Technologies for Increasing Seed Yield and Oil Content in Oilseed Crops

Presentation at CanolaWeek2017

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***Under the Private Securities Litigation Reform Act of 1995**

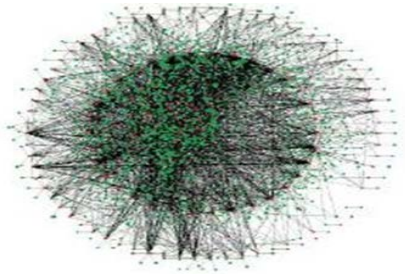
Company Overview and Objective

"Yield10 designs precise alterations to gene activity and the flow of carbon in food and feed crops to produce higher yields with lower inputs of land, water, or fertilizer"

- Leveraging a large historical investment in advanced metabolic engineering into a new arena
- Technology platforms and unique knowledge base span over 30 years of advanced metabolic engineering research experience and major accomplishments, including 19 years in crops
- Targeting over $15 billion of incremental value creation in North American crops
  - *Canola, soybean and corn*
- Headquartered in Woburn, MA USA
- Wholly owned Canadian subsidiary, Metabolix Oilseeds, located in Saskatoon
  - *Metabolix Oilseeds: R&D in oilseed crops*

Value Proposition

Value Proposition Driven by Yield and Oil Traits and Unique Capabilities



Major North American Commodity Crops

- Accelerate deployment with Ag majors
- Provide low hurdle to deploy and test yield traits in elite germplasm
- License agreements with milestones and participation in downstream economics

Specialty and Niche Crops including Nutritional Oils

- Form collaborations based on combining technologies to improve yield and/or improve nutritional value
- Focus on development of new products in food and animal feed
- Utilize technologies enabling a non-regulated path to market
- JV-type agreements with significant share of downstream economics

Yield10 Technology Platforms

- Accelerate innovation based on unique approach to identifying gene combinations for editing
- Access government grants and relationships with leading plant scientists
- R&D support for partner funded programs

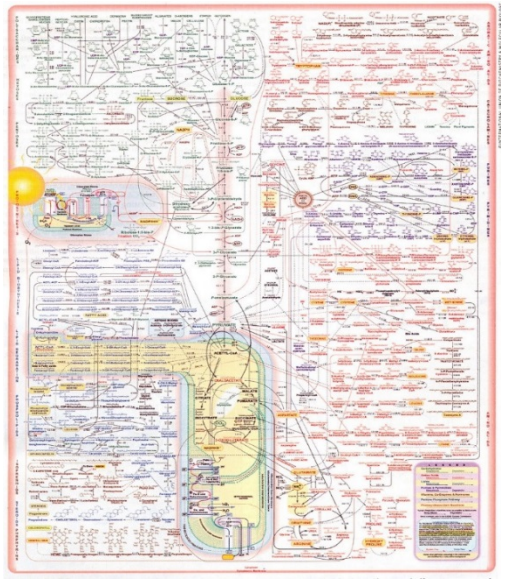
Increasing Yield is a Multi-Gene Problem

2800 traffic lights

Manhattan, Road map

Removing one stop light in Manhattan won't increase traffic flow from A to B

Crop metabolic map



Overexpressing a single enzyme or transcription factor won't increase carbon flow from photosynthesis to seed yield

Corn has about 2400 transcription factors

- Yield10: Two platforms to increase carbon flow and thus yield in plants
  - Our "Smart Carbon Grid" Platform allows us to identify combinations of genes to optimize crop metabolism or infrastructure
  - Our "T3 Platform" identifies combinations of transcription factors (gene switches) to increase crop performance
- Yield10 is integrating these platforms to create a "Google Earth" or "Waze"-like map of carbon flow (traffic) in crops

Rich Pipeline of Trait Genes in Development

CROP TRAITS IN DEVELOPMENT	
Business Area	**Current Status**
Seed Yield Traits-Regulated	
C3003	Camelina 1st and 2nd generation in field testing
	Canola 1st generation in field testing
	Soybean and rice in development
Seed/Oil Enhancing Traits-Non-Regulated	
C3004	Camelina testing underway
C3007	Camelina, canola editing underway
C3008a	Camelina non-regulated[1] status achieved
C3008a, C3008b and C3009 combinations	Camelina, editing of all 3 gene targets underway
Additional oil trait combinations	Research in progress
Yield Improvement Traits and Discovery Platform	
C4001 and C4003	Wheat program underway
	Rice transformation underway
	Corn transformation next step
C4002	Corn transformation next step
C4004	Editing in rice underway
C4004 plus 23 additional gene editing targets	Research with rice and wheat next step

Report Camelina and canola field test data Q4

Many opportunities exist for licensing and/or partnerships

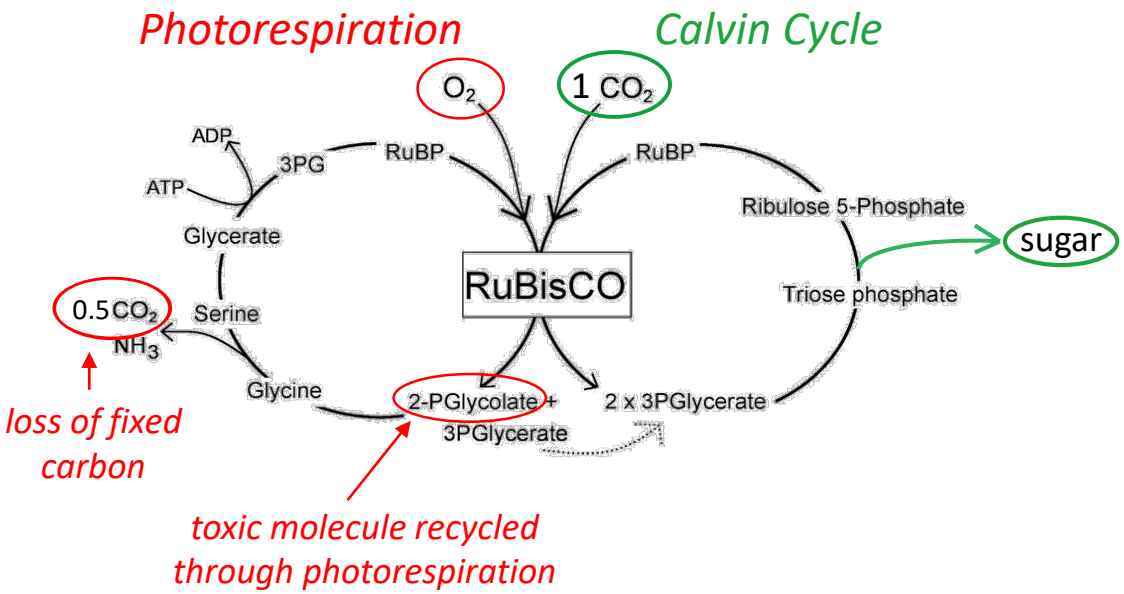
[1] *not regulated by USDA-APHIS in US, could be regulated by EPA and/or FDA*

Smart Carbon Grid: C3003

Photorespiration: A side reaction in crops having the C3 photosynthesis system that limits yield

- Many key food crops rely on C3 photosynthesis
  - *rice, wheat, soybean, canola, potato, etc.*
- Calvin cycle of photosynthesis, key enzyme RuBisCo fixes carbon dioxide producing sugar for plant growth
- C3 crops have considerable yield loss due to photorespiration, a competing wasteful cycle where RuBisCo fixes oxygen instead of carbon dioxide
  - *produces a toxic compound that must be removed*
  - *leads to significant fixed carbon and energy loss*
- Models suggest that photosynthesis could improve by 12-55% in the absence of photorespiration.
- A 5% reduction of photorespiration in soybean and wheat would increase yields estimated to add ~$500 million/year of economic value in the US *(Walker et al., 2016, Ann. Rev. Plant Biol. 67:17.1 – 17.23)*
- **C3003 is an algal gene believed to impact photorespiration**
- Mechanism of action under investigation by academic collaborator

C3 photosynthesis reactions



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C3003: Trait that Increases Seed Yield Likely by Impacting Photorespiration

- Yield10 and Metabolix Oilseeds have engineered Camelina and canola to express C3003 from constitutive (Gen 1) or seed specific (Gen2) promoters

	Crop/Trait	Year		
		2017	2018	2019
Translation	**Camelina** Gen 1 C3003	▪ 2016 field test data reported. Increase in seed yield observed		
Translation	**Camelina** Gen 2 C3003	▪ Greenhouse data, 24% seed yield increase ▪ Field test performed (*will report data soon*)	▪ Additional field tests	
Value Demonstration	**Canola** Gen 1 C3003	▪ Field test performed (*will report data soon*)	▪ Additional field tests	
Value Demonstration	**Canola** Gen 2 C3003		▪ Greenhouse data ▪ Field tests*	▪ Field tests
Value Demonstration	**Soybean** Gen 1 & Gen 2	▪ Greenhouse data from early generations	▪ Small scale field plots*	▪ Field tests
Value Demonstration	**Rice** Gen 1 & Gen 2		▪ Greenhouse data	

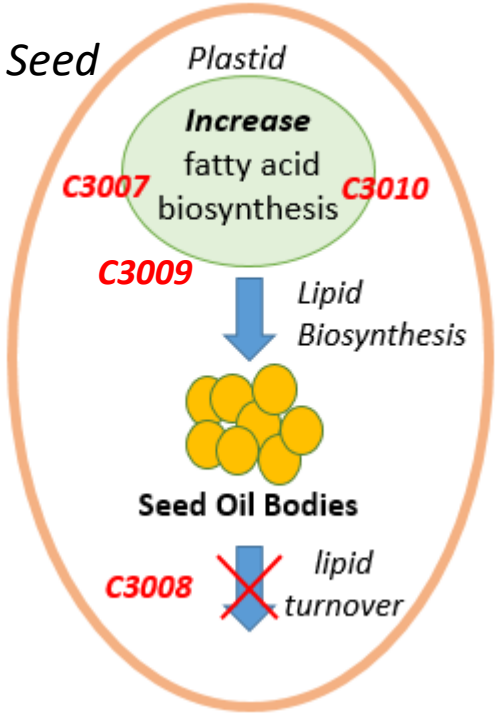
**dependent on CFIA permits and seed bulk-up timing*

Yield10: Traits for Boosting Seed Oil Content

- **Assembling combinations of traits to boost oil content of seeds through genome editing**

USDA-APHIS confirmed nonregulated status for our genome-edited C3008a Camelina line

- Yield10 submitted "Am I Regulated?" letter for C3008a
  - *First nonregulated trait submission to USDA-APHIS by Yield10*
- Developing multi-gene edited oilseed lines (C3008a, b, C3009) for future submission
- C3007 and C3010 also accessible through genome editing to increase oil content

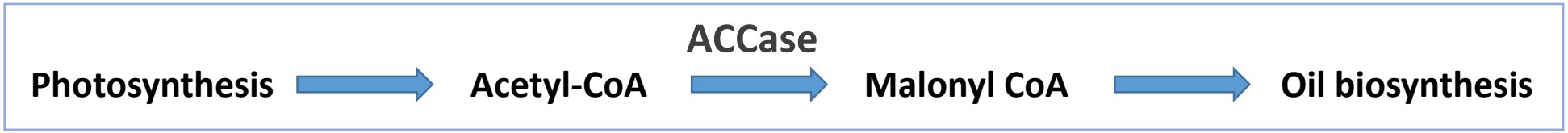


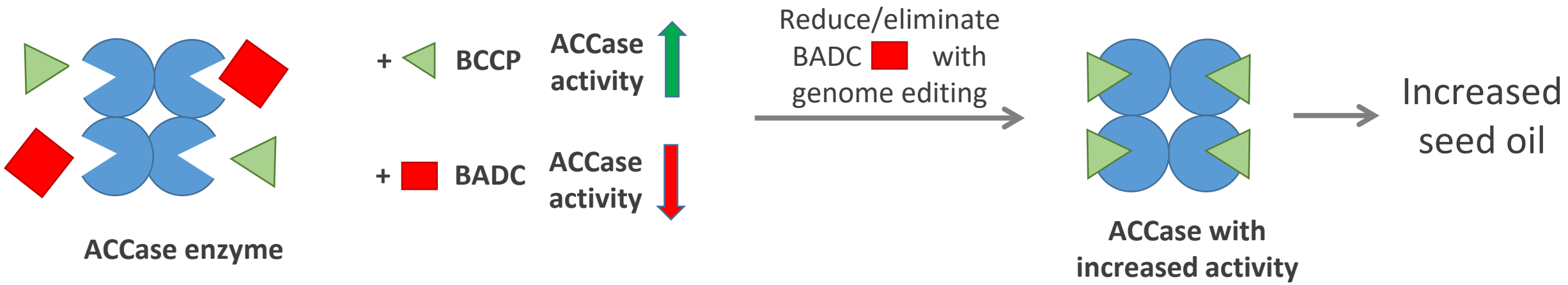
C3007 a promising target for boosting oil content in oilseed crops

- A scientific discovery from University of Missouri
- Controls a unique regulatory mechanism controlling a key point in the metabolic pathway for fatty acid and oil biosynthesis
- Potentially accessible through genome editing
- Combine C3007 with other genome edited traits to re-engineer oil biosynthesis

Editing of C3007 Trait: A Negative Regulator of a Key Enzyme in Oil Biosynthesis

- Acetyl-CoA carboxylase (ACCase) - a key enzyme in oil biosynthesis with a complex, multi-subunit enzyme structure
- BADC (C3007), a key negative regulator of ACCase *(Salie, M. et al., 2016, Plant Cell)*
- Use genome editing to reduce/eliminate availability of BADC (*red squares*) to increase the activity of the key ACCase enzyme to increase carbon for fatty acid biosynthetic pathway





BADC = biotin/lipoyl attachment domain containing proteins

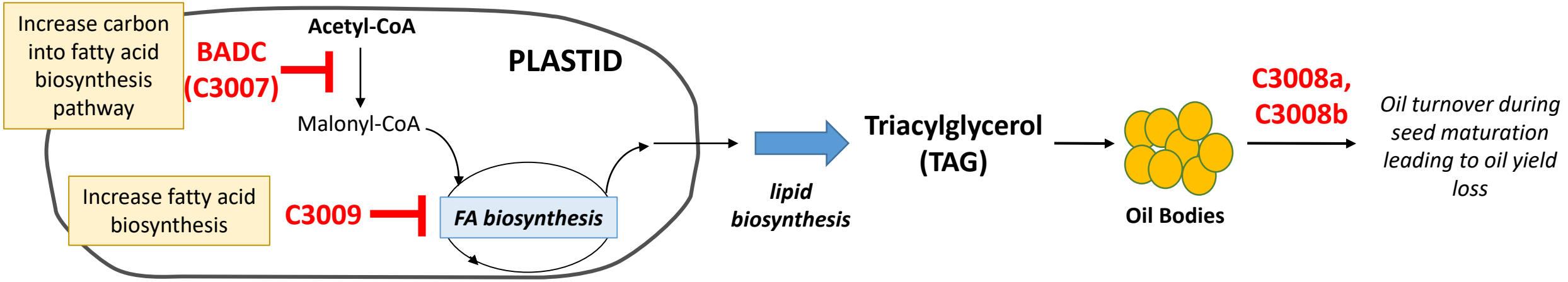
BCCP = biotin carboxyl carrier protein

Multiplex Editing to Target BADC Genes in Camelina and Canola

- Yield10 has exclusive option to license BADC technology from University of Missouri
- There are multiple types of BADC genes in plants *(Salie, M. et al., 2016, Plant Cell)*
- Yield10 has identified
  - *3 different BADC genes (9 alleles) in Camelina*
  - *3 different BADC genes (6 alleles) in canola*
- Yield10 working to edit combinations of BADC alleles in Camelina and canola to increase oil yield
  - *Target editing of all alleles*
  - *Target editing of only some alleles*

Multiplex Editing to Increase Seed Oil Content

- Combine BADC edits with edits to other genes in oil biosynthesis pathway
- Funded by US Department of Energy – BETO to Yield10 Bioscience with Metabolix Oilseeds as subawardee



- Progress with multiplex editing in allohexaploid Camelina

	Gene Targets, Plant 1		
Nature of edits obtained	C3008a	C3008b	C3009
Line type 1	X X _	X X X	X X X
Line type 2	X X X	X X _	X X X

X = mutation that leads to inactive protein
_ = allele that is difficult or impossible to mutate

- Progressing genome editing of BADC in Camelina

Gene Targets, Plant 2		
C3007a	C3007b	C3007c
In progress	In progress	In progress

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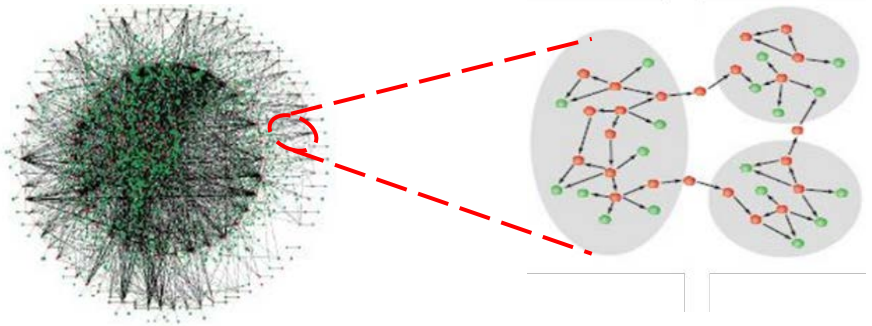
T3 Platform: Identify Global Regulatory Genes

- **Used transcriptome-based regulatory association networks to identify candidate global regulatory genes**
- **Global regulatory genes are transcription factors or "gene switches"**

Work with switchgrass as example

Identify candidate global regulatory genes to increase photosynthesis and biomass yield

Complex transcriptomics data



Gene interaction network

Functional modules

(modules = groups of genes associated with trait that target pathways of interest)

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

Generated transgenic plants to characterize candidate genes

- Transformed switchgrass with genes expressed from strong promoter active in green tissue
- Initial transgenic line analysis to pick best candidate lines for further characterization
  - Will present data for C4001

T3 Platform: C4001 Switchgrass Lines

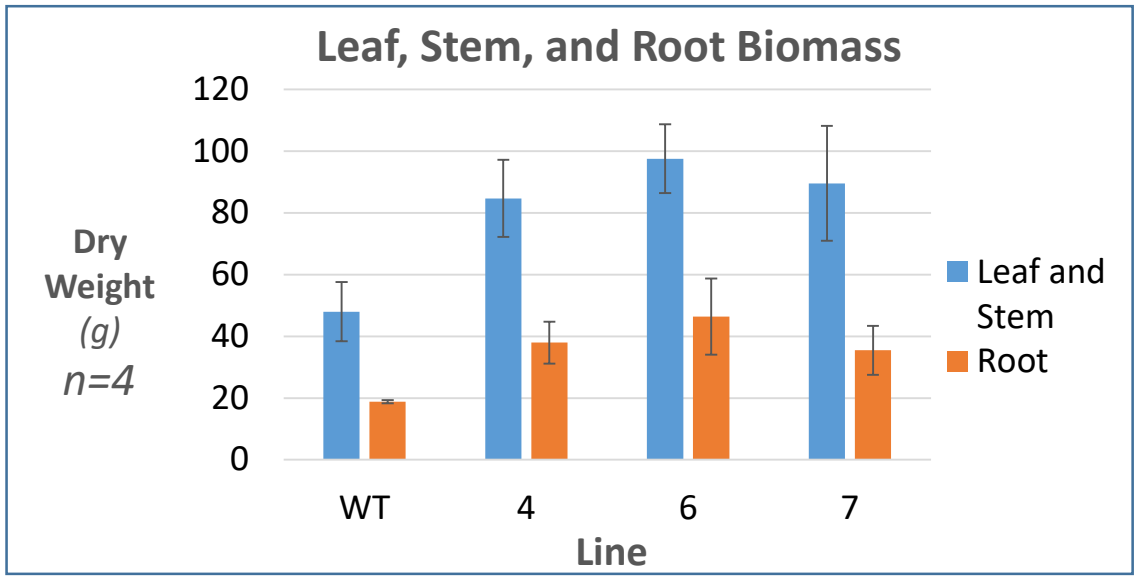
- Immature inflorescence derived cultures obtained from best primary transformants
- Plants regenerated from cultures, 4 plants from each line were grown in greenhouse (5 months)
- Panicles cut during growth (*requirement of greenhouse used*)

C4001

WT **4d** **6e** **7e**

Roots

WT **4d** **6e** **7e**



- Leaf and stem biomass, 75%-100% increase
- Root biomass, 85%-145% increase
- Parameters of photosynthesis increased *(electron transport rate around photosystems I and II)*
- ***Orthologs of C4001 found in canola and Camelina***

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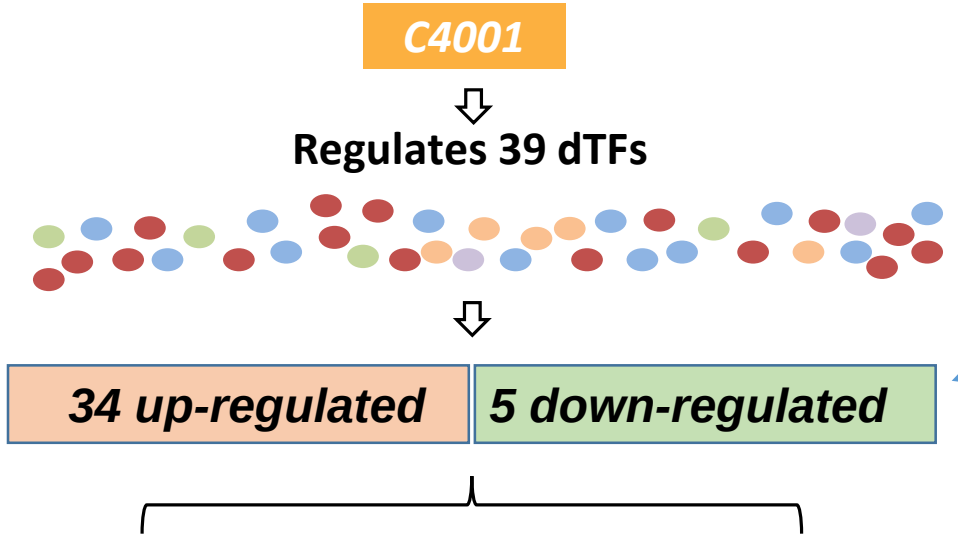
Microarray Analysis of C4001 Transgenic Switchgrass Lines

- High yielding lines useful for identifying pathways controlled by TFs and genome editing targets
- Multiple downstream transcription factors and key pathways are regulated in C4001 lines



- *Targets for genome editing*
- *Orthologs for downregulated genes present in Camelina & canola*

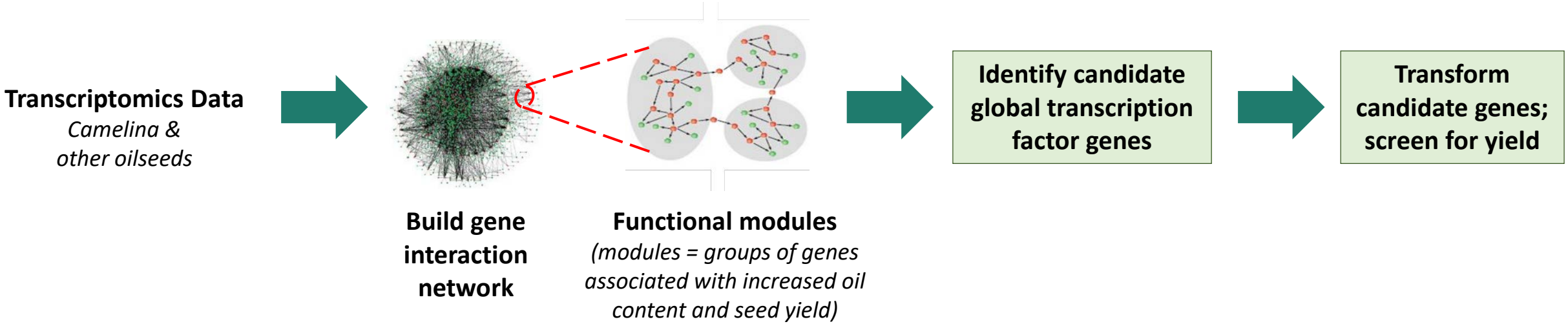
dTFs associated with key metabolic pathways and genes important for biomass, yield, & stress response

Photosynthesis (10)	Starch biosynthesis (6)	Photosynthetic electron transfer (4)	Carbohydrate metabolism (8)	Transport functions (21)	Protein metabolism & modifications (8)	Plant stress response (11)
Amino acid metabolism (7)	Plant hormone metabolism (9)	Lignin & cell wall metabolism (18)	Signal transduction (16)	Fatty acid & lipid metabolism (9)	Secondary metabolism (13)	Cytochrome P450 genes (7)

In process of testing select dTFs for function, three tested to date

Program to Increase Seed Yield and Oil Content in Camelina

- Funded by US Department of Energy
- Michigan State University lead (Danny Schnell, PI)
- Yield10 Bioscience and Metabolix Oilseeds are subawardees
- **<u>Goal Yield10 and Metabolix Oilseeds:</u>**
  - Use T3 platform (*transcriptome-based regulatory association networks*) to identify global regulatory genes that increase seed yield and oil content
  - Similar approach to previous work with switchgrass but with modules of increased oil content and seed yield



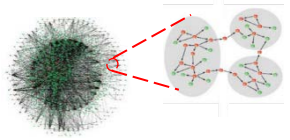
Next Generation Gene Discovery Approach

- Developing and beginning to validate predictive models to guide efforts in gene discovery

T3 Platform (Top down approach)

INPUT

Complex transcriptomics data

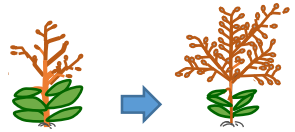


Gene interaction network
Functional modules target pathways of interest

OUTPUT 1

Candidate global regulatory genes

transform



Higher yielding plants

transcriptome analysis

OUTPUT 2

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

Gene Editing targets

Interaction of models

Flux Balance Analysis (Bottoms up approach)

All reactions in a system
- Enzymatic reactions
- Transport functions
- Inputs/Outputs (ATP, ADP, NADPH,….)

Incorporate thermodynamic information
- Avoid solutions that are thermodynamically unfavorable

Define problem
[directive to minimize or maximize certain flux(es)]
i.e. maximize biomass production

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

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Summary

- Yield10 Technology platform: unique approach for identifying gene combinations to increase yield
  - *Building and validating predictive models to discover and prioritize traits*
- Strong collaborations with multiple academic groups to enhance trait pipeline
- Yield10 is progressing traits to increase oil content and seed yield in canola
  - *Traits are also being progressed in other commodity crops such as soybean and rice*
- First canola field tests performed in 2017 growing season
- Employing both GMO and genome editing approaches to achieve goals
- Many opportunities exist for licensing, partnerships, and/or collaborations

Thank you

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