

Therapeutic peptides targeting PPI in clinical development: overview, mechanism of action and perspectives

Walter Cabri, Paolo Cantelmi, Dario Corbisiero, Tommaso Fantoni, Lucia Ferrazzano, Giulia Martelli, Alexia Mattellone and Alessandra Tolomelli*

Department of Chemistry “Giacomo Ciamician”, Alma Mater Studiorum University of Bologna, Via Selmi 2, 40126, Bologna (ITALY)

*** Correspondence:**

Corresponding Author

alessandra.tolomelli@unibo.it

Keywords: oligopeptides, clinical trials, protein-protein interactions, mode of action, route of administration

SUPPORTING MATERIAL

Table 1S: Peptides with protein-protein interaction against specific tumors under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure ^b	AA(UAA)	CLASS ^b	RoA
Dolcanatide (SP-333)	Bausch Health Companies Inc; National Cancer Institute	Guanylyl Cyclase-C Receptors	Preventing colorectal cancer	NCT03300570	1	nDEC(1)ELC(2)VNVAC(1)TGC(2)l	16	A	Oral
				NCT01983306	2				
BBT-401-1S (BBT-401)	Bridge Biotherapeutics Inc.	Pellino-1-Protein	Ulcerative Colitis	NCT04596293	2	U	4	H	Oral
Elsiglutide (ZP-1846)	Zealand Pharma	GLP-2 Receptor	Adjuvant therapy for Induced Diarrhea in colorectal cancer patients	NCT02383810	2	HGEGSFSSSELSTILDALAARDF IAWLIATKITDKKKKKK	39	A	SC
Ozarelix (D-63153)	Spectrum Pharmaceuticals	Gonadotropin-Releasing Hormone Receptor	Prostate Cancer	NCT01252693	2	Ac-D-2Nal-D-Phe(4-Cl)-D-3Pal-S-N(Me)Tyr-D-hCit-Nle-RPa-NH ₂	10(6)	A	SC
Fexapotide (NX-1207)	Nymox Pharmaceutical Corporation	-	Benign Prostatic Hyperplasia/Lower Urinary Tract	NCT01620515	2	IDQQVLSRIKLEIKRCL	17	U	I-PROSTAT
				NCT01846793	3				
Foxy-5 (Foxy 5)	WntResearch AB	Receptor of Wnt5a	Metastatic Prostate, Breast & Colon Cancer	NCT03883802	2	N-Formyl-MDGCEL	6	A	IV
				NCT02655952	1				
VT1021	Vigeo Therapeutics	CD36 And CD47	Solid Tumor	NCT03364400	1	U	5	U	U
EP-100	Esperance pharmaceuticals Inc.	Luteinizing Hormone Releasing Hormone Receptor	Ovarian Cancer, Breast Cancer	NCT00949559	1	KFAKFAKKFAKFAKKFAKQH WSYG-Lau-RPCONHBn	27(1)	A	IV
				NCT01485848	2				
Balixafortide^a (POL6326)	Polyphor Ltd.	Cxc Chemochine Receptor 4	Metastatic breast cancer	NCT03786094	3	AC(1)SAP-Dab-RYC(1)YQKPPYH	16(1)	H	Oral
				NCT01413568	1/2				
BNZ132-1-40 (BNZ-1)	Bioniz Therapeutics	IL-2, IL-9, IL-15 Cytokines	Cancer and autoimmune diseases	NCT03239392	1/2	IKEFLQRFIHIVQSIINTS	19	H	IV
ALM 201 (ALM201/0001; ALM-201)	Almac Discovery	Surface Receptor CD44	Solid Tumor, Ovarian Cancer	NCT03427073	1	IRQQPQDPPTETLELEVSPDPA S	23	H	SC
Tyroserleutide (YSL)	Shenzedn Kangzhe Pharmaceutical Co.	Protein Expression Of Cam;Activity of PI3K	Primary Hepatocellular Carcinoma	NCT03516448	3	YSL	3	U	Oral

Legenda: Nal: 2-naphtyl-alanine; Pal: palmitic acid; hCit: homocitrulline; Nle: norleucine; Lau: aminolauric acid; Dab: 2,4-diaminobutyric acid

^aBalixafortide is also active on another pathology: see Table 5. ^bA=Analogous; N=Native; H=Heterologous; U=Undisclosed.

Table 2S: Peptides with protein-protein interaction against uncontrolled inflammation and autoimmune response under clinical trial.

Name (alternative)	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure ^a	AA (UAA)	Class ^a	RoA	RoA
Forigerimod (Lupuzor™; IPP-201101)	ImmuPharma	T-cells	Systemic Lupus Erythematosus (SLE)	NCT03427151	3	RIHMOVYSKRO(p)SGKPRGYA FIEY	21 (1)	H	SC	SC
Difelikefalin (CR 845, KORSUVA®)	Cara Therapeutics	peripheral k-opioid receptor	Pruritus, postoperative pain	NCT03636269	NDA	fflk-[γ-(4-N-piperidiny)amino carboxylic acid]	5 (5)	H	IV	IV
				NCT03995212	2				Oral	Oral
				NCT04706975	2				Oral	Oral
				NCT02542384	2/3				IV	IV
EA 230 (Peptide 46)	Exponential Biotherapies	hormonal milieu	Systemic Inflammatory Response Syndrome (SIRS)	NCT03145220	2	AQGV	4	H	IV	IV
LSALT peptide (Metablok™)	Arch Biopartners	DPEP-1	Acute Respiratory Distress Syndrome (ARDS)	NCT04402957	2	NH3-LSALTSPSWLKYKAL-COOH	16	H	IV	IV
Brimapitide (AM-111, XG-102, Sonsuvi®)	Auris Medical	Mitogen-activated protein kinase 8	Acute Sensorineural Hearing Loss (ASNHL) and ocular inflammation	NCT02508337	3	dqsrvpqpflnlttrkprprrrrqrkkkrG	31 (30)	H	S-CONJUN C	SC
Timbetasin (RGN259, Thymosin B4, Thymosin beta-4)	RegeneRX Biopharmaceuticals	Thymosin β(4)	Dry eye	NCT03937882	3	Ac-SDKPDMAEIEKFDKSKLKKTE TQEKNPSPKETIEQEKQAGE S	43	A	OPHTH ALM	Ophthalm
TPX-100	OrthoTrophix	SIBILING proteins	Knee osteoarthritis	NCT02837900	2	U	U	U	I-ARTIC	I-Artic
Aviptadil (RLF-100™, ZYESAMI™)	NeuroRX and Relief Therapeutics Holding	VPAC1 on AT2 cells	Pulmonary Hypertension (PH) and Acute Respiratory Distress Syndrome (ARDS)	NCT04360096	3	HSDAVFTDNYTRLRKQMAV KKYLNLSILN	28	H	NASAL	Respir
Larazotide (AT-1001; INN-202; Larazotide acetate; SPD 550)	9 Meters Biopharma	Zonulin Receptor	Celiac disease	NCT03569007	3	GGVLVQPG	8	A	Oral	Oral

Legenda: (p)S: serine phosphate. ^aA=Analog; N=Native; H=Heterologous; U=Undisclosed.

Table 3S: Peptides with protein-protein interaction against hormonal hearing and visual genetic diseases under clinical trial.

Name (alternative)	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure	AA (UAA) ^a	Class ^a	RoA
HTL0030310	Sosei Heptares	Somatostatin receptor 5	Endocrine disorders	NCT03847207	1	U	U	U	SC
Vosoritide (BMN-111)	BioMarin Pharmaceutical	Fibroblast growth factor receptor 3; Atrial natriuretic factor receptor B	Achnondroplasia	NCT03424018 NCT04219007	NDA 2	PGQEHPNARKYKGANCKGLSK GC(1)FGLKLDRIKMSGLGC(1)	39	H	SC

^aA=Analog; N=Native; H=Heterologous; U=Undisclosed.

Table 4S: Peptides with protein-protein interaction designed from proglucagone fragments against diabetes, obesity, SBS and hyperinsulinemia under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure ^a	AA(UAA)	CLASS ^a	RoA
G3215	Imperial College	GLP-1R	Type 2 Diabetes Mellitus/Obesity	NCT02692040	1	U	U	A	SC
Noiglutide (HTI-2088; HS20004)	Jiangsu Hansoh Pharmaceutical	GLP-1R	Type 2 Diabetes Mellitus	NCT03848793	2	H-Aib- EGTFTSDVSSYLEEEAAKEFIAWLVRGGPSSGA PPPSK-Pal	40(1)	A	SC
PB-119 (PEG Exenatide)	PegBio Co. Ltd	GLP-1R	Type 2 Diabetes Mellitus	NCT04504370; NCT04504396	3	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSS GAPPPC(PEG)-NH ₂	39	A	SC
Avexitide (exendin 9-39)	Eiger BioPharmaceuticals	GLP-1R	Hyperinsulinemic Hypoglycemia	NCT04652479	2	DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS- NH ₂	31	A	SC
Apraglutide (FE203799)	VectivBio	GLP-2R	Short Bowel Syndrome	NCT04627025	3	HGDGSFSDE-Nle- FTILDLLAARDFINWLIQTKITD-NH ₂	33(2)	A	SC
Glepaglutide (ZP1848)	Zealand Pharma	GLP-2R	Short Bowel Syndrome	NCT03690206	3	HGEGTFSSELATILDALAARDFIAWLIATKITDK KKKKK-NH ₂	39	A	SC
Dapiglutide (ZP7570)	Zealand Pharma	GLP-1R/ GLP-2R	Short Bowel Syndrome	NCT04612517	1	U	U	U	SC
CT-868	Carmot Therapeutics	GLP-1R/ GIPR	Type 2 Diabetes Mellitus	ACTRN126180 01988246	1	U	U	U	SC
SCO-094 (TAK-094)	Scohia Pharma	GLP-1R/ GIPR	Type 2 Diabetes Mellitus	JapicCTI- 205323	1	U	U	U	SC
Tirzepatide (LY3298176)	Eli Lilly	GLP-1R/ GIPR	Type 2 Diabetes Mellitus	NCT03861039	3	Y-Aib-EGTFTSDYSI-Aib-LDKIAQK((AEEA) ₂ -γ-E- C20-diacid)-AFVQWLIAGGPSSGAPPPS -NH ₂	39(2)	A	SC
Pegapamodutide (LY2944876; TT401; MOD-601; OPK88003)	OPKO Health	GLP-1R/ GCCR	Type 2 Diabetes Mellitus	NCT03406377	2	H-Aib-QGTFTSDYSKYLDKSKKAQEFVQWLLN- Aib-GRNRNNIAC(MAL-PEG)-C(MAL-PEG)-NH ₂	39(2)	A	SC

BI456906 (ZP2929)	Zealand Pharma	GLP-1R/ GCGR	Type 2 Diabetes Mellitus/Obesity/ NASH	NCT04771273	2	U	U	U	SC
Cotadutide (MEDI0382)	Astra Zeneca	GLP-1R/ GCGR	Type 2 Diabetes Mellitus/Obesity	NCT03555994	2	HSQGTFTSDK(γ -E-Pal)- SEYLDSEARDFVAVLEAGG	30	A	SC
ALT-801 (SP1373; VPD-107)	AltImmune	GLP-1R/ GCGR	NASH	NCT04561245	1	H-Aib-QGTFTSDYSKYLD* K (GC18c)- AAK*EFIQWLLQT-NH ₂	29(1)	A	SC
AM833 (NN9838; NNC0174-0833)	Novo Nordisk	AMY	Obesity	NCT03856047	2	U	U	A	SC
LY3305677 (OXM3, IBI362)	Ely Lilly	GLP-1R/ GCGR	Obesity/Diabetes	NCT03928379	2	U	U	A	SC
PYY-1875 (NNC0165-1875)	Novo Nordisk	Y2R	Obesity	NCT03707990	1	U	U	A	SC
GT-001 (PeptideYY(3-36))	Gila Therapeutics	Y2R	Obesity/Diabetes	NCT03490786	1	IKPEAPGEDASPEELNRY ^a YASLRHYLNLVTRQR Y-NH ₂	34	N	TOPIC
LY3437943	Ely Lilly	GLP-1R/ GIPR/ GCGR	Obesity/Diabetes	NCT04143802	1	U	U	A	SC
Dasiglucagon (ZP 4207; HypoPal®)	Zealand Pharma	GCGR	Hyperinsulinemic Hypoglycemia/		NDA	HSQGTFTSDYSKYLD-Aib-ARAEFVKWLEST	29(1)	A	SC

Legenda: Aib: 2-aminoisobutyric acid; Pal: palmitic acid; Nle: norleucine; PEG: polyethylene glycol; AEEA: 8-amino-3,6-dioxaoctanoic acid dimer; C20-diacid: eicosanedioic acid; Mal: maleimide.

^aA=Analogous; N=Native; H=Heterologous; U=Undisclosed. ^b See text for detailed description of the structure.

Table 5S: Peptides as drug for the treatment of cardiovascular system and hypertension with protein-protein interaction under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure	AA (UAA)	Class ^b	RoA
Ularitide (Urodilatin)	Cardiorentis	Natriuretic peptide receptor-A	Acute Decompensate Heart Failure (ADHF)	NCT01661634	3	YAPRSLRRSSC(1)FGGRMDRIGASGLGC(1)NSFRY	32	A	IV
CN-105 (Ac-VSRRR-NH ₂)	AegisCN	LDL receptor	Intracerebral Hemorrhage/Stroke	NCT03168581	2	Ac-VSRRR-NH ₂	5	A	IV
Pemziviaptadil (PB1046, Vasomera™)	PhaseBio Pharmaceuticals	Vasoactive intestinal peptide type II receptor	Pulmonary Arterial Hypertension	NCT03556020	2	ELP-MHSDAVFTDNYTRLRKQMAVKKYLNSILN	29	A	SC
Nerinetide (NA-1, Tat-NR2B9c)	NoNO Inc.	PSD-95	Stroke, Acute	NCT04462536	3	YGRKKRRQRRRKLSSIESDVYGRKKRRQRRR	31	A	IV
Balixafortide^a (POL6326)	Polyphor Ltd.	Cxc Chemochine Receptor 4	Large Reperfused ST-Elevation Myocardial Infarction	NCT01905475	2	AC(1)SAP{Dab}RYC(1)YQKPPYH	16	H	Oral

Legenda: Dab: 2,4-diaminobutyric acid;

^aBalixafortide is also active on other pathologies: see Table 1. ^bA=Analogous; N=Native; H=Heterologous; U=Undisclosed

Table S6: Peptides as drug for the treatment of degenerative diseases with protein-protein interaction under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure	AA (UAA)	Class ^a	RoA
Alirinetide (GM6-GM604)	Genervon	Multi-target	Amniotropic lateral sclerosis	NCT01854294	2	FSRYAY	6	N	IV
Davunetide (NAP, AL-108)	Allon Therapeutics/University of California, San Francisco (UCSF)	Microtubule-associated protein modulators;	Progressive supranuclear palsy	NCT01056965	1	NAPVSIPQ	8	N	NASAL
RA101495 (Zilucoplan)	UCB Pharma	Complement C5 inhibitors	Myasthenia gravis	NCT04225871	3	Ac-K(1)-VERFD(1)-D(NMe)-G(tBu)-YW(Aza)-EYPG(Cy)-K-PEG-γ-E-Pal	15(4)	H	SC
NLY01 (TLY 001)	Neuraly	GLP-1R	Alzheimer/ Parkinson Disease	NCT04154072	2	HGEGTFTSDLSKQMEEEEAVRLFIEWLKNNGPSSGAPPPSC-PEG	40	A	SC

Legenda: W(Aza): 7-azatryptophan, G(Cy): N-cyclohexyl-glycine; Pal: palmitic acid; PEG: polyethylene glycol

^aA=Analogous; N=Native; H=Heterologous.

Table S7: Peptides as antibiotic and antiviral with protein-protein interaction under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure	AA (UAA)	Class ^a	RoA
Nangibotide (Motrem™, LR-12)	Inotrem	TREML1 protein inhibitors	Shock, Septic; COVID 2019 infections	NCT04055909 NCT04429334	2 2	LQEEDAGEYGCM-NH ₂	12	N	IV
Reltecimod (AB103)	Atox Bio	B7-2/CD28	necrotizing soft tissue infection.	NCT02469857	NDA	aSPMLVAYDa	10 (2)	A	IV
C16G2	armata pharm.	Mechanism unclear	Dental Caries	NCT03196219	2	TFFRLFNRSFTQALGKGGGKNLRIIRKGIHIKKY-NH ₂	35	A	Oral

^aA=Analog; N=Native; H=Heterologous.

Table S8: Peptides with protein-protein interaction against different pathologies under clinical trial.

Name	Company	Biological Target	Target Disease	Clinical Trial Identifier	Clinical Phase	Structure	AA (UAA)	Class ^a	RoA
Hepcidin (LJPC-401)	La Jolla Pharm.Com.	Ferroportin-1	Hereditary Hemochromatosis	NCT03395704	2	DTHFPIC(1)IFC(2)C(3)GC(2)C(4)HRSKC(3)GMC(4)C(1)KT	25	N	SC
Ghrelin (OXE-103, SUN11031)	Oxeia Biopharm.	Unclear	Concussion, Brain Traumatic Brain Injury	NCT04558346	2	GSS(octadecyl)FLSPEHQRVQQRKESKKPPAKLQPR	28	N	SC
Solnatide (AP-301)	Apeptico	ENaC	Acute lung injury; Adult respiratory distress syndrome.	NCT03567577	2	C(1)GQRETPEGAEAKPWYC(1)	17	A	NASAL
TAK639 (SHP 639)	Takeda	type B natriuretic peptide receptor	Ocular hypertension/primary open-angle glaucoma (POAG)	NCT03131167	1	(S)-N-octanoyl-nipecotic acid-F-(R)-(N', N') dimethylornithine-L-(3-hydroxy)PLDRI-NH ₂	9	H	OPHTHALM

^aA=Analog; N=Native; H=Heterologous.