Weighing risks (hazards) and benefits: lessons from biosafety

Zach N. Adelman, Dept of Entomology

Are there unique safety challenges surrounding these technologies?

No.

What are the specific concerns - human health/safety, the impacts to the environment/ecosystem etc.?

More than that. Assault on human values.

What are the biosafety concerns associated with contained laboratory research versus environmental release?

That the technology will escape control and permanently change the world.

The assessment of risk may be tricky but is the management (containment) any different from what we have today?

No.

Might we need to consider possible new risk management strategies (e.g. new approaches to biological containment – gene drive reversals, kill switches)

We might.

Gene Drive

Gene drive in the news

ScienceNews
MAGAZINE OF THE SOCIETY FOR SCIENCE & THE PUBLIC

News: Genetics,Ecology

In lab tests, this gene drive wiped out a population of mosquitoes

Success with the genetic engineering tool raises hopes of eliminating the malaria carrier

By Tina Hesman Saey 11:20am, September 24, 2018

Perspective

Received: 29 March 2018 Revised: 6 July 2018 Accepted article published: 12 July 2018 Published online in Wiley Online Library: 18 September 2018

(wileyonlinelibrary.com) DOI 10.1002/ps.5137

Gene drive systems: do they have a place in agricultural weed management?

Paul Neve*

Gene drives in our future: challenges of and opportunities for using a self-sustaining technology in pest and vector management

James P. Collins

From Environmental Release of Engineered Pests: Building an International Governance Framework Raleigh, NC, USA. 5-6 October 2016

Gene drive in the news

Vox

Gene drives could end malaria. And they just escaped a UN ban.

The most important international summit you haven't heard of, explained.

By Dylan Matthews | @dylanmatt | dylan@vox.com | Dec 7, 2018, 9:30am EST

The Economist

Extinction on demand

The promise and peril of gene drives

A new genetic-engineering technology should be used with care

EXPERIMENTAL POPULATION GENETICS OF MEIOTIC DRIVE SYSTEMS[1,2] I. PSEUDO-*Y* CHROMOSOMAL DRIVE AS A MEANS OF ELIMINATING CAGE POPULATIONS OF *DROSOPHILA MELANOGASTER*

TERRENCE W. LYTTLE[3]

Department of Genetics, University of Wisconsin, Madison, Wisconsin 53706

Manuscript received September 9, 1976
Revised copy received December 23, 1976

Rapid spread of a *P* element/*Adh* gene construct through experimental populations of *Drosophila melanogaster*

G. A. Meister and , T. A. Grigliatti

Genome, 1993, 36(6): 1169-1175, https://doi.org/10.1139/g93-155

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Historical Profiles and Perspectives

From Tucson to Genomics and Transgenics: The Vector Biology Network and the Emergence of Modern Vector Biology

Barry J. Beaty[1]*, Denis J. Prager[2], Anthony A. James[3,4], Marcelo Jacobs-Lorena[5], Louis H. Miller[6], John H. Law[7,8,9], Frank H. Collins[1], Fotis C. Kafatos[1]

"A seminal meeting entitled "Prospects for Malaria Control by Genetic Manipulation of its Vectors" was held January 27–31, 1991, in Tucson, Arizona, and was sponsored by The MacArthur Foundation, WHO-TDR, and the University of Arizona.

Participants included scientists with expertise in basic molecular biology, genetics, epidemiology, entomology, vector control, and public health.

By the end of the meeting, a consensus had emerged that the use of molecular approaches to vector and disease control should be pursued as a real possibility and not as an impossible dream. On this basis, TDR established a 20-year plan for the development of malaria refractory mosquitoes."

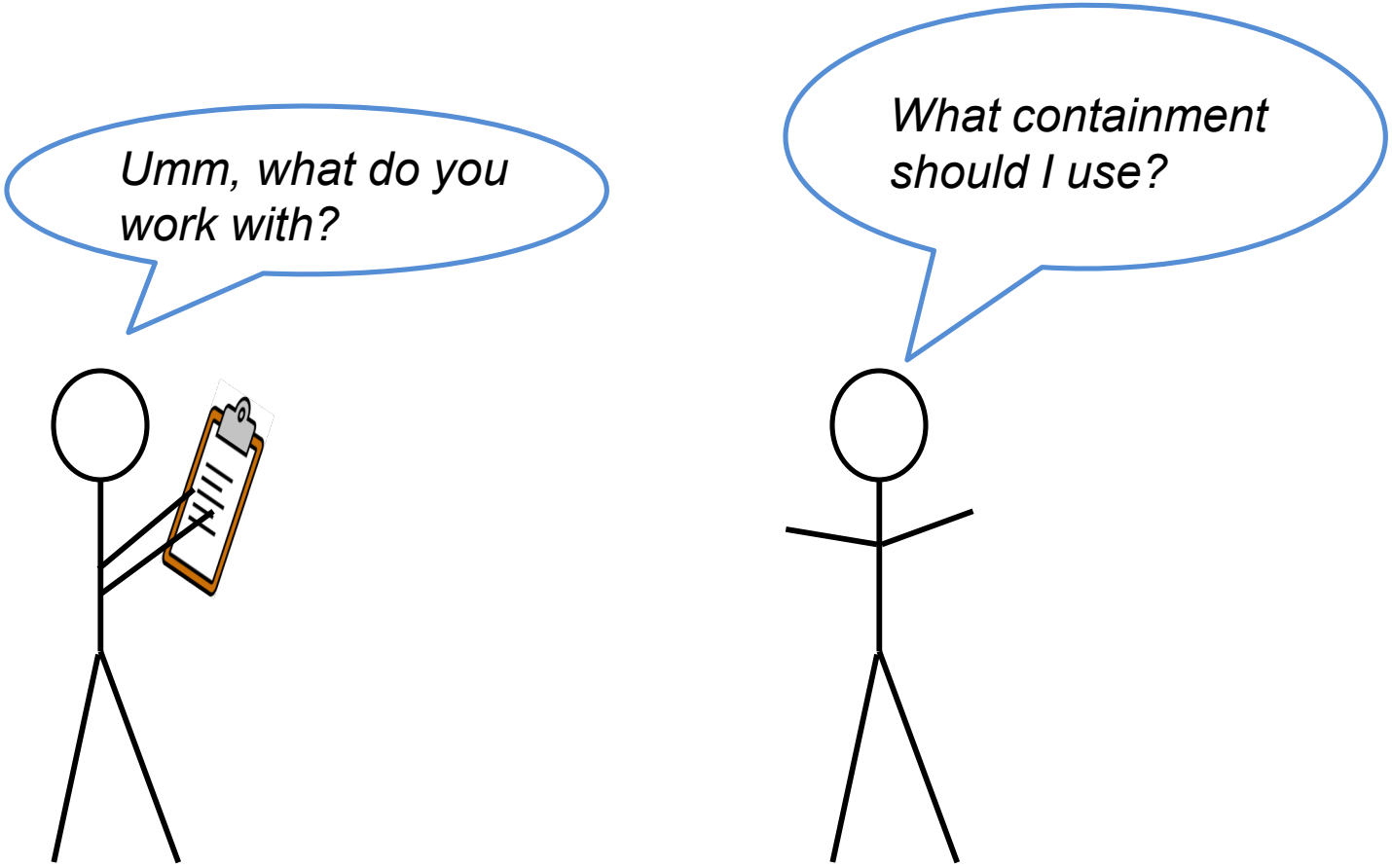
Gene Drive is:

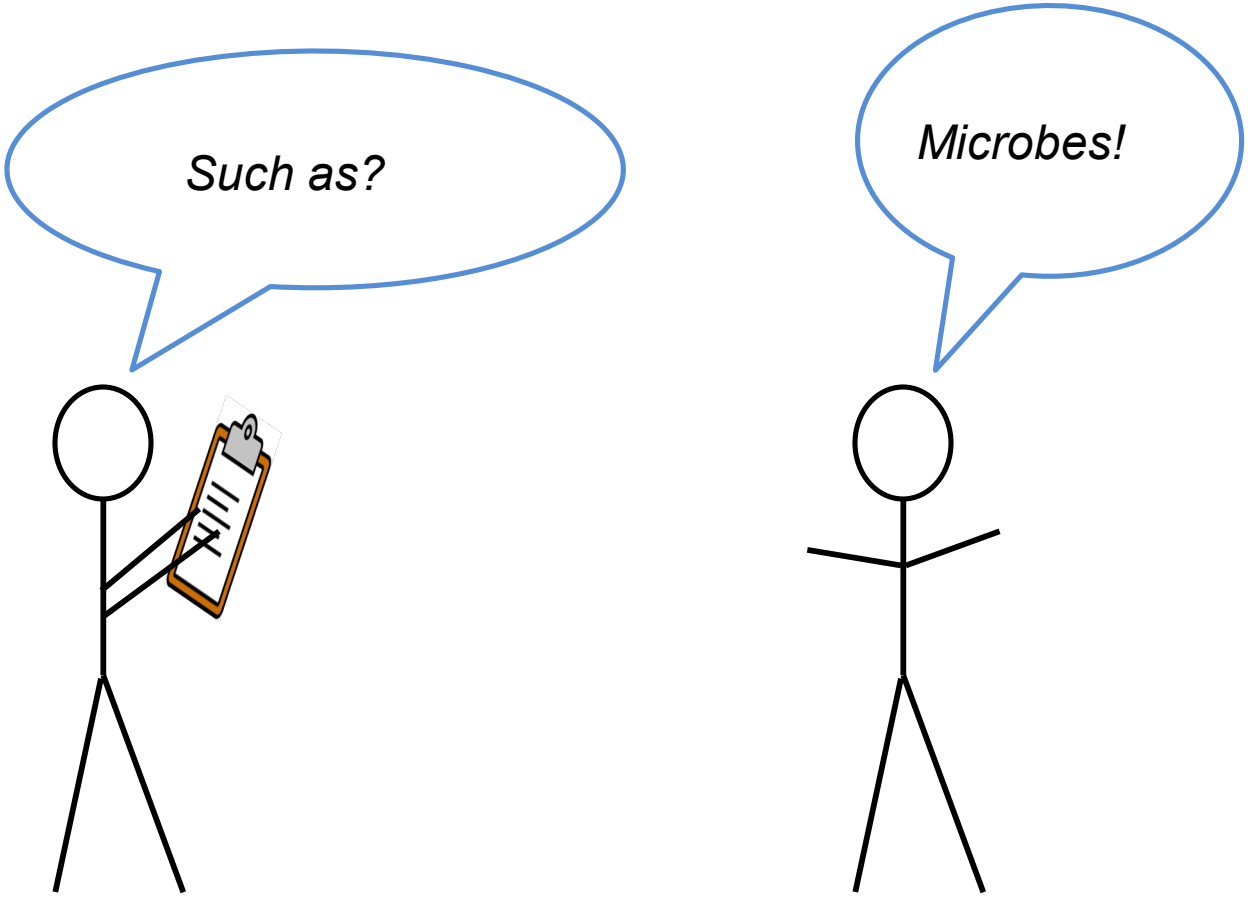
1) A completely new phenomenon in laboratory research

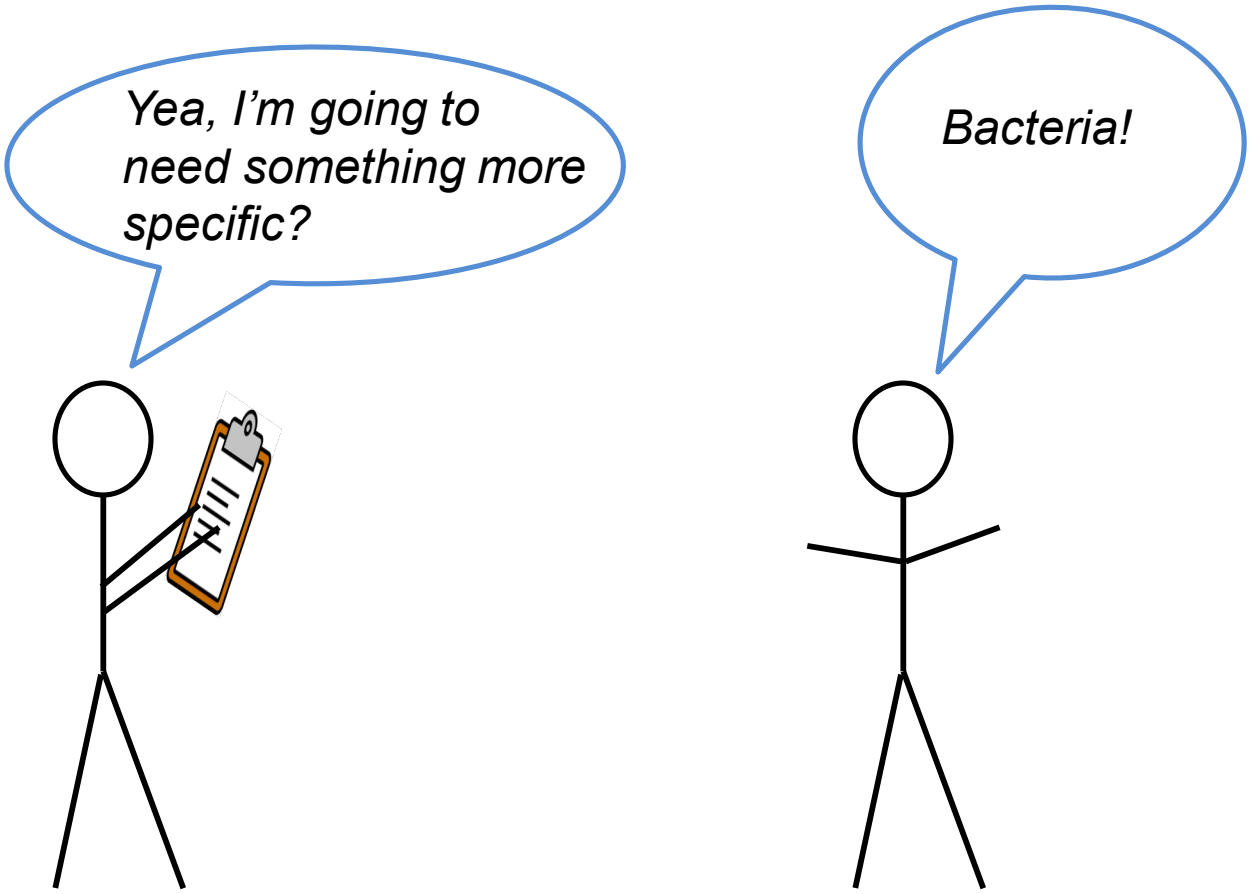
2) A process that completely breaks all laws of inheritance

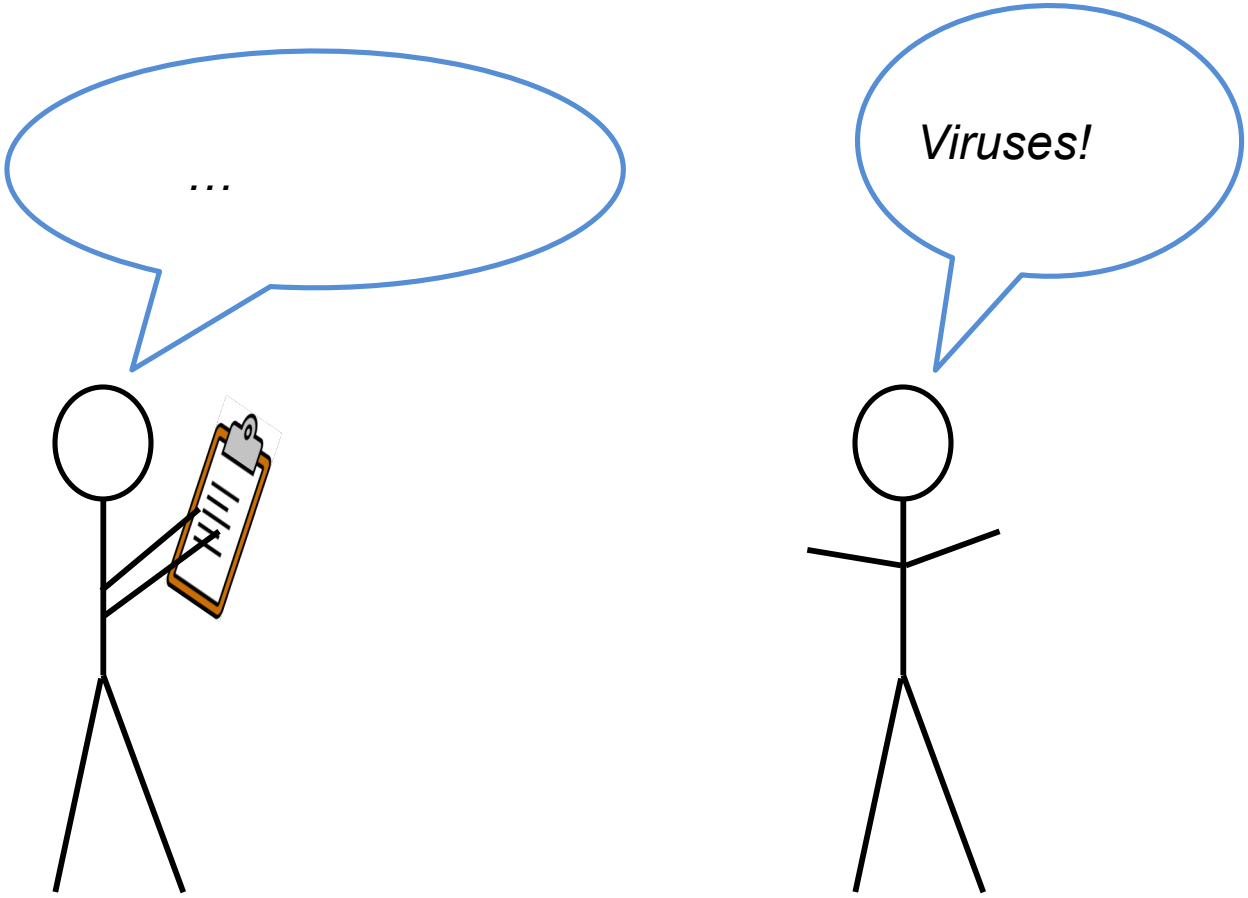
3) A really good way to get around town

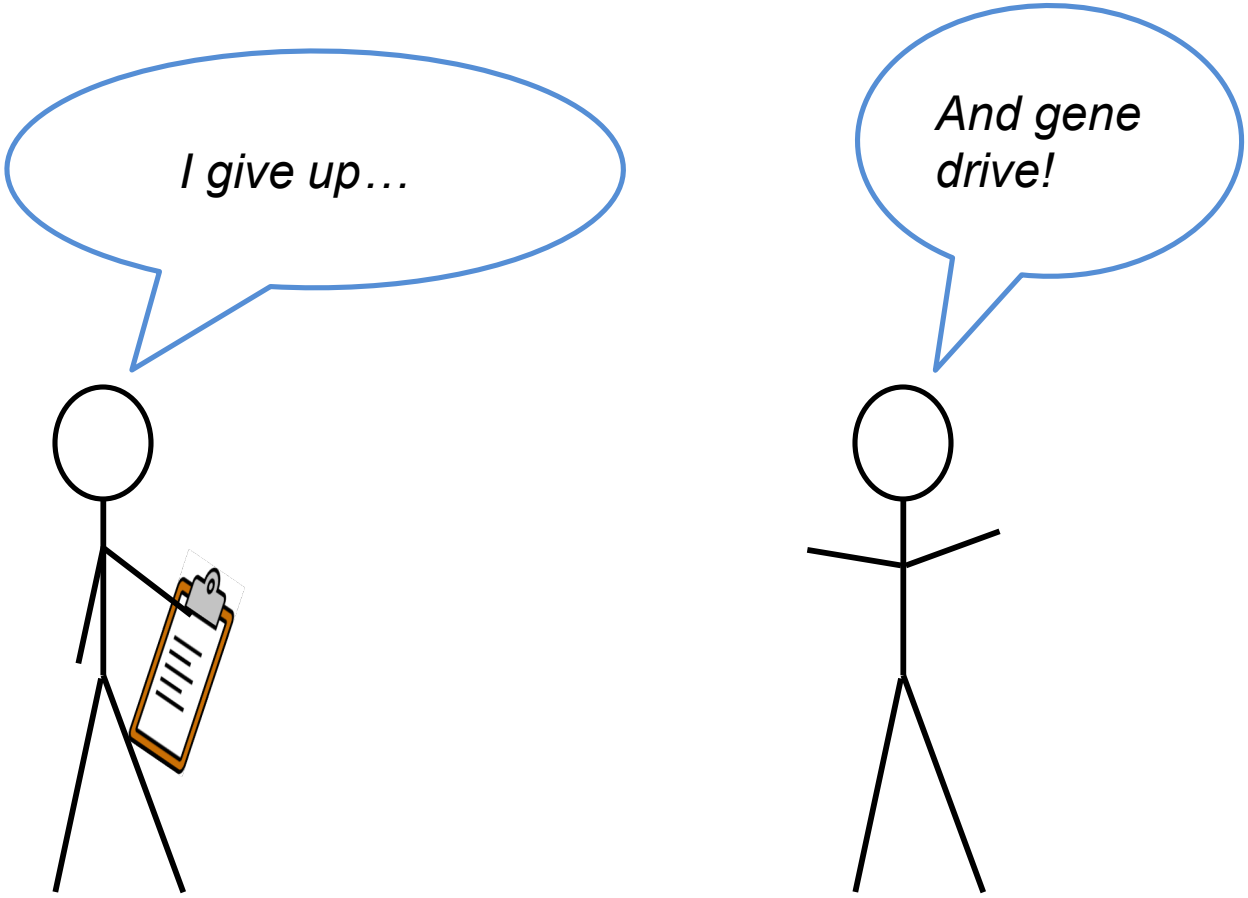
4) A term that has limited utility as a starting point for risk assessment.


Umm, what do you work with?
What containment should I use?

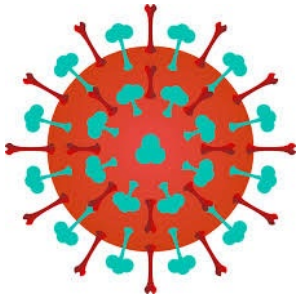

Such as?
Microbes!

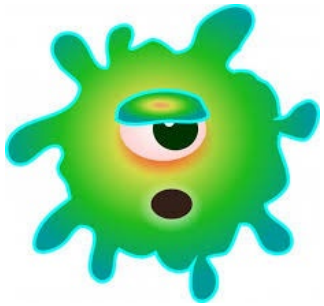

Yea, I'm going to need something more specific?
Bacteria!

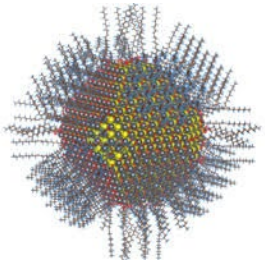

…
Viruses!


I give up…
And gene drive!

Agent

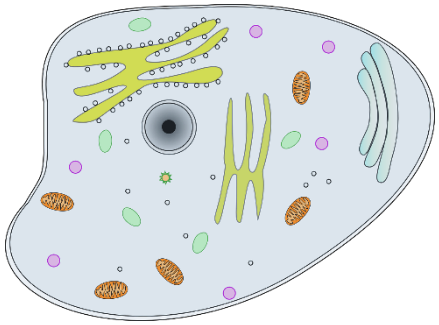


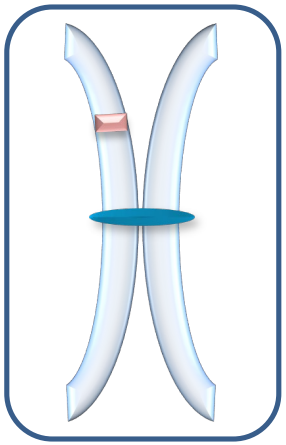




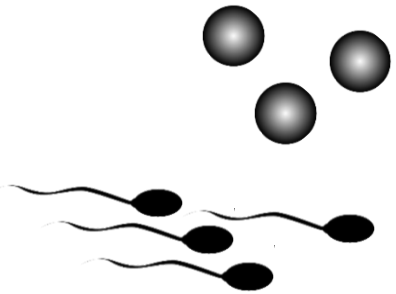
Risk Assessment does not change

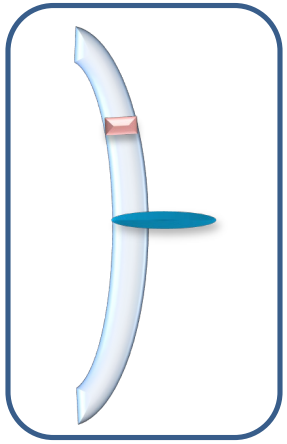
Mendelian inheritance of genes

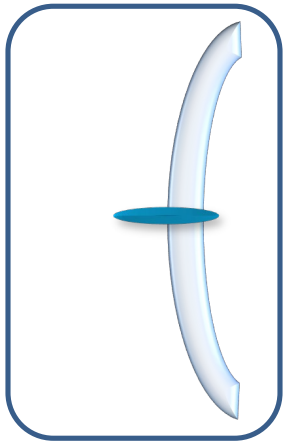




Diploid (2 copies of each chromosome)



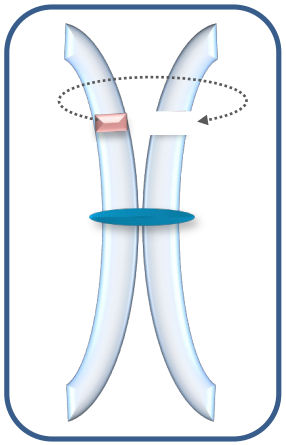




Half (50%) of gametes (eggs/sperm) carry the transgene

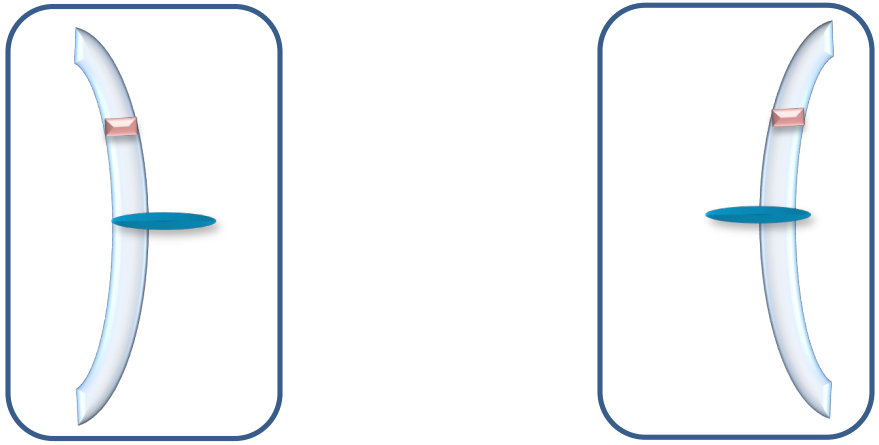
Haploid (1 copy of each chromosome)

Homing-based Gene Drive



Mode of inheritance is still the same

Diploid (2 copies of each chromosome)



All (100%) of gametes (eggs/sperm) carry the transgene

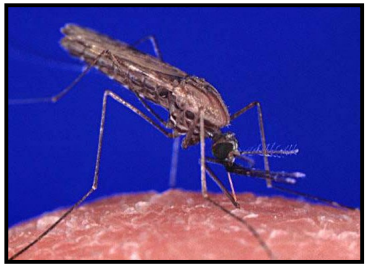
Haploid (1 copy of each chromosome)

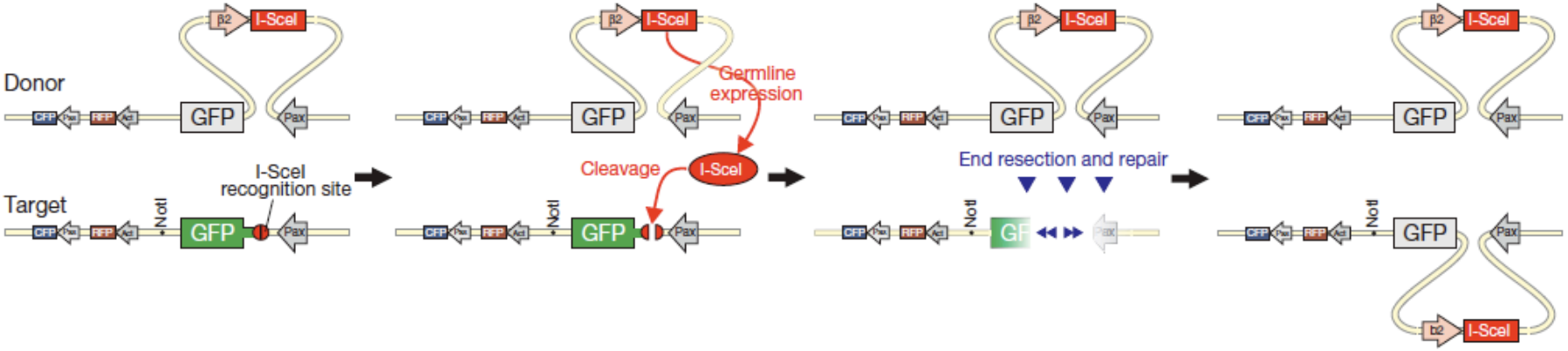
Homing-based Gene Drive

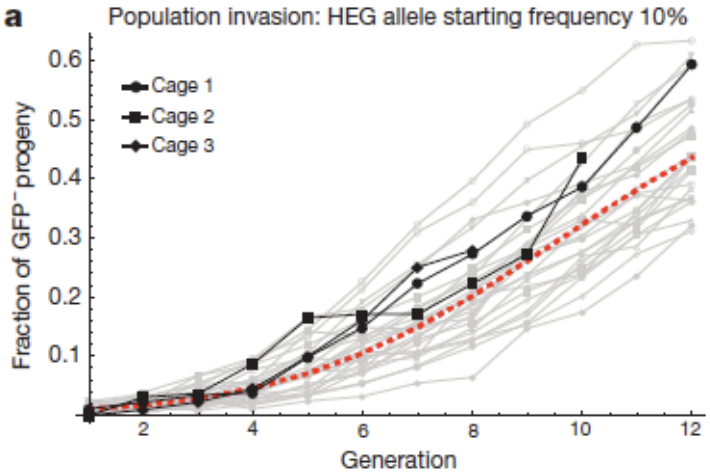
A synthetic homing endonuclease–based gene drive system in the human malaria mosquito

Nikolai Windbichler[1], Miriam Menichelli[1], Philippos Aris Papathanos[1], Summer B. Thyme[2,3], Hui Li[4], Umut Y. Ulge[4,5], Blake T. Hovde[6], David Baker[2,3,7], Raymond J. Monnat Jr[4,5,6], Austin Burt[1,8]* & Andrea Crisanti[1,9]*

212 | NATURE | VOL 473 | 12 MAY 2011







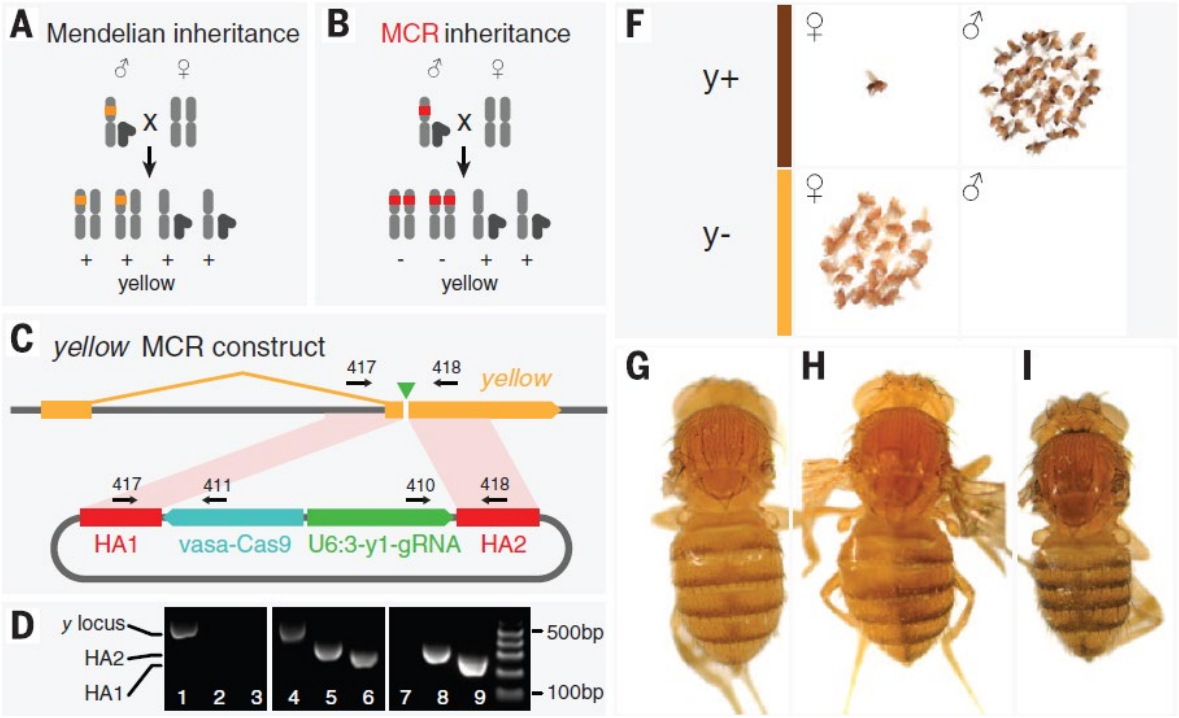
Homing-based Gene Drive

GENOME EDITING

The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations

Valentino M. Gantz* and Ethan Bier*

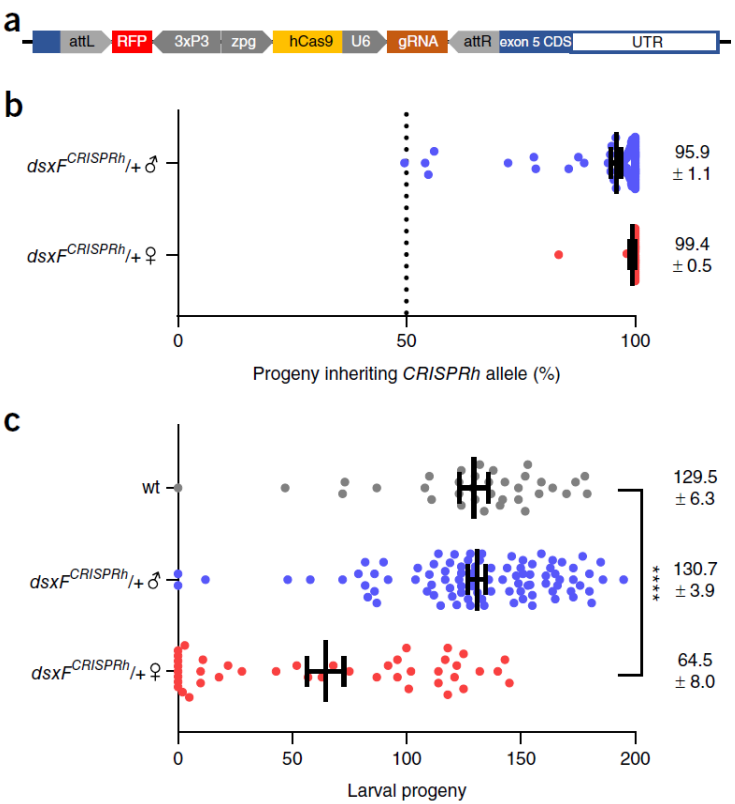
2015 Science ;348(6233):442-4.

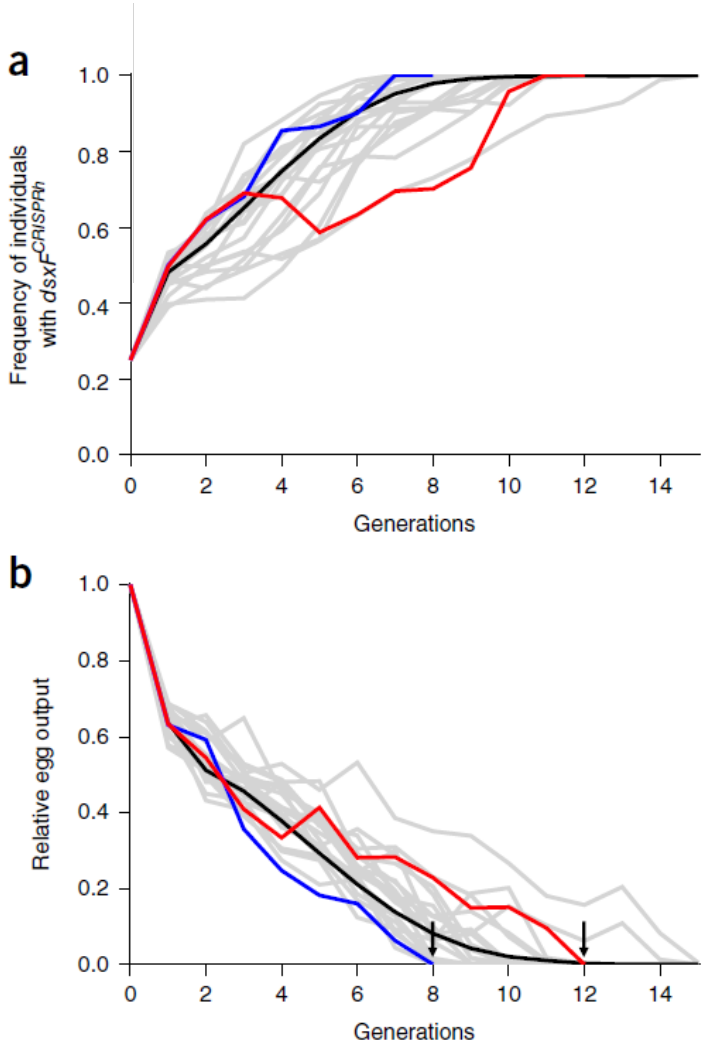


A new gene drive target shows no signs of resistance development

A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes

Kyros Kyrou[1,2], Andrew M Hammond[1,2], Roberto Galizi[1], Nace Kranjc[1], Austin Burt[1], Andrea K Beaghton[1], Tony Nolan[1] & Andrea Crisanti[1]

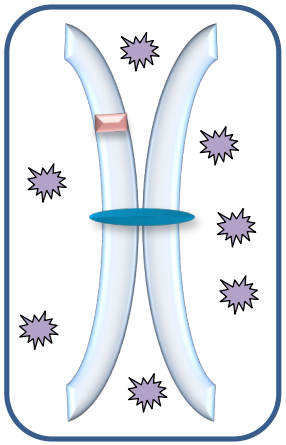




Homing-based gene drive: Same mechanism, completely different risk profiles

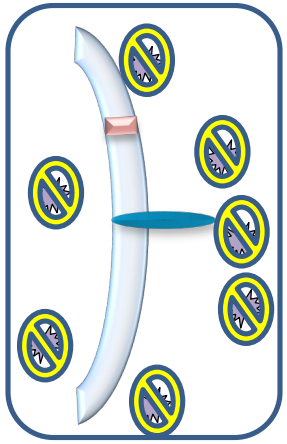
Nuclease	*Target*		*Potential for spread in environment*
I-SceI	I-SceI target		**None**, target site not present in any natural population
CRISPR	yellow		**Limited**, as gene is not essential and resistance was selected for rapidly
CRISPR	Gene involved in female sex determination		**Likely**, resistance was not selected for in laboratory populations. Target site conserved in wild populations.

Selective survival gene drive



Mode of inheritance is still the same

Diploid (2 copies of each chromosome)



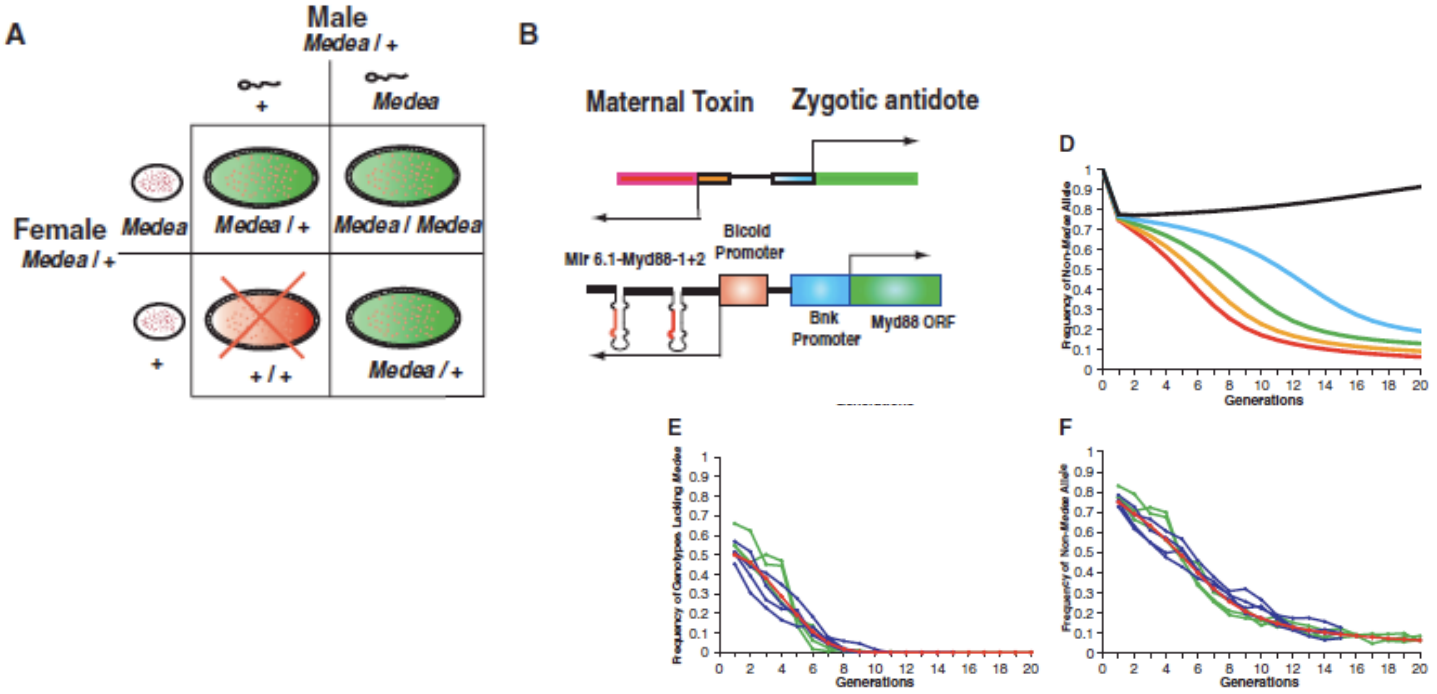
All (100%) of gametes (eggs/sperm) carry the transgene

Haploid (1 copy of each chromosome)

Gene Drive: MEDEA

A Synthetic Maternal-Effect Selfish Genetic Element Drives Population Replacement in *Drosophila*

Chun-Hong Chen,[1] Haixia Huang,[1] Catherine M. Ward,[1] Jessica T. Su,[1]
Lorian V. Schaeffer,[1] Ming Guo,[2] Bruce A. Hay[1]*



Concept can be adapted for targeting any maternally deposited transcript vital for embryo survival; Very stable, highly invasive.

Selective Survival: X-shredding in *An. gambiae*

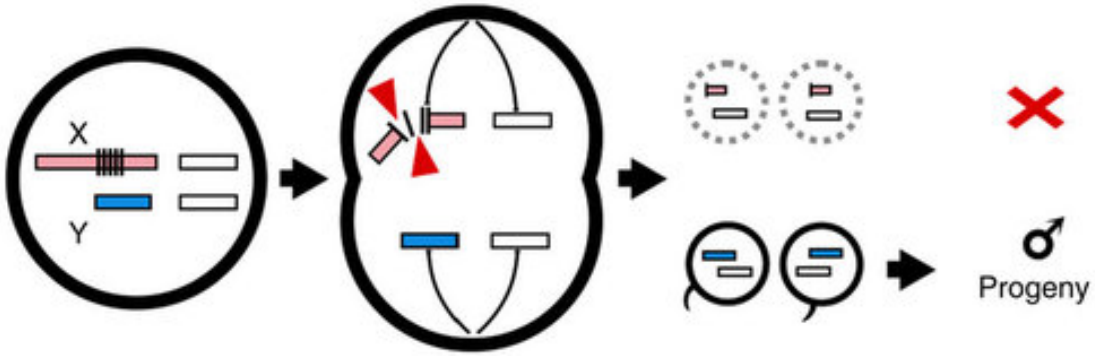
ARTICLE

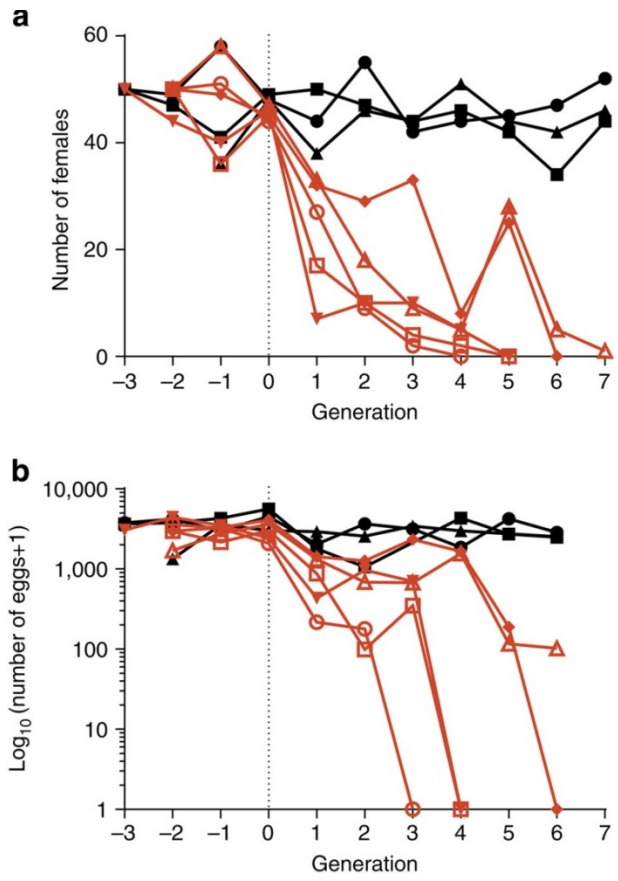
Received 12 Mar 2014 | Accepted 28 Apr 2014 | Published 10 Jun 2014

DOI: 10.1038/ncomms4977 OPEN

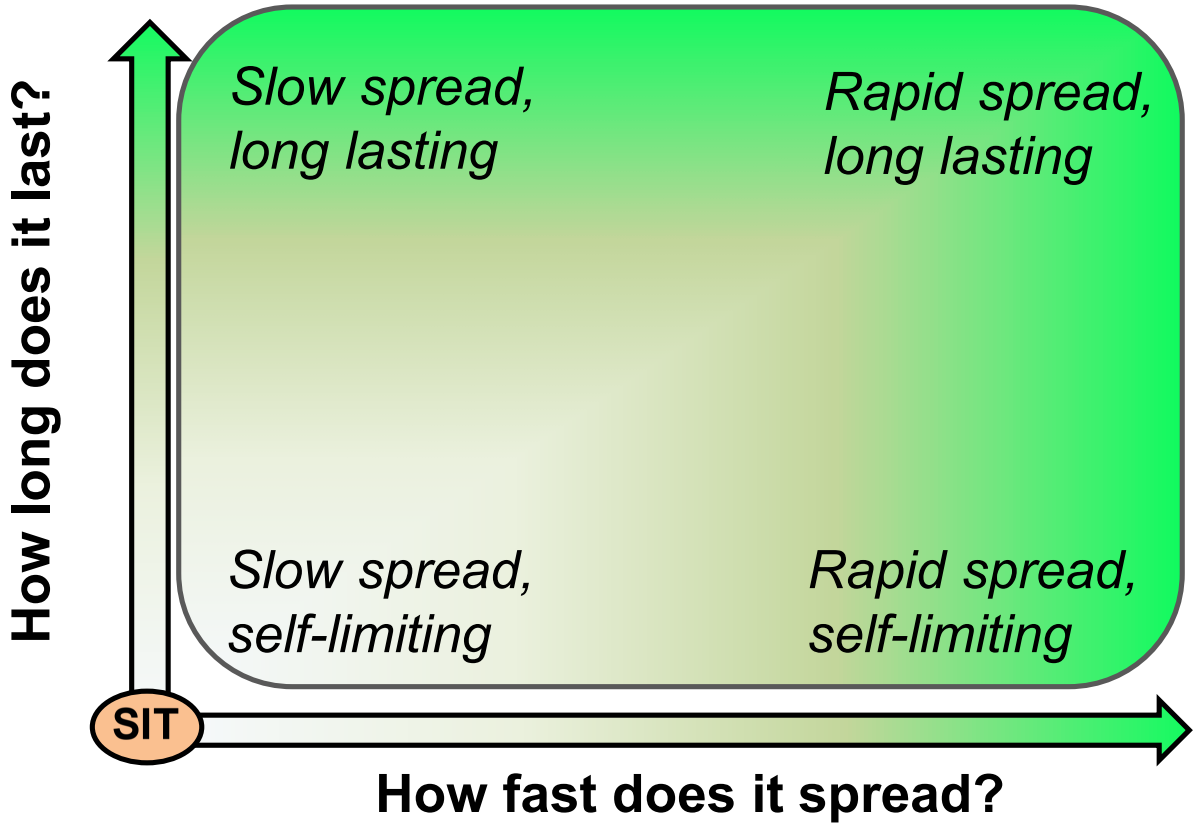
A synthetic sex ratio distortion system for the control of the human malaria mosquito

Roberto Galizi[1,2], Lindsey A. Doyle[3], Miriam Menichelli[1], Federica Bernardini[1], Anne Deredec[1], Austin Burt[1], Barry L. Stoddard[3], Nikolai Windbichler[1,*] & Andrea Crisanti[1,2,*]

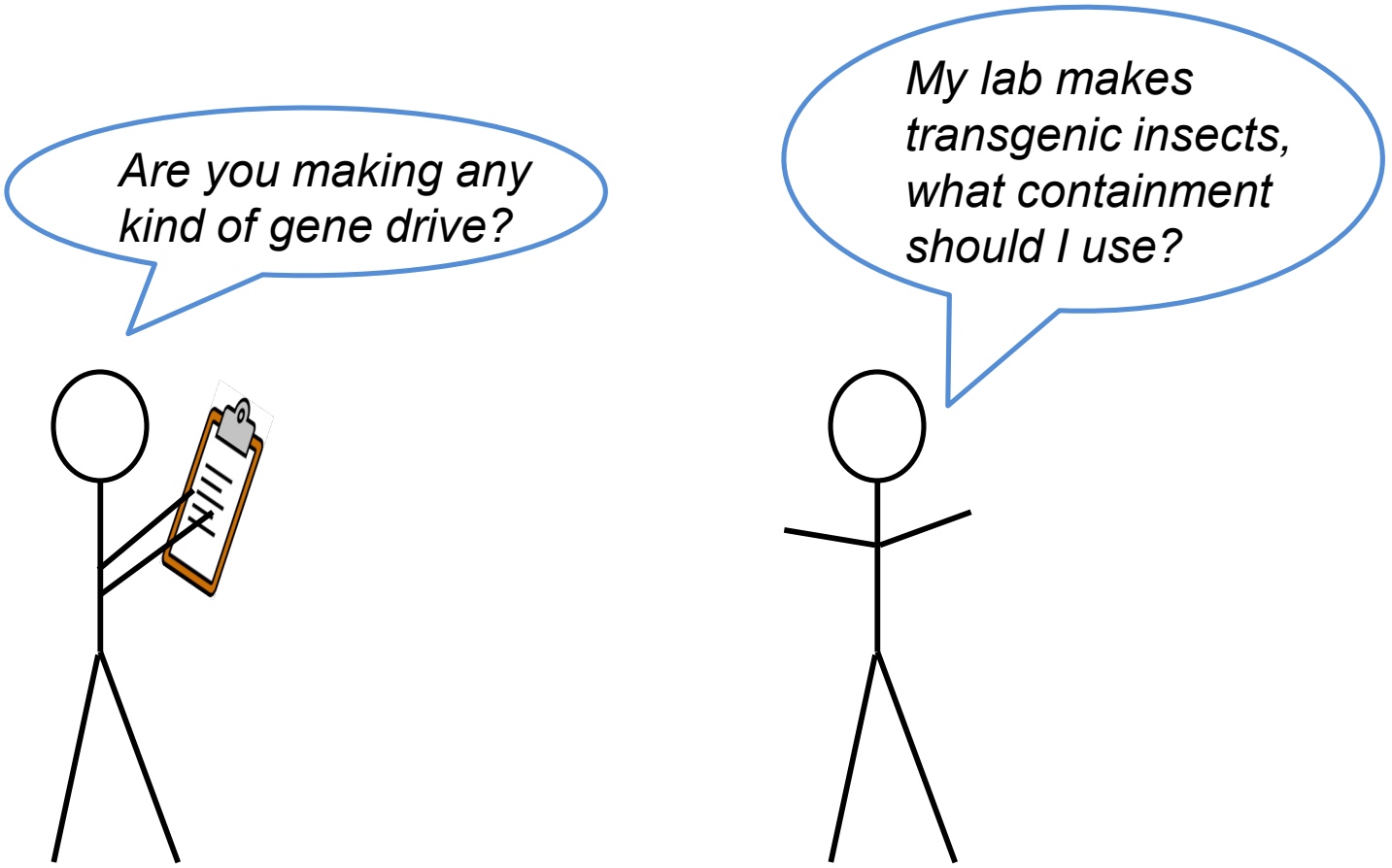


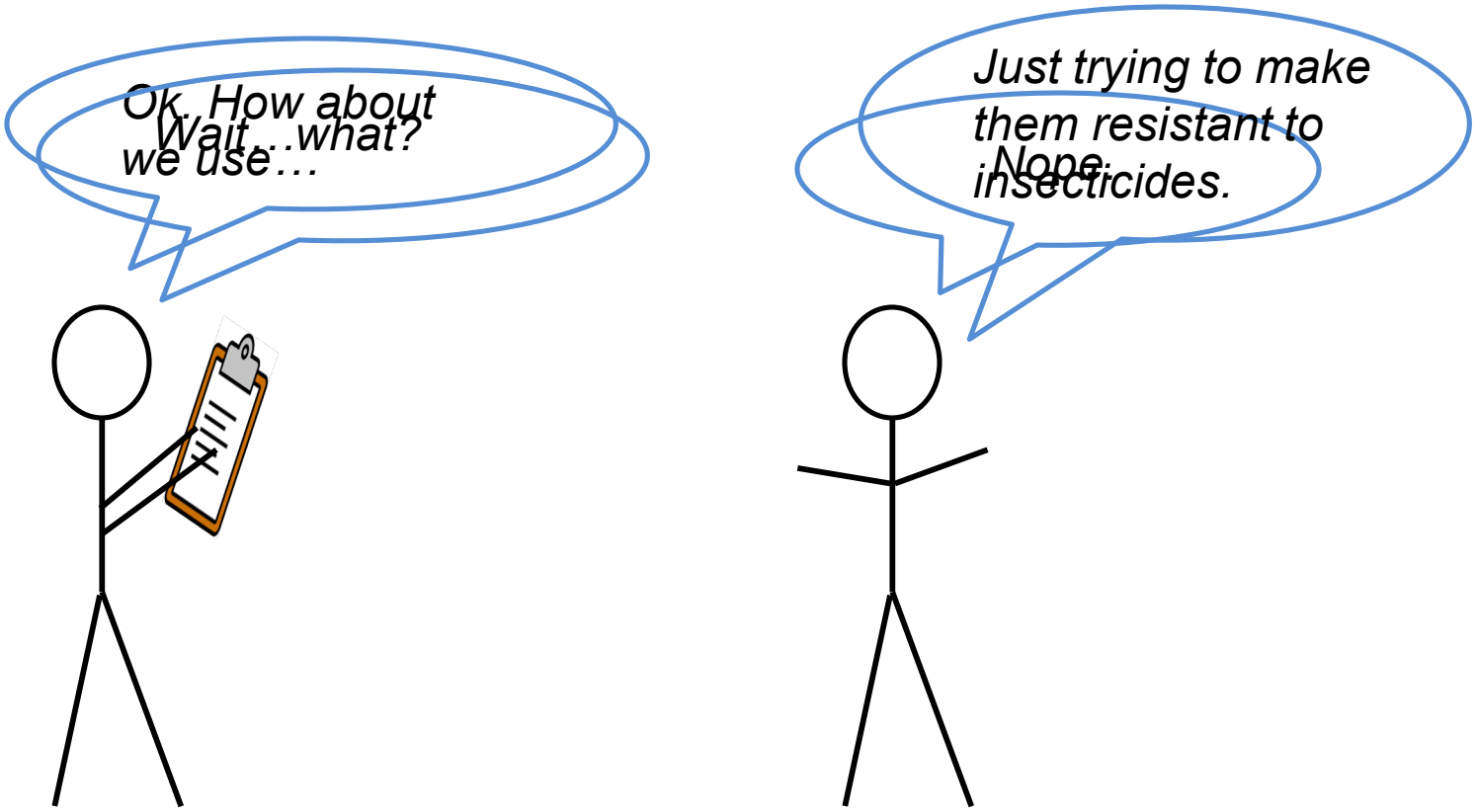


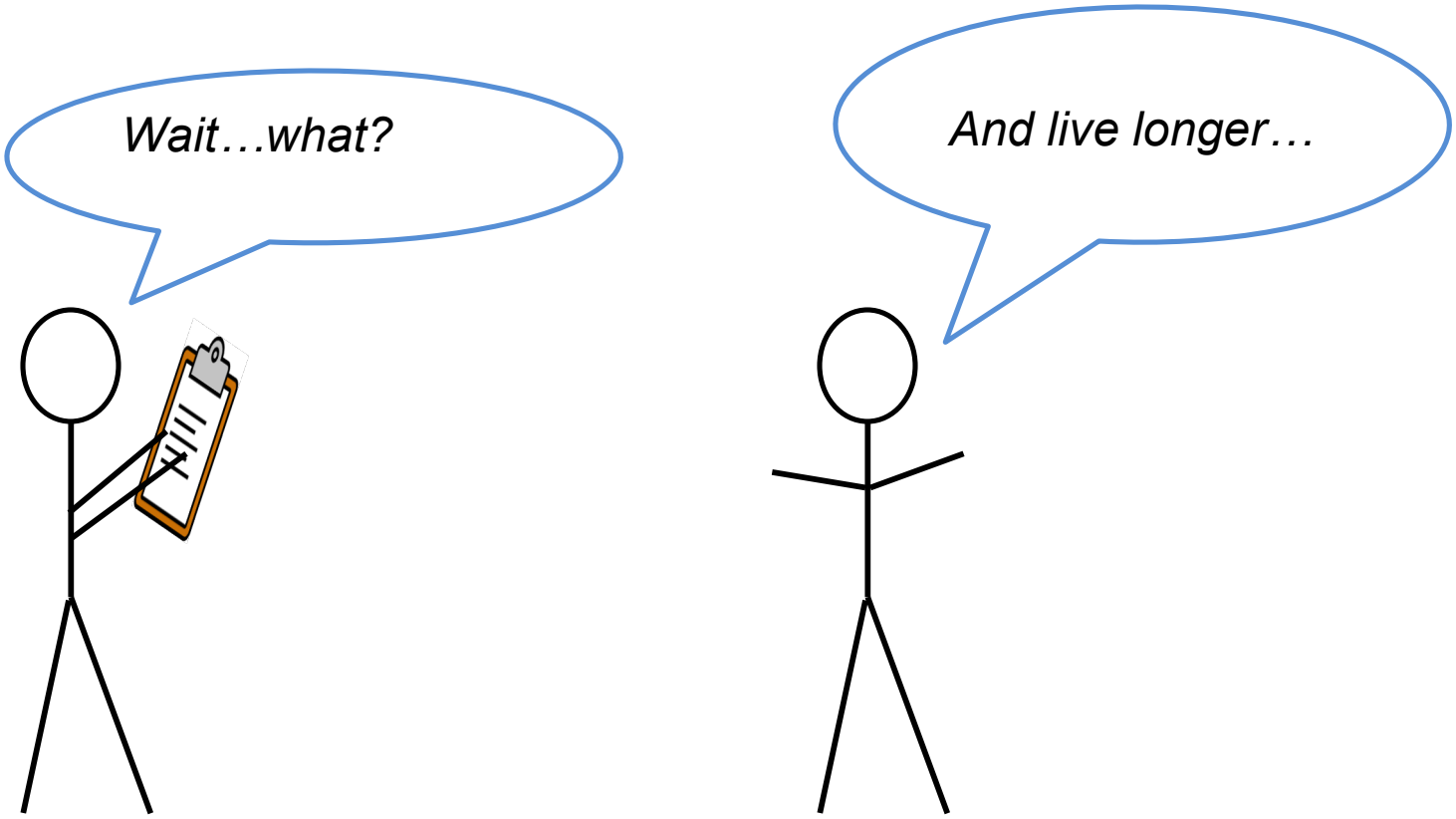
Any attempt to begin risk assessment based on the use of a particular technology has little chance of keeping up

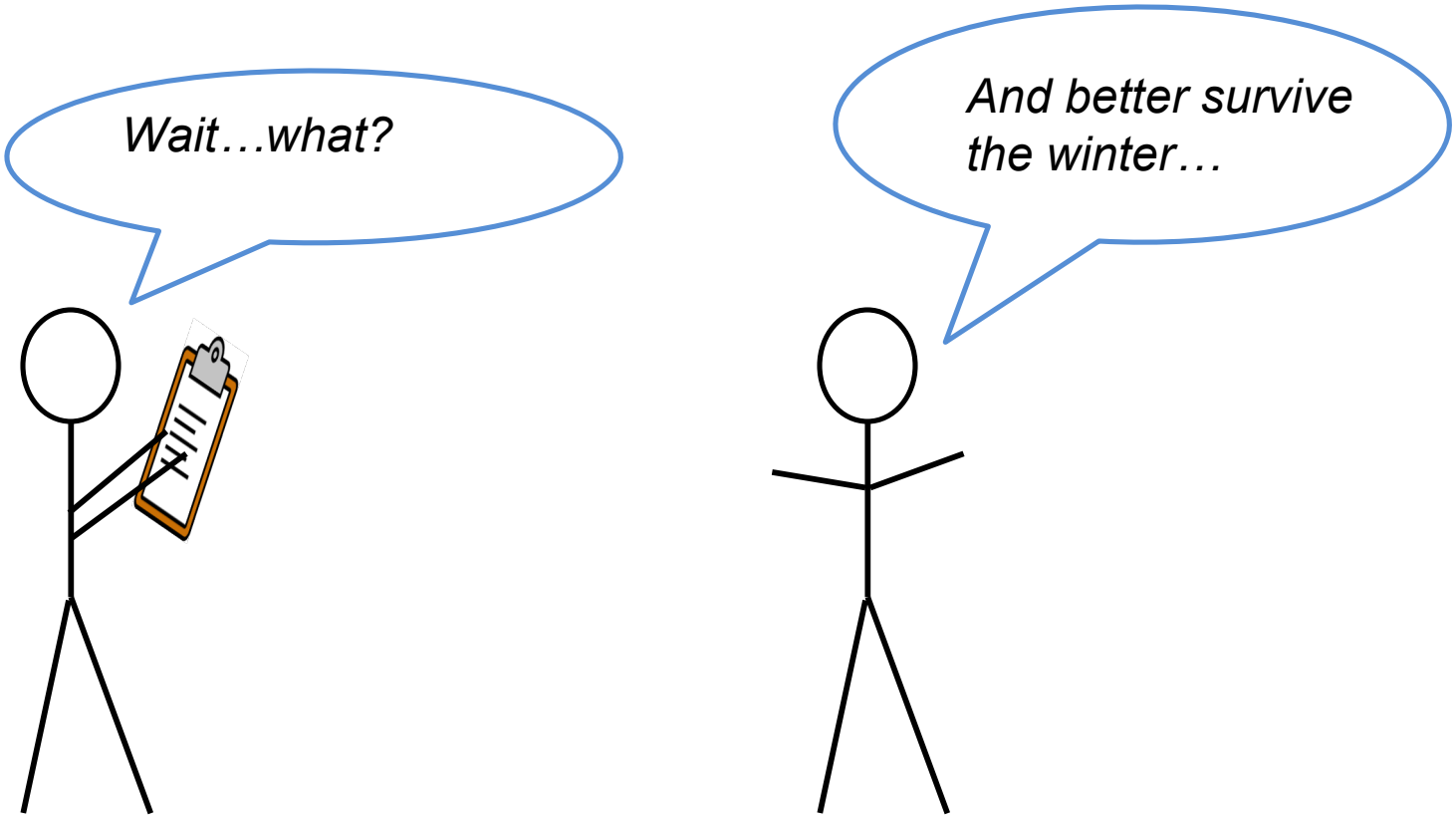


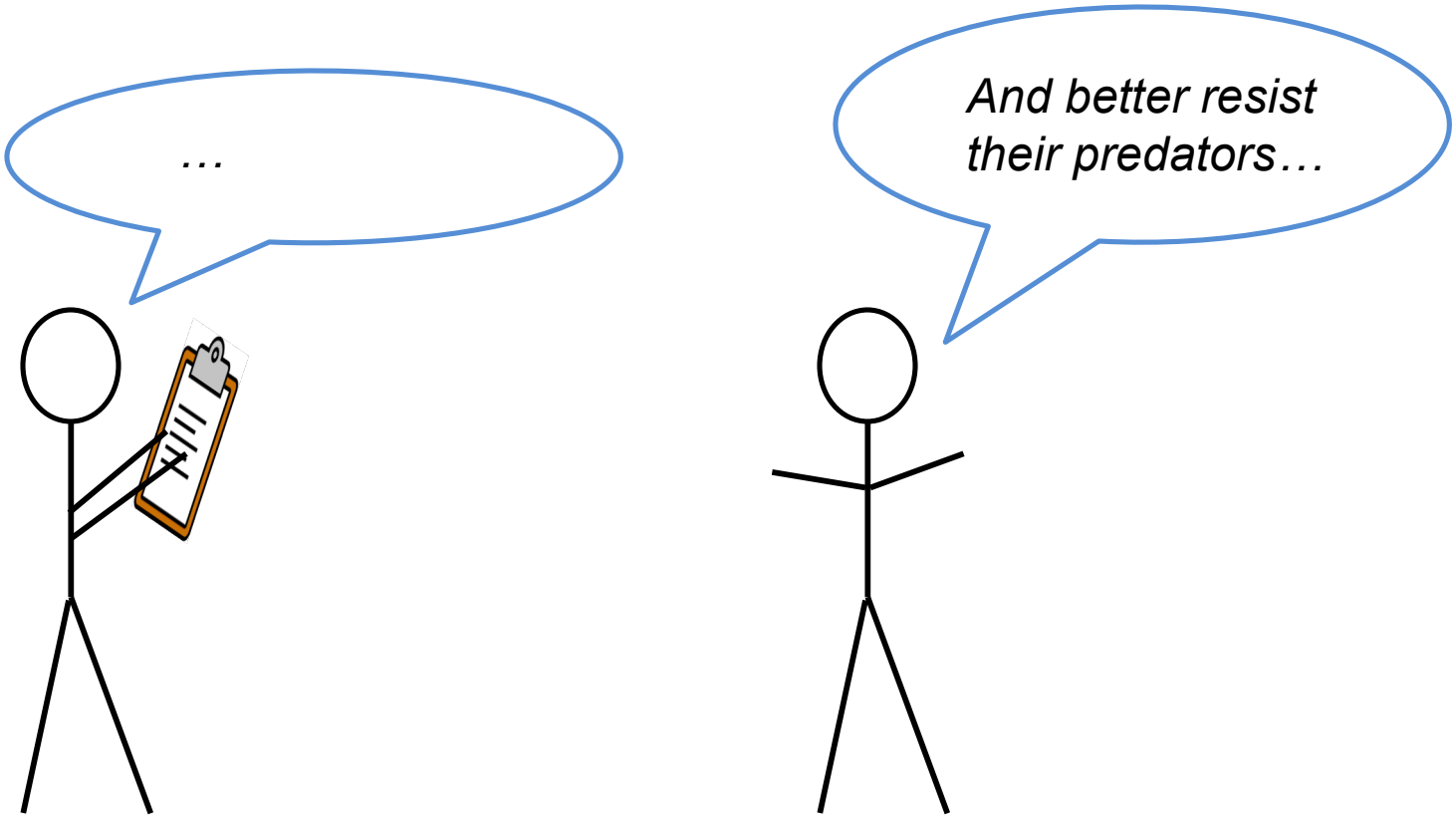
New technologies that might also result in gene drive have likely not been built yet


Are you making any kind of gene drive?
My lab makes transgenic insects, what containment should I use?


Ok. How about we use…
Wait…what?
Just trying to make them resistant to insecticides.
Nope.


Wait…what?
And live longer…


Wait…what?
And better survive the winter…


…
And better resist their predators…

Recombinant DNA has been secured through implementation of the NIH guidelines

Then	***Now***
Long-term colonization reduces fitness	Colonization not necessary
Random integrations	Precise integrations
Genetic bottlenecks due to transgenesis procedures further reduce fitness	Multiple identical integrations can limit genetic bottlenecks
Few organisms that could be transformed	Many organisms that could be transformed
Little genetic/genomic data to develop regulatory control elements	Immense genetic/genomic data to develop regulatory control elements
Little knowledge of genetic basis of important phenotypes	Improving knowledge of genetic basis of important phenotypes

A updated starting point for risk assessment of laboratory-based transgenic organisms

- Is the introduced transgene (or combination of transgenes) likely to persist or spread through a natural population if introduced?

Yes

Includes some gene drive transgenes, but also transgenes that provide a net benefit

No

Includes some gene drive transgenes, but also transgenes that are neutral or confer a disadvantage

Risk Assessment– Infectious Agents

Risk Group	Definition	Examples
1	Agents that are not associated with disease in healthy adult humans	*B. subtilis*
2	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are ***often*** available	*Salmonella*
3	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions ***may*** *be* available (high individual risk but low community risk)	Prions, HIV types 1 and 2
4	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are ***not usually*** available (high individual risk and high community risk)	Lassa virus, Ebola virus;

Safety Considerations – Transgenes

Risk Group	Definition	Gene Drive	No Gene Drive
?	Transgenes that are less fit than wild-type and cannot persist/spread in the wild	*Homing-drive (no target), Underdominance*	*EGFP inserted into vital gene*
?	Transgenes that may persist in the wild in the short term, but cannot spread	*Homing-drive (resistance alleles can be selected, target site limited)*	*EGFP inserted into neutral location*
?	Transgenes that may spread/persist in the wild in the long-term, but cannot transfer to new species	*Homing-drive (resistance alleles cannot be selected)*	Gene than confers increased disease/pesticide resistance (no hybridization)
?	Transgenes that are likely to spread/persist in the wild and present a significant risk of horizontal transfer to new species.	*Homing-drive (resistance alleles cannot be selected), target site conserved in related species*	Gene than confers increased disease/pesticide resistance (hybridization)

Containment conditions/practices set on case-by-case basis

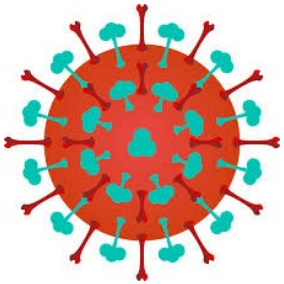
Challenges for Institutional review of transgenic arthropod research

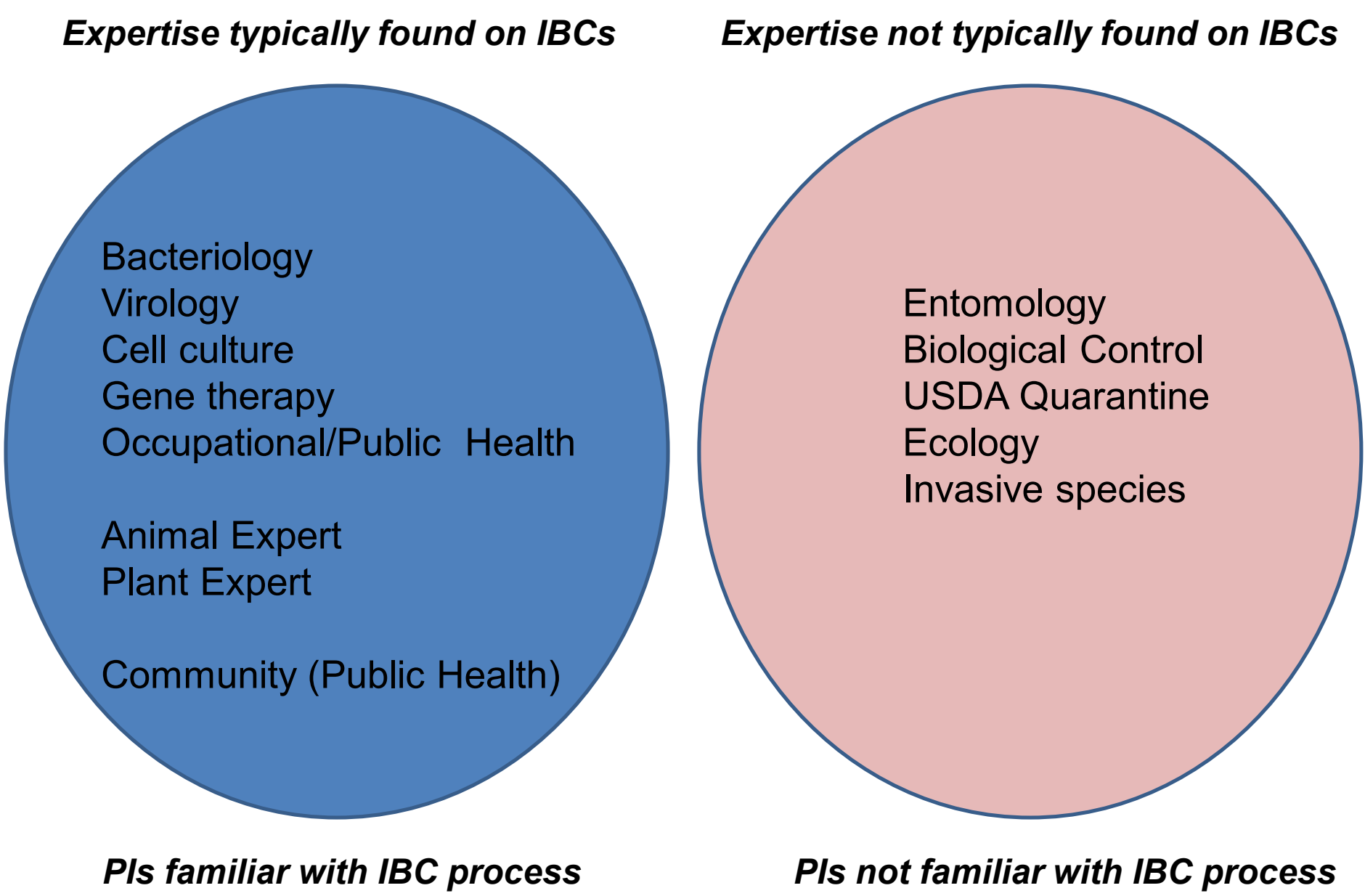
Transgenic arthropods alone present little risk to the health and safety of laboratory workers and thus may not be given as thorough a review as pathogen-based work or human gene therapy.

NIH/BMBL provides little to no specific guidance on containment for arthropods.

PIs may be less familiar with the NIH guidelines, principles of biosafety.

Biosafety: Protect those closest to danger, and everyone else is protected too.




Expertise typically found on IBCs
Expertise not typically found on IBCs
Bacteriology
Virology
Cell culture
Gene therapy
Occupational/Public Health
Animal Expert
Plant Expert
Community (Public Health)
Entomology
Biological Control
USDA Quarantine
Ecology
Invasive species
PIs familiar with IBC process
PIs not familiar with IBC process

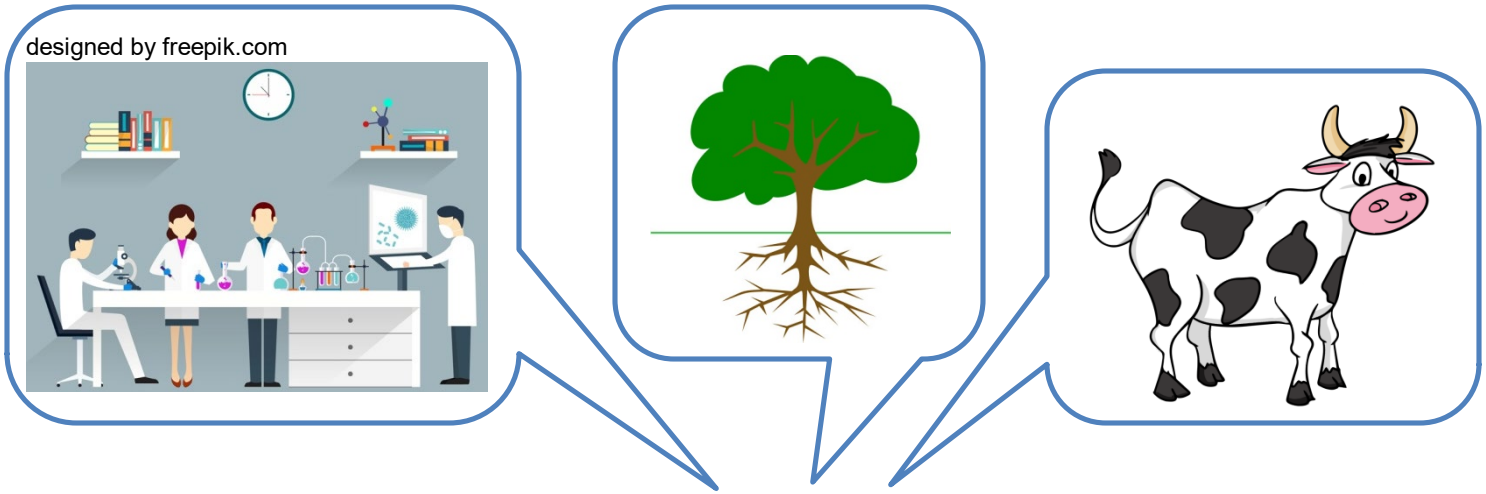
Risk assessment for laboratory research using transgenic arthropods

Transgenic arthropod

Section V-M. Determination of whether a ~~pathogen~~ has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of ~~plant diseases, crops~~, and ecosystems in the geographic area of the research.

???

Containment practices



- **Physical (Appendix G, P, Q)**
  - **Practices**
  - **Equipment**
  - **Facilities**
- **Biological (Appendix I)**
  - **Survival**
  - **Transmission**

No specific guidance for arthropod containment

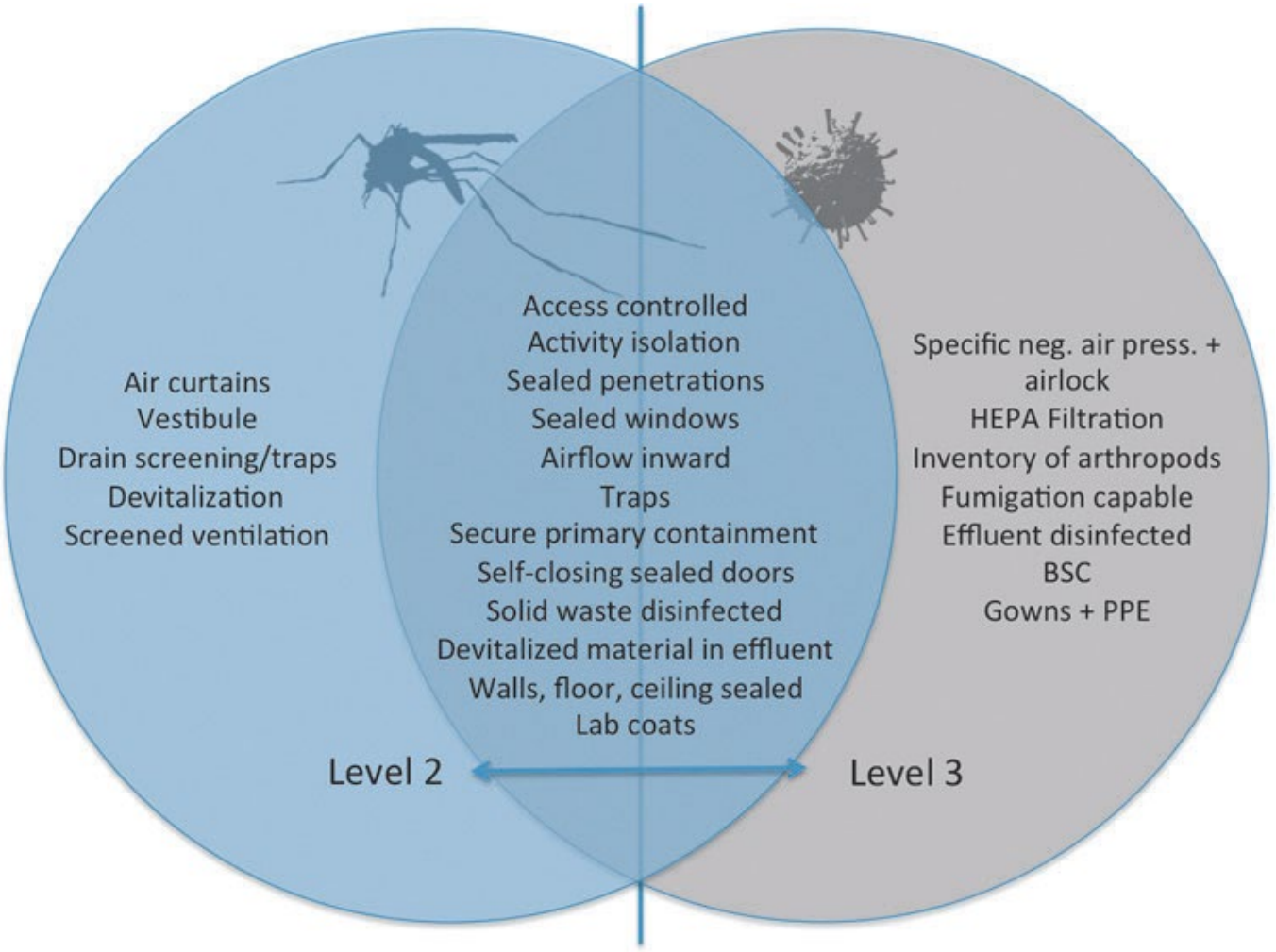
Modified from: NIH/OBA

Arthropod Containment Guidelines

- Developed by a subcommittee of the American Society of Tropical Medicine and Hygiene in 2003.
- Containment levels 1-4 to mirror handling pathogen-infected arthropods (based on agent BSL)
- Containment ACL-2 designated for genetically-modified arthropods.
- ACG do not mention gene drive, but current interpretations utilize ACL-2 as well.

ACG are not binding and may or may not be utilized by PIs/IBCs

ACGs are structured to contain both the vector and the microbial pathogen



Benedict et al (2018) VBZD

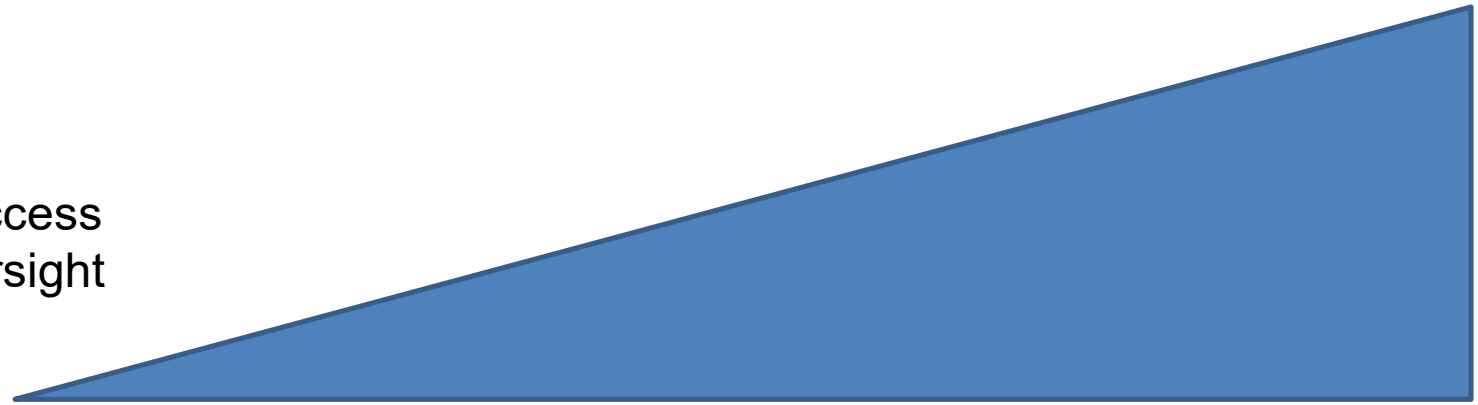
Risk Management

No different that work with pathogens:

- Work practices (SOPs, biosafety manuals)
- Safety equipment
- Personal protective equipment
- Training needs
- Facility design
- Security

As potential hazard increases, so do risk management strategies

Engineering controls
PPE
Training
Restricted access
Centralized oversight



Broad access
Self-oversight

Genetic mitigation approaches

Kill switches

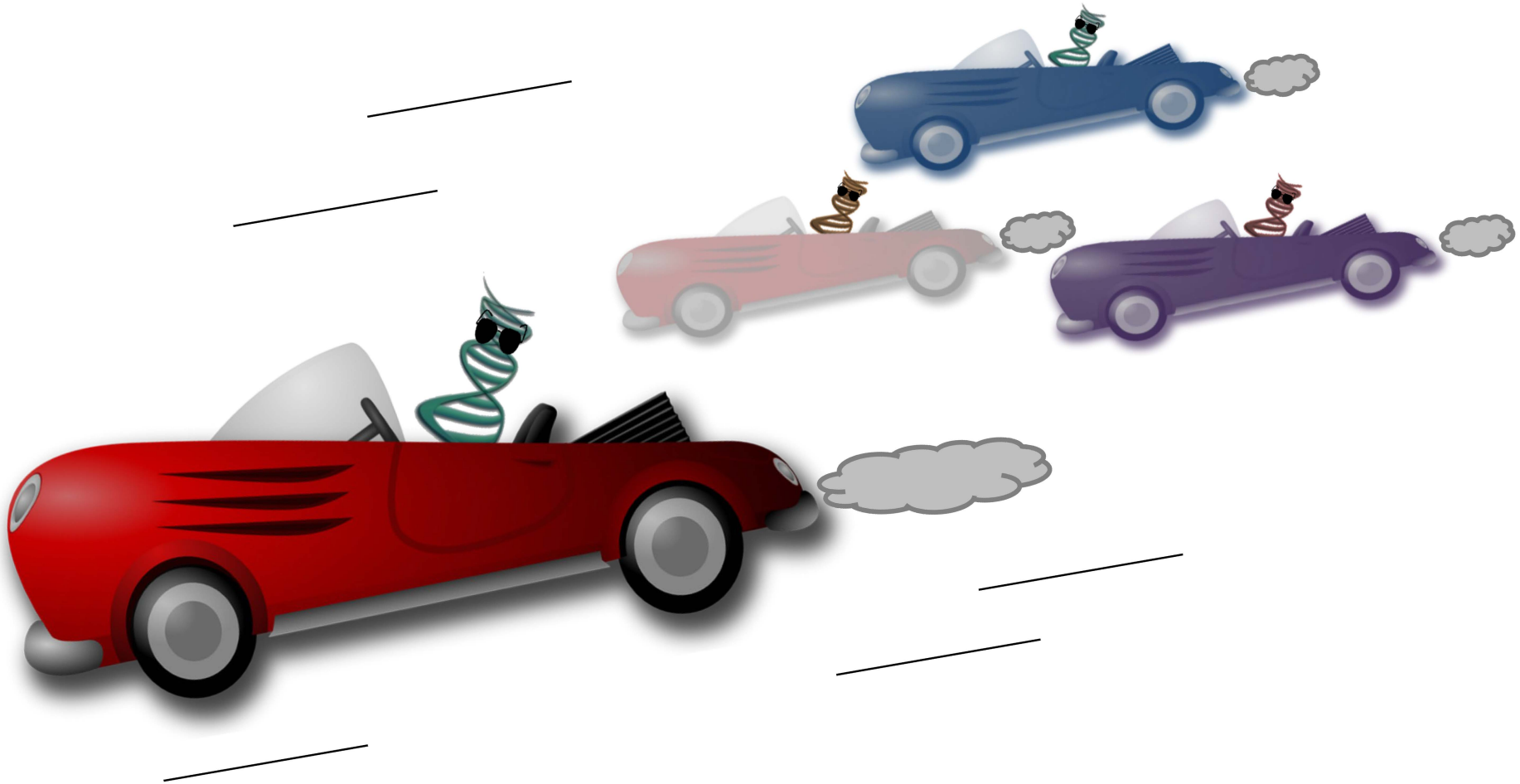
Inducible triggers

Split drives

Synthetic target sites

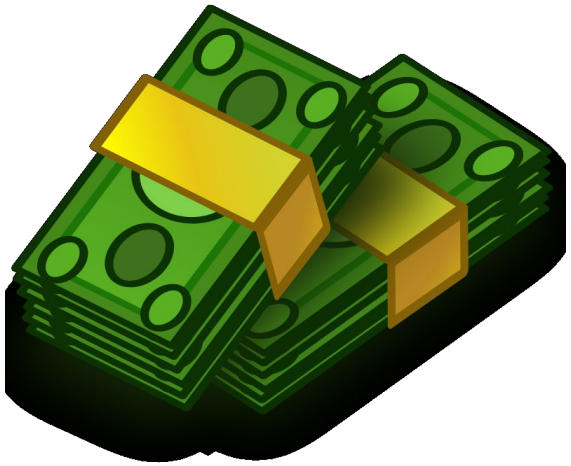
May also be experimental technologies

Need independent validation



The unfortunate history of new technologies

Product ***Profit*** ***Problems***



Changing the paradigm will take time

Problems ***Basic Research*** ***Product***