BIOGRAPHICAL SKETCH

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NAME: William R. Clarke, MD, MSc

eRA COMMONS USER NAME (credential, e.g., agency login): clarkewr

POSITION TITLE: CEO XLock Biosciences 0.51 FTE, Director of Drug Device and Diagnostic Accelerator, Boston Children's Hospital 0.49FTE

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Duke University	BA,	5/1974	Chemistry
Duke University	MSc	8/1979	Pharmacology
Duke University	MD	8/1979	Medicine
University of Washington	Combined Residencies	1/1983	Pediatrics and Anesthesiology
Children's Hospital of Philadelphia	Fellowship	6/1985	Pediatric Anesthesia and Critical Care
University of Pennsylvania	Post doc	7/1985-3/1987	Pulmonary pharmacology

A. Personal Statement

I have always focused my career on the interface between science and medicine. During my undergraduate degree in chemistry, I was fascinated with the chemistry of drug development process and the ability to help patients. While in medical school, I added three years of graduate school to obtain an MSc in pharmacology. Given my interest in medicine, pharmacology, and pediatrics, I decided to undertake two residencies - first in pediatrics, and second in anesthesiology, intending to obtain further training in pediatric critical care. During my residencies and fellowship, I developed an interest in pulmonary pharmacology and especially pulmonary hypertension so undertook a post-doctoral position in the laboratory of Dr. Bryan Marshall to deepen my basic skills in this area. The result was a series of publications that more fully defined the role of pulmonary arterial pO2 versus ventilating gas pO2 in the control of pulmonary vascular resistance (PVR), which is critical in caring for infants and children with complex congenital heart disease. This work elucidated the previously unclear phenomenon of severe increases in children with complex shunting lesions who were receiving high FiO2. At the University of Pennsylvania, I was intrigued by the then early work on idiopathic pulmonary hypertension treatment. Still maintaining this interest, I was recruited to the University of Washington, where I established a pulmonary hypertension clinic at Seattle Children's Hospital, which became the second largest pediatric pulmonary vascular disease center in the world, and directly led to my role as an initial investigator for the clinical trials of infused prostacyclin (Flolan®).

My clinical work in the peds ICU, and my interest in pediatric pulmonary vascular disease, redirected my focus to failed transitional circulation, the most prevalent cause of pulmonary vascular disease in infants and children. This propelled my most important work in delineating the formally mysterious but crucial role that phosphodiesterase type 5 (PDE5) plays in normal and diseased transitional circulation. My subsequent clinical work with early PDE5 inhibitors in treating neonatal pulmonary hypertension led to my recruitment into the pharmaceutical industry.

In industry, I applied my clinical and pharmacologic expertise to the research and development of novel therapeutics. As Director of Biology at GlaxoWellcome, I led target discovery and target validation. As Global Head of R and D at Amersham Health, I oversaw all aspects of Research, Development, Clinical, and Regulatory and thus developed a deep understanding of drug development, clinical trials, and registration. As CEO of Cellectar, I took “two scientists and an idea” through the founding of a company and a complex, yet successful, phase I trial of a novel therapeutic. I returned to a combined academic clinical and scientific role in 2010 as I missed taking care of kids. In this role, I was the Entrepreneur in Residence at the Medical College of Wisconsin, where I met and mentored the founders of Protein Foundry and XLock Biosciences, as well as several other faculty-led startup companies. In 2019, I was recruited to Boston Children’s Hospital to be the Faculty Director of the Drug, Device, and Diagnostic Accelerator along with a part-time clinical role. When approached by the XLock founders to lead the company as CEO, I was delighted. I am highly motivated to advance the development of XLock’s lead molecule and bring it to patients suffering from psoriatic arthritis. I deeply understand all aspects of what it takes to bring a therapeutic to market, and where to focus XLock's research efforts to turn the CCL20LD into a successful new drug.

Ongoing projects that I would like to highlight:

Source: NIH/NHLBI 1R43HL164271-01
PI: Clarke (Volkman co-PI)
Title: Development of an engineered CCL20 as a therapeutic molecule for chronic graft- versus-host disease
Dates: 6/15/2022-6/30/2023

B. Positions, Scientific Appointments, and Honors

Positions

October 2020 to Present XLock Biosciences, LLC
As Chief Executive Officer of XLock Biosciences, I utilize my decades of academic and industrial drug development experience to maintain a focus on risk reduction in the development of CCL20LD. I have emphasized the need for clear CMC progress and the early focus on industrial toxicology studies as these are often stumbling blocks in therapeutic development. I will direct the XLock team and coordinate efforts of academic subcontractors with project management assistance from Mr. Koplinski and scientific guidance from Dr. Volkman. Dr. Hwang will supervise the research team at UC Davis, the performance site. Dr. Dwinell will supervise the research team at MCW, the performance site for immune function studies and Dr. Peterson will lead the XLock protein design and manufacturing team.

April 2019 to Present - Boston Children’s Hospital
I am Senior Clinical Associate in perioperative medicine (pediatric anesthesiology and critical care) and the Faculty Director of the Drug, Device and Diagnostic Accelerator

September 2010- March 2019 - Medical College of Wisconsin
I was initially an Associate Professor, subsequently Full Professor of Anesthesiology and Pediatrics and the Entrepreneur in Residence. In the later role I spun out several new companies including Protein Foundry, LLC.

Jan 2007- Sept 2010 - Cellectar
As CEO, I took the embryonic Cellectar from 2 academic scientists with a great idea through a $14m fund raise, development of the lead and a successful phase 1 trial. Cellectar was purchased in October 2010. The molecule is now in several phase 3 trials.

April 2004-Dec. 2007 - GE Healthcare
Chief Medical Officer. GE purchased Amersham for access to our molecular imaging agent portfolio as well as our biosciences tools portfolio (for clarity, I did not oversee the biosciences tools part of Amersham, that was run by the previous Pharmacia leadership).

2000-March 2004 - Amersham plc
Global Head of R and D. I was recruited to Amersham to update their R and D processes. In this role I moved Amersham from 'traditional' imaging agents to develop new, molecular imaging agents including new PET imaging agents for amyloid and prostate cancer.

1996-Dec 1999 - GlaxoWellcome
Director of Biological Sciences. Biological Sciences was charged with target identification and validation for new therapeutic targets

1987-1996 - University of Washington
Assistant then Associate Professor of Anesthesiology and Pediatrics, and Founding Director of the University of Washington Pediatric Pulmonary Disease Center

Honors

1994 Elected Member, Association of University Anesthetists
1990 Young Investigator Award, Foundation for Anesthesia Education and Research
1988 B.B. Sankey Award for Excellence in Anesthesia Research, International Anesthesia Research Society
1988 J S Reading Award for Excellence in Critical Care Research, Southern Society of Critical Care
1974 Phi Lambda Upsilon, National Chemistry Honor Society

C. Contributions to Science. My initial contributions to science were in graduate school in the lab of Robert Lefkowitz at Duke University where I was the first to delineate the existence of an alpha-2 adrenergic receptor in the liver and define its binding and pharmacologic characteristics**.**

1) Control of pulmonary Vascular Tone by perfusate Po2 and inspired FiO2
My first truly independent first contribution to science was a series of studies, initially started in the laboratory of Dr. Bryan Marshall during my postdoc and then continued in my own laboratory at the University of Washington which revised our understanding of the variables which control the hypoxic pulmonary vasoconstriction response. In particular, these studies were the first to demonstrate and then to quantify the role that pulmonary perfusate pO2 plays in controlling pulmonary vascular tone. This is especially critical and relevant in the child with complex cyanotic cardiac disease and parallel circulations where we now understand that low perfusate (pulmonary arterial blood) pO2 can further constrict the pulmonary vascular bed, cause greater shunting and a self-reinforcing and potentially fatal cycle that results in catastrophic systemic hypoxia.

Spitzer AR, Davis J, **Clarke WR**, Berbaum J, and Fox W, Pulmonary hypertension, and persistent fetal circulation in the newborn *Clin. Perinatol*. 15:389-413, 1988.

Clarke WR, Gause G, Marshall RE, and Cassin S, The role of lung perfusate pO2 in the control of pulmonary vascular resistance of exteriorized fetal lambs *Respir. Physiol*. 79:19-32, 1990. 14.

Clarke WR, Haberkern CM, Zeh J, Powers K, Sharar SR, and Soltow LO'G, The HPV response is different with constant pressure versus constant flow perfusion *Resp. Physiol*. 94:75-90, 1993.

2) Role of PDE3 as a therapeutic in modulating PVR

My second contribution was to be one of the first, if not the first, to define the exact mechanism of the modulation of PVR by the PDE3 inhibitor amrinone. We were the first to show with detailed pressure-flow curve analysis that amrinone was a direct pulmonary vasodilator and did not 'reduce' calculated single-point PVR by simply raising cardiac output.

Clarke WR, Morray JP, Powers K, and Soltow LO'G, Amrinone reduces pulmonary vascular resistance elevated by U46619 in isolated perfused lungs *J. Cardiovas. Pharmacol*. 18:85-94, 1991.

Berger JI, Gibson RL, **Clarke W R**, Standaert TA, Redding GJ, Henderson WR and Truog WE, Effect of amrinone during group B streptococcus-induced pulmonary hypertension in piglets. *Pediatr. Pulmonol*. 16:303-310, 1993.

3) The Role of PDE3 Regulation in Normal and Diseased Neonatal Pulmonary Vascular Tone

My third contribution is that of which I am most proud because I see it used every day in children and adults in my care with pulmonary hypertension. I delineated the role of PDE5 in the control of normal and disease fetal/neonatal PVR and described the therapeutic role of PDE5 inhibitors in the treatment of pulmonary hypertension.

Uezono S, **Clarke WR**, Chambers A and Doepfner P, The type III phosphodiesterase inhibitor milrinone and type V inhibitor dipyridamole individually and synergistically reduce elevated PVR. *Pulmon. Pharmacol.* 7:81-89, 1994. 22.

Cohen AH, Hanson K, Morris K, McMurty IF, **Clarke WR** and Rodman, D M, Inhibition of 3'-5'-guanosine monophosphate-specific phosphodiesterase selectively vasodilates the pulmonary circulation in chronically hypoxic rats. *J. Clin. Invest*. 97:172-179, 1996.

Hanson KA, Ziegler JW, Rybalkin SD, Miller JW, Abman SH, **Clarke WR**, Chronic pulmonary hypertension increases fetal lung cGMP phosphodiesterase activity. *American Journal of Physiology: Lung Cellular and Molecular Physiology.* 1998. Nov; 275 (5pt1): L931-41

Hanson KA, Burns F, Beavo J, **Clarke WR**, Developmental Changes in lung cGMP phosphodiesterase-5 activity, protein and message. *American Journal of Respiratory Cell and Molecular Biology.* 1998 July; 158 (1):279-88

Ziegler JW, Ivy DD, Fox JJ, Kinsella JP, **Clarke WR** and Abman S H, Dipyridamole Potentiates Pulmonary Vasodilation Induced by Acetylcholine and Nitric Oxide in the Ovine Fetus. *Am. J. Respir. Crit. Care Med*. 157. 1104-1110, 1998.