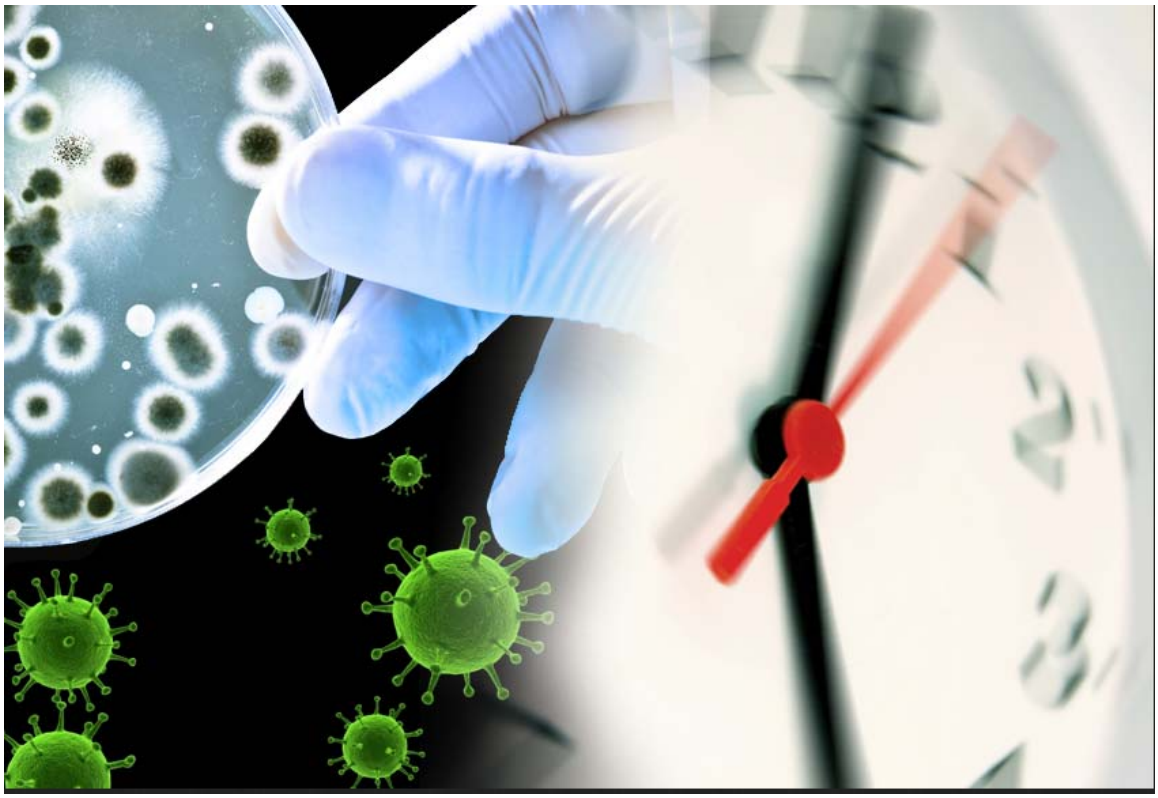


7-Day Biodefense

Military readiness and national security depend on the health and wellbeing of military servicemembers. The Department of Defense's (DoD) cumulative investment in personnel comprises the second-largest share of the total defense budget. As such, DoD seeks advances in healthcare to ensure warfighters can operate at peak performance.

Research into natural and synthetic pathogens, and treatments against them, is one plank of ensuring military readiness in the face of accidental and offensive biological threats to both warfighters and the supply chain supporting them. In this context, the 7-Day Biodefense program will seek to develop novel technologies focused on preventing infection by any emerging pathogen, sustaining survival once infected, and building immunity.

In recent years, global surveillance networks have determined an increase in the frequency and diversity with which new infectious micro-organisms are emerging. While this increase is due in part to improved reporting, multiple examples demonstrate it is also promulgated by changes in natural systems and possibly human activity.

The potential biological threat breaks down into two primary categories:

- Exposure to natural pathogens that are the result of: increased human-animal interface; increased population densities and co-location of vulnerable species with pathogen reservoirs; climate change, particularly affecting migration and spread of vectors; and narrowing of genetic diversity among food-animal stocks.
- Exposure to synthetic and highly diverse pathogens that have become easier to produce as biomedical and genetic-engineering technologies proliferate internationally; such pathogens could be used by adversaries for offensive purposes in a direct attack on warfighters or for covert sabotage of the agricultural industry that supports warfighters.

Together, these emerging threat agents challenge current medical countermeasures. Today's research and development cycle for countermeasures is ill-equipped for rapid response to emerging biological threats.

In response to the unspecified potential threat from emerging pathogens, the goal of the 7-Day Biodefense program is to develop innovative approaches to counter pathogens without regard to their exact nature. The methods being explored do not require prior knowledge of the pathogen and are broadly applicable to multiple, unrelated infectious agents.

The program consists of four technical areas investigating novel technologies to: 1) prevent infection; 2) sustain survival; 3) provide transient immunity; and 4) create persistent immunity.

- **H1N1 Acceleration (Blue Angel)**

  In May 2009, DARPA initiated the Blue Angel effort to identify ongoing programs to assist in the Government-wide response to the H1N1 pandemic. The Blue Angel program is an accelerated and integrated effort to deliver effective interventions for pandemic influenza. Blue Angel brings together the following technologies to form a comprehensive approach in response to a pandemic influenza or manmade outbreak: Predicting Health and Disease (PHD), a program to predict and diagnose individuals exposed to influenza before they are symptomatic; Modular IMmune In vitro Constructs (MIMIC®), a program to identify safe and effective treatments in a test tube; and Accelerated Manufacture of Pharmaceuticals (AMP), a capability for rapidly mass producing low-cost, vaccine-grade recombinant protein that has the potential for scale up to tens of millions of doses per month. In response to the 2009 H1N1 swine flu pandemic, Blue Angel programs are currently in a "live-fire test" to demonstrate a flexible and agile capability for the Defense Department to rapidly react and neutralize any natural or intentional pandemic disease.

  Predicting Health and Disease (PHD): PHD has developed a method for determining who will or will not become sick after exposure to a virus many days before symptoms appear, typically within 10 percent of the incubation period of a particular virus. This is accomplished using a highly accurate, mRNA-based

blood test. By identifying key biomarkers for host response to respiratory viral infections, PHD can categorize viral-exposed individuals into specific categories—those who will be sick, those individuals who are contagious, and those who are well. Accuracy of this method is 85-90 percent within hours of viral exposure and achieves near 100-percent detection after a few days. High accuracy of detection enables prevention, prediction of disease propagation, and appropriate early treatment of infected individuals.

Accelerated Manufacture of Pharmaceuticals (AMP): This program seeks to identify new ways to produce large amounts of high-quality vaccine-grade protein in less than 3 months in response to emerging and novel biologic threats. In response to the 2009 H1N1 swine flu pandemic, as a "live-fire test," the plant platform redirected its rapid scale-up process developed for avian influenza to the new H1N1 virus and produced a recombinant protein within 4 weeks.

Modular IMmune In vitro Constructs (MIMIC®): As animal studies are not always a good predictor of a vaccine's safety and efficacy in a human, the MIMIC® system will work in parallel with the AMP program to test the subunit of vaccine produced under the AMP program to ensure it is safe and immunogenic.

DARPA Makes 10 Million Strides in the Race to Contain a Hypothetical Pandemic

July 25, 2012

Rapid fire test of novel, plant-based production method delivers more than 10 million doses of H1N1 VLP influenza vaccine candidate in one month

U.S. military forces are the front line of U.S. national security, but as a globally deployed force they are also on the front line of any new pathogen-based health threat that may emerge. As overall human activity pushes ever further into previously undeveloped territory, the likelihood of exposure to new pandemic diseases increases.

The 2009 Army Posture Statement, cites a World Health Organization estimate of between 20 and 50 percent of the world's population being affected if a pandemic were to emerge. WHO forecasts "it may be six to nine months before a vaccine for a pandemic virus strain becomes available." In a separate report on pandemic influenza, the WHO describes several challenges to producing sufficient volumes of vaccine using current, egg-based protein-production technology, including the likelihood that two doses per person could be required due to the absence of pre-existing immunity.

In short, the potential for a pandemic exists and current technological limitations on defensive measures put the health and readiness of U.S. military forces at risk. A technological solution to increase the speed and adaptability of vaccine production is urgently needed to match the broad biological threat.

DARPA's Blue Angel program seeks to demonstrate a flexible and agile capability for the Department of Defense to rapidly react to and neutralize any natural or intentional pandemic disease. Building on a previous DARPA program, Accelerated Manufacture of Pharmaceuticals, Blue Angel targets new ways of producing large amounts of high-quality, vaccine-grade protein in less than three months in response to emerging and novel biological threats. One of the research avenues explores plant-made proteins for candidate vaccine production.

"Vaccinating susceptible populations during the initial stage of a pandemic is critical to containment," said Dr. Alan Magill, DARPA program manager. "We're looking at plant-based solutions to vaccine production as a more rapid and efficient alternative to the standard egg-based technologies, and the research is very promising."

In a recent milestone development under Blue Angel, researchers at Medicago Inc. produced more than 10 million doses (as defined in an animal model) of an H1N1 influenza vaccine candidate based on virus-like particles (VLP) in one month. Production adhered to Phase 1 appropriate current good manufacturing practices. The work was part of a "rapid fire" test that ran from March 25, 2012, to April 24, 2012, at a facility in Durham, NC. A third-party laboratory tested the production lots to confirm the immunogenicity of the vaccine candidate. Testing confirmed that a single dose of the H1N1 VLP influenza vaccine candidate induced protective levels of hemagglutinin antibodies in an animal model when combined with a standard aluminum adjuvant. The equivalent dose required to protect humans from natural disease can only be determined by future, prospective clinical trials.

"The results we've achieved here with plant-based production of vaccines represent both significant increase in scale and decrease in time-to-production over previous production capabilities in the same time period. The plant-made community is now better positioned to continue development and target FDA approval of candidate vaccines," Magill said. "Once the FDA has approved a plant-made vaccine candidate, the shorter production times of plant-made pharmaceuticals should allow DoD to be much better prepared to face whatever pandemic next emerges."

# # #

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HAC1 (H1N1) Formulated
BPR No.: BPR-988-00
Contents: 1.0 ml
Caution: New drug limited by
Date of Mfg.: 04 Jun 10
Manufactured By: WRAIR,
USA CMB



Prophecy (Pathogen Defeat)

Military readiness and national security depend on the health and wellbeing of military servicemembers. The Department of Defense's (DoD) cumulative investment in personnel comprises the second-largest share of the total defense budget. As such, DoD seeks advances in healthcare to ensure warfighters can operate at peak performance, and by focusing on prevention DoD may contain costs while enhancing readiness. In this context, the Prophecy (Pathogen Defeat) program will explore the evolution of viruses in the hopes of predicting viral mutations and ultimately developing drugs and vaccines in advance of need.

According to the National Institute of Allergy and Infectious Diseases, in the past 20 years, out of the newly recognized pathogens that impact human and animal health, approximately 44 percent are viruses. (1) Many of these pathogens, particularly RNA viruses, are characterized by a high mutation rate that allows them to rapidly adapt to a changing environment, as occurred in the 2009 H1N1 pandemic. Additionally, many viruses undergo more widespread genetic events (e.g., rearrangements, reassortments) that significantly alter the viral genome. These changes can produce virions capable of evading existing vaccine-acquired and convalescent immunity in humans and animals.

Current antiviral agents and vaccines are designed to protect against viruses that are already endemic, virulent and medically significant to human or animal health. Today's

antiviral therapy research-and-development cycle is reactive in posture, with new vaccines requiring months and new small-molecule inhibitors requiring years to counter emerging viruses.

With the exception of limited influenza viral-forecasting based on uneven global statistics, there is presently no reliable capability to predict viral reassortment or mutations responsible for the emergence of new viral strains. This capability gap leaves the military vulnerable to the detrimental health effects of future viral strains, and thus poses a significant risk to assured military readiness.

The Prophecy program seeks to transform the vaccine and drug development enterprise from observational and reactive to predictive and preemptive by spurring development of a multidisciplinary approach to predicting viral evolution. To achieve this objective, the three-phased program will focus on: 1) development of a viral-evolution platform for generating datasets used to build and validate algorithms predictive of viral evolution; 2) refinement of the platform to include mechanisms capable of controlling multiple selective pressures and accompanying predictive evolutionary models and algorithms; and 3) testing and validation of the system and algorithms using multiple selective pressures on at least three closely related virus strains in an experimental setting. Phase III will to attempt to replicate in a laboratory the viral mutations or evolutions that are documented to have occurred naturally.

References:

1. United States Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases (April 2011). *List of NIAID Emerging and Re-emerging Diseases*. Washington, DC: U.S. Department of Health and Human Services. Retrieved March 15, 2012 from http://www.niaid.nih.gov/topics/emerging/pages/list.aspx.

Microphysiological Systems

Recent DARPA research through the Accelerated Manufacture of Pharmaceuticals program has demonstrated the ability to accelerate production of millions of doses of vaccine using novel plant-based methods. Clinical trials, however, for vaccines, drugs or other biologics cannot be initiated without preclinical evidence of their safety in humans. Human safety and drug performance is not always effectively predicted through animal testing. And the Department of Defense needs to rapidly develop and field safe and effective medical countermeasures against biological threats to warfighters.

To create a pathway for the fielding of safe and effective countermeasures, DARPA has launched the Microphysiological Systems program. MPS will develop a platform that uses engineered human tissue to mimic human physiological systems. The interactions that candidate drugs and vaccines have with these mimics will accurately predict the safety and effectiveness that the countermeasures would have if administered to humans. As a result, only safe and effective countermeasures will be fully developed for potential

use in clinical trials while ineffective or toxic ones will be rejected early in the development process. The resulting platform should increase the quality and potentially the number of novel therapies that move through the pipeline and into clinical care.

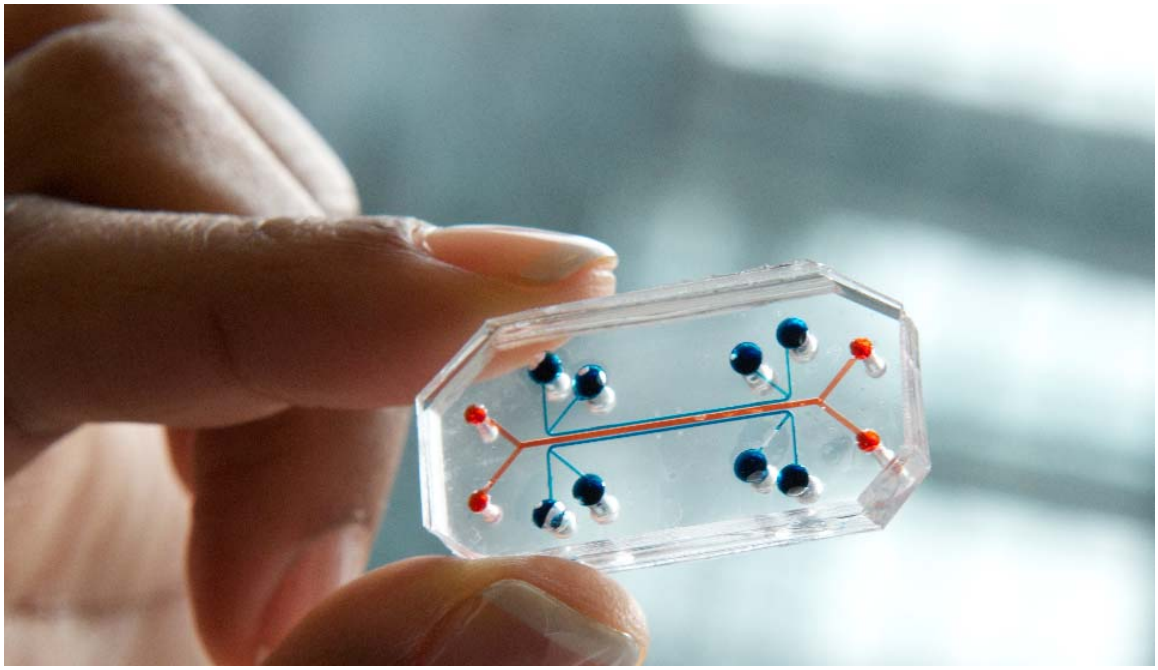
As a force protection measure, DoD has a requirement to protect warfighters from existing or emerging diseases, pandemics and bioterrorism. It has significant interest in developing viable medical countermeasures with an approach that includes aggressive research, removing barriers to innovation and developing capacity to respond quickly to threats.

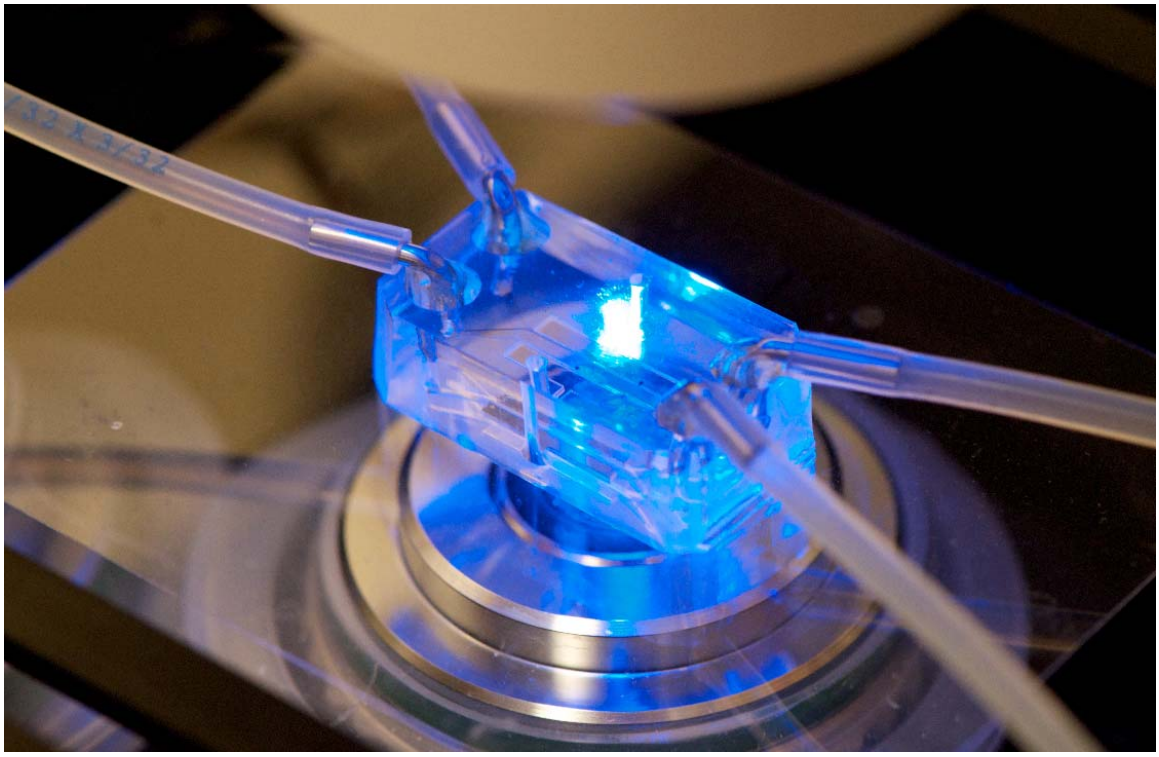
MPS research expects to concentrate in the following areas: A reconfigurable platform that permits simultaneous study of ten or more *in vitro* physiological systems, arranged in any sequence. The platform should be a flexible, user-friendly and reliable design that allows biological components to interact in a physiologically relevant manner and able to sustain the resident tissues for up to four weeks. Researchers developing the *in vitro* mimics should demonstrate that the engineered tissues function together to reproduce each of the human physiological systems. As these system mimics are integrated into a platform of increasing complexity, researchers should demonstrate that the platform reproduces the physiologically-relevant crosstalk between the systems that normally occurs in humans. To validate platform behavior and its potential value for evaluating drugs and vaccines, test compounds with known effects in humans will be applied to the platform. The effects that the test compounds have on the physiological system mimics will then be extrapolated to humans via computer modeling and compared to their health effects previously observed in humans. Research may also demonstrate how an infectious agent might affect the *in vitro* platform, thus providing an opportunity for scientists to study the infectious agent in a human-relevant manner.

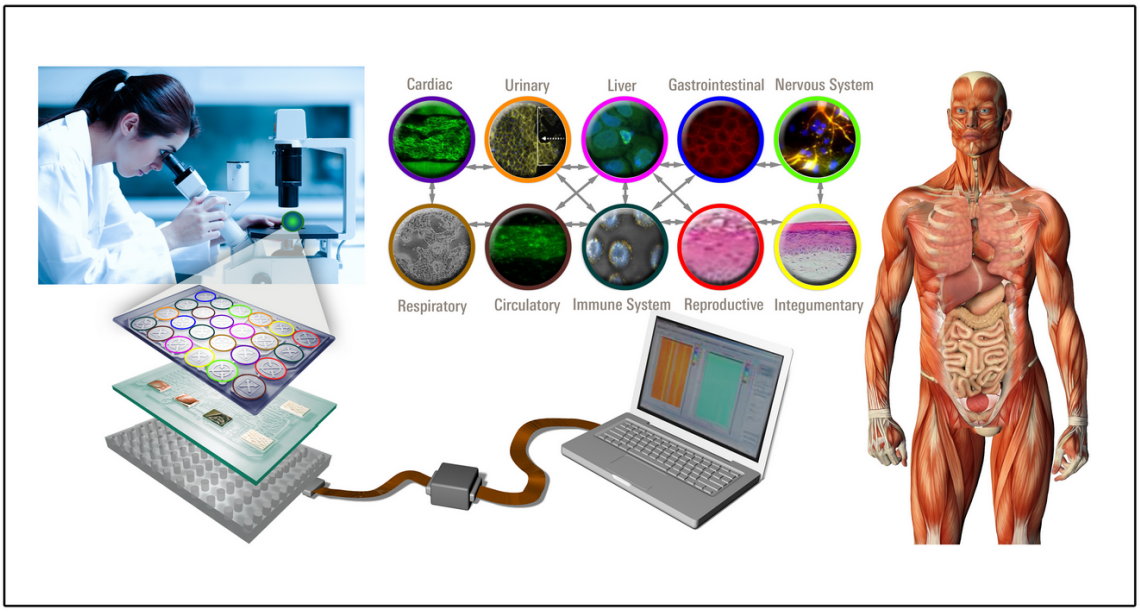
MPS is coordinating efforts with the National Institutes of Health, who is conducting separate but parallel research.

The Food and Drug Administration has been involved from this beginning to help ensure that regulatory challenges of reviewing drug safety and efficacy are considered before and during development.

DARPA published its Broad Agency Announcement Sep. 15, to solicit proposals from potential researchers.







DARPA TO DEVELOP PLATFORM FOR MORE EFFECTIVE TESTING OF DRUGS AND VACCINES

September 16, 2011

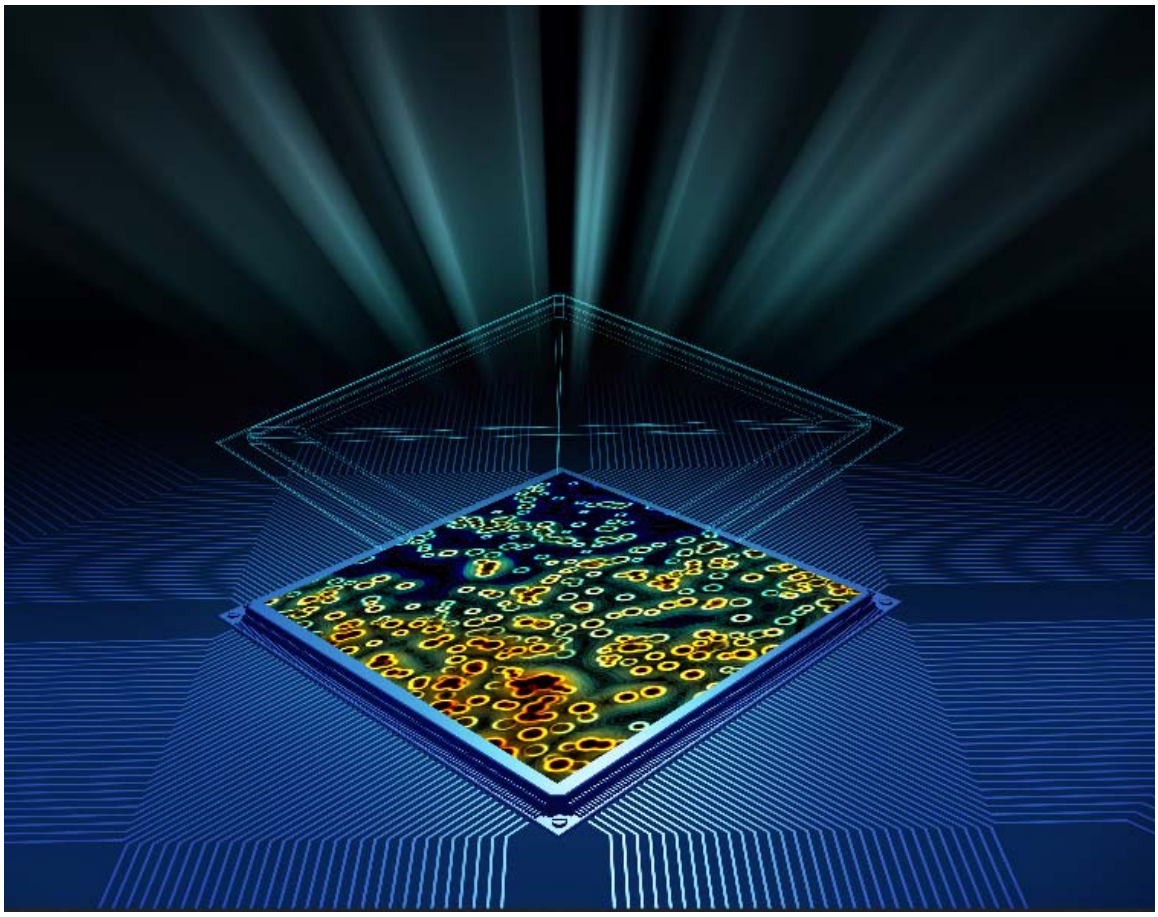
DARPA, NIH, FDA coordinate research efforts to develop chip to screen for safe and effective drugs and vaccines swiftly and efficiently

Recent DARPA research through the Accelerated Manufacture of Pharmaceuticals program has demonstrated the ability to accelerate production of millions of doses of vaccine using novel plant-based methods. Clinical trials, however, for vaccines, drugs or other biologics cannot be initiated without preclinical evidence of their safety in humans. Drug safety and effectiveness in humans are not always accurately predicted through animal testing. And the Department of Defense needs to rapidly develop and field safe and effective medical countermeasures against biological threats to U.S. warfighters.

To create a pathway for the fielding of safe and effective countermeasures, DARPA has launched the Microphysiological Systems program. MPS will develop a platform that uses engineered human tissue to mimic human physiological systems. The interactions that candidate drugs and vaccines have with these mimics will accurately predict the safety and effectiveness that the countermeasures would have if administered to humans. As a result, only safe and effective countermeasures will be fully developed for potential use in clinical trials while ineffective or toxic ones will be rejected early in the development process. The resulting platform should increase the quality and potentially the number of novel therapies that successfully move through the pipeline and into clinical care.

Success of these programs depends on active program management from each agency and strong collaboration among the research teams from all the organizations. DARPA researchers will concentrate their efforts on engineering platforms and the biology required for scientific proof of concept. The NIH's National Center for Advancing Translational Sciences will focus on developing complementary microphysiological systems to mimic human physiology and pathology by taking advantage of recent advances in the field. Both agencies will work closely with the U.S. Food and Drug Administration throughout the process. FDA will provide scientific input to help ensure that the regulatory challenges of reviewing drug safety and efficacy are considered before and during development.

"FDA is excited about this program to develop novel new platforms that can be used to screen drugs for safety and efficacy, without the use of animals and in a manner that better predicts what happens in people," said Margaret A. Hamburg, M.D., Commissioner of the U.S. Food and Drug Administration. "This cheaper, faster and more predictive approach to drug screening could speed the development and improve the evaluation of innovative medicines, bringing needed products to patients safer and faster."

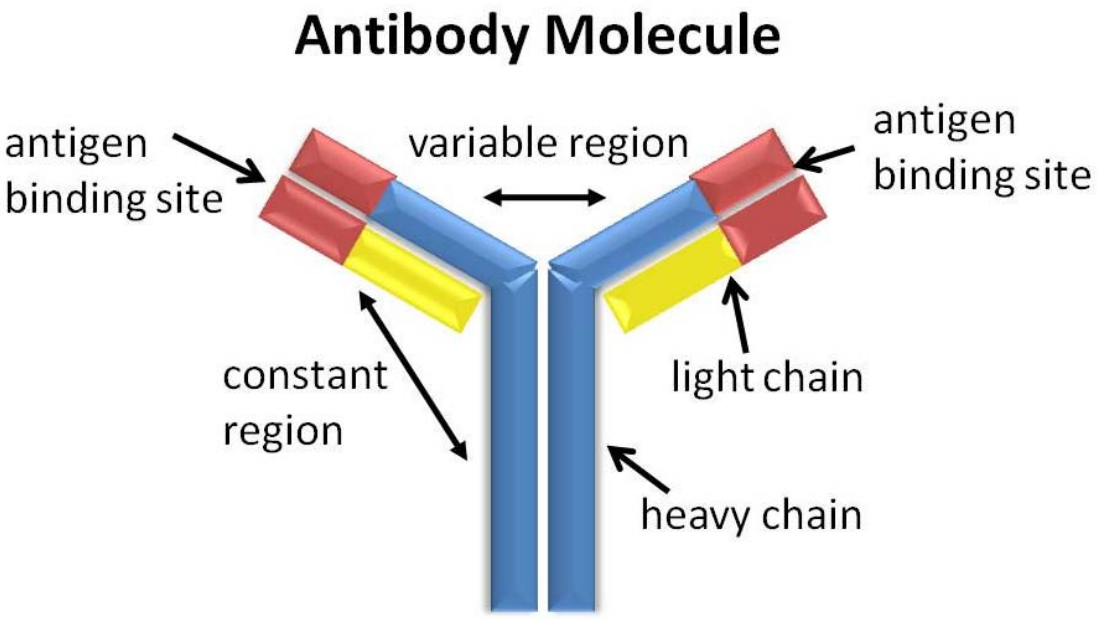


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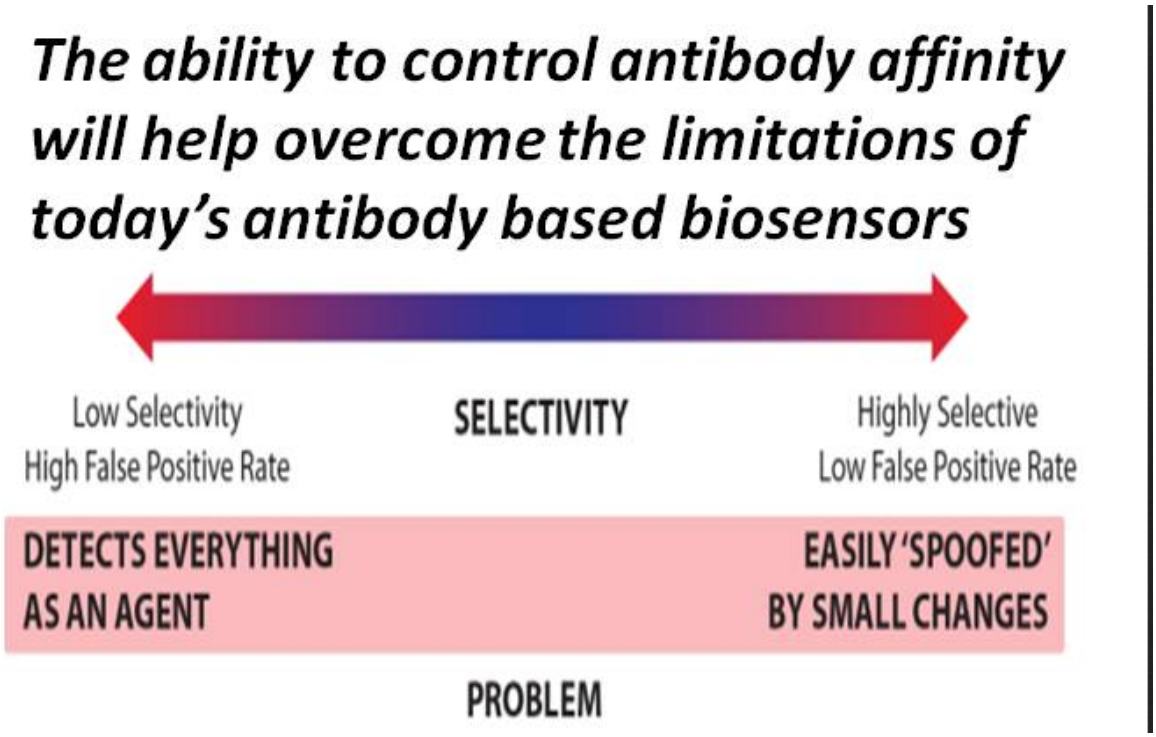
- **Antibody Technology Program (ATP)**

  Antibody-based biosensors provide the most reliable detection capability across the broadest range of biowarfare agents. They are, therefore, the preferred platform for DoD biosensor applications. Fragility of antibody molecules, however, and the short shelf life of antibody-based biosensors severely complicates their use outside the clinical laboratory environment. Additionally, the variability in affinity across various antibody systems has precluded development of multiplexing antibody arrays for biosensor applications. The vision of DARPA's Antibody Technology Program (ATP) is to develop and demonstrate approaches for achieving revolutionary improvements in the stability of antibodies while demonstrating the ability to control antibody affinity. DARPA believes achievement of these goals will ultimately enable the deployment of portable, multiplexing biosensors that operate well in the harsh environments encountered during some DoD missions.

  ATP seeks to develop and demonstrate technologies that enable antibody-based biosensors that operate in harsh environments and can be stored for up to 5 years with no loss in performance. The ability to control antibody affinity will enable development and deployment of biosensor arrays that detect multiple agents in a single platform.



ATP is exploring amino acid substitutions in the antibody structure to improve stability and control affinity



Biochronicity

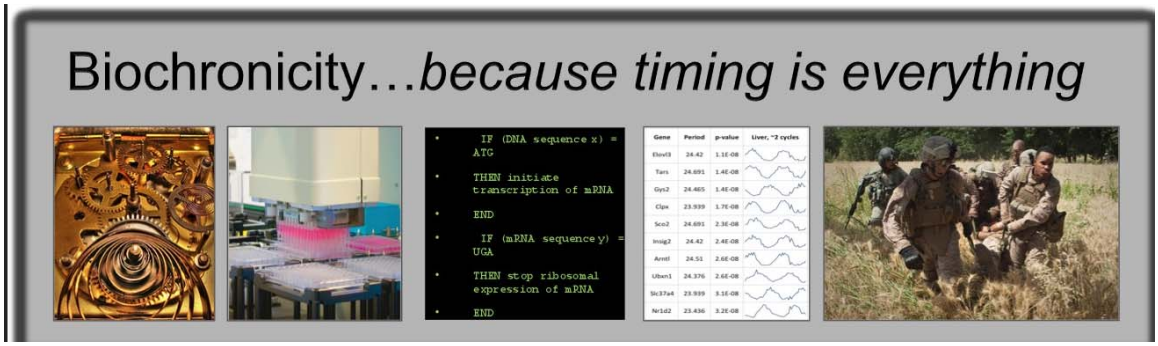
Military readiness and national security depend on the health and wellbeing of military servicemembers. DoD's cumulative investment in personnel comprises the second-largest share of the total defense budget. As such, DoD seeks advances in healthcare to ensure warfighters can operate at peak performance. In this context, the Biochronicity program will explore the role of time in biological functions in pursuit of breakthroughs in managing the effects of time on human physiology.

Time is a fundamental variable in all science, including biology. Biological clocks regulate almost every function in the human body, yet scientists lack a clear understanding of the coordination of timing on multiple scales to influence processes such as cell-cycle progression, growth, metabolism, aging and cell death.

The Biochronicity program is an interdisciplinary research effort that seeks to identify common spatio-temporal instructions, or "clock signatures," in biological organisms by using empirically derived data, as well as bioinformatics and data-mining techniques. Early phases of the program will aim to identify and validate networks of temporal regulators to enable development of predictive algorithms for time-dependent processes in biological organisms.

Fundamental advancements in the understanding of timing in biology could potentially contribute to many defense imperatives, including enhancing human combat performance, improving trauma care on the battlefield by expanding the window of

opportunity for medical treatment and surgical intervention, and understanding the mechanisms behind disease and managing their effects.



Chronicle of Lineage Indicative of Origins (CLIO)

Recent innovations in biotechnology have significantly reduced the cost, time, infrastructure and level of training required to manipulate genetic code and alter the behavior of an organism. Numerous defense missions could benefit from the resulting biotechnology capabilities, but prior to developing and fielding these capabilities, the Department of Defense must establish robust and enduring control features. These technologies are required to enable the public to reap the rewards of these advances while maintaining U.S. strategic technological advantage and minimizing the medical and environmental risk in the case of accidental or intentional misuse.

The Chronicle of Lineage Indicative of Origins (CLIO) program aims to use recent advances in synthetic biology to develop genomic and proteomic capabilities that promote safe, secure biological research, protect intellectual property and prevent unwanted release of microorganisms. To encourage user adoption and ensure the maintenance of CLIO systems, control and security capabilities will be designed to have little or no impact on the fitness of host organisms.

The CLIO program includes three tracks of research and development to support these goals:

1. The Gene Guards track seeks to develop technologies to ensure the safe handling of pathogenic organisms and prevent the adverse manipulation of these pathogens (i.e., addition of virulence factors, immune modulators or antibiotic-resistant genes).
2. The Attribution track seeks to develop technologies that protect intellectual property in the microbial genome and that can be analyzed to authenticate ownership and true origin.
3. The Memory track seeks to develop persistent encoding systems that document and record the chronology, nature of manipulation and environmental conditions in an organism's genome.

If successful, CLIO will establish enduring control elements that protect against intentionally harmful genetic engineering, prevent illegal acquisition or misuse of proprietary strains, provide novel forensic tools to assist in the investigation of biological incidents and allow responsible investigators to document compliance with safe biological manipulation practices. The program will advance the field of synthetic biology with new insight into the design and behavior of biological systems.

Education Dominance

Warfighters today must master a diverse set of physical and mental skills, often in a very compressed period. Measures of learning in this military environment often rely on qualitative and subjective assessment, with little opportunity to correct or redirect learning in mid-course.

The Education Dominance program will enable students to learn at their own pace, in their own style, with their own digital tutor. In this way, students will not simply memorize information, but will learn and understand the concepts upon which information is built. They will train to a standard of competence, not rote recall, to demonstrate significant improvements in mastery of complex concepts. Novices trained on Digital Tutor will acquire accelerated problem-solving capabilities that will enable them to compete with experienced operational experts. Education Dominance focuses on several key approaches:

- Replicating expert tutor behavior using knowledge engineering techniques.
- Modeling intrinsic motivation and memory to optimize learning and consolidation.
- Building student/tutor models based on abstractions of a wide range of student behaviors with live tutors.
- Incorporating remediation strategies to enable the Digital Tutor to provide targeted reinforcement.

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- **International Space Station SPHERES Integrated Research Experiments (InSPIRE)**

  The International Space Station (ISS) SPHERES Integrated Research Experiments (InSPIRE) program will leverage the human presence in space for rapid, iterative experimentation and design of space capabilities, and provide the next generation of scientists and engineers with exposure and experience in carrying out meaningful space experimentation economically and over reasonable time scales. The goal of InSPIRE is to design and prototype the next generation of Synchronized Position, Hold, Engage, and Reorient Experimental Satellites (SPHERES) satellites for use inside or outside the ISS as well as develop a science, technology, engineering and mathematics (STEM) outreach program to promulgate a DARPA SPHERES Challenge competition among high schools

across the United States. The InSPIRE program will use the DARPA-sponsored Synchronized Position, Hold, Engage, and Reorient Experimental Satellites (SPHERES) platform, which has flown onboard the International Space Station (ISS) since May 2006, to perform a series of multi-body formation flight experiments that necessitate a medium-duration zero-gravity environment.

High Energy Liquid Laser Area Defense System (HELLADS)

Enemy surface-to-air threats to manned and unmanned aircraft have become increasingly sophisticated, creating a need for rapid and effective response to this growing category of threats. High power lasers can provide a solution to this challenge, as they harness the speed and power of light to counter multiple threats. Laser weapon systems provide additional capability for offensive missions as well—adding precise targeting with low probability of collateral damage. For consideration as a weapon system on today's air assets though, these laser weapon systems must be lighter and more compact than the state-of-the-art has produced.

The goal of the HELLADS program is to develop a 150 kilowatt (kW) laser weapon system that is ten times smaller and lighter than current lasers of similar power, enabling integration onto tactical aircraft to defend against and defeat ground threats. With a weight goal of less than five kilograms per kilowatt, and volume of three cubic meters for the laser system, HELLADS seeks to enable high-energy lasers to be integrated onto tactical aircraft, significantly increasing engagement ranges compared to ground-based systems.

The program has completed laboratory testing of a fundamental building block for HELLADS, a single laser module that successfully demonstrated the ability to achieve high power and beam quality from a significantly lighter and smaller laser. The program is now in the final development phase where a second laser module will be built and combined with the first module to generate 150 kW of power.

Following the final development phase, the plan is for the laser to be transported to White Sands Missile Range for ground testing against rockets, mortars, surface-to-air missiles and to conduct simulated air-to-ground offensive missions.


Photo Illustration by DARPA


USAF
Photo Illustration by DARPA

- ## COMPACT HIGH-POWER LASER PROGRAM COMPLETES KEY MILESTONE

June 30, 2011

COMPACT HIGH-POWER LASER PROGRAM COMPLETES KEY MILESTONE

Enemy surface-to-air threats to manned and unmanned aircraft have become increasingly sophisticated, creating a need for rapid and effective response to this growing category of threats. A potential solution for countering these threats is high-powered lasers, which can harness the speed and power of light to counter multiple threats. But these lasers need to be lighter and require less space than current state-of-the-art for use on many of today's air assets. The goal of DARPA's High-Energy Liquid Laser Area Defense System (HELLADS) is to develop a 150 kilowatt (kW) laser weapon system that is ten times smaller and lighter than current lasers of similar power, enabling integration onto tactical aircraft to defend against and defeat ground threats.

DARPA recently completed laboratory testing of a fundamental building block for HELLADS, a single laser module that successfully demonstrated the ability to achieve high power and beam quality from a significantly lighter and smaller laser.

"Successful testing of the single laser module is a major accomplishment," said Richard Bagnell, DARPA's HELLADS program manager. "Advances in diodes, cooling, lightweight electronics, pumps, optics, and metal structures have made shrinking the size and weight possible without losing laser effectiveness."

The program now enters the final development phase where a second laser module will be built and combined with the first module to generate 150 kW of power. The goal is to have the 150 kW laser completed by the end of 2012.

Following the final development phase, plans call for the laser to be transported to White Sands Missile Range in the early-2013 timeframe for ground testing against rockets, mortars, surface-to-air missiles and to conduct simulated air-to-ground offensive missions.

DARPA is also in discussion with the Air Force about transitioning the technology to conduct an airborne demonstration following the ground testing phase.

- ## EXCALIBUR

In counterinsurgent, counter-terror campaigns, risks associated with conventional weapons in combat operations can severely limit their use and effectiveness,

particularly in urban environments. These risks are largely associated with challenges posed by confining intended effects to adversary combatants and forces. Even in cases when combat operations are deemed necessary, the consequences of collateral damage from conventional weapons can complicate and hinder the overall mission. Laboratory and field testing of high-power laser systems indicate irradiance levels for functional and lethal effects against a variety of adversary targets and surgical precision of such lasers against certain air and ground targets. However, existing high-power chemical laser systems are too large and too inefficient for deployment on tactical airborne platforms.

The DARPA Excalibur program will develop coherent optical phased array technologies to enable scalable laser weapons that are 10 times lighter and more compact than existing high-power chemical laser systems. The optical phased array architecture provides electro-optical systems with the same mission flexibility and performance enhancements that microwave phased arrays provide for RF systems and a multifunction Excalibur array may also perform laser radar, target designation, laser communications, and airborne-platform self protection tasks.

These phased arrays will coherently combine lower-power electrically driven lasers, such as diode lasers and fiber laser amplifiers. Coherently combinable single-mode diode lasers and fiber-based systems can provide overall laser efficiencies greater than 50 percent and 30 percent, respectively, while maintaining near-diffraction-limited beam quality. To produce a weapons-grade system, however, their output power must be increased without introducing additional optical phase noise and modal instability.

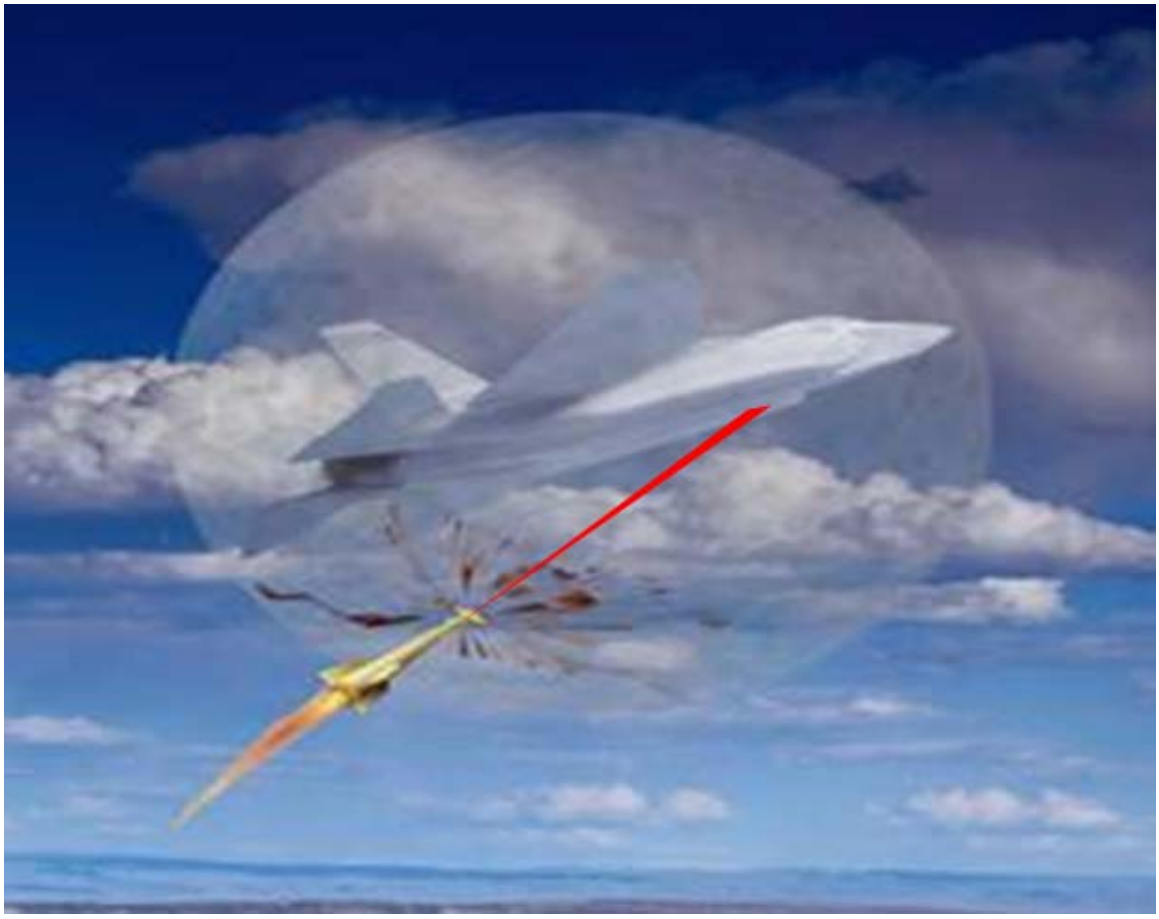
Beam-steering technologies will be pursued to make these arrays conformal with the airframe, to provide rapid retargeting across a large field of regard, and to compensate for the effects of atmospheric turbulence. The Excalibur program will demonstrate a high-power phased array of kW- class fiber laser amplifiers and investigate the limits of active optical phase-locking onto uncooperative targets under realistic conditions.

Once Excalibur's technical objectives are achieved, it is envisioned that a coherent array of 10's of subapertures, each driven with a multi-kW coherently combinable fiber laser amplifiers, would enable ~100 kW class laser systems for precision strikes against both ground and air targets. This technology will enable the practical use of high-power lasers on a broad spectrum of military platforms without degradation of their original missions.

Aero-Adaptive/Aero-Optic Beam Control (ABC)

The goal of the Aero-Adaptive/Aero-Optic Beam Control (ABC) program is to improve the performance of high energy lasers on tactical aircraft against targets in the aft field of regard. This program will optimize flow control strategies for pointing angles in the aft

field of regard and will also explore the ability of the flow control system to be synchronized with adaptive optics. This effort will initially focus on wind tunnel testing to prove the feasibility of steady and periodic flow control techniques to reduce or regularize the large scale turbulent structures surrounding an optical turret. These tests will culminate in a hardware-in-the-loop demonstration using flow control with an adaptive optics system in a full-scale wind tunnel test for the turret. Following successful wind tunnel demonstrations, a preliminary design of a flight test turret incorporating flow control will be undertaken.



- **Enabling Stress Resistance**

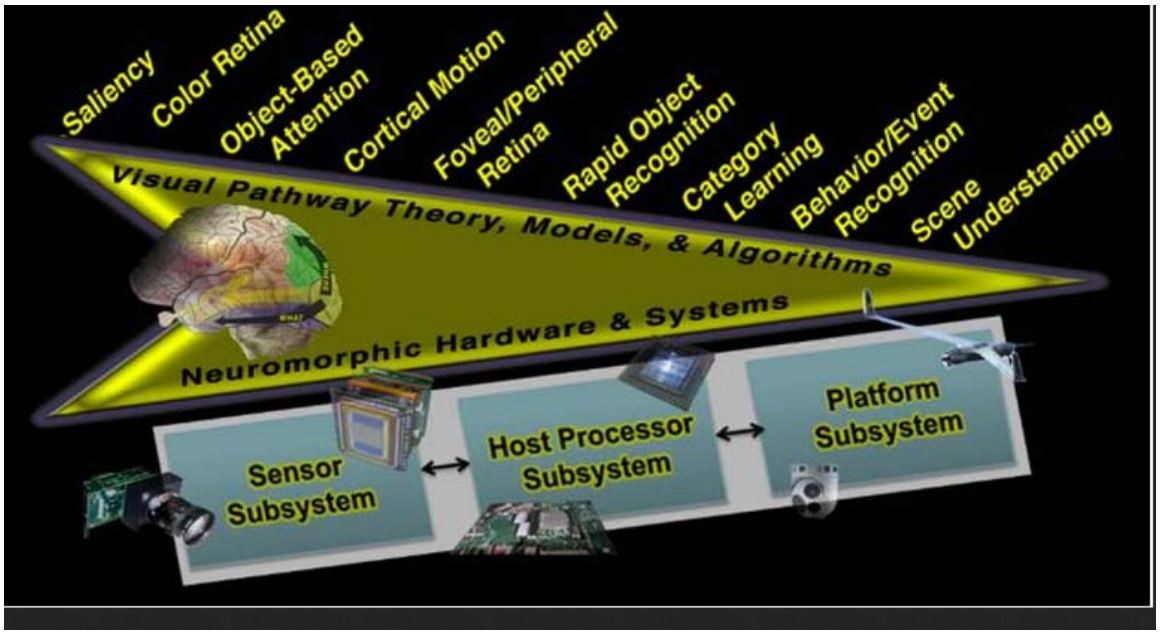
  Negative impacts of stress on the cognitive, emotional, and physical well-being of warfighters is irrefutable. Recent technological developments in neuroscience present the opportunity to address these challenges as never before. Novel molecular biological techniques, coupled with in vivo measurement technologies, can allow assessment of the effects of stress with extreme temporal and anatomical precision, leading to a better understanding of stress and opportunities for intervention.

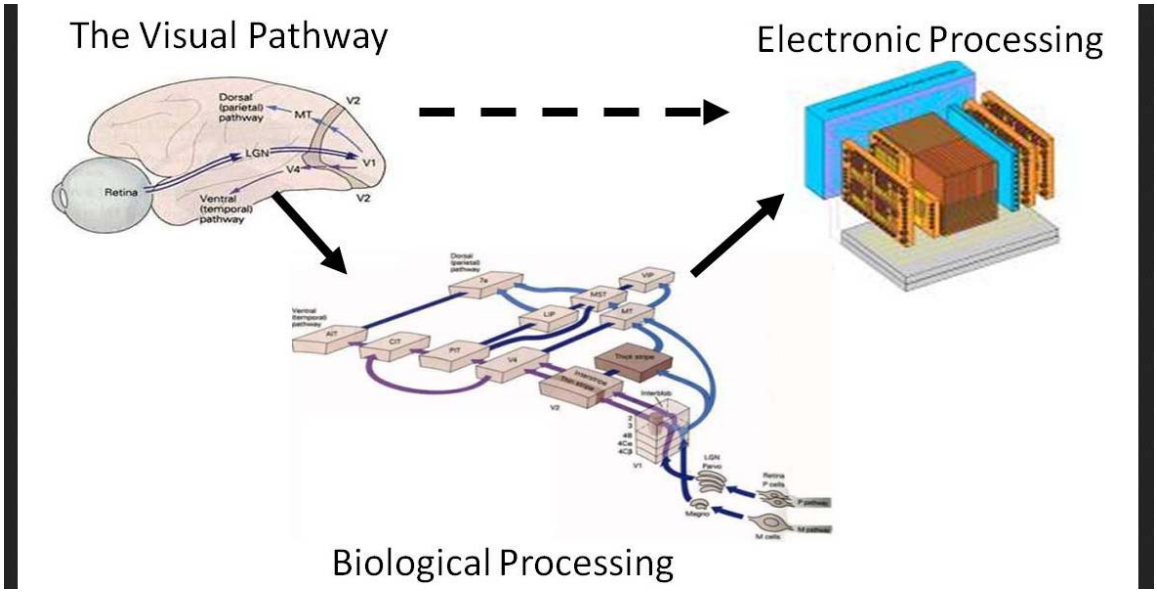
The Enabling Stress Resistance program will create a comprehensive, quantitative description of the impact of stress on the brain by leveraging revolutionary technologies and recent advances in molecular neurobiology, neuroimaging, and molecular pathway modeling. This program's objective is a proactive approach to stress mitigation starting with the development of a comprehensive animal model of the complex effects of multiple stressors on the brain. The program strives to develop and implement cognitive, behavioral, and pharmacological interventions
Neovision2

Biological vision systems have the ability to recognize, categorize, and learn new objects in fractions of a second. While animals and humans accomplish this seemingly effortlessly and constantly, computational vision systems have, to date, been unable to replicate this feat of biology. Until recently, the reason this translation between biology and computation has not occurred is a lack of quantitative data explaining mechanisms for visual scene processing in the brain. Visual neuroscience literature is rich with description, but lacks testable, model-based understanding of precise transformations that occur throughout visual pathways.

The Neovision2 program will develop an unattended, standalone system that can recognize relevant military objects in a wide range of ambient and environmental conditions through fusion of neuroscience and engineering. Integration of recent developments in understanding the mammalian visual pathway and advances in microelectronics will lead to the production of new revolutionary capabilities that will provide a new level of situational awareness for warfighters.

that will prevent the deleterious effects of stress on warfighters.





Rapid Altitude and Hypoxia Acclimatization (RAHA)

Military personnel rapidly deployed to extreme hypobaric or hypoxic conditions can experience high altitude illnesses and hypoxemia. Current approaches for mitigating effects of sudden altitude exposure and other forms of hypoxia involve the use of approved medications developed for other purposes. These approaches do not restore sea level physical performance, impose unacceptable adverse events, and potentially compromise natural acclimatization processes.

The Rapid Altitude and Hypoxia Acclimatization (RAHA) program goal is to demonstrate innovative, novel pharmacological, biological, and technological approaches to adapt to high altitudes (4,000–6,000 meters) and alleviate effects of high altitude illnesses and hypoxia.

Specifically, RAHA researchers will develop a fast-acting, short-duration therapeutic agent or strategy and a slow-acting, long-duration therapeutic agent or strategy that alone or in combination will reduce altitude-induced illness incidence or severity without impeding natural acclimatization processes.

By the end of Phase I, RAHA researchers will identify candidate processes and drug candidates suitable for an investigational new drug or investigational device exemption study. These novel products will be positioned for use in an FDA Phase I clinical trial.

Restorative Encoding Memory Integration Neural Device (REMIND)

Memory loss and inability to acquire new memories are common consequences of traumatic brain injury, and memory dysfunction is an expensive, long-term treatment

problem for the military. Recovery from loss of memory associated with critical work and life tasks is essential to the recovery of a brain-wounded warfighter. A biomimetic model of the hippocampus could serve as a neural prosthesis for lost cognitive function and memory impairment.

The Restorative Encoding Memory Integration Neural Device (REMIND) program will determine the nature and means by which short-term memory is encoded to enable restoration of memory through use of devices programmed to bypass injured regions of the brain. Researchers will demonstrate the ability to restore performance on a short-term memory task in animal models, as well as determine quantitative descriptive methods for describing the means and processes by which memory is encoded

Quantum effects in Biological Environments (QuBE)

Biological sensors often display high sensitivity, selectivity, and low false alarm rates while being fabricated and operated in dirty, noisy natural environments. Attempts to emulate these sensors synthetically have not fully met expectations. Recent evidence suggests that some biological sensors exploit nontrivial quantum mechanical effects to produce macroscopic output signals. Examples of such sensors include the highly efficient energy transfer properties of photosynthesis in plants, bacteria, and algae; magnetic field sensing used by some birds for navigation; and the ability of some animals to detect odors at the single molecule level. The Quantum Effects in Biological Environments (QuBE) program is laying the foundation for novel sensor designs by challenging the long-held view that biological sensors utilize primarily classical physics. QuBE will verify, understand, and exploit these effects to develop new scientific foundations for sensor technologies for military applications.

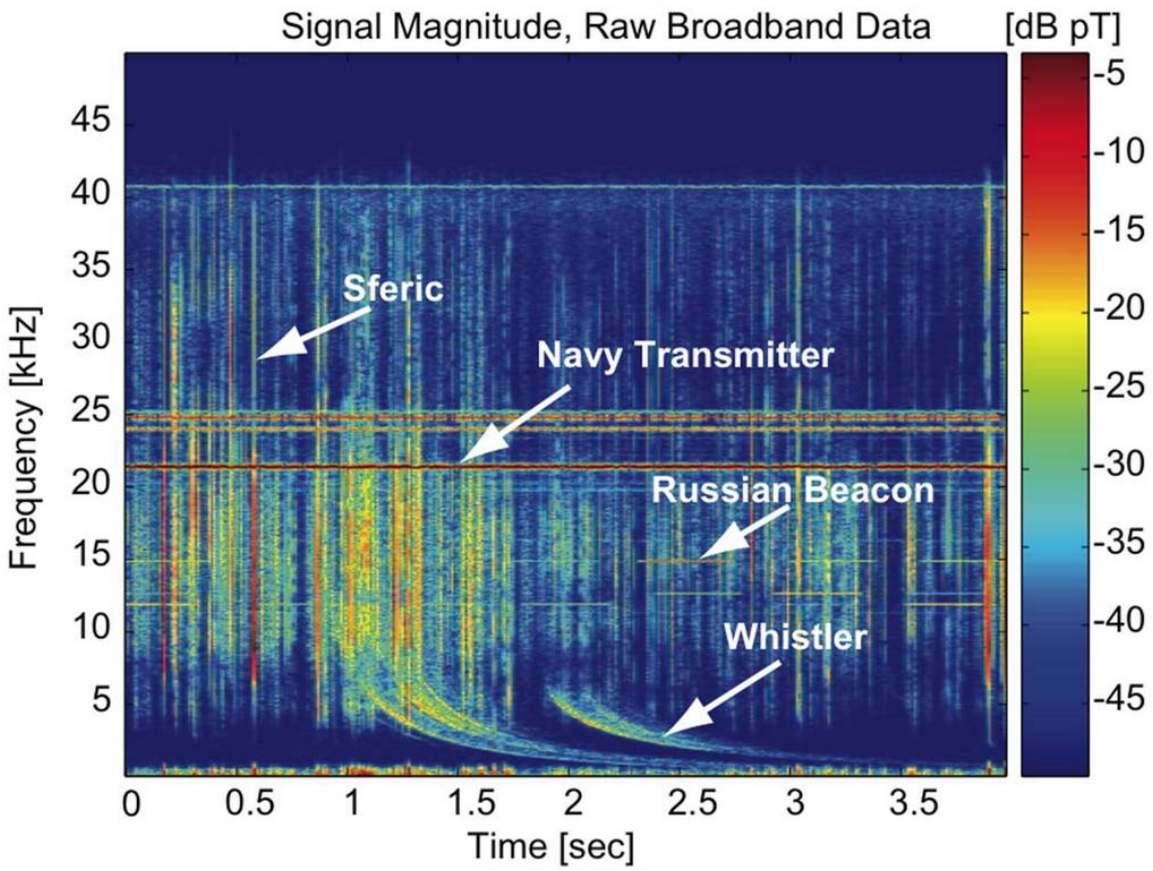
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Nimbus

Lightning can cause delays in operations, disrupt communications, destroy assets, and generally pose a deadly threat to military personnel. While lightning has been studied intermittently for decades, critical questions remain about how and why lighting initiates, how it spreads, and how it attaches to objects. Also unclear is how lightning generates its ionospheric components such as elves, sprites, and gigantic blue jets, or how it ties into the global charging circuit.

Nimbus is a fundamental science program focused on obtaining a comprehensive understanding of the lightning process, its associated emissions (such as x-rays), and its ionospheric components to better protect troops, ordnance, and other military assets.

This program will yield insights into other high-voltage, high-current electromagnetic phenomena.



Optical Radiation Cooling and Heating in Integrated Devices (ORCHID)

Micro- and nanoelectromechanical systems (MEMS and NEMS) are employed in many Department of Defense (DoD) systems. These devices find use in compact accelerometers and gyroscopes for stability control and inertial navigation and in switches for optical communication and data routing. Incredibly, these devices still operate many of orders of magnitude away from their ultimate limits. Techniques to reduce or overcome thermal noise in MEMS/NEMS devices are critical for realizing their full potential.

Optomechanical devices offer a novel, noncryogenic path toward sensing at the standard quantum limit (SQL). Ultimately, quantum (shot) noise limits the performance of many sensitive optical instruments including force sensors, trace gas detectors and laser gyroscopes. However, optomechanical devices can also control the quantum fluctuations of optical probes to reduce readout sensitivity below SQL, a technique known as squeezing.

The ORCHID program will leverage recent successes within the field of cavity-optomechanics to broadly explore the application space while driving technological development toward smaller and more robust devices capable of deployment in the

field. It is envisioned that such devices, once demonstrated by DARPA, will find broad application across DoD, particularly in the areas of force sensing and optical communication

- **Centers in Integrated Photonics Engineering Research (CIPHER)**

  In recent years there has been a dramatic increase in the number and duration of missions being carried out by autonomous and semi-autonomous platforms. The need for these platforms to operate remotely, for as long as possible, puts severe constraints on size, weight and power consumption of the sensing, processing, and communication systems they carry. These platforms operate in harsh conditions where mechanical ruggedness and thermal stability of the onboard systems are critically important. In addition to these constraints, the need to respond in a timely manner to a complex and dynamic battlefield environment and to evolving mission objectives must be satisfied. This combination of constraints and requirements necessitates revolutionary advances in microsystems that are able to change their behavior in an adaptive manner and dynamically allocate their internal resources. A new design approach for intelligent microsystems that goes well beyond current design strategies will be required to satisfy future military needs. This new system design paradigm will necessitate radically different device and materials infrastructure. To address the need for revolutionary advances in microsystems, DARPA engages the U.S. academic and industrial innovation system through the Centers in Integrated Photonics Engineering Research (CIPHER) program.

  The CIPHER program is pushing fundamental photonics research to address four critical military needs: mid-wave infrared laser communications, laser detection and ranging (LADAR), chem-bio sensing, and neurobiology. CIPHER seeks to advance current laser communications and laser imaging capabilities by providing a chip-scale solution that takes advantage of laser phase and amplitude coherence. The CIPHER program will advance the areas of chemistry and biology by investigating the next generation of multimodal photonic chem-bio sensing and fundamental interactions between neurons and light.

- **Quantum Entanglement Science and Technology (QuEST)**

  Fundamental discoveries in quantum information science have potential for dramatic impact on technologies related to modern military platforms. Key examples are the exponential speedup of critical computations such as with Shor's prime factoring quantum algorithm and secure quantum communication protocols. Other examples include sensing, image processing and metrology. While considerable progress has been made in recent years in understanding the fundamentals of quantum information science on both experimental and theoretical sides, many fundamental issues and challenges remain unresolved.

The goal of the Quantum Entanglement Science and Technology (QuEST) program is to investigate innovative approaches that enable revolutionary advances in the fundamental understanding of quantum information science related to small quantum systems.

The objective of QuEST is to identify and address the most important outstanding challenges and opportunities, both experimental and theoretical, and resolve or exploit them to enable revolutionary advances in the field of quantum information science and technology.

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- **Tip-Based Nanofabrication (TBN)**

  The goal of the Tip-Based Nanofabrication (TBN) program is to develop the capability to controllably manufacture nanostructures, specifically nanowires, nanotubes, and quantum dots, with nanometer-scale control over the size, orientation, and position of each nanostructure. TBN aims to enable this revolutionary capability with approaches that use functionalized AFM cantilevers and tips, due to their ability to manipulate environments at the submicrometer scale on the surface of a substrate, creating high temperatures, high fluxes, and high electric and magnetic fields, as well as optical and bio-inspired techniques.

  Controlled nanomanufacturing is presently not possible. The capability to grow, deposit, or manipulate nanostructures has been demonstrated in recent years, but these all suffer from significant deficiencies when viewed against controlled nanomanufacturing. For example, dense, aligned "forests" of carbon nanotubes can be grown, even with pregrowth lithography to define regions of growth. This technique, however, cannot controllably grow individual nanotubes or control their orientation or dimensions. There are also examples of quantum-dot growth from catalyst seeds with potential to create large arrays with high uniformity. There is no ability, though, for controlled manufacturing of patterned arrays of two different quantum dots, and there is no ability to repair the nonuniformity that typically arises from these growth processes. None of these emerging approaches appears to provide a path to controlled nanomanufacturing.

  The IBM Millipede program, a topographic data storage technology, demonstrated nanometer-scale parallel fabrication, detection and modification of indentations using an array of AFM cantilevers. This work includes many of the features of controlled nanomanufacturing and is strong motivation to consider AFM tips as potential tools for nanomanufacturing. Combined with the efforts at IBM to address problems with parallel operation, array manipulation, wear, materials, etc., the goal of TBN is to develop methods for controlled nanomanufacturing. Success in the program will enable many significant applications and although the program focuses on nanowires, nanotubes and

quantum dots, capabilities developed for this subset of nanostructures should be extendable to numerous other structures, materials and treatments.

- **Advanced X-Ray Integrated Sources (AXiS)**

  The primary goal of the AXiS program is to develop advanced x-ray source technology that will enable high contrast when imaging low-Z materials such as soft biological tissues. Imaging based on phase contrast is approximately 1000 times more sensitive than absorption contrast imaging for soft tissue and other low-Z materials. Currently, x-ray radiation required for accomplishing phase-contrast imaging can be generated only using large synchrotrons. Recent advances in accelerator and laser technologies suggest they might be exploited to enable much less expensive and smaller x-ray sources that could be readily deployed in military field hospitals or on selected military platforms to improve combat casualty care. They might also lead to new advanced imaging capabilities that most modern laboratories and hospitals could afford. The program will involve development of component technologies, including electron (cathode/beam) sources, electron accelerators, and undulators for compact, tunable x-ray sources, as well as integrated device development.

rogram in Ultrafast Laser Science and Engineering (PULSE)

Defense applications, such as geo-location, navigation, communication, coherent imaging and radar, depend on the generation and transmission of stable, agile electromagnetic radiation. Improved radiation sources—for example, lower noise microwaves or higher flux x-rays—could enhance existing capabilities and enable entirely new technologies.

The Program in Ultrafast Laser Science and Engineering (PULSE) seeks the technological means for such improved radiation sources. Through precise spectral engineering in the optical domain, more efficient and agile use may be made of the entire electromagnetic spectrum. By generating and engineering waves in the optical domain, where engineers already exercise exquisite stability and control, these waveforms may be down or up-converted to the desired wavelength.

PULSE will also aim to apply this technology to enable synchronization, metrology and communications applications spanning the electromagnetic spectrum, from radio frequencies to x-rays. By building on established ultrafast laser techniques, PULSE seeks to:

1. Develop agile, low phase-noise, portable radio frequency oscillators;
2. Demonstrate techniques compatible with worldwide distribution of the world's most accurate optical clocks;
3. Construct tabletop sources of coherent x-rays in the water window (3-5 nanometers); and
4. Produce efficient, isolated attosecond pulses as a stroboscopic probe of electron dynamics in materials.

During Phase 1, teams will develop components and conduct proof-of-principle demonstrations. In Phase 2, teams will shift focus to component integration and laboratory demonstrations aimed at achieving performance milestones. In Phase 3, teams will demonstrate their capabilities in a relevant defense operating environment.

Neuroscience

DSO develops and leverages neurophysiological sensors, neuro-imaging, cognitive science and molecular biology to provide support, protection and tactical advantage to warfighters who perform under the most challenging operational conditions. DSO is discovering and applying advances in neuroscience to improve warfighters' resilience to stress, increase the rate and quality of learning and training, defend against injury and enhance our warfighters' ability to exert influence. DSO's advances in neuroscience are leading to better sensors and novel neuro-morphic system architectures in the fields of computing, robotics and information integration, providing solutions to challenging issues. By harnessing the capabilities of neuroscience and fusing them with cutting edge electronics and the social sciences, DSO is bringing a new level of efficiency and situational awareness to provide warfighters with reliable information, training and tools to execute their missions.

- ## Materials

  The DSO Materials program seeks to advance material science on many technology fronts. Programs range from developing physics- and chemistry-based models that allow for the design of novel materials possessing radically improved or new properties, to innovative processing methods that dramatically reduce the cost of producing titanium metal and its alloys.

  DARPA's involvement with material science began in the early 1960s with the genesis of the Interdisciplinary Research Laboratories, which transformed into the National Science Foundation Materials Research Laboratories. DSO continues to advance the frontiers of material science by concentrating efforts on emerging capabilities and maintaining the interdisciplinary theme that generates many of the breakthroughs in this field.

  The DSO Materials program seeks to advance material science on many technology fronts. Programs range from developing physics- and chemistry-based models that allow for the design of novel materials possessing radically improved or new properties, to innovative processing methods that dramatically reduce the cost of producing titanium metal and its alloys. Mathematical and characterization tools are being generated to enable rapid design and development of new armor systems. Armor systems based on topological constructs are demonstrating an increase in performance not achievable with traditional approaches. Biologically inspired approaches to material synthesis and design are pervasive in many DSO initiatives. Future investments in the DSO Materials program will continue to explore the frontiers of material science, which include new science-based tools

for the development of new materials, novel materials for energy and water harvesting, new mechanical designs that exploit or challenge new materials and material systems, and innovative electromagnetic materials that will revolutionize the field of electronics. This aggressive vision to pursue the development of radically new materials and material systems is producing the critical technologies that will allow for the next generation of high-performance military platforms.

Novel Materials and Material Processes

Objectives: This focus area includes new materials concepts for lowering the weight and increasing the performance of aircraft, ground vehicles, and spacecraft structures. Techniques are being established for assessing damage evolution and predicting future performance of the structural materials in Defense platforms and systems through physics-based models and advanced interrogation tools. New, low-cost processing and fabrication techniques are being developed to enable expanded use of new materials and structures in Defense applications. The design and development of electromagnetic materials and material systems that have unique intrinsic or extrinsic properties are being pursued. Mathematical tools are under development that will reduce the complexity and increase efficiency of ab initio methods and allow for the discovery of novel materials and structures as well as new synthesis routes.

Multifunctional Materials and Material Systems

Objectives: As military systems and missions become more complicated, the development of materials that are dynamic in both shape and activity is becoming critical. In addition, the combination of functions, such as power generation of blast resistance, with structural loadbearing, is expected to yield markedly enhanced capabilities across multiple military platforms. Current projects in this focus area include revolutionary new armor systems that exploit unique high-strength steel/polymer composite hybrid configurations for military vehicles; an extremely small (less than 7.5 centimeters), ultralightweight (less than 10 grams) air vehicle system with the potential to perform indoor and outdoor military missions; and barriers that can be rapidly emplaced and reversed to allow fluid U.S. force movement.

Biologically Inspired Materials

Objectives: DSO's focus area in biologically inspired materials explores the emerging interfaces between biology and novel materials. Areas under development include systems that mimic the ability of plants to generate large strains while performing a robust structural function and circulatory systems to induce extreme changes in structural system properties.

Z-Man

U.S. warfighters operate in all manner of environments, including tight urban terrain. The safety and effectiveness of the warfighter demand maximum flexibility for maneuvering and responding to circumstances. To overcome obstacles and secure entrance and egress routes, warfighters frequently rely on ropes, ladders and related climbing tools. Such climbing tools cost valuable time to use, have limited application and add to the load warfighters are forced to carry during missions. The Z-Man programs aims to develop biologically inspired climbing aids to enable warfighters to scale vertical walls constructed from typical building materials, while carrying a full combat load, and without the use of ropes or ladders.

Geckos, spiders and small animals are the inspiration behind the Z-Man program. These creatures scale vertical surfaces using unique systems that exhibit strong reversible adhesion via van der Waals forces or hook-into-surface asperities. Z-Man seeks to build synthetic versions of these biological systems, optimize them for efficient human climbing and use them as novel climbing aids.

"Geckskin" is one output of the Z-Man program. It is a synthetically-fabricated reversible adhesive inspired by the gecko's ability to climb surfaces of various materials and roughness, including smooth surfaces like glass. Performers on Z-Man designed adhesive pads to mimic the gecko foot over multiple length scales, from the macroscopic foot tendons to the microscopic setae and spatulae, to maximize reversible van der Waals interactions with the surface.

Recent activities include:

- Fabrication of Geckskin (stiff fabric impregnated with an elastomer) that "drapes" over a surface to maximize compliance with the surface while reducing compliance in the load direction, thus enabling increased adhesion.
- A proof-of-concept demonstration of a 16-square-inch sheet of Geckskin adhering to a vertical glass wall while supporting a static load of up to 660 pounds.

Warrior Web

The amount of equipment and gear carried by today's dismounted warfighter can exceed 100 pounds, as troops conduct patrols for extended periods over rugged and hilly terrain. The added weight while bending, running, squatting, jumping and crawling in a tactical environment increases the risk of musculoskeletal injury, particularly on vulnerable areas such as ankles, knees and lumbar spine. Increased load weight also causes increase in physical fatigue, which further decreases the body's ability to perform warfighter tasks and protect against both acute and chronic injury.

The Warrior Web program seeks to develop the technologies required to prevent and reduce musculoskeletal injuries caused by dynamic events typically found in the warfighter's environment. The ultimate program goal is a lightweight, conformal under-suit that is transparent to the user (like a diver's wetsuit). The suit seeks to employ a system (or web) of closed-loop controlled actuation, transmission, and functional

structures that protect injury prone areas, focusing on the soft tissues that connect and interface with the skeletal system. Other novel technologies that prevent, reduce, ambulate, and assist with healing of acute and chronic musculoskeletal injuries are also being sought.

In addition to direct injury mitigation, Warrior Web will have the capacity to augment positive work done by the muscles, to reduce the physical burden, by leveraging the web structure to impart joint torque at the ankle, knee, and hip joints. The suit seeks to reduce the metabolic cost of carrying a typical assault load, as well as compensate for the weight of the suit itself, while consuming no more than 100 Watts of electric power from the battery source.

While injury mitigation is a primary goal, a Warrior Web suit system is not intended to interfere with current warfighter "soldier systems," such as external body armor, rather it aims to augment them to improve warfighter effectiveness.

The Warrior Web program will consist of two separate but related program tasks. Task A, called Warrior Web Alpha, seeks to develop a mix of core technologies critical to the realization of a Warrior Web capability. The Warrior Web Alpha effort examines five key Technology Areas: core injury mitigation technologies; comprehensive analytical representations; regenerative actuation; adaptive sensing and control; and suit human-to-wearer interface.

Part way through the Warrior Web program, Warrior Web Bravo, or Task B, is expected to develop an integrated suit capability by leveraging the technology developed by Task A efforts and incorporating the most appropriate breakthroughs into a suit that shows the best performance. The final suit is expected to be tested in appropriate mission profiles under realistic loads to evaluate performance.

Mathematics

DSO's mathematics program applies and develops new and existing mathematical tools that impact a broad continuum of DoD mission areas. The program is rooted in the tenet that DoD needs are best addressed by creating integrated teams of mathematicians and subject matter experts to address problems. This approach enables the rapid exploitation of new mathematical techniques to create new technologies as well as the translation of technological needs into challenge problems for the mathematics community to drive new research. Today's applied mathematics and computational research programs help achieve up-to-the-minute, cutting-edge superiority, while basic mathematical research programs secure the foundation for advanced science and technology programs in the future.

Applied and Computational Mathematics

Objectives: DSO's programs in the mathematical sciences span key application areas across the entire DoD mission. Applications being addressed include signal and image processing, biology, materials, sensing, and design of complex systems.

Fundamental Mathematics

Objectives: DSO's fundamental mathematics focus area includes the development of new theoretical mathematics with high potential for future applications. Current program themes include topological and geometric methods, extracting knowledge from data, and new approaches for conducting focused research to explore fundamental interconnections between key areas of mathematics where critical insights should lead to both new mathematics and innovative applications.

- **Graph-theoretic Research in Algorithms and the Phenomenology of Social Networks (GRAPHS)**

  The use of "backtracking" techniques when discovering network intrusion or in other types of cyberspace investigations has been popularized in books, films and on television. Recent evidence has shown that this kind of network analysis can also provide critical insights when used in DoD-relevant scenarios. Recall that networks are typically represented as graphs: nodes may denote people of interest, with edges signifying relationships or interactions. However, the science of network analysis is still in its infancy; currently, the structure of real-world networks is described only in terms of the most coarse and basic details, such as diameter, degree distribution, etc. In order to implement network analysis techniques efficiently and effectively, a more comprehensive grasp of their finer mathematical structure is needed.

  The Graph-theoretic Research in Algorithms and the Phenomenology of Social Networks (GRAPHS) program seeks quantitative understanding to enable determination of network function from its structure, while incorporating considerations such as time evolution. GRAPHS will build from the theory that telltale structures may be embedded in perhaps much larger networks, and that their presence is indicative of activity that warrants greater attention. Hence certain classes of subgraphs constitute "signals of interest," and GRAPHS aims to detect these.

  Given this objective, GRAPHS focuses on several capabilities that need to be developed and refined in the graphs. The first set is obvious: DoD requires analytic characterizations, both static and dynamic, of the structures of interest. In addition, GRAPHS must confront the fact that, unlike the situation in traditional signal processing, the signals of interest are not scalars or vectors. Hence, GRAPHS aims to develop new noise models, and consequently, new sampling theory. GRAPHS also seeks to incorporate information that derives from multiple networks; in the context of interpersonal social networks, people may be linked in various ways. Finally, GRAPHS will attempt to create new classes of

approximation algorithms that will enable signal detection in large networks on reasonable time scales. To be truly useful, GRAPHS algorithms must provide rigorous error bounds on their performance.

To date, DoD has been effective in the use of rigorous analytic and predictive methods for problems involving continuously valued variables (e.g., in performing tracking and other forms of signals processing); however, the development of similarly refined and robust methods for discrete data such as graphs and networks has not kept pace. What is needed is a comprehensive notion of state that characterizes networks of DoD interest, as well as a description of how this state may vary in both space and time. Also of interest is the creation of a theory of how heterogeneous networks interact.

The goal of the GRAPHS program is the development of a foundational, DoD-relevant framework that will enable analysis of network behavior on actionable time-scales in support of identifying, detecting and predicting exceptional events.

- **Surviving Blood Loss (SBL)**

The Surviving Blood Loss (SBL) program is developing novel strategies to radically extend the time injured warfighters can survive critical blood loss on the battlefield before initiation of fluid and blood resuscitation. Achieving this goal will allow increased time—as much as hours or days—for evacuation, triage, and initiation of supportive therapies. An interdisciplinary effort is underway to develop comprehensive understanding of energy production, metabolism, and oxygen use and to identify and control the protective mechanisms that preserve cellular function despite critically depressed oxygen delivery. Specific investigational focus areas include mechanisms to control the metabolic state on demand, including induction of a hibernation-like state, and development of low-volume therapies that reduce tissue demand for oxygen and metabolites when full resuscitation is not available.

Significant progress has been made achieving program goals including metabolic rate reduction using hydrogen sulfide—exposure to low levels of hydrogen sulfide were shown to induce a hibernation-like state in mammals, which is highly protective against blood loss or low-oxygen environments. The treatment is believed to reduce cellular oxygen consumption by reversibly inhibiting the mitochondrial enzyme cytochrome oxidase and by acting as an electron acceptor alternative for oxygen. Resistance to effects of trauma and blood loss were also demonstrated with a single dose of the female hormone 17β estradiol. The mechanism of action is likely related to induction of widespread adaptive mechanisms at the biochemical, cellular, and physiologic levels. Other promising approaches also under investigation include novel mitochondrial targeted anti-oxidants as well as therapeutics affecting the epigenetic response to stress.