages interact with K^+ and H^+ .

The unique supramolecular properties of cyclic *D, L*-cyclic peptides make them interesting scaffolds for the design of new ion transport systems. In 2020, Fuertes *et al.* designed dimeric symport ionophores based on pyridine-decorated cyclic peptides (Figure 4b) [52]. The α,γ -cyclic peptide scaffold provides the right topological disposition for the three pyridine moieties to coordinate ions. In the proposed transport mechanism, besides the expected cation recognition, pyridine units simultaneously coordinate with anions through anion- π interactions or hydrogen bonds having the same recognition motif for both ions. Furthermore, anion selectivity could be tuned by changing the pyridine isomer appended to the cyclic peptide. In a subsequent work, they used similar α,γ -cyclic peptide scaffolds that were functionalized with flexible pendants for the obtention of dimeric membrane-spanning ionophores (Figure 4c) [53]. These flexible pendants incorporated polar end groups that can reach both membrane sides inducing a transient permeable state. A small library of

Figure 4



Cyclic peptide-based ion transporters. **a)** Self-assembled cyclic *D, L*-peptides via β -sheet hydrogen bonding network into nanotubes with ion transport activity. **b)** Dimeric symport ionophores that recognize cations and anions through pyridine moieties. **c)** Dimeric membrane spanners that allow ion transport through transient membrane permeabilization. **d)** Dimeric supramolecular capsules that entrap and transport hydrated anion clusters.

oligoethylene glycol-based moieties were attached to the cyclic peptide scaffold via click chemistry leading to a library of compounds providing different transport behaviours. Recently, the same group exploited a similar cyclic peptide backbone for the generation of dimeric supramolecular capsules that entrapped hydrated anion clusters by the addition of *tris*(triazolyethyl)amine caps attached to a central peptide scaffold (Figure 4d) [54]. The obtained supramolecular capsules were also able to transport Cl^- across phospholipid bilayers through a symport H^+/Cl^- or antiport OH^-/Cl^- mechanism.

Beyond ions: peptide-based (bio)molecular carriers

Beyond their potential as membrane channels and ionophores, peptides have also been successfully applied for the transport of biologically relevant molecules across

lipid membranes [55]. We include here a short summary of the general design trends towards peptide molecular carriers to highlight the importance and versatility of these biocompatible scaffolds as broad membrane transporters. Amphiphilic peptide sequences were identified as potential supramolecular carriers for the transport of a wide range of molecular and biomolecular cargos [56,57]. Particularly, cationic amphiphilic polypeptides, either alone or in combination with other lipids or organic polymers, have been applied as suitable templates for the complexation and transport of nucleic acid cargos [58]. The hydrophobic enhancement of a dimer of the TAT peptide has also been shown to drive the cytosolic delivery of functional biomolecules *in vitro* and *in vivo* [59,60]. Arginine-rich peptides have been validated as efficient carriers for proteins in living cells [61]. It should be noted that polyarginines and peptides

derived from a segment of HIV-1 Tat protein (TAT peptide) can adhere to cell membranes and enhance different energy-dependent uptake pathways (e.g., macropinocytosis) [62]. Therefore, attenuated cationic lytic peptides have been designed to enhance macromolecular delivery taking advantage of these types of active internalization mechanisms [63]. Endosome-disruptive cytosolic peptides can also be engineered to trigger the endosomal escape of proteins and antibodies at minimized toxicity [64]. Our group introduced the use of dynamic covalent modification (e.g., hydrazone) to modify peptide sequences and obtain transient amphiphilic carriers for the efficient and nontoxic delivery of different nucleic acids and proteins [65,66]. Recently, intriguing liquid droplets from designed amphiphilic peptide sequences have also been shown to enable the efficient membrane transport of a broad range of biomolecular cargos [67,68].

Conclusions

The collection of examples included in this short review demonstrates the wide applicability and strong versatility of peptide scaffolds as membrane-targeted transporters for ions and molecular cargos. Either inspired by natural systems or applying innovative (semi)synthetic artificial designs, chemists have taken advantage of peptide properties to engineer channels and transport systems that would be otherwise hardly accessible. Peptide transporters are currently being developed by unimolecular and supramolecular strategies that employ different peptide sequences as membrane-embedded channels or as templating units of hybrid systems. As functional systems, new designs of peptide-based ion channels and carriers need to be oriented towards the improvement of the transport efficiency, the toxicity and the selectivity. Multiple examples have already shown the potential of the combination of synthetic parts and peptide templates for the assembly of functional molecular systems for membrane transport. The excellent properties of peptides in terms of synthetic accessibility, biocompatibility and topological control, will continue to encourage scientists to implement these scaffolds in their future design of innovative ion channels and membrane carriers.

Disclaimer

In the interest of conciseness, the examples included in this perspective have been limited to a representative collection of published structures and mechanistic studies. The authors apologise for any insightful reports that might have been let out in this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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- * of special interest
- ** of outstanding interest

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