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Ülo Langel
Department of Biochemistry and Biophysics
Stockholm University
Stockholm, Stockholms Län, Sweden

Institute of Technology
University of Tartu
Tartu, Estonia

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Contents

Abbreviations

Aa	Amino acid
Abz	2-Aminobenzoic acid
aCPP	Activatable cell-penetrating peptide
AD	Alzheimer's disease
Aib	α-Aminoisobutyric acid
ALA	5-Aminolevulinic acid
AMP	Antimicrobial peptides
APP	Amyloid precursor protein
ASO	Antisense oligonucleotide
ATTEMPTS	Antibody targeted triggered electrically modified prodrug type strategy
BBB	Blood-brain-barrier
BK	Bradykinin
bPrPp	Bovine prion protein
CaM	Calmodulin
Cas	CRISPR-associated protein systems
CatD	Cathepsin D
CD	Circular dichroism
CF	Carcoxyfluorescein
Chol	Cholesteryl
CLSM	Confocal laser scanning microscopy
CNS	Central nervous system
CPP	Cell-penetrating peptide
CRISPR	Clustered regularly interspaced short palindromic repeat
DDS	Drug delivery systems
DLS	Dynamic light scattering
DMD	Duchenne Muscular Dystrophy
DOX	Doxorubicin
DPC	Dodecylphosphocholine
DRBD	Double-stranded RNA-binding domain

EED	Endosomal escape domains
EGFR	Epidermal growth factor receptor
EM	Electron microscopy
EPR	Enhanced permeation and retention
ERT	Enzyme replacement therapy
FA	Folic acid
FAM	Arboxyfluorescein
FACS	Fluorescence activated cell sorting
FCS	Fluorescence correlation spectroscopy
FITC	Fluorescein isothiocyanate
Fl	Fluorescent label
FRET	Förster resonance energy transfer
GAGs	Glycosaminoglycans
GET	Glycosaminoglycan-binding enhanced transduction delivery system
GFP	Green fluorescent protein
GO	Graphene oxide
GPCR	G-protein coupled receptor
GUV	Giant unilamellar vesicles
HA	Haemagglutinin
hMSC	Human mesenchymal stem cell
HPLC	High performance liquid chromatography
HS	Heparan sulfate
HSC	Haematopoietic stem cell
Hsp70	Heat shock protein 70
HSPG	Heparan sulfate proteoglycan
IgG	Immunoglobulin G
iPS	Induced pluripotent stem cell
iRGD	Integrin-binding RGD motif
ITC	Isothermal titration calorimetry
JIP	JNK interacting protein
LF	Lactoferrin
LMWP	Low molecular weight protamine
LNA	Locked nucleic acid
LSP	Lysosomal sorting peptide
LUV	Large unilamellar vesicles
mAb	Monoclonal antibody
MAP	Membrane active peptide
MD	Molecular dynamics
MEND	Multifunctional envelope-type nanodevice
MHC	Major histocompatibility complex
MION	Magnetic iron oxide nanoparticles
miRNA	MicroRNA
MLV	Multilamellar vesicles
MMP	Matrix metalloprotease
MPP	Mitochondria-penetrating peptides

MRI	Magnetic resonance imaging
MS	Mass-spectrometry
MSC	Mesenchymal stem cells
mt	Mitochondria
MTS	Mitochondrial targeting sequence
NLC	Nanostructured lipid carrier
NLS	Nuclear localisation signal
NMR	Nuclear magnetic resonance
NP	Nanoparticle
NRP-1	Neuropilin-1
ON	Oligonucleotide
OVA	Ovalbumin
PACAP	Pituitary adenylate-cyclase-activating polypeptide
pAntp	*Drosophila* homeoprotein Antennapedia derived peptide
pArg	Poly-arginine, pR
PC	Phosphatidylcholine
PCM	Primary cardiomyocyte-targeting peptide
pDNA	Plasmid DNA
PDT	Photodynamic therapy
PDZ	A 80–90 aa domain found in the signaling proteins
PEG	Poly-ethylene glycol
PEI	Polyethylenimine
Pen	Penetratin
PET	Positron-emission tomography
PF	PepFect
pHLIP	pH low insertion peptides
Pip	PNA internalising peptide
PK	Protein kinase
PLA	Poly-l-arginine
PLGA	Poly(dl-lactic acid-co-glycolic acid)
PLL	Poly-l-lysine (PLL)
PMO	Phosphorodiamidate morpholino oligomers
PNA	Peptide nucleic acid
POPC	1-palmitoyl-2-oleoyl-snglycero-3-phosphocholine
POPG	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol
PPI	Protein-protein interaction
PS	Phosphorothioate ON
PSC	Pluripotent stem cells
PSP	Photo-sensitive peptide
PTD	Protein/peptide transduction domains
PTX	Paclitaxel (PTX)
QD	Quantum dots
R8	Octa-arginine
Rh	Rhodamine
ri	Retro-inverso

Rn	Poly-arginine
SAP	Sweet arrow peptide
SAR	Structure-activity studies
SCARA	Class A scavenger receptors
SCO	Splice correcting ON
scFv	Single chain variable fragment
SDS	Sodium dodecyl sulfate
SEM	Scanning electron microscope
siRNA	Short interfering RNA
SOD	Suoeroxide dismutase
SPPS	Solid phase peptide synthesis
SPT	Single particle tracking
SUV	Small unilamellar vesicles
TALENs	Transcription activator like effector nucleases
Tat	HIV-Tat derived CPP
TEM	Transmission electron microscopy
Tf	Transferrin
TF	Transcription factor
THP	Tumour homing peptide
TP	Transportan
TPP	Tumor penetrating peptide
TRITC	Tetramethyl rhodamine iso-thiocyanate
Yops	Human-pathogenic Yersinia plasmid-encoded Yersinia outer proteins
ZFNs	Zinc finger nucleases

Chapter 1
Introduction

Keywords CPP · Cell-penetrating peptide · Peptide · Shuttling · Translocation

The genesis of cell-penetrating peptide research (CPP; also known as prote/peptide transduction domains, PTD, or Trojan peptides) was born from the publication of two parallel landmark reports on an HIV tat trans-activator protein (Frankel and Pabo 1988; Green and Loewenstein 1988), now widely known to epitomise membrane shuttling proteins (but not to be confused with the shuttling proteins cycling back and forth through the nuclear pore complex (Goldfarb 1991)). Several follow up studies demonstrated that only a portion (residues 1–72 and 37–72) of the Tat protein was necessary for cellular uptake (Fawell et al. 1994). These findings were validated by complementary reports from the group of Alain Prochiantz (Joliot et al. 1991) on cellular internalization of the 60 aa homeodomain of Antennapedia (a *Drosophila* homeoprotein), and on a short 16 aa peptide, pAntp(43–58), later named penetratin, which was necessary and sufficient for this translocation (Derossi et al. 1994); patent application number 828995, filed 1992. Together, these seminal findings challenged the laws of cellular biochemistry and contested the traditional dogma that the cell plasma membrane was impermeable to proteins and peptides. As a recent example, SERPINA5 (protein C inhibitor) is a secreted protease inhibitor with broad protease reactivity, wide tissue distribution and demonstrable cellular internalization properties (Wahlmuller et al. 2017).

To date (fall 2018), CPPs have been cited in 5 000 scientific reports and at least four summary books have been dedicated to progress within the field, the most recent of which was published in 2015 (Langel 2015). The Web-site CPPsite 2.0 (http://crdd.osdd.net/raghava/cppsite/) database contains around 1700 unique, experimentally validated CPPs together with their secondary and tertiary structures. In silico CPP predictions show even higher numbers of such peptides, awaiting confirmation and application.

Certainly, these discoveries were preceded by several earlier reports on short bioactive peptides inducing intracellular events in a specific receptor-independent

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manner such as the peptide toxins mastoparan, melittin as well as neuropeptides bradykinin and substance P (Repke and Bienert 1987), reviewed in (Mousli et al. 1990) as well as the arginine-rich pituitary adenylate-cyclase-activating polypeptide (PACAP) (Tchoumi Neree et al. 2014). In 1969, quantitative studies of radioactively labelled D-Glu_2 confirmed, through morphological evidence, that it was taken up by pinocytosis and stored, intact, in macrophage lysosomes. Interestingly, this may be the very first study to analyse intracellular peptide uptake (Ehrenreich and Cohn 1969).

Antimicrobial peptides, AMPs, are other examples of short peptides which dose-dependently influence intracellular biology, not merely through processes such as membrane pore formation, but also through interacting directly with intracellular targets (Guilhelmelli et al. 2013), an observation which propounds their possible use as drug delivery vectors at non-toxic doses. CPPs and AMPs belong to the family of membrane active peptides (MAPs), both are positively charged peptides with the ability to cross cell membranes and deliver macromolecular cargo. Several CPPs, including penetratin, pVEC, TP10 and Tat, have been shown to have antimicrobial properties at higher doses. Several classical AMPs, for example magainin, lactoferrin and LL-37 have been shown to be cell-penetrating (Rydberg et al. 2012).

It seems in general that several CPPs carry more than a single function exemplified by antimicrobial peptides, neuropeptides or short protein mimics. More recently, multiple suggestions can be found for drug delivery by combinations of new modalities e.g. new generation peptides (bicyclic, hairpin, stapled etc.), oligonucleotides and other drugs (Valeur et al. 2017; Waldmann et al. 2017). Such combination of efficient modalities including CPPs, will further fuel the possibilities in drug delivery.

It is disturbing that not a single CPP-based drug has been approved yet for therapeutic use. It is a paradigm in CPP research that the peptides are taken up by virtually all cells, but in vivo CPPs only target a very limited number of cells and many tissues are hardly reached at all. A paradigm change towards a more opportunistic approach in CPP research has been proposed whereby the applications of CPPs should be focussed on those pathophysiologies for which the relevant target cells have been shown to be reached in vivo (Collado Camps and Brock 2017).

Undeniable, the complexities of their mechanisms of action, have rendered CPPs problematic to define, if indeed possible at all. Here we cite a recent definition of CPPs from (Langel 2015) in order to cover the topics reviewed herein.

Cell-penetrating peptides (CPPs) are relatively short peptides, 4–40 aa, with the ability to gain access to the cell interior by means of different mechanisms, mainly including endocytosis, and/or with the capacity to promote the intracellular effects by these peptides themselves, or by the delivered covalently or non-covalently conjugated bioactive cargoes.

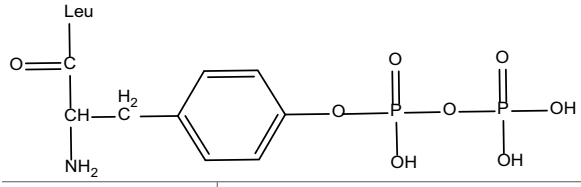
In this book, a summary and update of the most important areas of CPP research are presented, whilst hopefully raising relevant questions for further development. The selected CPP sequences are presented in Table 1.1 and discussed throughout the book. The methods for testing CPP mechanisms are discussed in detail. Various approaches for the testing of endocytotic pathways of CPP uptake are also described.

Table 1.1 Selection of cell-penetrating peptides

Most of the presented peptides have been synthesized and tested as C-terminal amides (not indicated), although in several cases it is impossible to certify; cysteamide modifications are indicated. The L-amino acids are presented in capital letters, D-amino acids are presented in lowercase letters

Ac indicates acetyl; Ahx or X is aminohexanoic acid; Aib is aminoisobutyric acid; B is β-alanine; Bpg is bishomopropargylglycine; Dmt is dimethyltyrosine; O is ornithine; pT is a phosphoryl-Thr; pS is a phosphoryl-Ser; Φ is l-2-naphthylalanine; ri denotes retro-inverso; * denotes staple tethering site

**



Name	Sequence
2	DSLKSYWYLQKFSWR (Kondo et al. 2012)
18A	DWLKAFYDKVAEKLKEAF (Datta et al. 2000)
α1H	KSKTEYYNAWAVWERNAP (Gomarasca et al. 2017)
α2H	GNGEQREMAVSRLRDCLDRQA (Gomarasca et al. 2017)
A22p	HTPGNSNKWKHLQENKKGRPRR (Shin et al. 2014)
Ac-18A-NH_2	DWLKAFYDKVAEKLKEAF) (Wimley and White 2000)
aCPP	Typical sequence R9GPLGLAGE8 (Li et al 2015)
AdVpVI(33-55)	Ac-GAFSWGSLWSGIKNFGSTVKNYG (Murayama et al. 2016)
AIP6	RLRWR (Wang et al. 2011)
all-d DsC18	Glrkrlrkfrnkikek (Bergmann et al. 2017)
αgliadin(31-43)	LGQQQPFPPQQPY (Paolella et al. 2018)
Alyteserin-2a	ILGKLLSTAAGLLSNL (Conlon et al. 2013)
ANG	TFFYGGSRGKRNNFKTEEY (Demeule et al. 2008)
ApoE(141–150)	Ac-LRKLRKRLLRX-Bpg-G (Shabanpoor et al. 2017)
ApoE-derived	Ac-LRKLRKRLLR (Tailhades et al. 2017)
Arf(1-22)	MVRRFLVTLRIRRACGPPRVRV (Johansson et al. 2008)
AT1002	FCIGRL (Gopalakrishnan et al. 2009)
AT1AR(304-318)	FLGKKFKKYFLQLLK (Östlund et al. 2005)

(continued)

Table 1.1 (continued)

Bac7	RRIRPRPPRLPRPRPRPLPFPRPGPRPIPRPL (Sadler et al. 2002)
BGPC7-FHV	RRRRNRTRRNRRRVR-RRFYGPV (Wongso et al. 2017)
Bim	EIWIAQELRRIGDEFNAYYARLLC (Kim et al. 2017)
BP16	KKLFKKILKKL (Soler et al. 2014)
BP100	KKLFKKILKYL (Eggenberger et al. 2009)
BPP13a	GGWPRPGPEIPP (Sciani et al. 2017)
bPrPp(1-30)	MVKSKIGSWILVLFVAMWSDVGLCKKRPKP (Magzoub et al. 2006)
BR2	RAGLQFPVGRLLRRLLR (Lim et al. 2013)
Buforin II	TRSSRAGLQFPVGRVIIRLLRK (Park et al.1998)
Buforin IIb	RAGLQFPVG[RLLR]$_3$ (Lee et al. 2008)
C6M1	RLWRLLWRLWRRLWRLLR (Jafari et al. 2014)
C105Y	CSIPPEVKFNKPFVYLI (Rhee and Davis 2006)
CADY	GLWRALWRLLRSLWRLLWRA cycteamide (Crombez et al. 2009a)
CAR	CARSKNKDC (Toba et al. 2014)
CA-Tat	KWKLFKKYGRKKRRQRRR (Lv et al. 2017)
CB5005 M	KLKLALALALA (Zhang et al. 2016)
CDB3	REDEDEIEW (Issaeva et al. 2003)
CendR	RPARPAR (Hu et al. 2014)
cFΦR4	cyclic FΦRRRRQ (Qian et al. 2014)
CGKRK	CGKRK (Griffin et al. 2017)
CIGB-300	cyclic CWMSPRHLGTC-Tat (Perera et al. 2012)
CIGB-552	Ac-HARIKpTFRRlKWKYKGKFW (Fernandez Masso et al. 2013)
CLIP6	KVRVRVRVpPTRVRERVK (Soudah et al. 2017)
CooP	ACGLSGLGVA (Hyvonen et al. 2014)
CpMTP	ARLLWLLRGLTLGTAPRRA (Jain and Chugh 2016)
CPNT	STSGTGKMTRAQRRAAARRNRA (Qi et al. 2011)
CPP1	(KFF)$_3$K (Patel et al. 2017)
CPP33	RLWMRWYSPRTRAYG (Lin et al. 2018)
CPP-C	PIEVCMYREP (Nakayama et al. 2011)
CPPecp	NYRWRCKNQN (Fu et al. 2017)
C-peptide	GPGLWERQAREHSERKKRRRESECKAA (Fan et al. 2016)
CRGDK	CRGDK (Zhao et al. 2018)
Crotamine	YKQCHKKGGHCFPKEKICLPPSSDFGKMDCRWRWKCCKKGSG (Rodrigues et al. 2012)
cSN50	AAVALLPAVLLALLAPVQRKRQKLMP (Torgerson et al. 1998)
65-2CTS	CPYVNQRPQKARYRNG (Percipalle et al. 2003)
CWR$_8$K	CWR$_8$K (Sasaki et al. 2008)
CyLoP-1	CRWRWKCCKK (Ponnappan et al. 2017)

(continued)

Table 1.1 (continued)

Cyt c(77–101)	GTKMIFVGIKKKEERADLIKKA (Howl and Jones 2015)
DAG	cyclic CDAGRKQKC (Mann et al. 2017)
D-JNKI-1	RPKRPTTLNLFPQVPRSQDT (Bonny et al. 2001)
DK17	DRQIKIWFQNRRMKWKK (Bera et al. 2016)
DLP	ACKTGSHNQCG (Kumar et al. 2015)
DMBT1-derived	GRVEVLYRGSW and GRVRVLYRGSW (Tuttolomondo et al. 2017)
dNP2	KIKKVKKKGRK-KIKKVKKKGRK (Lim et al. 2015)
DPV3	RKKRRRESRKKRRRES (Tacken et al. 2008)
DPV1047	CVKRGLKLRHVRPRVTRMDV (De Coupade et al. 2005)
DRTTLTN	DRTTLTN (Gennari et al. 2016)
DS4.3	RIMRILRILKLAR (Jeong et al. 2014)
Dynorphin A	YGGFLRRIRPKLKWDNQ (Marinova et al. 2005)
EA	GLKKLAELAHKLLKLGC (Yang et al. 2014)
EB1	LIRLWSHLIHIWFQNRRLKWKKK (Lundberg et al. 2007)
EF	GLKKLAELFHKLLKLGC (Yang et al. 2014)
EHB	RCSHYTGIRCSHMAATTAGIYTGIRCQHVVL-C6H (Cao et al. 2018)
EPRNEEK	EPRNEEK (Orihuela et al. 2009)
F3**	diphosphorylated dipeptide (Miao et al. 2016)
$G_4R_9L_4$	$G_4R_9L_4$ (Ramakrishna et al. 2014)
GALA	WEAALAEALAEALAEHLAEALAEALEALAA (Li et al. 2004)
GeT	KIAKLKAKIQKLKQKIAKLK (Rakowska et al. 2014)
gH625	HGLASTLTRWAHYNALIRAF (Galdiero et al. 2015)
Gi3α(346-355)	KNNLKECGLY (Jones et al. 2005)
Glu-Lys	EEEAAKKK (Lewis et al. 2010)
GV1001	EARPALLTSRLRFIPK (Kim et al. 2016a)
GWH1	GYNYAKKLANLAKKFANALW (Serna et al. 2017)
H2A derived	SGRGKQGGKARAKAKTRSSRAGLQFPVGRVHRLLRKG (Rosenbluh et al. 2004)
H6R6	H6R6 (Sun et al. 2017)
H16	H16 (Iwasaki et al. 2015)
HA2(1-23)	GLFGAIAGFIENGWEGMIDGWYG (Esbjörner et al. 2007)
HAIYPRH	HAIYPRH (Shteinfer-Kuzmine et al. 2017)
hBD3-3	GKCSTRGRKCCRRKK (Lee et al. 2015b)
HBP	GKRKKKGKGLGKKRDPCLRKYK (Luo et al. 2016)
hLF	KCFQWQRNMRKVRGPPVSCIKR (Duchardt et al. 2009)
Hph-1	YARVRRRGPRR (Jung et al. 2011)
HR9	CH_5-R_9-H_5C (Liu et al. 2013a)

(continued)

Table 1.1 (continued)

Hst5	DSHAKRHHGYKRKFHEKHHSHRGY (Luque-Ortega et al. 2008)
I1WL5W	WKKIWSKIKKLLK (Bi et al. 2014)
I4WL5W	IKKWWSKIKKLLK (Bi et al. 2014)
ID No.2	MAAWMRSLFSPLKKLWIRMH (Eudes and Macmillan 2014)
IMT-P8	RRWRRWNRFNRRRCR (Gautam et al. 2016)
INF	GLFEAIEGFIENGWEGMIDGWYGC (Pichon et al. 1997)
iNGR	CRNGRGPDC (Alberici et al. 2013)
isl-1	RVIRVWFQNKRCKDKK (Kilk et al. 2001)
JB9	cskc (Basu and Wickstrom, 1997)
JB434	R_9GGLAA-Aib-SGWKH_6 (Sangtani et al. 2018)
KAFAK	KAFAKLAARLYRKALARQLGVAA (Bartlett et al. 2013)
KALA	WEAKLAKALAKALAKHLAKALAKALKACEA (Wyman et al. 1997)
Kalata B1	polycyclic CGETCVGGTCNTPGCTCSWPVCTRNGLPV (Daly et al. 1999)
$(KFF)_3K$	$(KFF)_3K$ (Rownicki et al. 2017)
K-FGF	AAVLLPVLLAAP (Lin et al. 1995)
KH	$(KH)_9$ (Chuah et al. 2016)
KLA	KLAKLAKKLAKLAK (Huang et al. 2017)
KLAK	KLALKLALKALKAALKLA (Oehlke et al. 1998)
KLA-R7	KLAKLAKKLAKLAKGGRRRRRRR (Lemeshko, 2013)
KP	MAPTKRKGSCPGAAPNKKP (Villa-Cedillo et al. 2017)
KST peptide	STGKANKITITNDKGRLSK (Adachi et al. 2017)
L1−6	PLILLRLLR (Schmidt et al. 2017)
L5a	RRWQW (Liu et al. 2016a)
L17E	IWLTALKFLGKHAAKHEAKQQLSKL (Akishiba et al. 2017)
lactoferrampin(265-284)	DLIWKLLSKAQEKFGKNKSR (Reyes-Cortes et al. 2017)
lactoferricin(17-30)	FKCRRWQWRMKKLG (Reyes-Cortes et al. 2017)
lactoferrin(19-40)	KCFMWQEMLNKAGVPKLRCARK (Duchardt et al. 2009)
LAH1	KKLALALALALHALALALALKKA (Moulay et al. 2017)
LALF(31-52)	HYRIKPTFRRLKWKYKGKFW (Yanez et al. 2017)
LB	FKCRRWQWRMKKLGAPSITCVRRAF) (Liu et al. 2013b)
L-CPP	LAGRRRRRRRRRK (Liu et al. 2006)
LDP-NLS	KWRRKLKKLRPKKKRKV (Ponnappan and Chugh, 2017)
LE10	LELELELELELELELELELE (Antunes et al. 2013)
LF chimera	FKCRRWQWRMKKLG-K-RSKNKGFKEQAKSLLKWILD (Reyes-Cortes et al. 2017)

(continued)

Table 1.1 (continued)

linTT1	AKRGARSTA (Hunt et al. 2017)
LK	LKKLLKLLKKLLKLAG (Kim et al. 2016b)
LL37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES (Kim et al. 2016b)
LLIIL	LLIIL (Alaybeyoglu et al. 2017)
LMWP	VSRRRRRRGGRRRR (Chen et al. 2017d)
LP-12	HIITDPNMAEYL (Kumar et al. 2015)
LPAs	RC_nRC_nK (Gupta et al. 2011)
LTV	LTVSPWY (Chopra 2012)
lycosin-I	RKGWFKAMKSIAKFIAKEKLKEHL (Tan et al. 2017)
Lyp1	CGNKRTRGC (Fogal et al. 2008)
M918	MVTVLFRRLRIRRACGPPRVRV (El-Andaloussi et al. 2007)
Maurocalcine	GDCLPHLKLCKENKGCCSKKCKRRGTNIEKRCR (Poillot et al. 2010)
MAP	KLALKLALKALKAALKLA (Oehlke et al. 1998)
MAP12	LKTLTETLKELTKTLTEL (Oehlke et al. 2002)
MCoTI-I	polycyclic SGSDGGVCPKILQRCRRDSDCPGACICRGNGYCG (Camarero, 2017)
MCoTI-II	polycyclic CPKILKKCRRDSDCPGACICRGNGYCGSGSDGGV (Huang et al. 2015)
MFK	MFKLRAKIKVRLRAKIKL (Samuels et al. 2017)
Mgpe9	CRRLRHLRHHYRRRWHRFRC (Vij et al. 2016a)
MitP	INLKKLAKL(Aib)KKIL (Howl et al. 2018)
m(KLA)-iRGD	klaklakklakla-K-GG-iRGD (Qifan et al. 2016)
MMGP1	MLWSASMRIFASAFSTRGLGTRMLMYCSLPSRCWRK (Pushpanathan et al. 2013)
MPER fragment	ELDKWASLWNWFDITNWLWYIK (Song et al. 2009)
MPG	GALFLGFLGAAGSTMGA cysteamide (Morris et al. 1997)
MPG	GALFLGFLGAAGSTMGASQPKKKRKV cycteamide (Deshayes et al. 2005)
MPG-8	AFLGWLGAWGTMGWSPKKKRK (Crombez et al. 2009b)
mRVG	YTIWMPENPRPGTPCDIFTKSRGKRASNGGGRRRRRRRRR (Villa-Cedillo et al. 2017)
MT23	LPKQKRRQRRRM (Zhou et al. 2017)
mtCPP1	r-Dmt-OF (Cerrato et al. 2015)
MTM	AAVALLPAVLLALLAP (Fletcher et al. 2010)
MTD84	AVALVAVVAVA (Lim et al. 2014)
MTP	MLSLRQSIRFFK (Chuah et al. 2015a, b)
MTS	KGEGAAVLLPVLLAAPG (Zhao et al. 2001)
MTS1	AAVLLPVLLAAP (Rojas et al. 1998)
Mut3DPT-C9h	VKKKKIKAEIKIYVETLDDIFEQWAHSEDL (de la Torre et al. 2017)

(continued)

Table 1.1 (continued)

Myr-ApoE	Myr-LRKLRKRLLR (Tajik-Ahmadabad et al. 2017)
New modalities	Polycyclic, hairpin, stapled peptides for delivery (Valeur et al. 2017, Waldmann et al. 2017)
NF1	Stearyl-AGY(PO3)LLGKTNLKALAALAKKIL (Arukuusk et al. 2013)
NF51	δ-(Stearyl-AGYLLG)OINLKALAALAKKIL (Arukuusk et al. 2013)
NF55	δ-(Stearyl-AGYLLG)OINLKALAALAKAIL (Freimann et al. 2016)
NLS	PKKKRKV (Yoneda et al. 1992).
NLS-StAx-h	stapled RRWPRXILDXHVRRVWR (Dietrich et al. 2017)
NoLS	KKRTLRKNDRKKRC (Yao et al. 2015)
Novicidin	KNLRRIIRKGIHIIKKYF (Milosavljevic et al. 2016)
NPFSD	VLTNENPFSDP (Gong et al. 2016)
NYAD-1	stapled ITFEDLLDYYGP (Zhang et al. 2008)
Oct4-PTD	DVVRVWFCNRRQKGKR (Adachi et al. 2017)
P007	Ac-$(RAhxR)_4$-Ahx-βAla (Greer et al. 2014)
P1	LRRWSLG (Peng et al. 2017b)
P2	WKRTLRRL (Peng et al. 2017b)
P3	YGRKKRRQR (Tan et al. 2006)
P7	RRMKWKK (Watson et al. 2017)
P11	YGRKKRRQRRR (Zhao et al. 2011)
P11	HSDVHK (Bang et al. 2011)
P11LRR	P11LRR (Li et al. 2010)
P14LRR	$(P_L P_R P_R)_4$ (Brezden et al. 2016)
p18	LSTAADMQGVVTDGMASG (Taylor et al. 2009)
P21	KRKKKGKGLGKKRDPCLRKYK (Dixon et al. 2016)
P28	LSTAADMQGVVTDGMASGLDKDYLKPDD, Leu^{50}-Asp^{77} of azurin (Yamada et al. 2016)
p28	FLHSGTAVTCTYPALTPQWEGSDCTHRL (Signorelli et al. 2017)
p53 peptide MO6	Stapled TSF*EYWYLL* (Chee et al. 2014)
PAF26	Ac-rkkwfw (Lopez-Garcia et al. 2002)
PAS	GKPILFF (Woldetsadik et al. 2017)
pCLIP6	KVRVRVRVpP(pT)RVRERVK (Chen et al. 2017b)
pD-SP5	riPRPSPKMGV(pS)VS (Chen et al. 2017b)
PenetraMax	KWFKIQMQIRRWKNKR, L- and D- (Khafagy el et al. 2015)
Penetratin	RQIKIWFQNRRMKWKK (Derossi et al. 1994)
Pep-1	KETWWETWWTEWSQPKKKRKV cysteamide (Morris et al. 1997)
pepM	KLFMALVAFLRFLTIPPTAGILKRWGTI (Freire et al. 2014)
pepR	LKRWGTIKKSKAINVLRGFRKEIGRMLNILNRRRR (Freire et al. 2014)
Pept1	PLILLRLLRGQF (Marks et al. 2011)

(continued)

Table 1.1 (continued)

Peptide 599	GLFEAIEGFIENGWEGMIDGWYGGGGRRRRRRRRRK (Alexander-Bryant et al. 2015)
Pep42	Cyclic CTVALPGGYVRVC (Kim et al. 2006)
PepNeg	SGTQEEY (Neves-Coelho et al. 2017)
PepFect6	Stearyl-AGYLLGK(εTMQ)INLKALAALAKKIL, PF6 (El-Andaloussi et al. 2011)
PepFect14	Stearyl- AGYLLGKLLOOLAAAALOOLL (Ezzat et al. 2011)
PG1	RGGRLCYCRRRFCVCVGR (Liu et al. 2013b)
pHLIP	AEQNPIY-WARYADWLFTTPLLLLDLALLV-DADEGT (Andreev et al. 2010)
PHPs	H6-H10 peptides (Kimura et al. 2017)
PIP1	RXRRXRRXRIKILFQNRRMKWKK (Ivanova et al. 2008)
Pip5e	RXRRBRRXRILFQYRXRBRXRB (Betts et al. 2012)
Pip6a	Ac-RXRRBRRXRYQFLIRXRBRXRB (Lehto et al. 2014)
POD	CGGG(ARKKAAKA)$_4$ (Dasari et al. 2017)
PR9	FFLIPKG-R$_9$ (Liu et al. 2013a)
PTD	YARVRRRGPRRR (Dong et al. 2016)
PTD3	R9-ETWWETWWTEW (Kizaka-Kondoh et al. 2009)
PTD4	YARAAARQARA (McCusker et al. 2007)
Poly-Arg	Most popular R7 - R12 (Mitchell et al. 2000, Futaki, 2006)
pVEC	LLIILRRRIRKQAHAHSK (Elmquist et al. 2001)
Pyrrhocoricin	VDKGSYLPRPTPPRPIYNRN (Otvos et al. 2000)
R4K1	Stapled Ac-RRRRKS*LHRS*LQDS (Speltz et al. 2018)
R6dGR	R6dGR (Wang et al. 2017)
R8	R8 (Wender et al. 2001)
R8-dGR	R8dGR (Liu et al. 2016b)
R9-H4A2	Ac-YR9-HAHAHH (Okitsu et al. 2017)
R_6W_3	R_6W_3 (Bechara et al. 2013)
$R_{10}W_6$	$R_{10}W_6$ (Bechara et al. 2013)
RA9	RRAARRARR (Alhakamy et al. 2013)
RALA	WEARLARALARALARHLARALARALRACEA (McCarthy et al. 2014)
RDP	CKSVRTWNEI IPSKGCLRVG GRCHPHVNGG GRRRRRRRRC (Xiao et al. 2017)
REDV	REDV (Yang et al. 2016)

(continued)

Table 1.1 (continued)

RF	GLKKLARLFHKLLKLGC (Yang et al. 2014)
cRGDfC	Cyclic RGDfC (Wada et al. 2017)
iRGD	Cyclic CRGDKGPDC (Peng and Kopecek, 2015)
RGE	RGERPPR (Yu et al. 2017)
RH9	RRHHRRHRR (Alhakamy et al. 2013)
RL9	RRLLRRLRR (Alhakamy et al. 2013)
RL16	RRLRRLLRRLLRRLRR (Joanne et al. 2009)
RT53	RQIKIWFQNRRMKWKKAKLNAEKLKDFKIRLQYFARGLQV YIRQLRLALQGKT (Jagot-Lacoussiere et al. 2016)
RTP004	RKKRRQRRRG-K15-GRKKRRQRRR) (Lee et al. 2015a)
RV24	RRRRRRRRRGPGVTWTPQAWFQWV (Lo and Wang, 2012)
RVG	YTIWMPENPRPGTPCDIFTNSRGKRASNG (Kumar et al. 2007)
RVG-9R	YTIWMPENPRPGTPCDIFTNSRGKRASNGGGGRRRRRRRRR (Rassu et al. 2017)
RVG29	YTIWMPENPRPGTPCDIFTNSRGKRASNGGGGRRRRRRRRR (Villa-Cedillo et al. 2017)
RW9	RRWWRRWRR (Alhakamy et al. 2013)
RW16	RRWRRWWRRWWRRWRR (Jobin et al. 2013)
$(RXR)_4$	$(R\text{-}Ahx\text{-}R)_4$ (Saleh et al. 2010)
$(rXr)_4$	$(r\text{-}Ahx\text{-}r)_4$ (Vij et al. 2016b)
S155	VKKKKIKREI-KIAAQRYGRELRRMADEFHV (Haidar et al. 2017)
S4(13)-PV	ALWKTLLKKVLKAPKKKRKV (Mano et al. 2007)
SAP	VRLPPPVRLPPPVRLPPP (Pujals et al. 2006)
SAP(E)	VELPPPVELPPPVELPPP (Martin et al. 2011)
all-D-SAP	$(vrlppp)_3$ (Pujals et al. 2007)
SAPSp-lipo	stearyl-GGGGHGAHEHAGHEHAAGEHHAHE (Suzuki et al. 2017)
SAR6EW	SAR6EW (Im et al. 2017)
sC18	GLRKRLRKFRNKIKEK (Oren et al. 1999)
$(sC18)_2$	$(GLRKRLRKFRNKIKEK)_2$ (Gronewold et al. 2017)
SMTP motif,	LRLLR (Fuselier and Wimley, 2017)
SPACE	Cyclic ACTGSTQHQCG (Hsu and Mitragotri, 2011)
SRCRP2-11	GRVEVLYRGSW (Tuttolomondo et al. 2017)
STR-KV	$H_3K_3V_6$ (Pan et al. 2016)
SS-02	Dmt-r-FK (ALTA et al. 2017)
SS-20	F-r-FK (Alta et al. 2017)
SS-31	r-Dmt-KF (Zhao et al. 2005)
SynB1	RGGRLSYSRRRFSTSTGR (Rousselle et al. 2000)
T2	LVGVFH (Kumar et al. 2012)

(continued)

Table 1.1 (continued)

Tat(49-57)	RKKRRQRRR (Vives et al. 1997a)
Tat(48-60)	GRKKRRQRRRPPQ (Vives et al. 1997b)
Tat(44-57)	CGISYGRKKRRQRRR (Niesner et al. 2002)
Tat(37-72)	CFITKALGISYGRKKRRQRRRPPQGSQT-HQVSLSKQ (Fawell et al. 1994)
Tat analog	GRKKRRQR (Nguyen et al. 2008)
Tat-LK15	Tat-KLLKLLLKLLLKLLK (Peng et al. 2017a)
TCTP	MIIFRALISHKK (Bae et al. 2016)
TD-1	ACSSSPSKHCG (Chen et al. 2006)
TD2.2	SYWYRIVLSRTGRNGRLRVGRERPVLGESP (Heffernan et al. 2012)
TH peptide	GYLLGHINLHHLAHL-Aib-HHIL (Chen et al. 2017a)
TM2	PKKGSKKAVTKAQKKDGA (Kochurani et al. 2015)
Transportan	GWTLNSAGYLLGKINLKALAALAKKIL, TP (Pooga et al. 1998)
TP10	AGYLLGKINLKALAALAKKIL (Soomets et al. 2000)
TPk	VRRFkWWWkFLRR (Bahnsen et al. 2015)
Tpl	KWCFRVCYRGICYRRCRGK (Jain et al. 2015)
TPP	TKDNNLLGRFELSG (Gehrmann et al. 2014)
TT1	CKRGARSTA (Paasonen et al. 2016)
vAMP 059	INWKKWWQVFYTVV (Dias et al. 2017)
vCPP 0769	RRLTLRQLLGLGSRRRRRSR (Dias et al. 2017)
vCPP 2319	WRRRYRRWRRRRRWRRRPRR (Dias et al. 2017)
VDAC(1-26)	MAVPPTYADLGKSARDVFTKGYGFGL (Smilansky et al. 2015)
VP22	NAATATRGRSAASRPTQRPRAPARSASRPRRPVQ (Elliott and O'Hare, 1997)
V peptide	TVDNPASTTNKDKLFAVRK (Manosroi et al. 2014)
VT5	DPKGDPKGVTVTVTVTVTGKGDPKPD (Oehlke et al. 1997)
$W(RW)_4$	$W(RW)_4$ (Nasrolahi Shirazi et al. 2013)
Xentry	LCLR (Montrose et al. 2014)
X-pep	MAARLC (Adachi et al. 2017)
YKA	YKALRISRKLAK (Desai et al. 2014)
YTA2	YTAIAWVKAFIRKLRK (Lindgren et al. 2006)
YTA4	IAWVKAFIRKLRKGPLG (Lindgren et al. 2006)
Z2	FWIGGFIKKLKRSKLA (Chen et al. 2017c)
Z3	FKIKKFIGGLWRSKLA (Chen et al. 2017c)
Z12	KRYKNRVASRK**C**RAKFKQLLQHYREVAAAKSSENDRLRLLLK (Derouazi et al. 2015)
ZXR-1	FKIGGFIKKLWRSKLA (Chen et al. 2017c)

Different CPP uptake experiments are also compared since it is becoming clear that it is often best to apply several methods in a complementary manner in order to most comprehensively evaluate CPP uptake mechanisms due to the complexity of these processes. A brief summary of functionality issues of CPPs, both in vitro and in vivo are discussed.

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It was suggested that cell-penetrating proteins might represent a very ancient mechanism of communication between cells (Joliot and Prochiantz 2008) triggering signal transduction cascades inside cells yielding changes in the gene expression pattern (Prochiantz et al. 2014; Layalle et al. 2011). We are currently embracing many novel possibilities whereby our understanding of Nature's ancient machinery, can transform the very nature of our future therapeutic applications.

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