Online Supplement

Title: Artificial oxygen carriers- past, present and the future-a review of the most innovative and clinically relevant concepts

Running title: Update on concepts of artificial oxygen carriers

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Supplemental Table 1: Recent clinical trials with Hemopure

phase	trial number	locations	condition	status
II	NCT00479895	Netherlands	elective coronary revascularization	completed
II	NCT00317512	Netherlands, Belgium and Germany	elective coronary revascularization	completed with study results(Serruys et al., 2008)
II	ACTRN12615000522516	Australia	Bridging to hospital of shocked trauma patients	Ethics approval since 2013, not started yet
	2005-003639-30	UK	Tissue preservation during cardiopulmonary bypass	ongoing since 2005
II	2005-003637-41	UK	wound healing in patient with lower limp amputation	ongoing since 2005

Supplemental Table 2: Clinical studies on other HBOCs

HBOC	phase	trial number	locations	condition	status
Hemolink	II/III	NCT00038454	USA	Primary coronary artery bypass grafting in combination with intraoperative autologous blood donation	suspended since 2005
Polyheme	III	NCT00076648	USA	Bridging to hospital of shocked trauma patients	Unknown, study results(Moore et al., 2009a; Moore et al., 2009b)
Pyridoxalated hemoglobin polyoxyethylene conjugate	III	NCT00021502 2008-000504-92	USA Netherlands, Germany, Austria, UK, Spain, Belgium	Distributive shock + systemic inflammatory response syndrome	Discontinued in all countries due to low enrollment because of errors in study design. But completed as phase II(Elmer et al., 2012) study with study results(Kinasewitz et al., 2008)
Hemotech	I	Approved by the Ethics Committee of Kinshasa, Zaire (now Congo)	Congo	Sickle cell anemia in 9 children.	Completed with study results (Feola et al., 1992; Simoni et al., 2014)

Supplemental Table 3: Trials with Hemospan/ MP4OX and MP4CO

HBOC	phase	trial number	locations	condition	status
MP4OX	II	NCT00633659 2007-001538-15	Sweden	Chronic critical limb ischemia	completed prematurely ended
MP4OX	I, II	NCT00494949	Sweden	Reducing transfusion of RBCs in elective orthopedic surgery	completed with study results(Olofsson et al., 2006)
MP4OX	II	NCT00425334	USA	Reducing transfusion of RBCs in elective orthopedic surgery	completed
MP4OX	III	NCT00421200 2006-002513-12	Belgium, Czech Republic, Netherlands, Poland, Sweden, UK	Prevent hypotension in elective surgery	completed (Czech Republic, Belgium, Sweden, Netherlands with study results)(Olofsson et al., 2011) ongoing in UK (probably missing update: Sponsor terminated operations in 2013)
MP4OX	III	NCT00420277 2006-002514-35	Belgium, Czech Republic, Netherlands, Poland, Sweden, UK	Treating hypotension in elective surgery	completed in Czech Republic, Belgium, Sweden and Netherlands with study results(van der Linden et al., 2011) ongoing in UK (probably missing update: Sponsor terminated operations in 2013)
MP4OX	IIc	NCT01973504	Australia, Belgium, Brazil, France, Germany, Israel, New Zealand, Norway, South Africa, Switzerland, United Kingdom	MP4Ox in combination with standard treatment in severe trauma	2013 withdrawn prior to enrolment (probably missing update: Sponsor terminated operations in 2013)
MP4OX	IIb	NCT01262196 2010-023129-39	Australia, Austria, Brazil, Colombia, France, Germany, Israel, New Zealand, Norway, Singapore, South Africa, Spain, Switzerland, United Kingdom, Belgium, Italy	MP4Ox in combination with standard treatment in severe trauma	completed in all countries except Spain, Norway and Italy ongoing in Spain, Norway and Italy (probably missing update: Sponsor terminated operations in 2013)
MP4OX	IIa	NCT01004198 2009-013115-35	France, Germany, South Africa, UK	MP4Ox in combination with standard treatment in severe trauma	completed in all countries except France, ongoing in France (probably missing update: Sponsor terminated operations in 2013)
MP4CO	Ib	NCT01356485	France, Jamaica, Lebanon, UK	Stable sickle cell anemia	completed with study results(Keipert and Investigators, 2016)
MP4CO	II	NCT01925001 2013-001600-11	Bahrain, Belgium, Brazil, France, Lebanon, Netherlands, Qatar,	Vaso-occlusive crisis in sickle cell anemia	withdrawn prior to enrolment (Sponsor ceased operation)

			Turkey, United Kingdom		

Comment to Supplemental Table 3: Please note, that some clinical trials are still listed as "recruiting/ongoing" although the sponsor stopped funding and thereby terminated the study.

Supplemental Table 4: Clinical trials with Sanguinate

phase	trial number	Locations	condition	status
I	NCT01847222	Israel	Safety and pharmacokinetics in healthy volunteers	terminated due to completion of competing study (ACTRN126120010338 3)
I	ACTRN12612 001033831	Australia	Safety and pharmacokinetics in healthy volunteers	completed with study results(Misra et al., 2014)
I	NCT02754999	USA	Severe anemia	completed
II	NCT02323685	USA	delayed cerebral ischemia after acute aneurysmal subarachnoid hemorrhage	completed
Ib	NCT01848925	Colombia, Panama	Sickle cell disease	completed with study results(Misra et al., 2017)
I	NCT01374165	Israel	Sickle cell disease	suspended (cancelled)
II	NCT02600390	Panama, Dominican Republic	Sickle cell disease associated leg ulcer	completed
II	NCT02672540	Panama, Dominican Republic, Honduras, Colombia	Vaso-occlusive crisis in sickle cell disease	completed
II	NCT02411708	USA	Vaso-occlusive crisis in sickle cell disease	completed
II, III	NCT02490202	USA	Reduction of delayed graft function with infusion of Sanguinate prior to kidney transplantation	completed
Ib	NCT02437422	USA	Impact on humoral sensitization in end stage renal disease	completed
II	NCT02658162	Not provided	Reduction of delayed graft function in kidney transplant patients	withdrawn

Supplemental Table 5: Sophistically engineered Hgbs

product	**Idea**	**reference**
OxyVita	Linking of bovine Hgb-monomers via physiolocially present amide groups	Wollocko 2017(Wollocko et al., 2017)/ Jahr 2012(Jahr et al., 2012)
Poly-Hb-tempol	Glutaraldehyde polymerized porcine Hgb and tempol with SOD activity	Wu 2017(Wu et al., 2017)
Sanflow, VitalHeme (PNPH)	Polynitroxylated bovine Hgb	Brockman 2017(Brockman et al., 2017)'(LLC)
YQ23	Non-polymeric cross-linked tetrameric mammalian Hgb	Li, 2016(Li et al., 2017)'(Limited, 2017)
BAEGF-Hb	Antioxidative Bromoacethylethyleneglycol-ferulate-linked human Hgb	Guo, 2016(Guo et al., 2016)
PolyPHb/ bPEG-Hb	Polymerized human placenta Hgb/ pegylated bovine Hgb	Li 2015(Li et al., 2015)/ Wang, 2016(Wang et al., 2017b)

Supplemental Table 6: Standard Hgb plus engineered envelope

product	**Idea**	**reference**
HbVesicles	Human Hgb encapsulated in biocompatible liposomes	Sakai 2017(Sakai, 2017), Azuma 2017(Azuma et al., 2017), Kohno 2017(Kohno et al., 2017)
HbMP-700	Bovine Hgb in microparticles	Baeumler, 2014(Baumler et al., 2014), Kao, 2018(Kao et al., 2018)
ErythroMer	Human Hgb in tunable polymer shell, pH sensitive O_2-affinity	Pan, 2016(Pan et al., 2016; Kalocyte, 2017)
HbN	Bovine Hgb conjugated polymer micelles	Qi, 2016(Qi et al., 2016)
HbP	polymer encapsulated bovine Hgb	Lu 2016(Lu et al., 2016) and Li 2014(Li et al., 2014)
LEH	Human Hgb in liposomes	Yadav, 2016(Yadav et al., 2016), Fukui 2017(Fukui et al., 2017)
• Hb-PDA • PDA-Hb-microcapsules	• Antioxidative polydopamine-coated bovine Hgb nanocapsules • Polydopamine-coated bovine Hgb	• Wang, 2017(Wang et al., 2017a; Wang et al., 2018) • Yu, 2018(Yu et al., 2018)
Hemoact	Cluster of human Hgb + human albumin	Haruki, 2015(Haruki et al., 2015)
RBCM	RBC-like microgel particles loaded with bovine Hgb	Chen, 2012(Chen et al., 2012)
Mal-PEG-βXL-Hb	Inside-out pegylated Hgb	Webster, 2017(Webster et al., 2017)
Hemoglobin loaded nanoliposomes	Liposomes with human Hgb	Qu, 2017(Qu et al., 2017)
	Human Hgb adsorbed to silica nanoparticles	Devineau, 2018(Devineau et al., 2018)

Supplemental Table 7: Other artificial blood products in preclinical stage

product	**Idea**	**reference**
HemoCD	Iron-porphyrin/ cyclodextrin complex	Kitagishi, 2017(Kitagishi et al., 2017)
PEG-LtEC	Pegylated earthworm Hgb	Jani, 2017(Jani et al., 2017)
HrBOC	hemerythrin (from marine worms) copolymerized with glutarlaldehyde, human serum albumin or ruberythrin	Toma, 2018(Toma et al., 2018)
Cobalt-replaced myoglobin	Resulting in p50 of 37mmHg	Neya, 2014(Neya et al., 2014)
Cobaltporphyrin-based micelles	Hgb- free oxygen transporter in micelles	Shen, 2016(Shen et al., 2016)
LOMs/PHMs	Lipid-based oxygen microbubbles/Polymer hollow microparticles (stabilized thin wall)	Black, 2017(Black et al., 2017)/Seekell, 2016(Seekell et al., 2016)

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