

CRISPR Questions

- What are some of the potential pitfalls you could see happening on a societal scale if human genome editing were allowed without regulation in place?
- What are some methods you could foresee using to combat these drawbacks?
- How can the scientific and legal communities engage the public in a meaningful way to achieve a consensus on appropriate CRISPR policies and regulations?
- What are some questions you would include in an Human Rights Impact Assessment (HRIA) focused on human genome editing?

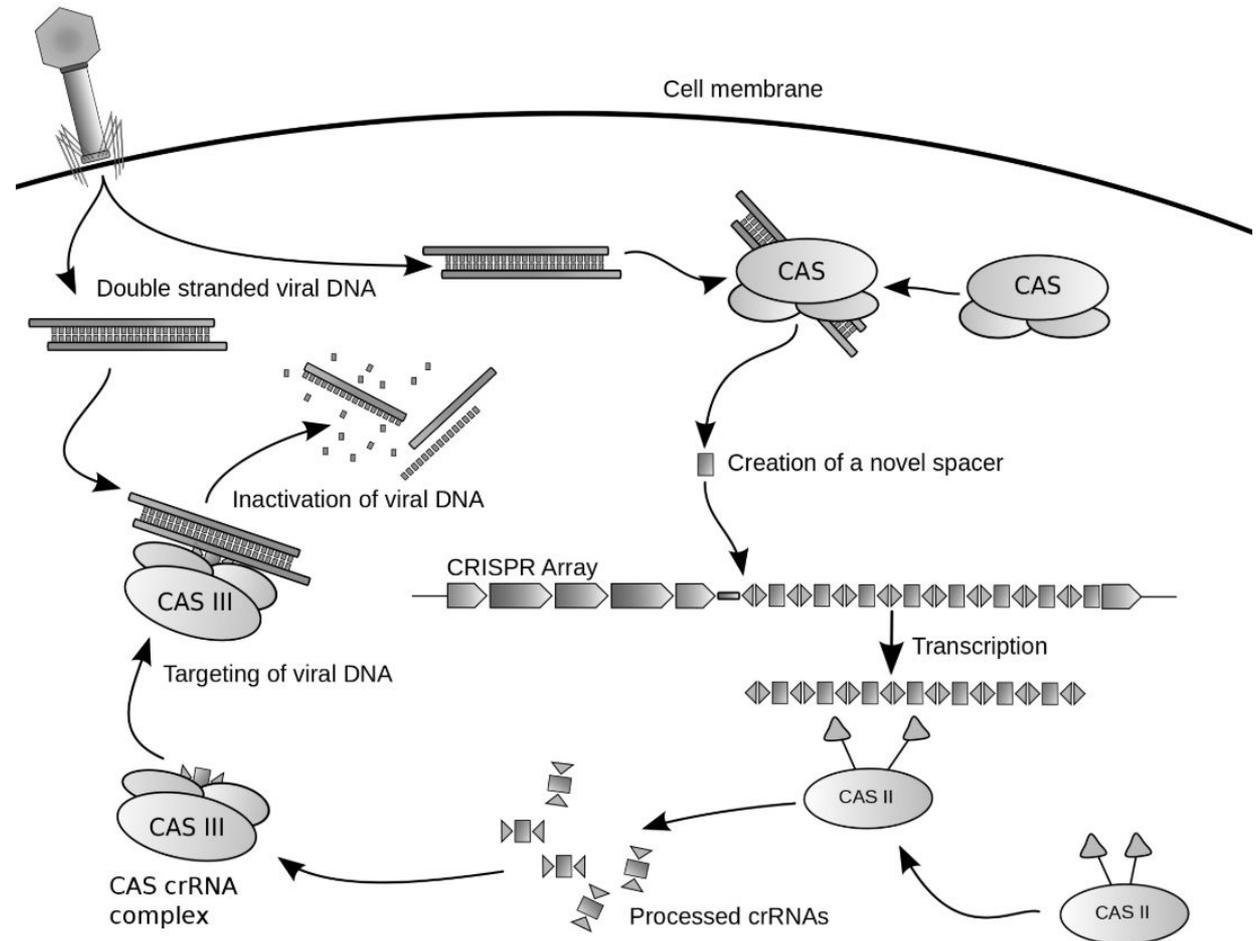
Human Genome Editing with CRISPR

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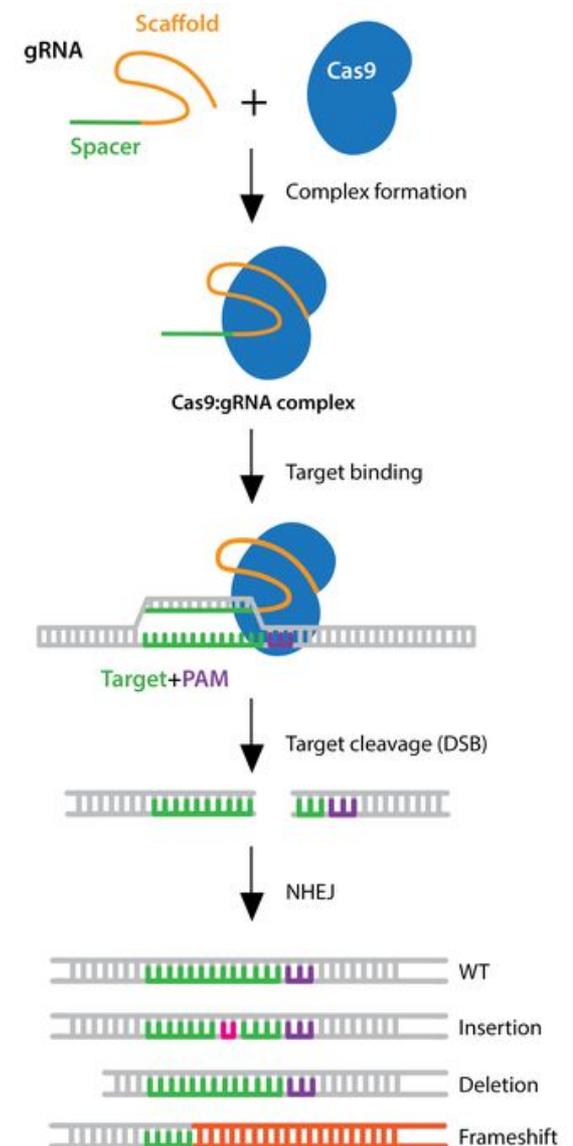
A Primer on the Science of CRISPR

- CRISPR provides a mechanism for bacterial adaptive immunity against bacteriophages
- Selective recognition and destruction of phage DNA



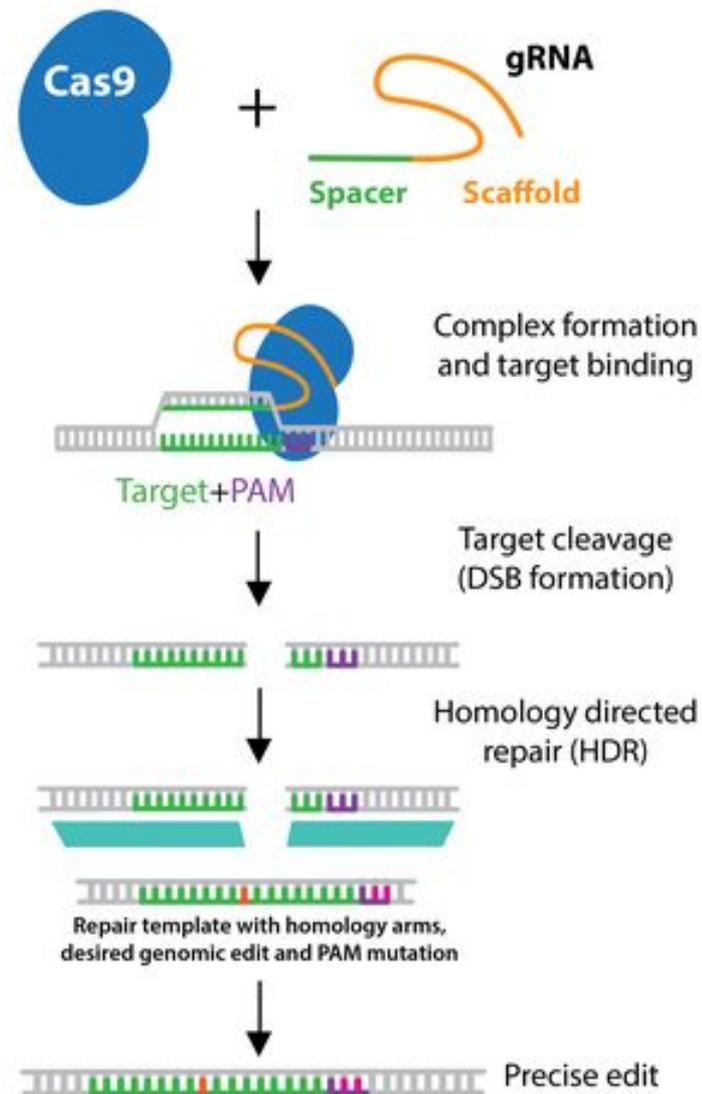
A Primer on the Science of CRISPR

- Generation of gene knockouts using guide RNA's (gRNA's) with a spacer complimentary to the gene of interest
 - Binding of Cas9 to the gRNA enables binding of the ribonucleoprotein complex to genomic DNA
 - The Protospacer Adjacent Motif (PAM) is a binding signal for Cas9
 - Binding of the gRNA spacer to the genomic DNA allows unwinding and a double strand break (DSB) by Cas9
 - Error-prone non-homologous end joining (NHEJ) results in mutations to the gene



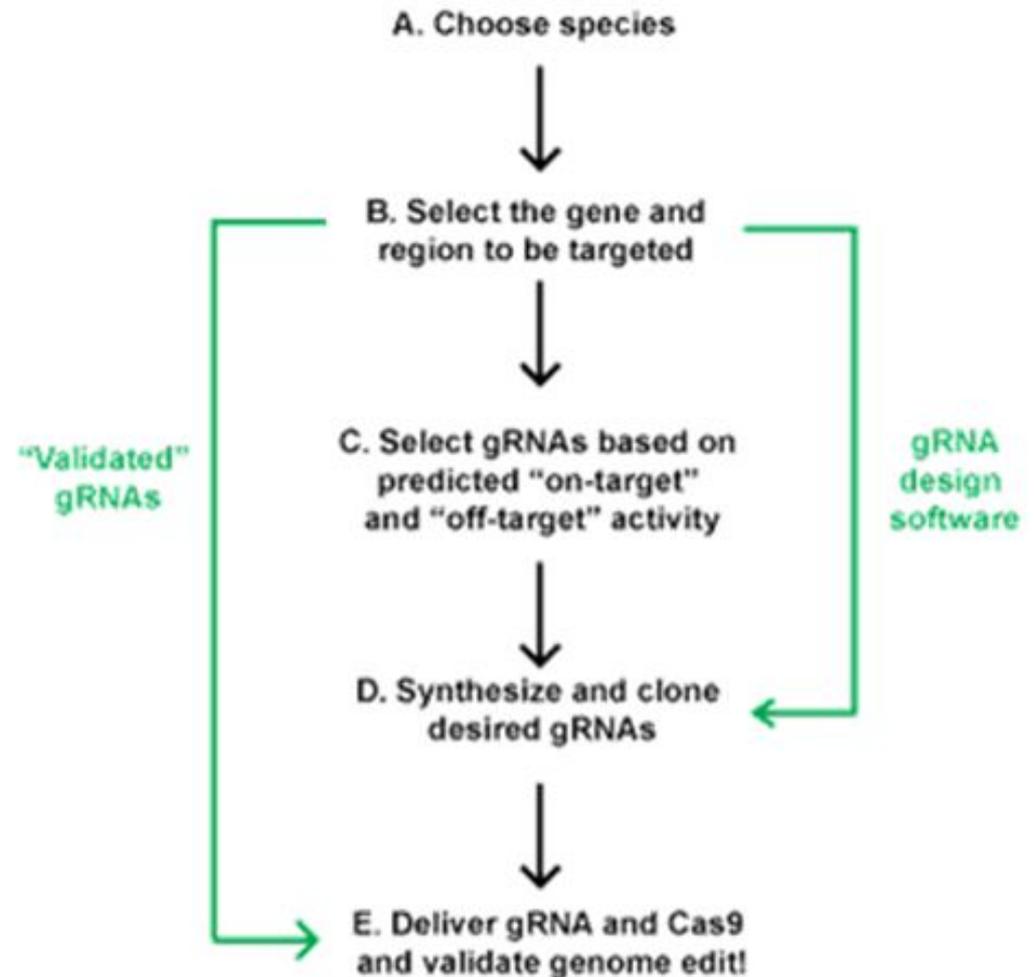
A Primer on the Science of CRISPR

- Precise Modifications Using Homology Directed Repair (HDR)
- Similar to knockout protocol except that repair template included
- Mutation of PAM in repair template necessary to prevent Cas9 recognition of template



A Primer on the Science of CRISPR

- CRISPR-specific software facilitates the production and validation of guide RNA's (gRNA's)
 - Other CRISPR molecular biology tools are freely shared among the scientific community



A Primer on the Science of CRISPR

- CRISPR has been modified to facilitate a variety of genetic manipulations

Genetic Manipulation	Application
Knockout	Permanently disrupt gene function in a particular cell type or organism without a specific preferred mutation
Edit	Generate a specific user-defined sequence change in a particular gene, such as generating a point mutation or inserting a tag
Repress or Interfere (CRISPRi)	Reduce expression of a particular gene(s) without permanently modifying the genome
Activate (CRISPRa)	Increase expression of an endogenous gene(s) without permanently modifying the genome

Sources

- <https://en.wikipedia.org/wiki/CRISPR>
- <https://www.addgene.org/guides/crispr/>

CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool

Risk/Benefit Considerations in CRISPR Technology

	Benefit(s)	Risk(s)/Harm(s)
Basic and pre-clinical research	<ol style="list-style-type: none">1) new model organisms and cell lines2) increased gene-editing efficiency3) high throughput screens4) novel drug targets5) access to totipotent cells6) identification of novel signaling, regulatory, and developmental pathways7) development of novel gene-editing approaches (base editing and RNA targeting)8) knowledge advancement	<ol style="list-style-type: none">1) experimentation involving human embryos is controversial and illegal in some countries2) potential for privacy and confidentiality breaches

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Translational and clinical medicine	<ol style="list-style-type: none">1) immunotherapy2) organoids3) novel drug targets4) artificial intelligence5) modification of pathological genes6) novel therapeutics and fertility applications7) procreative liberty8) ability to “fix” single base changes9) knowledge advancement10) potential for equitable access	<ol style="list-style-type: none">1) serious injury, disability, and/or death to research participant(s) and/or offspring2) blurry distinction between therapeutic and enhancement applications, leading to potential subtle or obvious exacerbation of inequalities3) misapplications4) eugenics5) potential for inequitable access and exacerbation of inequalities

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	Benefit(s)	Risk(s)/Harm(s)
Non-therapeutic applications	<ol style="list-style-type: none">1) enhancement to augment select faulty or human characteristics2) fortification of crops and livestock3) successful control of pests, invasive species, and reservoirs (gene drives)4) disease/infection control (e.g., malaria, dengue fever, Lyme and Chagas disease, schistosomiasis)5) ecosystem alteration to protect endangered species (gene drives)6) safety7) crop cultivation8) knowledge advancement	<ol style="list-style-type: none">1) eugenics2) exacerbation of racism and inequality3) theoretical risk for damage to ecosystems4) theoretical risk of misuse

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Risk/Benefit Considerations in CRISPR Technology

	Benefit(s)	Risk(s)/Harm(s)
Access to CRISPR technology	<ol style="list-style-type: none">1) inexpensive (technology itself)2) widely available3) profit, economic growth4) innovation	<ol style="list-style-type: none">1) price gouging2) prohibitively expensive applications
Regulations for clinical research involving human subjects	<ol style="list-style-type: none">1) established framework in some countries to manage research risk2) legal mechanisms for redress already exist, depending on location	<ol style="list-style-type: none">1) lack of appropriate supervisory infrastructure, oversight, and/or regulatory framework in many nations2) unclear how to supervise the research even in some countries with regulatory oversight3) over regulation might hinder progress

CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool

Risk/Benefit Considerations in CRISPR Technology

	Benefit(s)	Risk(s)/Harm(s)
National and international regulations, law, and policy	<ol style="list-style-type: none">1) prevention against misuses of technology2) safeguard against potential unethical conditions	<ol style="list-style-type: none">1) potential to encroach on societal autonomy limit discovery and progress2) difficult enforcement3) lack of uniformity

Thank You



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