

Divergence, Inc.

Developing
Safe and Effective Products
for the
Control of Plant Parasites

Andrew P. Kloek
Divergence, Inc.
www.divergence.com
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DIVERGENCE
The Nematode Genomics Company

Divergence Background

- > R&D company formed in 1999
 - *Dr. Jim McCarter; former leader of the parasitic nematode sequencing group at the Genome Sequencing Center*
- > Genome-based approach to the Discovery of Novel Nematicides and Nematode Resistant Plants
 - *Identifying genes essential to the nematode not present in humans or non-target species*
- > Focused on effective, safe and environmentally sound solutions
 - *Nematode specific targets allows for the design of controls which minimize the likelihood of toxicity to non-target species*



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Divergence in a Snapshot

Divergence Validated Genome-Based Discovery Platform

- Two Novel Nematicidal Chemistries advanced to development since 2000
- Efficacy of Chemistry Across a Range of Nematodes; Novel MOA
- Chemistry Based on Known Targets Selected To Avoid Toxicity
- Pre-Selects for Risk Reduction & Cost Reduction in Product Development
- Parallel Transgenic Development

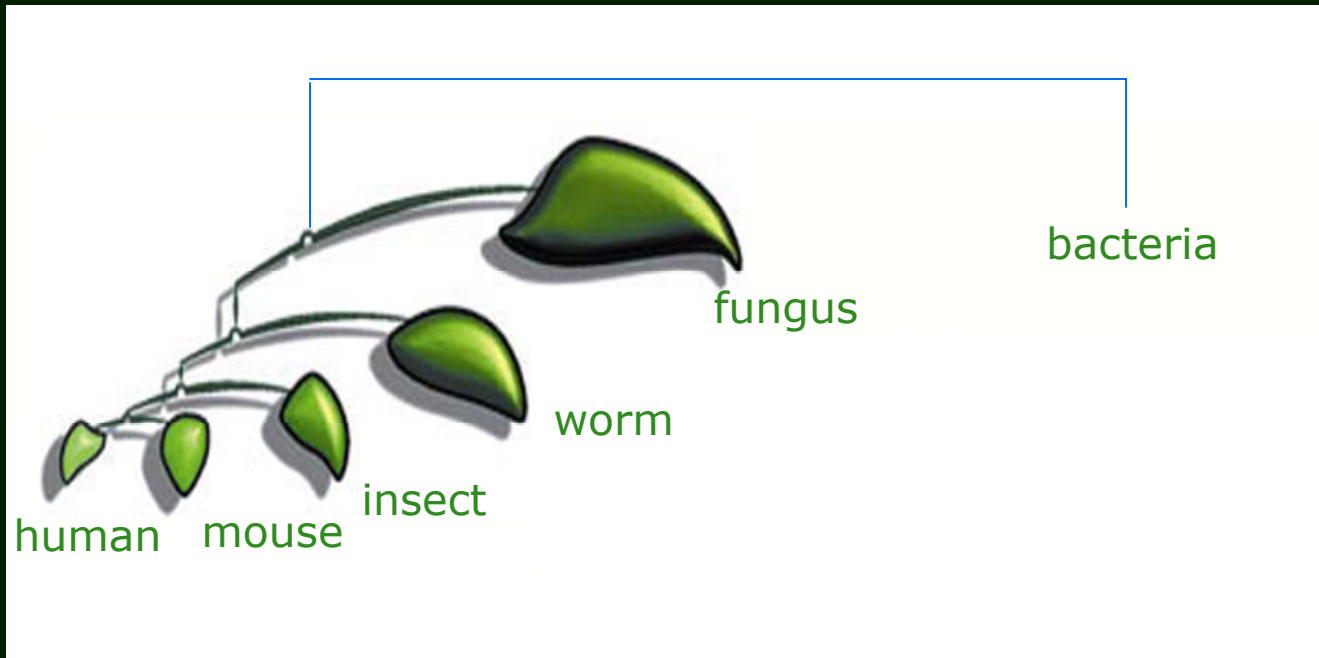
Funding, Grants, Awards

- Investors Include Industry Insiders - Vagelos, Shapiro, Gantz, etc.
- NIH Phase I & II SBIRs, 2 NSF Phase I SBIRs, National Corn Growers
- 4 Regional Awards in 2002 Recognizing Company & Founders



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Evolutionary Relationships Make Nematodes a Challenging Target



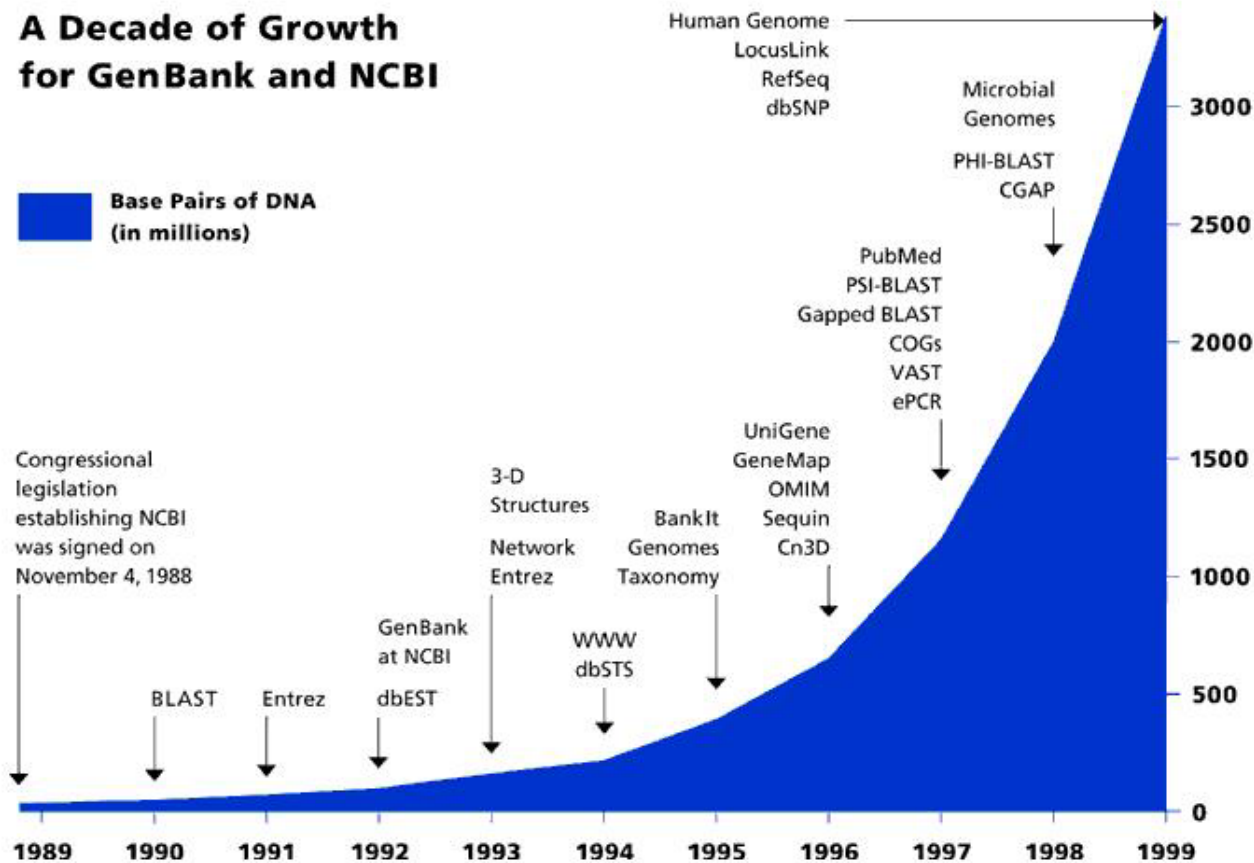
- Humans and Worms Share Nearly 1/2 Their Genes
 - Essential Genes Tend to Be Conserved Genes
- Finding Nematode specificity Requires Complete Genomes



Genomics: Explosion of Data in the late 1990's

A Decade of Growth for GenBank and NCBI

Base Pairs of DNA
(in millions)



3.3 billion



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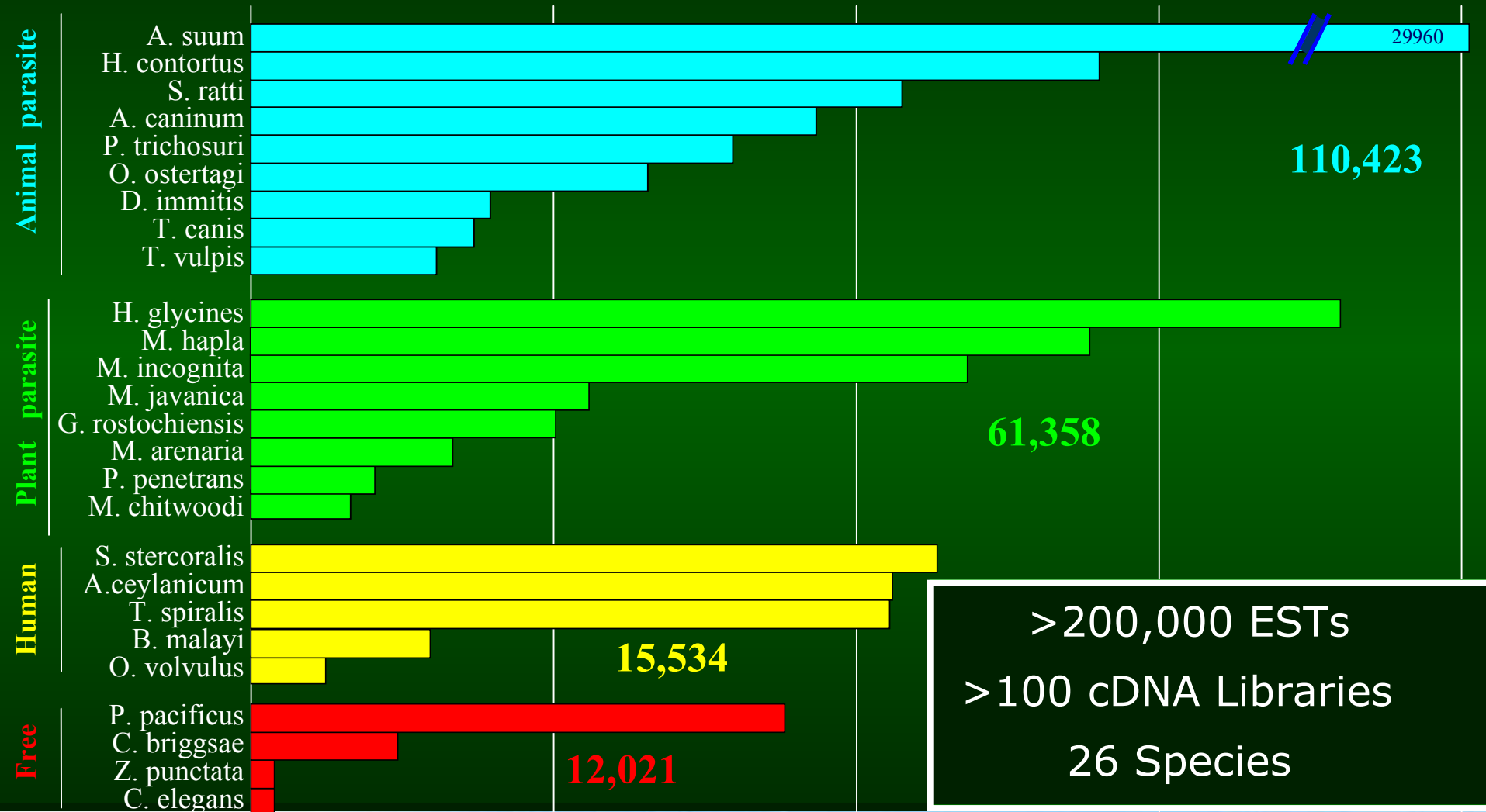
[illegible]

- St. Louis based GSC led first finished sequence of an animal, the nematode *C. elegans*, with Sanger Centre
- Sequenced significant portions of mouse/human genome
- World's Largest Effort in Parasitic Nematode Sequencing (235K ESTs)
- 26 Species; including 10 parasites of plants
- Extensive network of collaborators including leading academic labs
- \$2M+ in Support from NIH, NSF, Whitney Foundation, Merck – all data publicly available



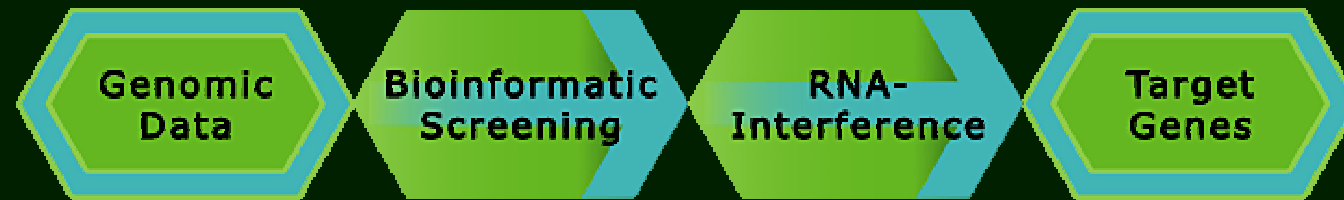
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GSC Nematode EST Totals, 4/03

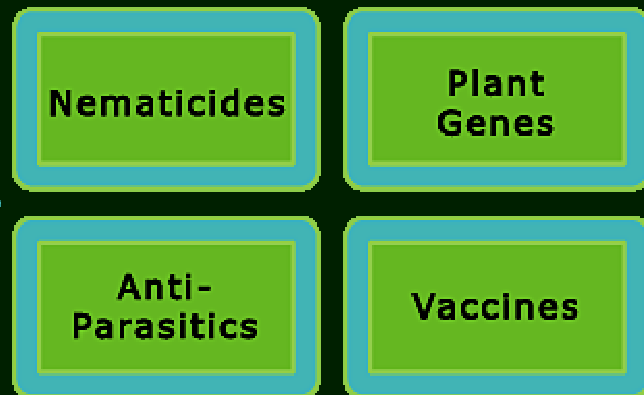
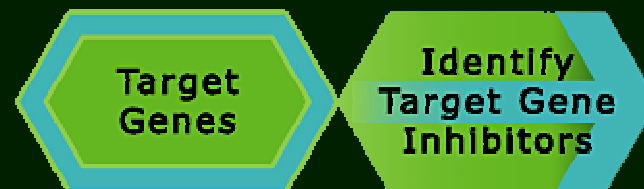


Divergence - Successful Discovery Platform

First Target Genes...

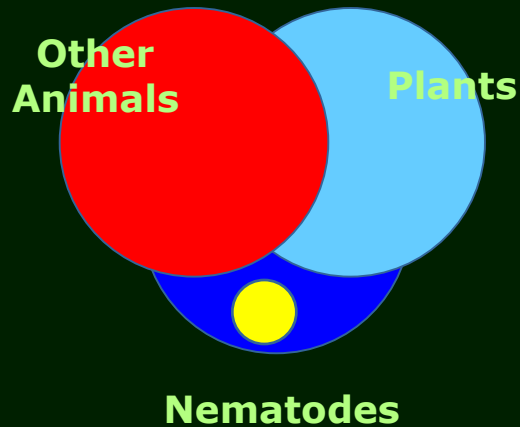


... Then Commercial Products



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Rational and Sequential Process for Harvesting Promising Leads from the Deluge of Data



*Not in human, required
for survival*

Bioinformatics Filter
20,000 > 1,000

Functional RNAi Filter
1,000 > 100

Curation
>100 Prioritized Gene
Leads



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Divergence Validated Target Genes Fall into Distinct Classes

I. Enzymes of known function with defined small molecule substrates
DIV8338, DIV3202, DIV3441



**Design & Test
Inhibitors**

II. Enzymes, channels, receptors with known function
DIV6916, DIV5704, DIV3876, etc.



**Hi-Thruput
Screens**

III. Secreted & transmembrane proteins on accessible surfaces (intestine, etc.)
DIV7429, DIV9015, DIV8907, etc.



**Transgenic &
Vaccine Approaches**

IV. Nematode Specific Proteins of unknown function
DIV5225, DIV0129, DIV9276



**Monitor
Literature**



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Two Approaches Toward Transgenic Control of Crop Parasitic Nematodes

1. Engineering plants to express small-molecule metabolic inhibitors that target nematode-specific biochemical pathways (Class I targets).
2. Engineering plants to produce small polypeptide inhibitors that specifically target essential proteins in the nematode intestine (Class III targets).



Class I Targets Allow Rapid Creation of Candidate Small-Molecule Inhibitors

I. Enzymes of known function with defined small molecule substrates

DIV8338, DIV3202, DIV3441



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Class I Example: DIV3202 and DIV3441

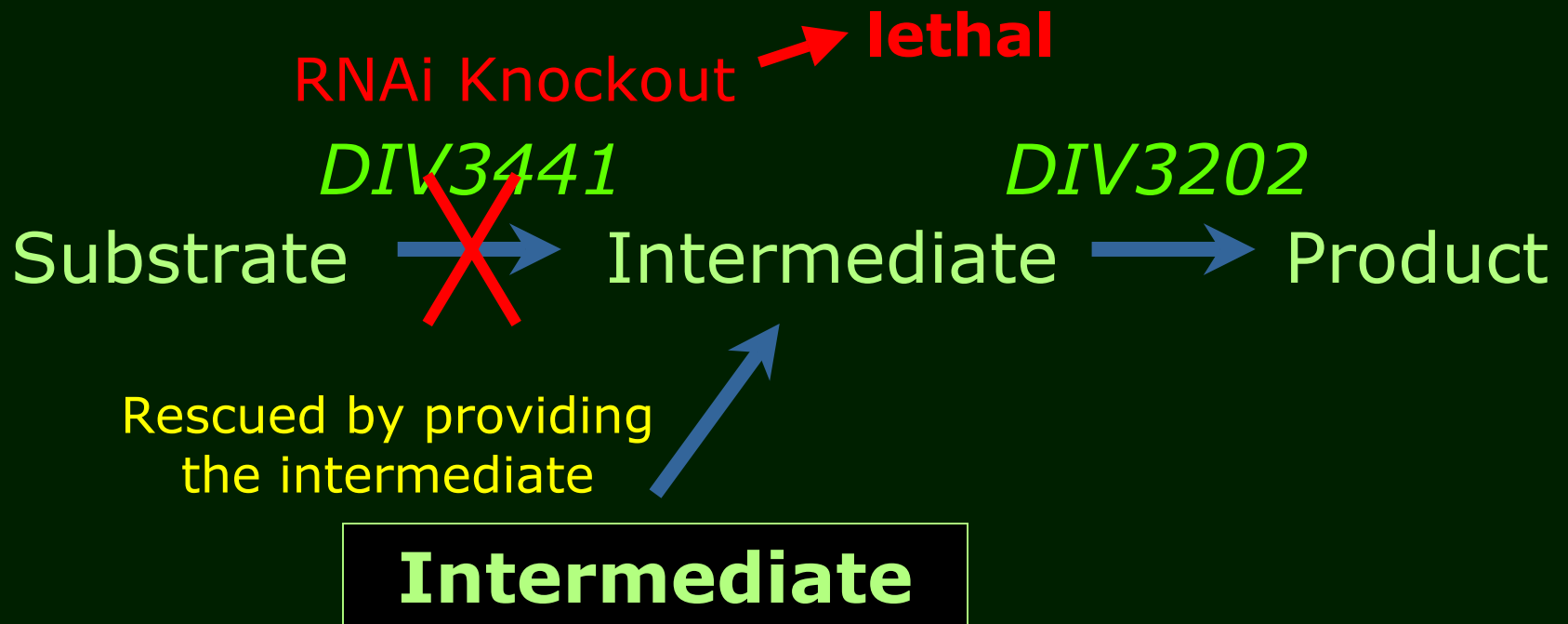
DIV3441 *DIV3202*
Substrate → Intermediate → Product

- Targets Work Sequentially in Enzymatic Pathway Not Found in Vertebrates
- Both Targets Essential in Multiple Steps During *C. elegans* Lifecycle
- Both Targets Present and Conserved in Many Parasitic Nematodes



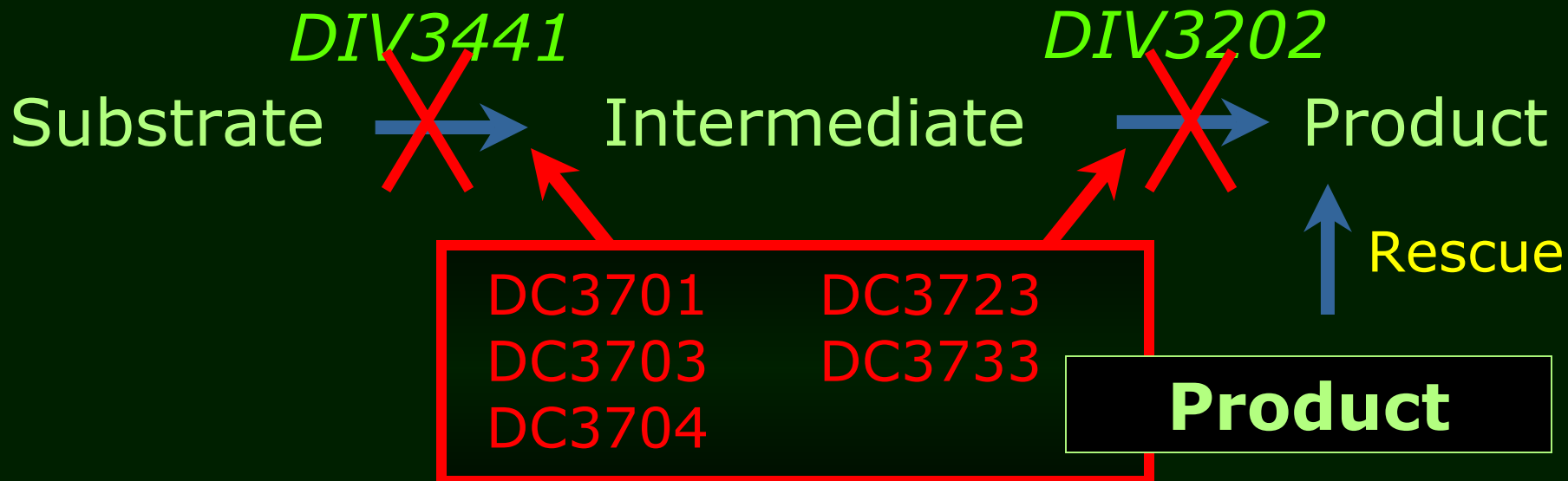
DIV3202 and DIV3441

- RNAi Knockouts of Either Target Can Be Rescued by a High Dose of Intermediate in Pathway



DIV3202 and DIV3441 Are Excellent Nematicide Targets

- In All 5 Cases, Chemical Knockout Can Be Rescued by a High Dose of Downstream Product in the Pathway
- Product Rescue Provides Basis for a In Vivo High Throughput Screen



Class I Example: DIV8338

DIV8338

Substrate → Product

- Target Works in Enzymatic Pathway Not Found in Vertebrates
- Target Essential in Multiple Steps During *C. elegans* Lifecycle
- Target Present and Conserved in Many Parasitic Nematodes



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DIV 8338 is an Excellent Target for both Chemical and Transgenic Products

- 10 Chemicals Selected Based on Structural Similarity to Substrates and Products in the Pathway
- In 5 Cases, Chemicals Were Nematicidal

DIV8338

Substrate  Product

DC7651

DC7647

DC7646

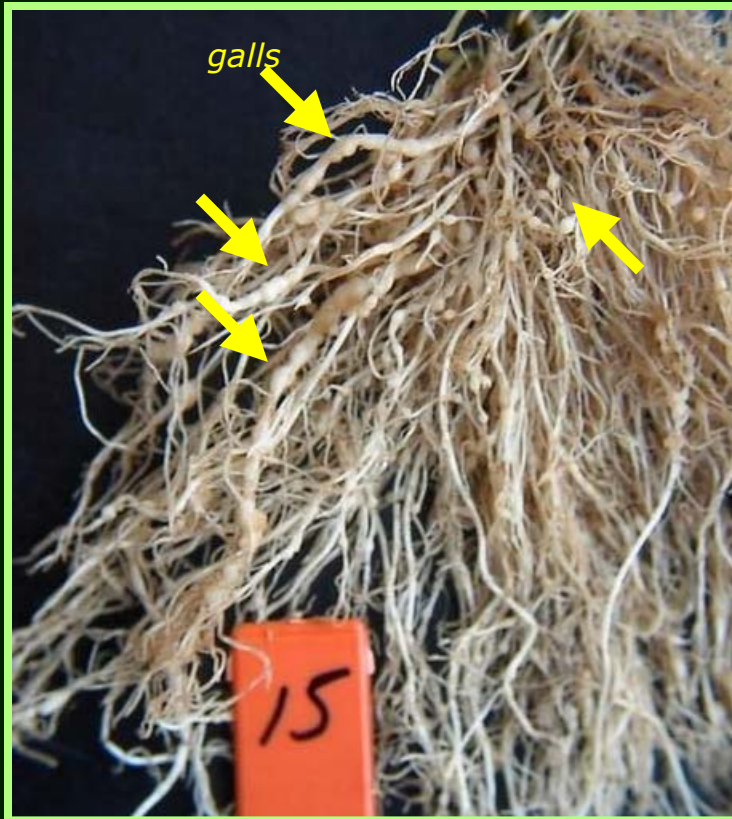
DC7653

DC3772



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Nematicidal Example



No treatment



DC7647/DC7651



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Transgenic Example: DIV8338

- Ideal for Chemical as well as Transgenic Development
- Several Inhibitors are Derivatives of Human-Consumed Plant-Derived Natural Products
- Plant Genes Controlling Production of These Products Have Been Cloned and are Being Tested in Transgenic "Hairy Roots" in the Lab

Control hairy roots infected
With Root Knot Nematode



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Class III Example: Intestinal Lumen Target Validation

- Of 5 Initial Targets Chosen, 4 Localize to the Intestine
- 2 Targets Are Known to Play Roles in Protein-Protein Interactions and Overexpression of these Peptides is Lethal to the Nematode
- Generation of Transgenic Plants Expressing these Peptides is in Progress



Divergence Alliances & Relationships



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Focus of Transgenic Development

- > Transgenic Nematode Control Solutions for Corn, Cotton and Soybeans
 - Research collaboration with NCGA
- > Capabilities for in-house development in model crops and academic partnered development in commercial germplasm
 - Gene or multiple genes to provide control of most economically significant nematodes (e.g. root-knot, reniform)
 - Stacked with other traits of interest
 - Backup genes to ensure resistance management/spectrum
 - Germplasm introduction based on geographical need



Summary

- > Excellent Safety Profile as targets unique to nematodes
- > Focused on transgenic solutions for row crop nematode control
- > Currently, two distinct approaches under development
 - Additional targets prioritized for advancement
- > Progressing through transgenic developmental milestones

