

Hiromi SAKAI

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Education:

2006 Ph.D. (D. Med. Sci.), School of Medicine, Keio University, Tokyo
1994 Ph.D. (D. Eng.), Polymer Chemistry, Graduate School of Sci. & Eng., Waseda University, Tokyo
1991 M.S., Polymer Chemistry, Graduate School of Sci. & Eng., Waseda University
1989 B.S., Applied Chemistry, School of Sci.&Eng., Waseda University

Research and Teaching Experiences:

2013 – Professor, Department of Chemistry, Nara Medical University
2011 – 2013 Associate Professor, Professor, Org. for Univ. Res. Initiatives, Waseda University
2010 – 2011 Associate Professor, Comprehensive Research Organization, Waseda University
2009 – 2013 Principal Investigator, Waseda Bioscience Res. Inst. in Singapore (WABIOS)
2004 – 2005 Visiting Lecturer at Tokyo Metropolitan University.
2002 – 2012 Visiting Lecturer & Assoc. Prof. at Keio Univ. Center for Integrated Med. Res.
2001 Visiting scholar at Dept. Bioengineering, Univ. of California, San Diego
1998 – 2010 Lecturer, Assoc. Professor at Adv. Res. Inst. for Sci. & Eng., Waseda University
1996 – 1998 Visiting Scholar at Dept. Bioengineering, Univ. of California, San Diego
(as an Overseas Research Fellow of JSPS).
1994 – 1996 Research fellow of Japan Society for the Promotion of Science (JSPS).

Academic Societies:

Soc. Blood Substitutes, Jpn (President) / Soc. Polymer Sci., Jpn / Jpn Soc. Artif. Organs / Am. Physiol. Soc.
/ Am. Chem. Soc. / Chem. Soc. Jpn / Int. Soc. Artif. Cells Blood Substitutes Biotechnol. (scientific advisory
board) / Jpn Soc. Microcirculation / Intern. Soc. Oxygen Transport Tissues / Journal of Artif. Cells Nanomed.
Biotechnol. (Editorial Board)

Honors:

Nov. 2019 Co-president, The 17th International Symposium on Blood Substitutes (XVII-ISBS)
Nov. 2008 Award for Outstanding Research on Membrane Technology
(Mukai Sci.&Technol. Foundation, Tokyo)
Dec 2006 Young Investigator Award (International Liposome Society, London)
Nov 2003 JSAO-Yoshimi Grant Award (Jpn Soc. Artificial Organs)
March 1994 Mizuno Award (Waseda Univ.) "Contribution to the Research of Artificial Red Cell"

Research Subjects:

artificial oxygen carriers / blood substitutes / molecular assembly / liposomes / redox and ligand binding of
hemoglobin / tissue oxygenation / biorheology & microhemodynamics / bioengineering / preclinical test, etc.

Grants (selected):

- (PI) Project for Translational Research, from Japan Agency for Medical Research and Development, AMED (2021-2023)
- (PI) Grants-in-aid for scientific research, from the Japan Society for the Promotion of Science (JSPS) (Scientific Research - B 21H03824) (2021-2023)
- Project Promoting Clinical Trials for Development of New Drugs and Medical Devices, from Japan Agency for Medical Research and Development, AMED (2018-2020)
- (PI) Grants-in-aid for scientific research from the Japan Society for the Promotion of Science (JSPS) (Scientific Research - B 17H02087) (2017-2019)
- (PI) Project Promoting Clinical Trials for Development of New Drugs and Medical Devices from Japan Agency for Medical Research and Development, AMED (2015-2017)

- (PI) Health and Labour Sciences Research Grants (Health Science Research Including Drug Innovation) from the Ministry of Health, Labour and Welfare (MHLW), Japan (2012-14)

Publications: 171 original articles in peer-reviewed journals, 112 review papers in journals or as chapters in books, and 14 patents.

List of Publication (Hiromi Sakai)

- (171) Y. Suzuki, K. Taguchi, T. Kure, H. Sakai, Y. Enoki, M. Otagiri, K. Matsumoto. Liposome-encapsulated methemoglobin as an antidote against cyanide poisoning. *J. Controlled Release* (in press)
- (170) B. Takase, Y. Higashimura, K. Hashimoto, H. Asahina, M. Ishihara, H. Sakai. Liposome-encapsulated hemoglobin (HbV) transfusion rescues rats undergoing progressive lethal 85% hemorrhage as a result of an anti-arrhythmogenic effect on the myocardium. *Artif. Organs* (in press)
- (169) T. Kure, H. Sakai. Preparation of artificial red cells (hemoglobin vesicles) using kneading method for high encapsulation efficiency. *ACS Biomaterials Science & Engineering* 7(6), 2835-2844 (2021). doi: 10.1021/acsbiomaterials.1c00424.
- (168) T. Matsuhira, H. Sakai. Entropy-driven supramolecular ring-opening polymerization of a cyclic hemoglobin monomer for constructing a hemoglobin-PEG alternating polymer with structural regularity. *Biomacromolecules* 22, 1944-1954 (2021) DOI: 10.1021/acs.biomac.1c00061
- (167) K. Shimanouchi, N. Rikihisa, Y. Saito, K. Iuchi, N. Tsumura, H. Sakai, N. Mitsukawa. Artificial red blood cells increase large vessel wall damage and decrease surrounding dermal tissue damage in a rabbit auricle model after subsequent flashlamp-pumped pulsed dye laser treatment. *J. Dermatol.* 48, 600-612 (2021) DOI: 10.1111/1346-8138.15805
- (166) Y. Yuki, K. Hagiwara, M. Kinoshita, H. Ishibashi, O. Ishida, D. Saitoh, H. Sakai, K. Terui. Efficacy of Resuscitative Transfusion with Hemoglobin Vesicles in the Management of Massive Obstetric Hemorrhage. *Am. J. Obstet. Gynecol.* 224(4), 398.e1-398.e11 (2021) DOI: 10.1016/j.ajog.2020.09.010
- (165) Y. Yoshida, T. Nagamori, E. Ishibazawa, H. Kobayashi, T. Kure, H. Sakai, D. Takahashi, M. Fujihara, H. Azuma. Contribution of long chain fatty acid to induction of myeloid-derived suppressor cell (MDSC)-like cells – Induction of MDSC by lipid vesicles (liposome) – *Immunopharmacol. Immunotoxicol.* 42(6), 614-624 (2020) DOI: 10.1080/08923973.2020.1837866
- (164) M. Tokuno, K. Taguchi, H. Sakai, S. Ohtsuki, K. Yamasaki, M. Otagiri. Evaluation of cytochrome P450-based drug metabolism in hemorrhagic shock rats that were transfused with native and an artificial red blood cell preparation, Hemoglobin-vesicles. *Drug Metab. Pharmacokinet.* 35(5), 417-424 (2020) doi: 10.1016/j.dmpk.2020.06.004.
- (163) M. Tokuno, K. Taguchi, H. Sakai, S. Ohtsuki, K. Yamasaki, M. Otagiri. Assessing cytochrome P450-based drug-drug interactions with Hemoglobin-vesicles, an artificial red blood cell preparation, in healthy rats. *Drug Metab. Pharmacokinet.* 35(5), 425-431 (2020) doi: 10.1016/j.dmpk.2020.06.005
- (162) K. Hagiwara, M. Kinoshita, D. Saitoh, Y. Morimoto, H. Sakai. Intraosseous Transfusion of Hemoglobin Vesicles in the Treatment of Hemorrhagic Shock and Collapsed Vessels in a Rabbit Model. *Transfusion* 60, 1400-1409 (2020) DOI: 10.1111/trf.15915
- (161) R. Hashimoto, M. Kohno, K. Oiwa, H. Onozawa, M. Watanabe, H. Horinouchi, H. Sakai, K. Kobayashi, M. Iwazaki. Immediate effects of systemic administration of normal and high O₂-affinity hemoglobin vesicles as a transfusion alternative in a rat pneumonectomy model. *BMJ Open Respiratory Res* 7, e000476 (2020) doi: 10.1136/bmjresp-2019-000476
- (160) T. Shonaka, N. Matsuno, H. Obara, R. Yoshikawa, Y. Nishikawa, Y. Ishihara, H. Bochimoto, M. Gochi, M. Otahi, H. Kanazawa, H. Azuma, H. Sakai, H. Fukuhara. Impact of human-derived hemoglobin based oxygen vesicles as a machine perfusion solution for liver donation after cardiac death in a pig model. *PLOS ONE* 14(12): e0226183 (2019). doi: 10.1371/journal.pone.0226183.
- (159) K. Hagiwara, M. Kinoshita, M. Takikawa, S. Takeoka, D. Saitoh, S. Seki, H. Sakai. Combination therapy using fibrinogen γ -chain peptide-coated, adenosine-5'-diphosphate-encapsulated liposomes and hemoglobin vesicles for trauma-induced massive hemorrhage in thrombocytopenic rabbits. *Transfusion* 59(10), 3186-3196 (2019) doi: 10.1111/trf.15427.
- (158) B. Takase, Y. Higashimura, K. Hashimoto, H. Asahina, Y. Tanaka, M. Ishihara, H. Sakai.

Myocardial Electrical Remodeling and Arrhythmogenic Substrate in Hemorrhagic Shock-Induced Heart: Anti-Arrhythmogenic Effect of Liposome-Encapsulated Hemoglobin (HbV) on Myocardium. *Shock* 52(3), 378-386 (2019) doi: 10.1097/SHK.0000000000001262.

(157) H. Sakai, C. Leong. Prolonged Functional Life Span of Artificial Red Cells in Blood Circulation by Repeated Methylene Blue Injections. *Artif. Cells, Nanomed. Biotechnol.* 47(1), 3123-3128 (2019) doi: 10.1080/21691401.2019.1645157

(156) T. Matsuhira, K. Yamamoto, H. Sakai. Ring opening polymerization of hemoglobin. *Biomacromolecules*, 20(4), 1592-1602 (2019) DOI: 10.1021/acs.biomac.8b01789

(155) M. Yamada, T. Matsuhira, K. Yamamoto, H. Sakai. Antioxidative pseudo-enzymatic mechanism of NAD(P)H coexisting with oxyhemoglobin for suppressed methemoglobin formation. *Biochemistry*, 58(10), 1400-1410 (2019) 10.1021/acs.biochem.8b01314.

(154) T. Shonaka, N. Matsuno, H. Obara, R. Yoshikawa, Y. Nishikawa, M. Gouchi, M. Otani, H. Takahashi, H. Azuma, H. Sakai, H. Furukawa. The application of perfusate with human-derived oxygen carrier solution under subnormothermic machine perfusion for donation after cardiac death (DCD) liver grafts in pigs. *Transplantation Proc.* 50, 2821-2825 (2018) DOI: 10.1016/j.transproceed.2018.02.184

(153) H. Sengyoku, T. Tsuchiya, T. Obata, R. Doi, Y. Hashimoto, M. Ishii, H. Sakai, N. Matsuo, D. Taniguchi, T. Suematsu, M. Lawn, K. Matsumoto, T. Miyazaki, T. Nagayasu. Sodium hydroxide based non-detergent decellularizing solution for rat lung. *Organogenesis* 14, 94-106 (2018) DOI: 10.1080/15476278.2018.1462432

(152) K. Hagiwara, M. Kinoshita, B. Takase, K. Hashimoto, D. Saitoh, S. Seki, Y. Nishida, H. Sakai. Efficacy of resuscitative transfusion with hemoglobin vesicles in the treatment of massive hemorrhage in rabbits with thrombocytopenic coagulopathy and its effect on hemostasis by platelet transfusion. *Shock* 50(3), 324-330 (2018). doi: 10.1097/SHK.0000000000001042.

(151) T. Matsuhira, T. Kure, K. Yamamoto, H. Sakai. Analysis of dimeric subunit exchange between PEG modified and native hemoglobins ($\alpha_2\beta_2$ tetramer) in an equilibrated state by intramolecular $\beta\beta$ -crosslinking. *Biomacromolecules* 19(8), 3412-3420 (2018) doi: 10.1021/acs.biomac.8b00728.

(150) N. Rikihisa, M. Tominaga, S. Watanabe, N. Mitsukawa, Y. Saito, H. Sakai. Intravenous injection of artificial red cells and subsequent dye laser irradiation causes deep vessel impairment in an animal model of port-wine stain. *Lasers Med. Sci.* 33(6), 1287-1293 (2018)

(149) S. Ghirmai, L. Bülow, H. Sakai. In vivo evaluation of electron mediators for the reduction of methemoglobin encapsulated in liposomes by using electron energies produced by red blood cell glycolysis. *Artif. Cells, Nanomedicine, Biotechnol.* 46(7), 1364-1372 (2018). <https://doi.org/10.1080/21691401.2017.1397003>

(148) K. Taguchi, S. Nagao, H. Maeda, H. Yanagisawa, H. Sakai, K. Yamasaki, H. Watanabe, M. Otagiri, T. Maruyama. Biomimetic carbon monoxide delivery based on hemoglobin vesicles ameliorates acute pancreatitis in mice via the regulation of macrophage and neutrophil activity. *Drug Delivery* 25(1), 1266-1274 (2018). <https://doi.org/10.1080/10717544.2018.1477860>

(147) M. Yamada, H. Sakai. The hidden antioxidative function of reduced nicotinamide adenine dinucleotide coexisting with hemoglobin. *ACS Chem. Biol.* 12(7), 1820-1829 (2017)

(146) M. Kohno, T. Ikeda, R. Hashimoto, Y. Izumi, M. Watanabe, H. Horinouchi, H. Sakai, K. Kobayashi, M. Iwazaki. Acute 40% exchange-transfusion with hemoglobin-vesicles in a mouse pneumonectomy model. *PLoS One* 12(6), e0178724 (2017)

(145) H. Azuma, Y. Yoshida, H. Takahashi, E. Ishibazawa, H. Kobayashi, H. Sakai, D. Takahashi, M. Fujihara. Liposomal microparticle injection can induce myeloid-derived suppressor cells (MDSC)-like cells in vivo. *Immunopharmacol. Immunotoxicol.* 39, 140-147 (2017).

(144) Y. Naito, H. Sakai, S. Inoue, M. Kawaguchi. Hemoglobin vesicles prolong the time to circulatory collapse in rats during apnea. *BMC Anesthesiol.* 17, 44 (2017)

(143) N. Rikihisa, S. Watanabe, K. Satoh, Y. Saito, H. Sakai. Photosensitizer Effects of Artificial Red Cells on Dye Laser Irradiation in an Animal Model Assuming Port-Wine Stain Treatment. *Plast.*

Reconstr. Surg. 139, 707e-716e (2017)

- (142) T. Kure, H. Sakai. Transmembrane difference in colloid osmotic pressure affects the lipid membrane fluidity of liposomes encapsulating a concentrated hemoglobin solution. *Langmuir* 33, 1533-1540 (2017)
- (141) S. Nagao, K. Taguchi, H. Sakai, K. Yamasaki, H. Watanabe, M. Otagiri, T. Maruyama. Carbon monoxide-bound hemoglobin vesicles ameliorate multiorgan injuries induced by severe acute pancreatitis in mice by their anti-inflammatory and antioxidative properties. *Int. J. Nanomedicine* 11, 5611-5620 (2016)
- (140) M. Tokuno, K. Taguchi, K. Yamasaki, H. Sakai, M. Otagiri. Superiority of resuscitation using long-term stored haemoglobin-vesicles over stored red blood cells regarding transfusion-related adverse effects in massive haemorrhagic rats. *PLoS One* 11, e0165557 (2016)
- (139) S. Nagao, K. Taguchi, Y. Miyazaki, V.T.G. Chuang, K. Yamasaki, H. Watanabe, H. Sakai, M. Otagiri, T. Maruyama. Evaluation of a new type of nano-sized carbon monoxide donor on treating mice with experimentally induced colitis. *J. Control. Release.* 234, 49-58 (2016)
- (138) S. Osaki, K. Yamamoto, T. Matsuhira, H. Sakai. Seasonal changes in the molecular weight of the *Nephila clavata* spider silk. *Polymer J.* 48, 659-663 (2016)
- (137) B. Namgung, H. Sakai, S. Kim. Influence of erythrocyte aggregation at pathological levels on cell-free marginal layer in a narrow circular tube. *Clin. Hemorheol. Microcirculation* 61, 445-457 (2016)
- (136) H. Li, H. Ohta, Y. Tahara, S. Nakamura, H. Izumi, Y. Matsushima, Y. Sunada, M. Nakagawa, J. Fukuchi, Y. Goto, K. Wada, M. Kaga, M. Inagaki, H. Yokota, S. Shibata, H. Sakai, K. Okamura, N. Yaegashi. Artificial oxygen carriers rescue placental hypoxia and improves fetal development in the rat pre-eclampsia model. *Sci. Rep.* 5, 15271 (2015)
- (135) K. Taguchi, S. Nagao, K. Yamasaki, H. Sakai, H. Seo, T. Maruyama, M. Otagiri. Biological responsiveness and metabolic performances of liposome-encapsulated hemoglobin (hemoglobin-vesicles) in apolipoprotein E-deficient mice after massive intravenous injection. *Biol. Pharm. Bull.* 38, 1606-1616 (2015)
- (134) K. Kettisen, L. Bulow, H. Sakai. Potential electron mediators to extract electron energies of RBC glycolysis for prolonged in vivo functional lifetime of hemoglobin-vesicles. *Bioconjugate Chem.* 26, 746-754 (2015)
- (133) J. Araki, H. Sakai, D. Takeuchi, Y. Kagaya, M. Naito, M. Mihara, M. Narushima, T. Iida, I. Koshima. Normothermic preservation of the rat hind limb with artificial oxygen-carrying hemoglobin vesicles. *Transplantation* 99, 687-692 (2015)
- (132) S. Nagao, K. Taguchi, H. Sakai, R. Tanaka, H. Horinouchi, H. Watanabe, K. Kobayashi, M. Otagiri, T. Maruyama. Carbon monoxide-bound hemoglobin-vesicles as a potential therapeutic agent for the treatment of bleomycin-induced pulmonary fibrosis. *Biomaterials* 35, 6553-6562 (Aug, 2014)
- (131) H. Sakai, B. Li, W. Lim, Y. Iga. Red blood cells donate electrons to methylene blue mediated chemical reduction of methemoglobin compartmentalized in liposome in blood. *Bioconjugate Chem.* 25, 1301-1310 (July, 2014)
- (130) M. Fujihara, D. Takahashi, H. Abe, H. Sakai, H. Horinouchi, K. Kobayashi, H. Ikeda, H. Azuma. Primary and secondary immune responses to keyhole limpet hemocyanin in rats after the infusion of hemoglobin vesicle, an artificial oxygen carrier. *Artif. Organs* 38, 234-238 (March, 2014)
- (129) H. Sakai, K. Ng, B. Li, N. Sugimura. Swine hemoglobin as a potential source of artificial oxygen carriers, hemoglobin-vesicles. *Artif. Cells Nanomedicine Biotechnol.* 41, 37-41 (2013).
- (128) K. Taguchi, H. Watanabe, H. Sakai, H. Horinouchi, K. Kobayashi, T. Maruyama, M. Otagiri. Fourteen-days observation and pharmacokinetic evaluation after massive intravenous infusion of hemoglobin-vesicles (artificial oxygen carriers) in cynomolgus monkeys. *J. Drug Metab. Toxicol.* 3, 1000128 (2012)
- (127) M. Kaga, H. Ohta, Y. Lee, R. Kamii, H. Yamamoto, S. Akiyama, S. Watanabe, T. Matsuda, Y. Kimura, S. Tsuchiya, H. Tei, L. Okamura, H. Sakai, N. Yaegashi. Physiological capacity of the

reticuloendothelial system for the degradation of hemoglobin-vesicles (artificial oxygen carriers) after massive intravenous doses by daily repeated infusion for 7 days in Pregnant rats and fetuses. *Life Sci.* 91, 420-428 (2012)

(126) H. Sakai, Y. Suzuki, K. Sou, M. Kano. Cardiopulmonary hemodynamic responses to the small injection of hemoglobin-vesicles (artificial oxygen carriers) in miniature pigs. *J. Biomed. Mater. Res. A*, 100A, 2668-2677 (Oct. 2012)

(125) A.G. Tsai, M. Intaglietta, H. Sakai, E. Delpy, C.D. la Rochelle, M. Rousselot, F. Zal. Microcirculation and NO-CO studies of a natural extracellular hemoglobin developed for an oxygen therapeutic carrier. *Current Drug Discovery Technol.* 9, 166-172 (2012, Sept)

(124) Y. Seishi, H. Horinouchi, H. Sakai, K. Kobayashi. Effect of the cellular-type artificial oxygen carrier Hb-vesicle as a resuscitative fluid for pre-hospital treatment: Experiments in a rat uncontrolled hemorrhagic shock model. *Shock* 38, 153-158 (2012, Aug).

(123) H. Sakai, K. Sou, H. Horinouchi, E. Tsuchida, K. Kobayashi. Removal of Hemoglobin-vesicles from circulating blood by using centrifugation and ultrafiltration. *Artif. Organs* 36, 202-209 (2012, Feb)

(122) M. Yamamoto, H. Horinouchi, Y. Seishi, N. Sato, M. Itoh, K. Kobayashi, H. Sakai, Fluid resuscitation of hemorrhagic shock with Hemoglobin vesicles in Beagle dogs: pilot study. *Artif. Cells Blood Substitutes Biotechnol.* 40, 179-195 (2012, Feb)

(121) H. Sakai, N. Miyagawa, H. Horinouchi, S. Takeoka, M. Takaori, E. Tsuchida, K. Kobayashi. Intravenous injection of Hb-vesicles (artificial oxygen carriers) after hemodilution with a series of plasma expanders (water-soluble biopolymers) in a rat repeated hemorrhage model. *Polymers Adv. Technol.* 22, 1216-1222 (2011, Aug)

(120) A. Niwa, T. Heike, K. Umeda, K. Oshima, I. Kato, H. Sakai, H. Suemori, T. Nakahata, M.K. Saito. A novel serum-free monolayer culture for orderly hematopoietic differentiation of human pluripotent cells via mesodermal progenitors". *PLoS ONE* 6, e22261 (2011, July)

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(118) D. Takahashi, H. Azuma, H. Sakai, K. Sou, D. Wakita, H. Abe, M. Fujihara, H. Horinouchi, K. Kobayashi, T. Nishimura, H. Ikeda. Phagocytosis of liposome particles by rat splenic immature monocytes makes them transiently and highly immunosuppressive in ex vivo culture condition. *J. Pharmacol. Exp. Therap.* 337, 42-49 (2011, April).

(117) K. Taguchi, Y. Iwao, H. Watanabe, D. Kadowaki, H. Sakai, K. Kobayashi, H. Horinouchi, T. Maruyama, M. Otagiri. Repeated injection of high dose of hemoglobin encapsulated liposomes (hemoglobin-vesicles) induces accelerated blood clearance in a hemorrhagic shock rat model. *Drug Metab. Dispos.* 39, 484-489 (2011, March)

(116) H. Sakai, N. Okuda, S. Takeoka, E. Tsuchida. Increased viscosity of hemoglobin-based oxygen carriers retards NO-binding when perfused through narrow gas-permeable tubes. *Microvasc. Res.* 81, 169-176 (2011, Feb.).

(115) K. Taguchi, M. Miyasato, H. Watanabe, H. Sakai, H. Horinouchi, K. Kobayashi, E. Tsuchida, T. Maruyama, M. Otagiri. Alteration in the pharmacokinetics of hemoglobin-vesicles in a rat model of chronic liver cirrhosis is associated with Kupffer cell phagocyte activity. *J. Pharmaceut. Sci.* 100, 775-783 (2011, Feb.).

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serum containing liposome vesicles. *Artif. Blood* 18, 91-95 (2010).

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(106) H. Sakai, M. Okamoto, E. Ikeda, H. Horinouchi, K. Kobayashi, E. Tsuchida. Histopathological changes of rat brain after direct injection of hemoglobin-vesicles (oxygen carriers) and neurological impact in an intracerebral hemorrhage model. *J. Biomed. Mater. Res.* 90A, 1107-1119 (2009, Sept).

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(99) M. Yamaguchi, M. Fujihara, S. Wakamoto, H. Sakai, S. Takeoka, E. Tsuchida, H. Hamada, H. Azuma, H. Ikeda. Effect of hemoglobin vesicles, cellular-type artificial oxygen carriers, on the *ex vivo* expansion of human hematopoietic stem/progenitor cells using a coculture system with human stromal cells. *ASAIO J.* 55, 200-205 (2009, May-June).

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(97) H. Sakai, Y. Seishi, Y. Obata, S. Takeoka, H. Horinouchi, E. Tsuchida, K. Kobayashi. Fluid

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