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Exploring Novel Approaches for Gene Target Selection & Trait Validation in Crops

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CRISPR&NBT
AgBio Congress 2019

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Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and may be beyond the Company's control, you should not rely on these statements as predictions of future events. Actual results could differ materially from those projected due to our history of losses, lack of market acceptance of our products and technologies, the complexity of technology development and relevant regulatory processes, market competition, changes in the local and national economies, and various other factors. All forward-looking statements contained herein speak only as of the date hereof, and the Company undertakes no obligation to update any forward-looking statements, whether to reflect new information, events or circumstances after the date hereof or otherwise, except as may be required by law.

*Under the Private Securities Litigation Reform Act of 1995

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"Yield10 develops high value seed yield traits for the agriculture and food industries"

TRAIT FACTORY

3-5 years

PRODUCTS

Efficiently developing superior traits for corn, soy, canola, wheat, rice and camelina

The "Trait Factory" leverages 26 years of Met-Eng investment/achievements

Optimizing photosynthesis and carbon efficiency to increase grain yield

Strong leadership and R&D team, operates in Boston, USA and Saskatoon, Canada

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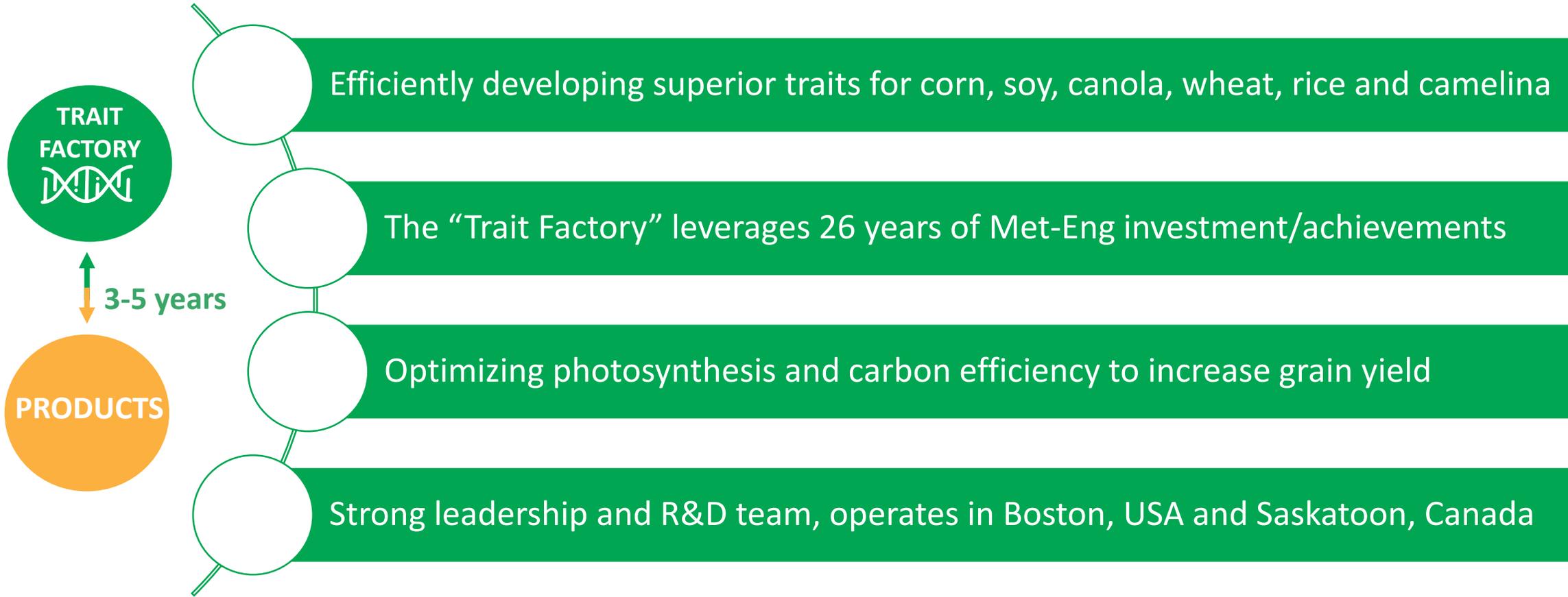
Yield10 combines advanced discovery with genome editing to develop valuable traits

TODAY

- Increased seed yield
- Increased oil content
- Improved stress resistance
- Increased biomass yield

TOMORROW

- Specialty oils and PHA biomaterials
- Winter cover crops

FUTURE

- Elimination of synthetic chemicals
- Disruptive seed sector business models

TRAIT FACTORY

3-5 years

PRODUCTS (TRAITS)

BIG DATA

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GRAIN 3.0 (Gene Ranking Artificial Intelligence Network)

- On some level a plant phenotype or trait reflects altered metabolism due to genetic variation
- GRAIN uses metabolism to rationally mine genomics data

Genomics Era

- Genome sequencing
- **"Qualitative"**
- Expensive time-consuming testing of thousands of single transgenes
- Molecular analysis of transgenics
- Molecular breeding markers etc.
- **Low ROI** - 2 decades

"Big Data"

Billions of Data Points

Data Mining

Grain Era

- **Facts** (Metabolic changes)
- **"Quantitative"**
- **High value gene targets**
  - Literature validation
  - IP white space
- **High ROI - ?**

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Big Data

Gene Targets

Environment

Metabolism

Gene Regulation

GRAIN

Engineered Plants

1 – 2 years

3 – 8 years

The "Trait Factory"
- Regulated traits 3-8 years
- Non-regulated traits 3-5 years

Development Pipeline

Commercial Products

- Genome-editing is a key tool to deploy new traits and unlock the value created using GRAIN

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Step-change increases in seed yield will likely require increased photosynthetic carbon fixation and delivery of the increased fixed carbon to the seed

- Identifying the right combination of genes is a key task
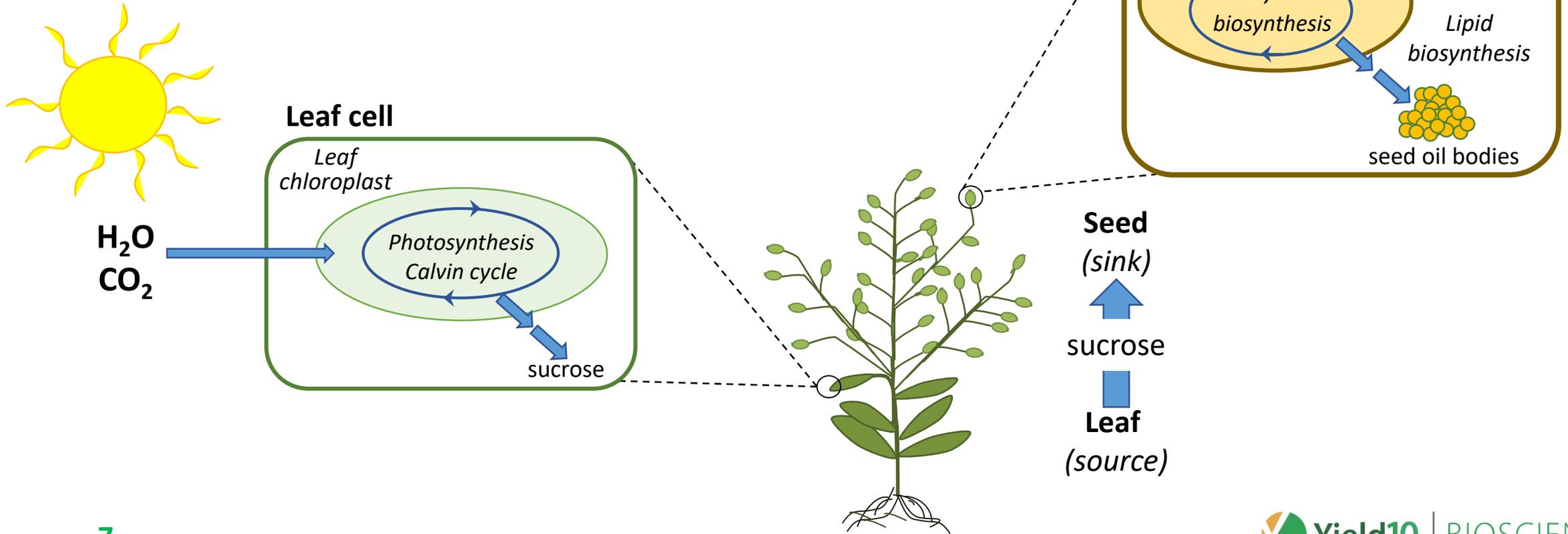
CROP SPECIFIC GENOMICS DATA

REGULATORY MODELING

METABOLIC MODELING

FAST FIELD TESTING

Environment

Metabolism

Gene Regulation

GRAIN 3.0

Actionable gene modifications leading to valuable, novel yield traits
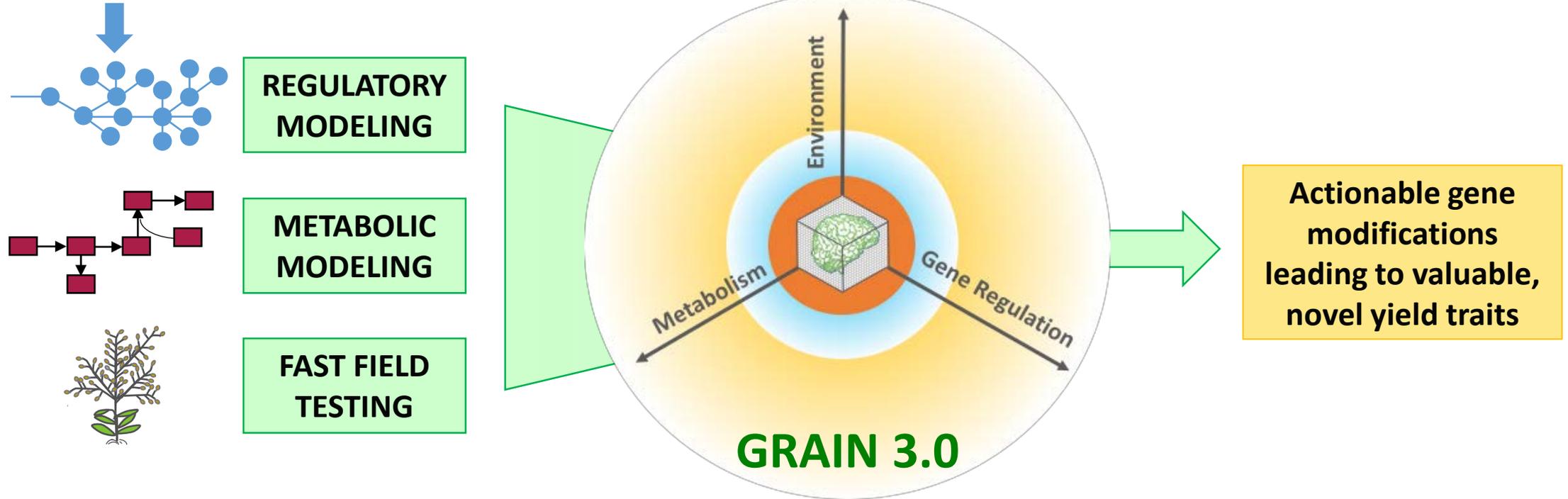
- Regulatory and metabolic modeling components, each component can generate its own set of gene targets
- Combining components provides unique tool where metabolic information can inform genomics decisions

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Metabolic modeling component based on flux balance analysis

- Contains all enzymatic reactions, transport functions, and cofactors (ATP, ADP, NADPH….) in plant system
- Incorporates thermodynamic information to avoid solutions that are thermodynamically unfavorable
- Define problem (e.g. maximize seed biomass production)

METABOLIC MODEL

INPUTS

light
CO_2
NO_3^-
etc.

LEAF

sugars

amino acids

leaf biomass

SEED

CO_2

seed biomass

MODEL OUTPUT

- Sets of ideal fluxes
- Theoretical yields
- Pathway comparisons or optimizations
- Alternative pathways to achieve goal
- Importance of individual genes to trait

GENE TARGETS

Yield10 Review Paper on Metabolic Engineering in Plants: Skraly et al., Metabolic engineering to increase crop yield: From concept to execution, 2018, Plant Science

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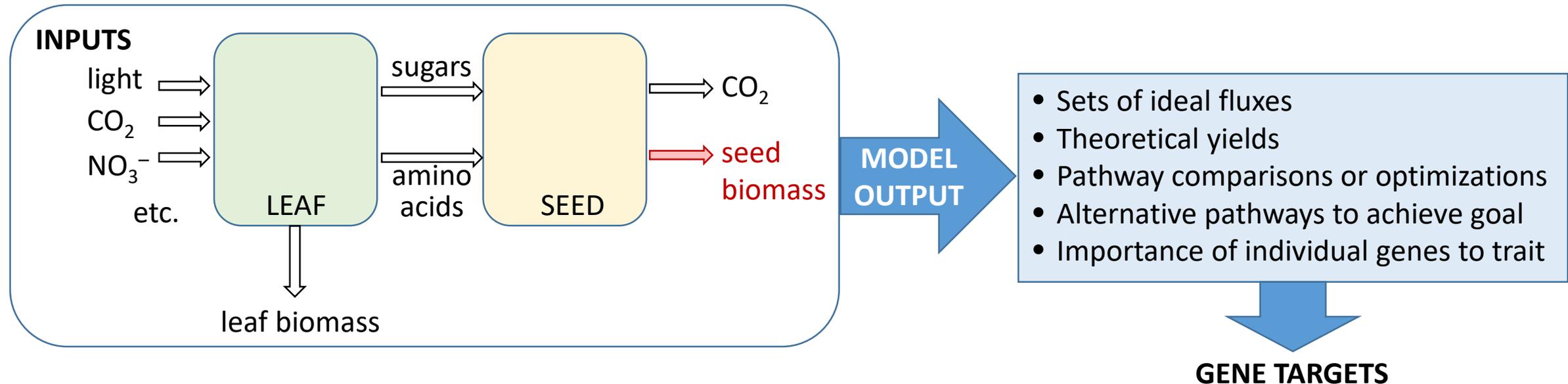
Overexpression of novel carbon fixation pathway in *Camelina sativa* increases seed yield

NET: 2 CO_2 + 2 HCO_3^- → oxaloacetate
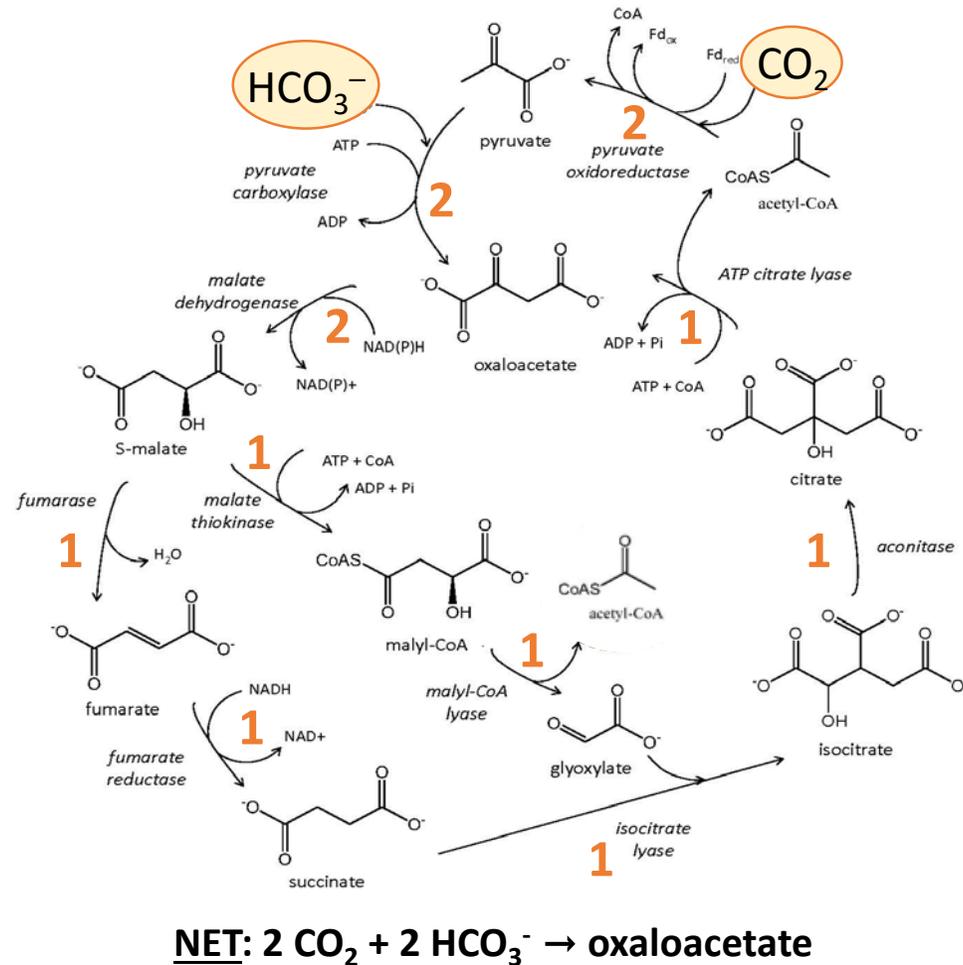
- Modeling predicts **112%** increase in maximum theoretical seed yield with novel pathway under photorespiratory conditions
- Experimental results show increase up to **128%**

Camelina greenhouse study: Seed yield in best plants

Novel Pathway Description: *Camelina sativa*, an oilseed at the nexus between model system and commercial crop. Malik et al., Plant Cell Rep., 2018
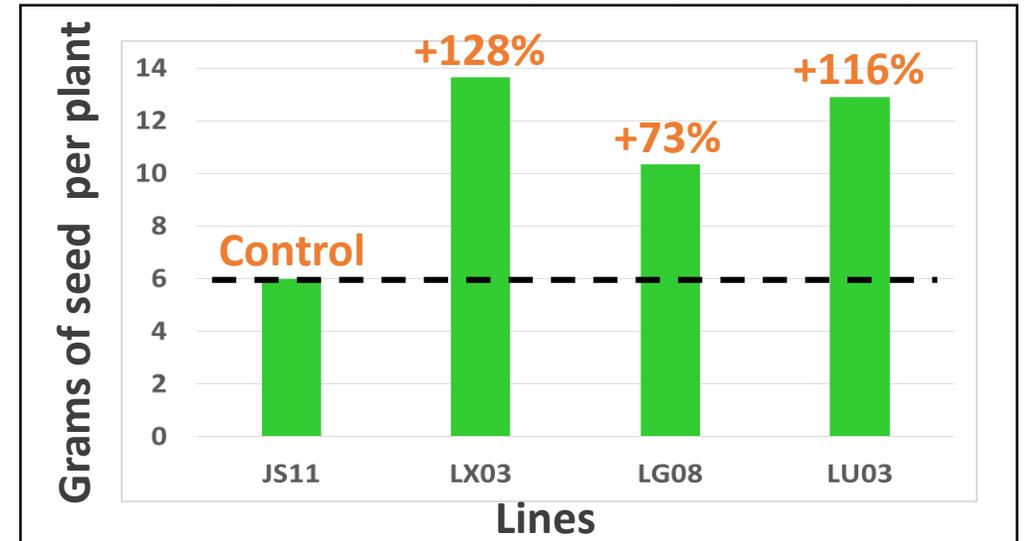
Transcriptome-based regulatory association networks convert big data into actionable gene targets

Complex transcriptomics data

Functional modules

Gene interaction network
Identify functional modules related to trait

OUTPUT 1

Gene 1
Gene 2
Gene 3

Transform

OUTPUT 2

Gene a	Gene d	Gene k
Gene q	Gene f	Gene y
Gene b	Gene s	Gene z
Gene m	Gene t	

Transcriptomics

Transcriptomics of high yielding plants:
A powerful resource for gene discovery

GENE EDITING TARGETS

Increased Yield

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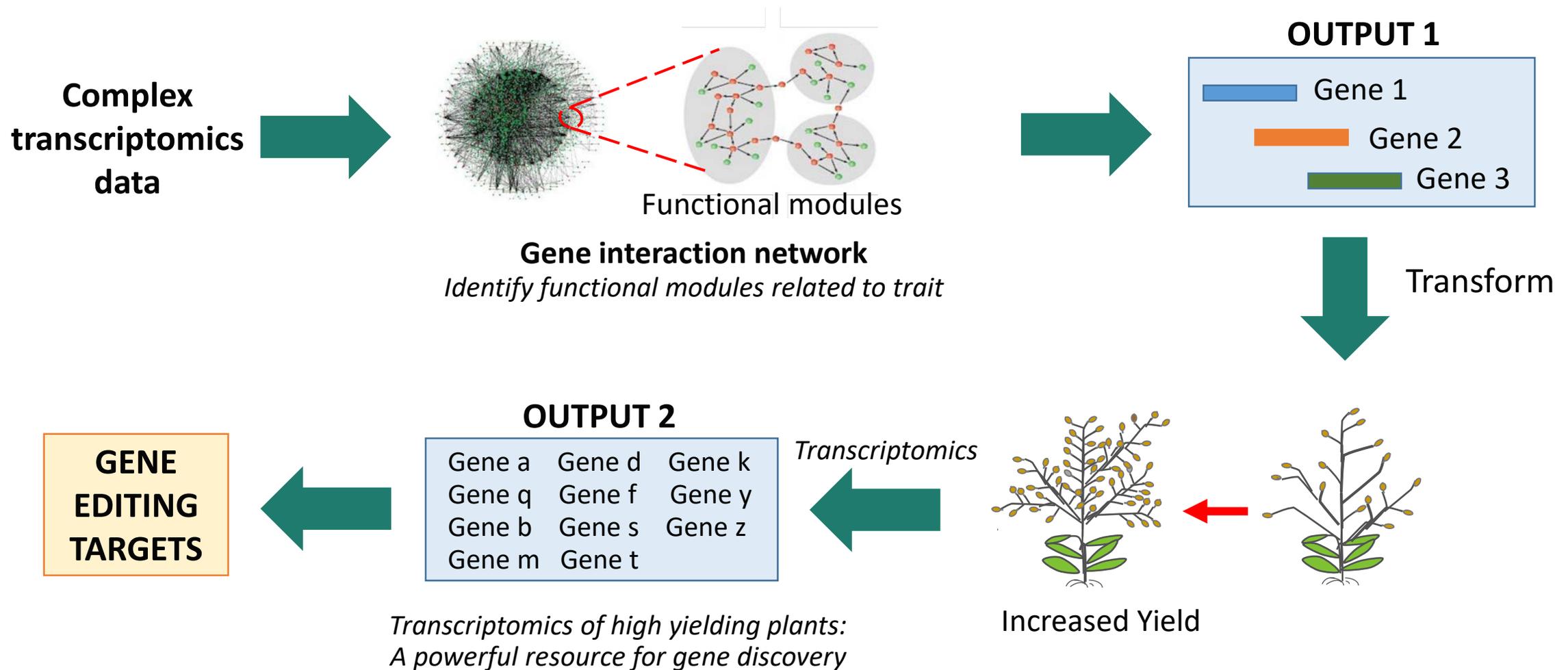
Work with switchgrass

- **Identify candidate global regulatory genes to increase photosynthesis and biomass yield**

Complex transcriptomics data

Gene interaction network

Functional modules

Global regulatory gene candidates identified (C4001, C4002, C4003)

transcription factors that interact with pathways of interest
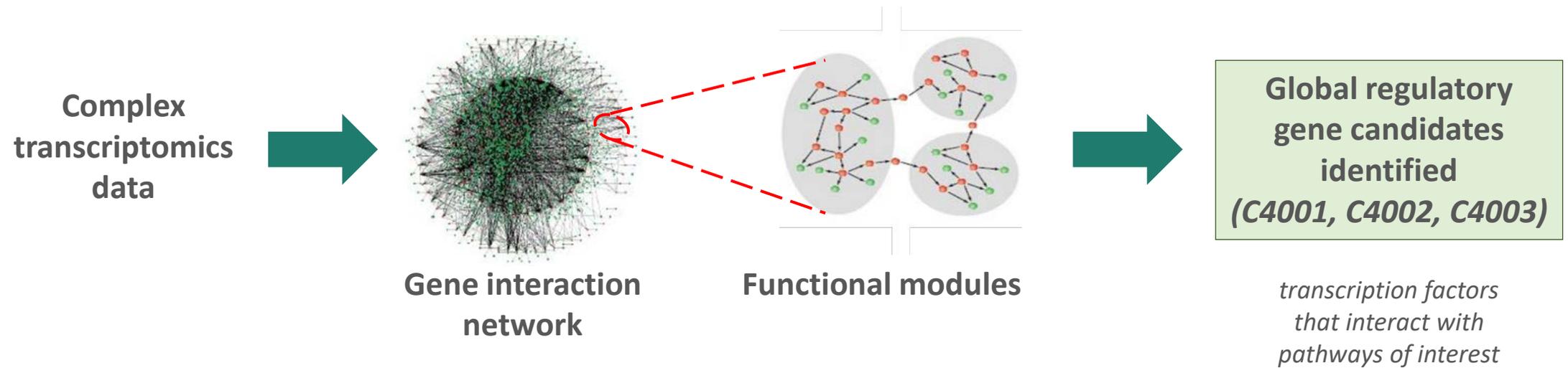
Functional modules of interest for increased biomass yield in switchgrass are enriched in genes related to photosynthesis and central carbon metabolism

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- Transgenic plants produced
  - *genes expressed from strong promoter active in green tissue*

- Increases in aboveground and root biomass observed

Work funded by DOE-EERE

For more data, see: *Ambavaram et al., Novel transcription factors PvBMY1 and PvBMY3 increase biomass yield in greenhouse-grown switchgrass (Panicum virgatum L.), 2018, Plant Science*

*n=4 plants, asterisks indicate levels of significance; * P ≤ 0.01, ** P ≤ 0.05*

C4001 *(PvBMY1)*
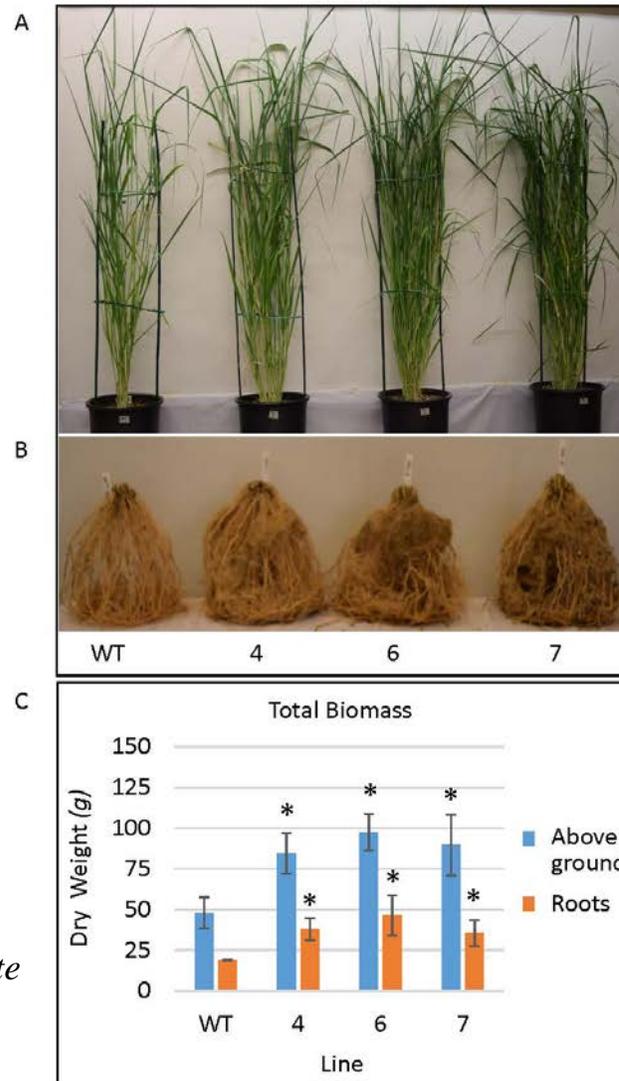
Leaves & stems, 75%-100% increase
Roots, 85-140% increase

C4003 *(PvBMY3)*
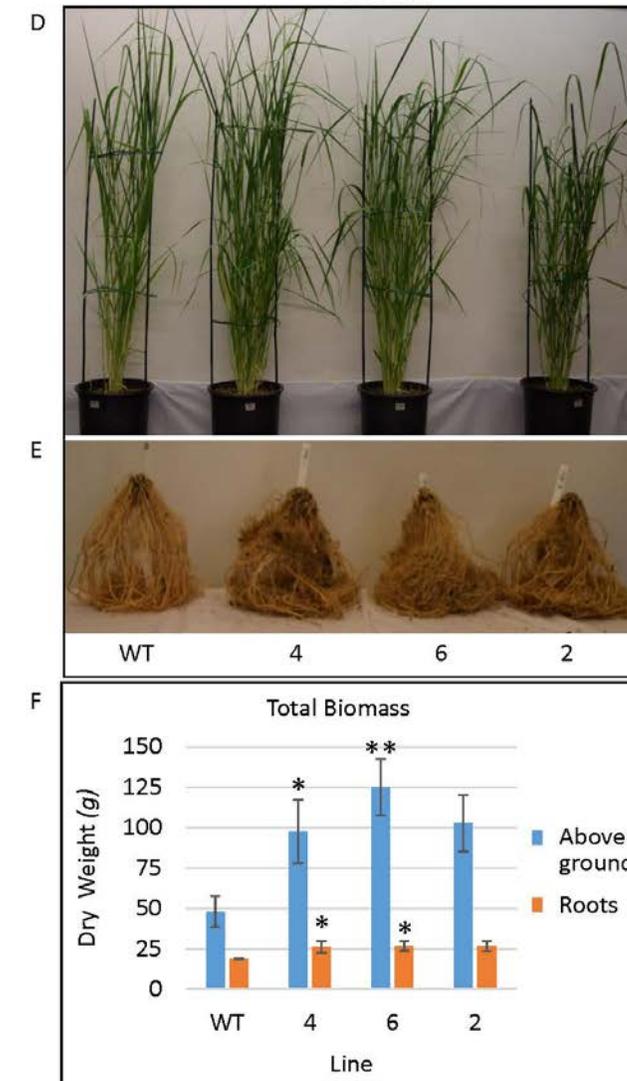
Leaves & stems, 100-160% increase
Roots, ~40% increase

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Various photosynthetic parameters measured. Primary difference observed in electron transport rate around photosystem I and II [ETR(I) and ETR(II)]
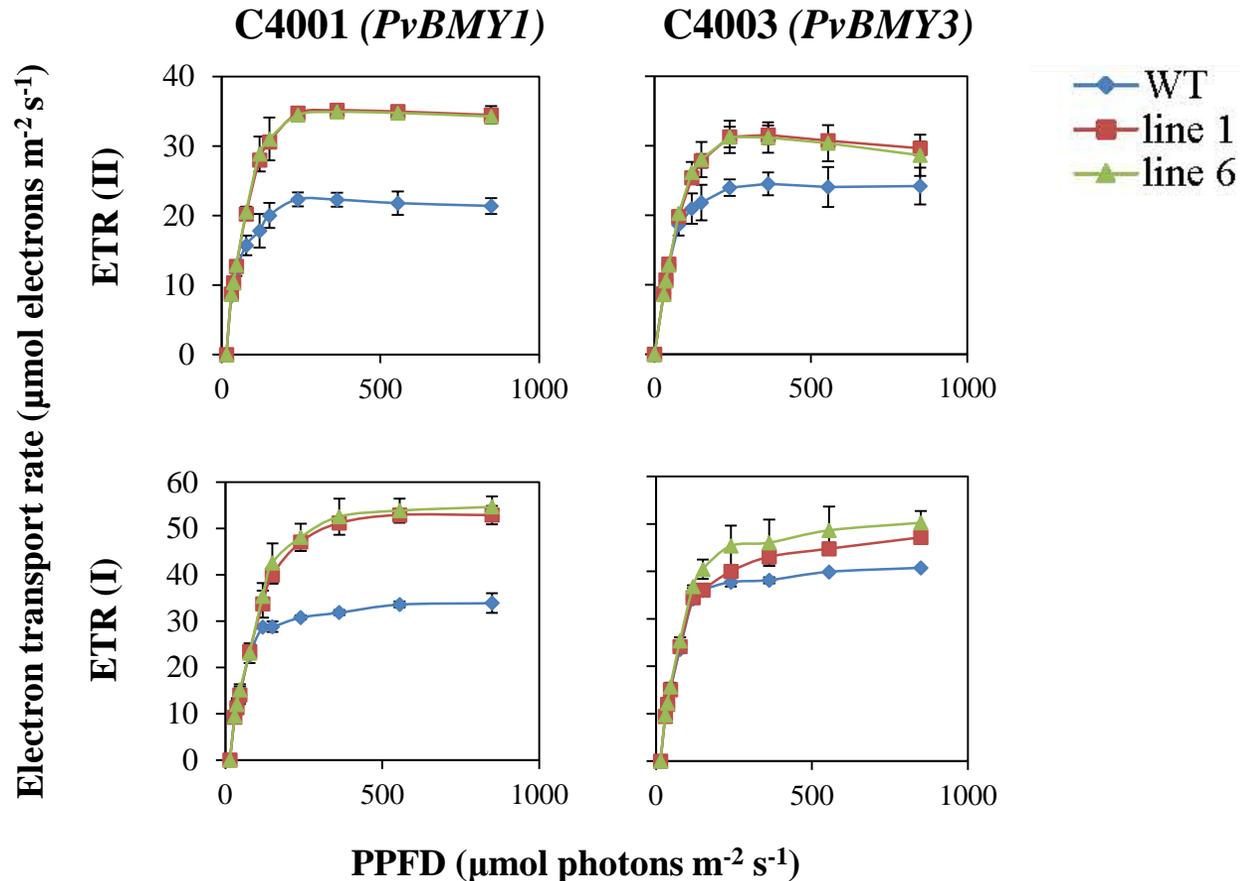
- Photosynthesis rate measurements using Dual-PAM-100 (Heinz Walz GmbH) in 2 month old plants with light adapted leaves on a sunny morning

- Leaf used

- *2nd leaf of a 2 month old plant*

- PPFD = photosynthetic photon flux density

Transcriptomics of high yielding switchgrass plants: A powerful resource for gene discovery

Overexpression of **C4004** in switchgrass

- Negative regulator of plant growth
- Good editing target
- Evaluating edits in rice and wheat

Control switchgrass   Transgenic C4004 Plants

Overexpression of **C4029** confers drought tolerance

Control switchgrass   Transgenic C4029 Plants

2 month old plants
3 weeks without water

Control switchgrass   Transgenic C4029 Plants

Biomass harvested
Regrowth analyzed after 30 days

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Combined modeling components to identify transcription factors (TFs) to increase oil and/or seed yield in industrial oilseed *Camelina sativa*

Camelina Genomics Data

REGULATORY MODELING

METABOLIC MODELING

GRAIN 3.0

Environment

Metabolism

Gene Regulation
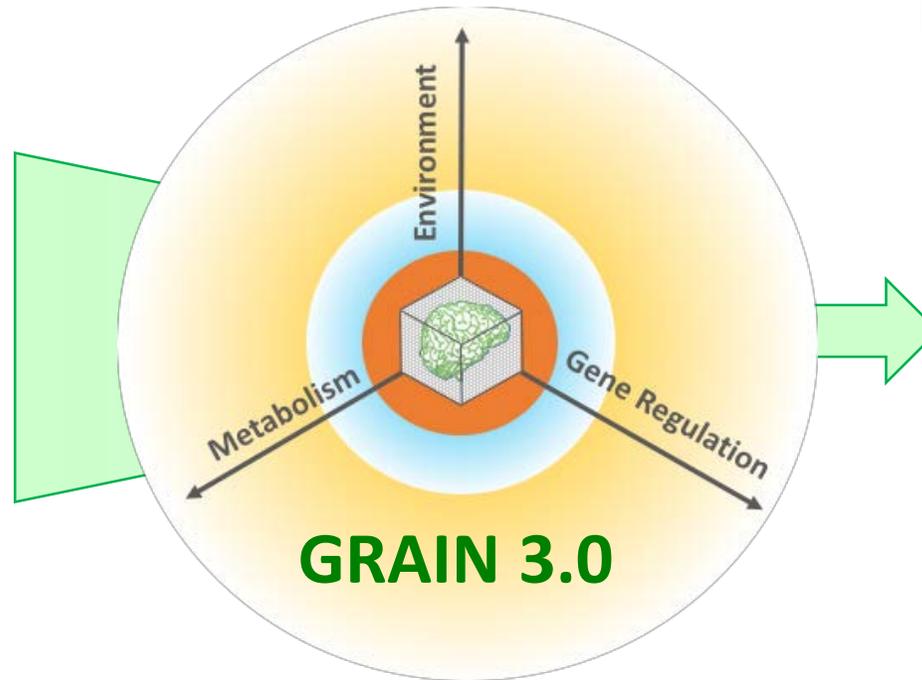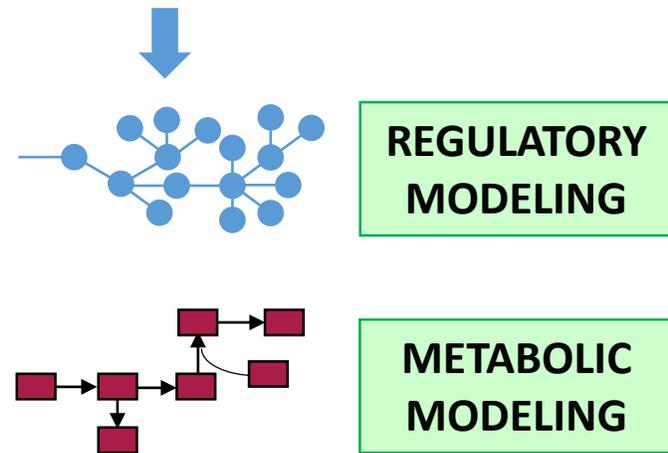
Prioritized List of Gene Targets

Identified TFs (Ranked)	
TF1 = WRI1	TF9
TF2 = WRI1	TF10
TF3 = WRI1	TF11
TF4 = MYB56	TF12
TF5	TF13
TF6	TF14
TF7	TF15 = MYB56
TF8	TF16 ….

- Ranked list of TFs obtained
- Known TFs that impact oil and/or seed yield observed in top spots in list validating approach
- **Many uncharacterized genes identified, IP white space**
- Currently pursuing multiple uncharacterized TFs

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PLOS ONE

### WRINKLED1, A Ubiquitous Regulator in Oil Accumulating Tissues from *Arabidopsis* Embryos to Oil Palm Mesocarp

Wei Ma ✉, Que Kong, Vincent Arondel, Aruna Kilaru, Philip D. Bates, Nicholas A. Thrower, Christoph Benning, John B. Ohlrogge

Wild-type seed

Wri1 mutant seed

JIPB ✦ Journal of Integrative Plant Biology
Serving the Plant Science community Since 1952 (Formerly Acta Botanica Sinica)
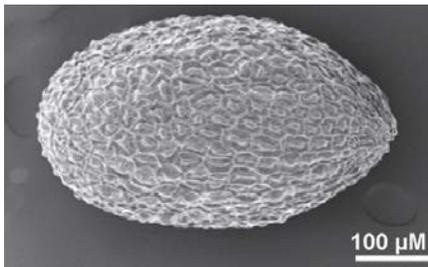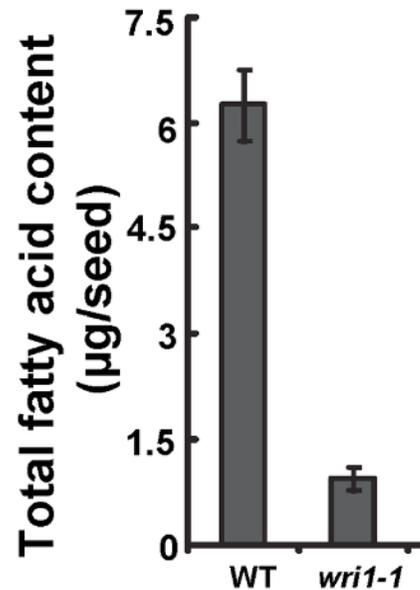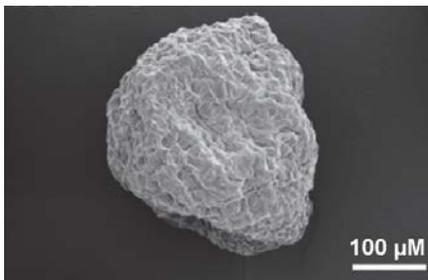
Research Article

MYB56 Encoding a R2R3 MYB Transcription Factor Regulates Seed Size in *Arabidopsis thaliana*

Yanjie Zhang, Wanqi Liang, Jianxin Shi, Jie Xu, Dabing Zhang ✉

| Wild-type seed | Mutant (myb56-1) | Mutant (myb56-2) |
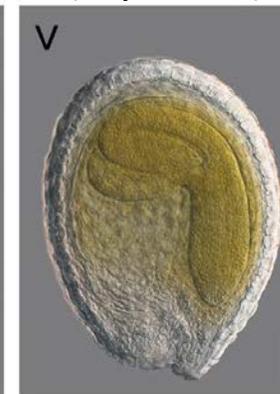
Scale bars = 100 μM

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- Development of advanced models
  - Camelina – in hand

- Develop crop-specific models
  - Canola
  - Soybean
  - Corn
  - Rice, wheat, potato, etc

- Identify gene targets for specific trait objectives
  - Targets for genome editing and transgenic approaches

- Multiple opportunities for collaborations

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For niche oils: cost of goods is driven by harvested oil/acre (= seed yield/acre x seed oil content)

Objective: Develop the best combination of gene edits to maximize oil/acre

C3008a
- Successful editing of all three copies of C3008a in Camelina
  - Camelina is an allohexaploid; each gene expected to be present in 3 copies
  - Received confirmation in 2017 that line is not regulated by USDA-APHIS
  - US field tests in progress

C3008a, C3008b, C3009
- Completed editing of three distinct genes of Camelina designed to increase oil
  - Simultaneous editing of 9 genes (3 target genes present in 3 copies each)
  - Received confirmation in 2018 that line is not regulated by USDA-APHIS
  - US field tests in progress

C3007 (BADC) and C3010
- Completed exclusive license to IP from University of Missouri (C3007 and C3010)
  - C3007 is a novel negative regulator of ACCase a key enzyme in fatty acid biosynthesis
  - Metabolix Oilseeds is currently editing the C3007 gene in Camelina and canola

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Commercial Strategy
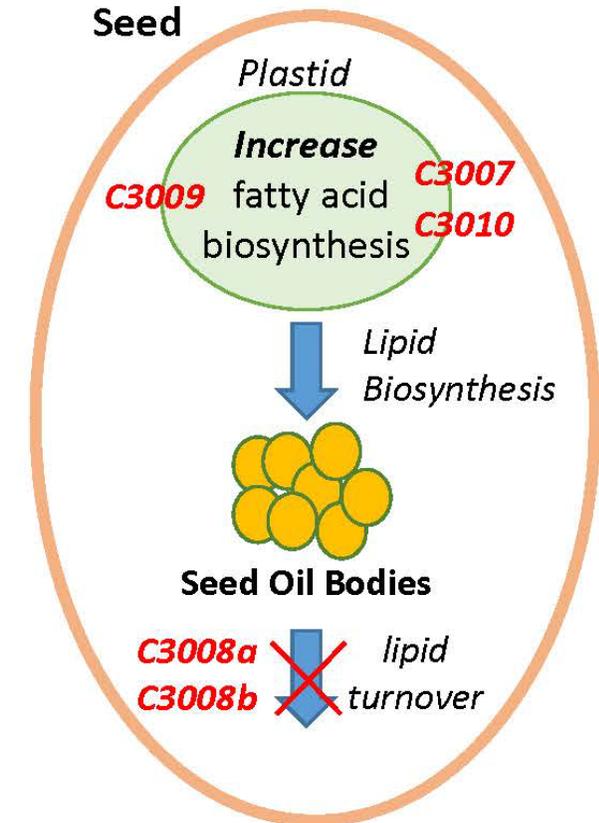
**Yield10 technologies enable multiple paths to value creation**

North American Commodity Crops
- Accelerate deployment with Ag majors
- License agreements with milestones and participation in downstream economics

Specialty and Niche Crops including Nutritional Oils
- Focus on development of high value products in food and animal feed
- Participation in the downstream business
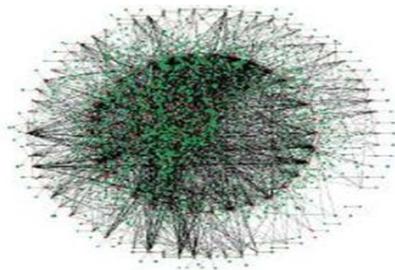
Technology Platforms
- "GRAIN" unique approach to identifying gene combinations for editing
- Non-dilutive funding and relationships with leading plant scientists
- R&D support for partner funded programs