

Tardigrade-based mRNA therapy for radioprotection

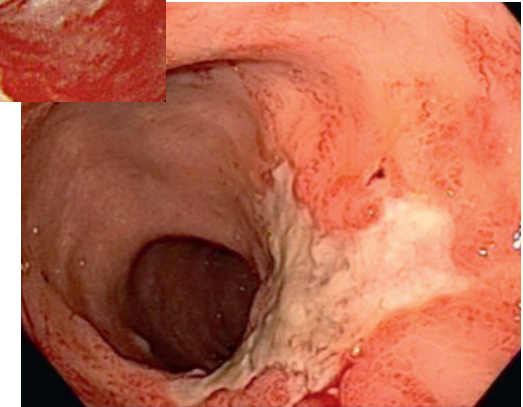
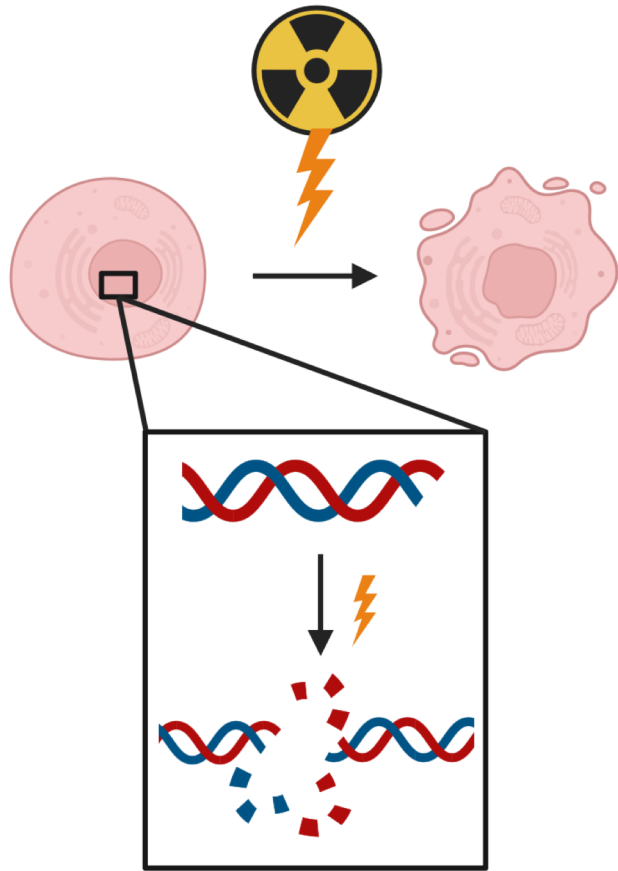
Gene Delivery and Gene Editing – Session 2

Ameya Kirtane, PhD

Brigham and Women's Hospital, Harvard Medical School

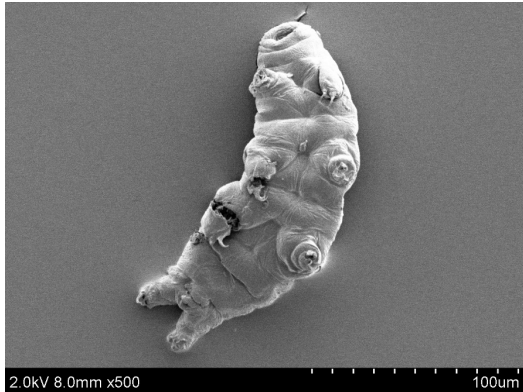


Radiation-induced mucositis



O Maria *et al.*, *Front. Oncol.*, 2017

Extremotolerant tardigrades



Tardigrade species	State	Radiotolerance (LD50)
<i>Macrobiotus aveolatus</i>	Dehydrated	5700 Gy
	Hydrated	4700 Gy
	Hydrated	2500 Gy
	Dehydrated	3000 Gy
<i>Richtersius coronifer</i>	Dehydrated	10240 Gy
	Dehydrated	2000 Gy
	Dehydrated	2000 Gy
	Dehydrated	2000 Gy
<i>Ramazzottius varieornatus</i>	Hydrated	4000 Gy
	Dehydrated	4000 Gy
<i>Hypsibius dujardini</i>	Hydrated	4180 Gy

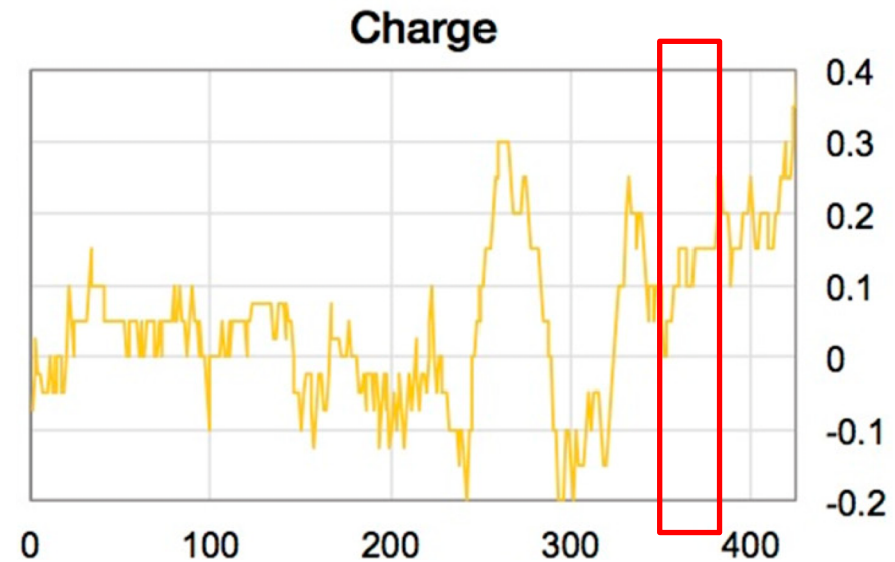
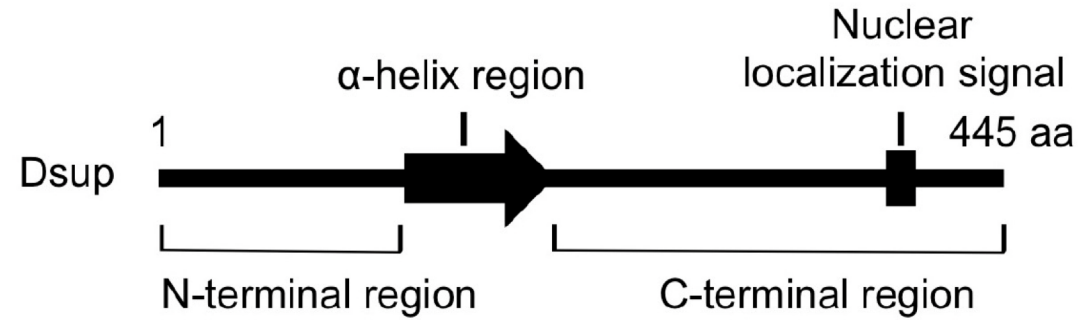
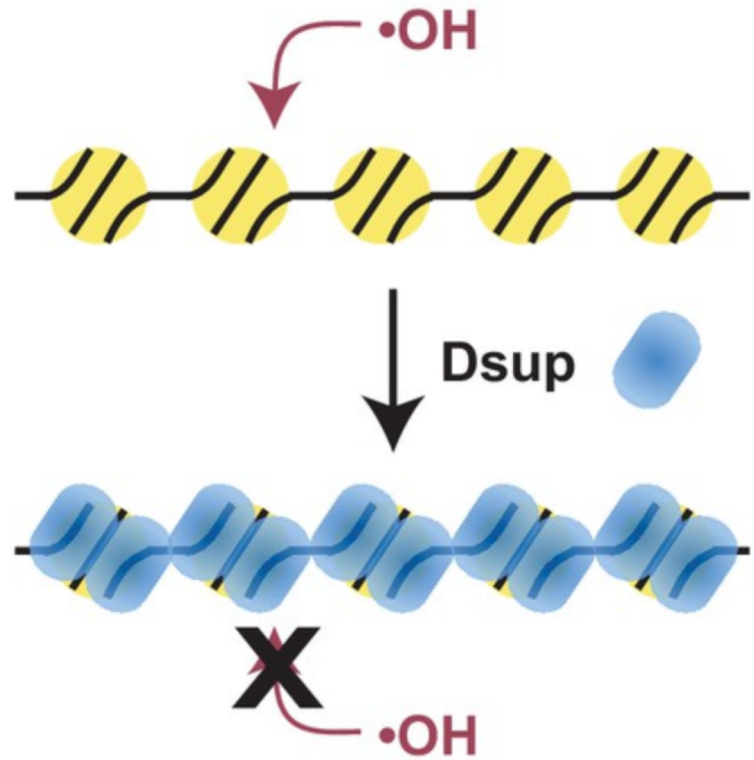
LD50 for humans is ~4 Gy

Hashimoto *et al.*, *Life*, 2017

Kirtane, Bi *et al.*, *Nature Biomedical Engineering*, *in press*

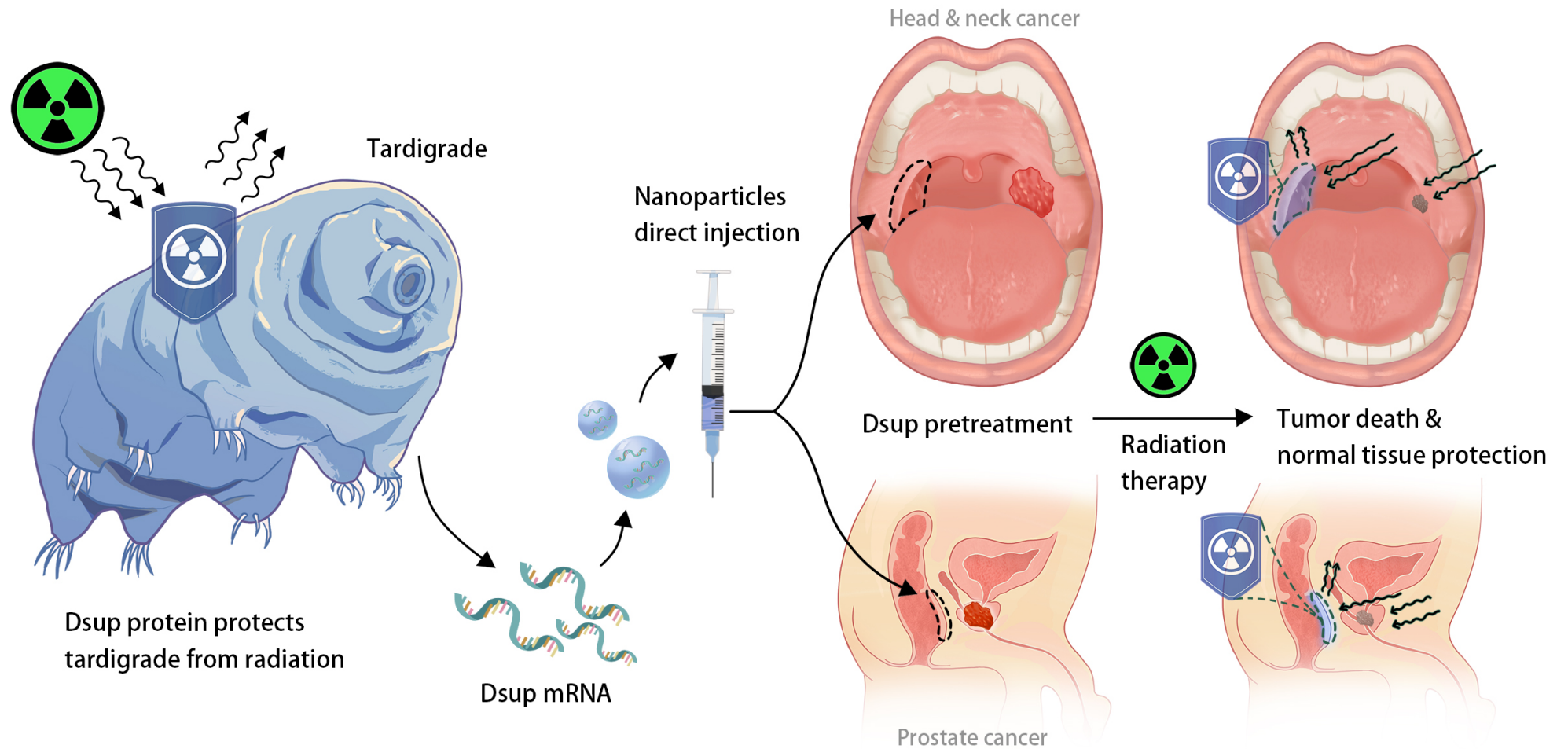


Tardigrade damage suppressor (Dsup) protein



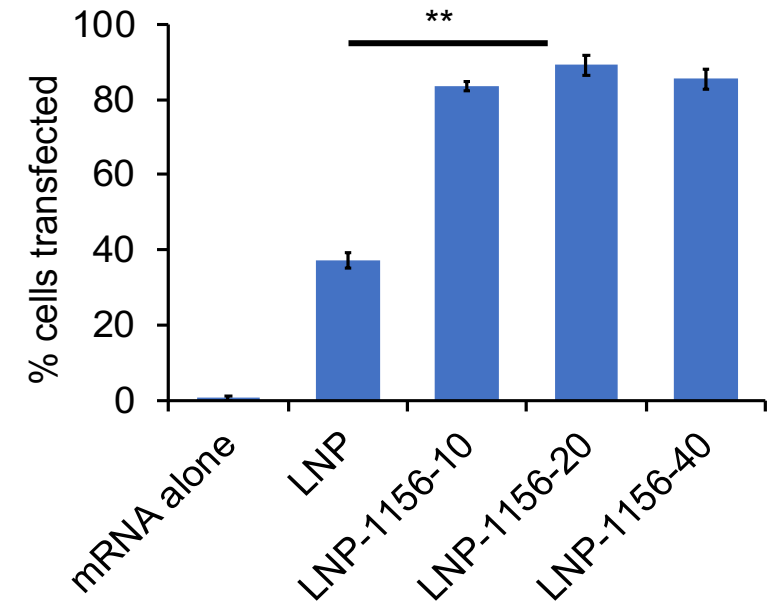
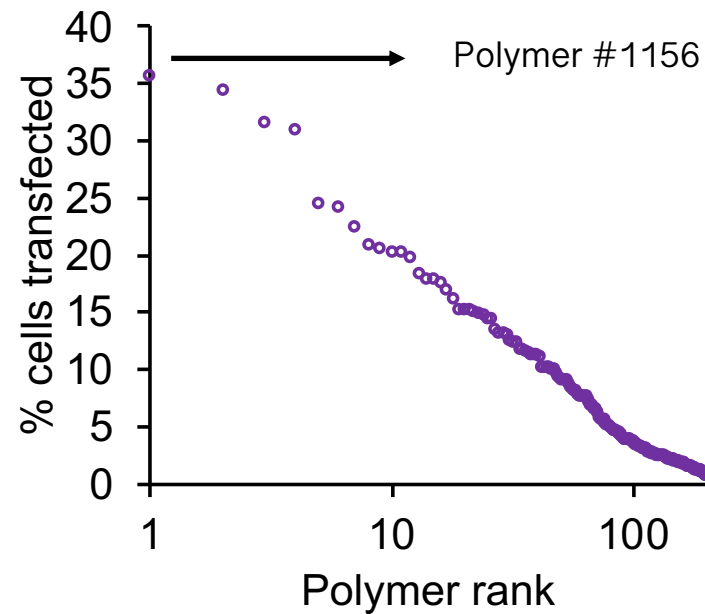
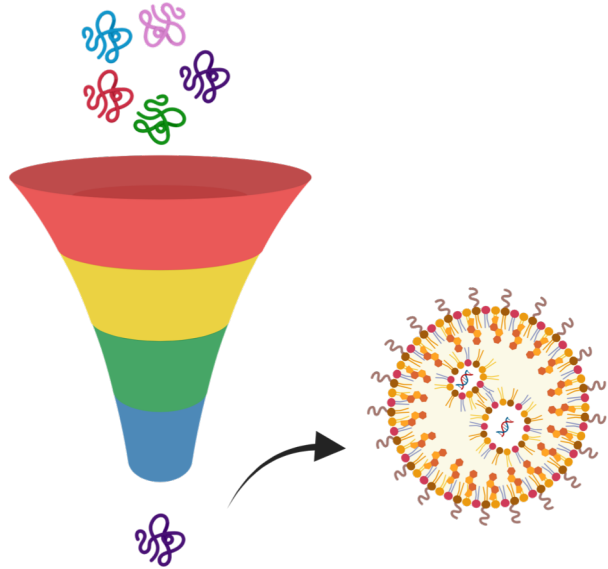
Hashimoto *et al.*, *Life*, 2017
Chavez *et al.*, *eLife*, 2019

Strategy

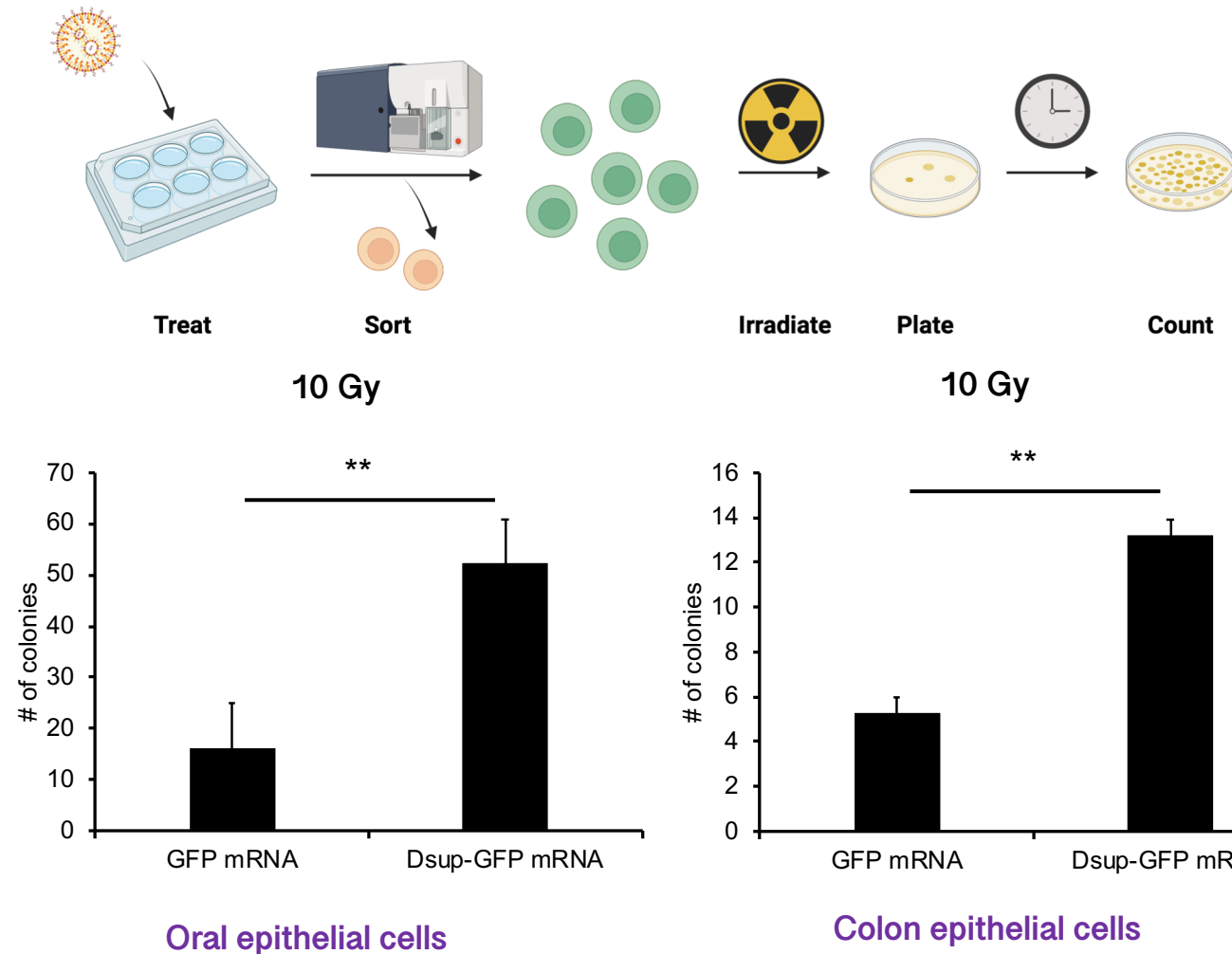


Kirtane, Bi *et al.*, *Nature Biomedical Engineering*, *in press*

Polymer-lipid nanoparticles produce potent transfection *in vitro*



DSup mRNA protects cells from radiation *in vitro*



Data is represented as mean + SD, n=5-10, *p<0.01, **p<0.005

DSup mRNA nanoparticles reduce DNA damage

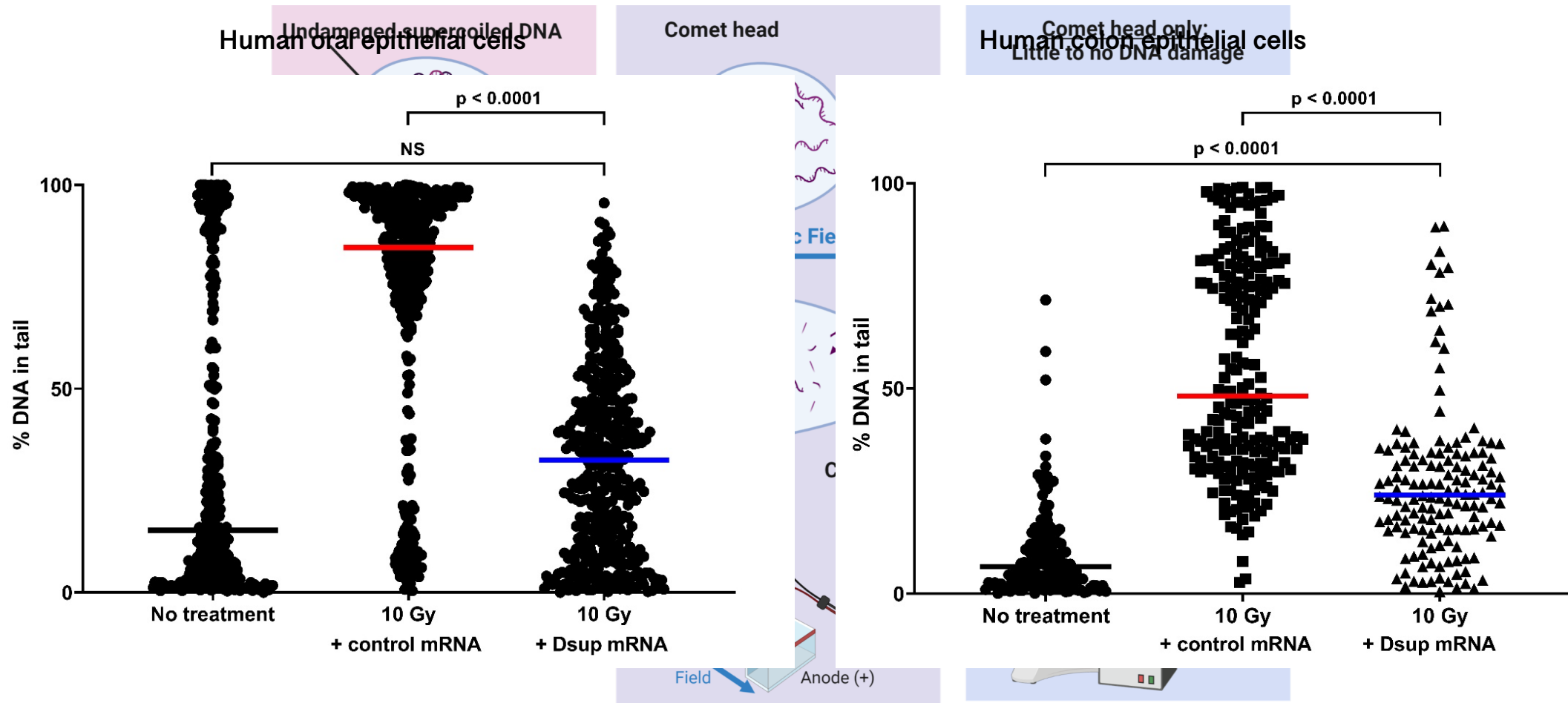
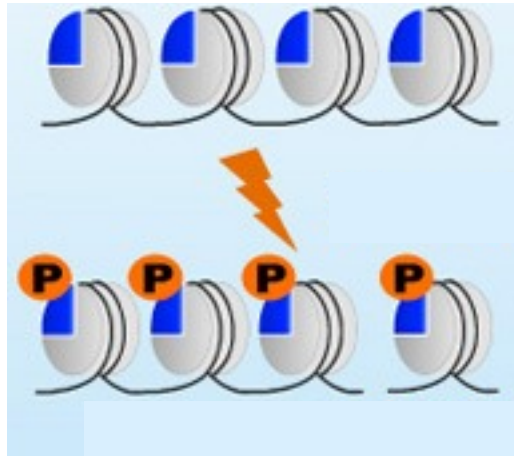


Image courtesy: Breed Diagnostics

DSup mRNA nanoparticles reduce DNA damage



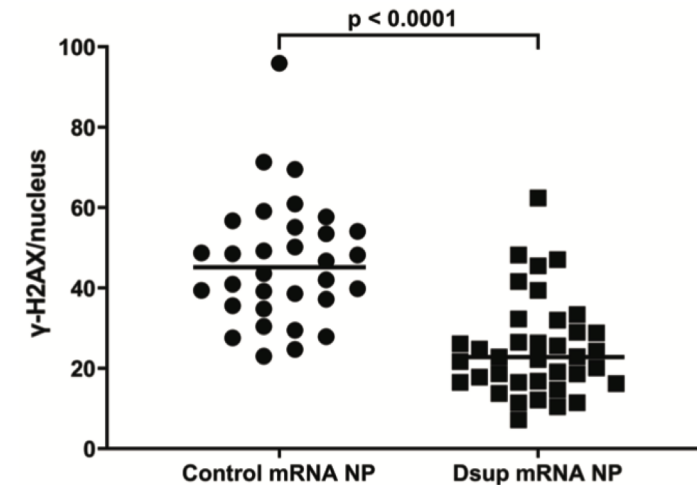
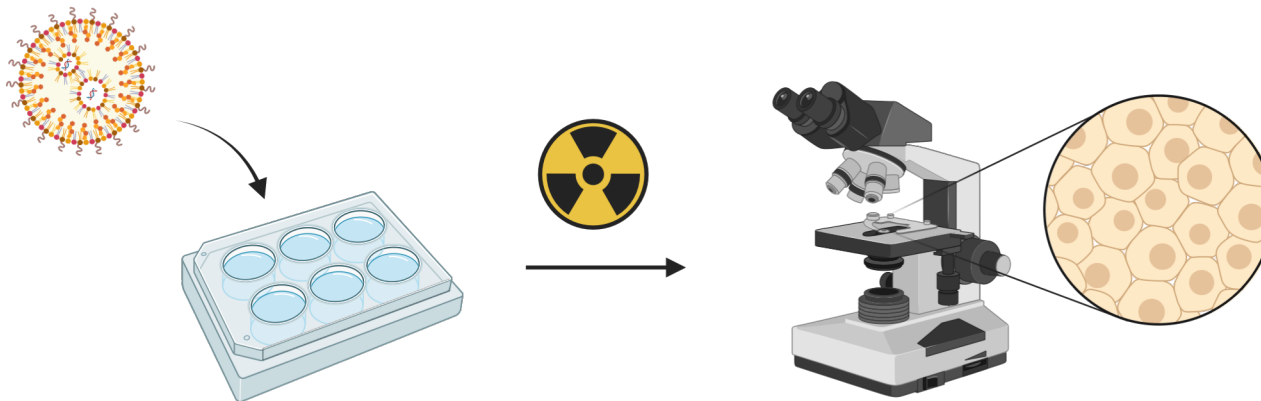
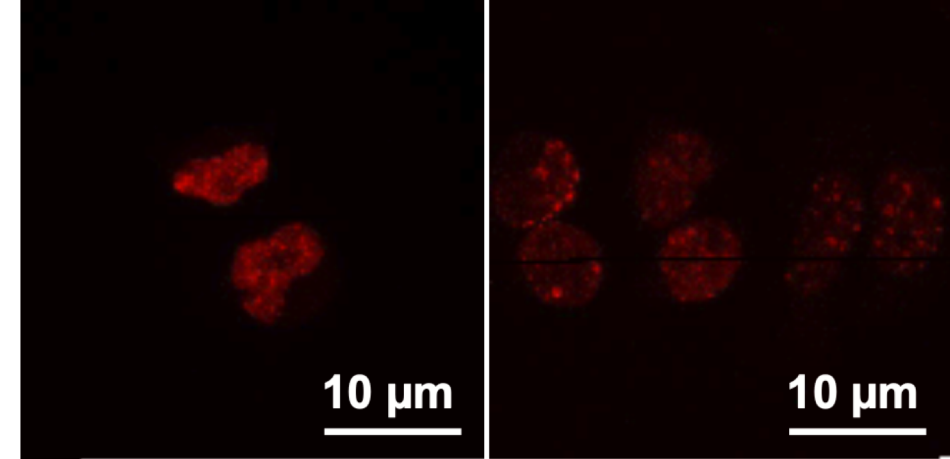
Histone
H2AX

gH2AX

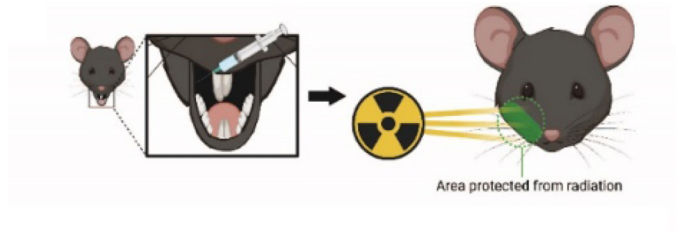
Gruosso *et al.*, EMBO Mol Med, 2016

Control mRNA NP

Dsup mRNA NP



DSup mRNA nanoparticles reduce DNA damage *in vivo*



Data is from 3
samples/mouse, 7 mice/
group; p values are
calculated using One-way
ANOVA, post-hoc Bonferroni



Summary

- Addition of cationic polymers to lipid nanoparticles enhances their transfection efficacy
- Pre-treatment with dsup-mRNA nanoparticles enhances resistance to radiation induced DNA damage



INTEGRATING
Delivery Science
ACROSS DISCIPLINES

