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DARPA'S 2019 BIOTECHNOLOGY PROJECT PROGRESS

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Abstract: The U.S. Defense Advanced Research Projects Agency (DARPA) is the leading agency responsible for pre-research on high-tech defense technologies in the United States. It is known for sensing and leading new trends in the future development of defense science and technology. This article provides an in-depth analysis of the progress of DARPA's biotechnology projects in 2019, and provides inspiration and reference, in order to provide valuable reference for the development of my country's national defense biotechnology.
Keywords: U.S. Defense Advanced Research Projects Agency; Biotechnology projects

1 INFECTIOUS DISEASE PREVENTION AND CONTROL FIELD

Defense Advanced Research Projects Agency (Defense Advanced Research Projects Agency) Search Projects Agency (DARPA) is responsible for the U.S. defense against high-tech The leading organization for technical pre-research work, known as the "global military science and technology development vane"[1]. In April 2014, DARPA announced the establishment of The Biotechnology Office marks that the U.S. military has a high degree of awareness of biotechnology huge military application potential, elevating it to the top priority for development Strategic height [2]. According to the 2020 budget report[3], DARPA Investment in the biotechnology field from 2018 to 2020 was US$3.38, US$3.90 and US$410 million respectively, showing a more sustained and stable expenditure. Hold mode. This article provides an in-depth analysis of DARPA biotechnology projects progress in 2019, and provide inspiration and reference to promote our Provide reference for research in military-related fields.

Infectious disease prevention and control focuses on viral infections and insect-borne diseases. With the acceleration of globalization, human destruction of the natural environment and the intensification of livestock production, the harm of zoonotic diseases is becoming increasingly serious. severe, leading to millions of deaths every year. Although the U.S. military is fighting against infectious diseases has rich experience in epidemic prevention and control, but because many regions around the world The lack of health facilities for the prevention and control of emerging infectious diseases poses a serious threat to the U.S. military's presence across the country. The rapid deployment of the ball presents challenges. To solve the above problems, DARPA In 2019, the Preventing Emerging Pathogenic Threats Project (Pre-venting Emerging Pathogenic Threats, PREEMPT), "Preexpression Project for Protective Alleles and Response Elements" (Pre-sumptive Expression of Protective Alleles and Re-sponse Elements, PREPARE) and "Insect-borne diseases should Key deployments have been made on the project "(ReVector)".

1.1 Prevention of Emerging Pathogenic Threats Program

In February 2019, DARPA announced contracts with Autonomous Therapeutics, Institut Pasteur, Montana State University, Pirbright Institute, and the University of California, Davis, to support PREEMPT [4] carry out.

According to the World Health Organization (WHO), there are approximately 60% of emerging infectious diseases are zoonoses, such as Ebola virus, Zika virus, avian influenza virus, Lassa fever virus and MERS virus etc., all originated from animals and eventually spread to humans, causing global concern. A major infectious disease outbreak broke out. The PREEMPT project effectively curbs viruses that infect humans at the source by discovering pathogens that may cause zoonotic diseases in animal and insect hosts and taking intervention measures to directly block the key link of cross-species transmission of pathogens from animals to humans. The occurrence of sexually transmitted diseases.

The PREEMPT project's research team consists of multidisciplinary researchers Composed, with rich professional knowledge and practical experience in infectious disease prevention and control The respective research focuses are as follows: ①Autonomous Therapeutics Company, which studies pathogenic viruses transmitted by avian and small mammal hosts pathogenic avian influenza viruses, and the tick-borne virus emerging from Crimea-Congo Blood fever virus; ②Institut Pasteur, studying several types that can spread widely arboviruses to animals or humans; ③Montana State University, research Study the pathogenicity and transmission routes of Henipavirus originating from bats. The genus Henipavirus contains several species classified by the National Institutes of Health and Severe diseases listed on the list of controlled agents by the Centers for Disease Control and Prevention (CDC) ④ Pirbright Research Institute, studying how to interfere with the mosquito-transmitted pathways of dengue virus, West Nile virus and Zika virus; ⑤ Add UC Davis, studying Lassa disease from rodents viruses and the pathogenicity and transmissibility of Ebola virus originating from rhesus monkeys Broadcasting channels, etc. At the same time, McMaster University's Institute of Ethics and Policy, CDC's Department of Laboratory Science and Safety and other institutions will provide ethical guidance for the project. DARPA plans to cooperate with WHO to explore ways to transform the results of this project in the future.

1.2 Preexpression Projects for Protective Alleles and Response Elements

In June 2019, DARPA announced partnerships with DNARx LLC, Georgia Institute of Technology, University of Massachusetts Medical School, and Columbia University University Irving Medical Center, University of California, San Francisco and other 5 locations The organization signed a contract to support the development of the PREPARE[5] project.
Influenza virus infection is an important challenge facing the U.S. military in the prevention and control of infectious disease epidemics. Due to the rapid mutation rate of viruses, currently available influenza vaccines often do not match seasonal influenza virus strains. Therefore, there is an urgent need to develop alternative new protection methods to effectively deal with influenza virus infection, a long-term health threat, and to reduce the burden of influenza vaccine development, storage, transportation and immunization. The PREPARE project develops programmable gene expression regulators to up-regulate or down-regulate the expression of specific genes, thereby quickly and powerfully activating the body's natural defense against influenza viruses and achieving timely and effective responses to expected threats.
The research team of the PREPARE project is taking a multi-pronged approach to carry out research on the prevention and treatment of influenza viruses. Its research focuses are as follows: ① DNARx LLC will develop a new DNA-encoded gene therapy to enhance the natural immunity of the nasal cavity and lungs. response and other protective functions to help patients fight influenza viruses; ② Georgia Institute of Technology will deliver gene expression regulators into the body to enhance the body's defense response and quickly prevent virus replication to protect the human body from various influenza viruses; ③ The University of Massachusetts Medical School will study new host and virus targeting sequences, including long non-coding RNA (lncRNA), which can be used to enhance host resistance to influenza viruses; ④ Columbia University Irving Medical Center will develop a Programmable gene expression regulators that can be administered orally trigger the protection and regeneration of intestinal cells while inducing protective responses in liver cells; ⑤ University of California, San Francisco, will activate intestinal cells through intravenous administration or oral therapeutic interventions. A natural defense response in tract and blood stem cells that can last for weeks.
The ultimate goal of the PREPARE program is to submit at least one product to the U.S. Food and Drug Administration (FDA) for a clinical trial new drug application. DARPA requires each research team to maintain close cooperation with the FDA during project implementation to ensure that the research plan and data meet FDA regulatory standards. In addition, all research must comply with relevant ethical requirements, that is, the research results of this project only regulate the expression of specific genes in the human body in a short period of time, and there are no risks such as permanent editing of the genome and potential off-target effects.

1.3 Insect-Borne Disease Response Project

In May 2019, DARPA released the “Response to Vector-borne Diseases Project” (ReVector) guidelines [6]. DARPA hopes that through the implementation of this project, U.S. soldiers will reduce the probability of contracting vector-borne diseases such as malaria, dengue fever, and chikungunya while working in the field.
Mosquito bites and insect-borne diseases have long been a problem in the United States A major challenge for military soldiers in field operations. Although the U.S. military has Equipped with mosquito nets, protective clothing, and insect repellent to avoid mosquito bites, these methods not only increase the burden of logistical support for the troops, but also increase the burden on the troops. On the one hand, it is impossible to accurately predict the frequency that will be used during deployment. rate and quantity, resulting in poor feasibility. ReVector project passed the modification Creates human skin microbiome to create mosquito protection within hours The bite is effective and lasts for about 2 weeks, greatly improving the force military operational effectiveness.
The key technical issue that the ReVector project needs to solve is the skin Modification of the microbiome. In addition to deciphering the relationship between microorganisms and human physiology In addition to the inherently complex interactions between Differences between microbiome groups. In addition, DARPA plans to cooperate with the U.S. Several federal regulatory agencies, including the FDA and Environmental Protection Agency, collaborate and invite Invite experts in the fields of ethics, law and sociology related to biotechnology Provide guidance for the project and provide support for subsequent clinical trials. Once the ReVector project comes to fruition, it will greatly improve the capabilities of U.S. military personnel The protective effect of military operations such as field operations and will be used in the treatment of infectious diseases It is widely used in the treatment of war injuries such as infection and wound healing.

2 HUMAN PERFORMANCE ENHANCEMENT FIELD

Human body performance enhancement focuses on brain-computer interface and mental health maintenance. As the new military revolution develops in depth, weapons and equipment are becoming increasingly sophisticated and sophisticated. It is complex and poses huge challenges to military personnel. Fighting to stay in the future Dominant in the environment, the US military has been committed to related research on human body performance enhancement. In 2019, DARPA focused on “next-generation nonsurgical neu-rotechnology” (N3), “new generation intelligent biological interface” (bridging the gap plus, BG+), and “Focused Pharmaceutical Program” (N3). Phar-ma) and other project research to enhance soldier effectiveness through technological means.

2.1 Next Generation non-Invasive Neurotechnology Project

In May 2019, DARPA announced a grant to Battelle to commemorate research Institute of Applied Physics, Carnegie Mellon University, Johns Hopkins University Six institutions including the Laboratory, Palo Alto Research Center, Rice University, and Tele-dyne Sciences provided financial support to carry out N3 project research [7]. The N3 project will

develop non-invasive and minimally invasive Two kinds of implantable neural interfaces use optical, acoustic and electromagnetic technologies to record neural activities at high speed and high resolution and send the brain's neural signals. Signal. Non-invasive neural interfaces require integrating sensors and other On one device, minimally invasive neural interfaces require the ingestion of various Chemicals help external sensors read brain information. this project Once successful, the U.S. military will have a wearable neural interface system that can Nowadays, neurotechnology is transformed from laboratory research to practical application.

The research team of the N3 project integrates research institutes, universities and enterprises. Its research focuses are as follows: ① Battelle Memorial Institute will develop a minimally invasive neural interface system that can connect external devices with electromagnetic signals that transmit neuron electrical signals. Nanosensors convert electrical signals from neurons into magnetic signals that can be recorded and processed by external devices. External magnetic signals can also be converted into neuron electrical signals, thereby achieving two-way communication; ② Carnegie Mellon University will use acoustics, Optical and other technologies are used to write records of the nonlinear response of neurons to electric fields into specific neurons; ③The Johns Hopkins University Applied Physics Laboratory will develop a non-invasive neural interface system based on optical technology. It will be able to directly measure changes in optical path lengths related to neural activity in neural tissue; ④ The Palo Alto Research Center will use the pairing of ultrasound and magnetic fields to generate local currents for neuromodulation to achieve deeper localization of the brain. Neuromodulation; ⑤ Rice University will develop and utilize diffuse optical tomography technology to infer and record neural activity by measuring light scattering in neural tissue, while using magnetogenetic methods to increase the sensitivity of neurons to magnetic fields; ⑥ Teledyne Science The company will use miniature optical pump magnetometers to detect small local magnetic fields associated with neural activity and conduct research on ultrasound-based writing of neuronal signals.

During the implementation of the N3 project, DARPA will invite legal and ethical experts to provide relevant opinions and suggestions, and consider the potential military and civilian value that the project may generate in the future. In addition, DARPA will work with U.S. federal regulatory agencies to guide research teams to submit relevant applications for new drugs and new devices to conduct clinical trials in subsequent stages.

2.2 New Generation Intelligent Biological Interface Project

In October 2019, DARPA launched the "New Generation Intelligent Biological Interface" project (BG+) [8]. The project promotes wound healing and functional recovery of the peripheral nervous system, such as respiratory function, bowel and bladder control, movement, touch, and proprioception, by comprehensively utilizing neuroscience technology, artificial intelligence technology, and biosensor technologies to provide healing services. Spinal cord injury offers the possibility.

Spinal cord injuries are common among U.S. soldiers participating in training and military operations A type of severe trauma that often occurs due to blocking or damaging the brain's connection to the The connection between bodies leads to irreversible physiological changes in injured soldiers Loss of function, causing paralysis and respiratory and cardiovascular system complication. In recent years, the U.S. military has been using neural interface technology to create Significant progress has been made in wound healing, but due to the differences between various types of injuries Differences, there is currently no neural interface that specifically addresses spinal cord injury technology. The BG+ project will develop and integrate technologies such as damage control, regenerative medicine, and functional recovery to provide medical support and optimal healing for patients at all stages of spinal cord injury (acute, subacute, and chronic). plan.

BG+ project will focus on improving healing of acute and subacute injuries As a result, chronically damaged body functions are restored. Usually, urgent Sexual injury occurs within 2 days after injury and is often accompanied by bleeding and inflammation. Subacute injury occurs 2 days to 2 weeks after injury, with scar formation and axonal die. Chronic injuries may involve limited function improvements. The research focus of the BG+ project is: ①Develop a series of A series of new regenerative medicine technologies and equipment, through intelligent biological interfaces Monitoring biomarkers directly related to injury to track spinal cord injury It can also provide treatments to intervene in injury and promote nerve regeneration. treatment methods, and in local trauma treatment facilities and military field hospitals widely used. ②Develop the brain connected to the nervous system and sensory organs Interface device to restore physiological functions of the body, such as bladder control. At the same time, minimize secondary complications and address spinal cord Long-term functional impairment may persist for years after injury.

2.3 Focus on Pharmaceutical Planning Projects

In September 2019, DARPA announced the launch of the "Focused Pharma Program" [9]. According to the U.S. Army According to a report released by the Ministry of Human Resources in 2018, the average among veterans 20 people commit suicide every day due to neuropsychiatric diseases, mental health Maintenance continues to be a huge challenge for U.S. soldiers. This item The aim is to develop rapid-acting drugs with long-lasting effects, which not only treat the symptoms of neuropsychiatric disorders, but also address their underlying the pathogenesis of.

Research shows that although the pathogenesis of various neuropsychiatric disorders may be very different, they all share a similar process- recurring, negative or negative thought processes. For example, patients with post-traumatic stress disorder will repeatedly recall negative feelings related to the trauma , patients with depression will negatively label normal events in the form of psychological suggestions, and patients with substance abuse and addiction will constantly remind themselves that certain drugs are part of their lives. necessities in. The goal of the Focused Pharmacy Initiative is to develop novel compounds that directly affect specific neurotransmitter signaling processes that are often associated with neurophysiological dysfunction.

Previously, DARPA combed through some research data from privately funded clinical trials. The results show that some specific controlled drugs that interact with serotonin (serotonin) receptors have rapid and long-lasting therapeutic effects in the treatment of chronic alcohol dependence, post-traumatic stress disorder and other neuropsychiatric diseases. However, these drugs act non-specifically on neurotransmitter receptors and receptor subtypes in the brain and indiscriminately activate many signal transduction pathways and produce a variety of serious adverse reactions, including hallucinations. These adverse effects and their possible unpredictable consequences prevent widespread use of these drugs in the U.S. military health care system. The new drugs developed by the "Focused Pharmaceutical Initiative" project will target and bind to specific neurotransmitter receptors and only activate specific neural signal transduction pathways to produce symptomatic treatment effects, thereby overcoming the limitations of existing treatment options. Given the scale of neuropsychiatric symptoms experienced by U.S. soldiers, this program will have huge returns if successful, providing the U.S. military health care system with new, safe and effective neuropsychiatric treatment options.

DARPA plans to develop section, the project will be reviewed to determine whether the novel compound can Effectively treat neuropsychiatric symptoms and avoid adverse effects. If the results of the midterm review are unsatisfactory, DARPA will terminate the program Continue implementation. The "Focus on Pharmaceuticals Initiative" project does not include human clinical trials However, DARPA requires the research team to be ready to submit an investigational new drug application to the US FDA at the end of the project.

3 ADVANCED BIONIC SYSTEMS FIELD

Advanced bionic systems focus on biosensor and intelligent bionic research. Natural evolution enables biological materials and bionic machinery to have the most reasonable and optimized structures and functions, which to a certain extent has become the "source of inspiration" for national defense biotechnology innovation. The U.S. military has included bionic materials as one of the five major categories of materials prioritized for development in the "new generation of national defense" in the 21st century, and bionic machinery has also become an important strategy for the development of new equipment. In 2019, DARPA focused on funding projects such as "Persistent Aquatic Biosensors" and "Tissue Regeneration Bioelectronics" to further promote research related to biosensors and intelligent bionics.

3.1 Persistent Aquatic Biosensor Project

In February 2019, DARPA's Biotechnology Office signed a "Persistent Aquatic Biosensor" (The research and development contract of the PALS project aims to study and make full use of the environmental sensing characteristics of marine organisms and strengthen the strategic monitoring capabilities of various types of waters [10].

The US military mainly uses tactical sensor networks for underwater monitoring, but the uncertainty of ocean currents and marine life activities will affect the monitoring results to a certain extent, and it is difficult to deploy to disputed waters. The PALS project will use hardware devices to capture the response signals of marine organisms to underwater vehicles, convert them into identifiable, actionable and useful information, communicate it to end users and analyze their behavioral characteristics.

NGC and other five units will make full use of marine life such as giant grouper, black sea bass and drum shrimp, as well as bioluminescent plankton. Innate perception ability, monitoring, recording and interpreting its behavioral characteristics. The reception and interpretation of sensory information poses challenges for monitoring hardware and software. Higher requirements, such as long-distance control, underwater wireless propagation speed and Reliability, sensing, distinguishing, collecting and processing weak signals in complex environments Ability etc. At the same time, the research team will use artificial intelligence technology to enhance Monitoring equipment’s ability to perceive the marine environment.

The PALS project integrates monitoring practices into the marine environment itself, once Achieving success will not only expand the scope of underwater monitoring, but also covertly and efficiently conduct comprehensive monitoring of underwater activities and trespassing targets, and at the same time provide Continuous underwater monitoring of disputed waters offers possibilities. In the future, the U.S. military plans to It plans to deploy biological sensing systems in its own waters and disputed areas to build a comprehensive underwater detection network.

3.2 Tissue Regeneration Bioelectronics Project

Explosion injuries, burns, and other traumas cause tremendous damage to the bones, skin, and nervous systems of U.S. soldiers, often requiring months or even days to recover. It takes years to recover, and sometimes even incurable sequelae. These lead to the time between soldiers being injured and leaving the army and returning to the army after recovering from injury. The distance between them is lengthened, which greatly weakens the combat capability of the troops. 2019 In February, DARPA released “Bioelectronics for Tissue Regeneration” (Bioelectronics for Tissue Regeneration). for tissue regeneration (BETR) project guide [11], the purpose is to By analyzing the wound healing processes of other organisms in nature, integrated Physical sensors and artificial intelligence technology accelerate the natural healing of human body wounds The integration process promotes the body’s rapid recovery and reduces complications. produce.

At present, the U.S. military usually uses methods to promote body tissue regeneration or self- Healing methods include plaster fixation of fractures or transplantation of donor ligaments and organs to replace non-renewable tissue. this trauma therapy The healing process is slow and incomplete due to scarring heal. The BETR project will develop new biosensors that use light biological, biochemical, bioelectronic, and mechanical signals to directly monitor the body physiological state of the body, and use methods such as data modeling and intelligent analysis to method, adjusting interventions based on

changes in trauma status, such as intervention Regulate immune responses, recruit endogenous stem cell types, guide stem cells Cell differentiation pathways, etc., to achieve rapid and intelligent healing of stubborn wounds.

4 Conclusion

Overall, the biotechnology projects deployed by DARPA in 2019 reflect its strategic pattern of both innovation leadership and demand orientation. On the one hand, DARPA has always adhered to the principle of "maintaining U.S. technology Leading position to prevent potential opponents from unexpectedly surpassing" this case Purpose, actively explore research and development activities focusing on disruptive technologies activities, such as using the sensory characteristics of marine organisms to the environment to thoroughly Change the current underwater surveillance model of the US military. On the other hand, DARPA Facing the realities faced by the US military such as infectious disease prevention and control and human body efficiency enhancement Demand advanced solutions. Such as studying viruses and animals, insects Interactions between parasites and human hosts to respond to emerging infectious diseases epidemic. Paying close attention to DARPA's future biotechnology development trends will help promote the development of my country's national defense science and technology and respond to potential threats. Provide valuable references.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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