DRACO

(Double-stranded RNA Activated Caspase Oligomerizer)
Broad-Spectrum Antiviral Therapeutics

Dr. Todd H. Rider

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A mighty creature is the germ,
Though smaller than the pachyderm.
His customary dwelling place
Is deep within the human race.
His childish pride he often pleases
By giving people strange diseases.
Do you, my poppet, feel infirm?
You probably contain a germ.

-Ogden Nash

DRACO Broad-Spectrum Antiviral Therapeutics

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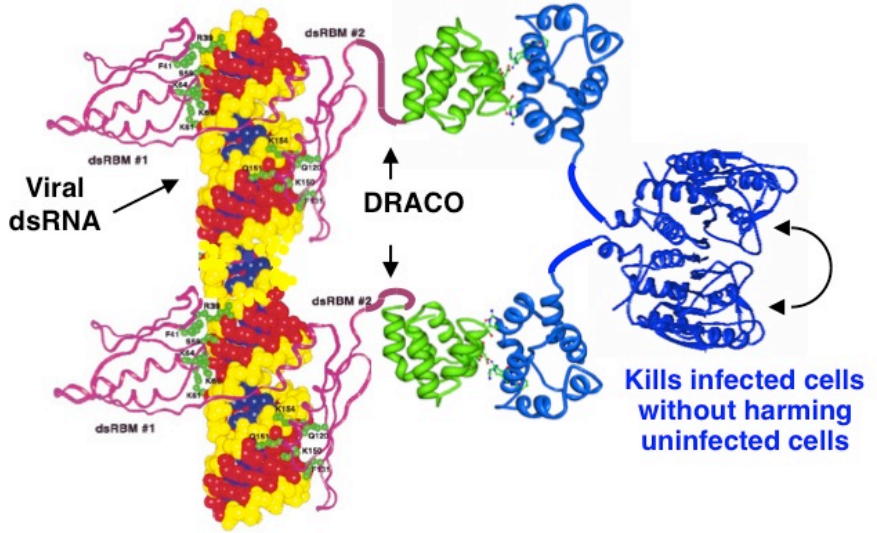
Broad-Spectrum Antiviral DRACO
(Double-stranded RNA Activated Caspase Oligomerizer)

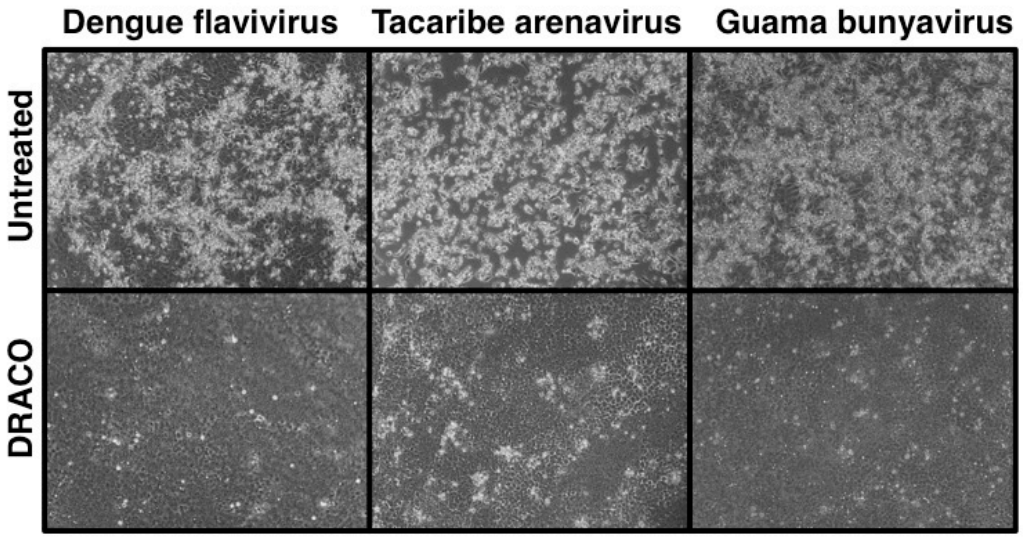


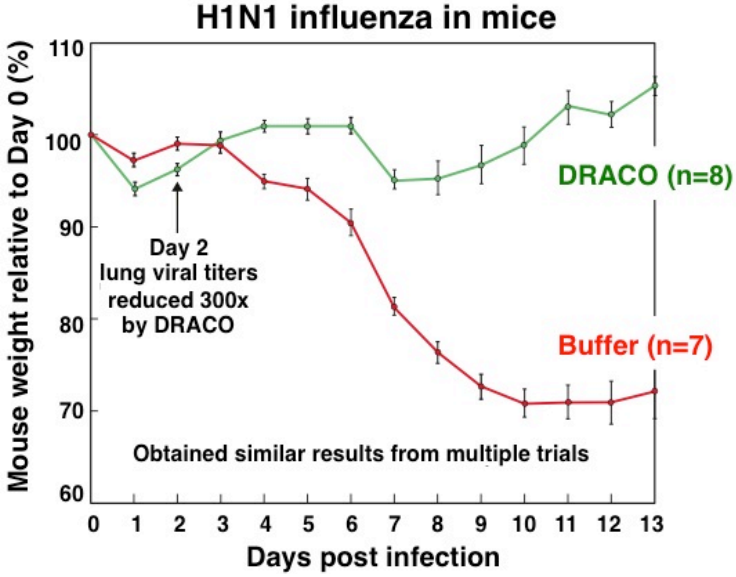
Demonstrated Antiviral Efficacy

Effective against 18 viruses:
- Dengue type 2 flavivirus
- Amapari arenavirus
- Tacaribe arenavirus
- Guama Be An 277 bunyavirus
- Guama Be Ar 12590 bunyavirus
- Influenza H1N1 A/PR/8/34
- Influenza H1N1 A/WS/33
- Adenovirus 5
- Murine adenovirus
- Reovirus 3
- Theiler's encephalomyelitis
- Rhinovirus 1B
- Rhinovirus 2
- Rhinovirus 14
- Rhinovirus 30
- Coronavirus TGEV Purdue
- Coronavirus TGEV Miller
- Coronavirus TGEV AR310

Nontoxic & effective in 13 cell types:
- Monkey Vero E6 kidney cells
- Normal human lung fibroblasts
- Normal human hepatocytes
- Normal human airway epithelial cells
- Normal human osteoblasts
- Normal human aortic muscle cells
- Human embryonic kidney 293 cells
- Human HeLa cells
- Pig ST cells
- Pig SK-RST cells
- Mouse L929 cells
- Mouse BALB/3T3 cells
- Mouse NIH/3T3 cells

Live mice—nontoxic, effective against:
- Influenza H1N1 A/PR/8/34
- Amapari arenavirus
- Tacaribe arenavirus
- Guama bunyavirus





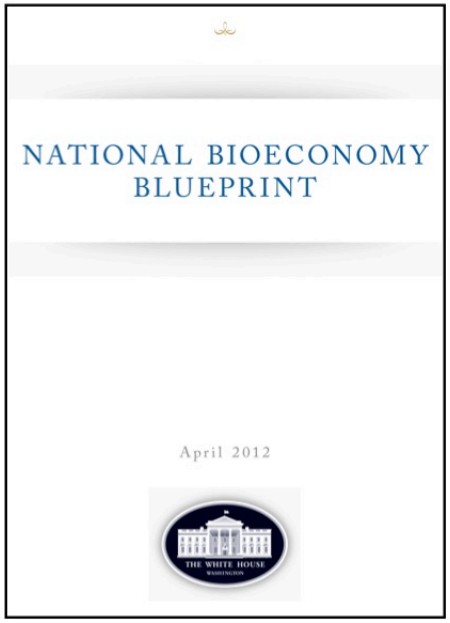
DRACO: Scientific and Public Reception

- First published in *PLoS ONE* (2011)
- Presented at numerous international conferences
- Protected by U.S. and international patents and patent applications

DRACO has been covered by:

U.S. News & World Report	*International Business Times*
Wall Street Journal	*Nature Biotechnology*
Bloomberg Business Week	*Boston Globe*
Technology Review	*Wired*
New Scientist	BBC
Popular Science	NPR
National Geographic	Discovery Channel
R&D Magazine	Etc.

One of *Time* magazine's top inventions of the year (Nov. 28, 2011, pp. 58, 78)



Called "visionary" by the White House (April 2012, p. 9)

Cover story in *Science Illustrated* (September 2012)

Featured on *BBC Horizon* TV program (May 2013)

Only a Few Antiviral Treatments Exist Now, And Those Have Major Disadvantages

Vaccines

Louis Pasteur preparing rabies vaccine

- Separate vaccines must be produced for each virus, or even each virus strain
- It is extremely difficult to create vaccines for some viruses
- To be effective, some vaccines must be administered before infection
- Viruses may be designed to evade existing vaccines

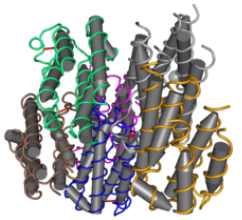
Drugs that target components used by specific viruses

Amantadine	Saquinavir	RNAi
↓	↓	↓
~~Influenza A M_2 channel~~	~~HIV protease~~	~~Specific pathogen gene~~

- Time-consuming and expensive to create drugs for each virus
- Drugs are so specific that resistant virus strains can easily arise naturally or artificially
- Some drugs can have serious adverse effects

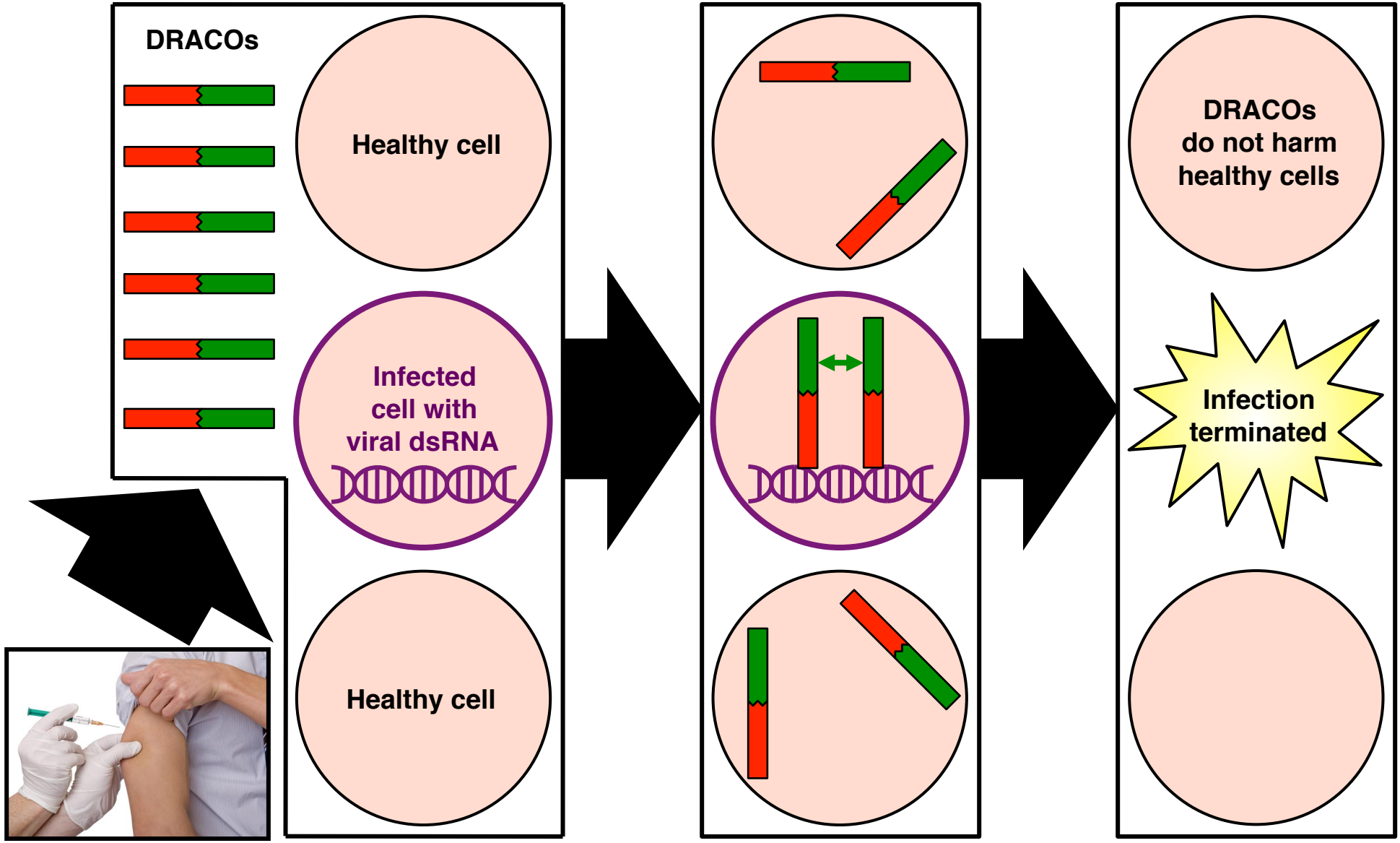
General immune system boosters

- Substances such as interferon have been tested since the 1950s
- This approach is ineffective against many pathogens
- Potential adverse effects include flu-like symptoms, autoimmune disease, shock, and death



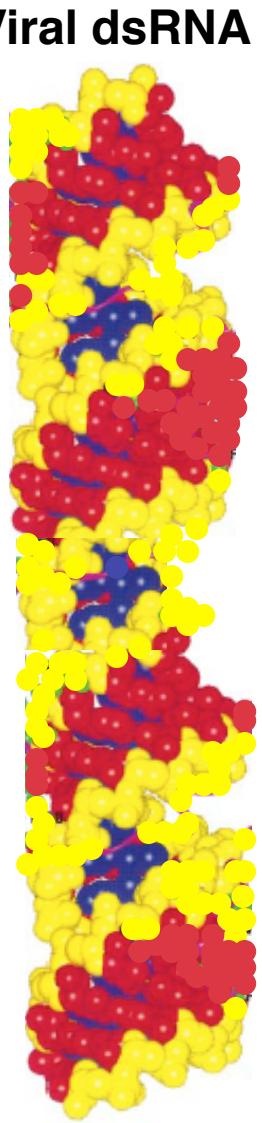
Interferon-α

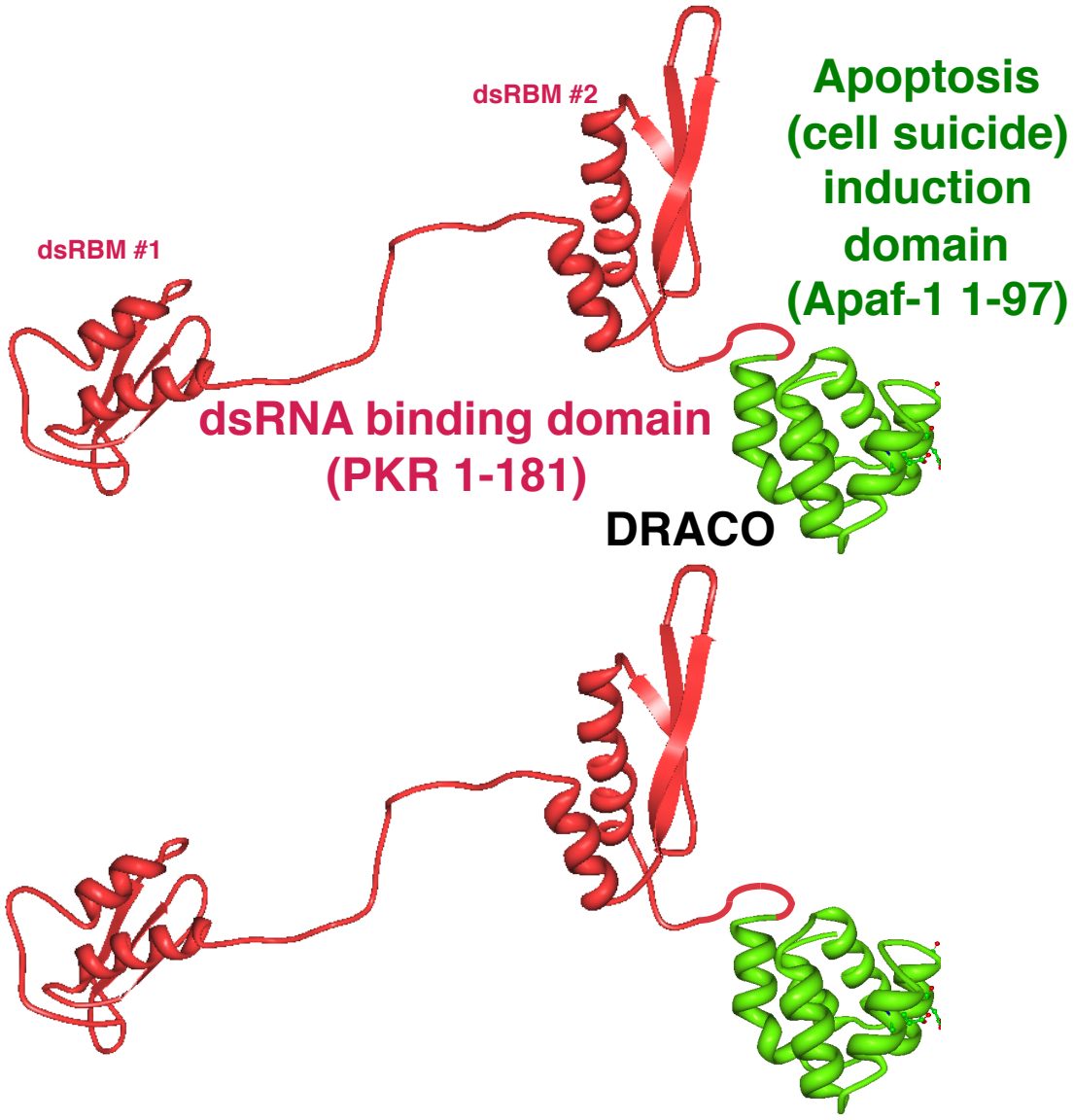
Double-stranded RNA Activated Caspase Oligomerizer (DRACO) Selectively Kills Virus-Infected Cells



Double-stranded RNA Activated Caspase Oligomerizer (DRACO) Selectively Kills Virus-Infected Cells

RNA and DNA viruses produce long double-stranded RNA (dsRNA), but uninfected mammalian cells do not





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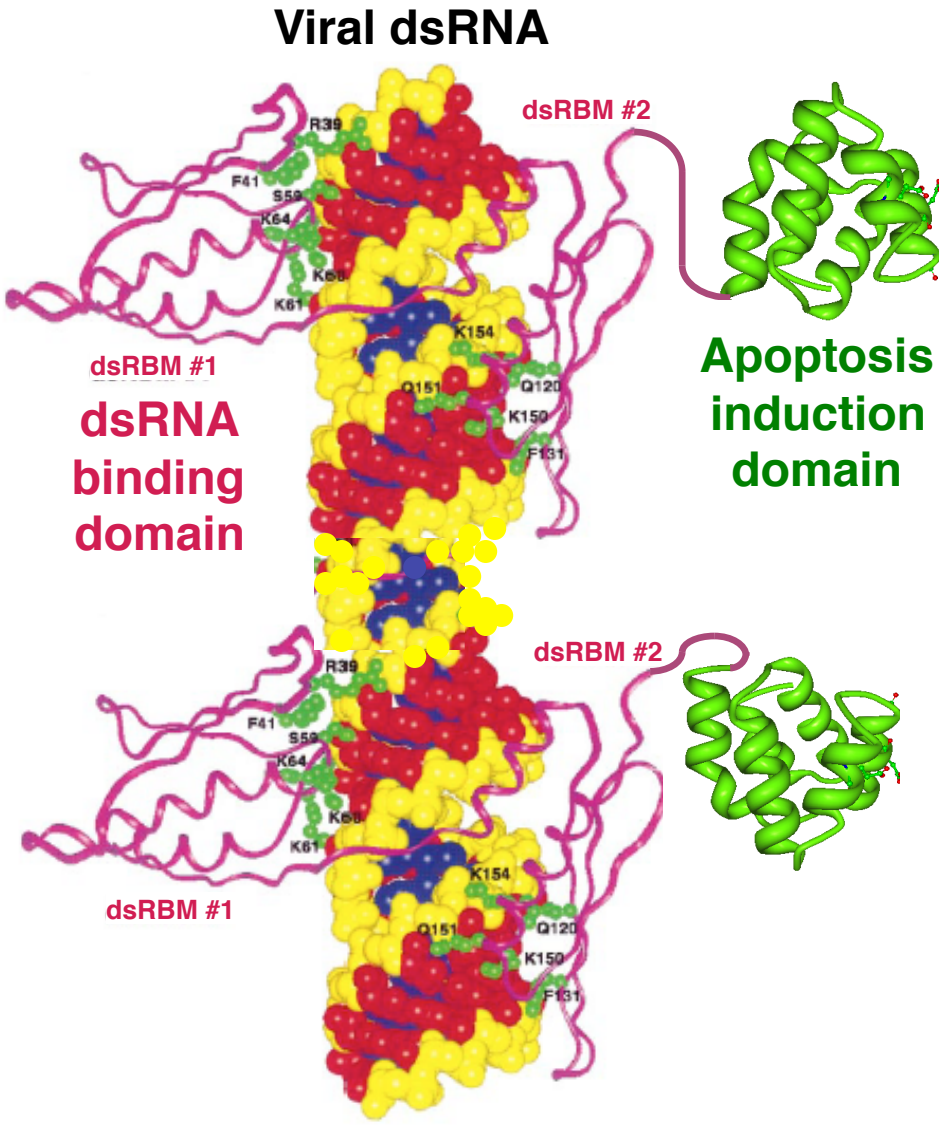
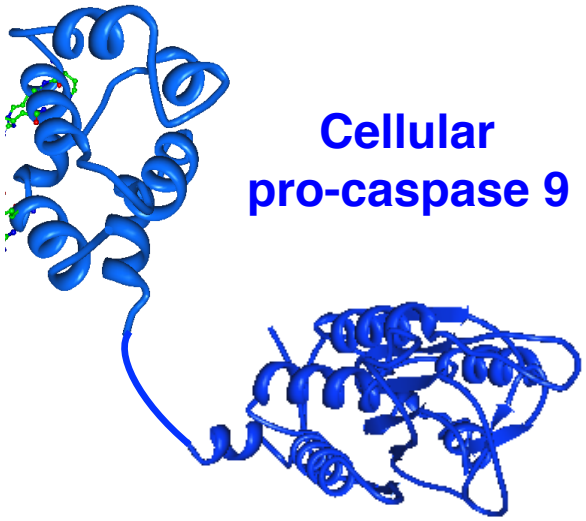
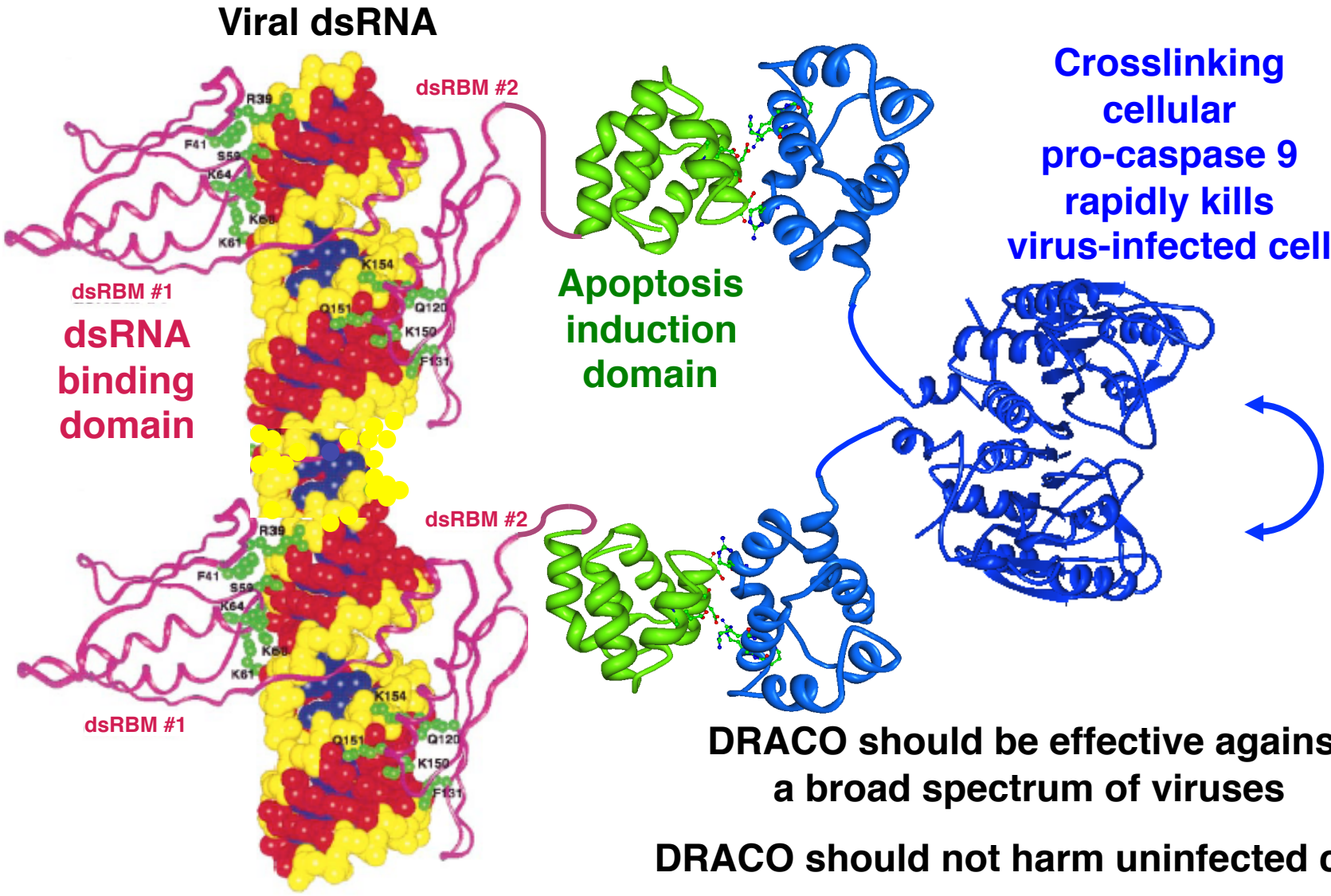




Double-stranded RNA Activated Caspase Oligomerizer (DRACO) Selectively Kills Virus-Infected Cells

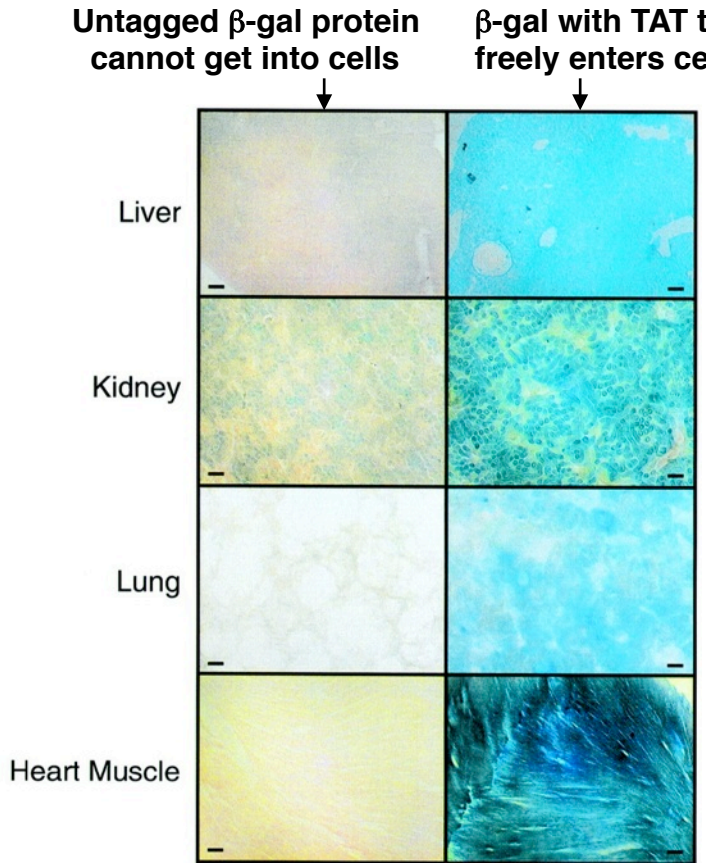


DRACO should be effective against a broad spectrum of viruses

DRACO should not harm uninfected cells

Use Protein Transduction Tags To Deliver DRACOs *in Vitro* and *in Vivo*

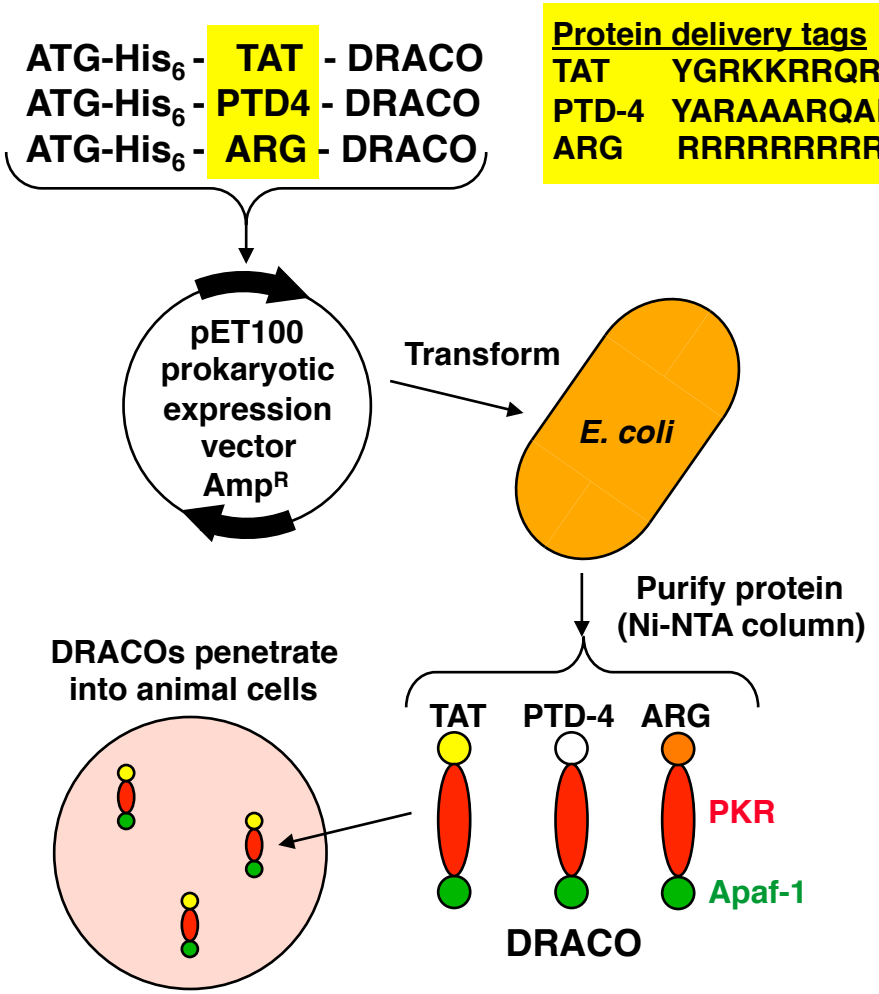
Other researchers showed that tags deliver any protein to all cell types in live mice



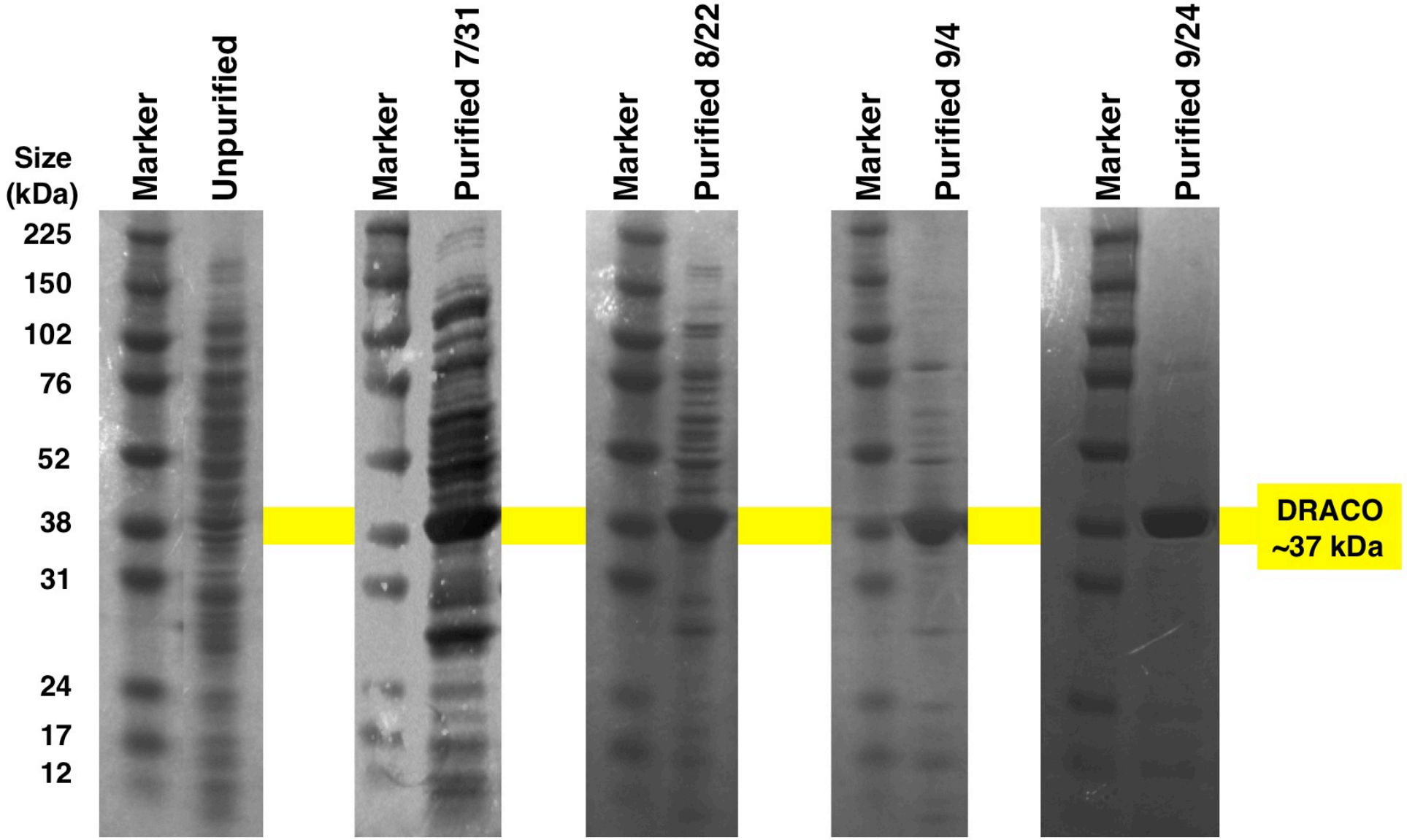
Ref: S. R. Schwarze *et al.* (1999) *Science* 285, 1569

- Also delivers β-galactosidase to brain, spleen, etc.
- No side effects in mice after 2 weeks of use

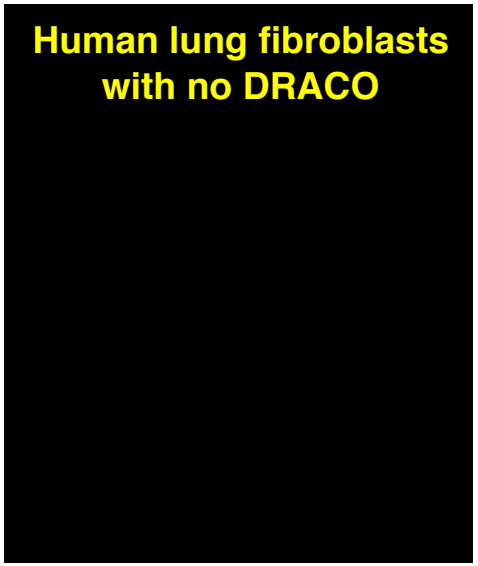
We have produced DRACOs with protein delivery tags

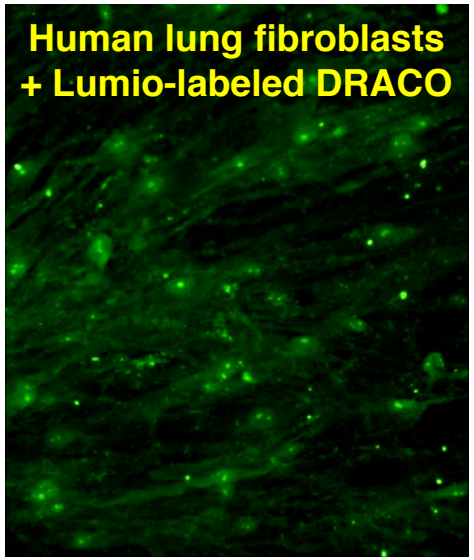


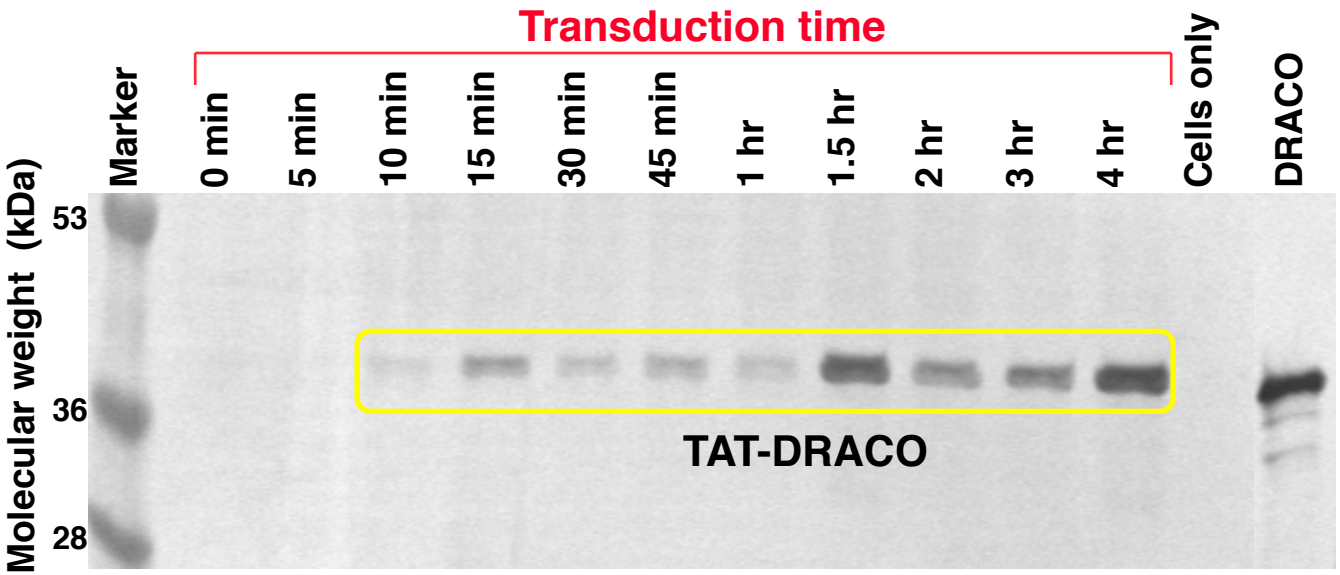
Improving the DRACO Purification Protocol

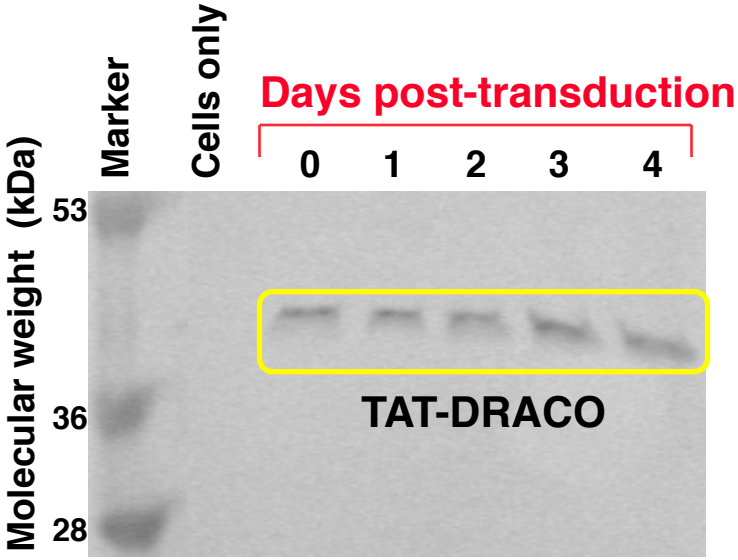


DRACO Penetrates into Cells within Minutes and Persists inside Cells for Days





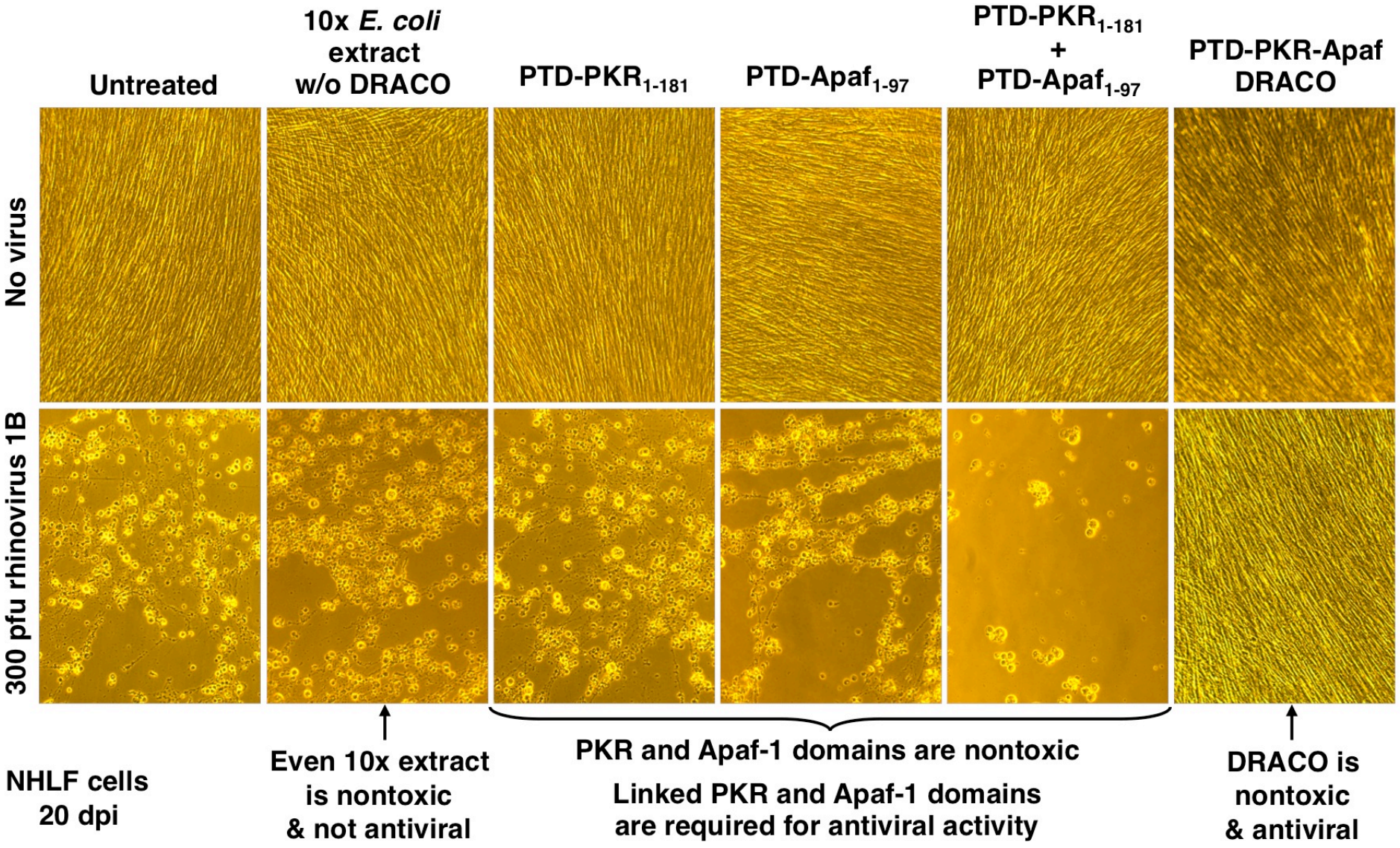




Similar results for other tags

We have also demonstrated that DRACO is effective when added up to at least 11 days before virus, or when any remaining extracellular DRACO is removed before adding virus

DRACO Is Effective Against Rhinovirus 1B in Normal Human Lung Fibroblasts



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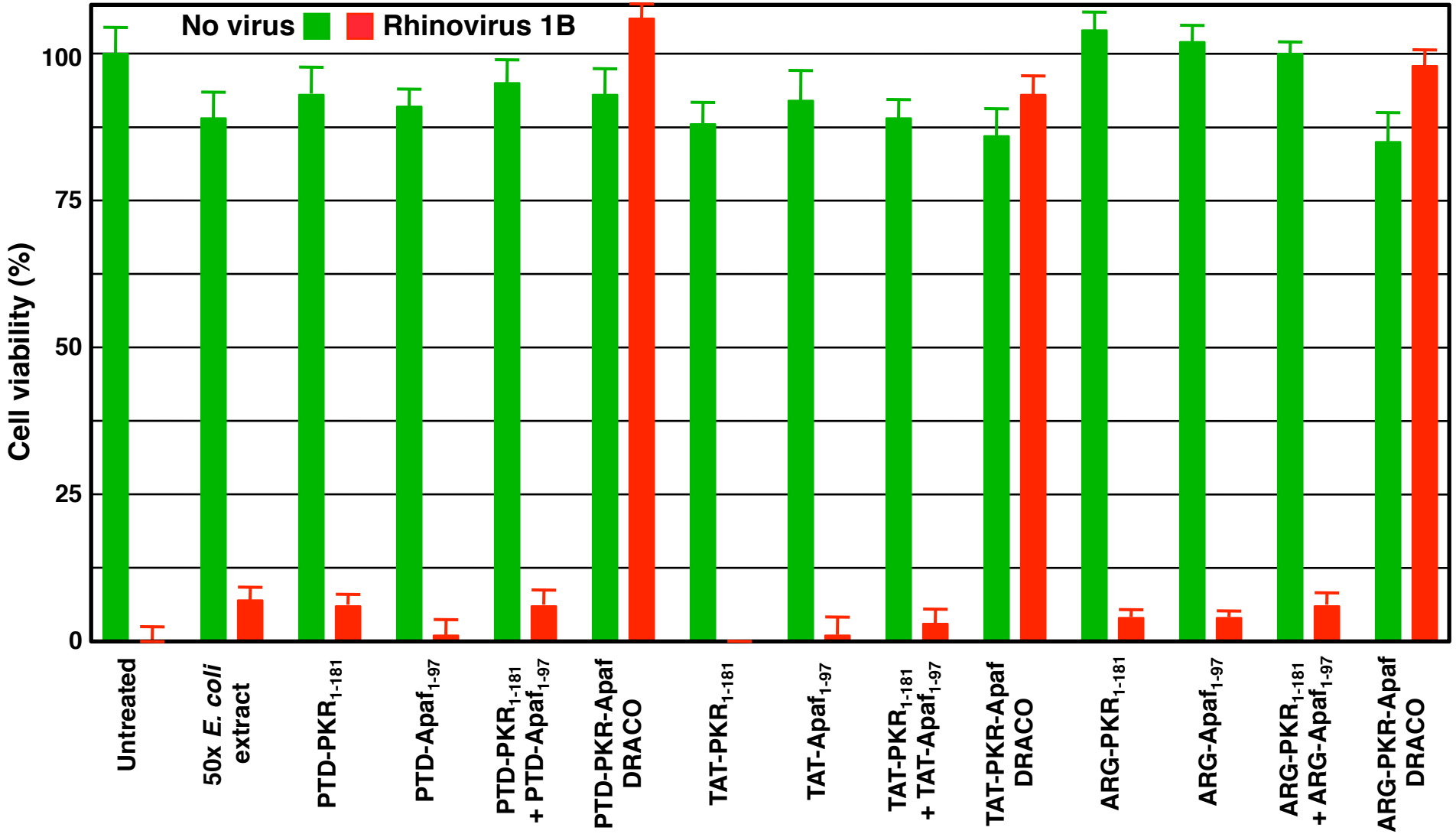
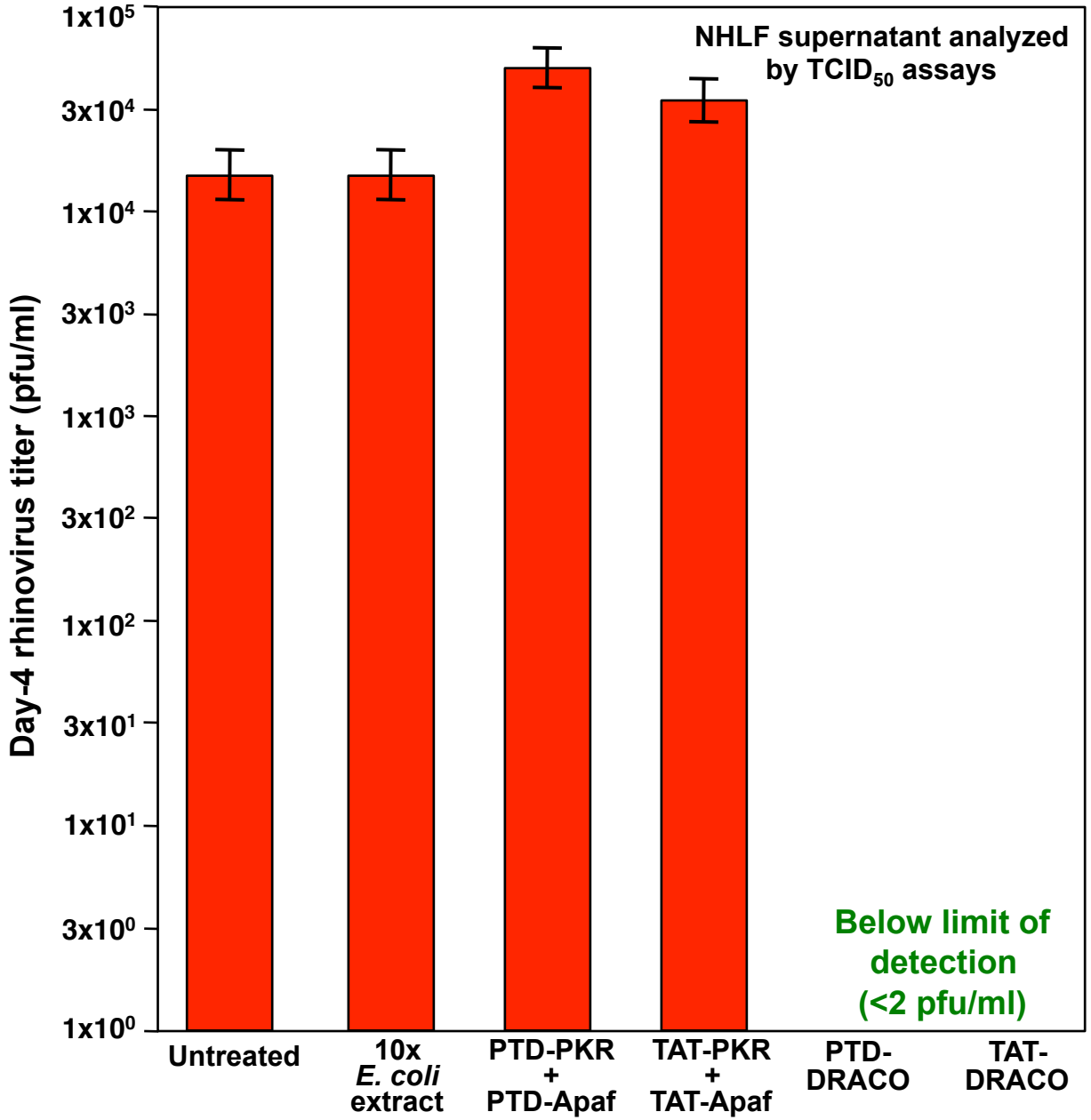
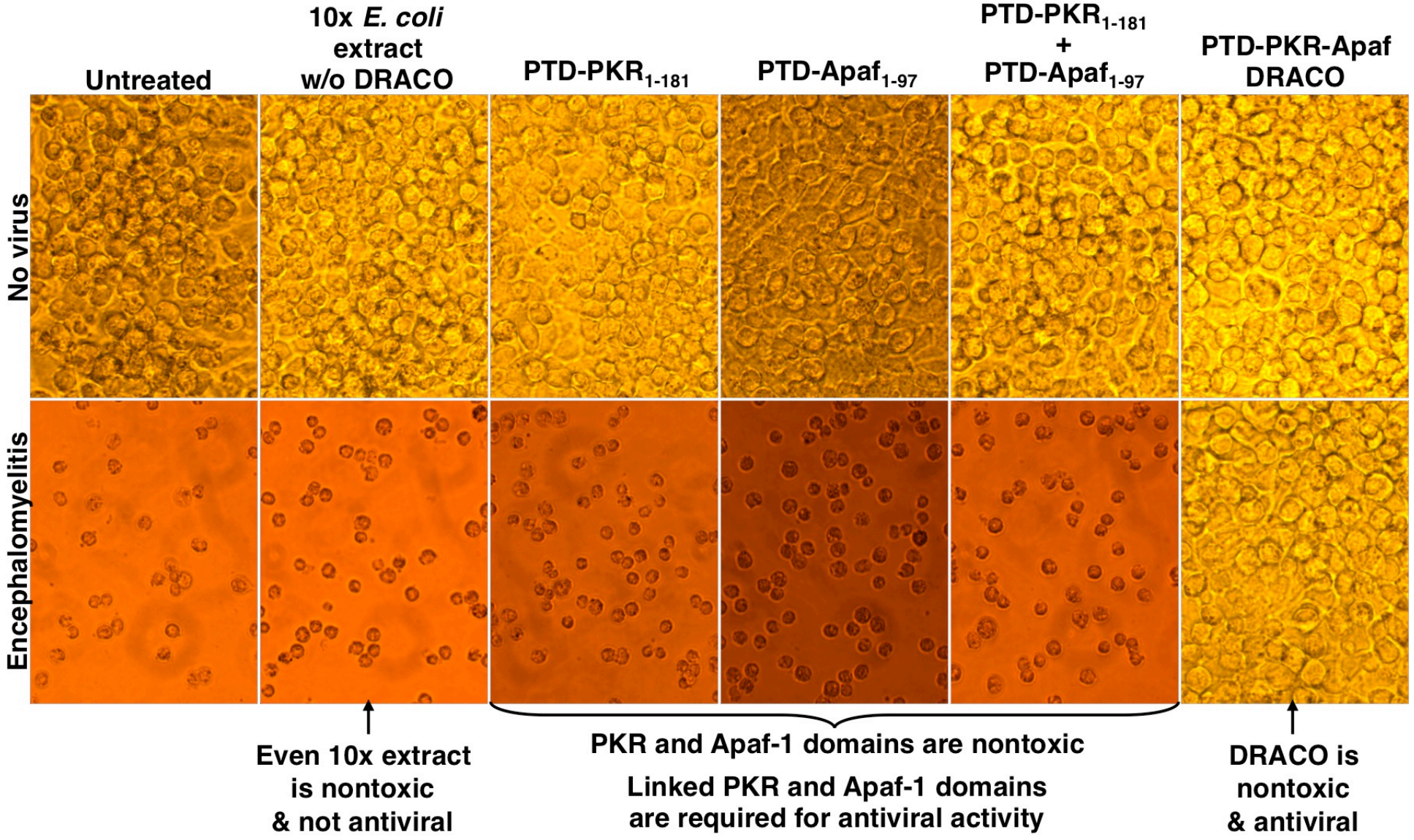


THR-13

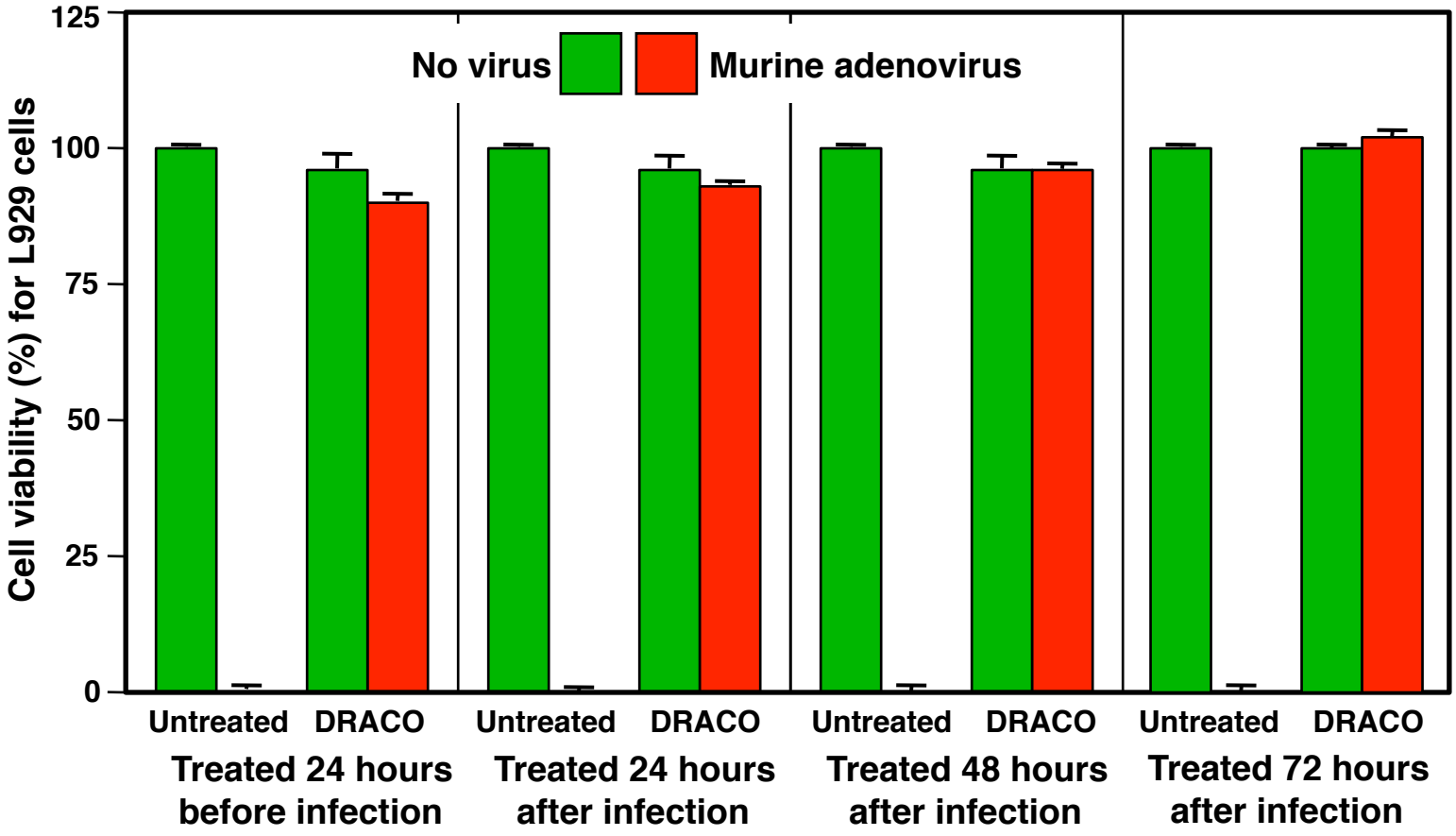
DRACO Reduces Rhinovirus Titers



DRACO Is Effective Against Theiler's Encephalomyelitis in Murine L929 Cells

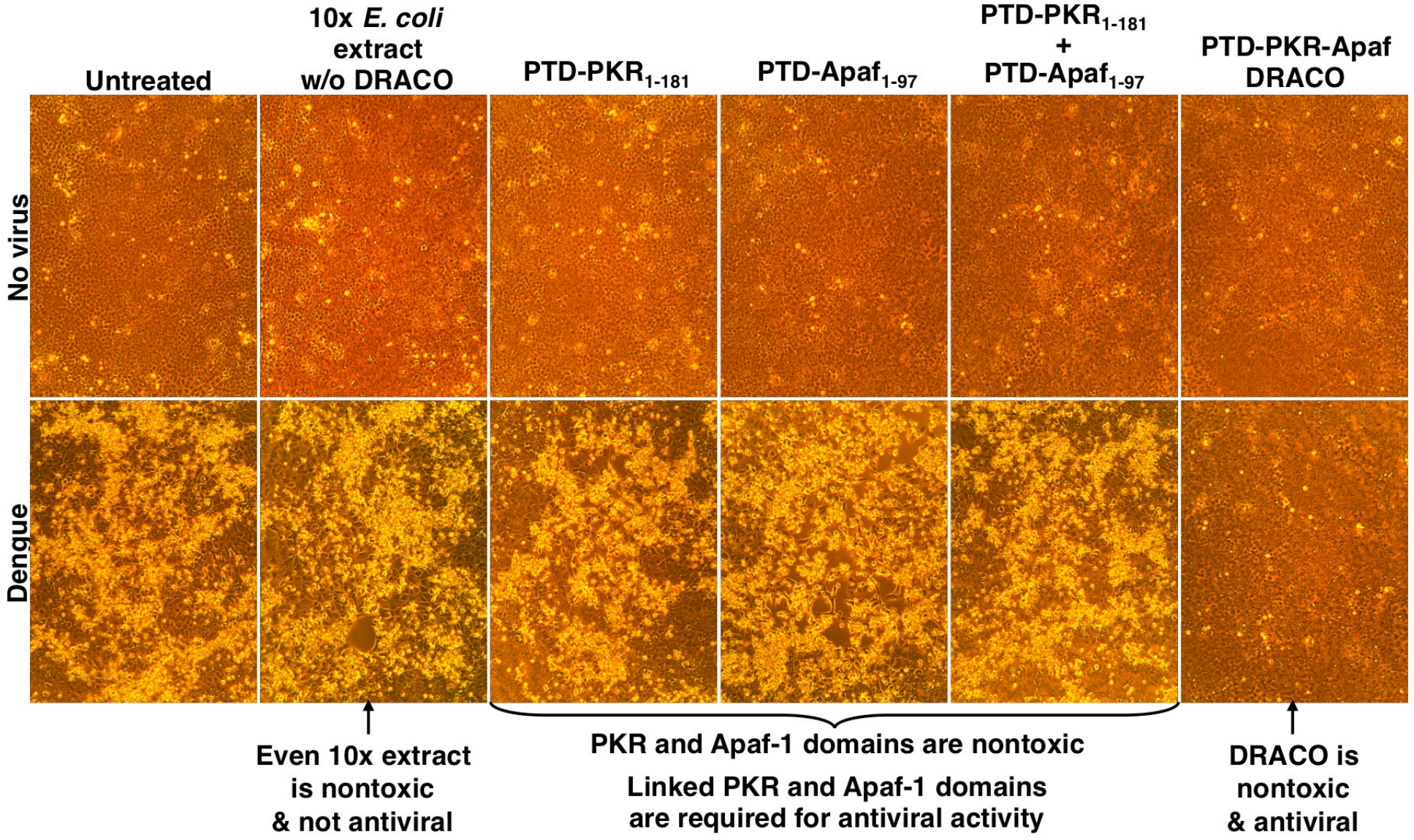


DRACO Is Effective Before or After Infection



Similar results for other viruses tested

DRACO Is Effective Against Dengue Hemorrhagic Fever Virus



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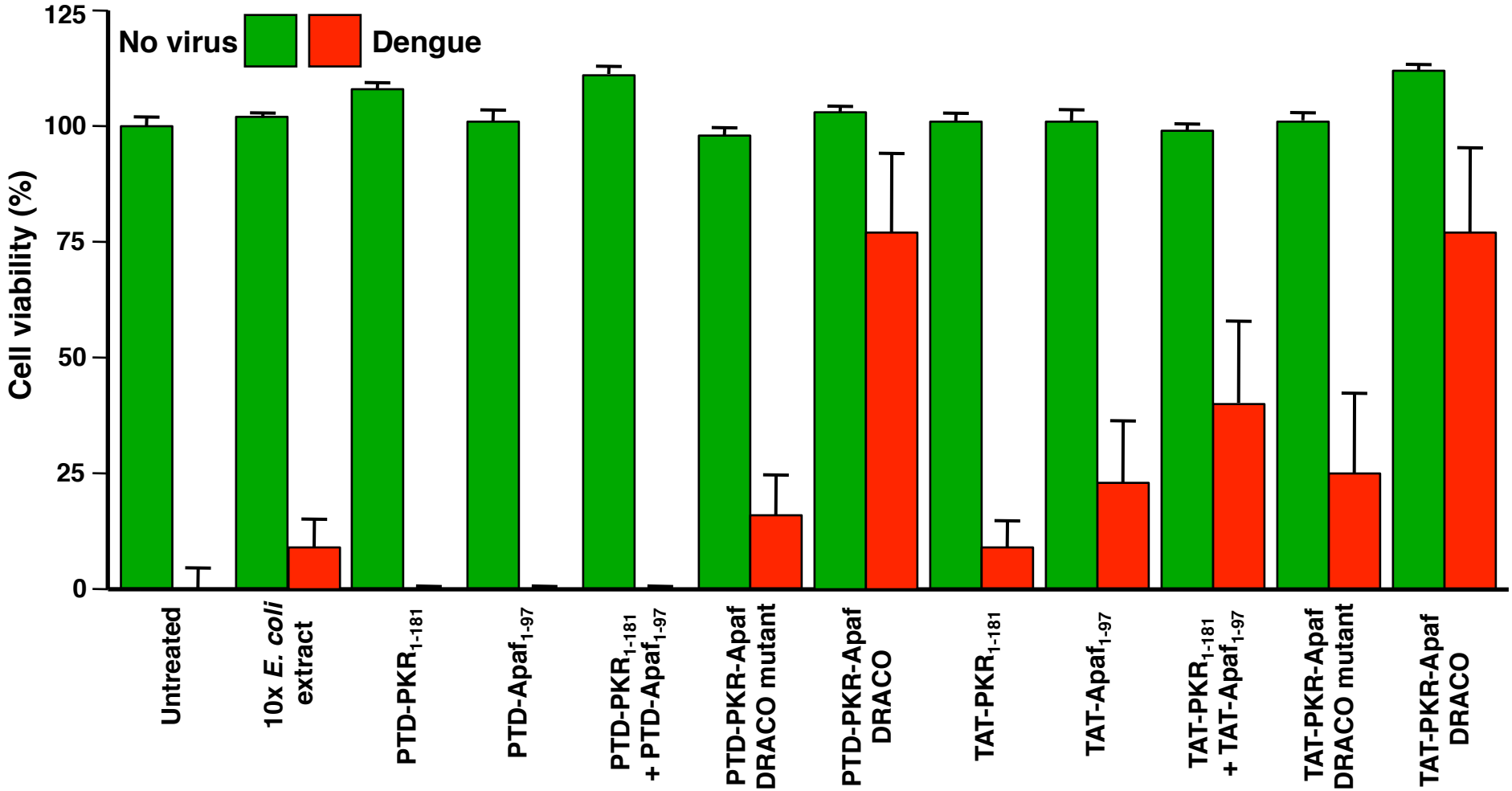
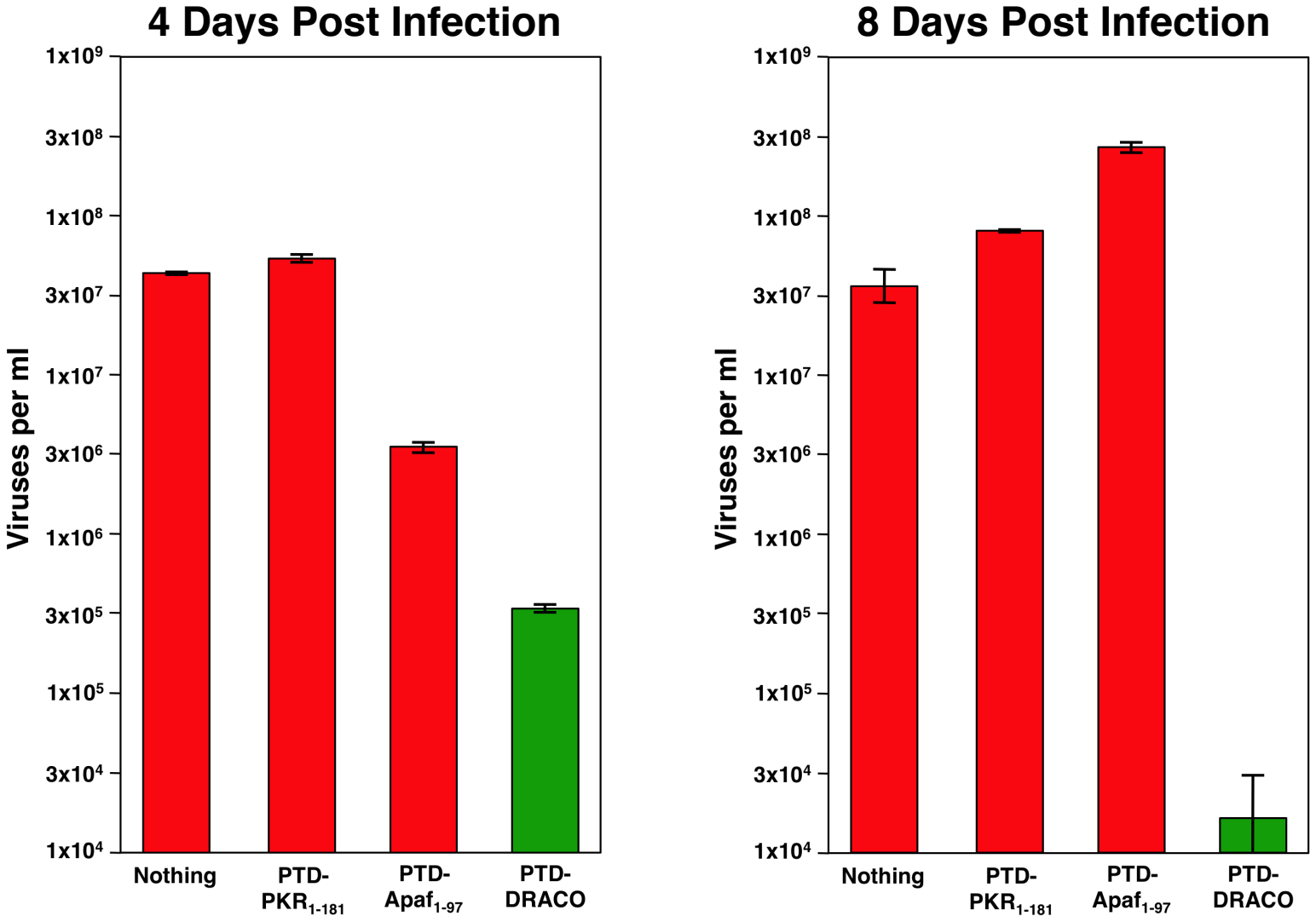
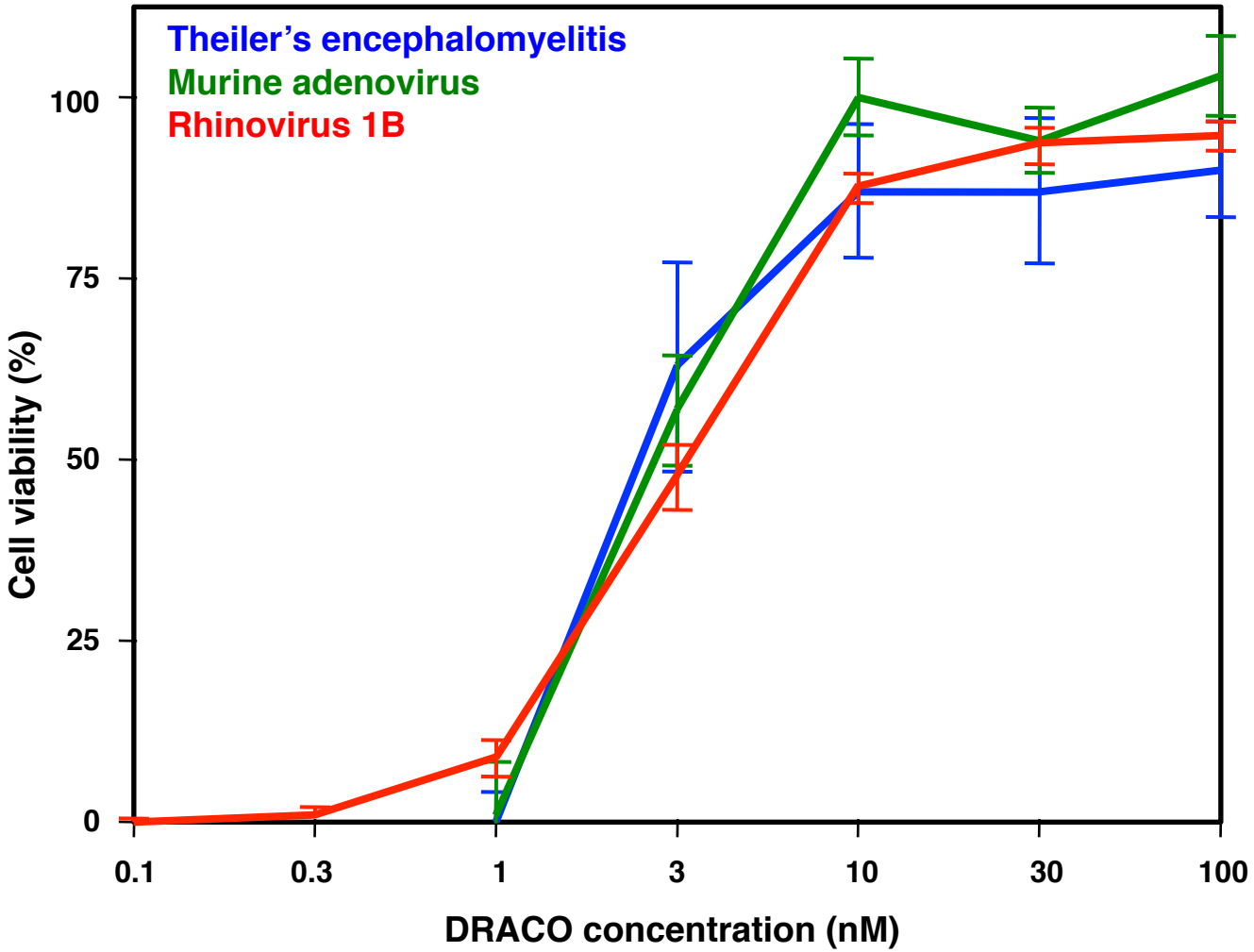


Preliminary Data Shows DRACO Reduces Titers of Hemorrhagic Fever Virus in Cells

RT-qPCR Viral Titers of Tacaribe Arenavirus in Vero E6 Cells

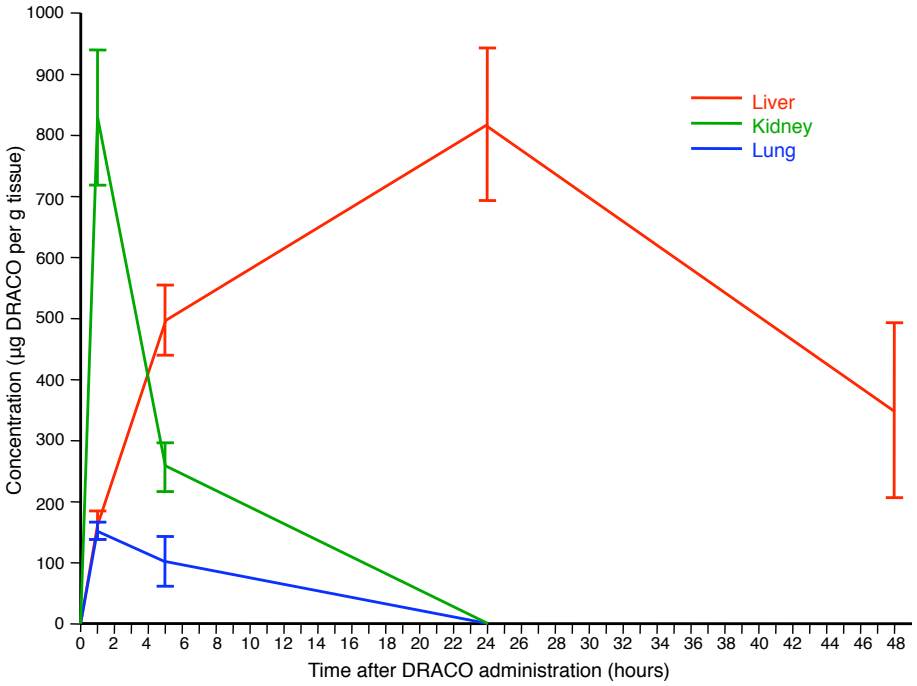


Median Effective Concentration (EC_{50}) for DRACO is ~2-3 nM

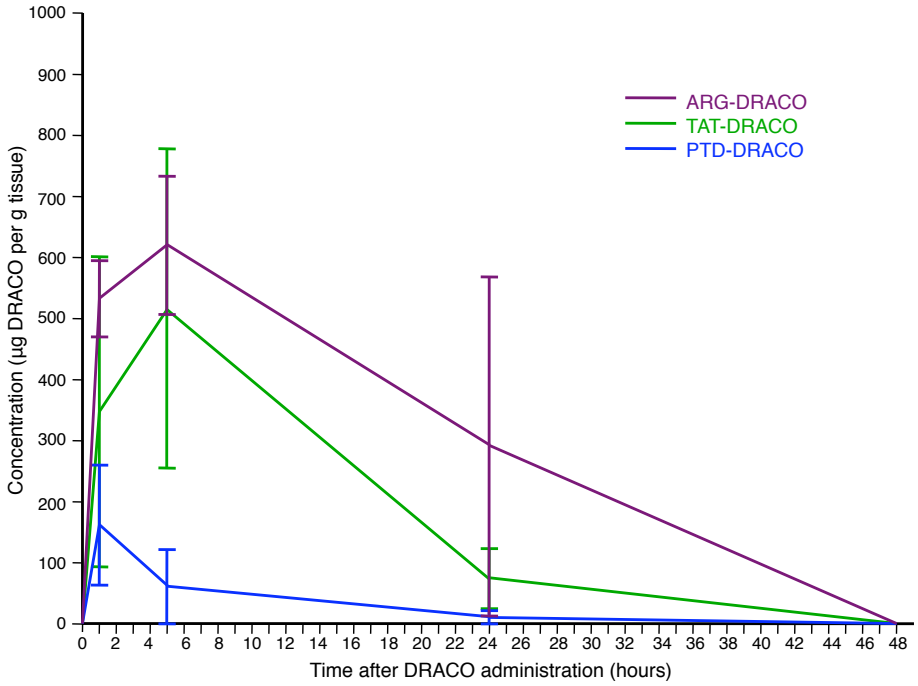


DRACO Is Nontoxic in Mice and Has Good Pharmacokinetics

Intraperitoneal administration (PTD-DRACO)

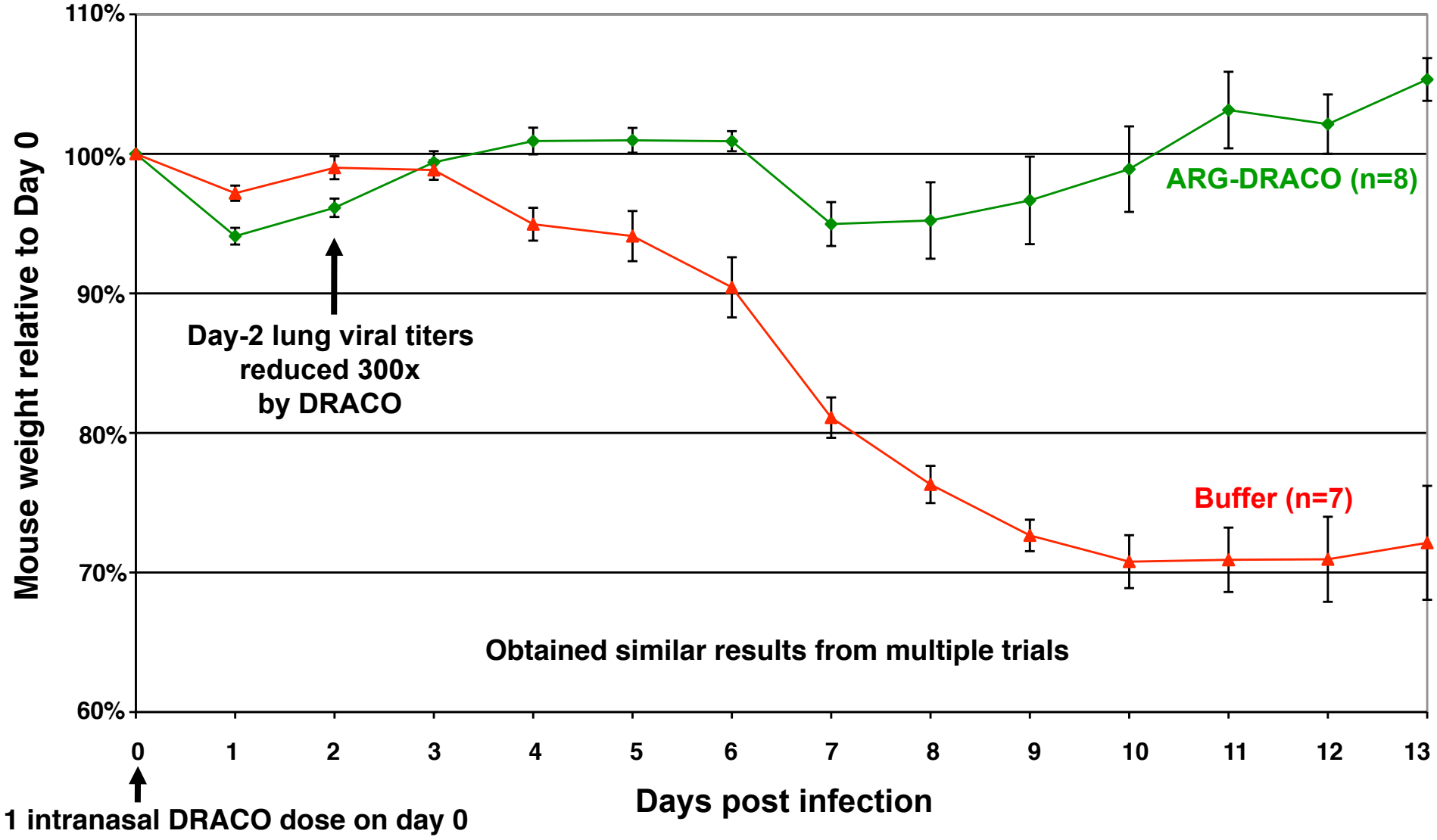


Intranasal administration (Lungs)

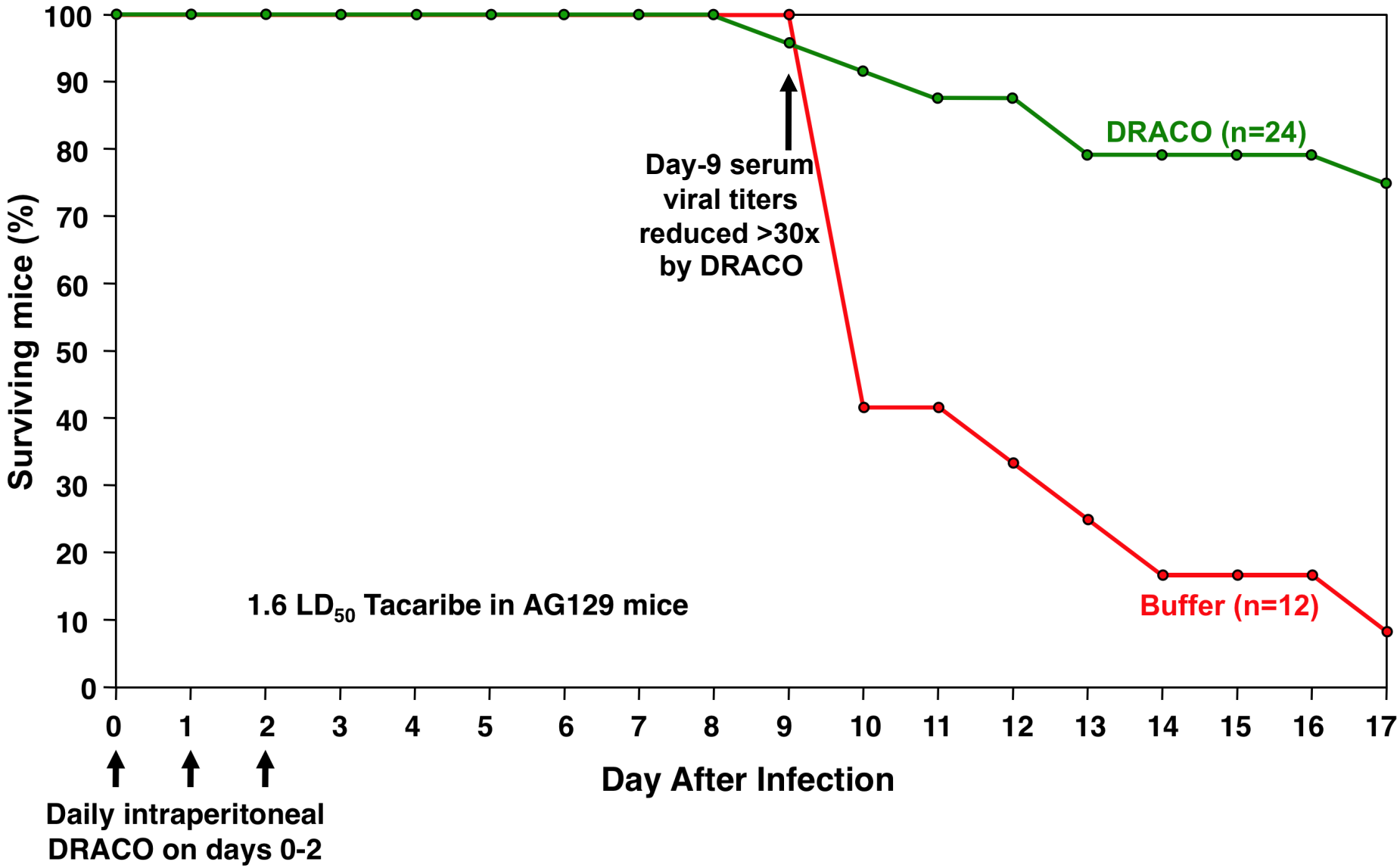


- **No apparent toxicity in live mice or in tissues examined during necropsy**
- **DRACO penetrates into all tissues tested and can persist 24-48 hours**
- **Different administration routes and delivery tags are better for different tissues**

Intranasal DRACO Greatly Improves Survival, Reduces Weight Loss, & Reduces Viral Titers in Mice Challenged with 1 LD_{50} H1N1 Influenza



Preliminary Data Shows DRACO Efficacy Against Tacaribe Hemorrhagic Fever Virus in AG129 Mice



THR-23

Some “Outbreak” Viruses of Potential Interest

Family	Virus	Human impact	Alternatives	BL2 model
Alpha-virus	Chikungunya	Now in Americas Years of pain	No	Cells: Yes Mice: Yes
Arena-virus	Junin, Lassa, etc.	Bioterrorism 25% mortality	No	Cells: Yes Mice: Yes
Bunya-virus	Rift Valley Fever, etc.	Bioterrorism Hemorrhagic fever	No	Cells: Yes Mice: Yes
Corona-virus	MERS	Epidemic? 25% mortality	No	Cells: Yes Mice: Yes
Filo-virus	Ebola	Bioterrorism <90% mortality	Some in human trials	Cells:Partial Mice: No
Pox-virus	Smallpox	Bioterrorism 50% mortality	No-engineered resistance	Cells: Yes Mice: Yes

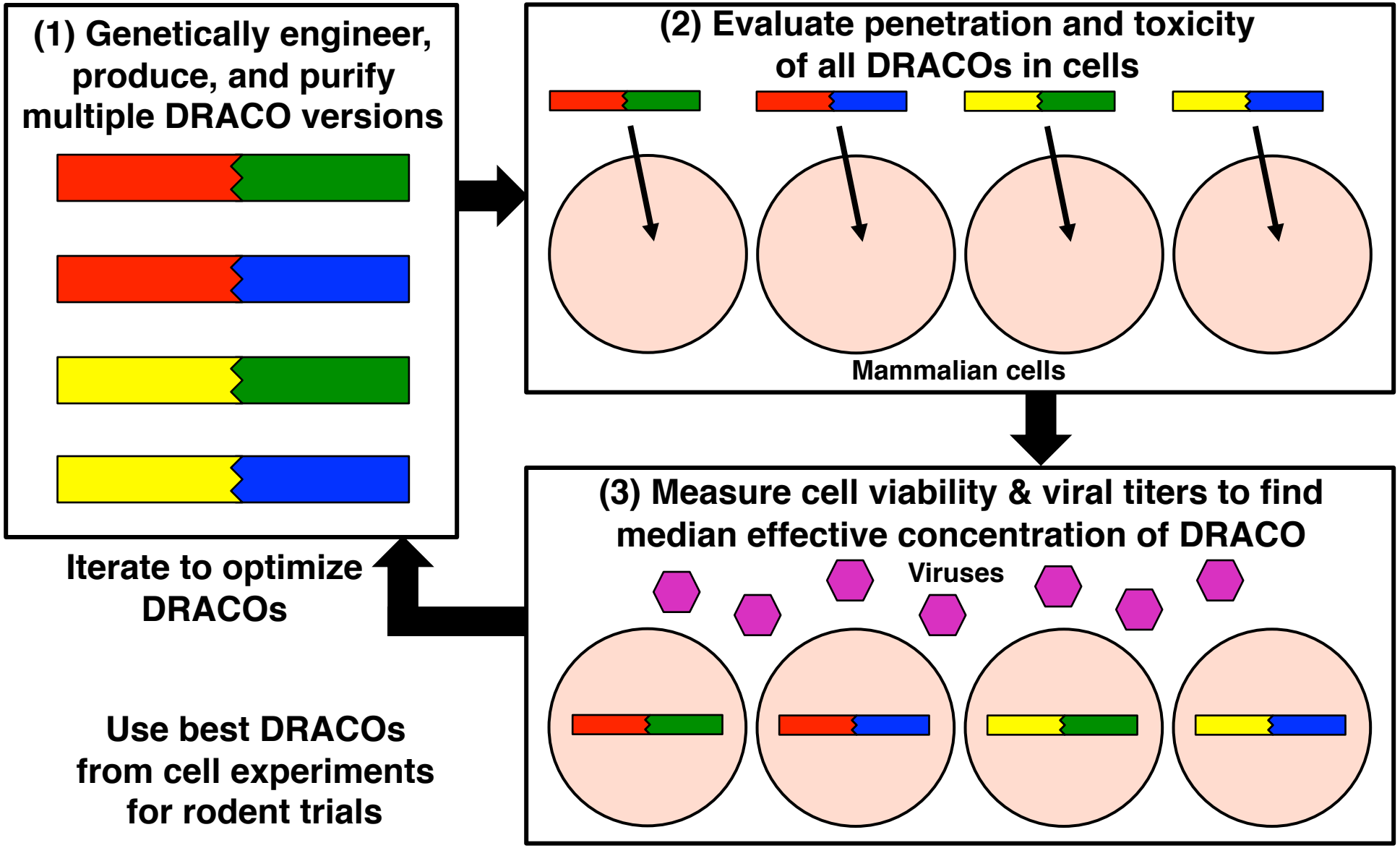
Some Clinical Viruses of Potential Interest (1 of 2)

Family	Virus	Human impact	Alternatives	BL2 model
Delta-virus	Hepatitis D	>20M infected >20,000 deaths/yr	HBV vaccine only	Cells:Partial Woodchuck:Y
Flavi-virus	Hepatitis C	200M infected >350,000 deaths/yr	Side effects, $$$	Cells: Yes Mice: Yes
Flavi-virus	Dengue Fever	500M/yr infected ~1M deaths/yr	Vaccines in development	Cells: Yes Mice: Yes
Hepadna-virus	Hepatitis B	>350M infected >600,000 deaths/yr	Vaccine Treatments ltd	Cells: Yes Mice: Yes
Hepe-virus	Hepatitis E	20M/yr infected >60,000 deaths/yr	Vaccines in development	Cells:Partial Rabbits: Yes

Some Clinical Viruses of Potential Interest (2 of 2)

Family	Virus	Human impact	Alternatives	BL2 model
Herpes-virus	Varicella Zoster	>3B infected Chronic infection	Treat but not cure	Cells: Yes Mice: Yes
Herpes-virus	Herpes Simplex	>500M infected Chronic infection	Treat but not cure	Cells: Yes Mice: Yes
Orthomyxo-virus	Influenza	5M/yr infected >250,000 deaths/yr	Very limited	Cells: Yes Mice: Yes
Paramyxo-virus	Respiratory Syncytial	Very serious for infants	No	Cells: Yes Mice: Yes
Picorna-virus	Hepatitis A	>30M infected >100,000 deaths/yr	Vaccine only	Cells: Yes Mice: Yes
Retro-viruses	HIV & other retroviruses	>35M infected:Health impact even w drugs	Treat not cure Resistance	Cells: Yes Mice: Yes

Potential Work to Optimize DRACOs in Cells (Structure-Activity Relationship or SAR Process)



Potential Work to Optimize DRACOs in Rodents

Test best DRACOs from cell experiments in rodent models of virus infection to find:

- Threshold for toxicity if any
- Tissue distribution
- Half-life
- Metabolized products
- Immunogenicity
- Median effective concentration against virus (morbidity and viral titers)
- Maximum time pre-infection for prophylactic DRACO administration
- Maximum time post-infection for therapeutic DRACO administration

Iterate DRACO designs to:

- Minimize toxicity and immunogenicity
- Maximize distribution and half-life
- Maximize efficacy against virus