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Walter Reed Army Institute of Research (WRAIR): Fifty Years of Achievements That Impact Science and Society

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ABSTRACT Thirty-four historical achievements since 1970 that emanated from scientific research at the Walter Army Institute of Research are identified and documented. Impact areas include vaccines, drug development, and clinical assays to prevent or treat infectious diseases; neuropsychiatric management of warrior performance and combat casualty; blood delivery management; and radiation protection.

INTRODUCTION

On June 22, 2018, the WRAIR held a day-long event that celebrated “125 Years of Infectious Disease Research at WRAIR.” In the program, it was noted that “WRAIR traces its roots back to the U.S. Army Medical School, one of the first public health and preventive medicine institutions in the United States.” The program further noted that “WRAIR’s modern mission has been redefined into two research centers of excellence, the Center for Infectious Disease Research (CIDR) and the Center for Military Psychiatry and Neuroscience (CMPN).” As a further historical note that was not in the program, on July 1, 2020, I celebrated 50 years of personal service at WRAIR—a period encompassing 39% of the history of WRAIR since its founding in 1893.

Having served continuously at WRAIR since 1970, at different intervals as an active duty medical officer, or as a civilian medical officer and supervisory scientist, or as an emeritus senior scientist, I have had a unique opportunity to visualize the impact of WRAIR on science and society over a 50-year period. WRAIR is a magnificent research institution that has had a dynamic flux of military and civilian scientists working on a wide range of scientific missions to support military readiness and operations. Like any great academic research institution, WRAIR is justifiably proud of its many

historic contributions that have benefited the missions of military practice and policy to support the aims of its sponsor, the U.S. Army. However, in many areas, military life is an inextricable reflection of civilian life, and some of the scientific advances coming from WRAIR as a mission-driven academic institution have also had dual-use effects on society as a whole. Here, I present a list of creative, innovative, pivotal, or enabling products; discoveries; inventions; concepts; or methods from WRAIR from 1970 through 2014 that have had an impact on military society and society in general.

Criteria for Selection

- One or more WRAIR scientific personnel must have been clearly involved (including active duty or civilian government employees, or WRAIR-embedded contract employees). This also includes WRAIR personnel in WRAIR-associated OCONUS satellite laboratories, such as Armed Forces Research Institute of Medical Sciences in Thailand, and others.
- For all forms of *scientific* research (basic or clinical) to be included, the work must have been the first of its kind, or have opened a completely new and continuing field of scientific research, or it must have resulted in a documented unique impact on society.
- For clinical research, successful phase 3 studies or earlier phase 1 or phase 2 clinical studies that contributed to ultimate the FDA licensing of the tested product are included.
- For a new invention having importance to the public, a U.S. patent must have been issued by the U.S. Patent and Trademark Office. An issued patent serves as a regulatory announcement of commercial timing and novelty, and out-licensing demonstrates entry of the invention into an active public market. In some cases,

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issuance and publication of a patent is cited as evidence of the timing of a benefit to society.

- For a novel method or concept to be included, it must have been uniquely created at WRAIR and resulted in general use in society.

Specific Exclusions

- Unsuccessful phase 3 trials, first-in-man phase 1 studies, or phase 2 studies that did not go further in the regulatory process and did not lead to regulatory approval of the tested product are excluded.
- Scientific research conducted by scientists in WRAIR or other military institutions has often resulted in outstanding purely scientific results that have been presented in the scientific literature. Although solutions to scientific problems do generally provide benefit by adding to scientific research supported by society as a whole, good science alone was not sufficient for inclusion in the present analysis unless it impacted uniquely in some way on society.

SELECTED ACHIEVEMENTS

The accounting of 34 WRAIR achievements that resulted in beneficial results, is shown in Table I. This is admittedly a subjective exercise assembled according to the criteria described, and others might wish to add or subtract from it; however, for each item, I supply specific evidence on which it is based.

DISCUSSION

WRAIR is a large post with a complex organization and broad mission. The authorized strength in CY 1990 was 798 military and civilian employees, many of whom were physicians and scientists, and this did not include numerous contractors. Hundreds of scientific publications and technical reports are generated each year, but among the vastness of output, only a few items are ultimately recognized over a period of time as having an impact on science or society. Some

achievements are recognized immediately: The successful phase 3 RV144 Thai HIV vaccine trial quickly changed the direction of the entire HIV vaccine field and gave hope to the public that an HIV vaccine was possible. Other achievements required years or even decades to achieve recognition: The 1995 FDA approval of amifostine (WR2721) as a drug for protecting normal tissue during radiation treatment of cancer came four decades after synthesis of the anti-radiation compound at WRAIR in the 1950s. Because of the inherent delay that often occurs in the process of historical recognition, the 50-year perspective presented in Table I pauses in 2014 as we await the emergence of historical impacts of the many recent and ongoing research efforts now being undertaken.

Failure to achieve an impact on science or society can have many different causes. The overall statistical “probability of success” for regulatory approval of candidate vaccines to infectious diseases overall is estimated to be only 33.4%.⁷⁵ Therefore, with reluctance, I have excluded many first-in-human phase 1 trials of interesting and exciting candidate vaccines, including those to chikungunya virus,⁷⁶ Ebola and Marburg viruses,⁷⁷ Middle East respiratory syndrome virus,^{78,79} and Zika virus,⁸⁰ because they have not yet been proved successful in a phase 3 trial and have not been licensed for human use by a national regulatory agency.

Scientific research is a competitive exercise, often requiring collaboration with groups of scientists at different institutions or companies. For example, the licensing by the FDA of the first Ebola virus vaccine resulted from competition among multiple different collaborative groups of scientists (including from WRAIR),⁷¹ with the winner of the competition (Merck) taking the prize that benefits all.⁸¹ The frenzied international recent attempts by more than 130 commercial and research groups to develop an effective SARS-CoV-2 vaccine provides a further example of such competition, and WRAIR is deeply immersed with its own military COVID-19 vaccine candidate.⁸² WRAIR is also at the forefront of discussions about

TABLE I. Selected Highlights in the History of WRAIR, 1970-2014⁴

1970—Development and demonstration of efficacy of the first effective meningococcal meningitis vaccine in a pivotal large-scale field trial. ^{1,2}
1971—Bivalent oral live adenovirus type 4 and type 7 vaccine tablets were created and FDA-approved for use in soldiers. ³⁻⁵
o The vaccine is administered to all recruits during basic training, and it retains its full protective potency for at least 6 years and probably much longer.
1975—Mefloquine (WR149240, brand name Lariam) antimalarial drug was first tested by WRAIR in humans. ⁶
o Mefloquine was approved by the FDA in 1989 and has been widely used for malaria prophylaxis among travelers.
1978—Synthesis of tafenoquine (WR238605), an analog of primaquine, a drug for treating and preventing relapse of <i>Plasmodium vivax</i> malaria which may occur months or years after initial infection. ⁷
o Tafenoquine was developed in association with SmithKline Beecham, resulting in the FDA approval in 2018.
1978—The first demonstration of the therapeutic potential of naloxone in shock and trauma. This specifically included hypovolemic shock, septic shock, spinal shock, and spinal cord injury, thus opening a new and ongoing field of scientific research. ⁸⁻¹³
o Naloxone (Narcan) is currently approved by the FDA as a therapeutic for opiate overdose.

TABLE I. (Continued)

- 1978—The first studies performed at WRAIR, establishing a new discipline in behavioral psychology called behavioral economics.^{14–18}
- o The referenced studies are among the most cited studies in the field of behavioral economics, with applications to predict abuse liability of novel psychoactive drugs and recently to predict demand for a COVID-19 vaccine.
- 1978—The first discovery and description of enhanced efficacy of liposomes as drug carriers for treatment of any type of infectious disease (originally used in an animal model of visceral leishmaniasis).¹⁹
- o Liposomal amphotericin B (AmBisome; Astellas Pharma US Inc.) was approved by the FDA for treatment of visceral leishmaniasis in 1997.
 - o U.S. patents issued to the Army inventors for above the technology in 1980 and 1981 were the 13th and 39th U.S. “liposome” patents of any type ever issued, out of 58,609 total U.S. liposome patents, as of January 20, 2020.
- 1984—Discovery of the genetic sequence of the circumsporozoite protein of the *Plasmodium falciparum* malaria parasite was a key historical milestone in the history of development of a successful vaccine against malaria.²⁰
- 1985—Discovery of heterosexual transmission of HIV-1/AIDS in the United States.²¹
- 1986—Creation of the widely used WR staging classification for HIV-1/AIDS.²²
- 1986—Creation of controlled human malaria infection (experimental infection of human volunteers) as a method for evaluating the efficacy of human malaria vaccines was a major step in the development of a successful malaria vaccine.²³
- 1986—Creation of the original prototype for the composition of the inactivated hepatitis A vaccine which was later licensed for human use by the FDA in 1995.²⁴
- 1987—Coining of the widely used term “grief leadership” in a report by the WRAIR’s Division of Neuropsychiatry about the human aftermath of the 1985 crash in Gander, Newfoundland, of a charter jet transport carrying 248 soldiers home from peacekeeping duties in the Sinai Desert.
- o “Leaders should provide grief leadership. Leaders who can express their sorrow, fear and sadness while continuing to function will provide a model for others to feel it acceptable to do the same.”^{25–27}
- 1987—Identification of repeat sequence peptides (NANP/NVDP) of the circumsporozoite protein of the *Plasmodium falciparum* malaria parasite as vaccine targets.²⁸ This was the key scientific breakthrough that enabled research leading to the development of the first approved human malaria vaccine (RTS,S; Mosquirix, GSK).
- 1987—Performed the first-ever human injection and evaluation of a malaria vaccine containing a recombinant protein.²⁹
- o A later improved vaccine containing a related recombinant protein (RTS,S; Mosquirix, GSK) was approved for large-scale testing under European Medicines Agency and World Health Organization auspices for prevention of malaria in infants in 3 sub-Saharan countries in Africa.
 - o COL Franklin K. Top, MC, USA (WRAIR director and commandant) was the first person injected.
- 1988—Halofantrine (WR171669, brand name Halfan), a blood antimalarial schizontozide drug effective against chloroquine- and sulfonamide/pyrimethamine-resistant malaria was first tested in humans in 1988.³⁰ Halofantrine was licensed for human use by the FDA in 1992.
- 1989—Performed the first-ever human injection and evaluation of a liposome-based candidate vaccine against an infectious disease (1989-1992).³¹
- o This also was the first-ever human injection of liposomes containing monophosphoryl lipid A and the first-ever human injection of a liposome-based malaria vaccine. COL Carl R. Alving, MC, USA was the first person injected.
- 1991—Creation of the WR repository and survey of compounds from the antimalarial drug development program.³²
- o The WR drug collection, overseen by the WRAIR Division of Experimental Therapeutics, comprises >800,000 highly characterized compounds that are physically maintained in a repository in Rockville, MD. Each drug is identified by a unique WR number.
- 1994—WRAIR (AFRIMS) served as the lead agency in the collaborative pivotal phase 3 trial for hepatitis A vaccine leading to licensing for human use by the FDA in 1995.³³
- 1995—Amifostine (WR2721) (Ethyol), the first broad-spectrum cytoprotectant approved in many countries for clinical use, is an analog of cysteamine and was originally developed by WRAIR in the 1950s as a radioprotective agent. It was approved for human use by the FDA in 1995 for protection of normal tissue during cancer radiation treatment.^{34,35}
- 1998—Discovery and founding of the field of transcutaneous immunization by skin patch; the invention, patenting, development, and out-licensing of the technology for vaccine application to Iomai Corp.^{36–43}
- 1999—Invention, patenting, demonstration of efficacy in 2003, and commercialization in 2011, of the Lethal Mosquito Breeding Container, known as Trap-N-Kill.^{44–47}
- o Product was distributed for reduction of *Aedes aegypti* mosquito populations.
- 1999—Invention, internal development, and demonstration of efficacy (in phase 3 testing) (2013) of WR279396, consisting of an aminoglycoside cream containing 15% paromomycin sulfate in a complex base to aid drug penetration for treatment of cutaneous leishmaniasis.^{48–51}
- 2000—Invention of the basis of the SOLX System for prolonged blood storage (LEUKOSEP HWB-600-XL Leukocyte Reduction Filtration System for Whole Blood with CPD Anticoagulant and SOLX).^{52,53} The system was approved for human use by the FDA in 2013.
- 2000—Atovaquone/proguanil (Malarone) was approved by the FDA for treatment or prevention of malaria in 2002. Development of drug combination strategies, dose-ranging preclinical and clinical studies, and pivotal efficacy trials were organized by WRAIR in partnership with GlaxoSmithKline.⁵⁴

TABLE I. (Continued)

2001—Invention of system and method for predicting human cognitive performance using data from an actigraph in 2001 that led to 2B-Alert App: A mobile application for real-time individualized prediction of alertness in 2019. ^{55–57}
2003—Invention of a system and method to predict human performance based on sleep history and circadian rhythm, called the SAFTE model. ^{58–61} <ul style="list-style-type: none"> o The SAFTE model was subsequently commercialized under license from the Army and is currently used by all the major U.S. Airlines and over 60 aviation and other organizations worldwide for predicting and managing fatigue in transportation and shiftwork. It has been incorporated into transportation policy by the Federal Railroad Administration and the Federal Aviation Administration.
2005—WRAIR conducted the pivotal large-scale field trial that validated the BinaxNow malaria rapid diagnostic test that was approved by the FDA in 2007. ^{62–64}
2009—WRAIR served as the lead agency in the collaborative first phase 2 efficacy testing of RTS,S/AS01 vaccine that subsequently became the first licensed malaria vaccine (Mosquirix, GSK). ⁶⁵
2009—WRAIR (AFRIMS) was the lead agency, together with many others, in the joint RV144 phase 3 trial of the first-ever, and only-to-date, HIV-1 vaccine to demonstrate protection against HIV infection. The trial involved more than 16,000 volunteers in Thailand, half vaccinated and half not vaccinated as a control group. ⁶⁶ <ul style="list-style-type: none"> o RV144 was rated number 2 on TIME magazine’s Top 10 Medical Breakthroughs list for 2009 and number 8 on their 50 Best Inventions of the Year. o “RV144 was the light at the time in the field, without which we may have given up,” said Dr. John Mascola, director of the National Institutes of Health Vaccine Research Center on World AIDS Day at WRAIR, on November 26, 2019. “In the last 10 years of HIV vaccine progress, RV144 is the anchor.”
2009—Created Vero cell-derived inactivated Japanese encephalitis virus technology that led to licensing of JEV vaccine (IXIARO, Intercell) for human use by the FDA in 2009. ⁶⁷
2013—Created, developed, patented, and out-licensed a novel immunotherapeutic vaccine technology against heroin and other opiates in collaboration with the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. ^{68–70}
2014—WRAIR investigators were the first to test in humans the subsequently FDA-licensed Ebola vaccine, rVSVΔG-ZEBOV-GP (Ervebo, Merck). ^{71–73}
2014—The CL Detect Rapid Test for Cutaneous Leishmaniasis. The CL Detect was developed by the Army in partnership with InBios International, Inc., the Institut Pasteur de Tunis in Tunisia, WRAIR, and the U.S. Army Small Business Innovation Research Program, and was approved by the FDA in 2014. ⁷⁴

^aThe listing of achievements in this table was prepared in 2020 but was limited to 2014 for technical reasons of historical delay. Hundreds of more recent and ongoing research projects at WRAIR, many of which include multi-year clinical research trials, new inventions and innovations under development, and basic research, are expected to emerge to add to the historical record, with the time of recognized future impact beyond 2020.

Abbreviations: AFRIMS, Armed Forces Research Institute of Medical Sciences; SAFTE, Sleep, Activity, Fatigue, and Task Effectiveness; WR, Walter Reed.

the possible use, and the ethics, of controlled human infection for accelerating SARS-CoV-2 vaccine development.⁸³ This is a model that is ethically informed from a historical standpoint, in part, by the controlled human malaria infection model developed at WRAIR in 1986 that has been highly useful and beneficial for malaria vaccine development.²³

WRAIR is competitive at the highest level as a scientific enterprise, and because of its mission needs, unique technology, and OCONUS capabilities, it is sometimes a linchpin research partner for investigating health problems that distinctively afflict both military and civilian personnel.

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Tracking down detailed evidence for the expanded list of WRAIR accomplishments over 50 years shown here utilized my own 50 years of personal experiences, personal papers, and collaborative interactions with many of the creators of WRAIR science and innovation. It was facilitated by the WRAIR-NMRC library, WRAIR historical archives, and online resources and also by consultations with individual WRAIR employees, contractors, and alumni, including Dr. Thomas J. Balkin, Dr. Leonard N. Binn, Ms. Lara M. D’Agaro, Dr. Kenneth H. Eckels, Dr. Alan Faden, Dr. Stephen R. Hursh and former WRAIR director and commandant COL C. Fred Tyner, MC, USA (Ret.).

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CONFLICT OF INTEREST STATEMENT

The author is a co-inventor of a patented, out-licensed, and government-owned heroin vaccine listed as a WRAIR achievement.

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