Safe Genes

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Proposers Day

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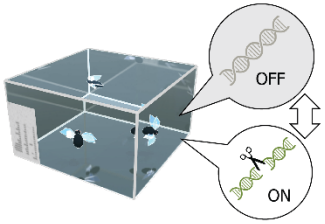
Safe Genes Program

Vision:
Create biological capabilities that enable the safe pursuit of advanced gene editing applications and protect against potential engineered genetic threats

Control of Gene Editing	Countermeasures and Prophylaxis	Genetic Remediation
		
Enable temporal, spatial, and reversible control of gene editors	Inhibit unwanted gene editing activity	Remove engineered genes from environments to return to baseline

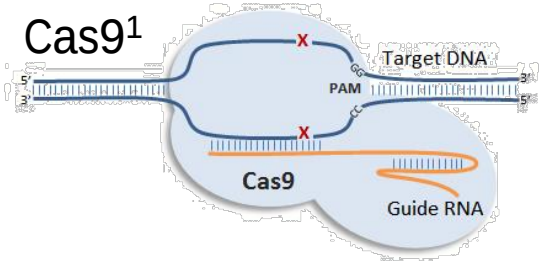
Goals:
- **build-in biosafety** for new biotechnologies at their inception
- provide a **toolkit** to enable previously unattainable applications in synthetic biology
- create an **understanding of what is possible, probable, and vulnerable** with regard to emergent gene editing biotechnologies

Rapid Advancement of Genome Editing Technologies

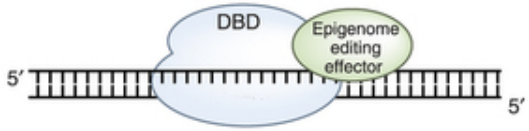
Genome editing advancements are outpacing biosafety & biosecurity advancements

Genome Editors

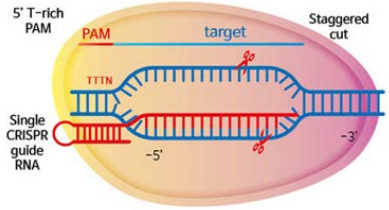
Cas9[1]



dCas9 + effector[2]



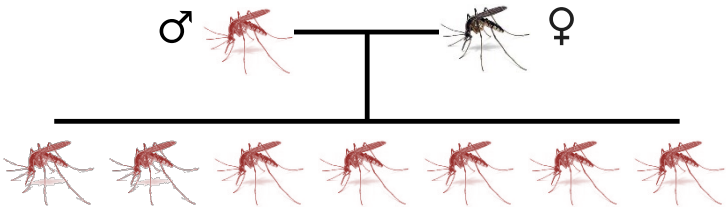
Cpf1[3]



etc...

Derivative Technologies

Gene drive Wildtype



Challenges:

- Lack of controls
- Lack of countermeasures
- Off target effects
- Need for empirical data, especially for derivative technologies

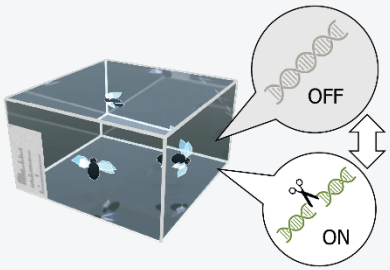
Challenges and unknowns create an opportunity cost

1. http://www.creative-animodel.com/; 2. Thakore et al, 2016; 3. Institute for Basic Science

A Toolkit for Innovation and Biosecurity

Objective: create a suite of tools that can be applied independently or in combination to safely pursue emergent opportunities in genome editing

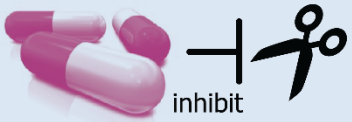
Control of Gene Editing



Enable temporal, spatial, and reversible control of gene editors

Technical Area 1 (TA1)

Countermeasures and Prophylaxis



Inhibit unwanted gene editing activity

Technical Area 2 (TA2)

Genetic Remediation

Remove engineered genes from environments to return to baseline

Technical Area 3 (TA3)

Safe Genes Notional Program Structure

3 Technical Areas:

TA1 - Controlling genome editing activity
TA2 - Countermeasures & Prophylaxis
TA3 - Genetic Remediation

All gene drive proposals **must** address TA1 *and* (TA2 or TA3), or all 3

All other proposals may address one, two, or all TAs in any combination

DARPA relevant applications:

Proposer-defined; may include:

- vector control
- ecosystem biodiversity protections
- novel cellular therapeutics
- biomanufacture
- etc...

Phase 1 (24 months)

Generate and Test Safe Genes Constructs

Generate, test, and characterize first generation Safe Genes constructs, culminating in *in vivo* proof of concept

Phase 2 Option (24 months)

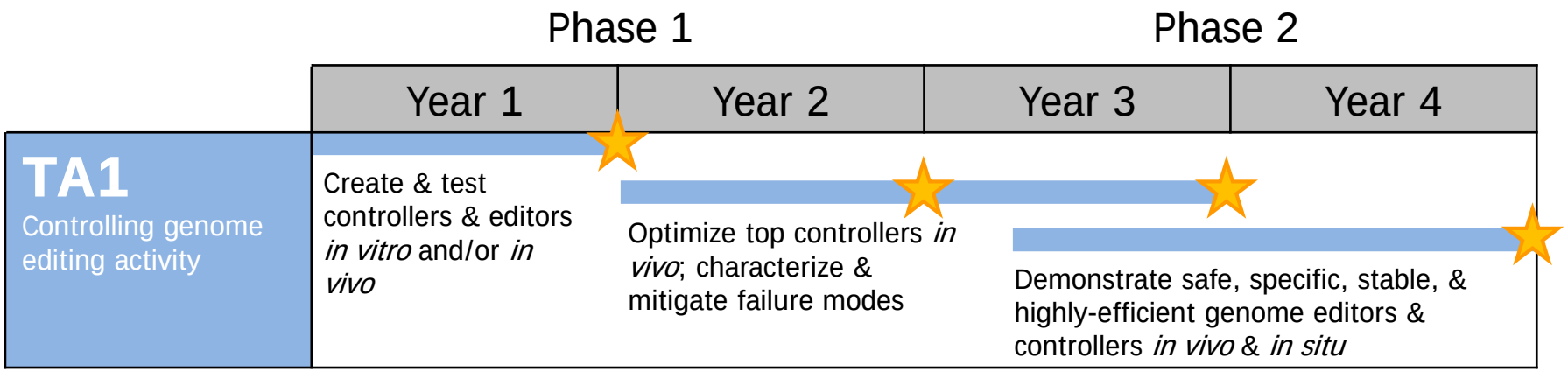
Demonstrate Safe Genes Capabilities

Second generation systems, building on Phase 1 technology, that enable efficient, safe, stable, and specific control (TA1), inhibition (TA2), and/or reversal (TA3) of genome editing activity *in vivo* and/or *in situ**

**simulated natural environments/contained systems only; open release not supported under this BAA*

TA1: Control of Gene Editing Activity

Objective: Create molecular constructs that provide **spatial, temporal, and reversible control** of genome editors in living systems

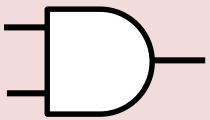


Must propose rigorous and quantitative metrics that address:

- Control efficacy
  - Temporal
  - Spatial
- Specificity
- Stability
- Safety

Deliverables

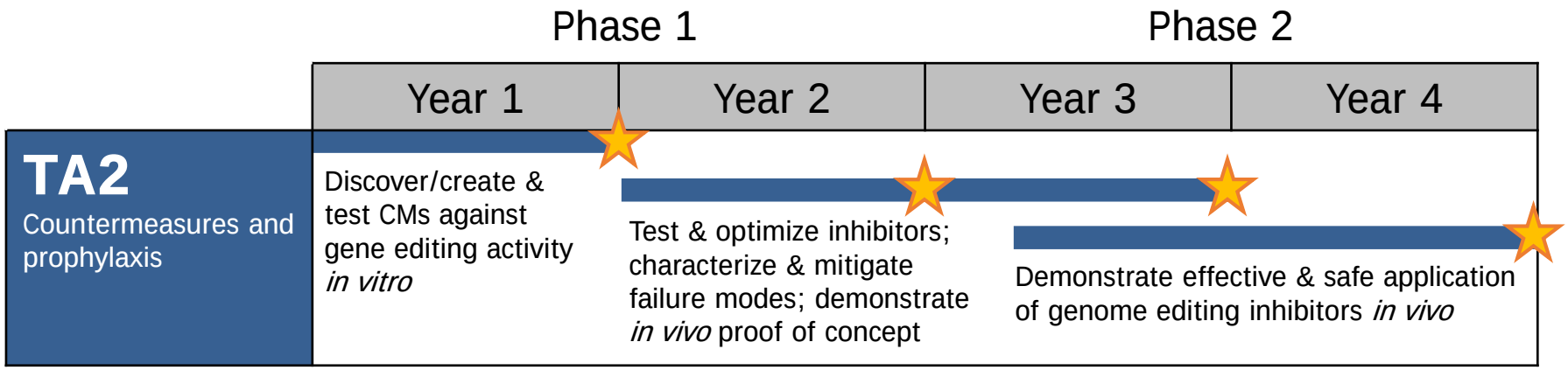
Controllable gene editors with high fidelity and efficacy



Better controllers, better editors

TA2: Countermeasures and Prophylaxis

Objective: Generate first-in-class **small molecule and/or molecular countermeasures** to prevent or limit unwanted genome editing activity



Must propose rigorous and quantitative metrics that address:

- Efficacy
- Specificity
- Safety
- Efficient Delivery
- Generalizability

Deliverables

Small molecule and molecular inhibitors that halt or prevent gene editing activity *in vivo*

First-in-class countermeasures

TA3: Genetic Remediation

Objective: Develop a capability to **eliminate unwanted engineered genes from environments** and restore systems to their baseline state

	Phase 1		Phase 2	
	Year 1	**Year 2**	**Year 3**	**Year 4**
TA3 Genetic remediation	Create & characterize transgenic & molecular tools to remediate genes from environments	Test & optimize target gene removal in small, contained populations; characterize & mitigate failure modes	Demonstrate efficient & specific target gene removal in contained populations & ecosystems	

Must propose rigorous and quantitative metrics that address:

- Efficacy
- Specificity
- Safety
- Stability
- Ecological impact

Deliverables

Molecular and transgenic tools to eliminate target genes from environments & restore baseline state

First-in-class gene remediation strategies

Images: bioBUBBLE, Biosphere

Additional Requirements

Data sharing

- All proposals must articulate a plan to share data with teams both internally to the Safe Genes performer group and externally with the broader research community

Ethical, Legal, and Societal Implications (ELSI)

- All proposals must articulate potential ELSI topics relevant to their proposed technology and describe plans for engagement throughout the program life cycle with DARPA ELSI experts and the broader community

Biosafety and Biocontainment

- All proposals must address lab safety protocols and biocontainment strategies for biosafety and containment

- Gene drive proposals must clearly articulate a detailed, **multilayered** biocontainment strategy for laboratory testing and cage trials
  - Include **monitoring and mitigation** measures for unintended release or outcomes
  - Consider physical, ecological, and molecular barriers

Ligand-dependent growth

Oxitec

bioBUBBLE

Safe Genes Program Logistics

BAA Released 9/15/2016 → Proposers Day 9/30/2016 → Abstracts Due 10/06/2016 → Full Proposals Due 11/17/2016

TIPS

- Read the BAA carefully
- Ask questions and check the Safe Genes FAQ document
  - Email questions to: SafeGenes@darpa.mil
  - FAQ: http://www.darpa.mil/work-with-us/opportunities
- Formation of complete teams with comprehensive expertise and capabilities is viewed as critical
  - Teaming is strongly encouraged
  - Teams applying to >1 TA are also encouraged to have a program coordinator/project manager
  - There is no bias for teams internal to one institution or across multiple institutions
    - But, effective communication and collaboration between teams is necessary

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