RNAi-based approaches to pest management in agricultural production systems

World Trade Organization
SPS Thematic Session on Emerging Risks and New Agricultural Technologies to Address Them

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GreenLight™ Biosciences

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Basic concepts of RNA in gene regulation

RNA is a naturally occurring biomolecule found in all cells

- **RNA interference (RNAi)** is a mechanism of gene regulation found in all eukaryotic cells
- **RNAi is triggered by dsRNA** that targets specific messenger RNA resulting in suppression of gene expression







Control of native genes
Fine-tuning regulation



Genome management
suppressing transposons



Defense
combating viruses

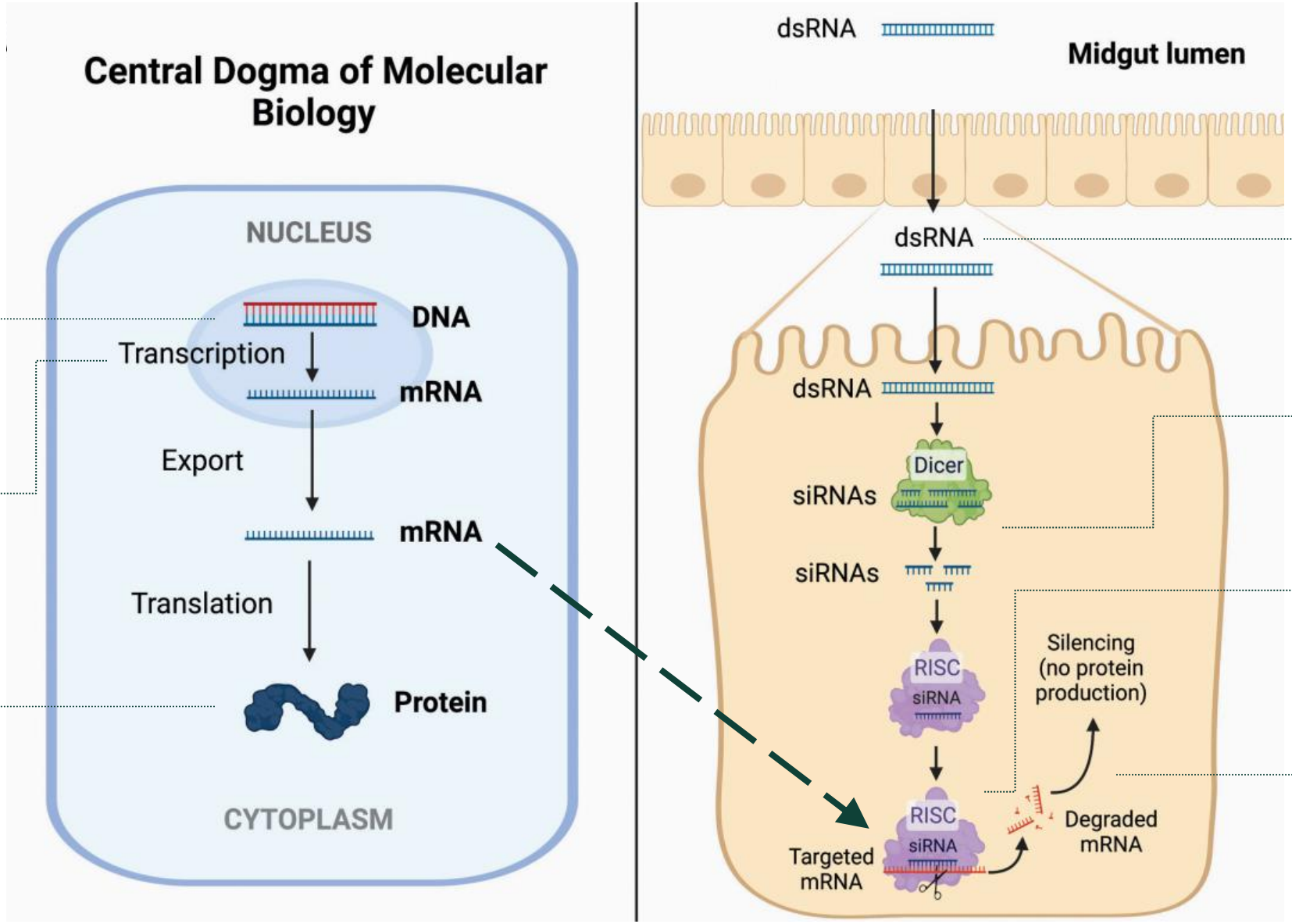
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WHAT is RNA interference (RNAi) and HOW does dsRNA work as a Biopesticide?

Inside the nucleus of each cell is the genetic blueprint, encoded in DNA

This information is transcribed (copied) into messenger RNA (mRNA)

Which gets translated by the cell's machinery to make specific proteins



The highly specific dsRNA is absorbed by target pest gut cells upon ingestion

Within the cell the dsRNA is processed by a pest's own protein complex into small interfering RNA (siRNA)

The active siRNA binds to mRNA with a matching sequence

The message encoded in the mRNA is effectively blocked. Production of a specific protein vital to the target pest is prevented

1. Velez et al. 2024

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RNAi in Agriculture

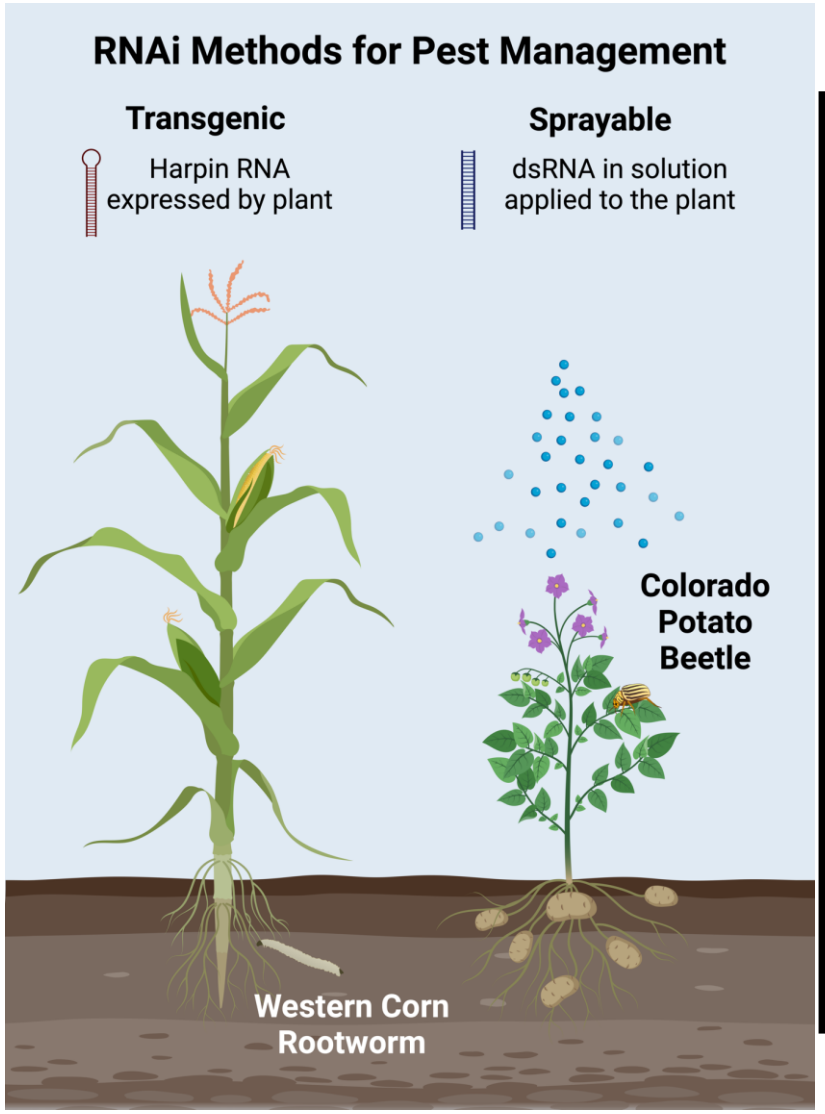
GMO

Host-Induced RNAi

Modify the plant to express dsRNA

Plant Incorporated Protectant (PIP):

e.g. Western Corn Rootworm DvSnf7 in SmartStax® PRO



Non-GMO

GreenLight Biosciences Technology

Spray-Induced RNAi

Externally applied dsRNA

- **Calantha™, first sprayable dsRNA registered by US EPA in 2023**
- **Submitted in Europe 2023, Registered in Ukraine 2024**

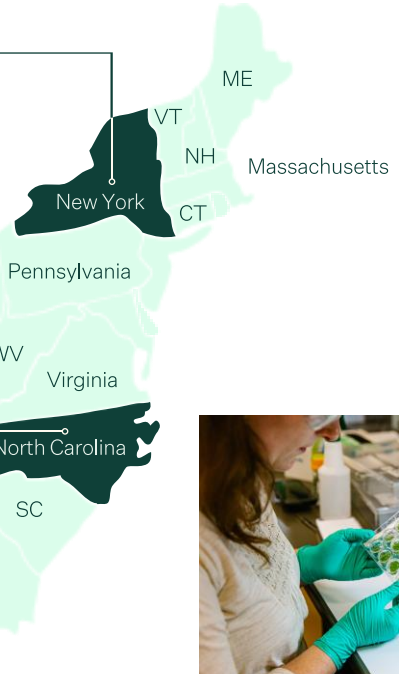
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GreenLight Biosciences has fully integrated capability for RNA commercialization

ROCHESTER, NY

- Pilot plant for manufacture of commercial products and R&D materials





RESEARCH TRIANGLE PARK, NC

- Research, discovery, field development, regulatory, and product development, marketing, sales, and business management





GRIMES, CA

- Field research station increases field trial capacity for regulatory submissions





SEVILLE, SPAIN

- Field research station to accelerate transition of research and discovery compounds



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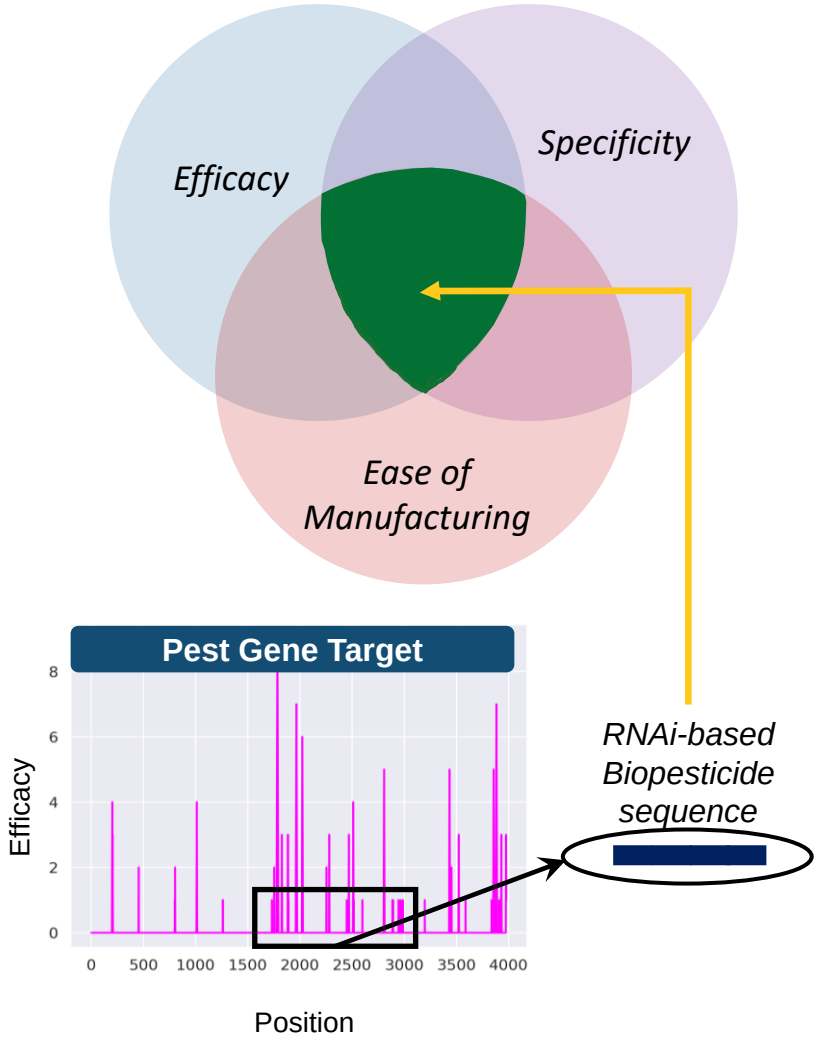
Targeted pest control: rational dsRNA sequence design

Efficacy
- Design sequences to target pest with high biological efficacy
- Use lab testing to inform and iterate on sequence design

Specificity
- Predict and mitigate potential impacts on humans and non-target organisms
- Thorough evaluation of registerability of dsRNA sequences

Ease of Manufacturing
- *In silico* evaluation of Ease of Manufacturing for sequences as part of our design process

Find most optimal sequences with input from lab testing



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GreenLight Biosciences Cell-free RNA Production Process

Manufacturing Operations in Rochester, New York

SCALE

Installed capacity of 500 kg per year, ready for expansion to 1,000 kg per year

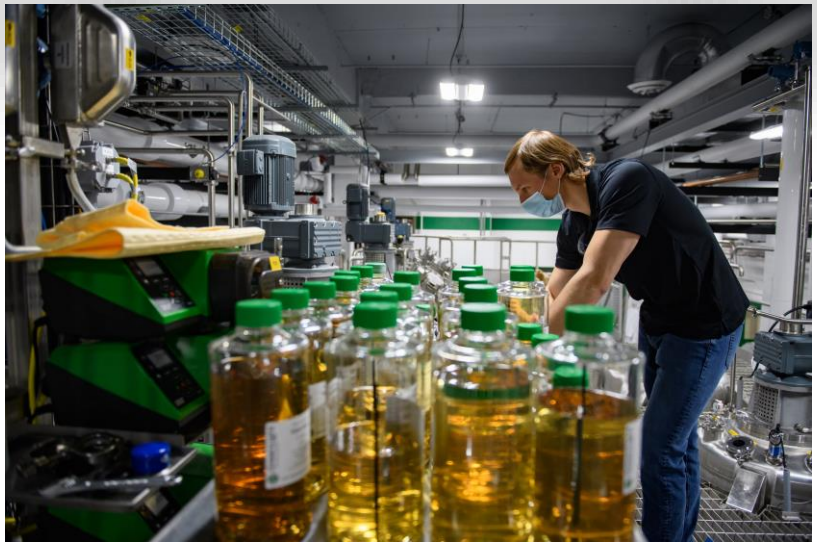
QUALITY

High quality RNA ensures consistent potency of active

COST

Quality RNA production at scale enables affordable pricing for farmers







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GreenLight Biosciences Products and Programs

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GreenLight Biosciences is the leader in RNA for crop protection

Proven proprietary pipeline that spans insecticides, fungicides, acaricides, and herbicides



Calantha™

- Description: dsRNA product for Colorado Potato Beetle (CPB). Calantha™ is the first-ever registered foliar-applied RNA product
- Target pest: *Leptinotarsa decemlineata* (CPB)
- First registration: Q4 2023 by US EPA



Vadescana

- Description: Mite control for bees. Designed to help address colony collapse syndrome by preventing proliferation of varroa mites
- Target pest: Varroa destructor mites
- Expected registration: 2024/2025



Unecyna

- Description: dsRNA fungicidal control for powdery mildew on grapes
- Target pest: *Erisyphe necator* (grape powdery mildew)
- Expected submission: 2024/2025



GreenLight Bio has solutions to capture market share in the $79B crop protection market

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Calantha™

GreenLight Bio's first of its kind solution for protection of potatoes against Colorado potato beetle, addressing a global market opportunity.

Calantha™ is the first registered sprayable dsRNA product

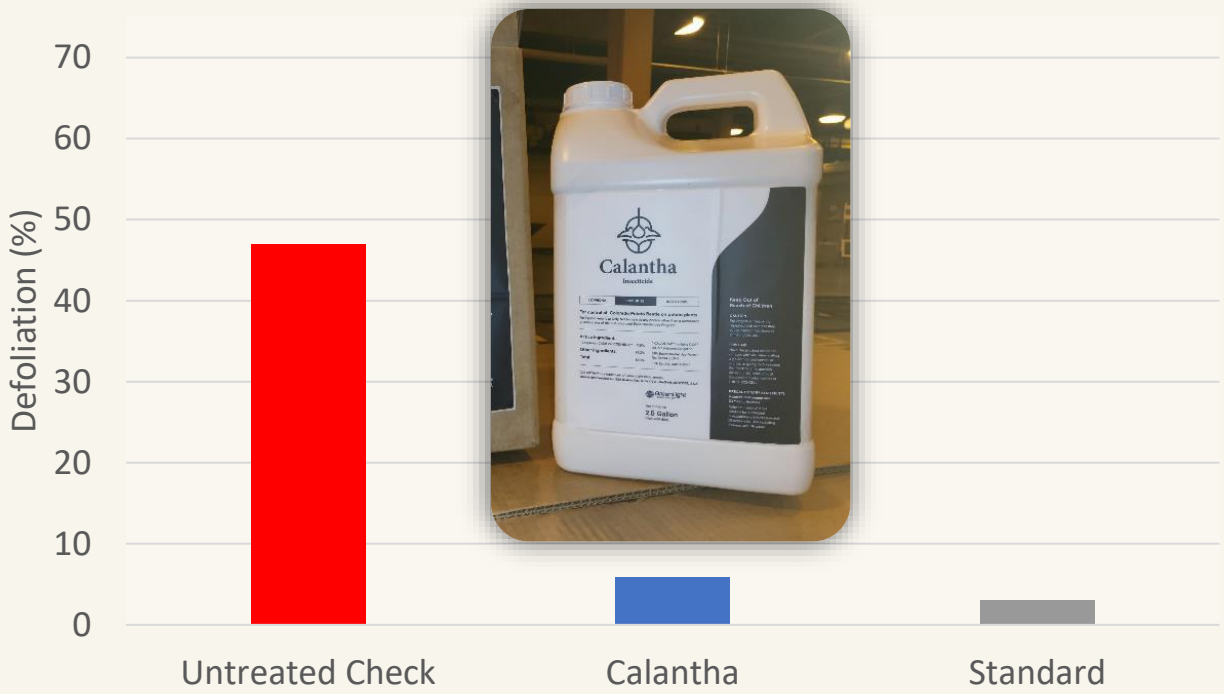
Registered by the US EPA in December 2023

IRAC Group 35

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Protects against crop damage by CPB

% CPB Defoliation from different foliar treatments



USA - Trial summary across 40 trials with >15% defoliation in untreated control plots from 2019-22

- Maine (10), Michigan (2), Minnesota (2), New York (8), North Dakota (4), Oregon (1), Virginia (1), Washington (5), Wisconsin (7)
- 2-3 foliar applications applied every 7 days ; data tahen ~3 weeks after first foliar application
- Industry standard insecticides included Spinosad, chlorantraniliprole, abamectin and lambda-cyhalothrin





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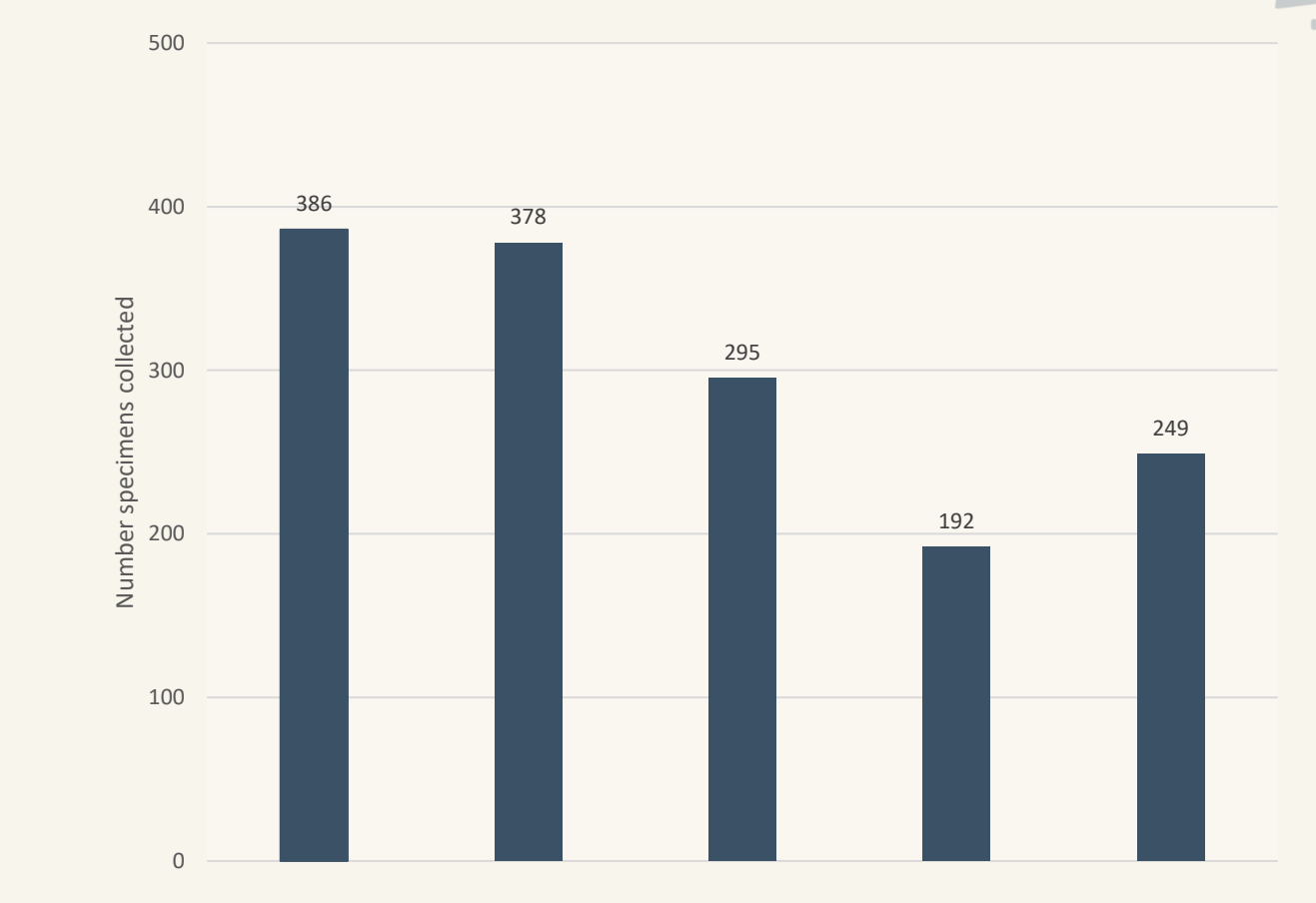
Calantha™ does not impact non-target arthropods

All studies performed confirm little to no impact on non-target organisms tested, leaving beneficials unaffected.

Abundance and specimen richness remained unaffected where Calantha™ was applied.

Neonicotinoid at planting and broad-spectrum insecticides impact populations.

Total number of above ground beneficial insect specimens collected during 2021 in Idaho



Soil appl.	None	None	Neonicotinoid	Neonicotinoid	Neonicotinoid
1st gen	None	**Calantha**	Avermectin	Neonic+pyreth	Spinosyn
2ndgen	None	**Calantha**	pyrethroid	Avermectin	Diamide

All treatments included +/- soil neonic / 3 foliar apps to 1st generation CPB / 2 apps to 2nd generation CPB. Samples collected ~every 2 weeks with vacuum sampler.
** Part of 2-year study across the USA*

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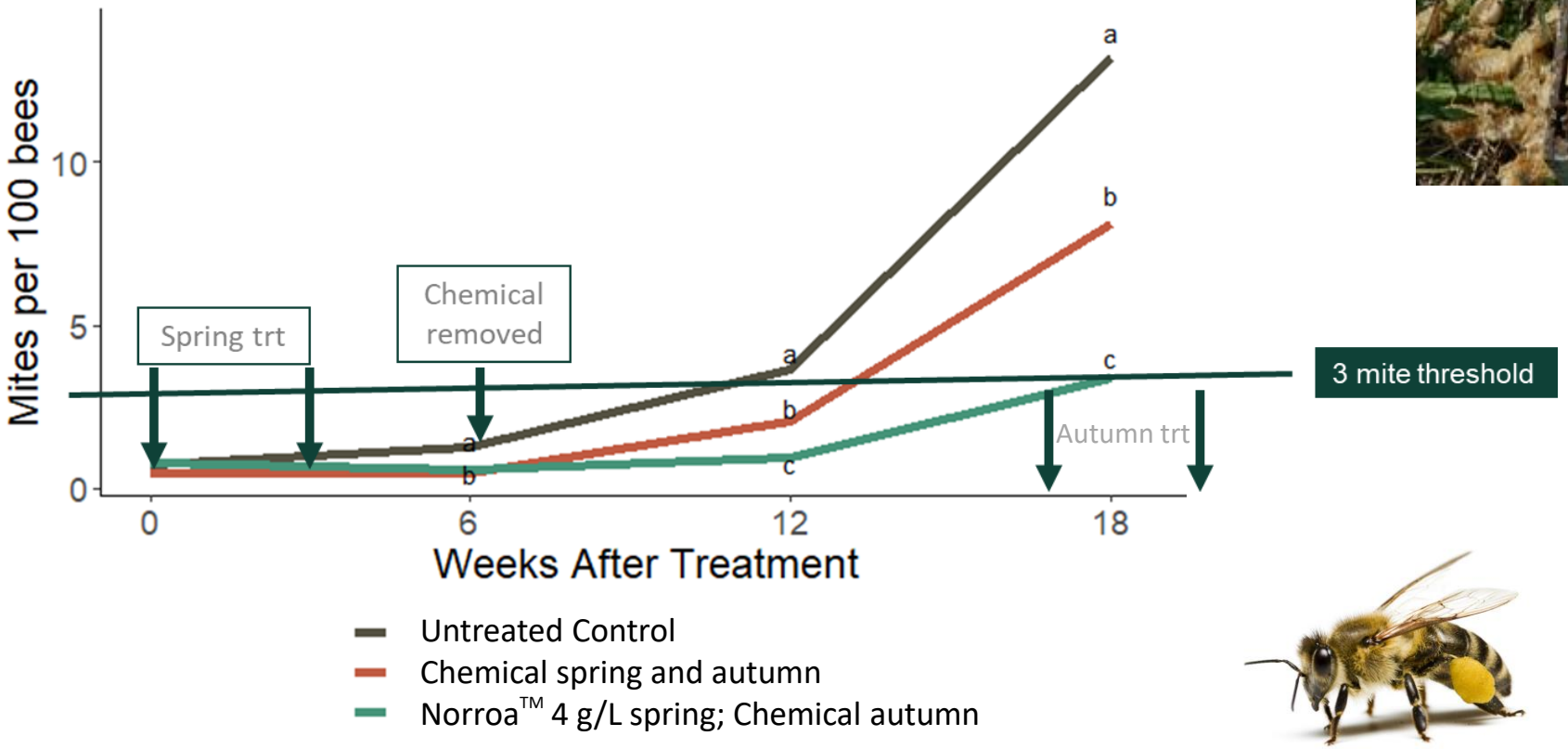
Bee Protection Program

US EPA submission in February 2023 for a dsRNA product to protect honeybees from the parasitic Varroa mite

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dsRNA control of Varroa mites in beehives

Norroa™ controls Varroa mite infestations





- Norroa™ was the only treatment to maintain mite numbers below threshold (3 mites/100 bees) until the autumn treatment was applied
- Norroa™ application in the spring provides longer and more effective mite control
- **Improved beehive health**

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Powdery mildew - Grapes

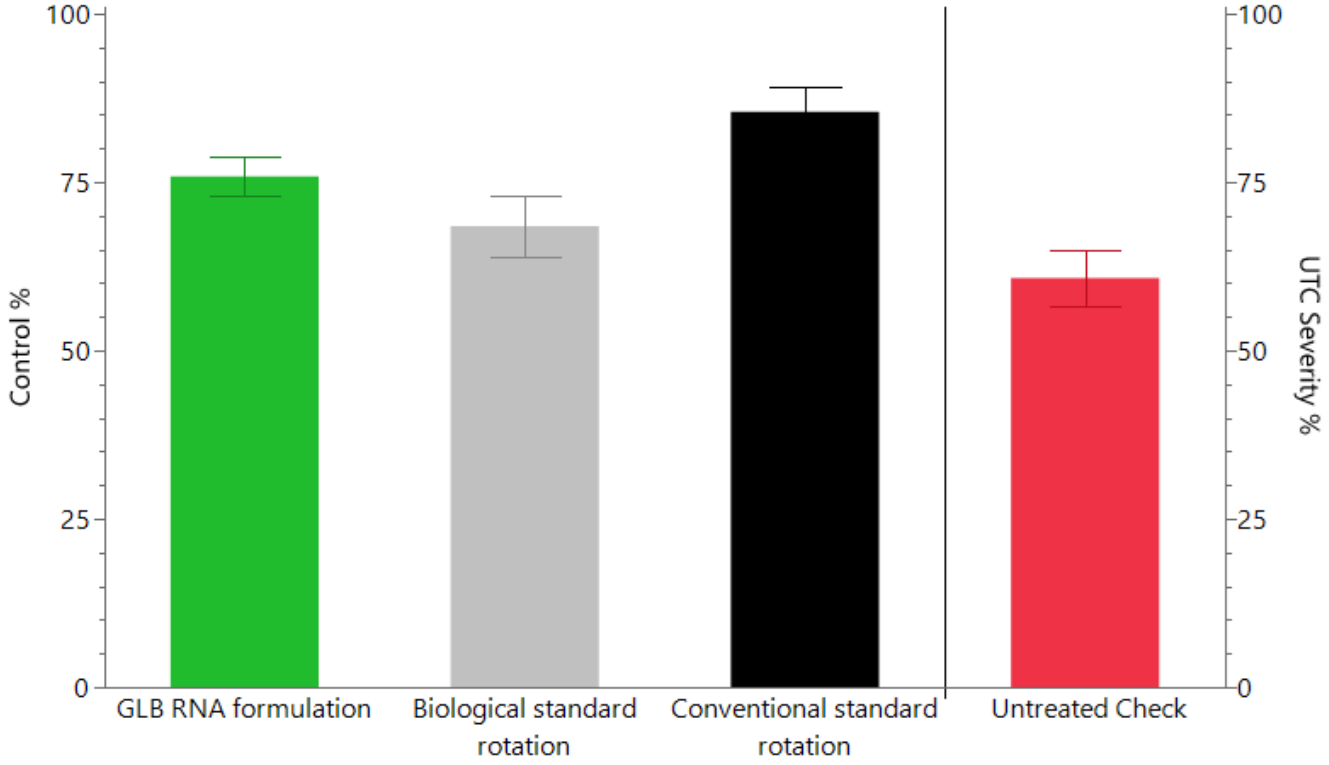
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Sprayable dsRNA control of Grape Powdery Mildew



- dsRNA provided similar control to the season long conventional program under medium to heavy disease pressure
- Regulatory-ready formulation was extensively tested across Europe and the USA providing consistent results
- Product entering regulatory phase

Average PM control on bunches of 15 trials (ES & USA) in 2023



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Global Regulatory Engagement

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GreenLight Biosciences Technology – Regulatory

GLB RNA solutions meet the diverse needs of regulators, farmers, and consumers

GLB dsRNA is registered, under review, or in discussion with regulators around the world

United States Environmental Protection Agency

Comissão Técnica Nacional CTNBio de Biossegurança

Australian Government
Australian Pesticides and Veterinary Medicines Authority

Federal Office of Consumer Protection and Food Safety

Government of Canada / Gouvernement du Canada

What regulators, growers and consumers are looking for:

RNA	Quality
✓	Specificity of action – not broad spectrum
✓	Minimal toxicity – humans and Non-Target Organisms
✓	Degrades rapidly in the environment
✓	Low to no residue
✓	Low dose rate
✓	Use in Integrated Pest Management (IPM) programs
✓	Non-GMO
✓	Compatibility with current Agricultural Practices
✓	Maintains Non-Target Organism diversity post-application

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Challenges

Communicate Exciting Novel technology within current Regulatory Frameworks

Informing stakeholders of new technology

- Science of novel technology and mode of action
- Communicating specificity and benefits to regulators and growers
- Relevance of standard study requirements
- Regulatory agencies experience/expertise with novel technologies

Adapting to current regulatory structures

- Acceptance of ‘waiver’ positions versus studies to meet standard guideline/study requirements – Cost, time, regulatory value
- Review and acceptance of ‘non-standard’ studies more appropriate for evaluation of dsRNA
- Acceptance of bioinformatics as a tool in risk assessment
- Cost of generating data not relevant to dsRNA in addition to new dsRNA-specific data

Managing long timelines

- Review times
- Shortage of technology expertise in regulatory agencies
- Priority setting for novel technologies

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Conclusions

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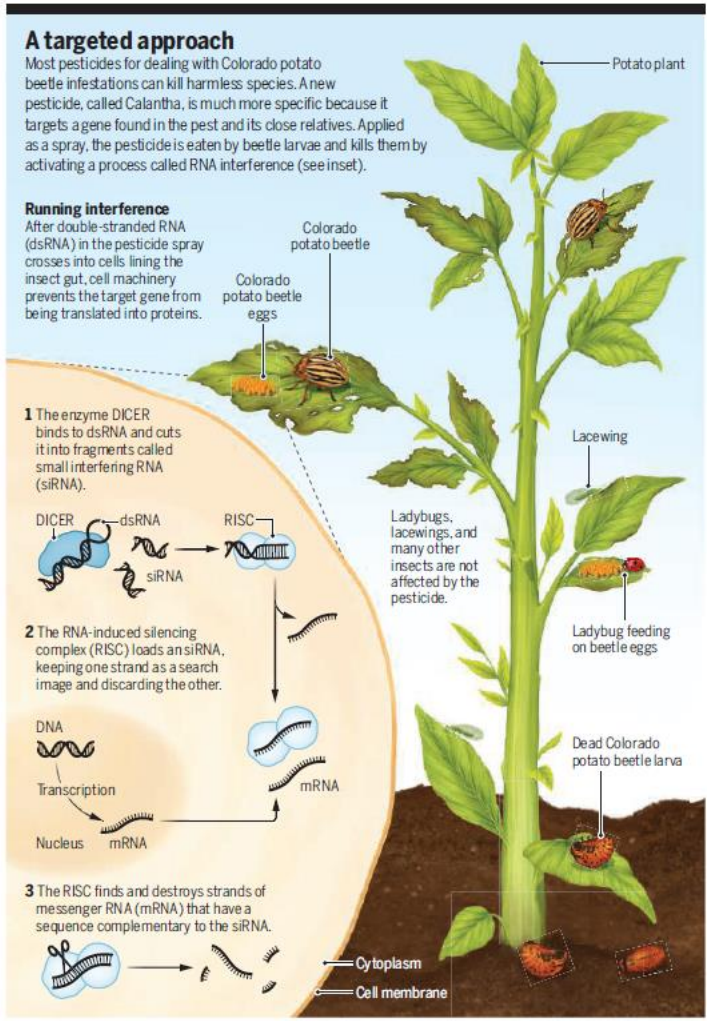
Summary: RNA biopesticides

Key points

- Grower benefits:
  - Non-GMO alternative to conventional insecticides
  - Valuable new Mode of Action
  - Fits grower programs for pest control
- Sustainability: Highly effective alternative to conventional insecticides
  - Targeted, preserves biodiversity
  - Rapidly degrades in the environment
  - Excellent safety profile for human health and non-target organisms
- Challenges:
  - Regulatory frameworks differ across jurisdictions
  - Ensuring resistance management requirements are followed







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Note: Norroa is currently under review at US EPA and not available for commercial sale.

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Thank You

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