RNAs: Risks and Hazards in the RNA World

GMO-Free Regions, Berlin, May 7, 2015

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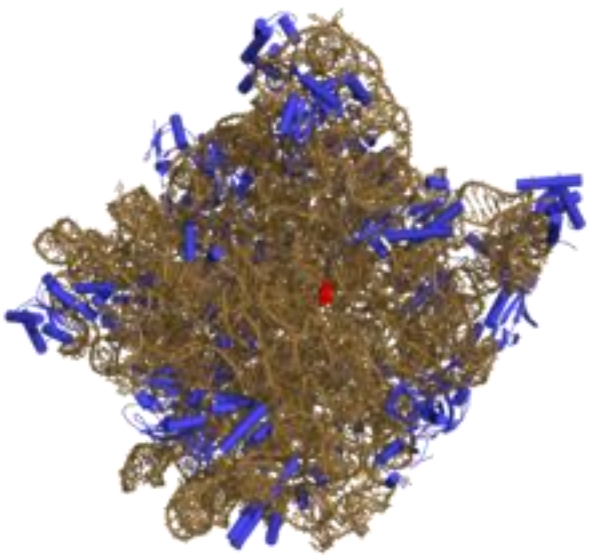

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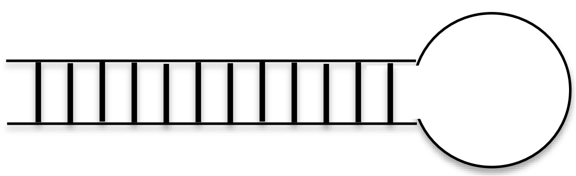
RNA interference GMO Crops Commercialised in the US

1) Treus Omega 3 Oil Soybean (Pioneer)

2) Non-browning “Arctic” Apple (Okanagan Specialty Fruits)

3) “Innate” low bruising/low acrylamide Potato (JR Simplot)

4) Vistive Gold low linolenic acid Soybean (Monsanto)



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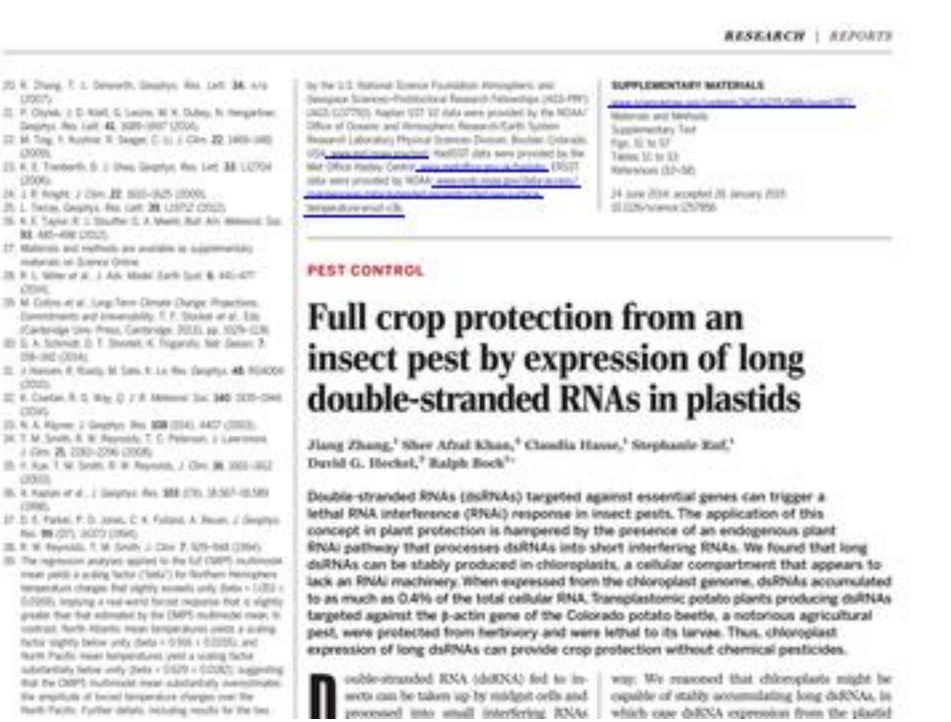
Pesticidal activities of interfering RNAs



RESEARCH | REPORTS

PEST CONTROL

Full crop protection from an insect pest by expression of long double-stranded RNAs in plastids

Jiang Zhang,[1] Sher Afzal Khan,[1] Claudia Hasse,[1] Stephanie Kaf,[1] David G. Heckel,[2] Ralph Bock[1]*

Double-stranded RNAs (dsRNAs) targeted against essential genes can trigger a lethal RNA interference (RNAi) response in insect pests. The application of this concept in plant protection is hampered by the presence of an endogenous plant RNAi pathway that processes dsRNAs into short interfering RNAs. We found that long dsRNAs can be stably produced in chloroplasts, a cellular compartment that appears to lack an RNAi machinery. When expressed from the chloroplast genome, dsRNAs accumulated to as much as 0.4% of the total cellular RNA. Transplastomic potato plants producing dsRNAs targeted against the β-actin gene of the Colorado potato beetle, a notorious agricultural pest, were protected from herbivory and were lethal to its larvae. Thus, chloroplast expression of long dsRNAs can provide crop protection without chemical pesticides.

"By targeting essential insect genes, dsRNAs can be developed into highly species-specific insecticides." – Zhang et al *Science* 2015

"the inbuilt gene specificity of this process offers the potential to design dsRNAs that kill one or a few species but have no effect on non-target species" – Whyard, S. in *Science* 2015

Two Big Buts:

1) Data show that binding of short RNAs to genes is generally not specific
2) Vertebrate cells are highly sensitive to long dsRNAs

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The Standard Framing of Biology

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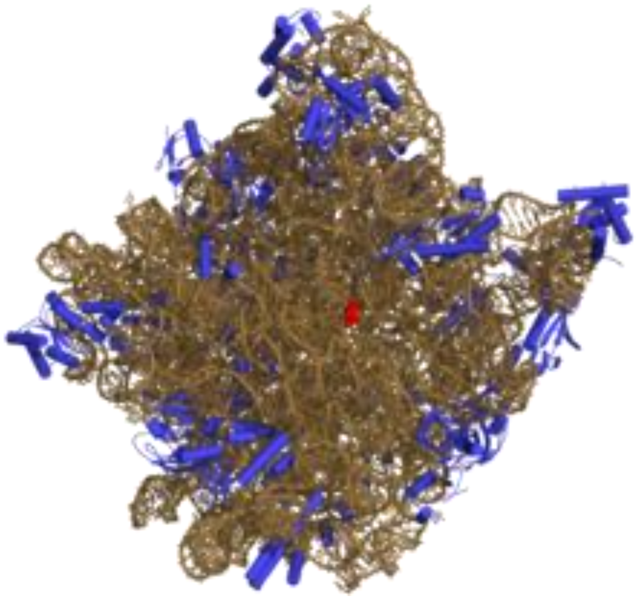
Appreciating the RNA World: The Bacterial 50S Ribosomal Subunit



Blue: Protein
Brown: RNA
Red: Active site

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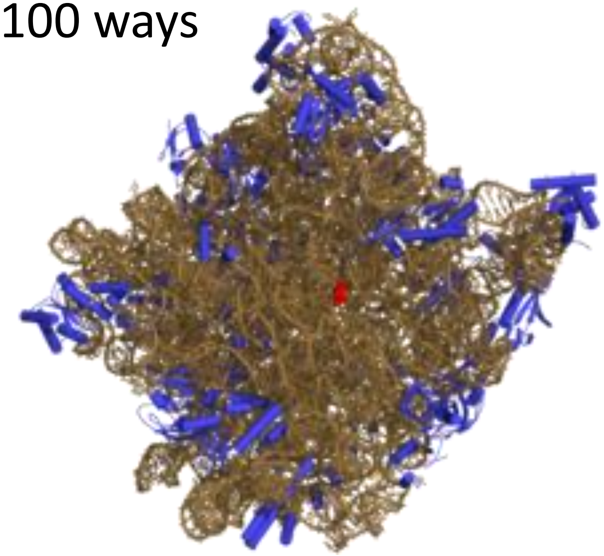
The Diversity and Complexity of RNA functions: RNA is NOT Just Like DNA!

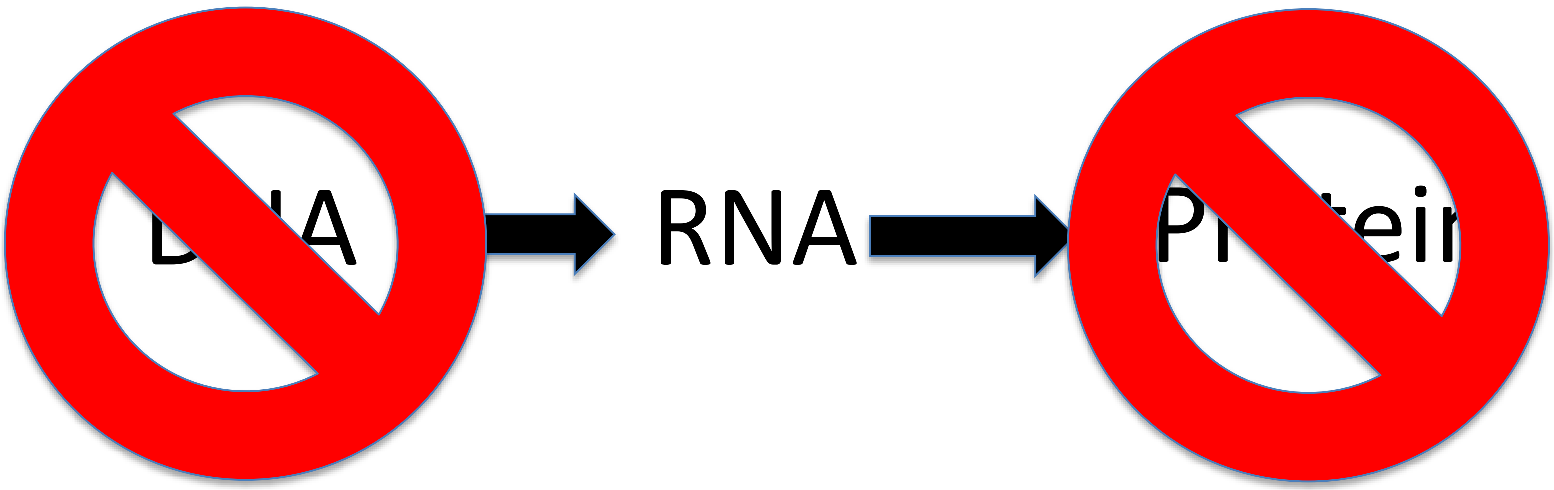
The RNA that makes protein (mRNA) is less than 1% of all cellular RNA
RNAs have non Watson-Crick base pairing: G:A and G:U
Highly flexible in structure
RNA bases can be structurally modified in more than 100 ways
Highly mobile inside organisms
RNA is sticky and chemically reactive (ie. Unstable)
Other structural modifications
Longest evolutionary history (more integrated)



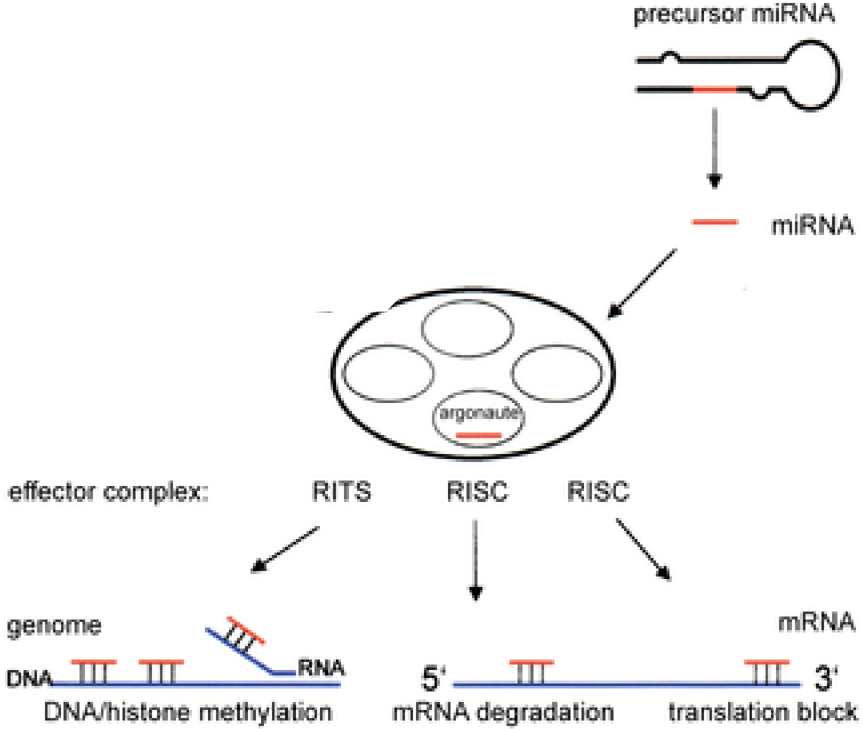
Important Implications:

1) RNA is not like DNA (Not amenable to the assumptions).
2) The RNA world is highly complex and poorly understood
3) We don’t even have the tools to understand it.
(E.g. the properties of RNA reside in its shape)

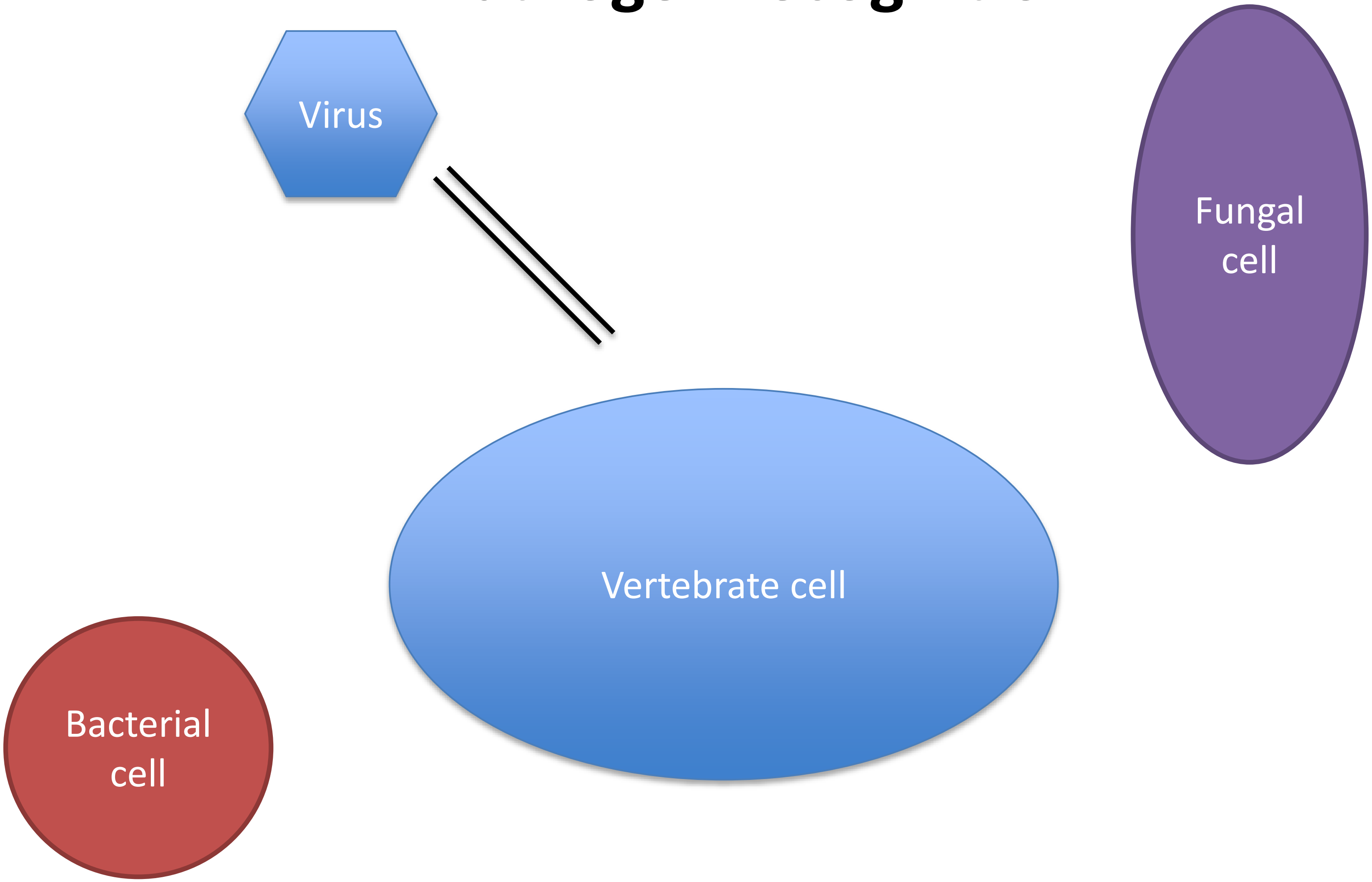
The Key to Biology?



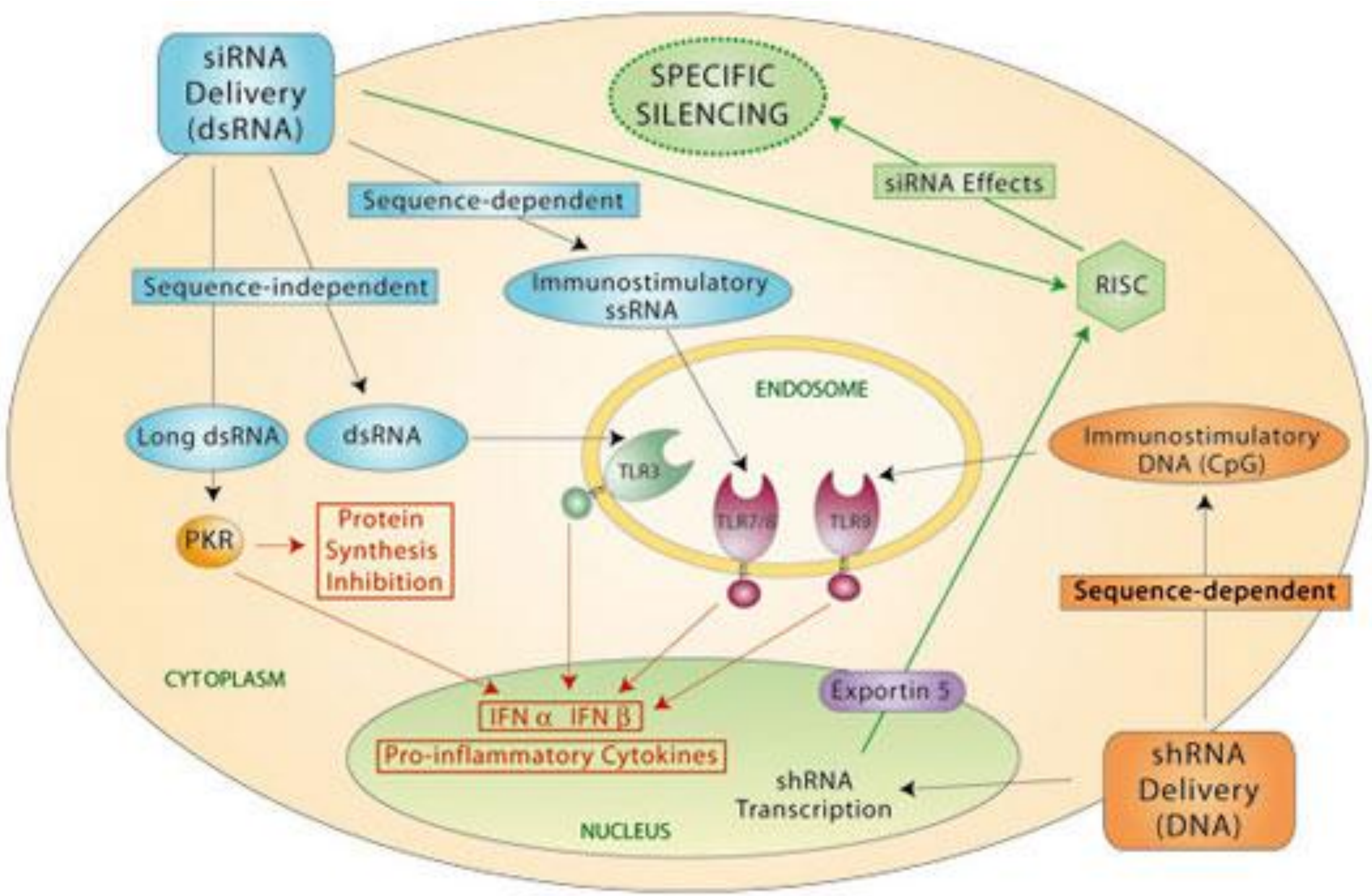
The Theory of RNA Interference in Plants: a) Gene regulation



Pathogen recognition



RNA Interference in (Vertebrate) Animals



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Some Medical Trials of Large dsRNAs to Test Effects on Vertebrates

Adamson R.H. and Fabro S. (1969) Embryotoxic effects of PolyI.PolyC. *Nature* **223**: 718.

Absher M., and Stinebring W. (1969) Toxic properties of a synthetic double-stranded RNA. *Nature* **223**: 715-717.

de Clercq E., Stewart W.E., and de Somer P. (1972) Interferon production linked to toxicity of Polyriboinosinic acid-Polyribocytidylic acid. *Infection and Immunity* **6**: 344-7.

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Toxic Reactions to Injected long dsRNAs in Diverse Mammals

Consequence	Species	References
Fever	Guinea pig, Cow, Goat, Rabbit	Lindsay et al. 1969; Cooper et al. 1988; McVicar et al. 1973
Defects in liver function	Mouse, Dog	Phillips et al. 1971; Morahan et al. 1972
Leukopenia	Dog	Phillips et al. 1971
Autoimmunity	Mouse	Steinberg et al. 1969
Growth rate defects/Weight loss	Rat, Dog, Mouse	Leonard et al. 1969; Phillips et al. 1971
Hypoglycemia	Mouse	Vignaux and Gresser 1981
Ocular toxicity	Rabbit	Ostler et al. 1970
Embryo toxicity	Rabbit, Mouse	Adamson and Fabro 1969; de Fougerolles and Baines 1987; Lin et al. 2006; Shimada et al. 2003
Inhibition of mitosis	Mouse	Serota and Baserga 1970; Jahiel et al 1971
Thymus degeneration	Mouse, Rat	Leonard et al. 1969
Lethality	Mouse, Dog, Goat, Rat, Rabbit, Monkey	Absher and Stinebring 1969; Ostler et al. 1970; Phillips et al. 1971; Homan et al. 1972; McVicar et al. 1973; Vignaux and Gresser 1981

Thank you

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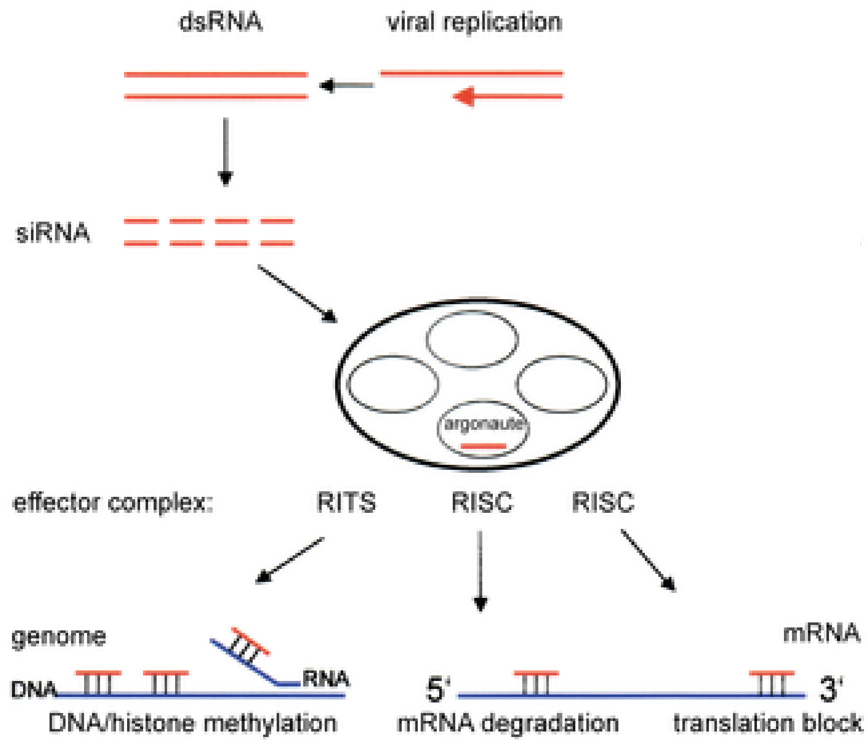
The Theory of RNA Interference in Plants: a) Gene regulation b) anti-viral defence



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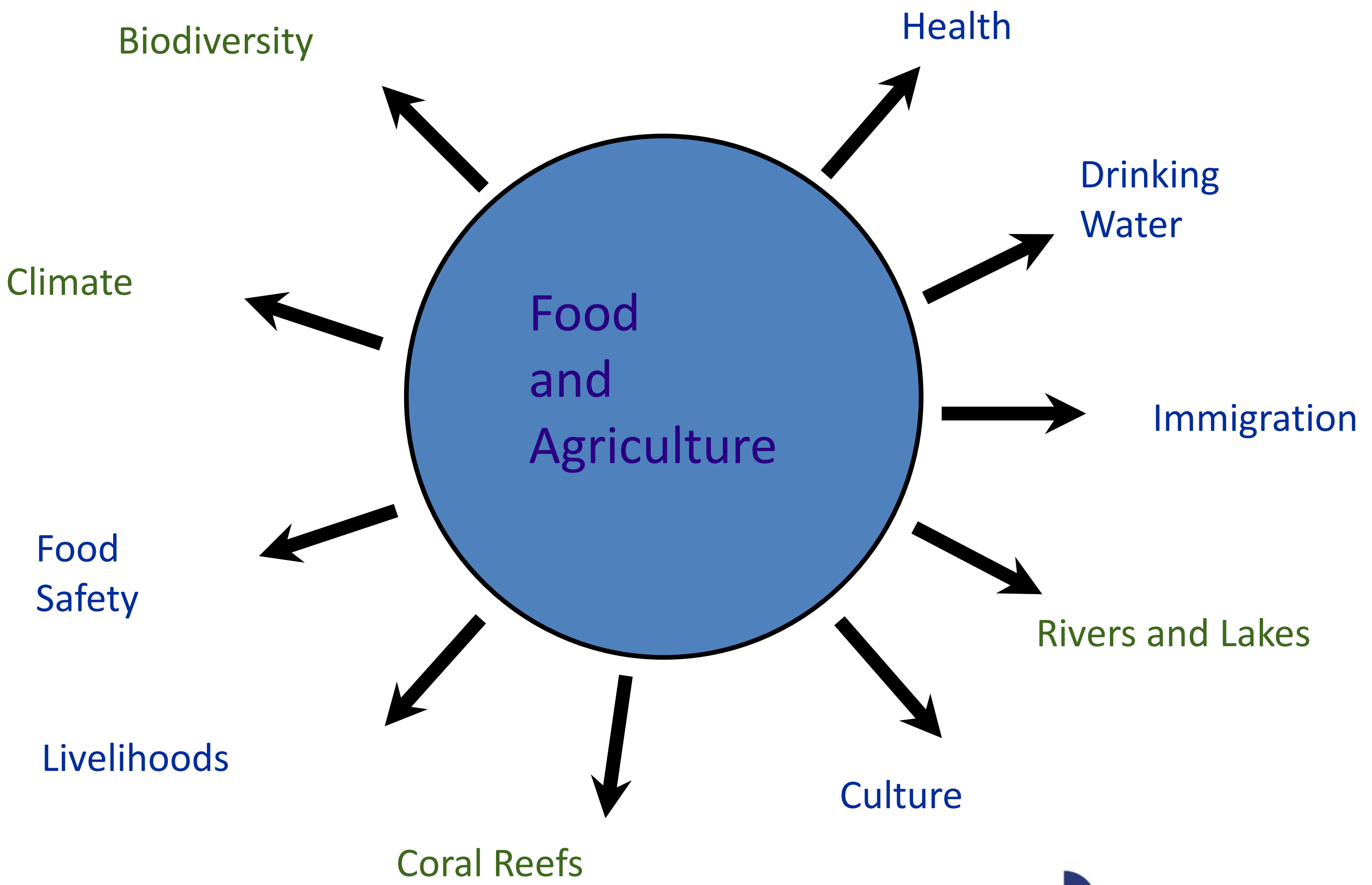
The Multifunctionality of Food and Agriculture



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