Research Advances in Stem Cell Therapy for Erectile Dysfunction – BioDrugs

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Declarations:

Funding: No funding received for preparation of this manuscript.

Competing interests: The authors declare that they have no competing interests.

Supplementary table 1 Summarizes stem cell studies aimed at ED in cavernous nerve injury

Author (year)	animal model	stem cell type	Transplant method	transfection	Follow-up time	number	Erectile function	Histological\ molecular
Bochinski e al. ^[1] (2004)	t CNI rat	Neuronal ESC labeled with GFP	ICI or MPG	BDNF	3 month	5x10 ³	CNS	NOS,tyrosine hydroxylase,NF
Kim et al. ^[2] (2006)	CNI rat	MDSCs	ICI	lacZ	2 and 4 weeks	1x10 ⁶	CNS	positively stained with PGP 9.5, lacZ
Fall et al. ^[3] (2009)	BCNA rat	BMMNC labeled with PKH-26	ICI	-	3 and 5 weeks	1x10 ⁷	CNS	nNOS,eNOS,cavernosal cellular
Albersen e al. ^[4] (2010)	t CNI rat	ADSCs labeled with Edu and ADSC-derived lysate	ICI	-	4 weeks	1x10 ⁶	CNS	nNOS,a-SMA,reticular subtype III collagen
Kendirci e al. ^[5] (2010)	t CNI rat	multipotent stromal cells	ICI	p75 derived GFP transgenic	4 weeks	5x10 ⁵	CNS	VEGF,NGF,BDNF,FGF,IGF
Lin et al. ^[6] (2011)	CNI rat	ADSCs labeled with Edu	ICI	-	2 and 7 days	1x10 ⁶	-	cell index
Lin et al. ^[7] (2011)	CNI rat	ADSCs labeled with Edu	ICI	-	3 months	-	CNS	S100,nNOS
Woo et al. ^[8] (2011)	CNI rat	MDSCs labeled with PKH-26	ICI	-	4 weeks	1x10 ⁶	CNS	cGMP level
Fandel et al. ^[9] (2012)	CNI rat	ADSCs labeled with Edu	ICI or around the dorsal nerve	-	1,3,7 days and 4 weeks	2x10 ⁶	CNS	nNOS,SDF-1
SJ Kim et al. ^[10] (2012) CNI rat	BMSCs	MPG	-	4 weeks	1x10 ⁶	CNS	nNOS,eNOS
SJ Kim et al. ^[11] (2012) CNI rat	BMSCs labeled with PKH-26	MPG	BDNF	4 weeks	1x10 ⁶	CNS	nNOS,eNOS
Kovanecz e al. ^[12] (2012)	t CNI and aging rat	MDSCs	-	Oral sildenafil	42 days	1x10 ⁶	CNS	Collagen,α-SMA,nNOS,NF-70,Calponin 1,SHP-2,BAX,BDNF,PDE5

Piao et al. ^[13] (2012)	CNI rat	ADSCs labeled with PKH-26	around the cavernous nerve	BDNF	4 weeks	1x10 ⁶	CNS	nNOS,eNOS,cGMP
Qiu et al. ^[14] (2012)	CNI rat	ADSCs labeled with Edu	tail-vein;	-	17 weeks	1x10 ⁶	CNS	nNOS,a-SMA,vWF,S-100
Qiu et al. ^[15] (2012)	CNI rat	ADSCs derived SVF	ICI	-	12 weeks	2x10 ⁶	CNS	nNOS,NF,Smooth muscle
Jeong et al. ^[16] (2013)	CNI rat	ADSCs	around the cavernous nerve	BDNF; Oral udenafil	4 weeks	1x10 ⁶	CNS	nNOS,VEGF,SMA,cGMP
You et al. ^[17] (2013)	CNI rat	ADSCs labeled with Cell STALKER	PPI or ICI	-	4 weeks	1x10 ⁶	CNS	nNOS,α-SMA,β-actin
You et al. ^[18] (2013)	CNI rat	BMSCs labeled with Cell STALKER	PPI or ICI	-	4 weeks	1x10 ⁶	CNS	nNOS
IG Kim et al. ^[19] (2013)	CNI rat	ADSCs labeled with PKH-26	around the cavernous nerve	NGF	4 weeks	1x10 ⁶	CNS	eNOS,α-SMA
Choi et al. ^[20] (2013)	CNI rat	BMSCs and HTSCs labeled with CM-DiI	PPI	-	4 weeks	1x10 ⁷	CNS	Stem-121 [™] ,β-tubulin class III
Ying et al. ^[21] (2013)	CNI rat	ADSCs	ICI	-	3 months	1x10 ⁶	CNS	nNOS,β-actin
Ying et al. ^[22] (2014)	CNI rat	ADSCs autologous vein graft	-	-	3 mongths	1x10 ⁶	CNS	nNOS
Miyamoto et al. ^[23] (2014)	CNI rat	endothelial progenitor cells	around the cavernous nerve	CD133+ cells	4days and 12 weeks	1x10 ⁴	CNS	nNOS,vWF,α-SMA,HNA,NGF,VEGF
Mangir et al. ^[24] (2014)	CNI rat	ADCSs	ICI	-	4 weeks	1×105	CNS	nNOS
Lee et al. ^[25] (2014)	CNI rat	hADSCs labeled with PKH-26	around the cavernous nerve	BDNF,bFGF	4 weeks	1x10 ⁶	CNS	bFGF,nNOS,β-III tubulin;α-SMA;β-actin;cGMP level
Ryu et al. ^[26] (2014)	CNI rat	BMSCs labeled with PKH-26	ICI + IPI	-	2 weeks	3×10^5	CNS	PECAM-1, phosphohistone H3, α -actin, nNOS, NF, β -actin
Bae et al ^[27] (2014)	CNI rat	MSC	ICI	-	4 weeks	1x10 ⁶	CNS	bFGF,F-actin,cGMP level
Xu et al. ^[28] (2014)	CNI rat	ADSCs labeled with EdU	ICI	-	1, 3 ,7 ,14 and 28 days	2× 10 ⁶	CNS	nNOS,RECA-1,α-SMA
Yang et al. ^[29] (2015)	CNI rat	EdU-labeled ADSC	ICI	-	1 and 4 week	1x10 ⁶	CNS	NGF,VEGF,Neurturin,nNOS
Takayanagi et al. ^[30] (2015)	CNI rat	BMSCs labeled with PKH-26	right external jugular vein	-	1 hour and 2 weeks	1x10 ⁶	CNS	GDNF,neurturin
You et al. ^[31] (2015)	CNI rat	SVF and ADSCs labeled with PKH-26	ICI	-	4 weeks	1x10 ⁶	CNS	α-SMA,eNOS,vWF,nNOS
Zhu et al. ^[32] (2015)	CNI rat	HUCBMSCs	ICI	-	1,3,7,28 days	2x10 ⁶	CNS	nNOS, a-SMA
Chen et al. ^[33] (2016)	CNI rat	ADSCs labeled with Edu	ICI	-	2,7 and 14days	1×10^{6}	CNS	nNOS,S100,PEDF,Akt,eNOS
Jeon et al. ^[34] (2016)	CNI rat	ADSCs labeled with CM-Dil	around CNI	-	4 weeks	1×10^{6}	CNS	β-III tubulin,α-SMA,VEGF,nNOS,eNOS,cGMP levels
Yang et al. ^[35] (2016)	CNI rat	USCs	ICI	PEDF	4 weeks	1×10 ⁶	CNS	nNOS, CD31,eNOS, muscle to collagen ratio,NF,S100, Nestin, TGF- β
Lin et al. ^[36] (2016)	CNI rat	ADSCs	ICI and nanotechnology approach	-	1,3,5 and 9 days	1×10^{6}	CNS	α-SMA,PECAM-1
Martínez-Salamanca et al. ^[37] (2016)	CNI rat	BMSCs	ICI	-	4 weeks	1×10^{6}	CNS	NO,fibrosis
Wang et al. ^[38] (2018)	CNI rat	BMSCs	ICI	-	0, 2, 4 and 7 days	4×10 ⁵	CNS	vWF,VE-cadherin,eNOS
Wu et al. ^[39] (2018)	CNI rat	ADSCs	ICI and nanotechnology approach	-	0, 1, and 3 days	2×10^{5}	CNS	α-SMA,β III tubulin,CD31
Zheng et al. ^[40] (2018)	CNI rat	ADSCs	ICI	miR-34a	4 weeks	1×10^{6}	CNS	S100β,GFAP,P75
Matsuda et al. ^[41] (2018)	CNI rat	BMSCs	CVI	-	4 weeks	1×10^{6}	CNS	smooth muscle-to-collagen ratios
Fang et al. ^[42] (2018)	CNI rat	BMSCs+EPCs	ICI	-	2 weeks	1×10^{6}	CNS	PECAM-1,a-actin,caspase-3,nNOS,MBP,S100β
Ying et al. ^[43] (2019)	CNI rat	ADSCs	ICI	-	4 weeks	1×10^{6}	CNS	nNOS,Smooth muscle /collagen ratio
Ge et al. ^[44] (2019)	CNI rat	ADSCs	ICI	-	4 weeks	1×10^{6}	CNS	NGF,NT-3,S100β,P75,transcription-3
Chen et al. ^[45] (2019)	CNI rat	iMSC and ADSCs labeled with PKH-67	ICI	-	4 weeks	1×10^{6}	CNS	nNOS, vWF,eNOS, SMA,Desmin,S100β,caspase-3
Yang et al. ^[46] (2020)	CNI rat	ADSCs	around the MPG	VEGF and GDNF	2 weeks	1.5×10^{6}	CNS	Neurofilament-H,nNOS,Desmin,HIF-1α,RECA-1,VEGF,GDNF,S100β
Gu et al. ^[47] (2020)	CNI rat	PSCs labeled withmKATE-renLUC	ICI	-	1, 6, and 12 weeks	2.5 × 107	CNS	nNOS,f desmin,RECA-1,eNOS
Yang et al. ^[48] (2020)	CNI rat	ADSCs	ICI,CVI,PPI	BDNF	4 weeks	1×10^{6}	CNS	nNOS

Chen et al. ^[49] (2021)	CNI rat	ADSCs labeled with Edu	ICI	-	4 weeks	1×10^6 or 2×10^6	CNS	nNOS,smooth muscle/collagen ratio
Zheng et al. ^[50] (2020)	CNI rat	ADSCs	ICI	ł	÷	5×10^{5}	CNS	S100,GFAP,P75,nNOS, β-actin
Zou er al. ^[51] (2021)	CNI rat	MDSCs labeled with GFP	ICI	miRNA-126	4 weeks	1×10^{6}	CNS	CD31,vWF,VEGF,IRS1,KLF10
Zheng et al. ^[52] (2021)	CNI rat	ADSCs labeled with CM-Dil	ICI or CVI	-	1,2 and 4 weeks	1×10^{6}	CNS	SMA,nNOS
Wu et al. ^[53] (2021)	CNI rat	hGMSCs	around the MPG	-	2 weeks	1×10^{6}	CNS	nNOS,α-SMA,eNOS,NGF,MBP
Kim et al. ^[54] (2021)	CNI rat	BMSCs	around the CNI	nanofibrous scaffolds	2 and 4 weeks	1×10^{6}	CNS	NF, MAP2, MBP, peripherin, vWF, SMA, NF
Jung er al. ^[55] (2021)	CNI rat	BMSCs labeled with PKH-67	around the CNI	Oxygen carrier loaded hollow micro particles	1, 2, and 4 weeks	1x10 ⁶	CNS	a-SMA, nNOS, eNOS,M3, cGMP
Ti et al. ^[56] (2022)	CNI rat	ADSCs or CBMSCs labeled with PKH-26	ICI	-	4 and 12weeks	1×10^{6}	CNS	nNOS,α-SMA,CD31,NT4,VEGF,MMP 1,MMP 3
Zhang et al. ^[57] (2022)	CNI rat	ADSCs labeled with PKH-67	ICI	lipopolysaccharide	2 weeks	1×10^{6}	CNS	SMA,desmin,MBP,HGF,fibronectin,TGF-β1
He et al. ^[58] (2022)	CNI rat	ADSCs	ICI	VEGF&Smad7	4 weeks	1×10^{6}	CNS	TGF-β1,α-SMA,nNOS,RhoA/ROCK,α-tubulin
Shao et al. ^[59] (2022)	CNI rat	ADSCs labeled with PKH-26	ICI	an EPO-loaded multifunctional hydrogel	4 weeks	$1 imes 10^{6}$	CNS	α-SMA,eNOS,nNOS,Caspase-3,BAX,Bcl-2,GAPDH, GFAP, Tuj1

Cavernous nerve injury=CNI; Embryonic stem cells=ESC; green fluorescent protein=GFP; Intracorporal injection=ICI; major pelvic ganglion=MPG; Cavernosal nerve electrostimulation=CNS; Nitric oxide synthase=NOS; Intracavernosal pressure=ICP; Mean arterial pressure=MAP; green fluorescence protein=GFP; brain-derived neurotrophic factor=BDNF; muscle-derived stem cells=MMNC; Neuronal nitric oxide synthase=nNOS; Endothelial nitric oxide synthase=eNOS; Adipose tissue-derived stem cells=ADSCs; Smooth muscle actin= SMA; fibroblast growth factor=FGF; vascular endothelial growth factor=VEGF; Nerve growth factor=IGF; vascular endothelial growth factor=VEGF; Nerve growth facto 2-containing protein tyrosine phosphatase=SHP-2; muscle-derived stem cells=MDSC; von Willebrand factor=VEGF; periprostatic implantation=PPI; testis-derived stem cells=HTSC; human nuclear antigen=HNA; intraperitoneal injection=IPI; filamentous actin=F-actin, autologous stromal vascular fraction=SVF; von Willebrand factor=vWF; pigment epithelium-derived factor=PEDF; glial fibrillary acidic protein=GFAP; caudal vein injection = CVI; insulin receptor substrate 1=IRS1; Krüppel-like factor=KLF10; periprostatic injection =PPI; oplacental stem cells =PSCs; muscarinicacetylcholine receptor 3=M3; cyclic guanosine monophosphatemonomeric= cGMP;Katushka far red fluorescent protein= mKATE; endothelial cell antigen-1 =RECA-1; human gingiva-derived MSCs =hGMSCs; , nerve growth factor =NGF; myelin basic protein =MBP;

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Author (year)	animal model	stem cell type	Transplant method	transfection	Follow-up time	number	Erectile function	Histological\ molecular
Garcia et al ^[1] (2010)	DMED rats	ADSCs	ICI	-	three weeks	1×10^{6}	CNS	nNOS,RECA
Qiu et al ^[2] (2011)	DMED rats	BMSCs labeled with CM- DiI	ICI	-	four weeks	4×10^{5}	CNS	a-SMA,vWF,CD31, calponin,
Nishimatsu et al ^[3] (2012)	DMED rats	ADSCs labeled with PKH- 26	ICI	-	four weeks	5×10^{5}	CNS	eNOS,VE-cadherin
Sun et al ^[4] (2012)	DMED rats	BMSCs labeled with CM- DiI	ICI	-	four weeks	5×10^{6}	CNS	nNOS,NF,VEGF,NGF,BDNF
Qiu et al ^[5] (2012)	DMED rats	MSCs labeled with CM-DiI	ICI	VEGF164	four weeks	$5 imes 10^6$	CNS	VEGF
Liu et al ^[6] (2013)	DMED rats	ADSCs labeled with GFP	ICI	VEGF	one and four weeks	1×10^{6}	CNS	VEGF,eNOS,vWF,CD31,smooth muscle/collagen ratio
He et al ^[7] (2014)	DMED rats	BMSCs	ICI	KCNMA1	four weeks	1×10^{6}	CNS	KCNMA1
Liu et al ^[8] (2015)	DMED rats	ADSCs labeled with GFP	ICI	HGF	one months	2x10 ⁶	CNS	HGF,eNOS,PECAM-1,SMA,P-Akt, Akt,Bcl-2,P-Smad2,Smad2,Cleaved- caspase3,Bcl-xl,TGIF
Wang et al ^[9] (2015)	DMED rats	ADSCs labeled with CM- DiI	ICI	-	four weeks	1×10 ⁶	CNS	VEGF,CD31,bFGF, BDNF,GDNF,SDF-1,CXCR4,vWF,nNOS,α-SMA,HIF- 1α,Ang-1
Ryu et al ^[10] (2016)	DMED rats	MSCs	ICI	-	two weeks	3×10 ⁵	CNS	eNOS,nNOS,PECAM-1,α-SMA, NF,
Lu et al ^[11] (2016)	DMED rats	ADSCs labeled with GFP	ICI	PEDF	two weeks	1×10 ⁶	CNS	BDNF,NGF,nNOS,β-III tubulin,cGMP
Zhou et al ^[12] (2016)	DMED rats	ADSCs labeled with CM- DiI	ICI	-	four weeks	1×106	CNS	α-SMA,vWF,VEGF ,nNOS,AGEs,RAGE,NF-κB
Sun et al ^{[13}] (2017)	DMED rats	BMSCs	ICI	Bcl-2	three days and four weeks	5×106	CNS	Bcl-2
Wang et al ^[14] (2017)	DMED rats	MSCs	ICI	-	four weeks	1×10^{6}	CNS	vWF,a-SMA,p-STAT3,p-Akt,Csp3,Bax,BcL-2
Sun et al ^[15] (2018)	DMED rats	BMSCs	ICI	-	zero,two,four ,seven days	5×10 ⁶	CNS	MEG3,FOXM1,VEGF
Zhu et al ^[16] (2018)	DMED rats	MSCs labeled with CM-DiI	ICI	low-energy shock waves	eight weeks	1×10^{6}	CNS	VEGF,SDF-1,PECAM,NGF,PDNF,nNOS,eNOS,pAKT,AKT,β-actin,PARP,LC-3
Ouyang et al ^[17] (2019)	DMED rats	USCs	ICI	-	four weeks	2x10 ⁵	CNS	nNOS,CD31,eNOS,cell/collagen ratio.
Zhang et al ^[18] (2019)	DMED rats	USCs	ICI	-	four weeks	1x10 ⁶	CNS	LC3-II,LC3-I,PCNA,Beclin1,p62,CD31, eNOS,VEGFRA,VEGFR2
Zhang et al ^[19] (2019)	DMED rats	ADSCs	ICI	iNOS	two weeks	5x10 ⁵	CNS	NO,cGMP,TGF-β1, collagen I, collagen IV,smooth muscle
Chen et al ^[20] (2019)	DMED rats	ADSCs、BMSCs	ICI	-	four weeks	BMSC:1x107;ADSC:1x106	CNS	eNOS
Zhang et al ^[21] (2019)	DMED rats	ADSCs labeled with EdU	ICI	myocardin	one and three weeks	1×10^{6}	CNS	α-SMA,calponin,collagen I,Bcl-2, Bax, cleaved-caspase3
Yang et al ^[22] (2020)	DMED rats	ADSCs、EPCs	ICI	-	four weeks	ADSCs:1×106,EPCs:1×106; ADSCs/EPCs:0.5×106/0.5×106	CNS	CD31,vWF,KDR,VEGF,SDF-1, eNOS
Yang et al ^[23] (2020)	DMED rats	ADSCs	ICI	phosphodiesterase type 5 siRNA	one and two weeks	5x10 ⁵	CNS	PDE5, IGF-1, VEGF, smooth muscle/collagen ratio
Wang et al ^[24] (2020)	DMED rats	MSCs labeled with CM-DiI	ICI	-	two weeks	1×10 ⁶	CNS	$\alpha\text{-}SMA, vWF, Nrf2, HO-1, Bax, Caspase3, Cleaved-Caspase3, Bcl-2, Beclin1, 62, LC3II/I$
Sun et al ^[25] (2020)	DMED rats	BMSCs	ICI	LncRNA MALAT1	-	5x10 ⁶	CNS	VEGF,MALAT1,vWF,VE-cadherin,eNOS, NO level, cGMP, smooth muscle-to- collagen ratio
Zhou et al ^[26] (2021)	DMED rats	ADSCs	ICI	Knockdown of miR- 423- 5p	eight weeks	1x10 ⁶	CNS	eNOS,VEGF
Shin et al ^[27] (2021)	DMED rats	MSCs	ICI	SDF-1,ESWT	four weeks eight weeks	1×10 ⁶	CNS	α-SMA,SDF-1,nNOS
Liu et al ^[28] (2022)	DMED rats	ADSCs	ICI	LIPUS	two and four weeks	1x10 ⁶	CNS	eNOS,vWF,CXCL12,FGF2,VEGF,ERK,NGF,HGF,IGF1,

Table 2 Summarizes stem cell studies aimed at DMED

Feng et al ^[29] (2022)	DMED rats	UC-MSCs	ICI and VI	-	four weeks	1x10 ⁶	CNS	cGMP,MDA,SOD,Fe,eNOS,nNOS,ROS,GPX4,ACSL 4,smooth muscle to collagen,SLC7A11,LPCAT3,ALOX15
Mukti et al ^[30] (2022)	DMED rats	UC-MSCs	ICI	-	-	1x10 ⁶ ;3x10 ⁶	-	TGF-β,α-SMA,collagen
Wang et al ^[31] (2022)	DMED rats	UC-MSCs	ICI	-	four weeks	1 x10 ⁶	CNS	TLR4,eNOS,VEGF,Smooth muscle/collagen ratio
Luo et al ^[32] (2022)	DMED rats	ADSCs	ICI	shNLRP3	four weeks	1×10^{6}	CNS	NLRP 3,SDF-1,VEGFA,FGF 2
Quaade et al ^[33] (2022)	DMED rats	ADSCs	ICI	-	four weeks	1×10^{6}	CNS	Procollagen1,PACAM-1,α-SMA、eNOS、nNOS

platelet endothelial cell adhesion molecule-1=PECAM-1; transcription co-inhibition factor=TGIF; vascular endothelial cell=VEC; pigment epithelium-derived factor =PEDF; B cell lymphoma-2=Bcl-2; advanced glycation end products=AGEs; rabbit anti-receptor for AGE =RAGE;Light chain 3=LC3;Poly-ADP-ribose polymerase=PARP;Inducible nitric oxide synthase =iNOS;metastasis-associated lung adenocarcinoma transcript 1=MALAT1;malondialdehyde=MDA;superoxide dismutase=SOD;Umbilical Cord-Derived Mesenchymal Stem Cells=UC-MSCs;TLR4=Toll-like receptor 4;ROS=reactive oxygen species; lipopolysaccharide-inducible=LIX; chemokine=CXC; TIMP metallopeptidase inhibitor 1;TIMP-1; interleukin-1a =IL-1a;macrophage inflammatory protein 3a=MIP-3a;maternally expressed gene 3=MEG3;

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