Breakthrough Biological Technologies for National Security

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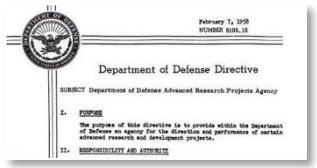
Director, Biological Technologies Office (BTO)

Briefing Prepared for Research Outreach

04 February 2022

DARPA's Mission: Breakthrough Technologies for National Security


Department of Defense Directive

SUBJECT Department of Defense Advanced Research Projects Agency

I. PURPOSE

The purpose of this directive is to provide within the Department of Defense an agency for the direction and performance of certain advanced research and development projects.

II. RESPONSIBILITY AND APPROVITY

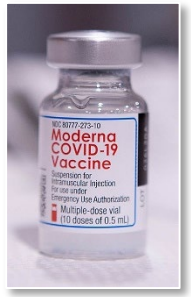
1958: DARPA Founded

1963: Arecibo Observatory

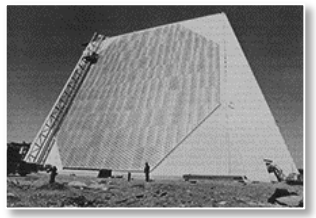
1977: Stealth Technology

1988: UAVs

2004: Autonomous Vehicle Grand Challenge



2014: mRNA Vaccine



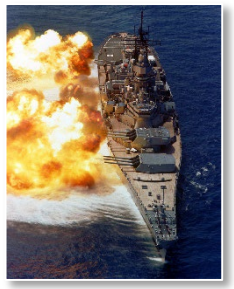
1959: Phased Array RADAR

1969: ARPANET

1984: X-29 Aircraft

2013: Blast Gauge

1960s | **1970s** | **1980s** | **1990s** | **2000s** | **2010s** | **2020s**



The Heilmeier Catechism

DARPA operates on the principle that generating big rewards requires taking big risks. But how does the Agency determine what risks are worth taking?

George H. Heilmeier, a former DARPA director (1975-1977), crafted a set of questions known as the "Heilmeier Catechism" to help Agency officials think through and evaluate proposed research programs.

1. What are you trying to do?
2. How is it done today, and what are the limits of current practice?
3. What is new in your approach and why do you think it will be successful?
4. Who cares? If you are successful, what difference will it make?
5. What are the risks?
6. How much will it cost?
7. How long will it take?
8. What are the mid-term and final “exams” to check for success?

BTO Drives Ethical, Legal, and Social Issue (ELSI) Engagement to Ensure Responsible Technology Development

Goal: Flexible ELSI framework to accommodate changing technical & policy landscape

Expert Analysis and Perspective

On Neurotechnology


Review

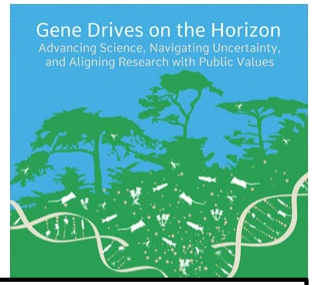
October 17, 2019

Ethical Challenges of Risk, Informed Consent, and Posttrial Responsibilities in Human Research With Neural Devices

A Review

Saskia Hendriks, MD, PhD[1,2]; Christine Grady, RN, PhD[1]; Khara M. Ramos, PhD[2]; et al

On Gene Drives




Neuroethics Guiding Principles for the NIH BRAIN Initiative

Henry T. Greely, Christine Grady, Khara M. Ramos, Winston Chiong, James Eberwine, Nita A. Farahany, L. Syd M Johnson, Bradley T. Hyman, Steven E. Hyman, Karen S. Rommelfanger, and Elba E. Serrano

Journal of Neuroscience 12 December 2018, 38 (50) 10586-10588; DOI: https://doi.org/10.1523/JNEUROSCI.2077-18.2018

Responsible Media Engagement


DARPA DEFENSE ADVANCED RESEARCH PROJECTS AGENCY ABOUT US / OUR RESEARCH /

Defense Advanced Research Projects Agency › News And Events › Setting a Safe Course for Gene Editing Research

Setting a Safe Course for Gene Editing Research

Safe Genes program aims to build a biosafety and biosecurity toolkit to reduce potential risks and encourage innovation in the field of genome editing

OUTREACH@DARPA.MIL
9/7/2016

Regular ELSI Meetings – Opportunity for Comment on Ongoing Efforts

Issue and Stakeholder Communication → Program Integration → Responsiveness and Transition

- New Start Discussion
- Ad Hoc Discussion
- Event Driven Interaction
- Meeting Participation

Harnessing Biology to Support the Warfighter

BTO develops capabilities that embrace the unique properties of biology—adaptation, resiliency, complexity—to revolutionize how the United States defends the homeland and prepares and protects its Warfighters

Ways to engage with DARPA

Opportunity	Audience	Topic Specificity	Timing	Duration
Program Specific Broad Agency Announcement (BAA)	General Research	Narrow	Irregular	Up to 5 years (Multiple phases)
Office-wide BAA	General Research	Broad	Rolling	~1 year
Small Business SBIR/STTR	Small Business	Narrow	Rolling	Up to 3+ years (Multiple phases)
Young Faculty Award	Tenure Track Assistant/Associate Professors	Narrow	Annual	Up to 2+ years
Transition Partner	Gov't/Commercial	Narrow	Program Dependent	Partner Dependent
Program Manager	Academia/Gov't/ Industry	Narrow	Rolling	2-4 years

Visit darpa.mil for more information

DIGET Program Overview

Detect It with Gene Editing Technologies

CDR Jean-Paul Chretien, M.D., Ph.D., MC, USN

Program Manager
Biological Technologies Office (BTO)

DIGET

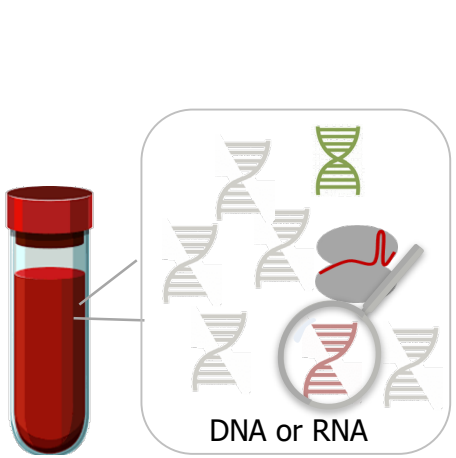
DETECT IT WITH GENE EDITING TECHNOLOGIES

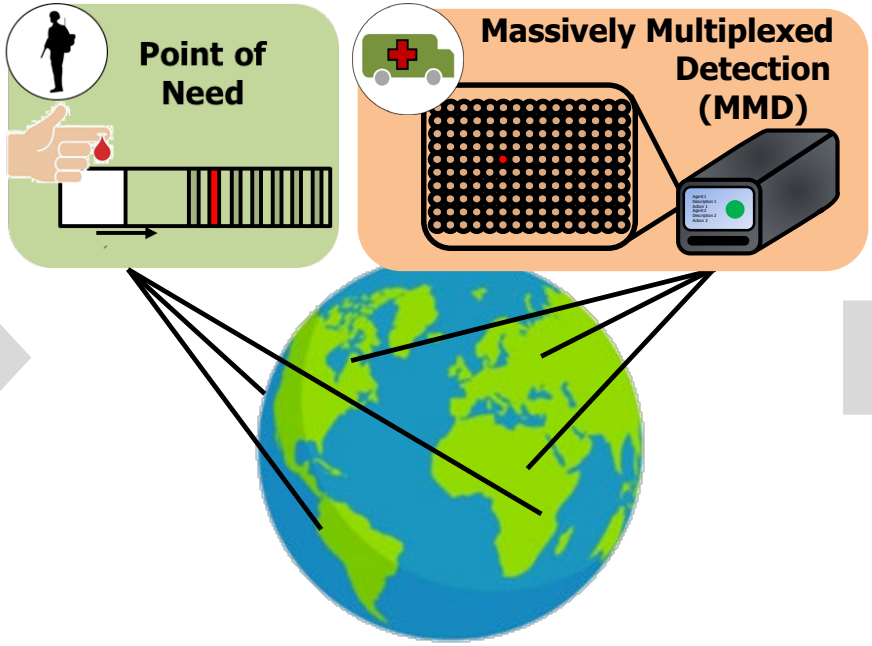
February 4, 2022

DARPA

DIGET Vision
Detect Any Threat, Any Time, Anywhere

Problem: Current diagnostic (Dx) and biosurveillance (BSV) capabilities cannot outpace disease outbreaks, detect emergent threats, or be readily available to operators for decision-making at point of need





Detect
Leverage DARPA gene editing discovery pipeline for nucleic acid detection

Deploy
Integrate novel detection chemistries for high-trust field-forward, distributed capabilities

Decide
Provide comprehensive and specific information to support decision-making and prevent emergent disease outbreaks

Vision: Develop technologies to **detect any threat, any time, anywhere** to support DoD stabilization and readiness

DIGET Technical Areas

Two Integrated Technical Areas, Two Devices Deployed

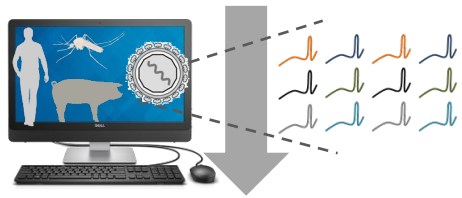
DIGET will create an end-to-end capability for gene editing based detection to support mission needs

TA1: Detection Assay Design and Development

Design

Computational pipeline

All possible genomes



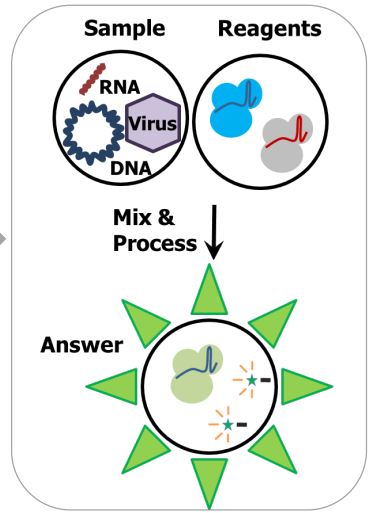
Minimal set of target probes to cover maximal sequence space

Detect and Develop

Enzymes, reporters, and assays

Detection enzymes

Reporters

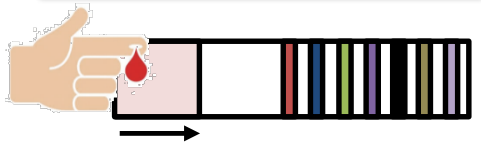


Assays

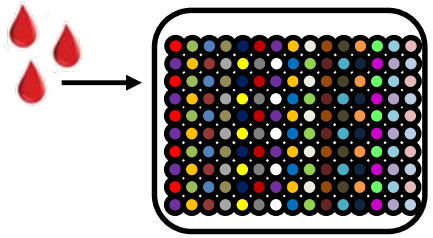
TA2: Device Development and Deployment

Integrate & Prototype

<15 min sample-to-answer



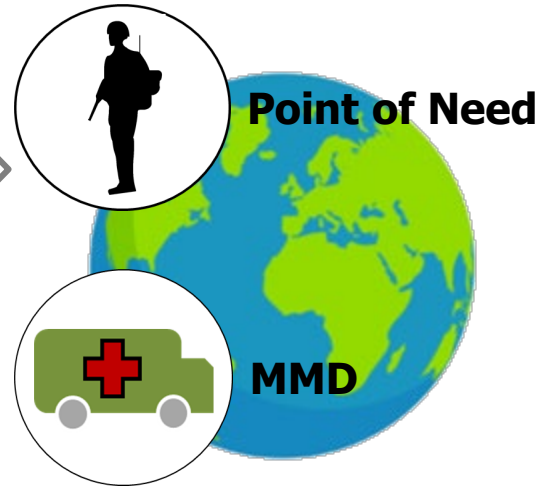
Simple, matrix-based hand-held devices



Massively multiplexed devices with disposable cartridges

Deploy

Fieldable capabilities

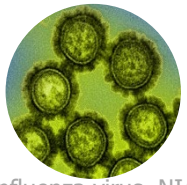


All proposers **must** address both TAs

All proposers **must** develop 2 devices

Public Health and National Security Focus Areas

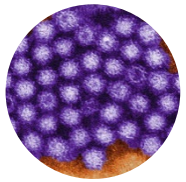
DoD-Relevant Panels



Influenza virus, NIAID

Marburg virus, NIAID

Aedes aegypti, CDC



Norovirus, health.mil

Bacteria, NIGMS

- Respiratory illnesses
- Febrile illness
- Vector-borne illness
- Gastrointestinal illness
- Sepsis

All proposers **must** focus on at least two DoD relevant panels designated by DARPA

One of these DoD-relevant panels **must** address **disease severity** (e.g., through host biomarkers)

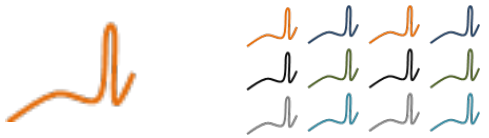
Proposers **may** include additional panels with commercial/industrial transition potential

CONOPS – New Capabilities for Regional Stabilization (Notional)

Enhancing Standard of Care, Preparedness, and Situational Awareness

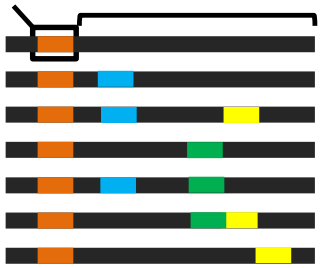
Broad and specific detection probes at the ready

Broad **Strain Specific**

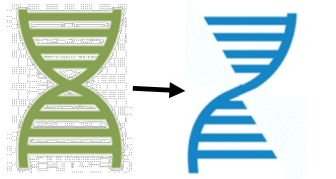


Pathogen

Viral genomes



Host

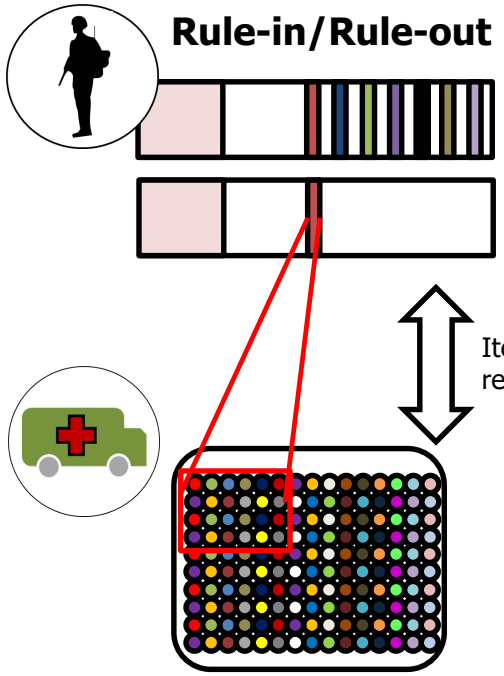


DNA Genotype

RNA Biomarker

Interoperable & reconfigurable assays

Rule-in/Rule-out



Iterate and reconfigure

Characterize and/or surveil

Mobile capability CONOPS:

1) If/then secondary test
2) Continuous biosurveillance
3) Assess disease severity

Actionable information for decision-making

"You don't have Ebola."

SAMUEL MAMBO/REUTERS

"You have dengue fever."

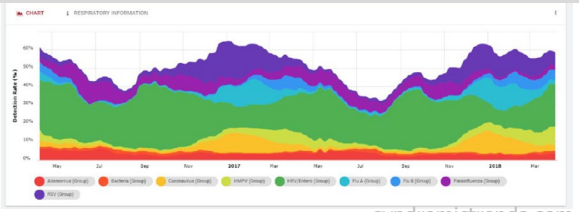
"Specifically, you have Dengue serotype 1."

"You also have drug-resistant malaria."

"Host cytokine levels are high indicating severe disease state."

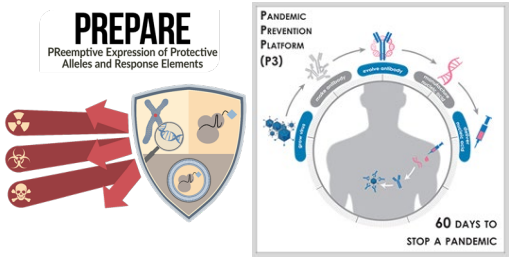
Stabilization through better decision-making and situational awareness

Detect outbreak early/BSV



syndromictrends.com

Firebreak spread of disease via quarantine and/or MCMs



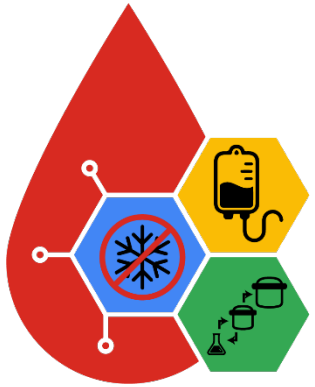
Stop outbreak

FSHARP Program Overview

Fieldable Solutions for Hemorrhage with bio-Artificial Resuscitation Products

CDR Jean-Paul Chretien, M.D., Ph.D., MC, USN

Program Manager
Biological Technologies Office (BTO)



FSHARP

February 4, 2022

DARPA

Fieldable Solutions for Hemorrhage with bio-Artificial Resuscitation Products (FSHARP)

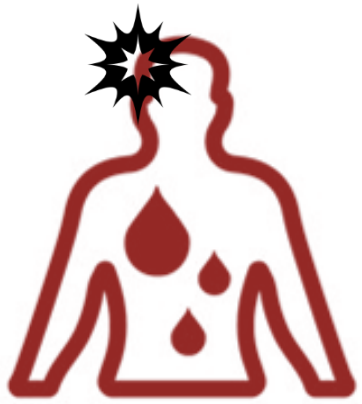
FSHARP

DoD Problem: The DoD faces challenges in replacing lost blood in forward settings, which could become even more significant in prolonged field care and mass casualty scenarios.

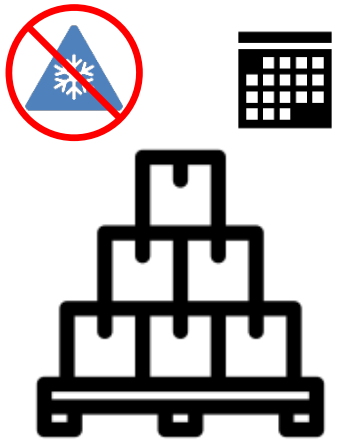
Trauma and hemorrhage in austere environments without immediate MEDEVAC

Military medical support for civil mass casualty response

Shelf-stable bio-artificial whole blood substitutes



Address complex trauma physiology



Able to be stockpiled without cold-storage for long durations

Rapidly, easily reconstituted

BTO Vision: A field-deployable, shelf-stable whole blood substitute as a hemorrhage countermeasure to sustain warfighters and civilian casualties in austere, pre-hospital settings.

Current preferred hemorrhage resuscitation: whole blood

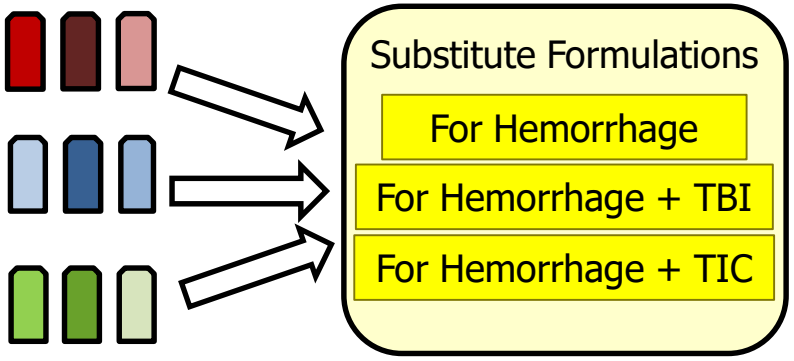
- Whole blood is the optimal resuscitation fluid for treating hemorrhagic shock: Butler et al., J Spec Oper Med 2018.
  - Replaces coagulation factors and platelets.
  - Reverses volume deficit.
  - Restores oxygen-carrying capacity.
- Use of whole blood (stored or fresh) in far-forward settings has logistical challenges:
  - Cold-storage requirement.
  - Limited shelf life requires frequent resupplying.
  - Possible insufficient donor supply for mass casualty.
  - Inability to screen for pathogens in the field.

Photo by Spc. Matthew Diaz
https://www.dvidshub.net/image/418360/blood

Reliance on scarce whole blood resources could be alleviated with a shelf-stable, bio-synthetic alternative.

FSHARP Technical Areas

TA1
Blood Substitute Development

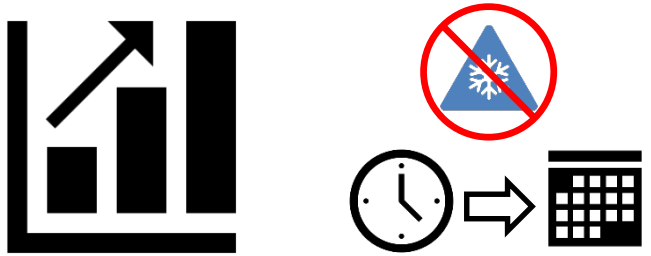


- Synthetic/semi-synthetic components that perform the critical functions of blood in trauma resuscitation.
- Bundles of co-administered components for specific clinical trauma pathophysiologies.

Deliverable: Bio-artificial blood product substitutes that are safe and achieve near parity to natural whole blood functionality.

TA1 Components

TA2
Methods for Manufacturing and Stabilization



- Formulations and methods compatible with scale-up to meet DoD needs.
- Rapidly re-constituted and administered.
- Shelf-stable without cold requirement.

Deliverable: Processes, preservatives, and apparatuses capable of consistent, timely production of shelf-stable TA1 products.

Biology for National Security

Matthew J. Pava, Ph.D.
Program Manager
DARPA Biological Technologies Office

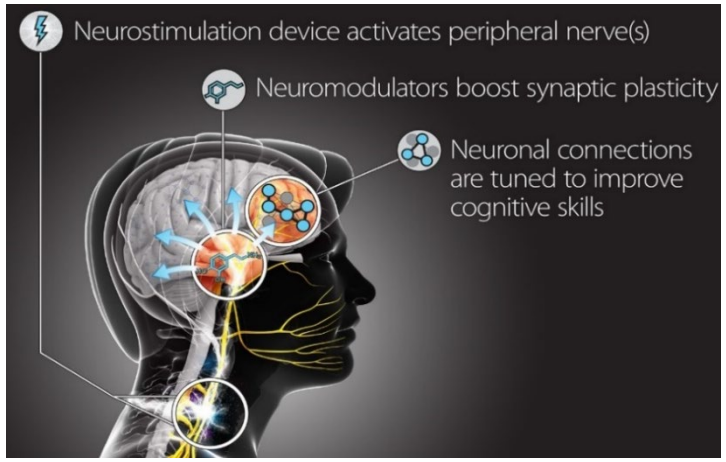
Briefing prepared for BTO Research Outreach

February 4, 2022

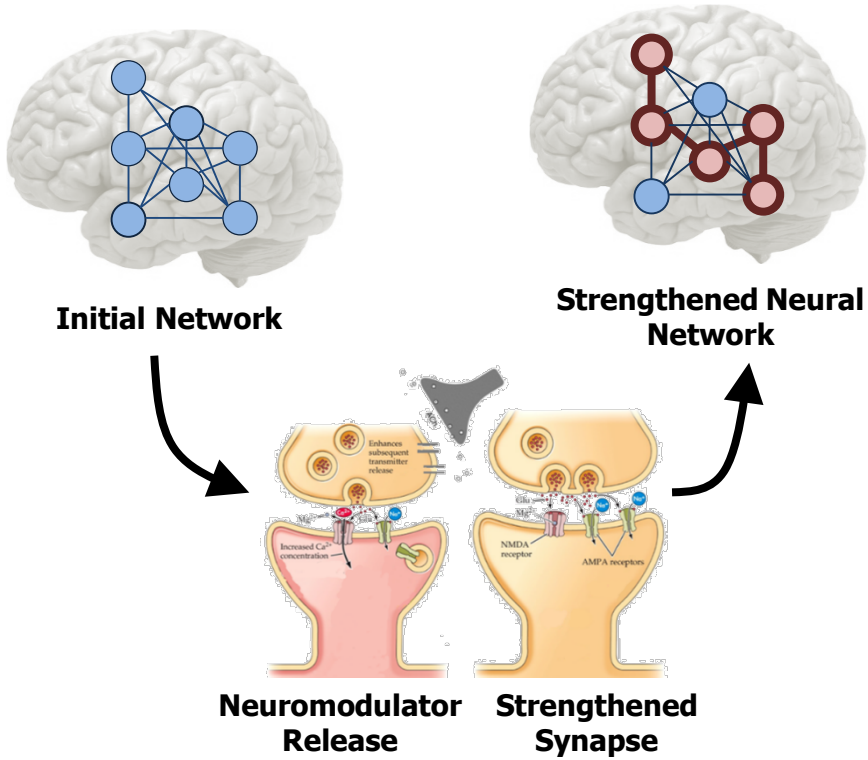
Targeted Neuroplasticity Training (TNT)

DoD Need: As training personnel is time consuming and low yield, demands of proficiency from various agencies suggest the need for accelerated training methods.

Peripheral Nerve Stimulation Engages Neuromodulatory Circuitry



Training Protocols Engage Task-specific Brain Regions



Goal:

Train personnel **faster** & achieve **superior** cognitive abilities

Program Vision: Enhance skill learning in healthy adults by using noninvasive peripheral nerve stimulation to promote synaptic plasticity in the brain

TNT technical challenges and approaches

Current methods for training, learning, and cognitive improvement

Behavioral

Memorization; Repetition; Practice

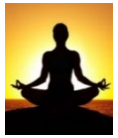
lumosity

Pharmacological

Amphetamines; Nicotine; Caffeine; Methylphenidate

Holistic Approaches

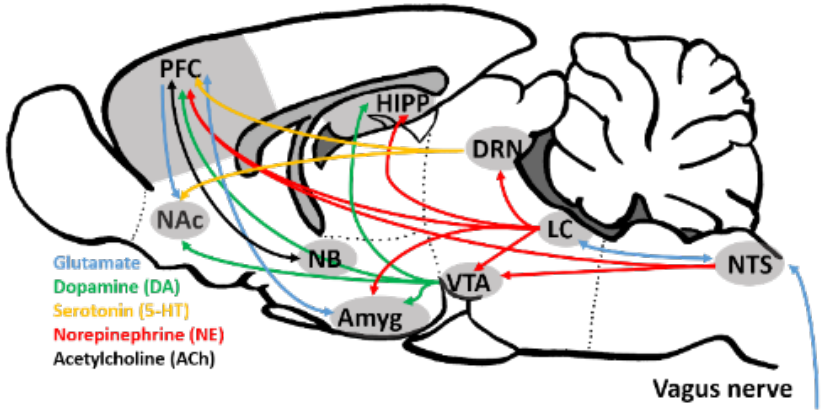
Socialization; Meditation; Exercise



TA1: Biological Foundations

Assess behavioral and neural circuitry changes in animal models using invasive and non-invasive nerve stimulation

Potential Connectivity Map



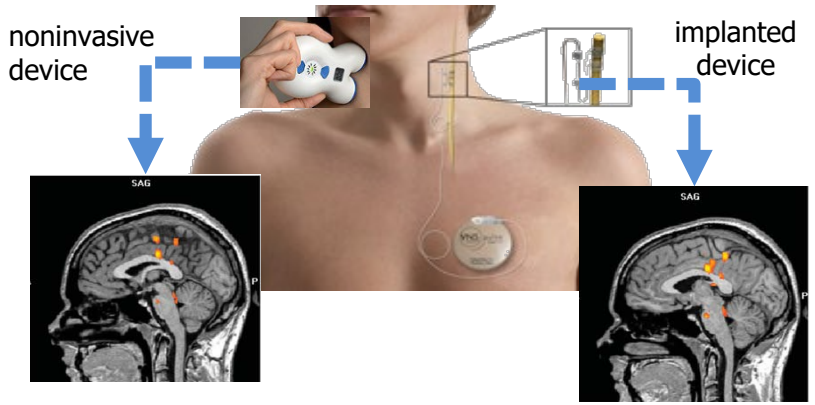
Challenges:

- Determine whether specific nerve engagement is required or if general sensory arousal also results in similar improvements in behavior
- Establish physiological responses for stimulus verification

TA2: Applications for Humans

Demonstrate improvements in cognitive and motor skills in humans using non-invasive nerve stimulation

Differential response to stimulus modality?



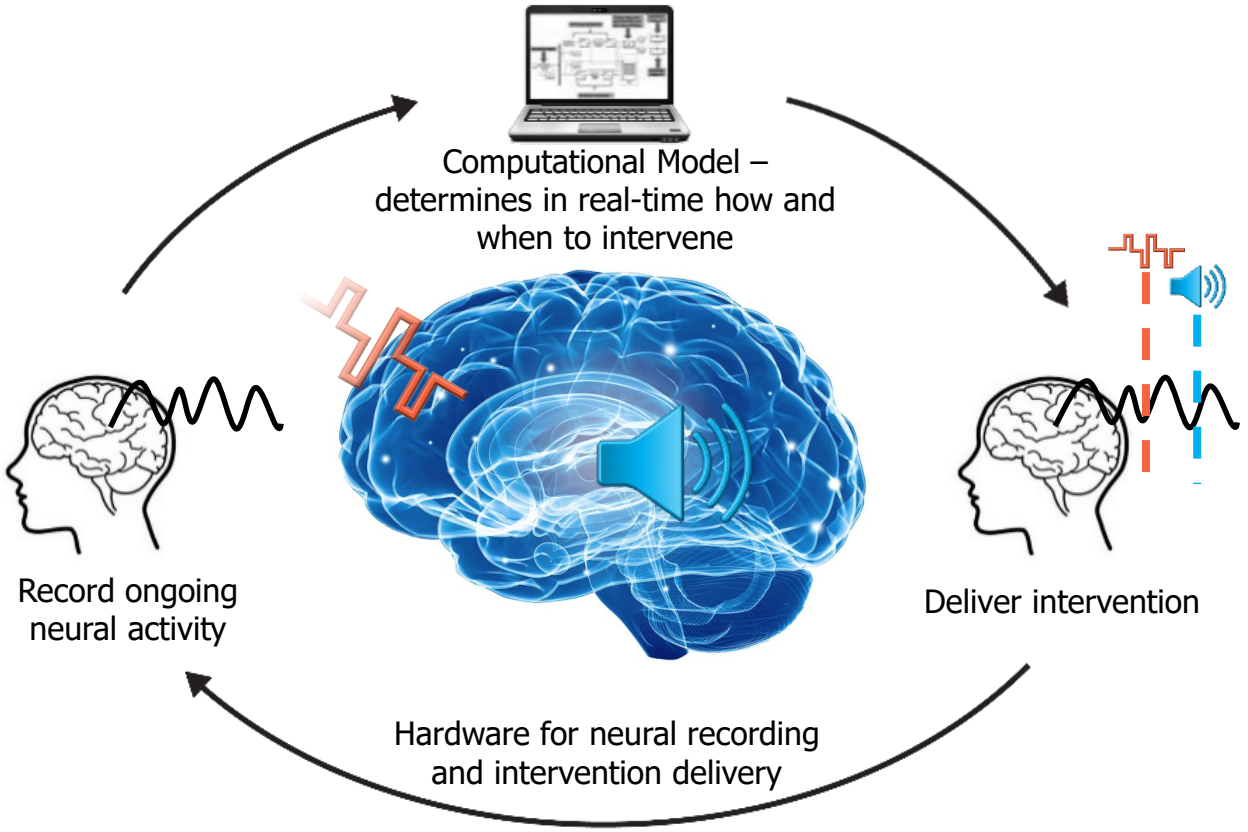
Challenges:

- Evaluate whether noninvasive peripheral nerve stimulation generates same outcomes as invasive stimulation
- Translate animal stimulation response profiles to humans

Restoring Active Memory (RAM)

DoD Need: Warfighters living with traumatic brain injury often experience deficits in forming and recalling memories; healthy warfighters require lengthy training to learn new operational skills.

- Develop computational models of neurobiological mechanisms underlying memory and skill learning in humans
- Create a portable neural device for memory restoration in humans
- Enable non-invasive memory enhancement



Program Vision: Memory restoration and enhancement in humans

RAM Replay: Technical challenges and approaches

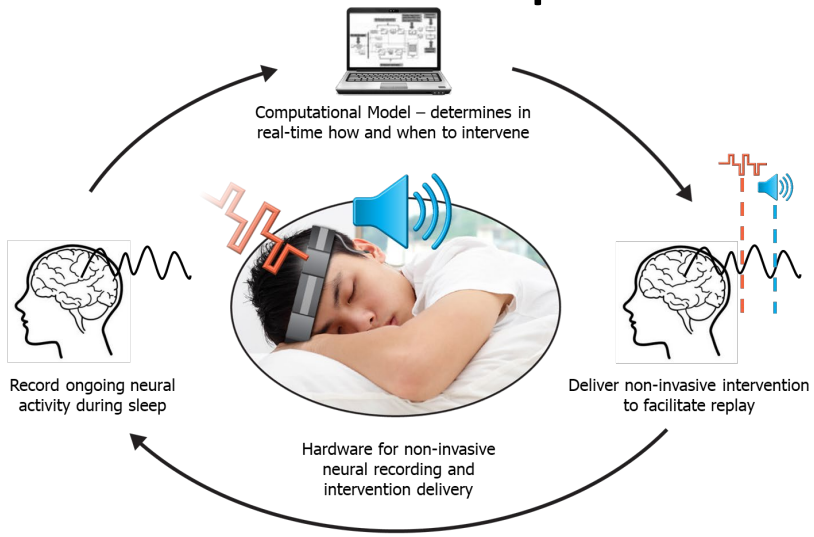
State of the Art

Nootropics

Brain Training

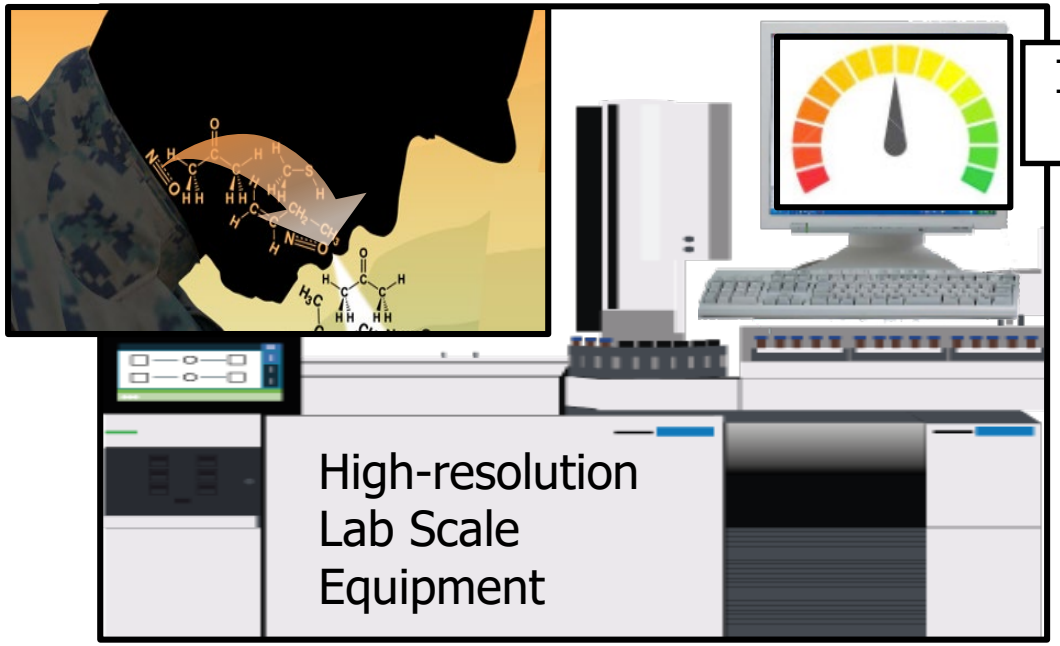
- Do not target specific functional networks in the brain
- Independent of ongoing dynamic brain function

Next Generation Closed-loop Interventions



- Spatiotemporally specific interventions to modulate functional networks in the brain
- Monitor real-time changes in brain state to deliver targeted intervention parameters

Small Study: Fatigue Assessment via Breath (FAB)



Immediate Results

Mitigation Potential

MISSION: ABORTED

- **Change Personnel**
- **Mandate Crew Rest**

- ✓ Tabletop or kiosk fatigue testing using clinical equipment
- ✓ Available at military installations or shipboard only
- ✓ Uses gold standard high resolution gas chromatography mass spectrometry instrumentation (or better)
- ✓ Enables testing prior to high priority and high risk missions

- ✓ Objective quantification of fatigue state(s)
- ✓ Identify performance/readiness impairment
- ✓ Test results can be made available to commanders

FAB GOALS

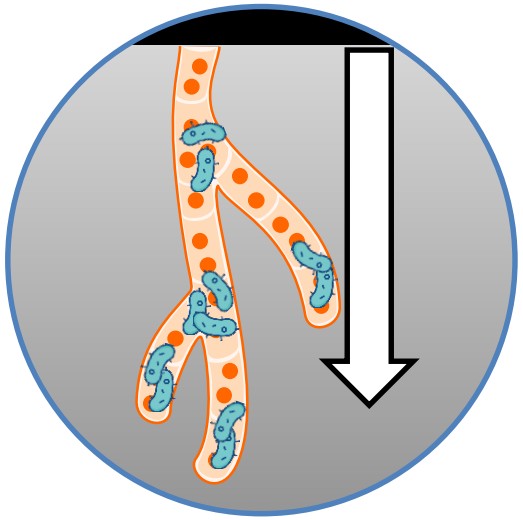
- Demonstrate reliable breath-based objective quantification of fatigue and impairment due to fatigue state(s)
- Enable objective individual and unit readiness information to be provided to commanders to prevent mishaps

YFA 2022* Topic: Engineered Cellular Symbiosis (ECS)

DoD Need: Legacy concrete-based infrastructure is prone to degradation but possesses neither self-healing nor defect-reporting capabilities

Research and develop engineered, self-sustaining prokaryotic-eukaryotic symbiotic systems that can:

Thrive within a cementitious environment



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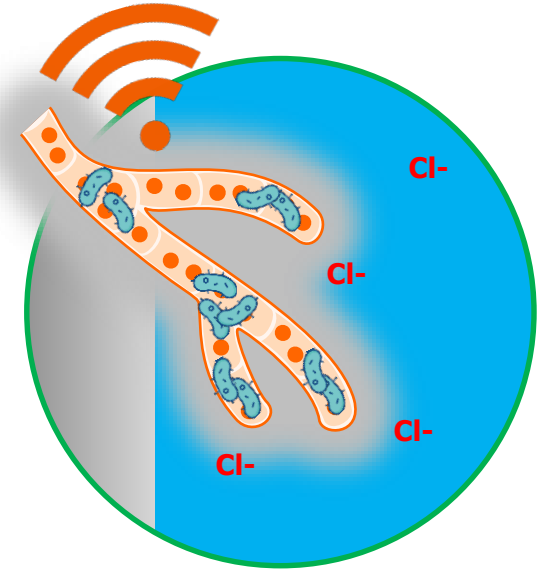
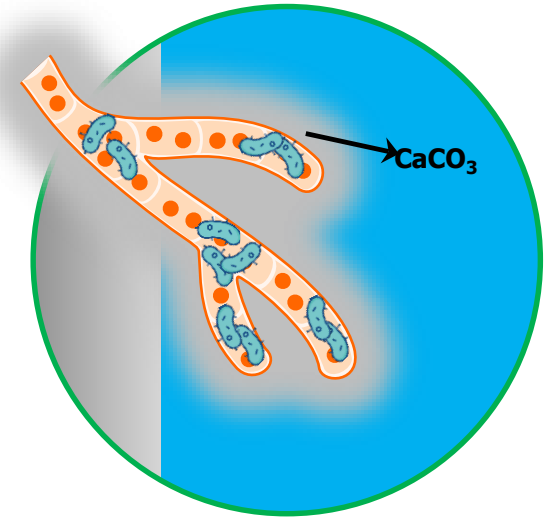
Sense and report environmental factors



&/or

Synthesize materials for in situ repair



*YFA full proposal submission deadline was 25 Jan 2022

YFA Topic Vision: Engineer biological, cross kingdom symbiotic systems that can integrate with existing concrete materials to augment inspection and repair

Biomanufacturing: Delivering New Operational Capabilities

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Briefing Prepared for BTO Research Outreach Event
February 4th, 2022

Living Foundries: 1000 Molecules (1KM)

Challenge
Biomanufacturing & US Department of Defense (DoD) Relevance

The DoD currently lacks a biomanufacturing capability to generate molecules and materials that are high-value, cost-effective, domestically sourced, and high-performing for a broad range of applications

DoD Challenge

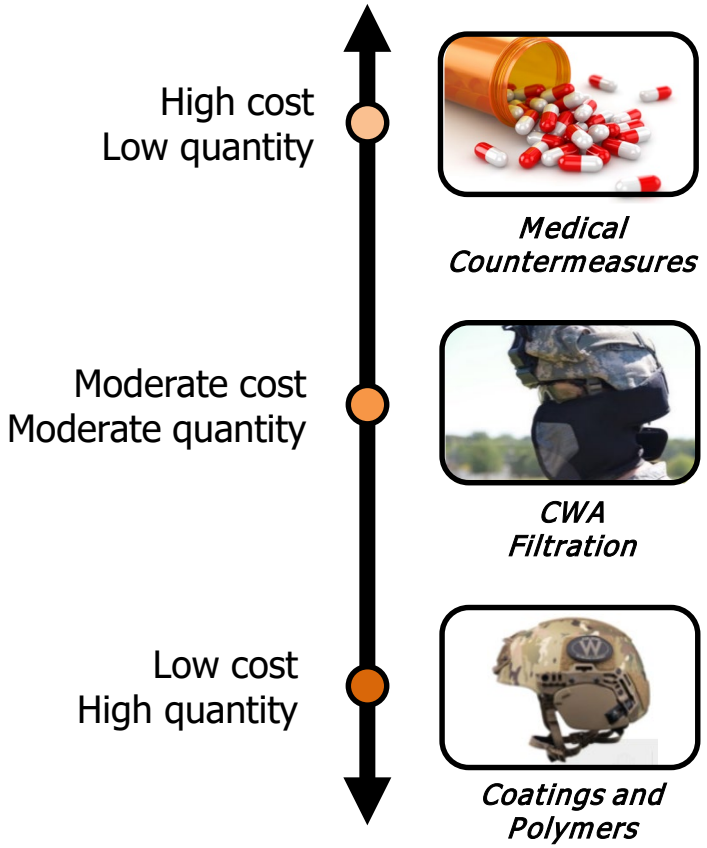
The DoD faces challenges for critical molecules & materials manufacture including:

- Limited performance
- High cost & volatile pricing
- Limited domestic access
- Logistical burden and footprint
- Slow, cumbersome, and lacks versatility

Living Foundries: 1000 Molecules Mission

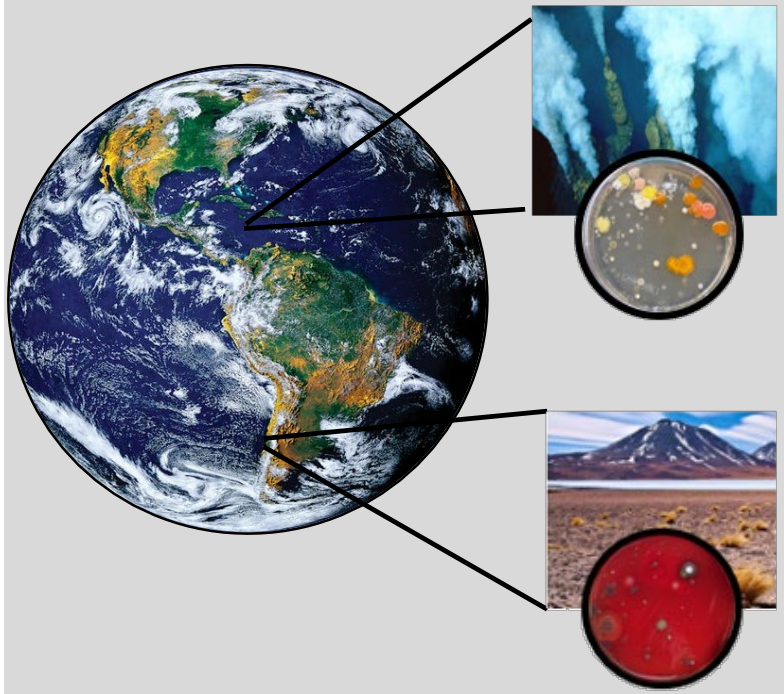
The 1000 Molecules program is developing a pipeline to enable the bio-manufacture of critical molecules & materials that are:

- Cost effective
- Customizable for enhanced performance
- Sourced domestically
- Versatile, scalable, and agile



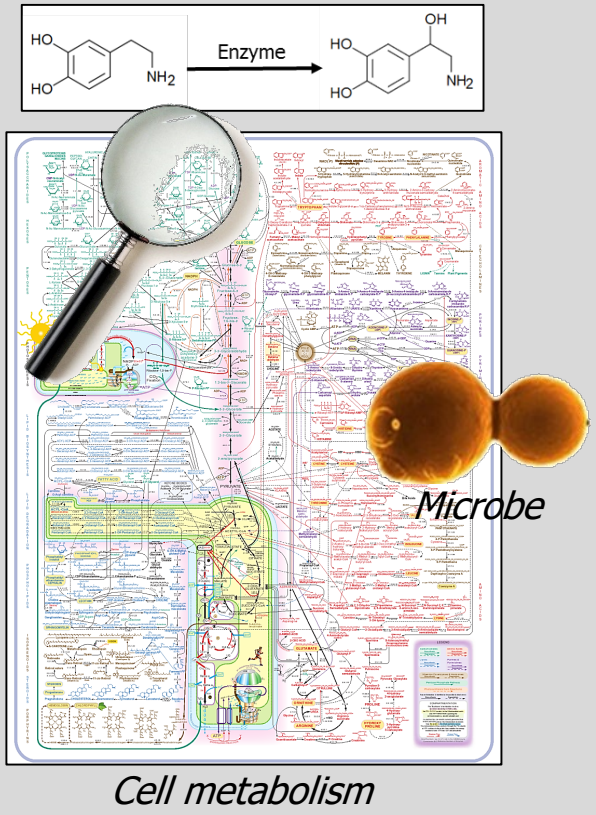
Opportunity
Harnessing Natural Products for Biomanufacturing of Molecules and Materials

From natural chemical reactions



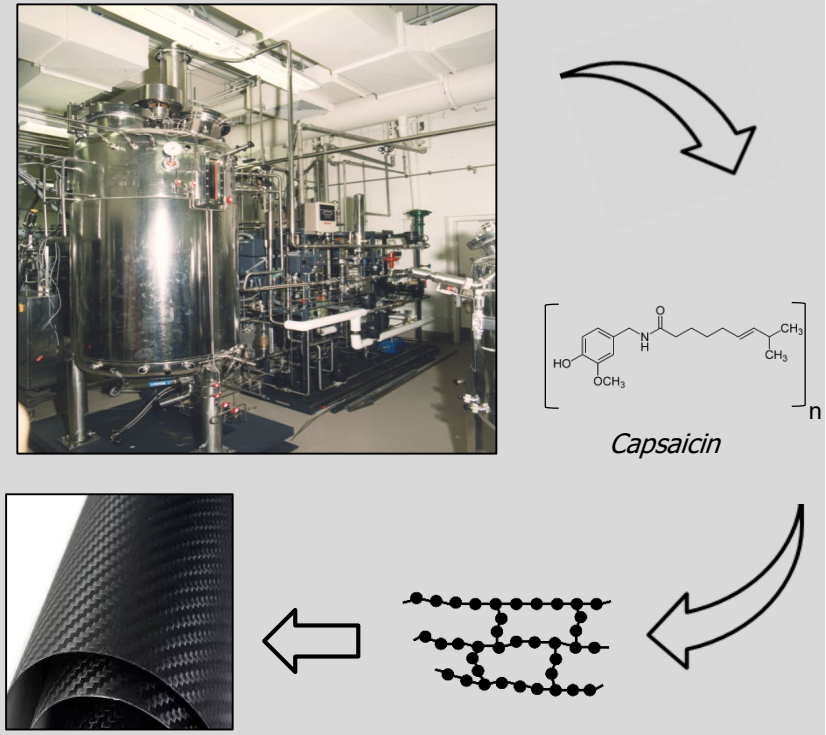
Understanding Earth's biological and metabolic diversity for a broad range of natural chemical reactions

To newly engineered reactions



Assembling genes from different biological sources to form new biosynthetic pathways and new metabolism

To biomanufacturing new materials

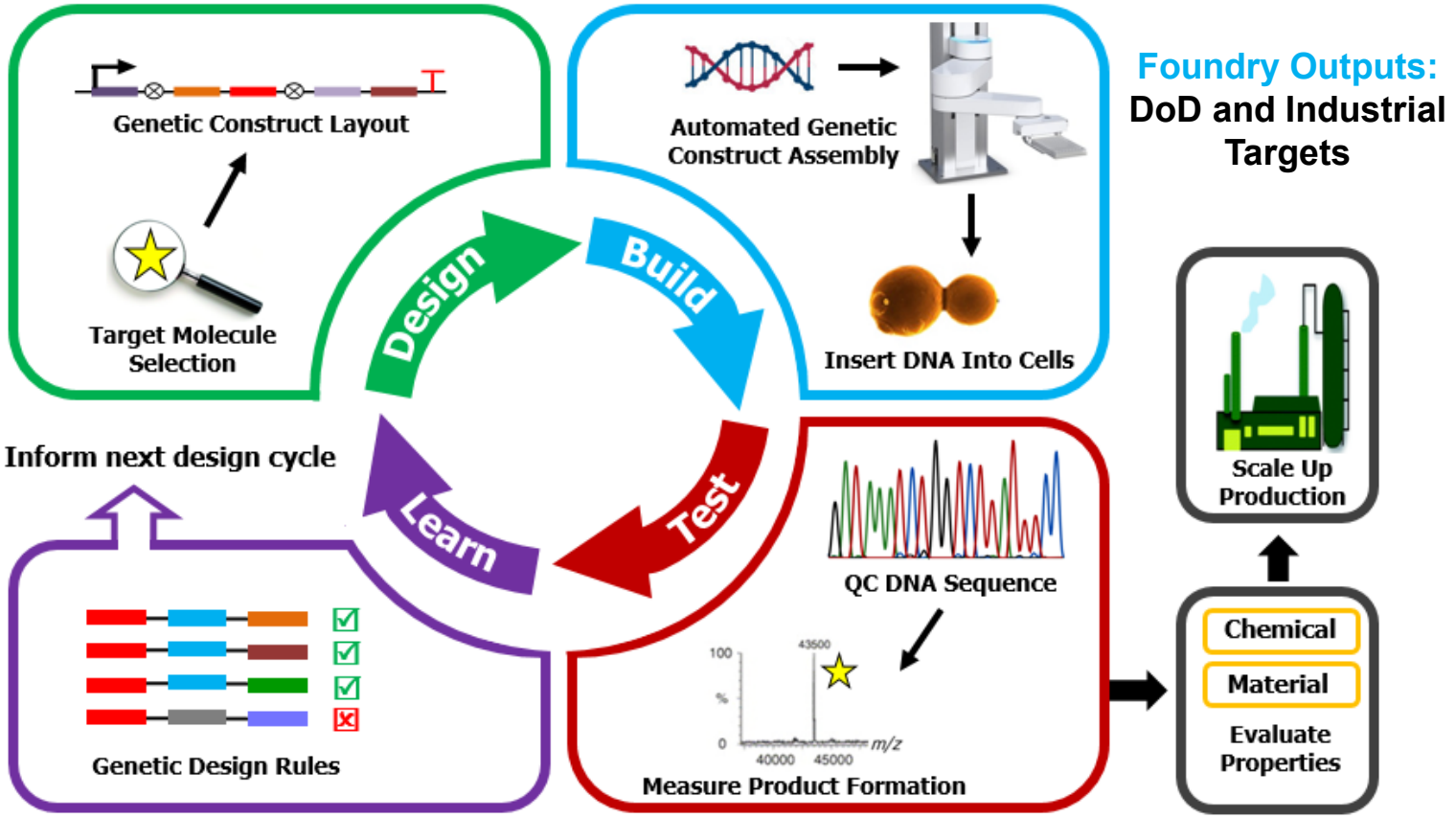


Producing and scaling molecule production for DoD and industry that can bolster, augment, and even replace existing supply chains

Program Overview - Living Foundries: 1000 Molecules

Design, Automation, and Infrastructure for Biofoundries

DoD Problem: The DoD lacks a biomanufacturing capability for critical molecules and materials that is high-value, cost-effective, domestically sourced, and high-performing



Foundry Outputs:
DoD and Industrial Targets

Performers

Amyris | **MIT-Broad Foundry** | **Zymergen**

T&E Partners

Air Force Research Laboratory (AFRL)

Naval Air Warfare Center Weapons Division (NAWCWD) – China Lake

U.S. Army Combat Capabilities Development Command – Army Research Laboratory (CCDC-ARL)

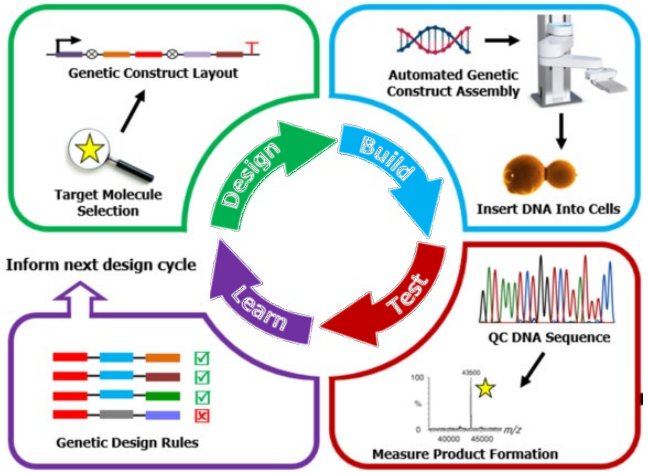
U.S. Army Combat Capabilities Development Command – Chemical Biological Center (CCDC-CBC)

Vision: Develop a versatile rapid design and prototyping foundry for engineering biology

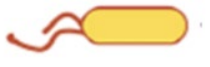
Living Foundries Capability

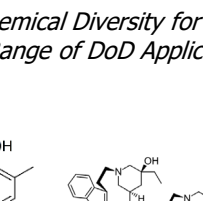
Increase Adaptability While Reducing Logistical Burdens

Initial capability development performed at foundry



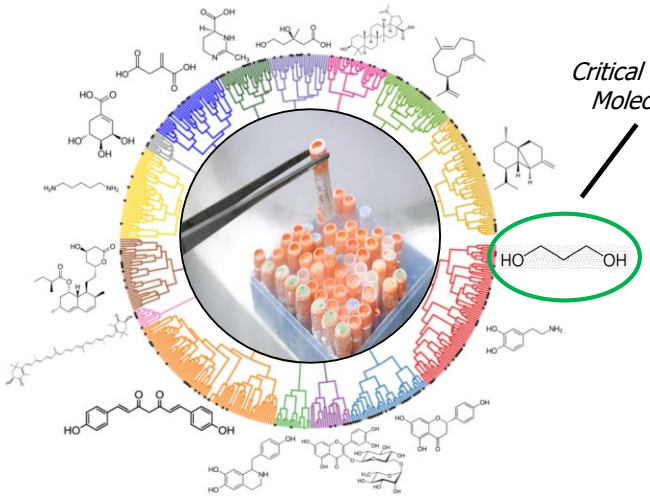
Chassis Organisms



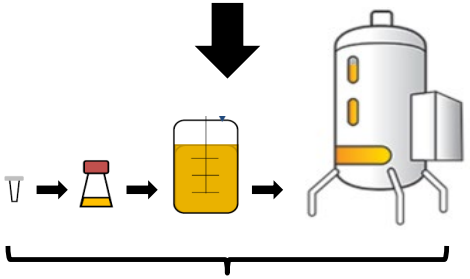


Chemical Diversity for a Wide Range of DoD Applications

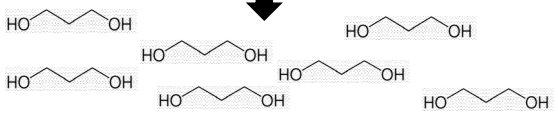
Developed capabilities can be stored for on-demand production



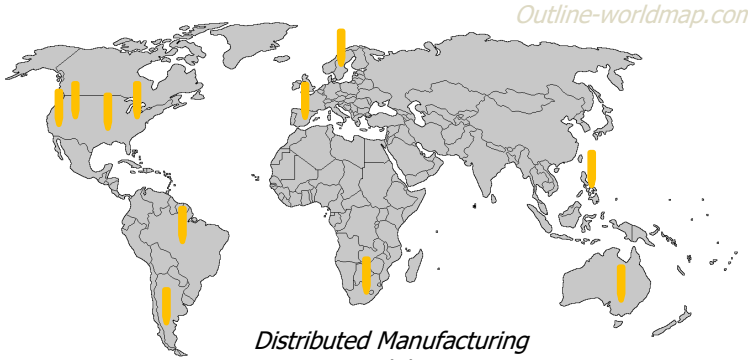
Critical Need Molecule



From Freezer to Industrial Scale Production ~2 Weeks



On-demand production can decrease logistical burden



Distributed Manufacturing Capabilities

Amyris

Economy of Scope Manufacturing

Domestically Sourced Renewable Supply Chains

Biologically Sourced Molecules with Enhanced Performance:
Enabling New Operational Capabilities

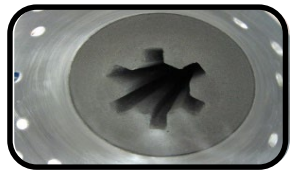
New biologically derived materials can replace or compliment a range of current DoD capabilities

Testing & Evaluation Partners

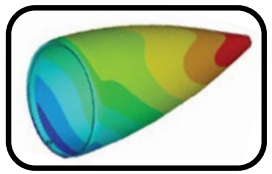
NAWCWD – China Lake *U.S. Army CCDC – CBC* *AFRL – RX/RQ*

Fire Resistant Composites

High Density Fuels



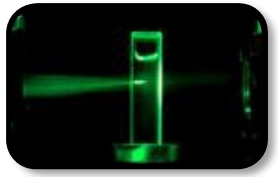
Solid Fuel Ram Jet Propellants



Thermostable Polymers for Radomes

Gas Storage (OBOGs)

Optical Materials (Liquid Crystals)

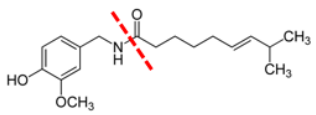


Optical Power Limiters

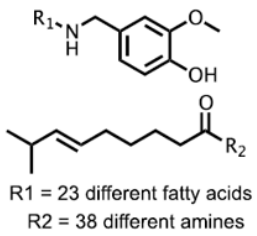
Living Foundries: 1000 Molecules

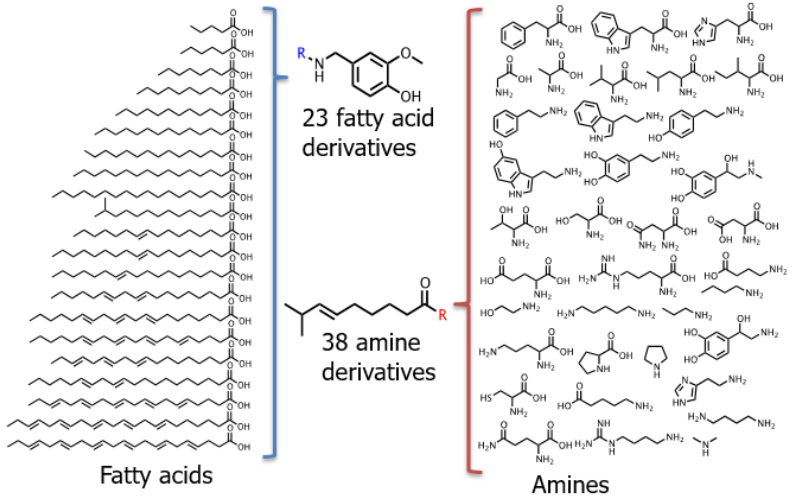
How Biology Does it Better

Derivatization and rapid prototyping: polymers



Capsaicin

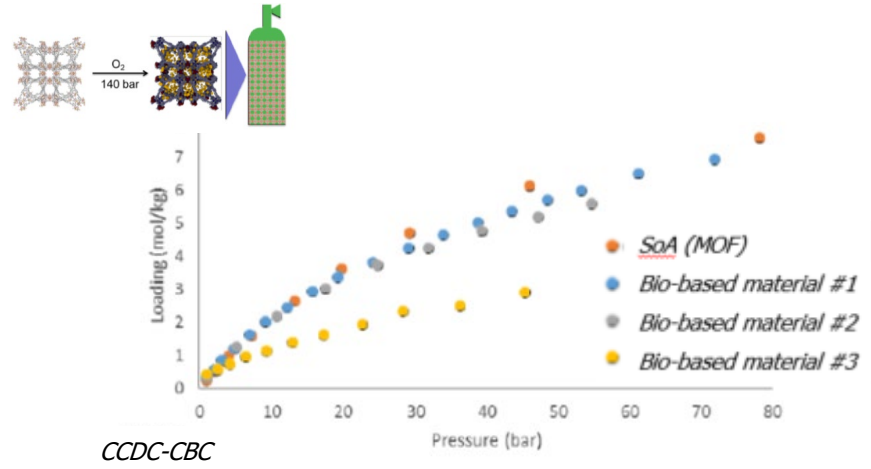




MIT-Broad

Access greater chemical diversity rapidly through biology to accelerate materials science

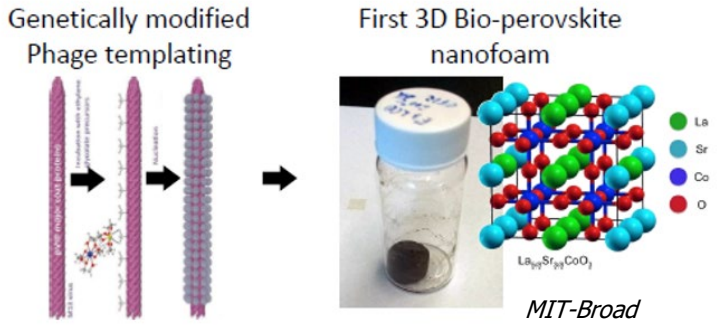
New functionalities: gas storage



CCDC-CBC

Create novel materials that are not reliant on rare earth metals; show equivalent or better functionality

New materials: surface catalysts



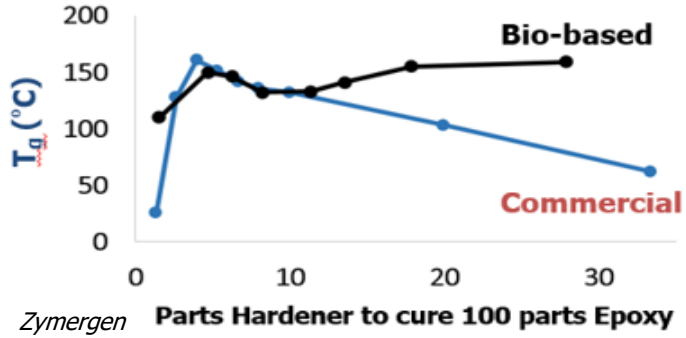
MIT-Broad

Templates	Perovskite	BET S.A.	A.T. °C
Phage E3/880 nm	$LaCoO_3$	16.9	600
Phage E3/880 nm	$LaMnO_3$	15.6	700
Citrate	$LaCoO_3$	8.6	500
Citrate	$LaMnO_3$	10.5	700

Templates	Perovskite	BET S.A.	A.T. °C
Phage E3/880 nm	$LaCoO_3$	16.9	600
Phage E3/400 nm	$LaCoO_3$	23.46	550
Phage E3/200 nm	$LaCoO_3$	14.65	550
Phage E3/100 nm	$LaCoO_3$	26.29	550

Increase reactive surfaces through biologically templated materials

Better performance: epoxies

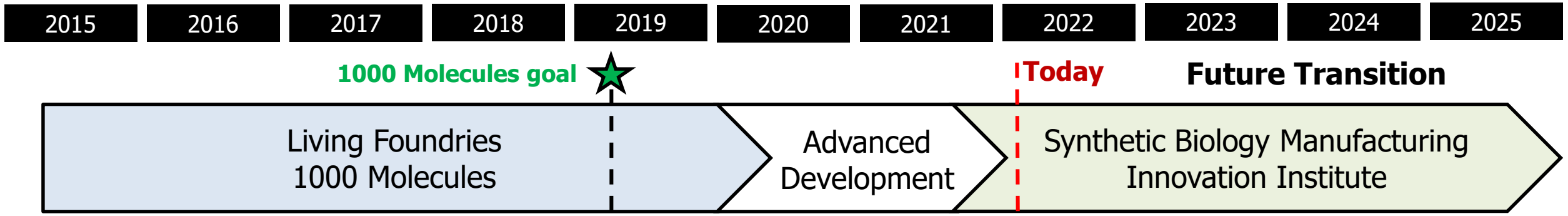


Zymergen

Improve physical properties of materials through biology

Living Foundries: 1000 Molecules Status

On Track to Meet and Exceed Program Goals – Focus on Transition



Living Foundries Funding

Advanced Development
Funding FY20-21

DoD ManTech MII Funding FY21-25

Stakeholders

AFRL RX/RQ | **U.S. Army CCDC-CBC** | **NAWCWD China Lake** | **U.S. Army ARL** | **SOCOM** | **DoD OSD** | **DTRA** | **DoD ManTech**

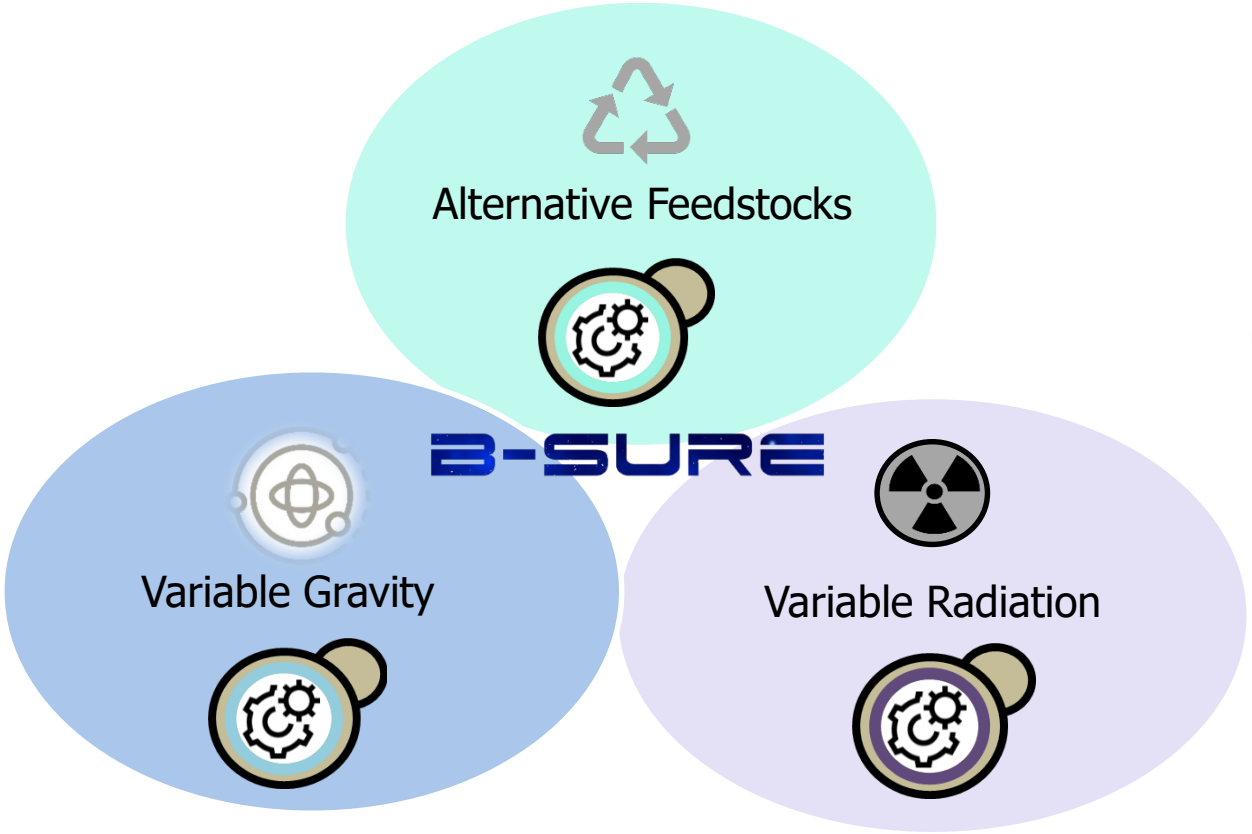
Biomanufacturing: Survival, Utility, and Reliability beyond Earth (B-SURE)

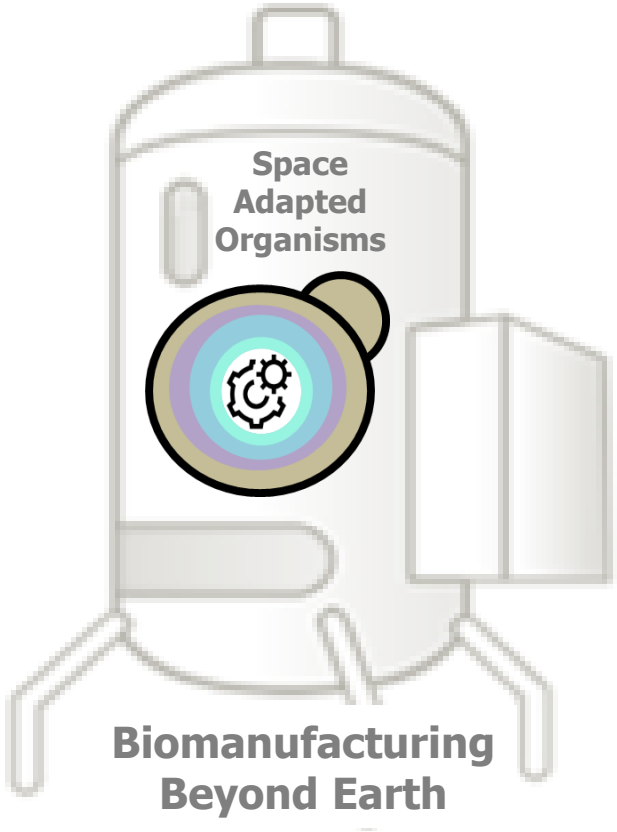
Biomanufacturing: Survival, Utility, and Reliability beyond Earth

B-SURE

Biomanufacturing: Survival, Utility and Reliability beyond Earth (B-SURE)

DoD Problem: Material logistics and supply chains for the space domain are complex and tenuous





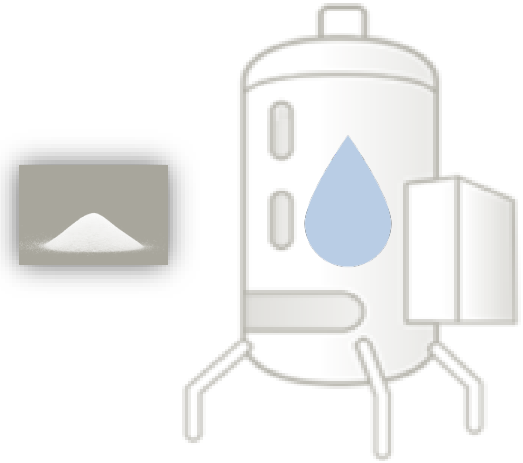
B-SURE Vision: Develop a fundamental understanding of microbial capabilities for bioproduction in space and biomanufacturing as a potential novel solution for in-space manufacturing

Biomanufacturing can help meet DoD priorities of the future

Future operational doctrine in the space domain is predicated on in space manufacturing for a ready supply of materials

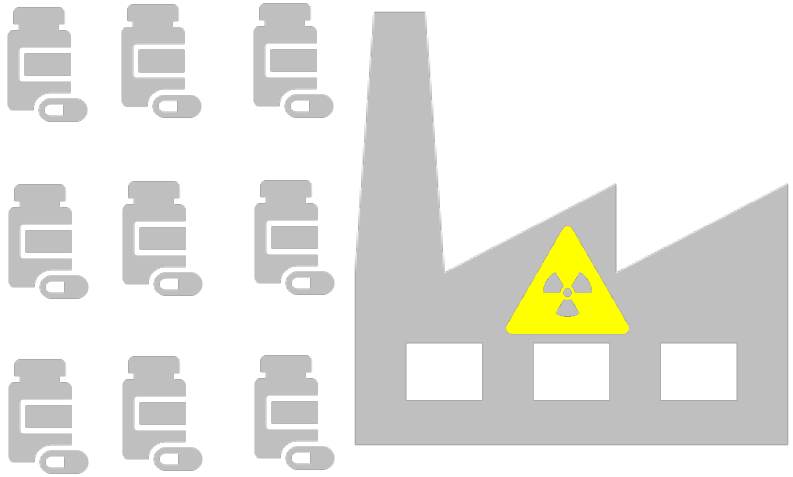
USSF Space Capstone

Biomanufacturing



- Common feedstock and fermentation hardware
- Water based and non-toxic
- Simple to operate
- Processes adaptable to microgravity

Traditional Manufacturing



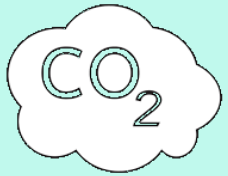
- Many Feedstocks and Reagents Required
- Flammable, Volatile, Corrosive, Toxic; Requires highly skilled operators
- Many processes are gravity dependent

DoD Application: Inform capability development for in-space manufacturing and future CONOPS

B-SURE will test biomanufacturing variables in support of future space operations

18 Month – Early Phase Program

Track 1: Alternative Feedstocks



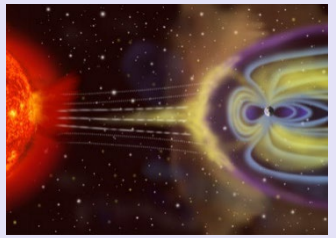
Carbon Dioxide

Human waste

Lunar Regolith

What local resources can be metabolically utilized?

Track 3: Variable Radiation



What adaptations enable high productivity in GCR?

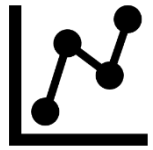
Track 2: Variable Gravity

High Altitude Balloon Flight

International Space Station

What adaptations enable high productivity in low gravity?

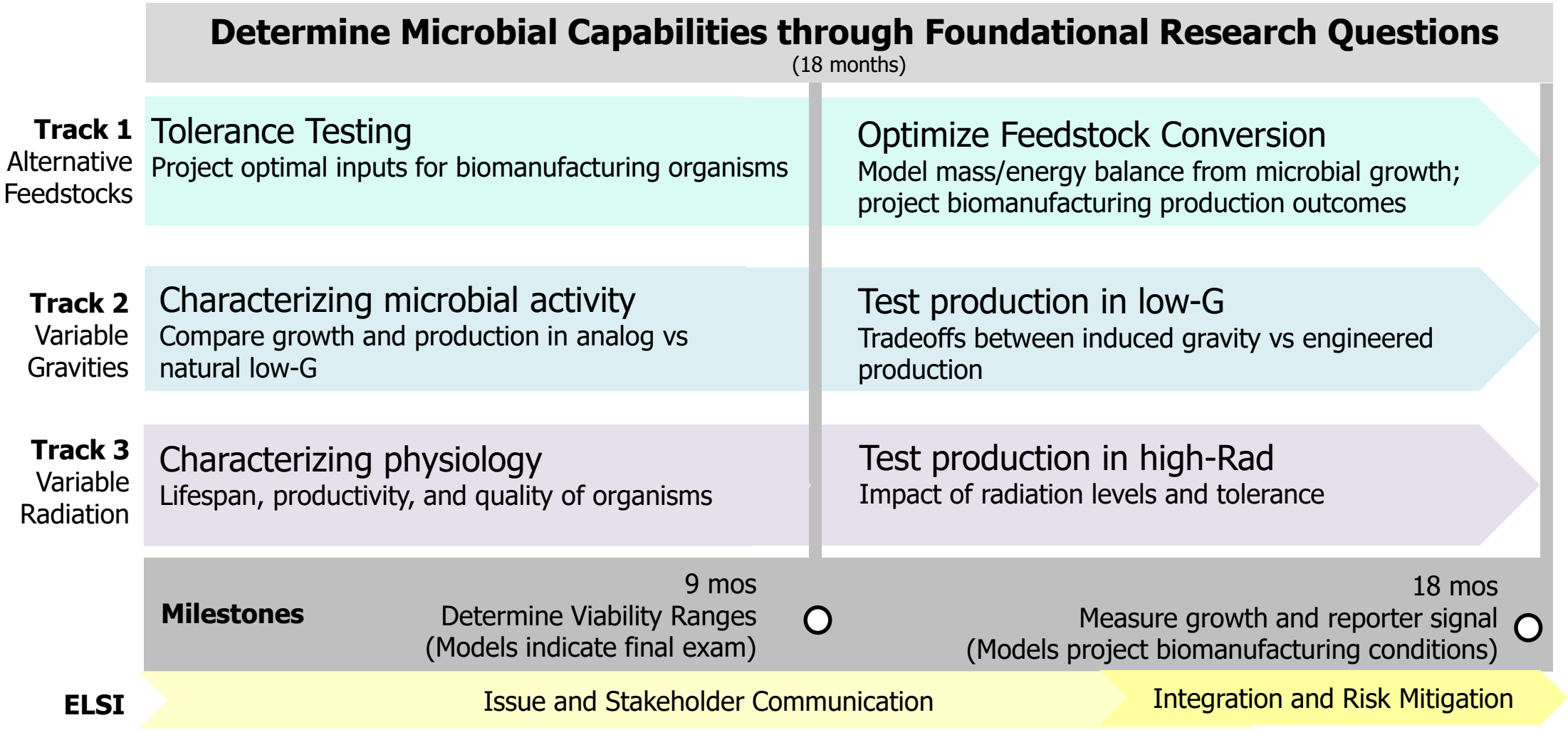
Modeling Logistics and Viability of Biomanufacturing



Included in all proposals

Under what circumstances is biomanufacturing viable in the space economy?

Test Tracks and Schedule



Goal: Generates data on variables of microbial engineering for in-situ resource utilization (ISRU) biomanufacturing proof-of-concept, outlining the potential in-space manufacturing capability and future space economy

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