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Editors

Blood Substitutes and Oxygen Biotherapeutics

Second Edition

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I am deeply grateful to those who have steadfastly pursued clinically applicable blood substitutes (now referred to as oxygen therapeutics). Their visions, wisdom, and unwavering efforts made this book possible! I would also like to extend my heartfelt appreciation to my mentors throughout my 40-year medical career, in China and the United States, Drs. Shouxi Zhang, Guxin Xiao, Suisheng Xia, Shiao Jin, J. Jane Matjasko, KC Wong, Jerry Levy, Michael A. Golden, and Alan D. Kaye. I am especially thankful to my dear family, my wife Marilyn Li, MD, whose forbearance and support over four decades have been nothing short of extraordinary; my daughter, Cindy Liu, MS, a highly talented software engineer; and my son Geoffrey Liu, MD, a devoted physician in his own right. The arrival of my grandson, Ari Liu, has brought immeasurable joy and happiness to our lives. As we look forward to the release of the second edition, I am hopeful that within the next decade, we will see one or two FDA-approved oxygen therapeutic products reach the clinical arena!

Henry Liu

– To my wife Dr. Kim Kaye for being the best spouse a man could ask for in his life.

– To my mother, Florence Feldman, who, while enduring a lifetime of pain and suffering with seven back surgeries, taught me tremendous things, including to accomplish tasks with the highest of quality and to reach my dreams and goals.

– To my brother Dr. Adam M. Kaye, Pharm.D., for his loving support and help over a lifetime.

– To all my teachers and colleagues at the University of Arizona in Tucson, Ochsner Clinic in New Orleans, Massachusetts General Hospital/Harvard School of Medicine in Boston, Tulane School of Medicine in New Orleans, Texas Tech Health Sciences Center in Lubbock, LSU School of Medicine in New Orleans, and LSU School of Medicine in Shreveport.

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My deepest appreciation to my wife, Dr. Jamielynn Hanam-Jahr, for putting up with me during all my multiple projects for 40 years. Her steadfastness to our relationship and family is noteworthy. To my children, Rachel Jahr, for her devotion and graphic design contribution, and to my son, Jacob Jahr, for his service, I am indebted to you both.

Jonathan S. Jahr

Foreword: Blood Substitutes: Lessons Learned and Future Directions

The entirety of this book has been organized with multiple chapters on Artificial Oxygen Carriers, Plasma/Transfusion Medicine, and Platelets/Hemostasis, addressing the past and present study of blood substitutes in great detail. This Foreword will provide insight into synthesizing the key lessons learned and propose where the field could progress in the future, creating a pathway forward toward regulatory approval.

Artificial Oxygen Carriers/Hemoglobin-Based Oxygen Carriers

Lessons Learned

Despite over 70 years of clinical investigation and continuing active preclinical and clinical development of a multitude of potential products, almost none have reached regulatory approval for commercialization in humans, and none in the United States. Experience has demonstrated that for multiple reasons, hemoglobin-based oxygen carriers (HBOCs) in earlier development, and probably future iterations, would not be commercialized as an equivalent to packed red blood cells. However, there would appear to be specific indications and uses where HBOCs would clearly fill an unmet medical therapeutic need. Despite prior challenges, active development of HBOC variants is ongoing.

Future Directions

The failure to develop HBOCs as a red blood cell equivalent has led, over the past few years, to an incremental approach with proposed limited indications, with advancements over time; examples are those restricted to military or civilian use when blood is unavailable or delivery is hindered by cold-chain requirements, ex vivo use (e.g., HEMO2life®), mediation of focal ischemia such as acute ischemic stroke (e.g., PP-007, previously Sanguinate™), as well as other potential specific indications related to properties of hemoglobin, such as delivery of antitumor gases/medications or to enhance radiosensitivity of tumors.

Future HBOCs will have to address safety issues inherent in the earlier iterations of HBOCs. Additionally, a critical review of the clinical experience with HBOCs brings up questions of actual efficacy. Both efficacy and safety, of course, must be addressed in any trials preparatory to regulatory approval. For non-inferiority trials, critical attention will need to be given to the a priori establishment of an appropriate non-inferiority margin. An ethical framework will need to be established to develop clinical trials that will be able to accrue adequate numbers of subjects with or without a placebo arm. Given the regulatory success in the EU of a marine lugworm hemoglobin for clinical use (ex vivo, to date), searches for additional sources of annelid large cell-free hemoglobins may continue. Additional design elements will likely include methods of encapsulating hemoglobin in synthetic shells or microparticles. Production of stem-cell-derived red blood cells may also be on the horizon. Methods of prolonging donated red cell storage will likely be actively investigated.

Hopefully, there will be eventual regulatory approval of product(s) allowing pre-hospital transfusion/infusion in the field by a paramedic-level practitioner, and/or allow transfusion of hemoglobin into hospitalized patients who cannot be successfully crossmatched. Additionally, approval for use in pediatric patients would be expected. Standardized potency is desirable, where one unit would be roughly equivalent to the hemoglobin in a unit of red cells or whole blood. Products should also be available for veterinary use. It is hoped that these products would be priced at a cost equivalent to natural blood products. Given the much longer shelf life compared to natural blood products, there is a potential cost savings due to less wastage. Such products could be stored in advance for potential mass casualty events. Finally, one could envision HBOCs used for blood doping as a performance enhancer for the military or, even, for competitive athletes, with appropriate safeguards for fairness.

Additionally, it is likely that various modified (i.e., dried) components may be combined into the equivalent of whole blood, either by co-packaging (i.e., three separate components in one box) or potentially into a combination product (adding a fluid to one bag for a whole blood equivalent). In this regard, new methods of infusing hemoglobin may also include modifications of red cells, for example, altering red cell surface characteristics to render them agnostic to the recipient's blood type.

Plasma

Lessons Learned

Dried plasma (lyophilized and sprayed) was massively used during World War II. Several lyophilized products are currently available ex-US and two are currently available in the United States, restricted to use by the military. With time, physicochemical analyses have improved over what was available 80 years ago, making the requirements for approval higher. The equivalence of lyophilized versus spray-dried products remains to be delineated and specific plasma components are likely different.

Future Directions

As with HBOCs, the approval of dried plasmas will depend on whether a limited indication (e.g., for the military in austere conditions) or a full indication (equivalence to liquid or frozen plasma) is sought. Both products currently approved under emergency use authorization for the American military come in glass bottles, cumbersome and fragile in extreme field conditions. Clearly, packaging in plastic will be preferable for pre-hospital use at least. It may be that marketing of a device for preparing dried plasma to blood centers versus marketing mass-produced dried plasma to them may compete in the marketplace. As with hemoglobin, the development of a combined product of hemoglobin with plasma and platelet-like particles as a dried whole-blood equivalent would be a consequential advantage in trauma care.

Based on nonclinical work in rodents, there has been very preliminary work evaluating plasma from young (i.e., young adult) donors in mediating both the effects of aging and the treatment of neurodegenerative diseases such as Parkinson's disease. The ultimate efficacy of this approach, as well as how to supply a potentially large amount of plasma from youthful donors, remains unclear, as does the potential isolation of any responsible specific factor(s). Think willow tree bark (effective) versus aspirin (better).

Platelets and Platelet-like Particles

Lessons Learned

Unlike HBOCs and dried plasma, there has been little FDA experience with platelet-like particles, and no published guidance. Similarly, as of this date the FDA has not agreed on a standard to evaluate in vitro efficacy.

Future Directions

It is unclear now whether the field will eventually veer toward lyophilized platelets, platelet-mimetic particles, platelet membrane preparations, fully synthetic platelets, several of these or something else. Additional methods of prolonging platelet preservation are likely in progress. And as for plasma and HBOC, the development of a whole blood equivalent of all three components would be extremely attractive, particularly for trauma care.

Summary

In conclusion, this significant and important text provides the necessary knowledge and advancements in the field for clinicians and scientists worldwide. It also allows us to better pave the way for future development of currently available products as well as new ones, to be able to deliver oxygen-carrying capacity, coagulation factors and platelets with the promise of providing an alternative to autologous or allogeneic blood. These novel products can be valuable assets for clinicians and scientists, and therefore, this text is valuable to help ascertain where we have been, where we are today, and our prospects for the future.

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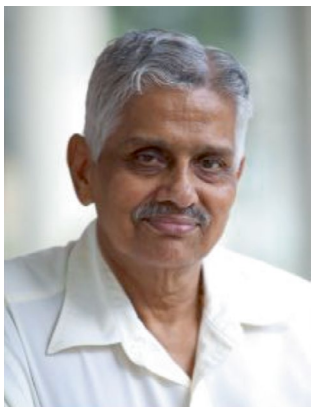
In Memoriam: Dr. Seetharama Acharya



Dr. Seetharama Acharya (1941–2024)

Dr. Acharya was a distinguished scientist, widely recognized for his pioneering work in protein chemistry and protein engineering. His groundbreaking research included the development of chimeric hemoglobins to investigate inhibition of sickle cell β-chain polymerization by nonhuman chimeric α-chains. His studies in blood substitutes spanned over three decades, encompassing transgenic hemoglobins, cross-linked hemoglobins, and innovative PEGylation chemistries that continue to influence the field even today.

Dr. Acharya's research focused on the structure and functions of PEGylated hemoglobin and albumin. He had multiple collaborations with academicians and industries like DNX Therapeutics, Prolong Therapeutics, Sangart Inc., Spectra Bio Labs, and many more. He authored over 100 peer-reviewed publications, book chapters, and scientific presentations, and had dozens of US patents. Among his notable achievements was the development of extension-arm PEGylated hemoglobin-based oxygen therapeutics (HBOCs) and PEGylated albumin. His extension-arm PEGylation chemistry was used by Sangart Inc. to develop MP4. His work helped define the development of the next generation of acellular oxygen therapeutics.

His distinguished career began in 1970 at the prestigious Indian Institute of Science in Bangalore, India, where he earned his doctorate in biochemistry. That same year, he moved to the United States, beginning a prolific research journey at Yale University under Dr. Frederic Richards as a molecular biophysicist. His pursuit of scientific excellence continued at the National Institutes of Health alongside Nobel Laureate Dr. Christian Anfinsen and Dr. Hiroshi Taniuchi, followed by a tenure at the renowned Moore and Stein laboratory at Rockefeller University.

Dr. Acharya moved to the Albert Einstein College of Medicine in 1987, serving as an Associate Professor in the Division of Hematology and collaborating with Dr. Ronald Nagel at the Sickle Cell Comprehensive Center. Promoted to Professor of Medicine in 1990, his expertise was further recognized through additional appointments in Oncology and Developmental

and Molecular Biology. After 30 years of dedicated research and teaching, he retired in 2017 as Professor Emeritus.

From his doctoral roots in Bangalore to the halls of Yale and the NIH, Dr. Acharya dedicated his life to the complexities of biochemistry and the betterment of human health. As a Professor Emeritus at Albert Einstein College of Medicine, he was more than a scientist; he was a mentor who fostered enduring relationships and a husband whose 15 years of care for his wife, Dr. Belur Manjula, spoke volumes of his capacity for love.

Having spent his final years in Seattle near his son Vivek and his cherished grandchildren, Dr. Acharya leaves a void in both the scientific world and the hearts of his family. His intellect was matched only by his generosity of spirit.

Ashok Malavalli
Chief of Operations
Vivosang Inc.

In Memoriam: Jan Simoni, D.V.M., Ph.D.

Jan Simoni was a leader in the blood substitute field and devoted much of his illustrious research career in advancing the field of hemoglobin-based oxygen delivery therapeutics as well as performing basic and translational science and clinical research. His research contributed significantly to the fields of blood substitutes, biotechnology, biomaterials, surgery, nephrology, and cardiology. Aside from his work in blood substitutes, he contributed to important preclinical and clinical studies of renal function, acid-base balance, atherosclerosis, and hematology. He leaves a distinguished legacy, with over 400 papers, book chapters, monographs, scientific conference articles, and US and international patents.

Dr. Simoni received a Doctor of Veterinary Medicine degree from the School of Veterinary Medicine at the University of Environmental and Life Science in Wroclaw, Poland, in 1975 and went on to receive his Ph.D. in Pathophysiology and Radiobiology in 1984. He then moved to the Texas Tech University Health Sciences Center in Lubbock, Texas, to perform a postdoctoral fellowship under Dr. Peter C. Canizaro, Dr. Mario Feola, and Dr. G. Tom Shires. For the next four decades, he continued his research career at Texas Tech and moved up the faculty ranks to become Research Professor of Surgery and Clinical Associate Professor of Internal Medicine in the Division of Nephrology and Interventional Cardiology.

Importantly, Jan also brought his biomedical discoveries and innovations to industry. Together with Dr. Mario Feola, he engaged with HemoBioTech, Inc., as a co-founder to commercialize bovine hemoglobin that was modified with ATP, adenosine, and glutathione cross-linking. This innovative approach was based on foundational research that he and his collaborators had initiated and was licensed to Texas Tech University. This novel product was designed not only to carry oxygen but also to stimulate erythropoiesis and limit the toxicity associated with unmodified cell-free hemoglobin. In a small study of children with sickle cell anemia, it was found to relieve the pain associated with a vaso-occlusive crisis. Subsequently, Jan was Founder and CEO of the Texas HemoBioTherapeutics and BioInnovation Center, which worked to further the development of artificial oxygen carriers and precision oncology. In addition, he served as a scientific consultant at Immutrix, Inc., and participated in developing their new technology for the purification of blood by the removal of unwanted inflammatory mediators and toxins so that the blood could be used safely in extracorporeal perfusion systems.

More recently, Jan served as Vice President for Manufacturing at AntiRadical Therapeutics, LLC. Here, he oversaw the manufacturing of large quantities of GLP-grade SanFlow, a PEGylated bovine hemoglobin that underwent polynitroxylation to provide intrinsic antioxidant properties. Moreover, the hemoglobin was stored in its carboxy state to limit methemoglobin formation and thereby extend its shelf life. Upon transfusion, the carbon monoxide dissociates from the heme and the resulting low level of carbon monoxide acts as an anti-inflammatory agent without significantly limiting oxygen transport. Importantly, resuscitation with this product was found to protect the brain from neurotrauma even when combined with hemorrhagic hypotension in mice, guinea pigs, and pigs. It was also effective in reducing infarct volume in a rat model of ischemic stroke.

Jan worked to promote the growing field of blood substitutes and artificial organs through scientific conferences and specialty journals. He was a member of the Editorial Board of

Artificial Organs and *Chemico-Biological Interactions*, and Section Editor for Tissue Engineering/Biomaterials of the *American Society for Artificial Internal Organs* (*ASAIO*) *Journal*. He was a key contributor to the many conferences on blood substitutes and artificial organs over the past four decades.

Dr. Simoni brought enthusiasm, inquisitiveness, and scientific rigor not only to the field of blood substitutes, but also to a broader range of novel therapeutic platforms at the interface of surgery, nephrology, interventional cardiology, biotechnology, and molecular biology. His leadership and insights in these fields will surely be missed.

By Prof. Raymond Koehler
John's Hopkins University

In Memoriam: Andrea Mozzarelli

Andrea Mozzarelli, Full Professor of Biochemistry at the University of Parma, passed away suddenly in 2024 among his beloved mountains of the Apennines. His scientific career spanned nearly 50 years, during which he distinguished himself as an internationally recognized scientist and a much-loved professor at the University of Parma.

His scientific career began in 1974, when he graduated in chemistry under the supervision of Professor Gian Luigi Rossi. He joined the University of Parma at a very young age as a research assistant, drawn to the chemistry of biological molecules, and especially to proteins. In 1984–85, he worked in the United States at the National Institutes of Health in Bethesda, where he conducted groundbreaking studies on sickle cell anemia, published in leading international journals. Upon returning to Italy, he advanced through the academic ranks, becoming Associate Professor and later, in 2000, Full Professor of Biochemistry at the Faculty of Pharmacy of the University of Parma.

His scientific interests were broad, ranging from the structure-function relationship of hemoglobin to protein engineering, the study of enzymes involved in the production of NMDA receptor agonists, the structural biology of multienzyme complexes, and the three-dimensional characterization of bacterial enzymatic assemblies. His work had a profound impact on science, laying the foundation for future advances in therapeutic and pharmaceutical research. Over his career, he authored more than 250 peer-reviewed publications.

In the last decade of his career, building on his extensive studies of hemoglobin structure and function, he began working on hemoglobin-based oxygen carriers, quickly establishing an international reputation in the field. In particular, he organized the International conferences "International Visions on Blood Substitutes. Hemoglobin-Based Oxygen Carriers: from Chemistry to Clinic" (2006), the "XII International Symposium on Blood Substitutes" (2009), and the "XVIIth International Conference on Oxygen Binding and Sensing Proteins" (2012).

His scientific excellence was recognized both nationally and internationally. He coordinated the Protein Group of the Italian Society of Biochemistry and Molecular Biology, obtained funding from the European Community, the US National Institutes of Health, and several governmental and private agencies, and established collaborations with leading scientists worldwide. Among them were Nobel laureate Max Perutz, William Eaton—his mentor at the NIH and thereafter a lifelong friend—, Donald Abraham, Bob Noble, Andras Eke, and Tatiana Demidkina, who also recently passed away.

Andrea's colleagues, who shared the earliest stages of his career, remember him for his intellectual generosity, his scientific rigor, and his ability to cultivate long-lasting collaborations. To younger scientists, he taught the principles of research: beginning with ethics and curiosity, and the willingness to venture into new directions.

Andrea Mozzarelli's legacy extends beyond his publications and collaborations. He inspired generations of students, many of whom have followed in his footsteps to become professors and researchers at the University of Parma or at other prestigious institutions. His ability to transmit passion for science, along with competence, dedication, and humanity, was a defining aspect of his career.

His absence leaves a deep void, but his influence will endure in the science and in the people he shaped.

By Prof. Leif Bulow
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