CELL-PERMEABLE PEPTIDES

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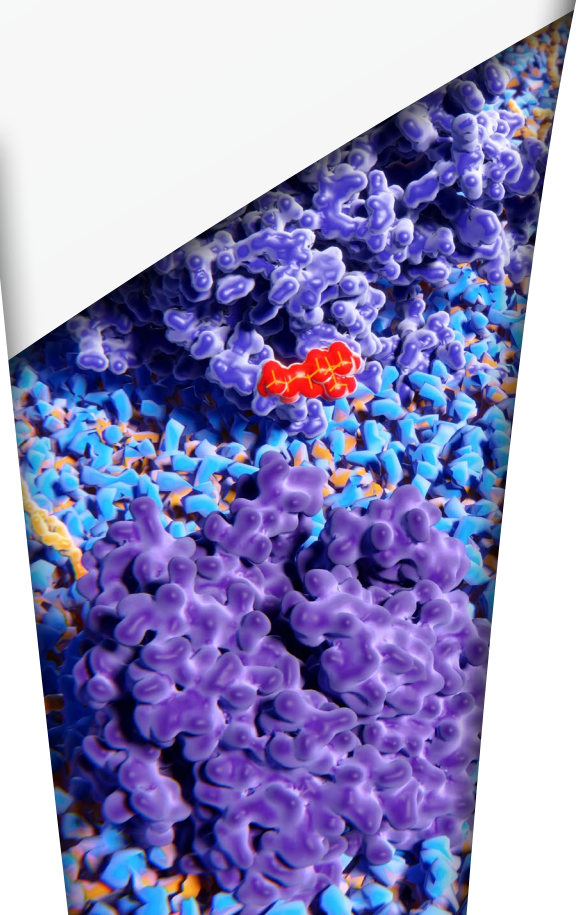

PROTEIN TRANSDUCTION DOMAINS (PTDs)

Cell-penetrating peptides (CPPs) constitute a promising tool for the cellular import of drug cargos. They have been successfully applied for *in vitro* and *in vivo* delivery of a variety of therapeutic molecules including plasmids, DNA, oligonucleotides, siRNA, PNA, proteins, peptides, low molecular weight drugs, liposomes, and nanoparticles.

Introduction

Delivery of therapeutic agents into cells through their membrane (cellular uptake) is a topic of profound importance to medicinal chemists and for the pharmaceutical industry and has always proved to be a challenging task especially in the delivery of large molecules. The plasma membrane prevents direct translocation of hydrophilic macromolecules by acting as a barrier to efficient and controlled intracellular delivery. A drug must be either highly lipophilic or very small to stand a chance of cellular internalization and it is difficult to ascertain a generic mechanism for drug uptake. These restrictions mean that the repertoire of possible drug molecules is limited. Similarly, novel therapeutic approaches such as gene and protein therapy also have limited potential due to the cell-impermeable nature of peptides and oligonucleotides. The existing methods for delivery of macromolecules, such as viral vectors and membrane perturbation techniques, can result in high toxicity, immunogenicity and low delivery yield.

CELL-PERMEABLE PEPTIDES (CPPs)

are short peptides that are able to pass the cell membrane. CPPs have found use for transporting cargo molecules as fluorophores, drugs, nucleic acids or proteins into cells.
Typically, CPPs contain a large proportion of positively charged amino acids, especially arginine, or an alternating sequence of charged and non-polar residues.

Discovery and potential of cell-permeable peptides

In 1988, Frankel and Pabo observed the remarkable ability of HIV-Tat protein to enter cells and translocate into the nucleus. Mutagenesis studies of the protein showed that the region between residues 47–57 (sequence: YGRKKRRQRRR) is important for cellular uptake. Soon after, in 1991, the group of Prochiantz and Derossi demonstrated that the antennapedia homeodomain protein of *Drosophila melanogaster* could be internalized by neuronal cells. This discovery subsequently led to the identification of a hexadecapeptide, penetratin, derived from the third helix of the homeodomain of antennapedia.Since then, the number of known natural and synthetic peptides with cell-penetrating capabilities has continued to grow (Table 1).
These peptides which are able to penetrate the cell membrane and enter the cell are known as cell-penetrating peptides. They are also known as protein transduction domains (PTDs), membrane translocating

Protein-derived	Chimeric	De novo designed
HIV-tat Protein HIV-1 tat (47-57) YGRKKRRQRRR	Galanin-Mastoparan Transportan GWTLNSAGYLLGKINLKALAALAKKIL	Oligoarginines Octa/nona-arginine RRRRRRRR(R)
Antennapedia homeoprotein Penetratin (Antp homeobox (43-58) amide) RQIKIWFQNRRMKWKK-NH_2	HIV rev -SV40 large T-antigen Pep-1 KETWWETWWTEWSQPKKKRKV	MAP KLAL KLALKLALKALKAALKLA
Herpes simplex Virus HSV-1 VP-22 DAATATRGRSAASRPTERPRAPAR-SASRPRRPVD	HIV gp41-SV40 T-antigen MPG GALFLGFLGAAGSTMGAWSQPK-KKRKV	KADY Ac-GLWRALWRLLRSLWRLLWKA-cysteamide
VE-Cadherin pVEC LLIILRRRIRKQAHAHSK-NH_2	p14 ARF M-918 MVTVLFRRLRIRRASGPPRVRV-NH_2	KALA WEAKLAKALAKALAKHLAKAL-AKALKACEA

Table 1: Examples of different CPPs that are protein-derived, chimeric sequences, or de novo designed peptides.

sequences (MTSs) or Trojan peptides. PTDs were identified in transcription factors, bacterial or viral surface proteins, toxins, amphipathic helix-forming peptides and in ligands of membrane-bound receptors or adhesion proteins.

CPPs can be broadly classified as protein-derived, chimeric (synthetic peptides combining partial sequneces of natural peptides), or synthetic, as shown in Table 1. These short peptides with less than 40 amino acids share common features such as positively charged amino acids, hydrophobicity and amphipathicity. The discovery and the ability of these peptides to traverse the cell membrane opened up a new avenue for drug delivery. Transport of therapeutically significant biomolecules across the membrane into the cell can be facilitated by attaching them to CPPs. A major breakthrough in the CPP field came from the first proofs-of-concept of their *in vivo* application, by the groups of Dowdy, for the delivery of small peptides and large proteins and of Langel, for delivery of peptide nucleic acids (PNAs) using the chimeric peptide transportan, derived from the N-terminal fragment of the neuropeptide galanin, linked to mastoparan, a wasp venom peptide. Since then, several CPPs that are able to trigger the movement of a cargo across the cell membrane into the cytoplasm have been designed.

Numerous cargo molecules have been attached to CPPs for cellular delivery. These include plasmid, DNA, oligonucleotides, siRNA, PNAs, proteins, peptides, liposomes, low molecular weight drugs, antibodies, nanoparticles, antibiotics, enzymes and enzyme substrates.

Methods of attaching CPPs to cargos

CPPs are usually connected via a covalent linkage to the cargo molecule. Proteins and peptides can be attached to CPPs through a disulfide bond (by modifying CPP and peptide/protein with cysteine) or through cross-linkers. Most CPP-nucleic acid complexes that have been proposed so far are formed through covalent bonding. Different strategies include cleavable disulfide, amide, thiazolidine, oxime and hydrazine linkages. Short interfering RNA (siRNA) can be covalently linked to transportan and penetratin by disulfide linkage at the 5'-end of the sense strands of siRNA to target luciferase or eGFP mRNA reporters. A stable covalent linkage between the cargo and CPP is not always necessary for translocation as simple mixing of two entities was shown to be efficient. The synthetic covalent bond between CPP and nucleic

The natural cell-permeable peptides mastoparan and mastoparan X have been isolated from the venoms of the wasps *Vespula lewisii* and *Vespa xanthoptera*, respectively. Both show the typical alternation of positively charged and lipophilic amino acids.
Crotamine, another natural CPP has been isolated from the venom of the South American rattlesnake *Crotalus durissus terrificus.*

acid may alter the biological activity of the latter. In 1997, the first non-covalent CPP for delivery of nucleic acids, called MPG (see Table 1) was designed by the group of Heitz and Divita closely followed by development of Pep-1 for non-covalent cellular delivery of proteins and peptides by Morris et al. in 2001. The groups of Wender and of Futaki demonstrated that oligoarginine sequences (Arg_8) were sufficient to drive molecules into cells and proposed that their uptake mechanism involves a bidentate hydrogen-bonding interaction between the guanidinium moieties of the arginine residues and phosphate groups in the membrane. Thus, a new non-covalent strategy requiring no chemical modification with short amphipathic CPPs, like MPG and Pep-1 as carriers has been successfully applied for delivery of cargoes. These non-covalent conjugates are formed through either electrostatic or hydrophobic interactions. With this method, cargoes such as nucleic acids and proteins could be efficiently delivered while maintaining full biological activity. MPG forms highly stable complexes with siRNA with a low degradation rate and can be easily functionalized for specific targeting, which are major advantages compared with the covalent CPP technology.

Mechanism of CPP translocation across the cell membrane

The exact molecular pathways underlying cellular uptake of a cargo attached to a CPP are not clear. Different CPPs have varying hydrophobicity, charge and amphiphilicity. The size and chemical properties of cargos are also different. Hence, generalizing the interaction of these complex molecules and cell membrane is not easy. For docking and cellular uptake, two major mechanisms have been considered: the endosomal pathways composed of endocytotic entry followed by endosomal escape, and direct cell membrane penetration. Peptides that have a high affinity for membranes have a higher propensity to be internalized by a non-endocytic mechanism than peptides with a lower affinity. CPPs with low molecular weight cargos may also enter without vesicle formation and facilitate access to all intracellular compartments.

Different stages of cell penetration via endocytosis are depicted in Figure 1. According to this mechanism, CPPs are first simply adsorbed at the cell, followed by endocytosis of membrane, vesicle formation, formation of endosomes in which the conjugate is trapped, and endosomal release.

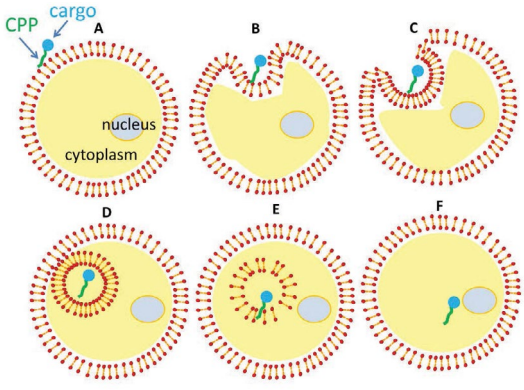

Figure1:
Cell penetration via endocytosis.
A: Membrane interaction;
B: Endocytosis;
C: Vesicle formation;
D: Endosome;
E: Endosomal release;
F: CPP conjugate in cytoplasm.

Drug delivery: CPP-drug conjugates in clinical trials

Research and clinical studies on the transport and delivery of therapeutics into cellular targets using cell-penetrating peptides has been progressing well in recent years. Several companies started working on clinical development of CPPs, for topical and systemic administration of different therapeutic molecules. The first CPP clinical trial was initiated by Cellgate Inc. for topical delivery of cyclosporine linked to polyarginine (CGC1072) and entered phase II trials in 2003 for the treatment of psoriasis.

This is an example of local application of a CPP-drug conjugate (local CPP-mediated delivery). However, despite an efficient uptake of the chimera, the release of the free drug was not rapid enough to compete with clearance. A list of different CPP-based drugs which entered clinical trial is shown in Table 2.

The therapeutic 28-amino acid cell-penetrating peptide p28 is derived from azurin, a redox protein secreted from the pathogen *Pseudomonas aeruginosa,* produces a post-translational increase in p53 by inhibiting its ubiquitination in cancerous cells. In few of these cases therapeutic agents are covalently linked either directly or through a linker to the CPP carrier. In KAI-9803, KAI-1678 and KAI-1455, the cargo peptide is attached to Tat peptide via a disulfide bond between additional cysteines at the

CPP	Sequence	Drug	Structure/ Sequence	Indication/ Status
p28 Azurin (50-77)	LSTAADMQGVVTDG-MASGLDKDYLKPDD	Azurin-p28 (NSC745104)	LSTAADMQGVVTDG-MASGLDKDYLKPDD	Progressive CNS tumors/ phase 1
TAT 48-57	GRKKRRQRRR	XG-102 (D-JNKI-1)	GRKKRRQRRR-PP-RPKRPTTLNLF-PQVPRSQDT	Hearing loss/stroke
TAT 47–57	YGRKKRRQRRR	KAI-9803 (Delcasertib)	CYGRKKRRQRRR | CSFNSYELGSL	Myocardial infarction/ phase 2b
TAT 47–57	YGRKKRRQRRR	KAI-1678	CYGRKKRRQRRR | CEAVSLKPT	Pain/phase 2a
TAT 47-57	YGRKKRRQRRR	KAI-1455	CYGRKKRRQRRR | CHDAPIGYD	Cytoprotection/phase 1
Vectocell® peptide	CVKRGLKLRHVR-PRVTRMDV	DTS-108	SN38-BCH-CVKRGLKLRHVRP	Colon cancer/phase 1

Table 2: CPP based drug delivery: CPP-drug conjugates which have entered clinical trials so far

N-termini of both entities. The cargo peptides SFNSYELGSL and EAVSLKPTC are δ protein kinase C (δPKC) and ε protein kinase C (εPKC) specific inhibitors, respectively and HDAPIGYD is a εPKC activator peptide. DTS-108 is a Vectocell® peptide-SN38 prodrug generated by esterification of the 10-hydroxyl group of SN38 to a hetero-bifunctional cross-linker (BCH) linked to Vectocell® peptide DPV1047 (CVKRGLKLRH-VRPRVTRMDV).

Conclusions

Extensive research on the design and *in vivo* applications of cell-penetrating peptides during the last two decades has demonstrated the potential of these compounds in molecular medicine. With the aid of CPPs, delivery of therapeutic biomolecules such as oligonucleotides and proteins can be better managed in terms of efficiency, cytotoxicity and biocompatibility. CPPs can associate with an extensive range of cargo types either via covalent linkage or non-covalent interaction. One of the limitations of CPPs is the non-specific cellular uptake which limits their potential for drug delivery to specific cellular targets such as tumor cells. Fortunately, a number of recently developed CPPs have shown high affinity for specific cell types or intracellular destinations. A recently discovered CPP known as 'crotamine' has shown unusually high affinity for actively proliferating cells. Another example lies with MPG, a synthetic CPP derived from the SV40 virus. Originally designed for nuclear delivery of siRNA, it has recently been altered to target the cytoplasm. Recently, "activatable" CPPs were introduced to address the problem of tissue non-specificity of CPPs. Constructs have been described that are "activated" either outside or inside the cells. Another solution to the problem of cellular non-specificity of CPPs will be, starting from the sequences of well-established cell-targeting peptides, to design new peptides that combine both targeting and internalization properties.

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The C-terminal part of human calcitonin, hCT (9-32), LGTYTQDFNK-FHTFPQTAIGVGAP-NH_2, and shorter C-terminal fragments act as CPP.

CELL-PERMEABLE PEPTIDES

A plethora of cell-penetrating peptides has been described in the literature. The choice of the optimal carrier not only depends on the cellular target but also on the type of cargo molecule.

If you don't find the CPP you require in this brochure, please contact our Custom Synthesis department to get a quote. If your requirements advance from research scale to process development and cGMP manufacturing, we are ready to support you with our framework of cGMP production facilities and dedicated regulatory affairs staff.

ARGININE OLIGOMERS

H-Arg-Arg-Arg-Arg-Arg-Arg-OH
(Hexa-L-arginine)
4028946
RRRRRR

H-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-NH$_2$
(Hexa-D-arginine-amide)
4028946
rrrrrr-NH$_2$

H-Arg-Arg-Arg-Arg-Arg-Arg-Arg-OH
(Hepta-L-arginine)
4041657
RRRRRRR

H-Arg-Arg-Arg-Arg-Arg-Arg-Arg-Arg-OH NEW
(Octa-L-Arginine)
4065816
RRRRRRRR

H-Arg-Arg-Arg-Arg-Arg-Arg-Arg-Arg-Arg-OH
(Nona-L-arginine)
4040952
RRRRRRRRR

H-Cys(Npys)-Arg-Arg-Arg-Arg-Arg-Arg-Arg-Arg-Arg-OH
(Cys(Npys)-Nona-L-arginine amide)
4091599
C(Npys)RRRRRRRRR-NH$_2$

H-Cys(Npys)-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-D-Arg-OH
(Cys(Npys)-Nona-D-arginine amide)
4091590
C(Npys)rrrrrrrrr-NH$_2$

ANTENNAPEDIA PEPTIDES

Penetratin
(Antennapedia Homeobox (43-58) amide)
4036091
RQIKIWFQNRRMKWKK-NH$_2$

FITC-εAhx-Antennapedia Homeobox (43-58) amide
FITC-ε-aminocaproyl-Antp Homeobox (43-58) amide)
4045699
FITC-εAhx-RQIKIWFQNRRMKWKK-NH$_2$

HIV-1 tat FRAGMENTS

(Cys^{46})-HIV-1 tat Protein (46-57) amide NEW
4049177
CYGRKKRRQRRR-NH$_2$

5-FAM-HIV-1 tat Protein (46-57) amide
4091600
(5-FAM)-YGRKKRRQRRR-NH$_2$

5(6)-TAMRA-HIV-1 tat Protein (46-57) amide
4091601
(5(6)-TAMRA)-YGRKKRRQRRR-NH$_2$

HIV-1 tat Protein (47-57)
4048761
YGRKKRRQRRR

HIV-1 tat FRAGMENTS (CONTINUED)

(Cys^{47})-HIV-1 tat Protein (47-57)
4066788
CGRKKRRQRRR

HIV-1 tat Protein (49-57)
4039739
RKKRRQRRR

TAT 2-4 NEW
4095685
YGRKKRRQRRRGYGRKKRRQRRRG

MASTOPARAN

Mastoparan
4013168
INLKALAALAKKIL-NH_2

Mastoparan-7
4030846
INLKALAALAKALL-NH_2

Mastoparan-X
4013767
INWKGIAAMAKKLL-NH_2

MISCELLANEOUS PRODUCTS

Calcitonin (9-32) (free acid) (human) NEW
4077804
LGTYTQDFNKFHTFPQTAIGVGAP

Hel-13-5
(Pulmonary Surfactant Model Peptide)
4091591
KLLKLLLKLWLKLLKLLL

KALA Amphipathic Peptide
4030798
WEAKLAKALAKALAKHLAKALAKAL-KACEA

Pep-1 cysteamide NEW
4039296
Ac-KETWWETWWTEWSQPKKKRKV-cysteamide

RVG-9R
(Rabies Virus Glycoprotein (194-221) Nonaarginine Chimer)
4058134
YTIWMPENPRPGTPCDIFTNSRG-KRASNGGGGRRRRRRRRR

SV40 Nuclear Transport Signal Peptide Analog
(NLS)
4026251
CGYGPKKKRKVGG

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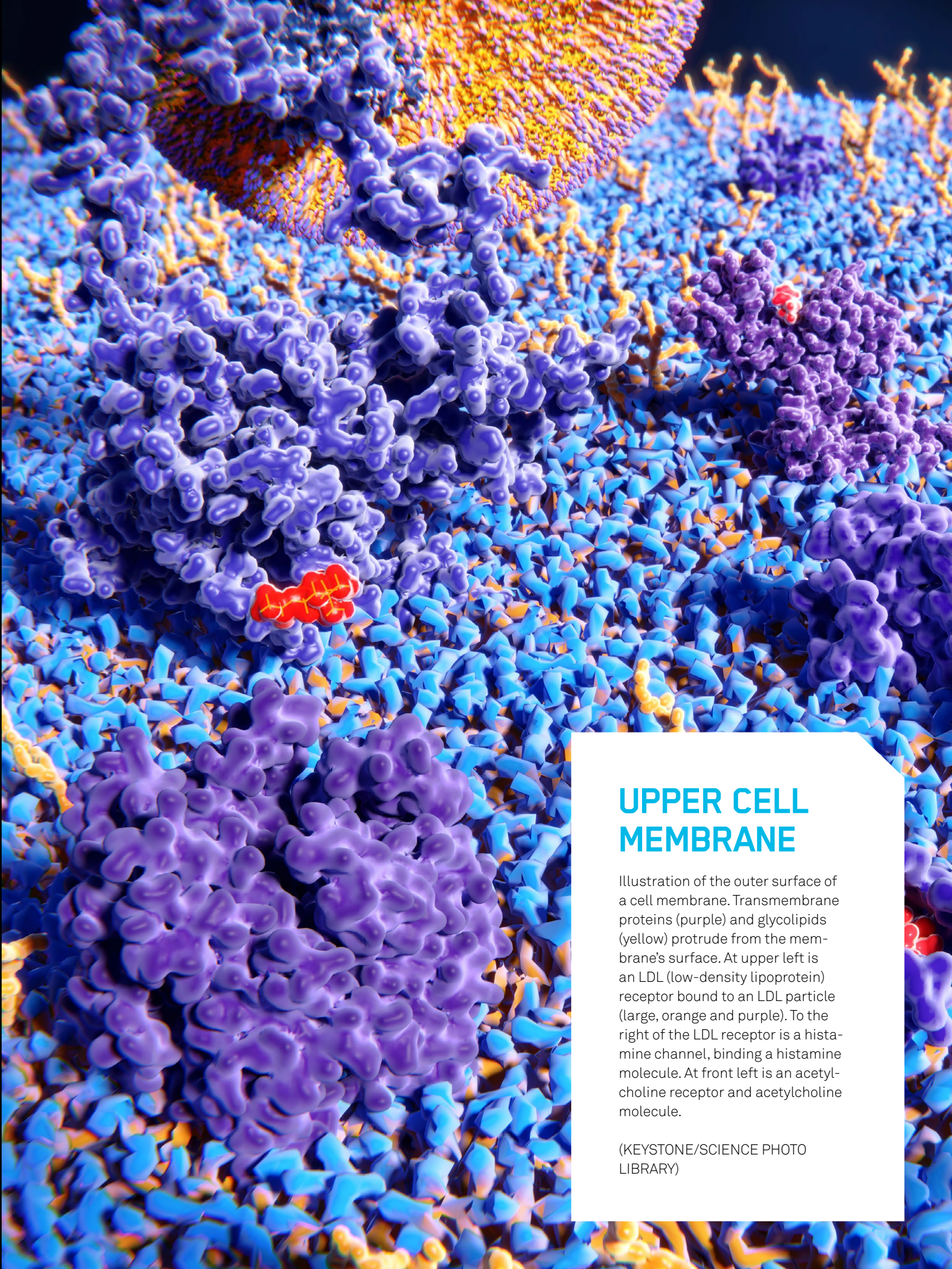

UPPER CELL MEMBRANE

Illustration of the outer surface of a cell membrane. Transmembrane proteins (purple) and glycolipids (yellow) protrude from the membrane's surface. At upper left is an LDL (low-density lipoprotein) receptor bound to an LDL particle (large, orange and purple). To the right of the LDL receptor is a histamine channel, binding a histamine molecule. At front left is an acetylcholine receptor and acetylcholine molecule.

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