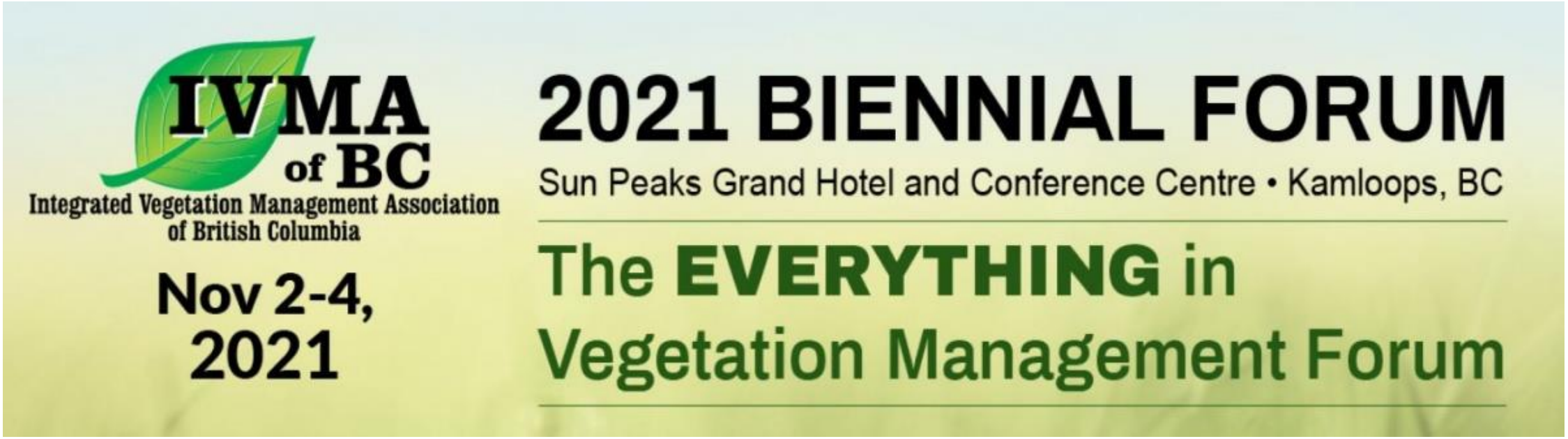


Facts, Fiction, and the Future of Chemical and Biological Herbicides

Ronny Priefer, PhD

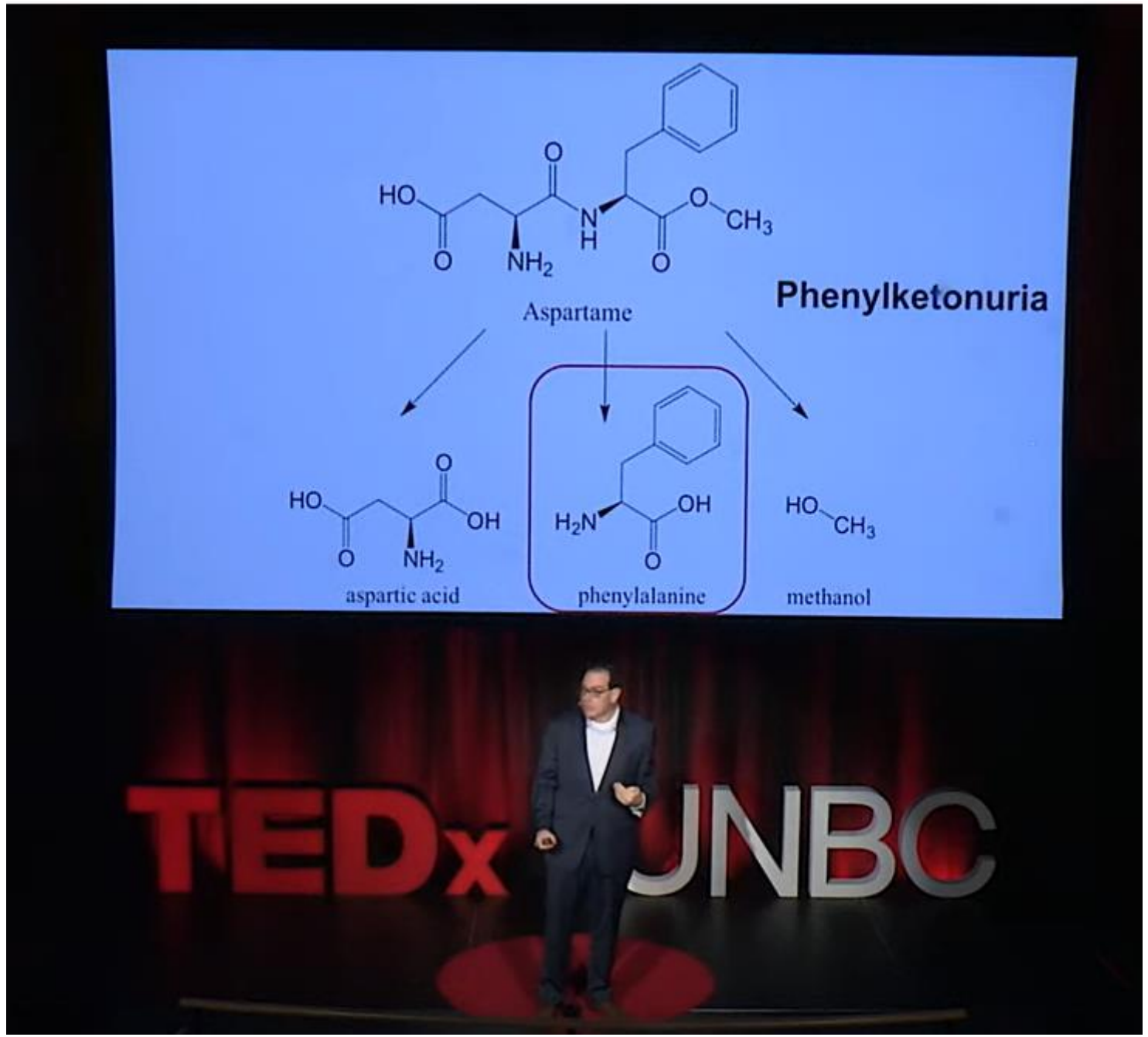
Department of Pharmaceutical Sciences

Massachusetts College of Pharmacy and Health Sciences University

Who I am

- Canadian (now dual American Citizen)
- BSc from the University of Northern British Columbia (1998)
- PhD from McGill University (2003)
- Worked in industry
  - Neurochem Inc (worked on Alzheimer's and epilepsy) (2003 - 2004)
  - Starks Associates (contract research) (2004 - 2005)
- Worked in academia
  - Niagara University (2005 - 2012)
  - Western New England University (2012 - 2018)
  - Massachusetts College of Pharmacy and Health Sciences University (2019 -)
- Serial entrepreneur
  - Acid Reign Where
  - Primurlyn
  - Breath Health
  - New England Breath Technologies
  - SAER


The Growing
Fear of
SCIENCE!
TEDx
UNBC


Phenylketonuria
Aspartame
aspartic acid
phenylalanine
methanol
TEDx JNBC

The Growing Fear of Science | Ronny Priefer | TEDxUNBC

2,527 views • Mar 27, 2020

82 1 SHARE SAVE ...

j0seph 1 year ago

Dr. Priefer is one of my professors. Nice to see him up here.

2 REPLY

BelieveInYourDreams 1 year ago

Thanks for talking of this argument. Thanks to Science, Technology and Innovation, we are going farther. Thanks to all scientists.

1 REPLY

D

David P 10 months ago

Nice talk 👍

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Rayeemon _ 1 year ago

That's my professor!!

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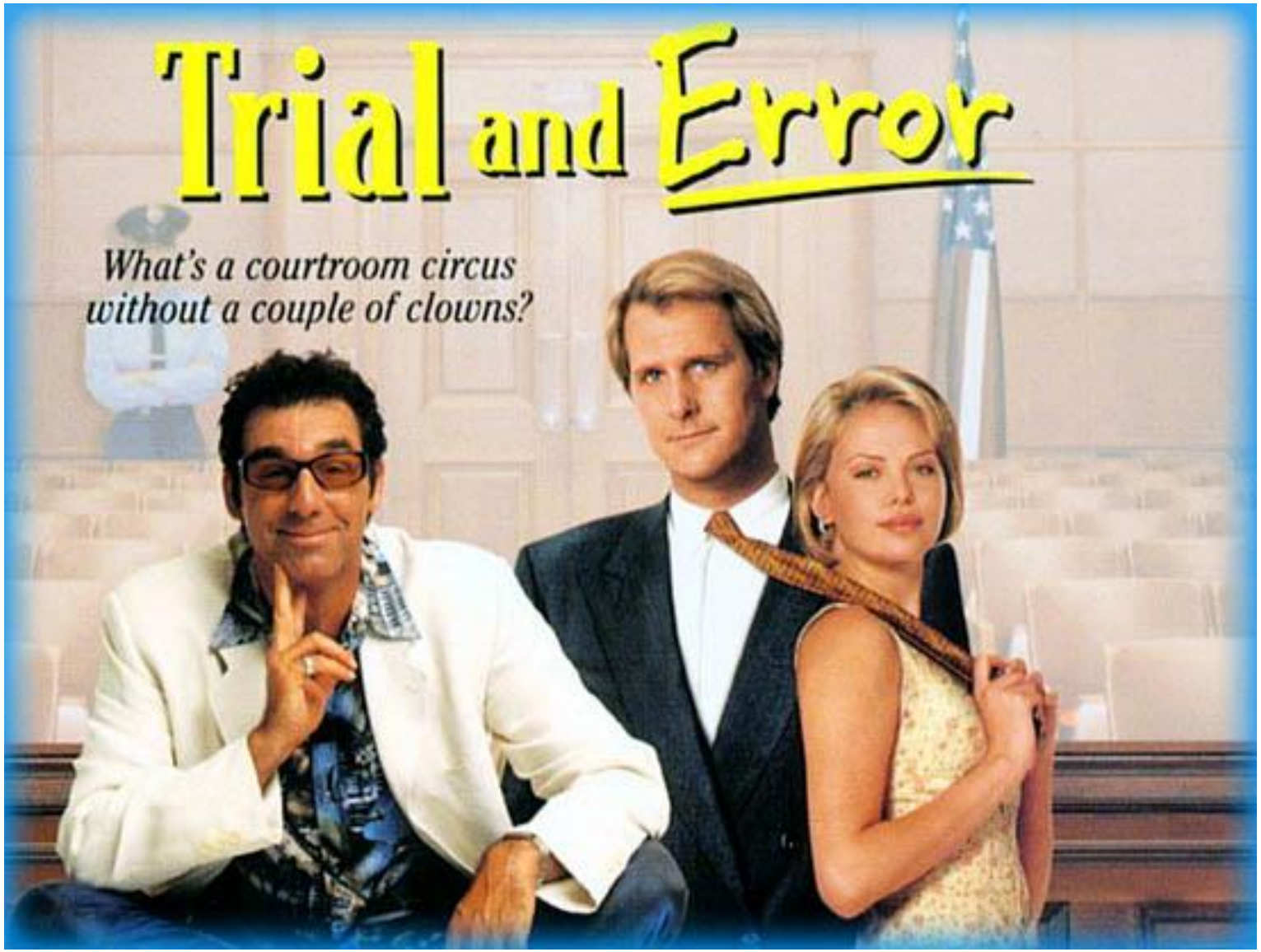
Daniel C. Freteval 1 year ago

Is he in the aspartame paycheck? :D

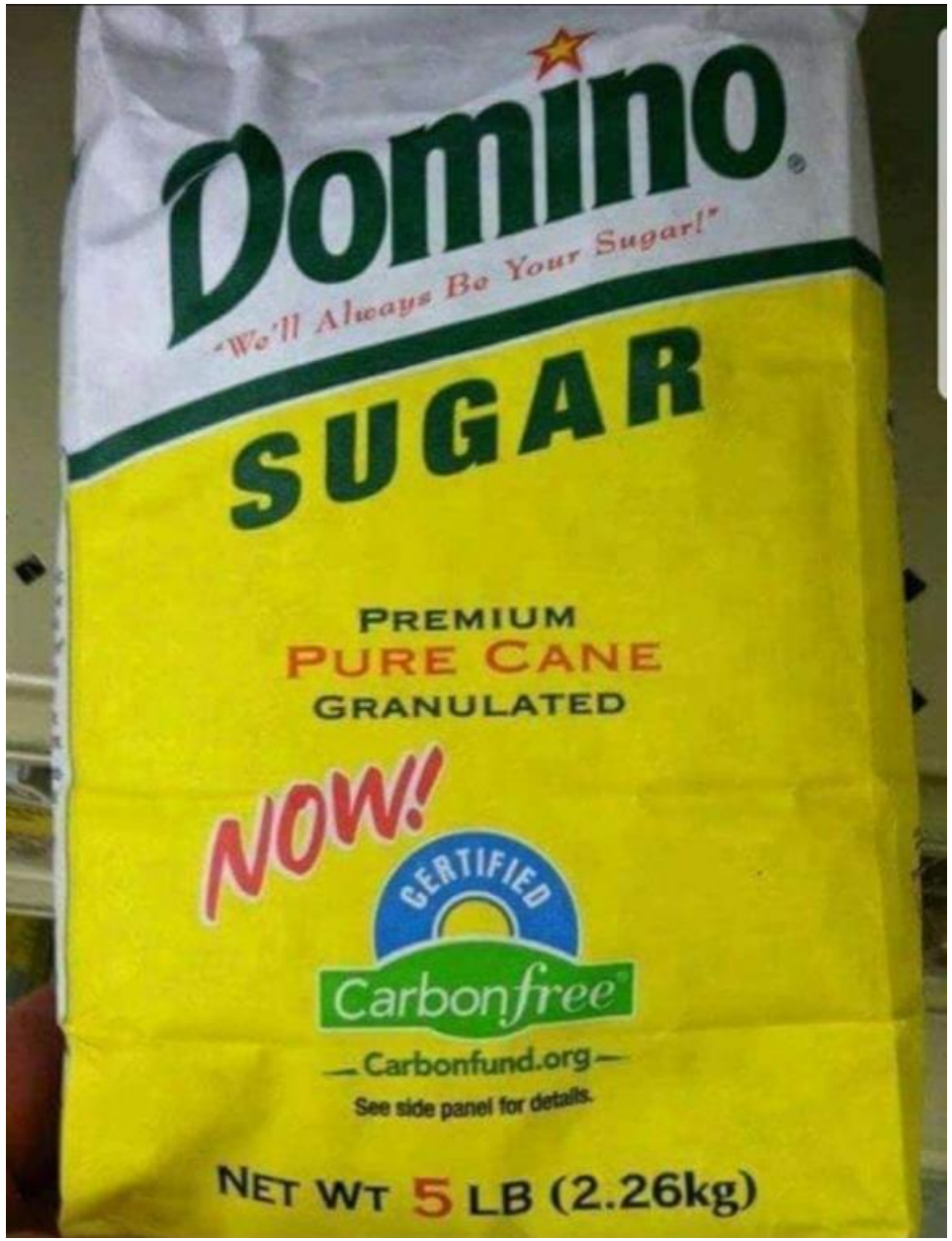
REPLY



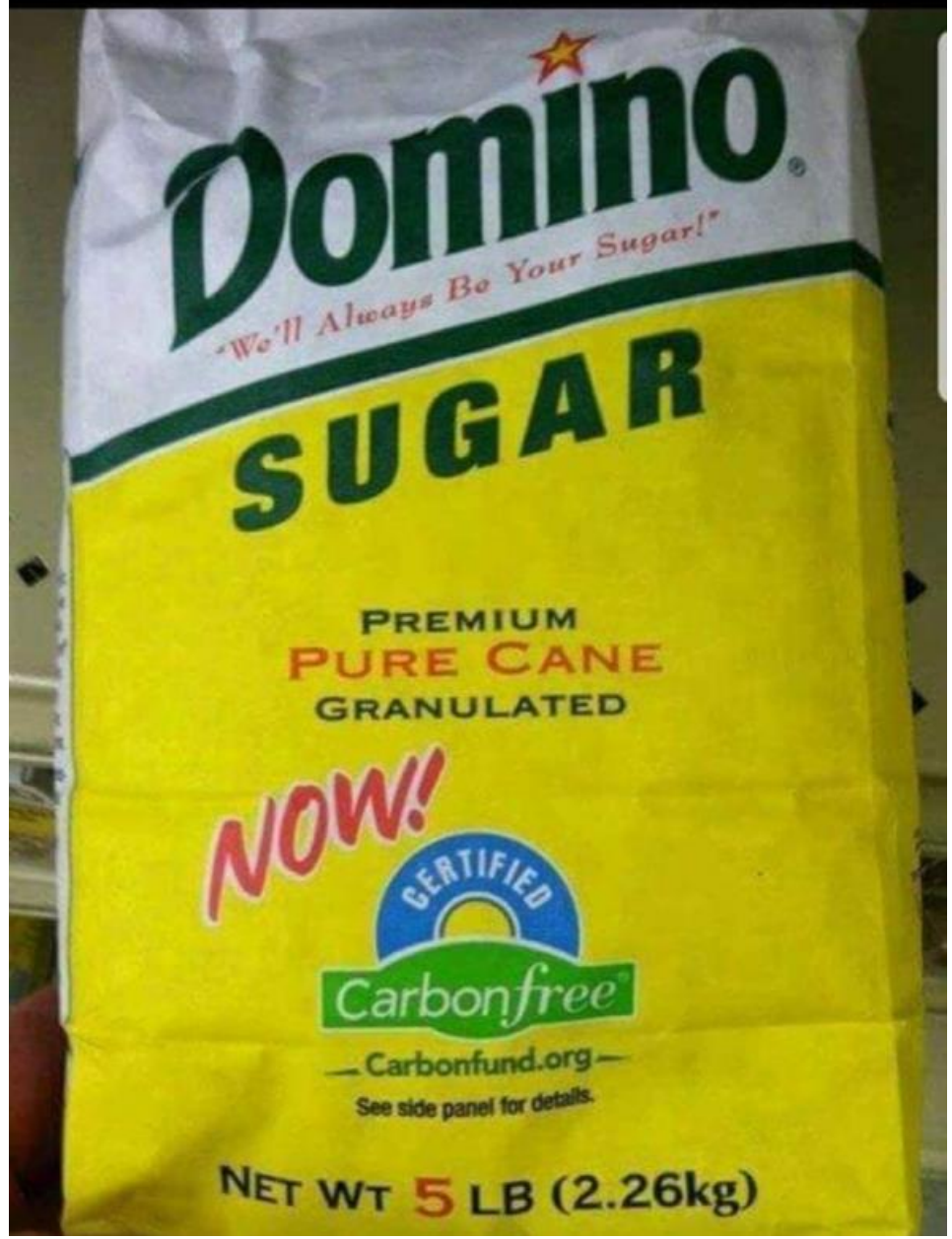
Michael Richards, Jeff Daniels, Charlize Theron

5.8/10 IMDb	50% Rotten Tomatoes

Budget	$25 million
Box Office	$14.6 million


Domino
"We'll Always Be Your Sugar!"
SUGAR
PREMIUM
PURE CANE
GRANULATED
NOW!
CERTIFIED
Carbonfree
Carbonfund.org
See side panel for details.
NET WT 5 LB (2.26kg)

Certified carbon free sugar. Because screw the twelve carbon atoms needed to make sugar...

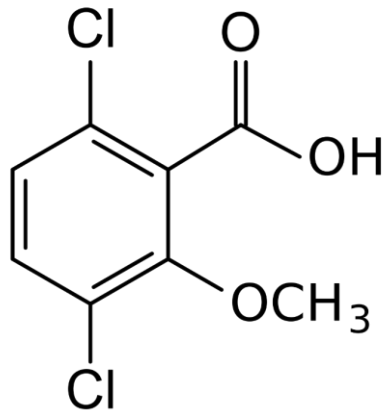



PRESENT
PAST
FUTURE

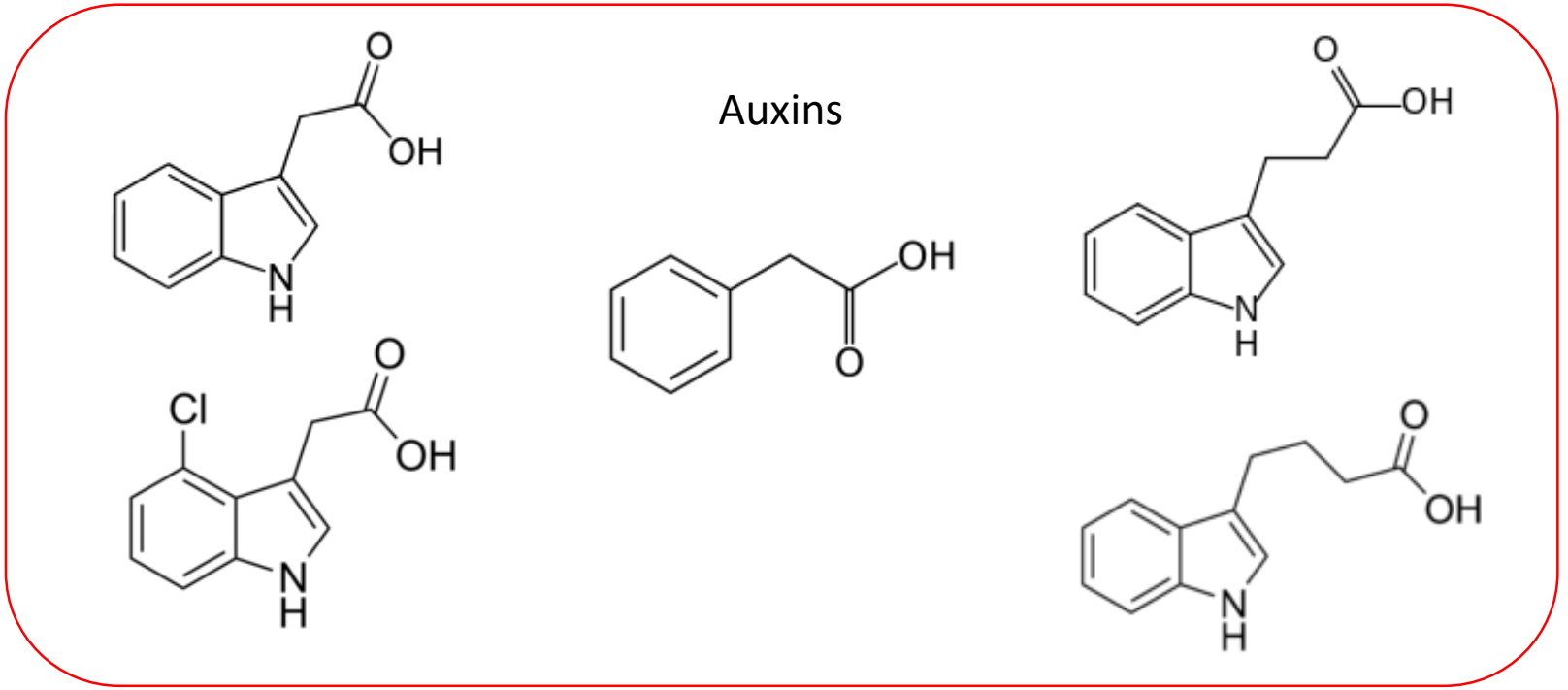
Dicamba

Dianat, Banvel, Diablo, Oracle, Vanquish

- Broad-spectrum herbicide
- Act to increase plant growth by mimicking the plant hormones, auxins
- When used, plants grow abnormally in uncontrollable ways, leading to death



Dicamba

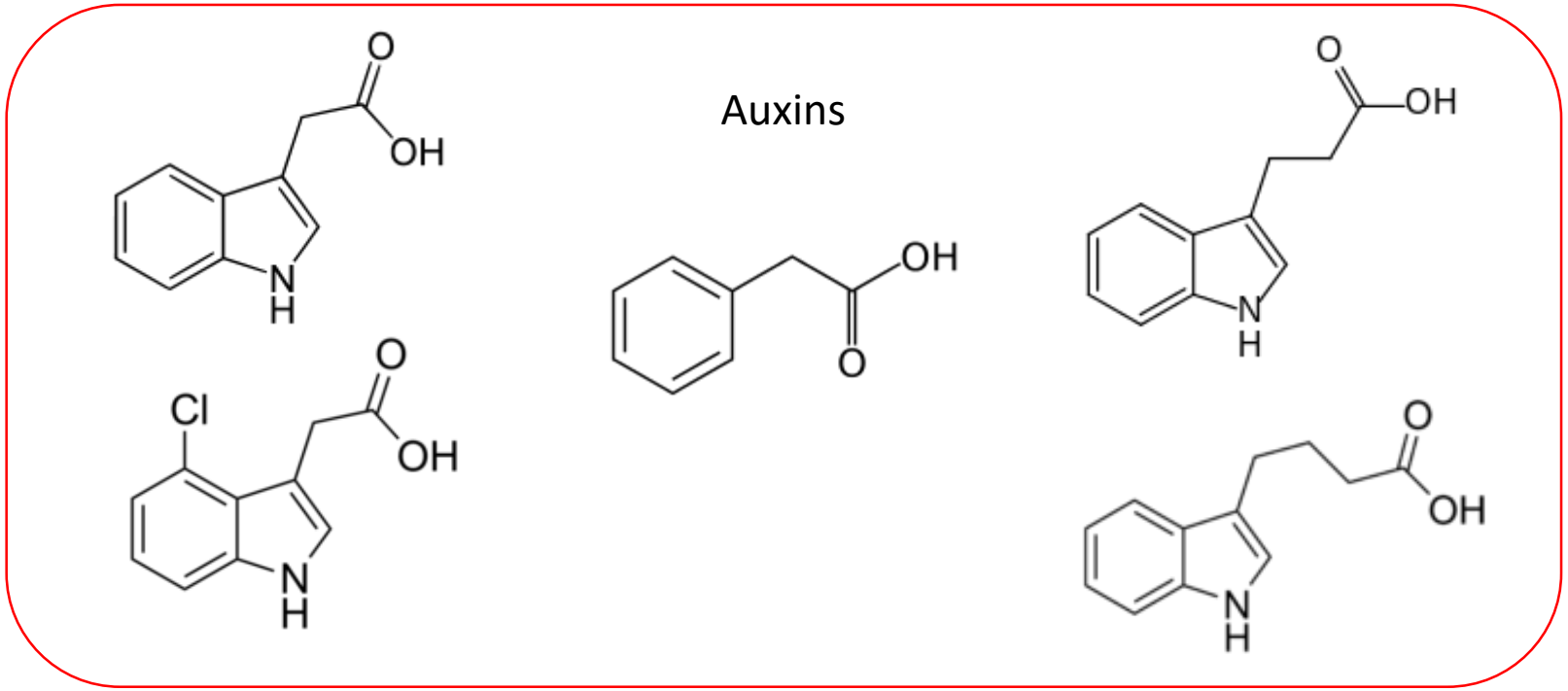


TIME TO THINK LIKE THE INTERNET

Where a little knowledge can do more damage than good

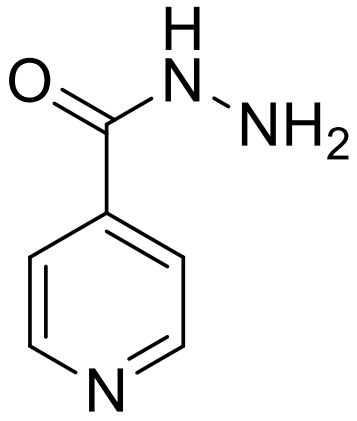
Auxins

- A class of plant hormones with some morphogen-like characteristics.
- Plays an important role in the coordination of many growth processes in the plant life cycles and development.

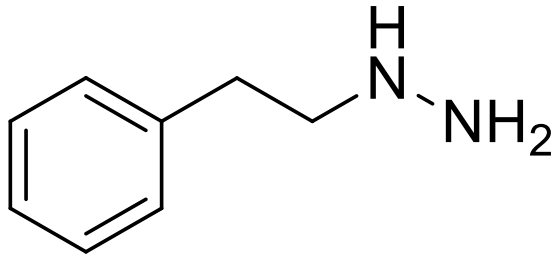


Monoamine Oxidase Inhibitors (MAOIs)

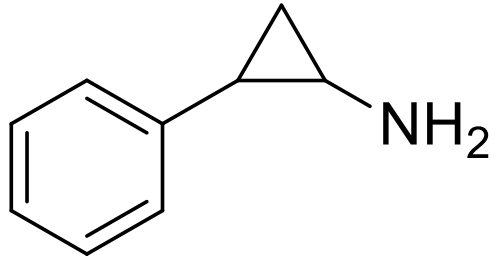
- Isoniazid is an anti-tuberculosis drug which also has powerful antidepressant properties.
- This became the forerunner of the MAOIs.
- This led to the field of hydrazine and non-hydrazine MAOIs.



Isoniazid



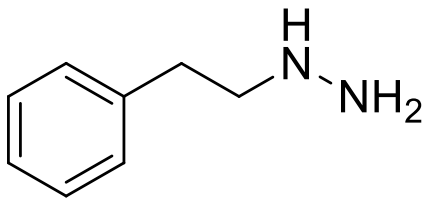
Phenelzine



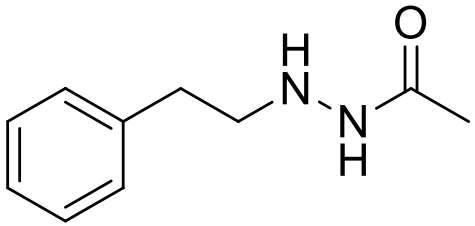
Tranylcypromine

Monoamine Oxidase Inhibitors (MAOIs)

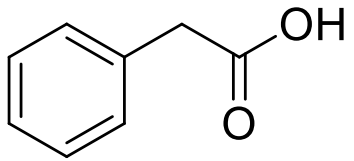
- Phenelzine irreversible inhibitor of MAO-A and MAO-B.
- MAOIs are potentially dangerous in patients with binge eating and purging behavior.
- *N*-acetylation and oxidation are the major metabolites.



Phenelzine

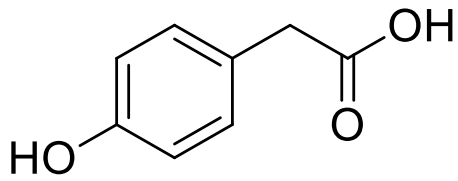


N-acetylphenelzine



Phenylacetic acid

Known metabolites

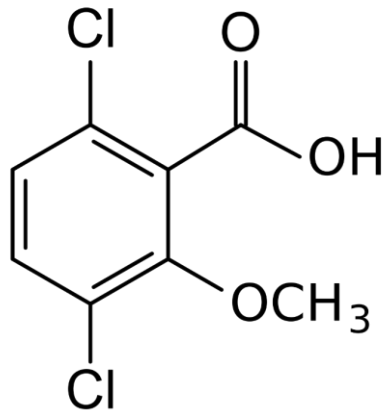


4-Hydroxyphenylacetic acid

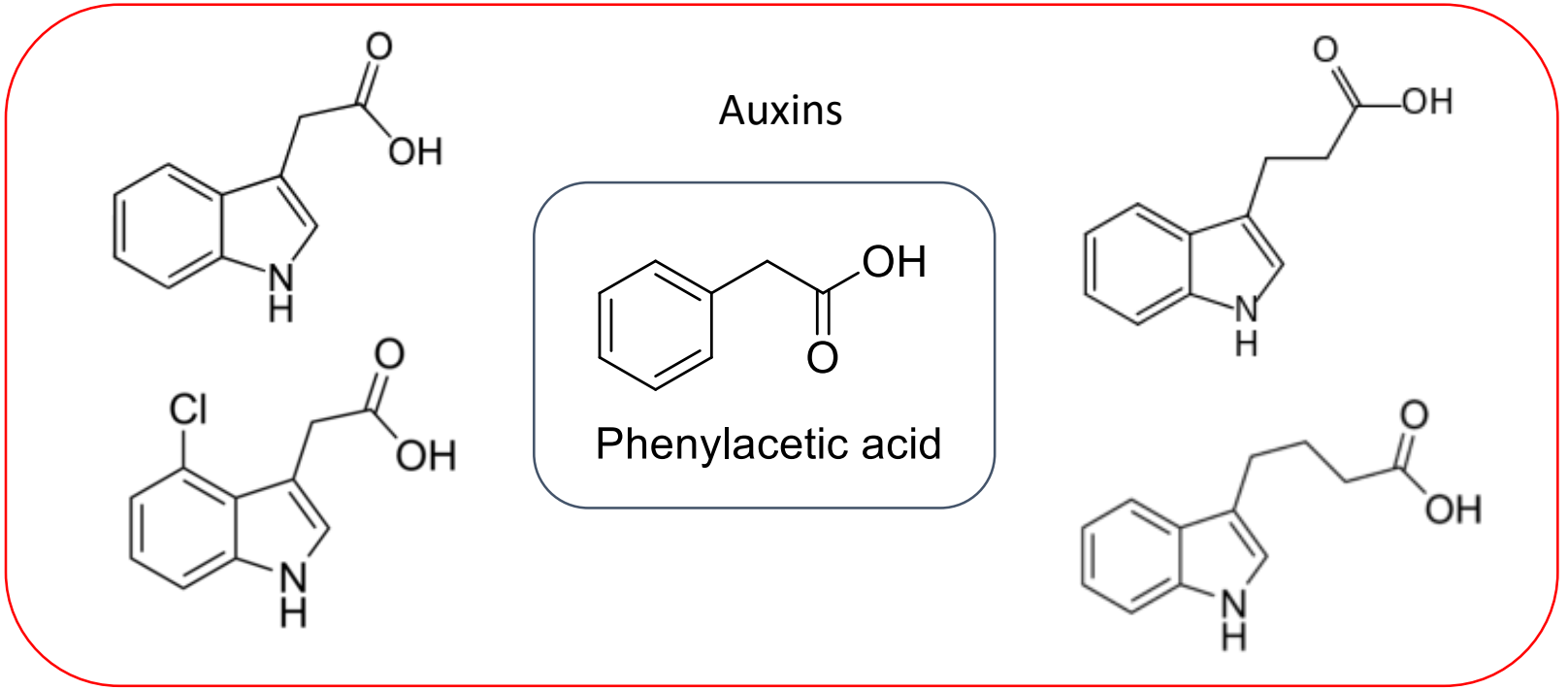
Dicamba

Dianat, Banvel, Diablo, Oracle, Vanquish

- Plays an important role in the coordination of many growth processes in the plant life cycles and development.
- Auxins play a key role in coordination of many growth and behavioral processes in plant life cycles and are essential for plant body development.

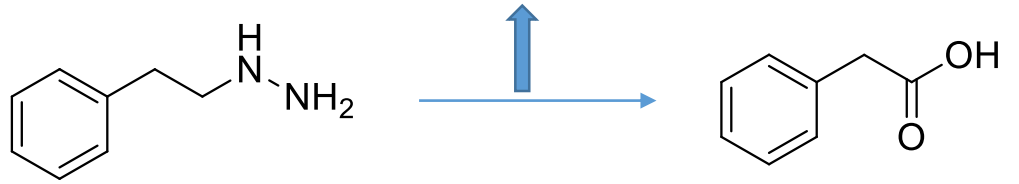


Dicamba



TIME TO THINK LIKE THE INTERNET

1) PAA is a metabolite of the antidepressant, Phenelzine



Phenelzine

Phenylacetic acid

TIME TO THINK LIKE THE INTERNET

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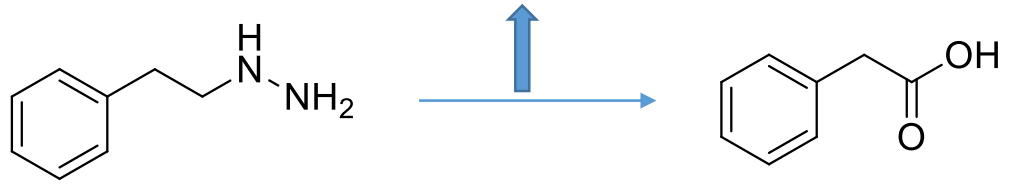
2) PAA is an auxin



Phenelzine

Phenylacetic acid

TIME TO THINK LIKE THE INTERNET

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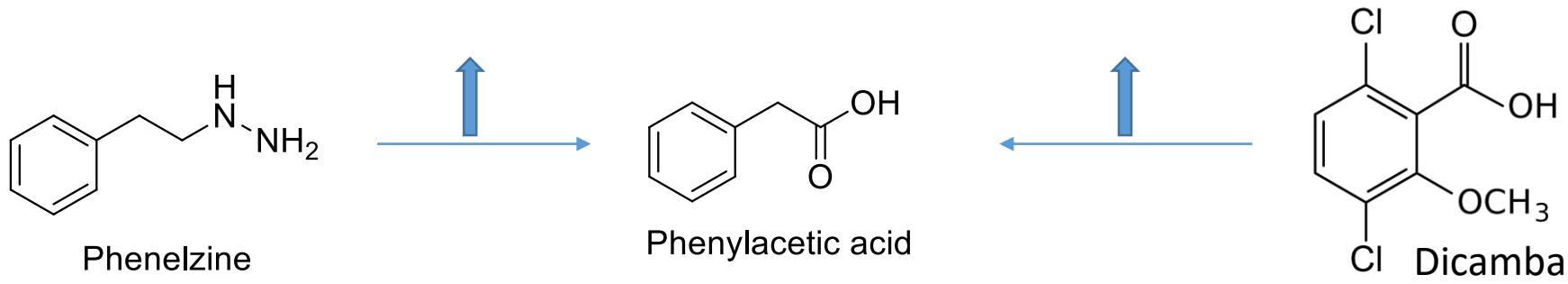
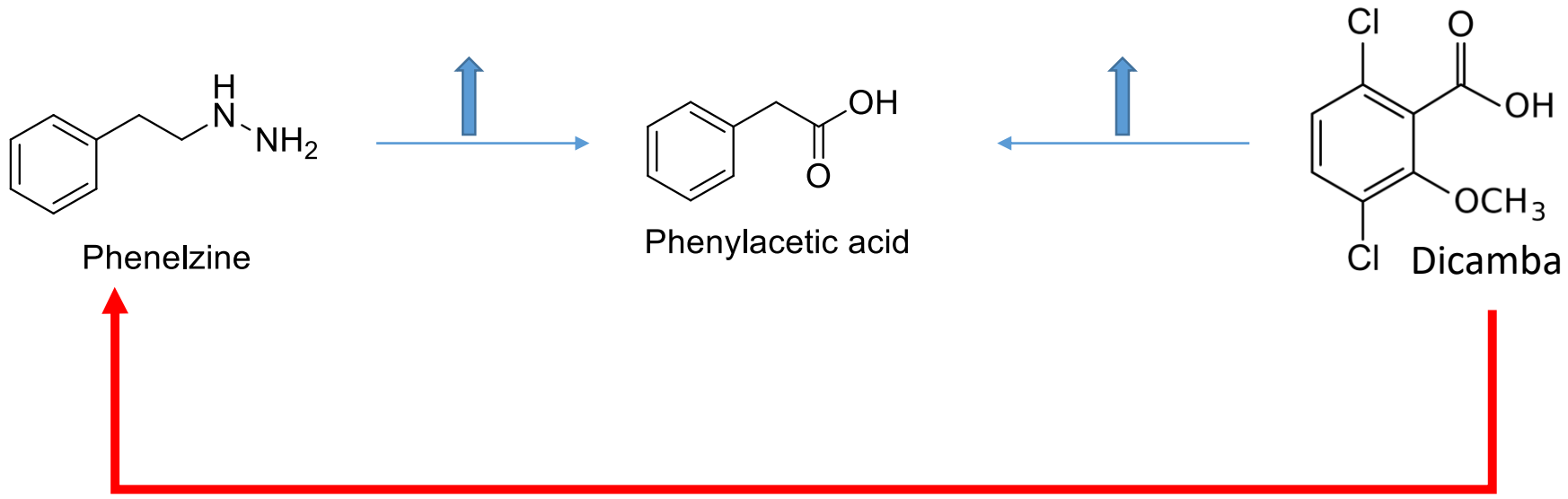
2) PAA is an auxin
3) Dicamba works by increasing PAA levels



Phenelzine Phenylacetic acid Dicamba

TIME TO THINK LIKE THE INTERNET

1) PAA is a metabolite of the antidepressant, Phenelzine
2) PAA is an auxin
3) Dicamba works by increasing PAA levels
4) Therefore, Dicamba must also act as an antidepressant



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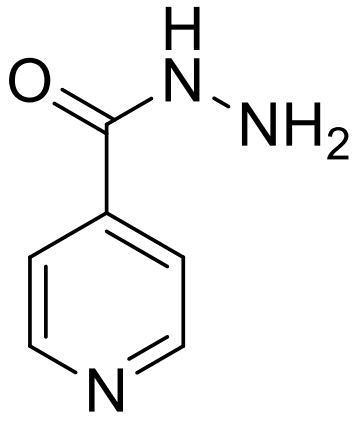
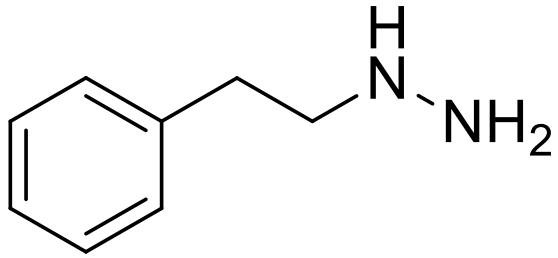
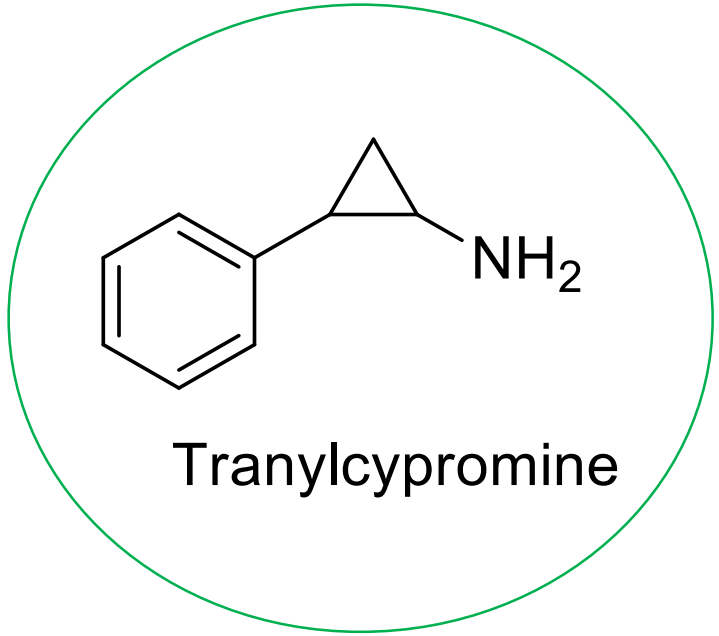


Isoniazid



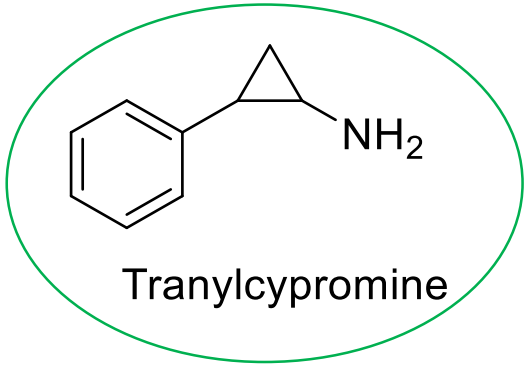
Phenelzine



Tranylcypromine

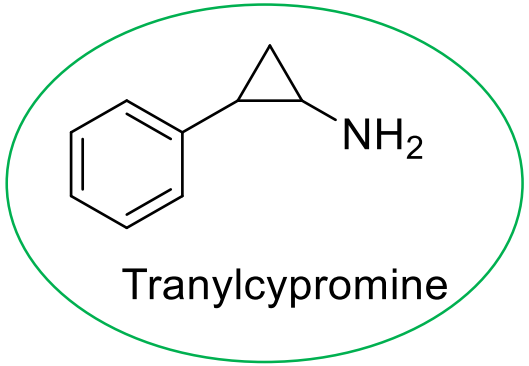
Monoamine Oxidase Inhibitors (MAOIs)

- Tranylcypromine is a non-hydrazine MAOI.



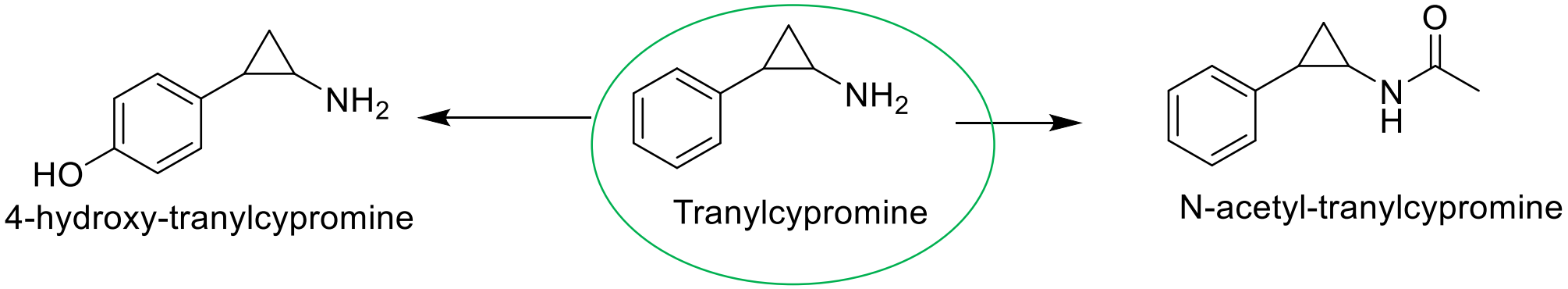
Monoamine Oxidase Inhibitors (MAOIs)

- Tranylcypromine is a non-hydrazine MAOI.
- It is an irreversible inhibitor of MAO-A and MAO-B.



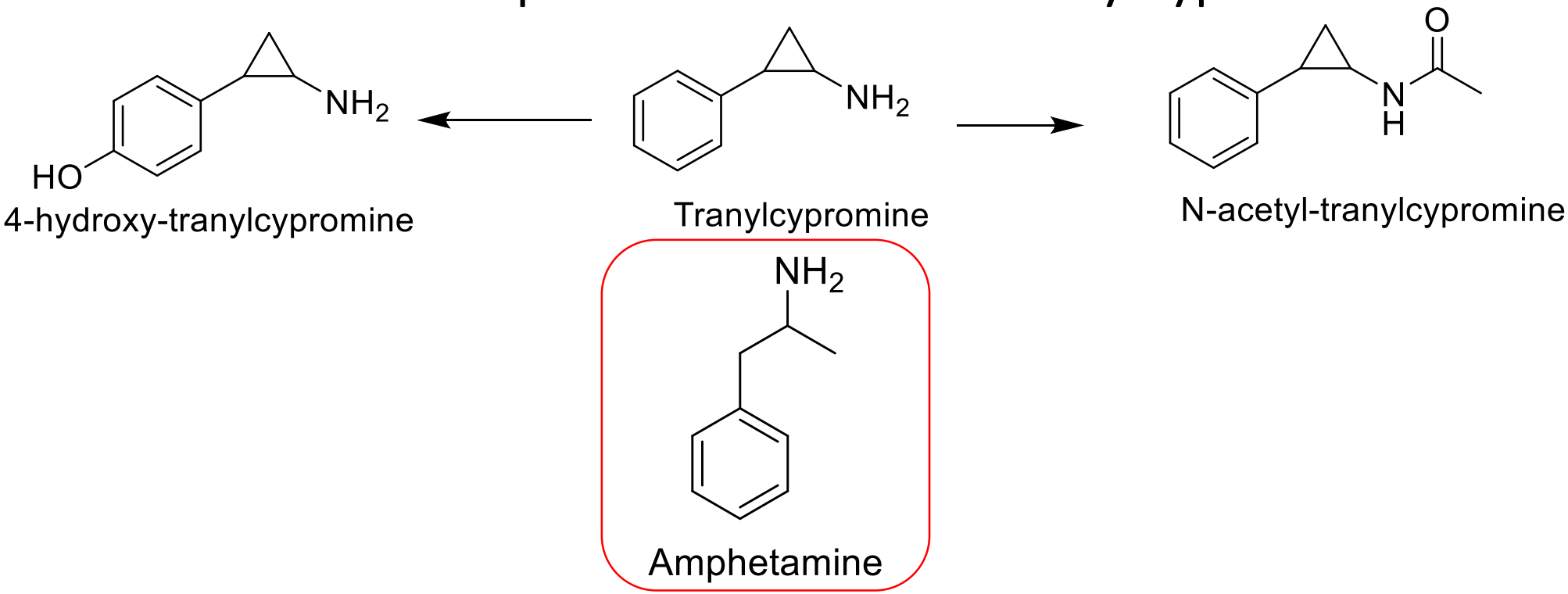
Monoamine Oxidase Inhibitors (MAOIs)

- Tranylcypromine is a non-hydrazine MAOI.
- It is an irreversible inhibitor of MAO-A and MAO-B.
- Metabolism is *N*-acetylation and aromatic hydroxylation.



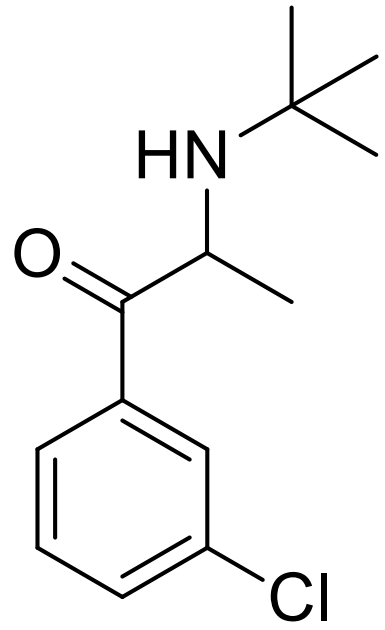
Monoamine Oxidase Inhibitors (MAOIs)

- Tranylcypromine is a non-hydrazine MAOI.
- It is an irreversible inhibitor of MAO-A and MAO-B.
- Metabolism is *N*-acetylation and aromatic hydroxylation.
- NOT metabolized to amphetamine as was initially hyped.



Dopamine and Norepinephrine Reuptake Inhibitors (DNRIs)

- Bupropion is a selective inhibitor of Dopamine reuptake at the presynaptic neuronal membrane is also a Norepinephrine Reuptake
- Bupropion is a noncompetitive antagonist of several nicotinic receptors; and thus has been used in smoking cessation programs (Zyban)



Bupropion

Bupropion: The “Poor Man’s Cocaine”? A Case Report

Ryan A. Anderson, D.O.
Chief Resident, Lehigh Valley Health Network

'Bath Salts' Drug Suspected In Miami Face-Eating Attack

May 30, 2012 · 12:50 PM ET

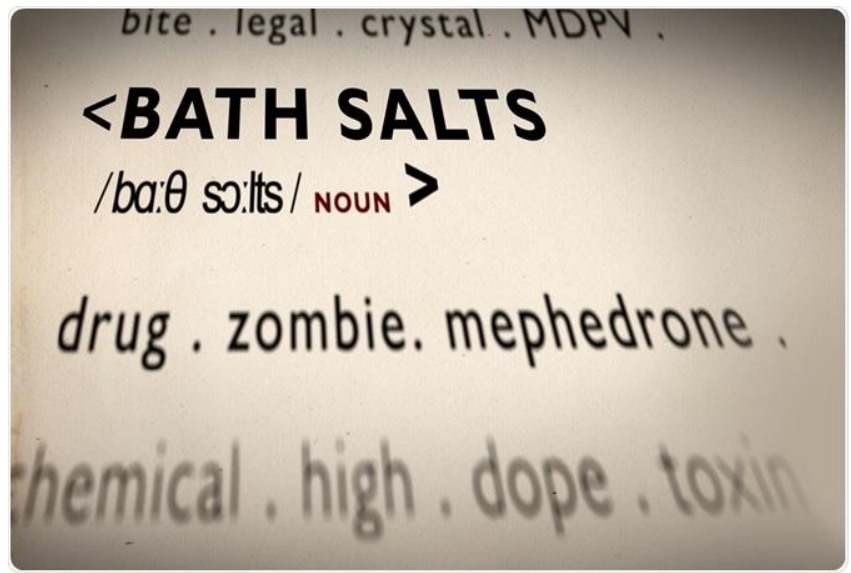
Bath Salts Had Role in Face-Eating?

MIAMI ZOMBIE

Updated Apr. 21, 2017 4:58PM ET / Published May. 29, 2012 1:48PM ET

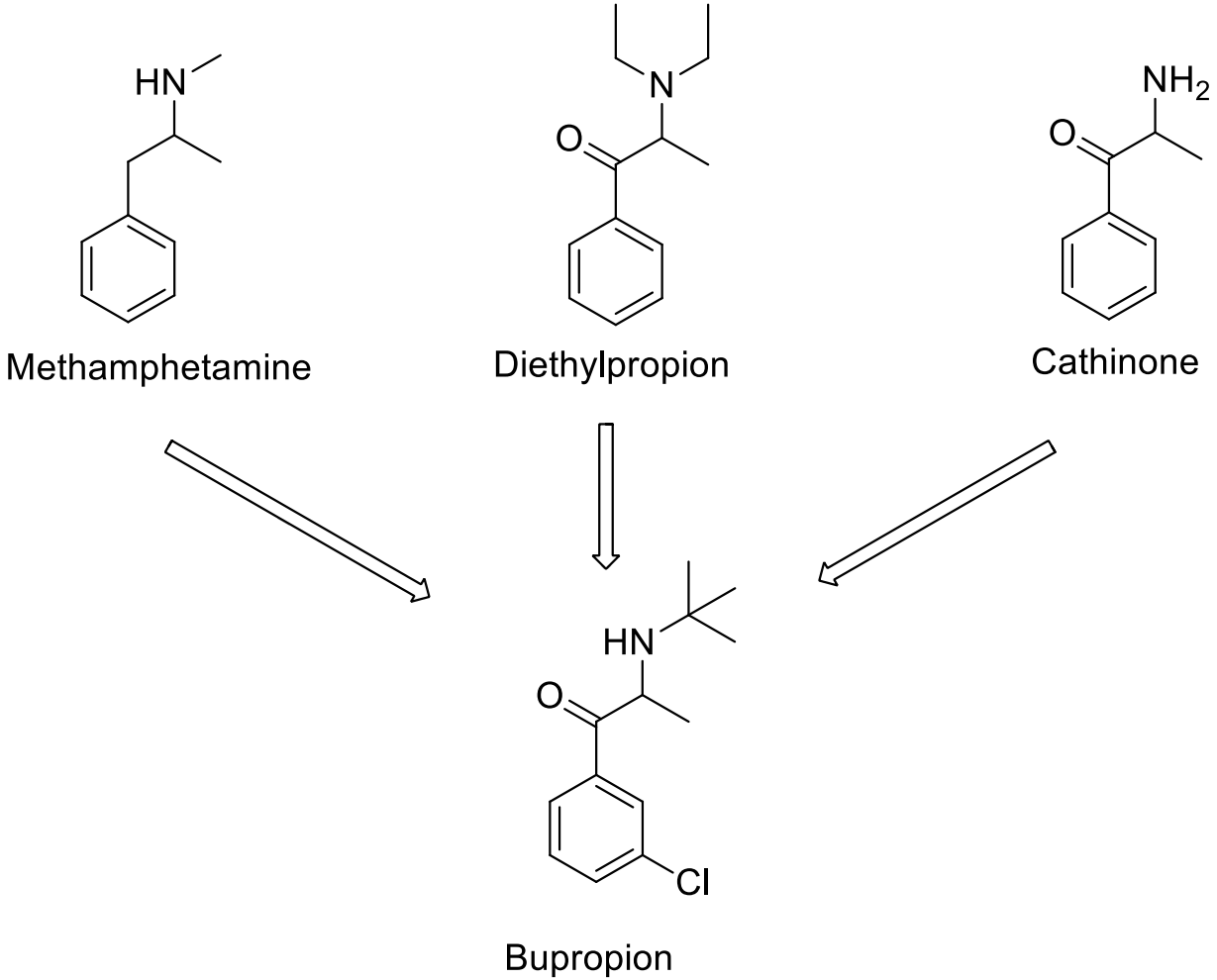
Face-Eating Cannibal Attack May Be Latest in String of 'Bath Salts' Incidents

By **ABC News**
June 1, 2012, 10:10 AM • 6 min read



Dopamine and Norepinephrine Reuptake Inhibitors (DNRIs)

- Bupropion is structurally similar to the CNS stimulant, methamphetamine; the diet suppressant, diethylpropion; as well as cathinone (“bath salt” family)



WHEN ARE NUMBERS NOT JUST NUMBERS

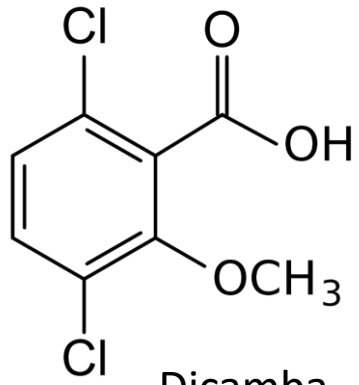
Where facts stay facts but are made to look scary

Dicamba

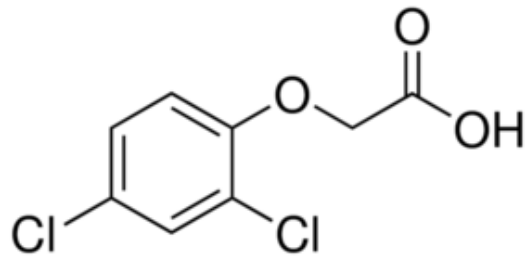
Dianat, Banvel, Diablo, Oracle, Vanquish

2,4-Dichlorophenoxyacetic acid (2,4-D)

Hedonal, Trinoxol



Dicamba

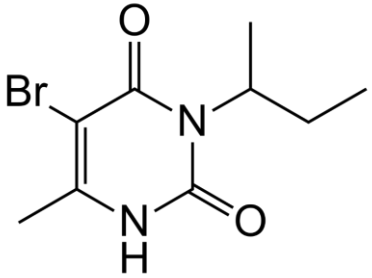


2,4-D

- Both Dicamba and 2,4-D can inhibit the acetylcholinesterase of animals
- LD_{50} of Dicamba in rats is 1,707mg/kg
- This is translated to be 3.5ounces for a 60kg in humans
  - Notice the use of ounces!!!
  - Equally accurate but less scary is 102,420mg for a 60kg human or 102g for 60 kg
  - Also, what is the average weight of an American male?
    - 198lbs (i.e. 90kg)
  - Thus, lethal dose for an average male is 153g.
- As a comparison LD_{50} of 2,4-D in rats is 639mg/kg to 1,646mg/kg.

Bromacil

Bromazil, Borea, Bromax 4G, Cynogan, Uragan



Bromacil

- Broad-spectrum herbicide
- Works by interfering with photosynthesis
- Nonselective weed and brush control
- LD_{50} of 5,200mg/kg [Dicamba LD_{50}: 1,707mg/kg]
- Irritant to skin, eyes, and respiratory tract
- There are quite a few safety precautions that should be taken when dealing with Bromacil. Dry formulations containing bromacil must bear the word "Caution" and liquid formulas must signal "Warning.“ Care should be exercised when spraying Bromacil on plants because it will also stop the photosynthesis of the adjacent non-target plants, therefore killing them. Bromacil should never be used in residential or recreation areas for risk of exposure. Bromacil is slightly toxic if individuals accidentally eat or touch residues and practically nontoxic if inhaled. Bromacil is a mild eye irritant and a very slight skin irritant. It is not a skin sensitizer. In studies using laboratory animals, bromaci is slightly toxic by the oral, dermal, and inhalation routes and has been placed in Toxicity Category IV (the lowest of four categories) for these effects. This herbicide should be stored in a cool, dry place and after any handling a thorough hand-washing is advised.
- In regards to occupational exposure, the National Institute for Occupational Safety and Health has recommended workers handing bromacil not exceed an exposure of 1 ppm (10 mg/m^3) over an eight-hour time-weighted average.

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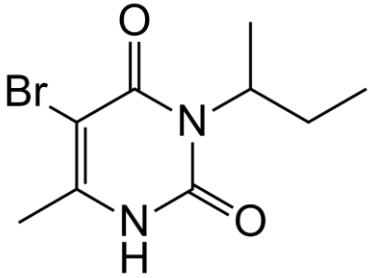

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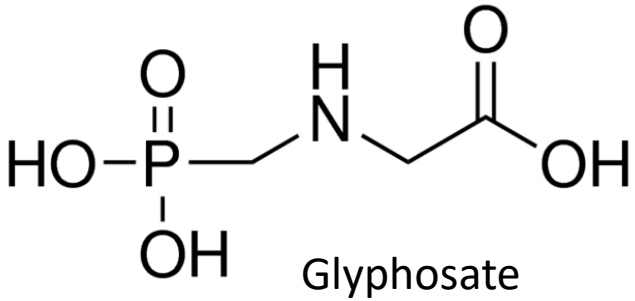
Glyphosate
Roundup



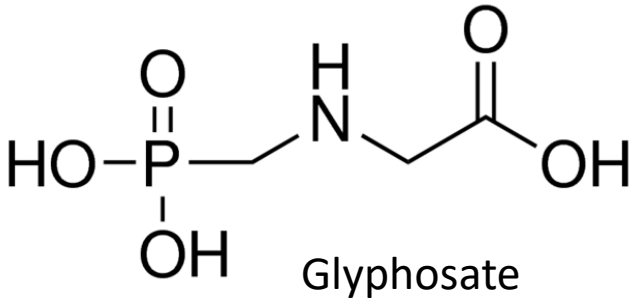
Glyphosate

- Broad-spectrum herbicide
- Inhibits the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase (i.e. shikimate pathway).
- Famous due to the DeWayne Lee Johnson lawsuit related to his non-Hodgkin lymphoma diagnosis.
- LD_{50} of 4,300mg/kg in rats
  - Recall that Dicamba has a LD_{50} of 1,707mg/kg and Bromacil is 5,200mg/kg

Other LD_{50} (rats)

Vitamin C	11,900mg/kg
Alcohol	7,060mg/kg
Fructose	4,000mg/kg
Caffeine	192mg/kg
Cocaine	72mg/kg

Glyphosate
Roundup



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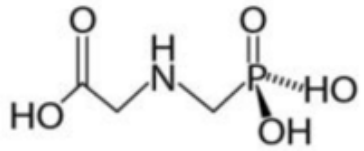
- Famous due to the DeWayne Lee Johnson lawsuit related to his non-Hodgkin lymphoma diagnosis.
- LD_{50} of 4,300mg/kg in rats
  - Recall that Dicamba has a LD_{50} of 1,707mg/kg and Bromacil is 5,200mg/kg
- In an analysis of 601 cases of glyphosate ingestion, 27% were asymptomatic and 64% had minor symptoms. Approximately 5.5% had moderate to severe poisoning and 3.2% of the patients died.[1]
- Most moderate to severe symptomatic cases have been associated with intentional (suicidal) ingestion.[1-3]
- Most, if not all of the symptoms may actually be related to the organic surfactant with which glyphosate is combined with.
- Regulatory agencies such as: Health Canada, European Food Safety Authority, Food and Agriculture Organization of the United Nations, World Health Organization, and the United States Environmental Protection Agency all concluded that glyphosate was unlikely to pose a carcinogenic risk to humans.
- Texas A&M University's AgriLife reported that glyphosate was the least toxic of all plant-killing herbicides that they tested.

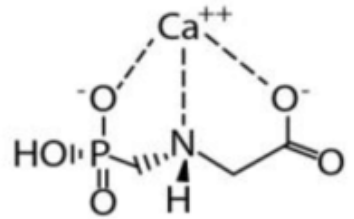
[1]Clin Toxicol 2010;48(2):129-136 [2]Clin Toxicol 2010;48:718-724 [3]Clin Toxicol 2006;44:329-332.

Long Half Life



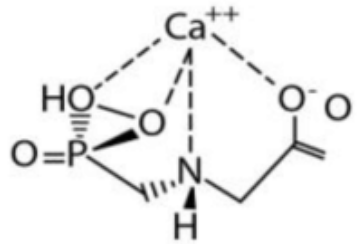
Glyphosate

Long half life- up to many years



Tridentate ligand

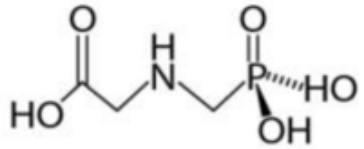
(Madsen et al. 1978)



Tetradentate ligand

(Subramaniam and hoggard 1988)

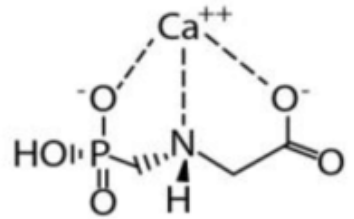
Long Half Life



Glyphosate

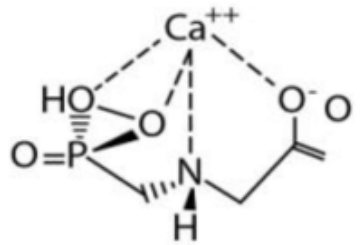
In hard water

Long half life- up to many years



Tridentate ligand

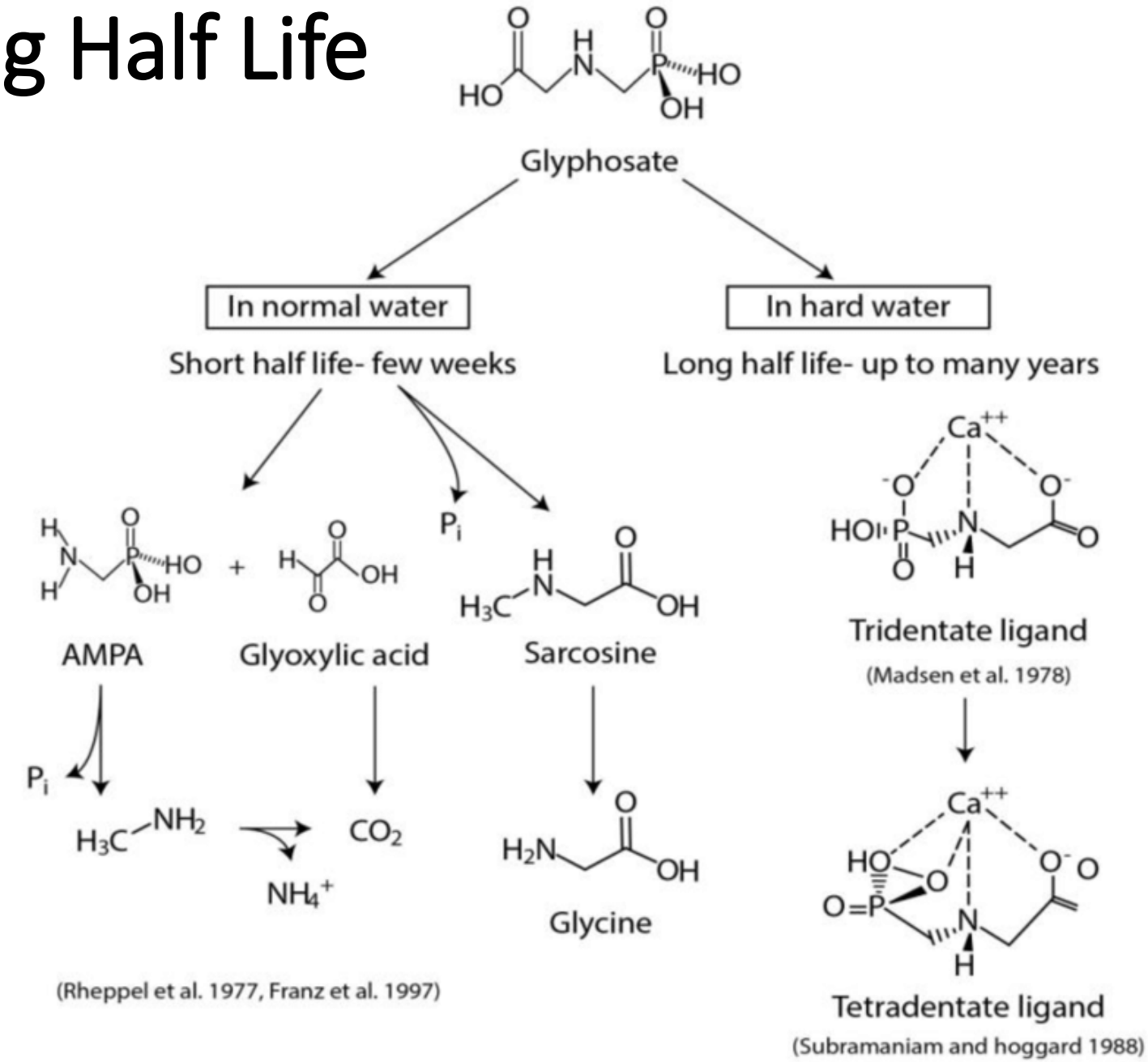
(Madsen et al. 1978)

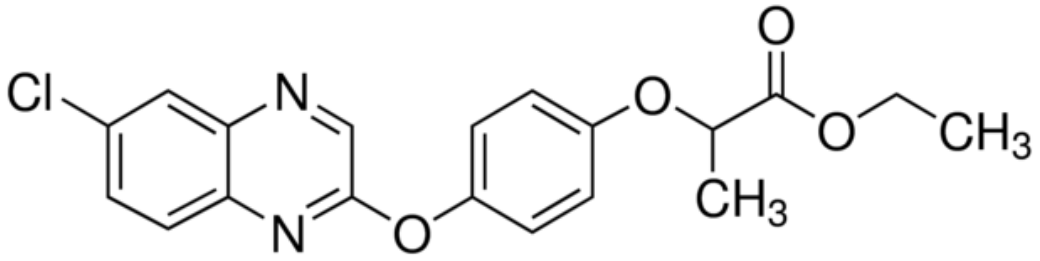


Tetradentate ligand

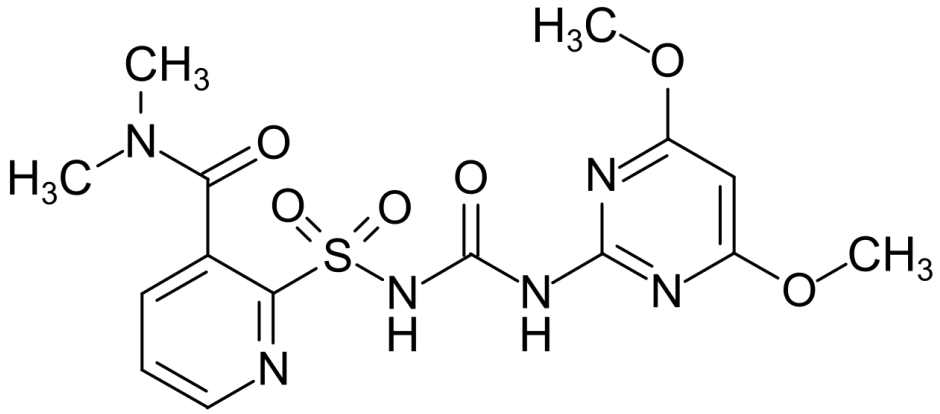
(Subramaniam and hoggard 1988)

Short vs Long Half Life

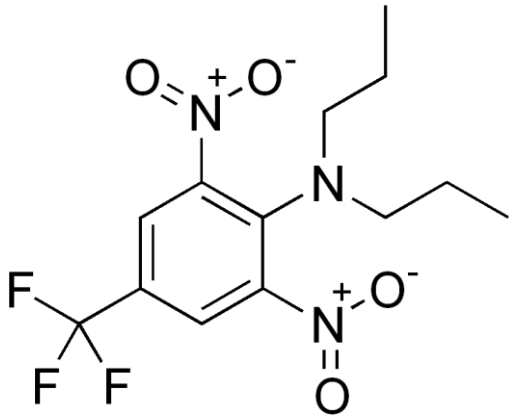




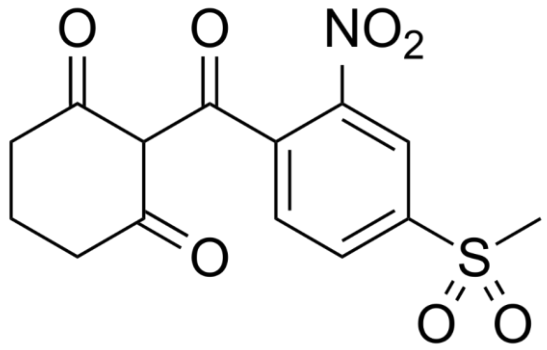
Quizalofop (Assure II)



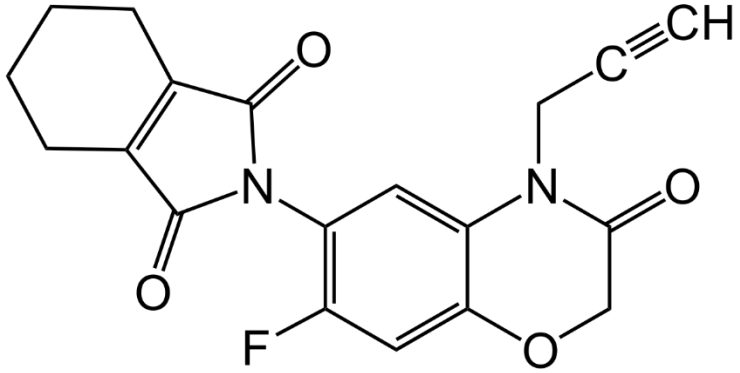
Nicosulfuron (Pursuit)



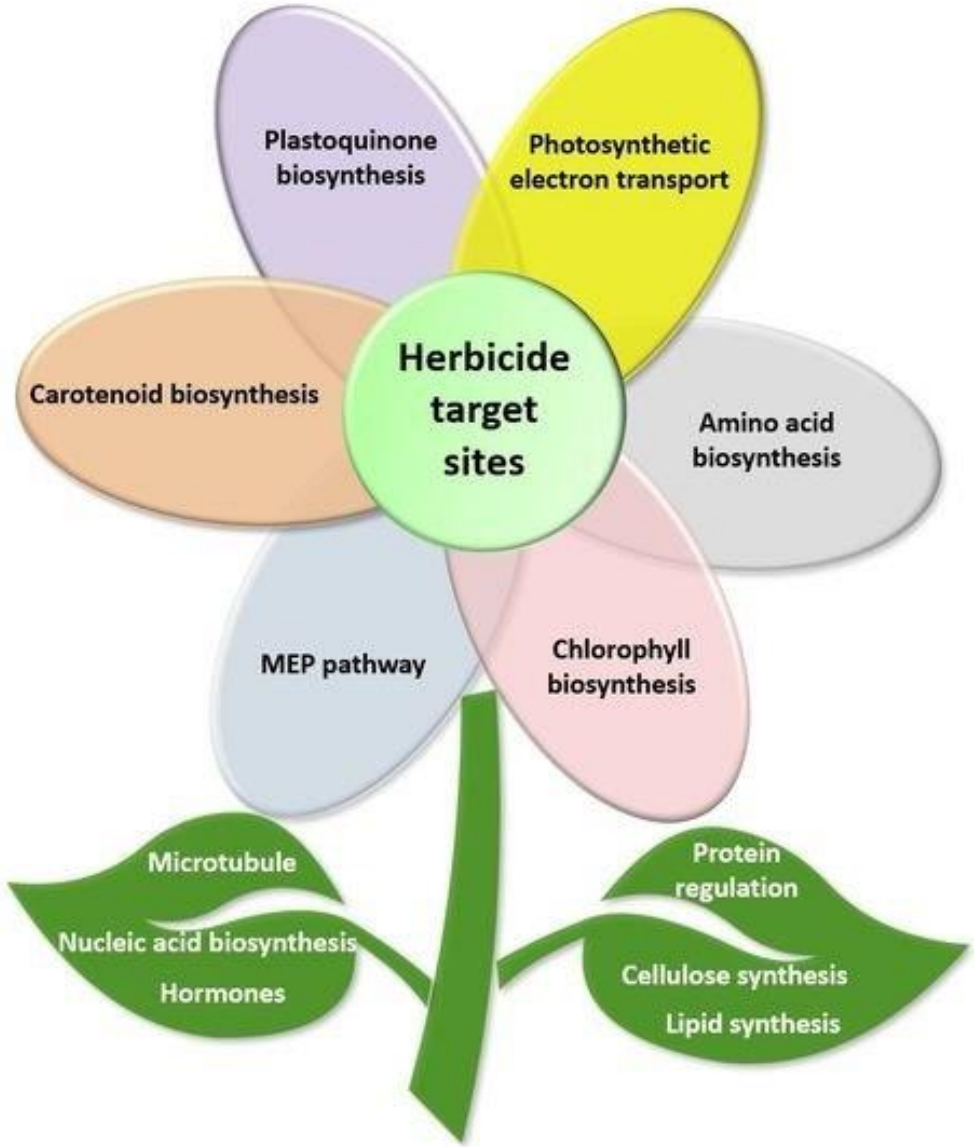
Triflualin (Treflan)



Mesotrione (Callisto)



Flumioxazin (Valor)



Herbicide mode of action classification[1] with example herbicides

Group	Mode of Action	Family[2]	Common name	Trade name
1	ACC-ase inhibitor	'fops'	quiazalofop	Assure II
		'dims'	clethodim	Select
2	ALS inhibitors	sulfonylurea	nicosulfuron	Accent
		imidazolinone	imazethapyr	Pursuit
		-	flumetsulam	
3	Mitosis inhibitors	dinitroalinine	trifluralin	Treflan
4	Synthetic auxins	phenoxy	2,4-D	many
		-	dicamba	Clarity
5	Photosystem II inhibitor[3]	triazine	atrazine	many
6	Photosystem II inhibitor[3]	-	bromoxynil	Buctril
9	EPSPS inhibitor	-	glyphosate	Roundup
10	Glutamine synthetase inhibitor	-	glufosinate	Ignite
13	Carotene inhibitor	-	clomozone	Command
14	PPO inhibitors	diphenylether	fomesafen	Reflex
		-	flumioxazin	Valor
15	Lipid inhibitors	acetamide	metolachlor	Dual
		-	dimethenamid-P	Outlook
19	Auxin transport inhibitor	-	diflufenzopyr	Status
22	Photosystem I inhibitor	bipyridilliums	paraquat	Gramoxone
27	HPPD inhibitor	triketones	tembotrione	Laudis
		-	mesotrione	Callisto

[1]Weed Science Society of America Mechanism of Action. Only groups used in corn and soybean included in the table.
[2]Family name listed for groups with multiple herbicides.
[3]Group 5 and 6 herbicides bind at different locations of the same target site.

Future

Overcoming Resistance

and

Overcoming Social Fears

through

Novel Approaches

Resistance

Non-glyphosate-resistant marestail (left) and glyphosate-resistant marestail (right)

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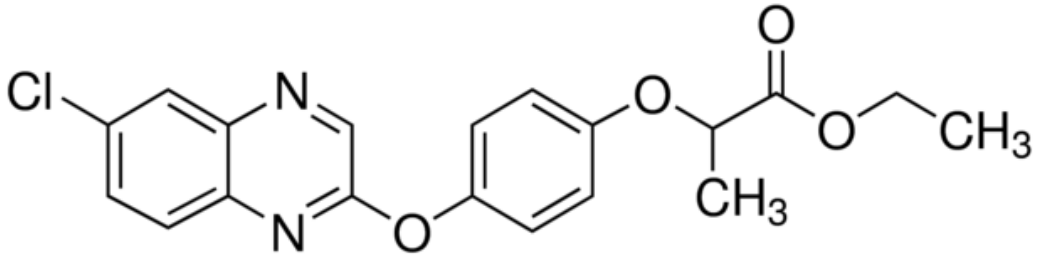
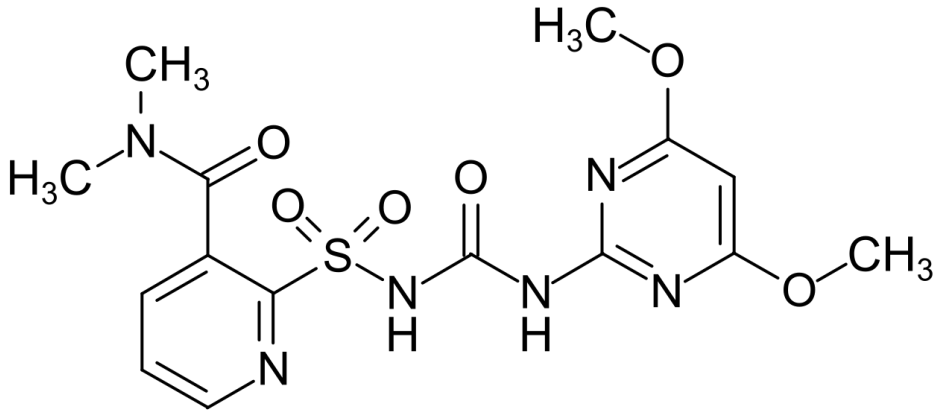
Structure Activity Relationship (SAR) studies

New Targets

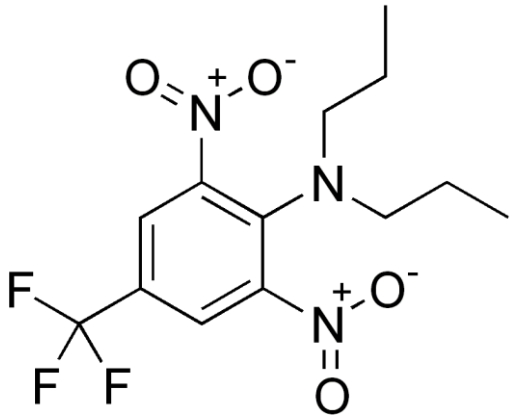
Cocktail of herbicides



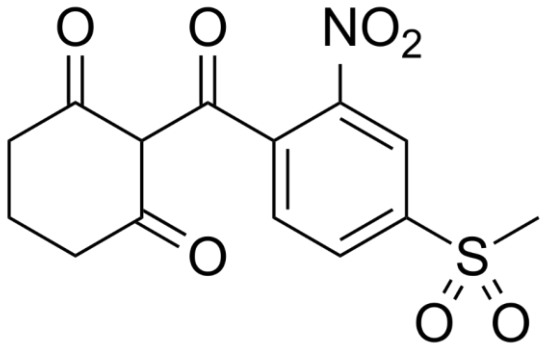
Quizalofop (Assure II)
[ACC-ase inhibitor]



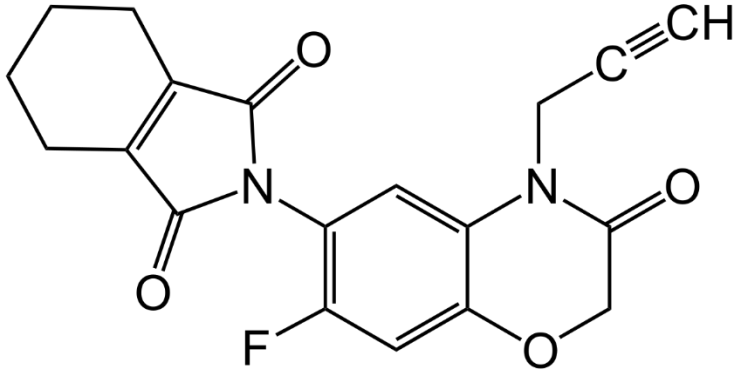
Nicosulfuron (Pursuit)
[ALS inhibitor]



Triflualin (Treflan)
[Mitosis inhibitor]



Mesotrione (Callisto)
[HPPD inhibitor]



Flumioxazin (Valor)
[PPO inhibitor]

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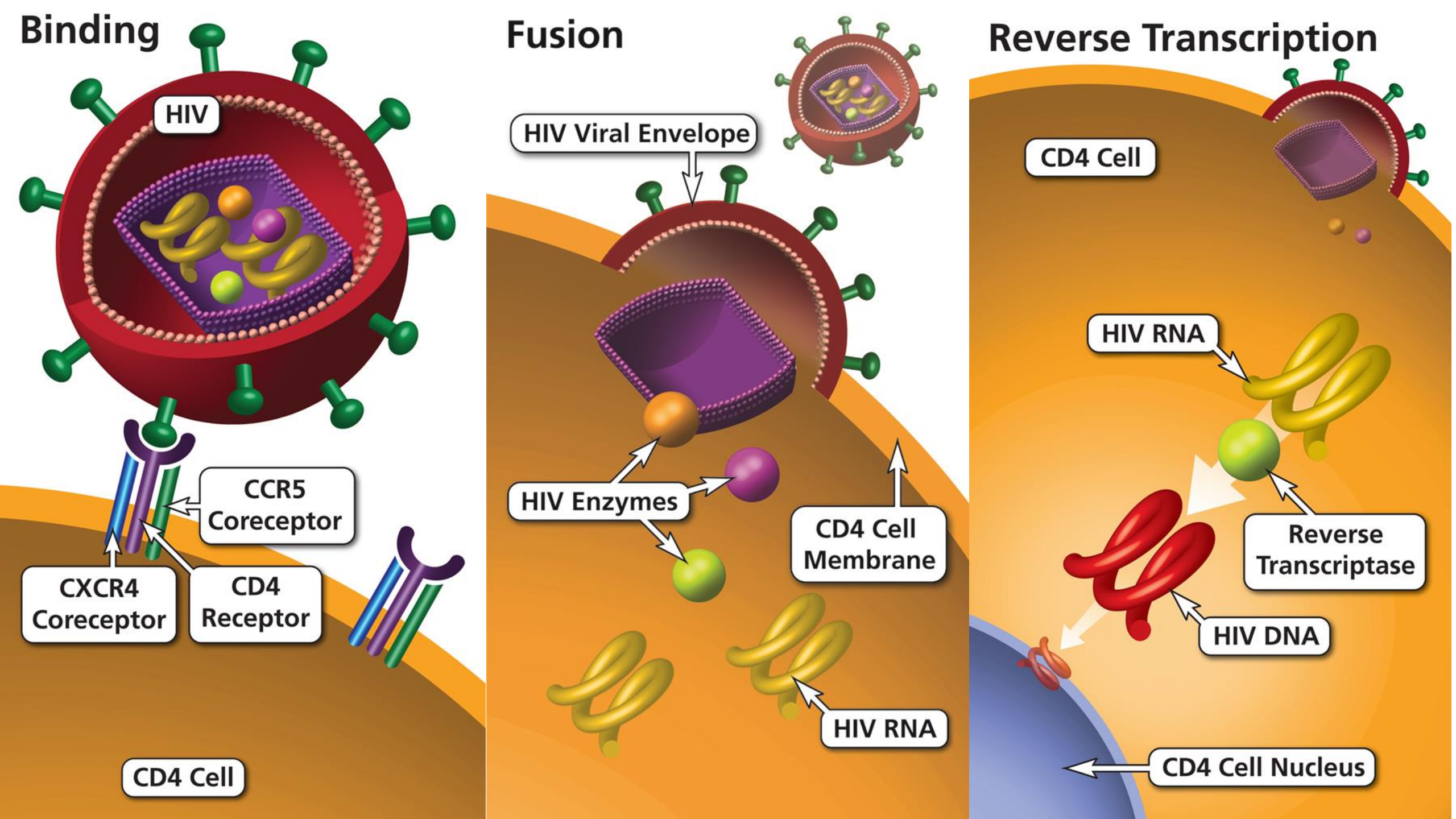
Structure Activity Relationship (SAR) studies

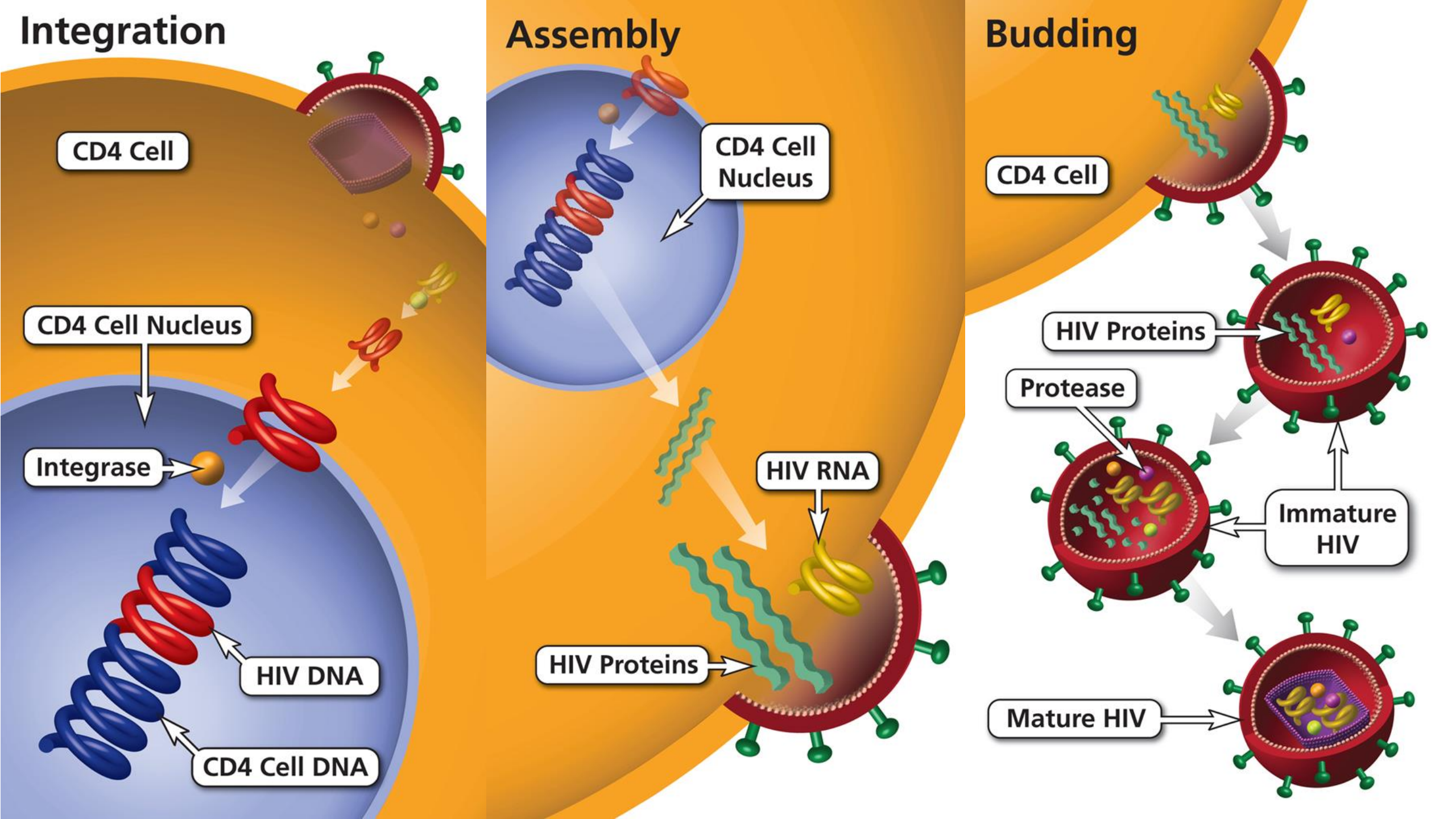
New Targets

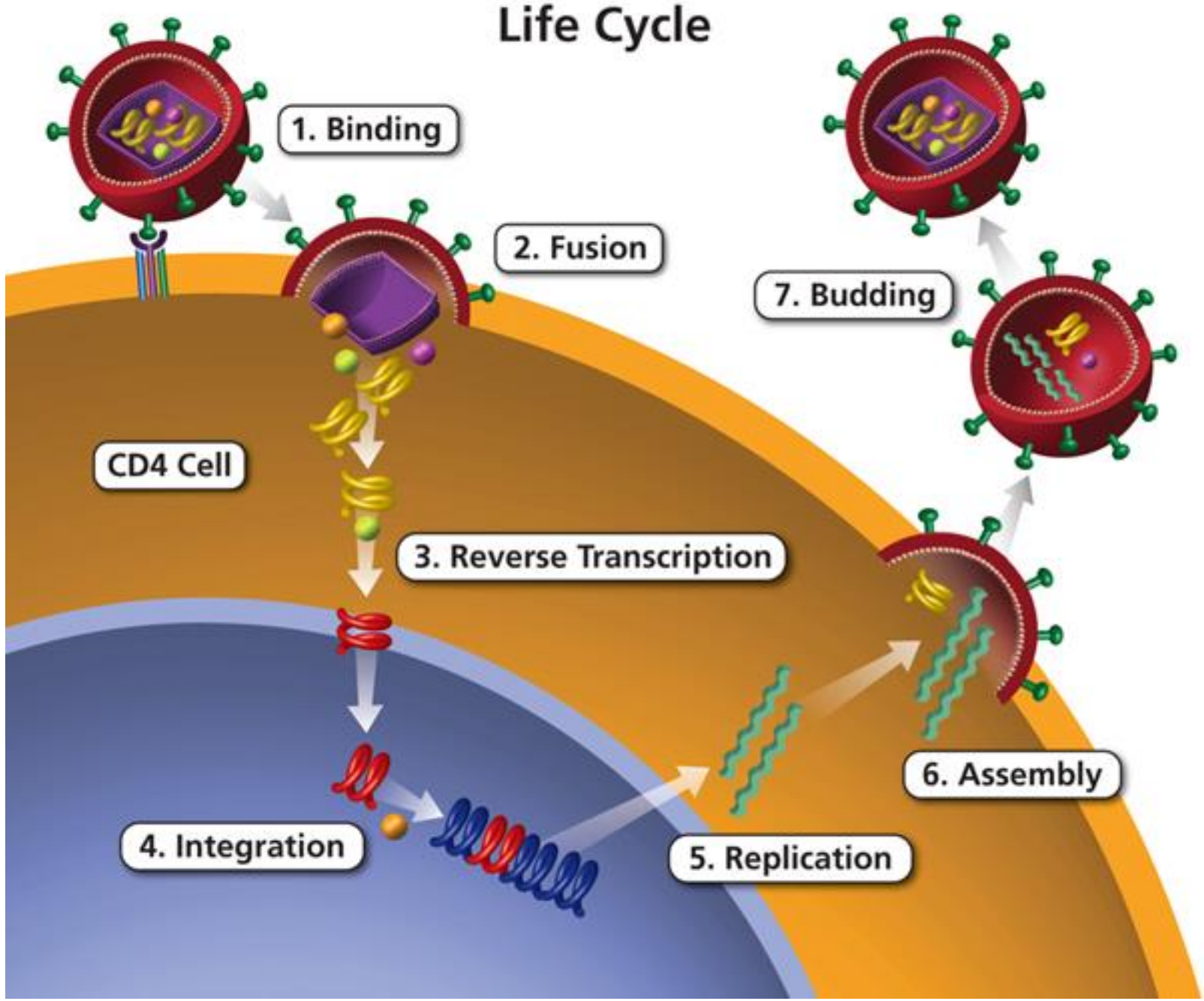
Cocktail of herbicides

What is the commonality of virtually all herbicides???

They are classic small molecule approaches


Binding
HIV
CCR5 Coreceptor
CXCR4 Coreceptor
CD4 Receptor
CD4 Cell
Fusion
HIV Viral Envelope
HIV Enzymes
CD4 Cell Membrane
HIV RNA
Reverse Transcription
CD4 Cell
HIV RNA
Reverse Transcriptase
HIV DNA
CD4 Cell Nucleus


Integration
CD4 Cell
CD4 Cell Nucleus
Integrase
HIV DNA
CD4 Cell DNA
Assembly
CD4 Cell Nucleus
HIV RNA
HIV Proteins
Budding
CD4 Cell
HIV Proteins
Protease
Immature HIV
Mature HIV


Life Cycle
1. Binding
2. Fusion
CD4 Cell
3. Reverse Transcription
4. Integration
5. Replication
6. Assembly
7. Budding

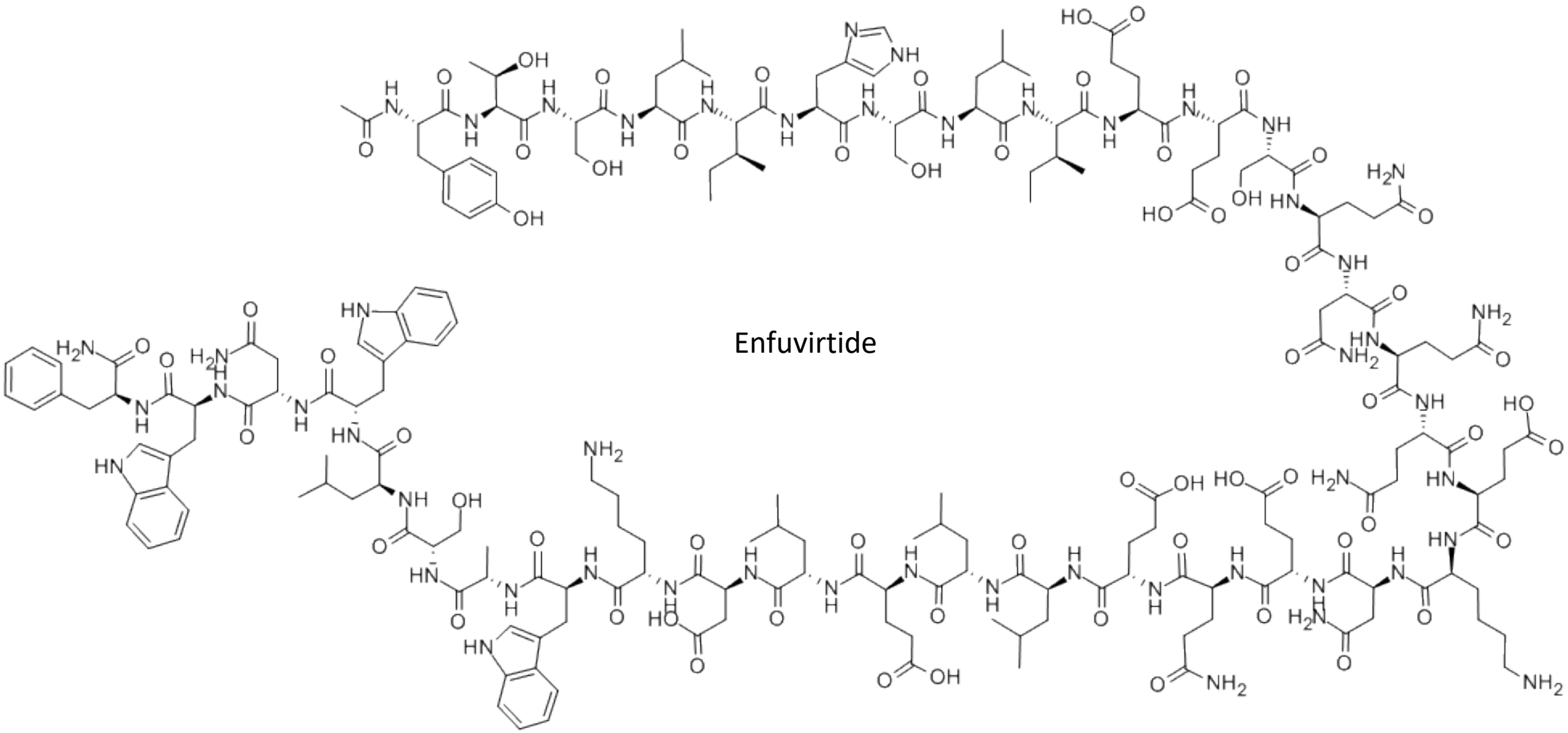
Anti-HIV Agents

- Binding inhibitors (CCR5 inhibitors)
- Fusion inhibitors
- Reverse Transcriptase Inhibitors
  - Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
  - Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Integrase inhibitors
- HIV Protease Inhibitors

Anti-HIV Agents

- Binding inhibitors (CCR5 inhibitors)
- Fusion inhibitors Enfuvirtide (biologic and NO primary resistance)
- Reverse Transcriptase Inhibitors
  - Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
  - Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Integrase inhibitors
- HIV Protease Inhibitors

BIOLOGIC



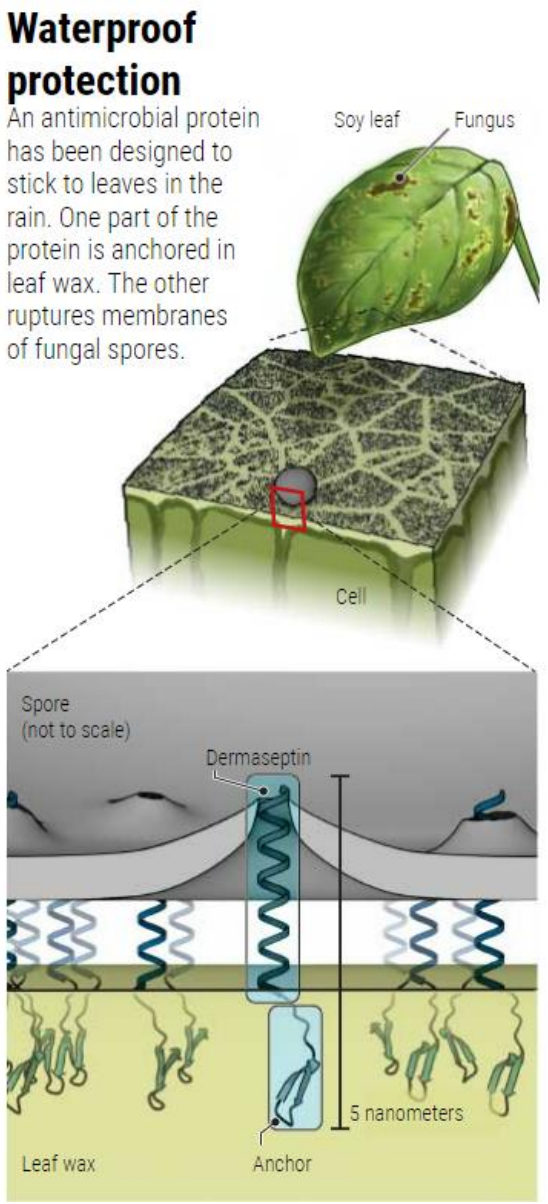
Enfuvirtide

Make plants more susceptible to existing herbicides

It’s already being examined with pesticides

Designer peptides kill soybean rust, a major threat that requires heavy fungicide use

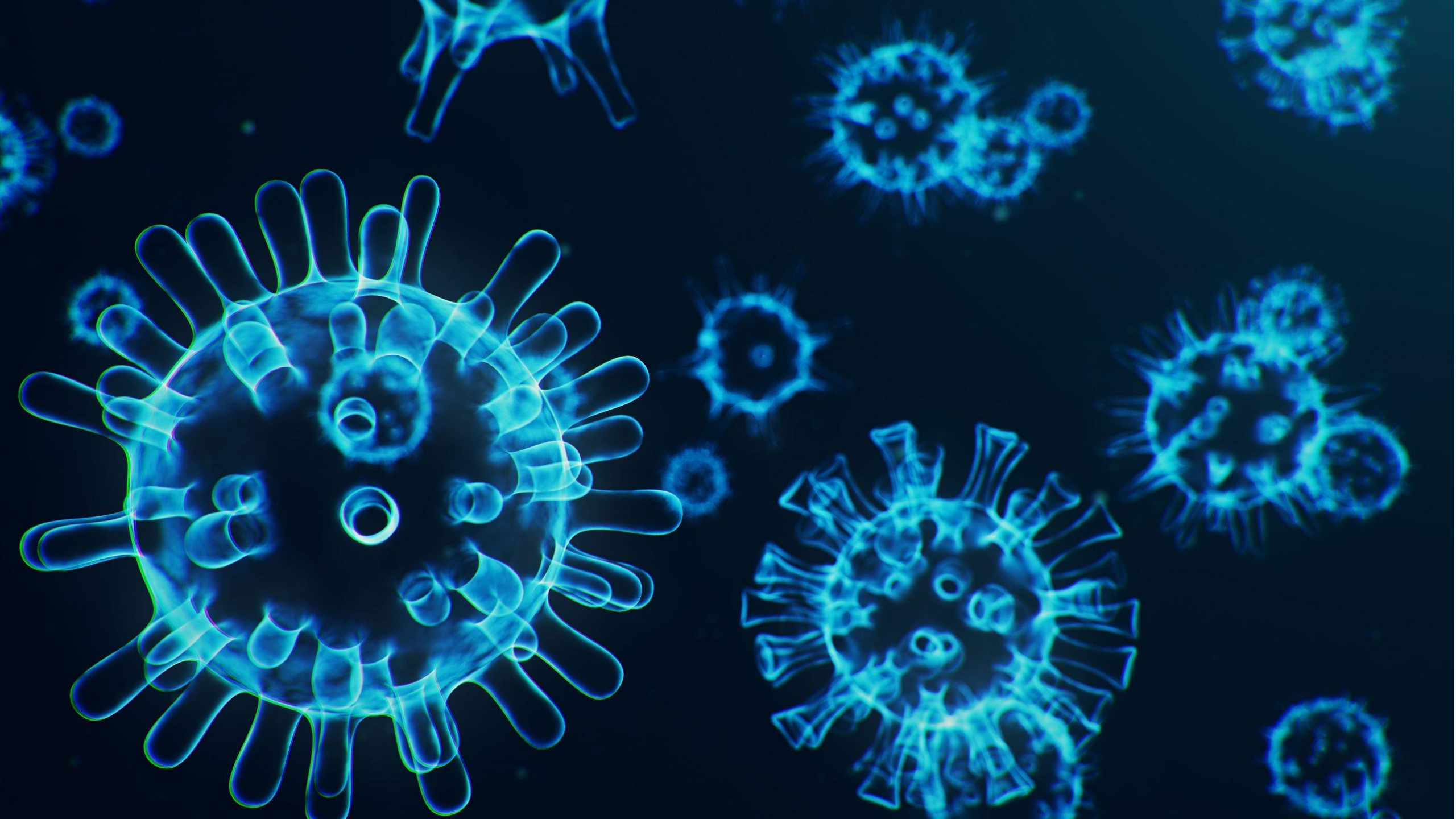
- A peptide embeds itself in the waxy surface of a leaf, holding tight in the rain
- Another peptide (Dermaseptin) juts out like a spear to attack microbial pests
  - Dermaseptin attacks a broad array of microbes, including bacteria and fungi
  - Pathogens are much less likely to evolve resistance because it is difficult to change the basic structure of cell membranes
- Thus, instead of second peptide, attach a herbicide as the “payload.”
- Less agent needed, less soil absorbance, “safer”, therefore better marketing.

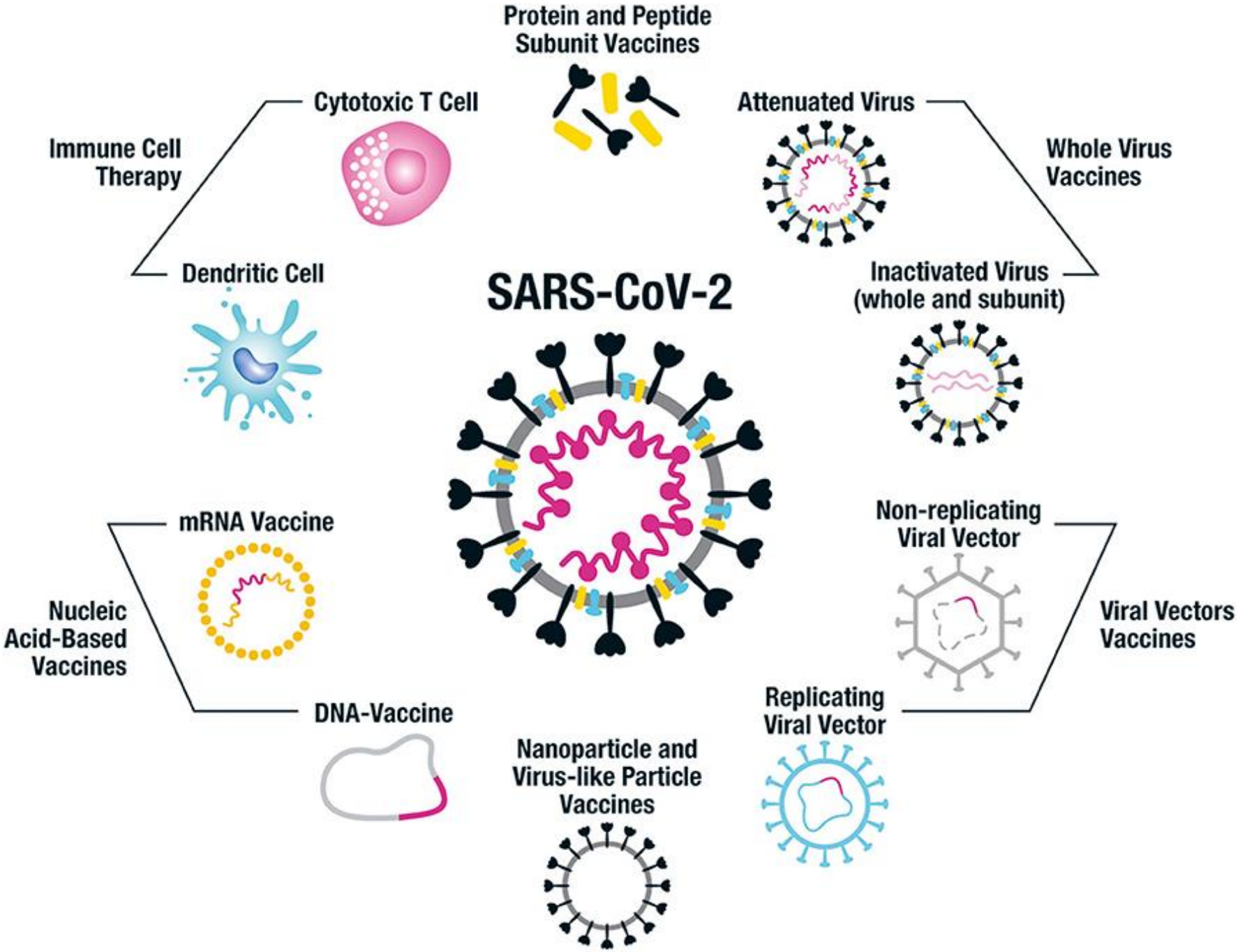


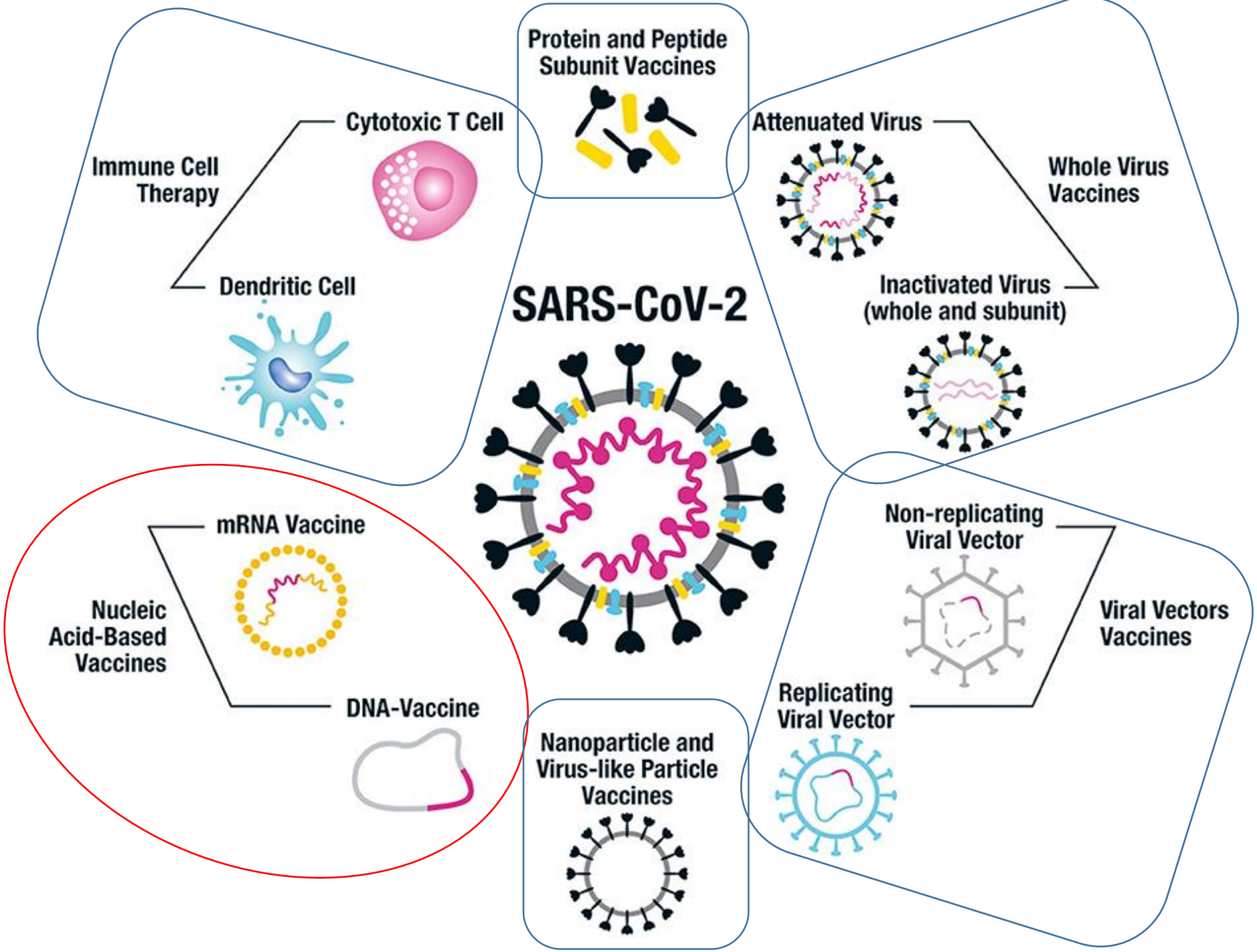
Stokstad E. *Science,* 2019 (doi: 10.1126/science.aax8199)

New targeted approach

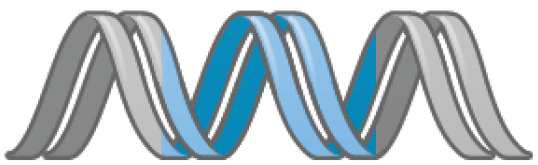
Take advantage of novel drug delivery advances

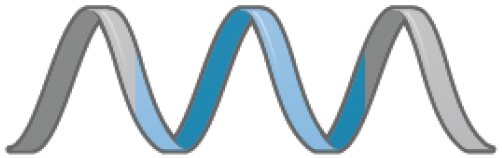



Protein and Peptide Subunit Vaccines
Cytotoxic T Cell
Immune Cell Therapy
Attenuated Virus
Whole Virus Vaccines
Dendritic Cell
SARS-CoV-2
Inactivated Virus (whole and subunit)
mRNA Vaccine
Non-replicating Viral Vector
Nucleic Acid-Based Vaccines
Viral Vectors Vaccines
DNA-Vaccine
Replicating Viral Vector
Nanoparticle and Virus-like Particle Vaccines


Protein and Peptide Subunit Vaccines
Immune Cell Therapy
Cytotoxic T Cell
Dendritic Cell
Attenuated Virus
Whole Virus Vaccines
Inactivated Virus (whole and subunit)
SARS-CoV-2
mRNA Vaccine
Nucleic Acid-Based Vaccines
DNA-Vaccine
Non-replicating Viral Vector
Viral Vectors Vaccines
Replicating Viral Vector
Nanoparticle and Virus-like Particle Vaccines

DNA → mRNA → Protein





STORAGE

DNA stores instructions for proteins in the nucleus

SOFTWARE

mRNA is a temporary set of instructions for cells to make a protein; mRNA is made using DNA

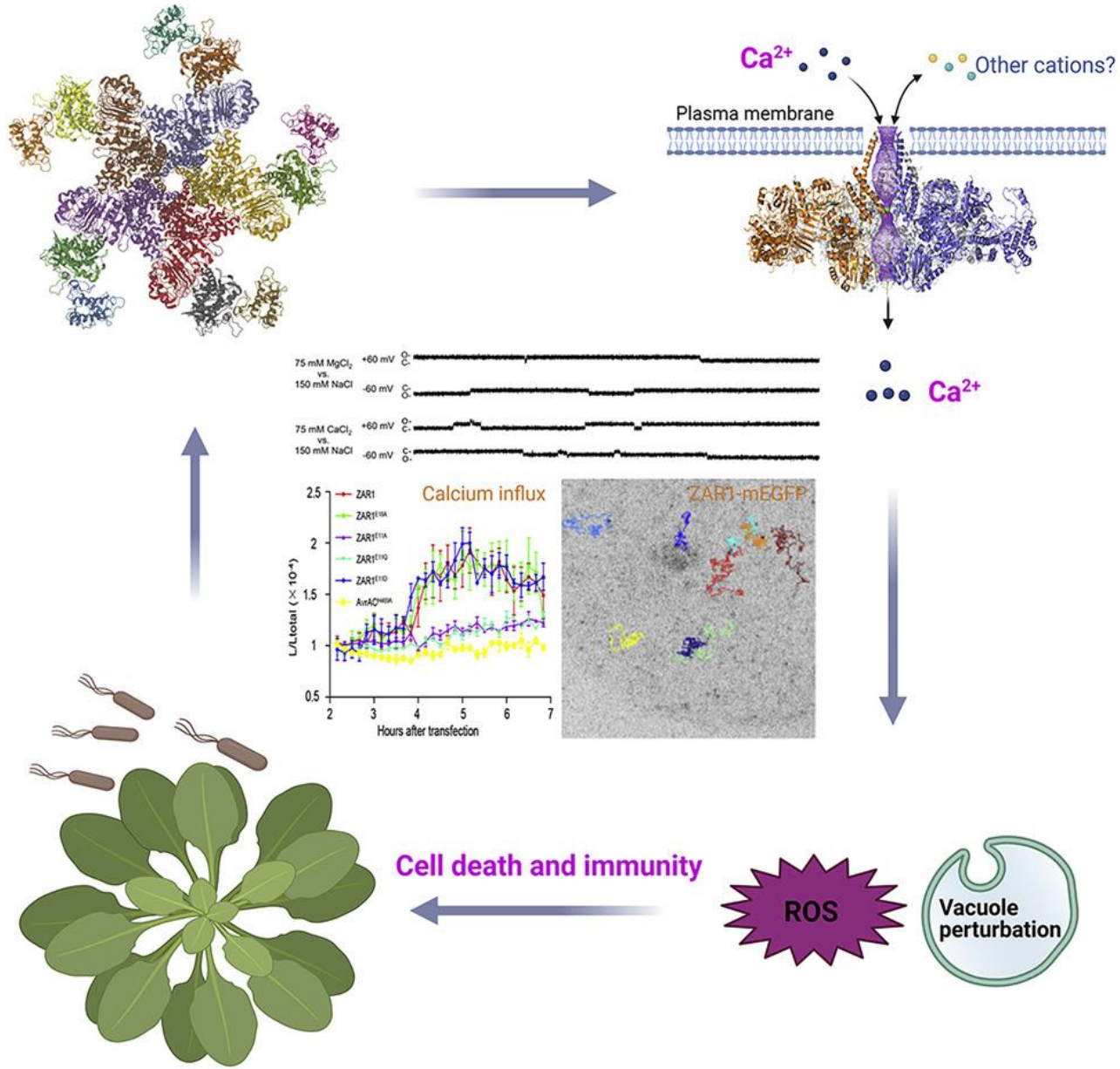
APPLICATIONS

Proteins form the basis of life by performing the functions required by every cell; proteins are made using mRNA

The ZAR1 resistosome is a calcium-permeable channel triggering plant immune signaling

- Nucleotide-binding, leucine-rich repeat receptors (NLRs) are major immune receptors in plants.
- Upon activation, the NLR protein, ZAR1 forms a pentameric resistosome and triggers immune responses and cell death in plants.

Bi G, Min S, Li N, Liang X, Hu M, Wang J, Zou M, Deng Y, Li Q, Huang S, Li J, Chai J, He K, Chen Y-H, Zhou J-M. *Cell* 2021;184(13):3528-3541.

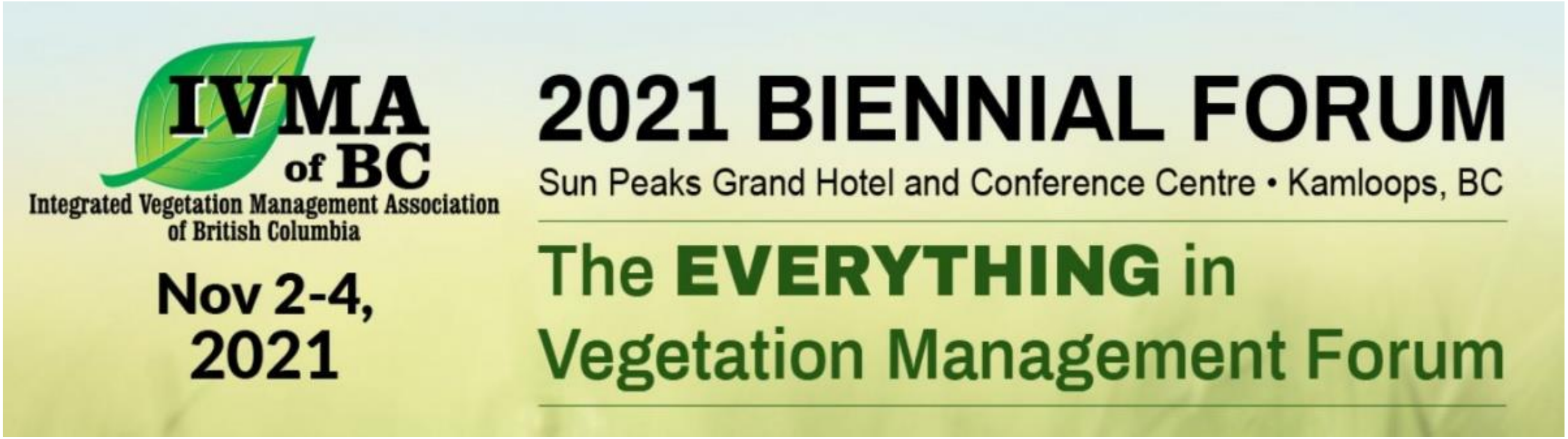

Ca2+
Other cations?
Plasma membrane
75 mM MgCl2
vs.
150 mM NaCl
+60 mV
-60 mV
75 mM CaCl2
vs.
150 mM NaCl
+60 mV
-60 mV
Ca2+
Calcium influx
ZAR1
ZAR1E10A
ZAR1E11A
ZAR1E11Q
ZAR1E11D
AvrAC H40A
L/Ltotal (× 10-4)
Hours after transfection
ZAR1-mEGFP
Cell death and immunity
ROS
Vacuole perturbation

The ZAR1 resistosome is a calcium-permeable channel triggering plant immune signaling

- Nucleotide-binding, leucine-rich repeat receptors (NLRs) are major immune receptors in plants.
- Upon activation, the NLR protein, ZAR1 forms a pentameric resistosome and triggers immune responses and cell death in plants.
- Pre-assembled ZAR1 resistosome were incorporated into planar lipid-bilayers and displayed calcium-permeable cation-selective channel activity.
- Activation of ZAR1 in the plants Ca^{2+} influx, perturbation of subcellular structures, production of reactive oxygen species, and cell death.

Bi G, Min S, Li N, Liang X, Hu M, Wang J, Zou M, Deng Y, Li Q, Huang S, Li J, Chai J, He K, Chen Y-H, Zhou J-M. *Cell* 2021;184(13):3528-3541.


The Enemy OF CREATIVITY -IS- SELF Doubt



Facts, Fiction, and the Future of Chemical and Biological Herbicides

Ronny Priefer, PhD

Department of Pharmaceutical Sciences

Massachusetts College of Pharmacy and Health Sciences University