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Fluids and Barriers of the CNS

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The legacy of William M. Pardridge (1947–2024) on the science and fields concerned with the physiology of the blood-brain barrier and the transport of drugs to the brain

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Abstract
This article highlights the scientific achievements and professional career of William M. Pardridge, who passed away on 18th of June 2024. He was born in 1947 in Bethesda, Maryland, USA. William, known affectionately as Bill, was one of the most influential researchers in the blood-brain barrier (BBB) field. Bill's research contributions to the field spun over 6 decades at the University of California, Los Angeles, and it was focused on the molecular physiology of the BBB, including the carrier-mediated transport of nutrients and small molecule drugs, the receptor-mediated transport of peptides and molecular Trojan horses, gene therapy of the brain with Trojan horse liposomes, and BBB genomics and proteomics. He founded ArmaGen Inc. in 2004, a biotech company that provided the basis for the treatment of CNS disorders with the molecular Trojan horse technology. This technology continues to be widely used in academia and in the biotech industry. He has been a cherished friend and mentor to many within the BBB community.

Dr. William M. Pardridge (Fig. 1), our colleague and dear friend, passed away on the 18th of June 2024. William, known affectionately as Bill, received a Medical Degree from the Pennsylvania State University in 1974. After internship and residence at the Boston University Medical Center, and a fellowship in Endocrinology at the University of California, Los Angeles (UCLA), he was appointed Assistant Professor of Medicine at UCLA in 1978. He remained at the same institution, and he was appointed Distinguished Professor, Emeritus, in 2013. Bill is considered by his peers a highly regarded scientist in the blood-brain barrier (BBB) field, and his legacy includes over 500 publications, numerous patents, and numerous postdoctoral trainees who continue to advance the BBB field. Bill supported his work with innumerable research grants awarded by the NIH and other public institutions and private foundations.

Bill was introduced to the field of the blood-brain barrier (BBB) in the laboratory of William Oldendorf in the summer of 1970, where he learned a method called the Brain Uptake Index (BUI) to study BBB transport. During the summer of 1971, as a medical student, Bill used the BUI method to initiate his own research on the BBB transport of drugs, and this work led to his first publications [1, 2]. Bill opened his permanent laboratory as an

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Fig. 1 Photograph of William M. Pardridge

Assistant Professor at UCLA and extended his work on the BBB to the transport of hormones, including thyroid hormones, steroid hormones, and neuropeptides. The work on thyroid and steroid hormone transport led to the hypothesis of plasma protein-mediated transport of hormones, and this was the focus of his work from 1978 to 1988 [3, 4]. The neuropeptide work prompted Bill to move from the in vivo physiology of BBB transport, as examined by the BUI method, to the in vitro cell biology of BBB transport with the use of capillaries isolated from fresh animal brain, and the human autopsy brain. The isolated brain capillary investigations led to the development of the field of receptor-mediated transport (RMT) of peptides across the BBB, and the discovery of the BBB molecular Trojan horse (MTH) as a brain biologics drug delivery technology, for which he received a US patent in 1989 [5]. In the 1980s, Bill maintained his interest in the BBB transport of nutrients, and in the 1990s and 2000s in the development of the genetic engineering of IgG fusion proteins.

The work on BBB transport of nutrients focused initially on the carrier-mediated transport (CMT) of glucose and amino acids, and Bill was the first to combine the principles of in vivo capillary physiology transport, as embodied in the Kety-Renkin-Crone equation, with enzyme kinetics, as described in the Michaelis-Menten Eqs. [6, 7]. Bill published an understanding of the kinetics of BBB transport of nutrients and provided insight into the molecular regulation of the intermediary metabolism of the brain [8]. This work progressed to the cellular level, where he investigated the kinetics of amino acid transport at the human BBB using capillaries isolated from human autopsy brain [9], and then to the molecular biology of the BBB CMT systems, which led to the molecular cloning of the GLUT1 glucose transporter, the LAT1 large neutral amino acid transporter, and the CNT2 purine nucleoside transporter [10–13]. The CMT systems are encoded by members of the Solute Carrier (SLC) gene family, which now totals nearly 500 genes. In order to understand which of the many SLC transporters function at the BBB, it would be necessary to know the Substrate Transporter Profile (STP) of the cloned BBB transporter and the STP of CMT transport across the BBB in vivo. Bill compiled this information and proposed a new Dual Track high throughput screening of small molecule drug libraries to isolate drug leads that have high affinity for both the drug target on brain cells, to mediate drug action in brain, and high affinity for a given BBB CMT system, to enable drug transport from blood to brain [14].

The discovery of the Molecular Trojan Horse (MTH) technology emerged from a linear sequence of discoveries in Bill's laboratory. In 1980, he developed a methodology for the isolation of brain capillaries, which form the BBB in vivo, from animal, and then human autopsy brain, and characterized BBB receptors for endogenous peptides, including the human BBB receptor for insulin [15]. This work was extended to the receptors for transferrin, insulin-like growth factors, and leptin at the human BBB. By the mid-1980s, the work on the human BBB insulin receptor led to the hypothesis that the BBB insulin receptor served to cause the receptor-mediated transport (RMT) of insulin from blood to brain [15]. The discovery of RMT processes at the BBB led to the idea of using endogenous peptides as molecular Trojan horses to ferry drugs across the BBB, via transport on the endogenous receptor-mediated transport (RMT) systems, and this idea was first published in 1986 [16]. Subsequently, receptor-specific peptidomimetic monoclonal antibodies (MAb) were developed as a BBB MTH, which targeted either the endogenous transferrin receptor (TfR) [17, 18] or insulin receptor at the BBB [19]. The potential of the MTH strategy for brain drug delivery was further validated in the early 1990s by the demonstration of pharmacological activity in vivo. Using MTH based on a MAb against the rat transferrin receptor, these studies provided proof that CNS pharmacological effects can be readily achieved after systemic administration of a nerve growth factor or a vasoactive neuropeptide [20, 21].The MAb against the insulin receptor targeted the human insulin receptor (HIR), so this antibody could be developed as a BBB Trojan horse for drug delivery to the human brain [22]. The HIRMAb cross reacted with the insulin receptor of Old-World primates, such as the Rhesus monkey, and it was shown that the antibody penetrated the primate BBB at a level of 2–3% of injected

dose/brain [19], which is comparable to the brain uptake of lipid soluble small molecules. The discovery of an antibody of mouse origin that rapidly penetrated the BBB in monkeys [19] was followed by the genetic engineering, expression, and validation of chimeric and humanized forms of this HIRMAb [23]. The availability of the genes encoding the heavy chain and the light chain of the engineered HIRMAb enabled the subsequent genetic engineering of IgG fusion proteins for BBB drug delivery of biologic drugs. In order to commercialize this technology, Bill founded ArmaGen Technologies, Inc. with Dr. Ruben J. Boado, in Santa Monica, CA, in 2004. The engineering and validation of numerous brain-penetrating lgG fusion proteins were successfully completed. These fusion proteins included neurotrophins [24–26], therapeutic antibodies [27], lysosomal enzymes [28–33], and decoy receptors [34]. It was shown that almost any type of biologic pharmaceutical can be re-engineered as an IgG fusion protein for penetration of the BBB [35–37], and this approach was initially extensively studied in several rodent models of CNS diseases [38–41]. The MTH technology applied to IgG-fusion proteins was successfully used in phase I/II/III clinical trials with valanafusp alpha and lepunafusp alfa in Hurler syndrome MPSI [42, 43] and pabinafusp alfa in Hunter syndrome MPSII [44]. Pabinafusp alfa was the first brain-penetrating biological approved by a regulatory agency for the treatment of Hunter MPSII syndrome [45]. The efficacy of a brain penetrating IgG-fusion protein with palmitoyl protein thioesterase-1, designated AGT-194 [33], was also demonstrated in a patient with neuronal ceroid lipofuscinosis type 1 (CLN1 disease) under its compassionate use [46].

The discovery of BBB-penetrating receptor-specific molecular Trojan horses enabled the design of Trojan horse liposomes (THLs) for the non-viral, non-invasive delivery of plasmid DNA to brain [47–49]. The intravenous injection in the adult Rhesus monkey of a reporter gene encapsulated in THLs enabled global expression of the transgene in all parts of the primate brain [50, 51]. The THL technology was also used in mouse or rat models of neural disease. For the treatment of experimental brain cancer, a plasmid DNA encoding a short hairpin RNA (shRNA) against the epidermal growth factor receptor (EGFR) mRNA was encapsulated in the THL and targeted to a human cancer in mouse brain with combined HIRMAb and TfRMAb Trojan horses [52]. Weekly treatment of mice with intra-cranial brain cancer with the MAb-targeted THLs resulted in a 100% increase in survival time [52]. Therapeutic levels of a lysosomal enzyme, glucuronidase (GUSB), were achieved in GUSB null mice with TfRMAb-targeted THL delivery to brain of a GUSB expression plasmid DNA [53]. The THL technology was also successfully applied to an experimental rat model of Parkinson's disease (PD) with intravenous treatment with THLs carrying a plasmid DNA that encoded for glial-derived neurotrophic factor (GDNF), a PD-specific neurotrophin [54]. The expression of the GDNF transgene was confined to the striatum by placement of the GDNF gene under the influence of the tyrosine hydroxylase gene promoter, showing increased expression of striatum TH and marked reduction in the PD's symptoms [54, 55].

The underlying theme of Bill's applied research on BBB transport was that new technology for the brain delivery of recombinant proteins, plasmid DNA, and small molecules can originate from the initial discovery of the basic science of endogenous RMT and CMT systems at the BBB. To facilitate the discovery of new BBB genes, Bill applied the emerging genomics technologies within the BBB field. BBB-specific genes for the rat BBB were discovered with the suppression subtractive hybridization methodology [56]. This technology was also applied to the human BBB [57]. This work led to several novel findings, as exemplified by the isolation of a previously unknown gene that encoded for a novel anion transporter, named BBB specific transporter type 1 (BSAT1), and which is now known as SL01C1 in the SLC gene family nomenclature. BSAT1 also showed an unusual dual affinity for both organic anions, such as estradiol glucuronide, and thyroxine [58]. Bill's work was also extended to the use of proteomics-based approach to the discovery of novel BBB genes [59]. His work on BBB genomics/proteomics may overall provide an understanding of the role of the brain microvasculature in brain disease and to the discovery of new targets for brain drug delivery.

Bill will be greatly missed. We will miss him for his contribution to science but also for his work as mentor to young scientists. His pioneering work on the drug delivery to the brain has inspired countless scientists to continue his legacy and to develop a new generation of brain-penetrating biologicals for the treatment of CNS disorders. His understanding of the physiology of the BBB is very well summarized in one of his latest publications [60].

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RB is co-inventor of patents on the delivery of biological drugs to the brain.

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