



# What if Biotechnology is the only answer to HLB?

June 16, 2016

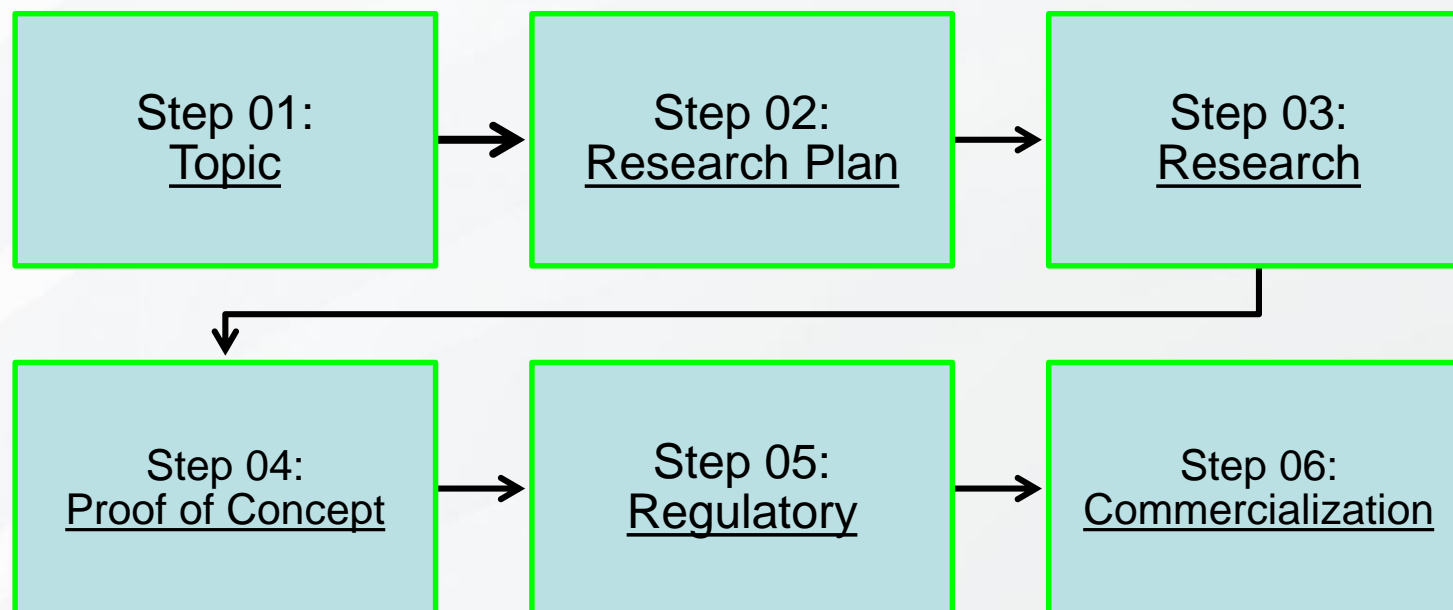
# Why is Southern Gardens Involved in Research?



# Southern Gardens Disease Research

- Finding a solution to the HLB Greening disease requires multiple steps to putting the answer “behind the tractor”.
- 4 steps –
  - Research
  - Regulatory Approval
  - Horticultural/Agricultural Production
  - Consumer Approval

# How a normal research project should work...



# How Greening research is done...

Next Step:

Step 01  
Topic: Greening

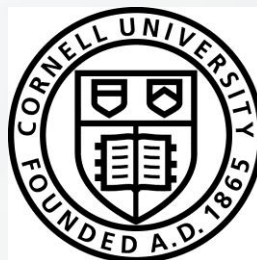
Commercialization – Research Plan – Research – Proof of Concept – Regulatory





# Research Projects

- Texas A & M University
  - Disease resistant plants
- Integrated Plant Genetics
  - Disease resistant plants
- Cornell University
  - Insect resistant plants
- AgroMed LLC
  - Identification of synthetic resistance genes
- University of Florida
  - Gene delivery system
- USDA
  - Screening of potential genes



# Southern Gardens Disease Research

- Two parallel approaches
  - GMO trees
  - CTV viral vector
- GMO trees
  - All citrus and multiple growing regions
  - More traditional approach; agencies familiar
- CTV viral vector
  - Genetically altered microbial pesticide
  - Plant pest
  - New to the agencies

# Southern Gardens Disease Research

- Among other things, SGC is working on solutions using biotech
  - Long term approach: GMO trees
  - Short/medium term approach: Viral delivery system
- Although there are multiple target genes, the one that is furthest along is an antimicrobial peptide from spinach (Texas A & M)
  - Spinach defensin(s)
- Citrus presents some unique challenges for deregulation



# Southern Gardens Disease Research

- GMO Transgenic Trees
  - Progressing with transgenic trees with spinach defensin technologies
  - Current situation:
    - Screening of multiple lines (200+)
    - Lack of flowering is an issue (juvenility)
    - Transgenic rootstocks will probably be required
  - From an agency perspective, we will be counting heavily on the “Extension” process

# Southern Gardens Disease Research

- GMO Transgenic Trees
  - Ideally, looking for immunity
  - Testing
    - Greenhouse
    - Field
  - Field testing is done under USDA-APHIS-BRS permits
    - 3 years
    - Defined conditions

# Southern Gardens Disease Research

- CTV – Plant Immunization
  - Basic principal is to use a virus to deliver a gene into the plant
  - Many advantages
    - One product can be used across multiple varieties
    - Juvenility is not an issue
    - Production potential is not an issue
    - Can be delivered to a subset of already existing trees
    - Can be deployed more quickly than a traditional transgenic approach
    - Consumer acceptance

# Southern Gardens Disease Research

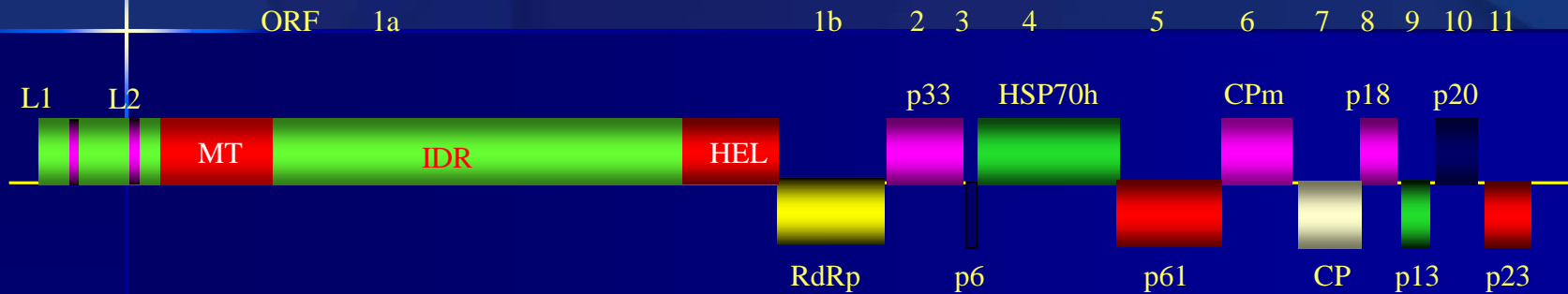


# Southern Gardens Disease Research

- CTV is the delivery mechanism (the gun)
  - Bullets can include:
    - Spinach defensin
    - Synthetic AMPS
    - RNAi
    - Others
- Currently have two field trials under permit
  - One with multiple AMPS and genes
    - Not commercial
  - One with a commercial track
    - Spinach defensins in multiple locations within the vector
    - Synthetic AMPS

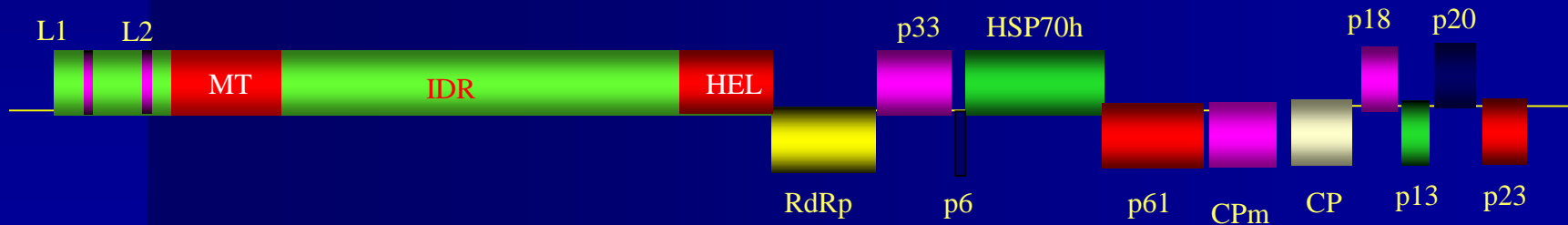


# CTV genome



## CTV-based expression vector

foreign gene



# SGC Research – Greenhouse Trials





# SGC Research – Greenhouse Trials





# SGC Research – Field Trials



# Southern Gardens Disease Research

- 2 Different Technologies
  - Both are related and must go through regulatory process
  - Transgenic trees
    - PIP (EPA)
    - Plant pest (APHIS)
  - Viral vector with spinach defensin
    - Microbial pesticide (EPA)
    - Plant pest (APHIS)
  - Regulatory challenges are similar
    - But different.....



# Advantages and disadvantages to both Technologies

## GMO trees

- More traditional approach for agencies
- Validated technology
- Should be widely portable
- Need to do each variety
- Juvenility and horticultural testing
- More expensive as every line is a new regulatory event

## CTVvv

- One construct will work across multiple varieties
- Deployed quickly
- Easily amenable to stacking
- Benefits with consumers (non-GMO)
- New to the agencies
- Deploying a plant pest

# Regulatory Approval

- EPA regulates the sale, distribution, and use of pesticides in order to protect health and the environment (EUPs)
- USDA (APHIS) is responsible for protecting agriculture from pests and diseases and has regulatory oversight over products of modern biotechnology that could pose such a risk
- FDA is responsible for ensuring the safety and proper labeling of all plant-derived foods and feeds, including those developed through biotechnology

# Regulatory Approval

- Currently meeting with the agencies 2-4 (more?) times a year
  - Primarily with USDA and EPA
- We are different than most other “biotech crops”
  - Need to have versus nice to have
- We are a perennial tree crop
  - Can’t back cross a trait into a variety
  - Many varieties/species (types)

# Regulatory Approval – EPA & GMO

- EUP- allows for greater than 10ac of trials
- For the transgenic tree defensin project, we have an EUP that allows:
  - 400 ac in Florida
  - 200 ac in Texas
  - Two defensins, plus a combination of the two
  - Initially 4 specific plant lines, but now any plant lines or citrus variety containing the specific defensins (in allowed constructs)
    - To our knowledge, this is a first

# Regulatory Approval – EPA & GMO

- We have many more lines being tested and it is likely that we may have lines better than those in the current EUP
- The EUP process is:
  - Tedious
  - Costly
  - Takes time
  - Is restrictive
    - Specific lines
    - Specific constructs



# Regulatory Approval – EPA & Viral Vector

- Have a new EUP amendment submission for large scale planting of the CTV viral vector containing spinach defensins
  - Defensins alone or in combination
  - Any variety of citrus
  - Multiple locations within the state of Florida
- Expect approval in July 2016
  - Will begin planting a smaller trial (~10ac) in mid-2016

# Regulatory Approval – EPA

- Temporary Tolerance Exemption
  - Temporary tolerances are granted by the EPA to allow holders of an EUP to use the products that come off the trials in the EUP
  - A petition for a temporary tolerance or an exemption must be submitted with the application for the EUP (if not a crop destruct)
  - In the case of spinach defensins in transgenic trees, a tolerance exemption was granted
    - Based on the data that was submitted, there were no toxicity issues
    - The defensin is already in the food chain

# Regulatory Approval – APHIS

- Traditional approach is to deregulate by event and backcross this in to breeding program
  - Not practical in citrus
  - Have to transform scion and rootstocks
    - Can't afford to do this in the traditional sense
- Counting heavily on the “Extension” process
  - Must deregulate one item and then request an “extension” of the determination of non-regulated status for similar products
  - Functional equivalence (trait, crop, phenotype)
    - Will still require some data (molecular characterization, phenotype changes if any, narrative, etc.)

# Regulatory Approval – EPA

- Plan is to submit a new petition for a temporary tolerance exemption to cover all spinach defensins.
  - GMO trees
  - Viral vector trees

# Regulatory Approval – FDACS

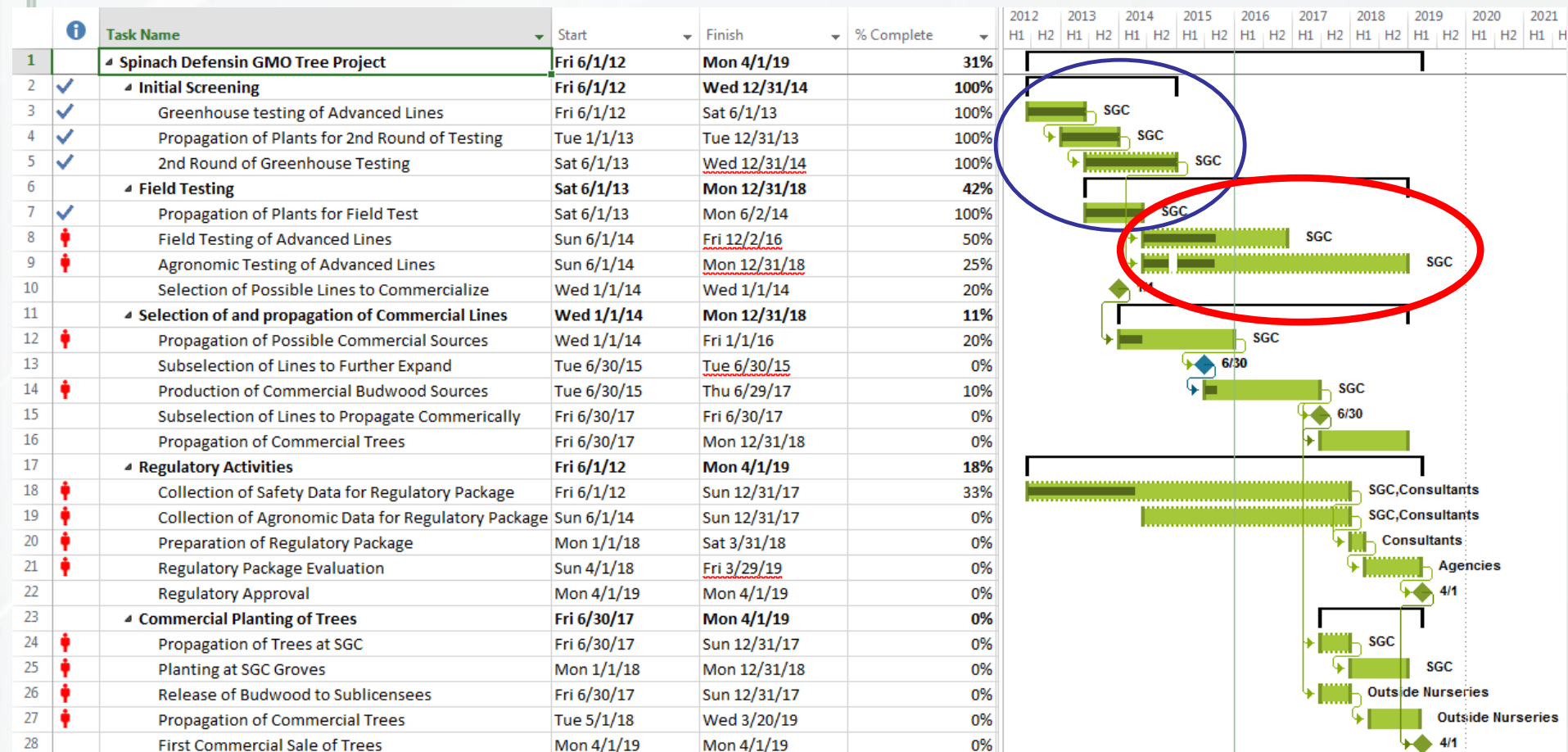
- Departmental Permit
  - Material from Texas is grown in FDACS approved greenhouse
    - Never in field in Texas
    - Derived from tissue culture
  - Prior to shipment, nucleic acids extracted and sent to Dr. Sieburth at Bureau of Budwood Registration for molecular testing
  - Phytosanitary certificate issued in Texas, inspected by FDACS inspector in Florida on arrival (and prior to opening)
  - No commercial propagations can be made from these materials after the research is finished.



# Regulatory Approval – Global

- Global approval
  - Have started the process to determine the landscape for approval of a transgenic tree-based and viral vector deployed commercialization of spinach defensins for both primary and secondary products
    - 5 key markets in addition to the US
      - Canada
      - Japan
      - Korea
      - Israel
      - EU

# Commercialization Time Line - GMO




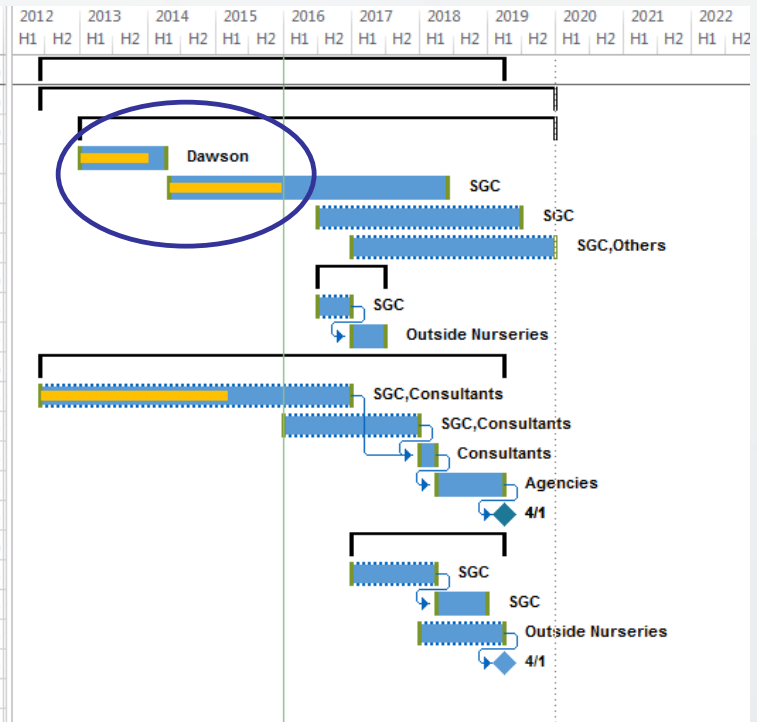
UNITED STATES  
SUGAR  
CORPORATION



SOUTHERN  
GARDENS  
CITRUS

# Commercialization Time Line - CTV

	 Task Name	Start	Finish	% Complete	
1	▶ Spinach Defensin GMO Tree Project	Fri 6/1/12	Mon 4/1/19	31%	
29	▶ CTVvv Defensin Project	Fri 6/1/12	Tue 12/31/19	23%	
30	▶ Screening	Tue 1/1/13	Tue 12/31/19	23%	
31	Greenhouse/Growth Room Screening	Tue 1/1/13	Tue 4/15/14	78%	
32	Kress Block Field Trial	Thu 5/1/14	Fri 6/1/18	40%	
33	Large Multi Construct Trial	Fri 7/1/16	Sun 6/30/19	0%	
34	Multilocation Trials	Sun 1/1/17	Tue 12/31/19	0%	
35	▶ Selection and Propagation of Commercial Lines	Fri 7/1/16	Mon 7/3/17	0%	
36	Establishment of Budwood trees	Fri 7/1/16	Sat 12/31/16	0%	
37	Distribution of Budwood to Sublicensees	Mon 1/2/17	Mon 7/3/17	0%	
38	▶ Regulatory Activities	Fri 6/1/12	Wed 4/3/19	35%	
39	Collection of Safety Data for Regulatory Package	Fri 6/1/12	Sat 12/31/16	60%	
40	Collection of Agronomic Data for Regulatory Package	Fri 1/1/16	Sun 12/31/17	0%	
41	Preparation of Regulatory Package	Mon 1/1/18	Mon 4/2/18	0%	
42	Regulatory Package Evaluation	Tue 4/3/18	Wed 4/3/19	0%	
43	Regulatory Approval	Mon 4/1/19	Mon 4/1/19	0%	
44	▶ Commercial Planting of Trees	Sun 1/1/17	Mon 4/1/19	0%	
45	Propagation of Commercial Trees for SGC	Sun 1/1/17	Sat 3/31/18	0%	
46	Planting at SGC Groves	Mon 4/2/18	Tue 1/1/19	0%	
47	Propagation of Commercial Trees	Mon 1/1/18	Sat 3/30/19	0%	
48	First Commercial Sale of Trees	Mon 4/1/19	Mon 4/1/19	0%	



# Agriculture and Florida Industry

- Technology and the Florida citrus industry –
  - From the beginning, Southern Gardens has committed that technology would be available.
  - What is the cost to “put the technology behind the tractor?”
  - Must have a Return on Investment
  - What is the model that works for all?

# Agriculture – State Nursery Capacity

	2015	2014	2013	2012	2011	2010
Number Propagations Reported (million) (*)	4.44	4.71	4.70	3.94	3.14	3.00
Nurseries Increasing Production	15	25	18	26	22	18
Nurseries Decreasing Production	33	21	24	14	17	24
New or Resumed Production	6	5	6	7	3	3
Nurseries Not Propagating	4	1	4	2	6	2
Total Active Nurseries (**)	58	52	52	49	48	47
Average Propagations Per Nursery	82,188	90,624	97,932	83,672	74,517	66,520
(*) 1989 - 7.24 million propagations						
(**) 1988 - 94 active nurseries						

- Note – 65% of propagations are shipped trees.

# Consumer Approval

- Once the EPA, FDA and USDA have completed their reviews and a GM product can be sold to the public, we know it is safe for the environment, people, and animals, but.....
  - We still have to ensure the public has the facts:
- Source of the gene is important:
  - ~~Crab~~
  - ~~Human~~
  - ~~Pig~~
- How it is presented is important
  - Nice to have vs. necessary
  - Other benefits



# Consumer Approval

- Also working on:
  - Consumer acceptance
    - Proactively to improve general acceptance
      - Consumers
      - Retailers
    - Legal preparation for the eventual law suits
    - Spinach defensins already in the food supply and acceptable.
  - Freedom to operate
  - Stewardship issues
    - “Defensins plus”
    - Second mode of action

# Consumer Approval

- With ever-increasing global travel and commerce, new exotic pathogens, weeds, and insect pests are spread around the world at a faster rate than ever before. These create severe problems which threaten entire crops.
- As climate changes, pests are often able to thrive in new places or at different times of year than in the past, creating much more difficult control issues.
- **What if greening is the example of future pest and disease issues in agriculture?**

# Consumer Approval

- Why BioTech?
  - Conventional breeding solutions take decades at best; new pest challenges don't give us that luxury.
  - Modern genetic engineering technology could be a very logical way to protect crops.
  - Technology is progressing very rapidly.
  - Genetics that drive quality are complex, so we have good reason to stick with the best varieties we know.
  - Consumers demand quality but also expect products that require minimal pesticide inputs and are not harmful to environment.
  - Consumers in the United States have never been hungry.

# Consumer Approval

- Questions that are unanswered –
  - Will consumers accept BioTech orange juice?
    - 85% of processed food today contains GMO's.
  - Would a reduction of current chemical usage outweigh BioTech's usage in orange juice?
  - Can foreign competition avoid BioTech orange juice?
  - Without biotechnology, can we effectively reduce fruit costs (inputs and increased production) so as to reduce price to the consumer to stimulate purchase?

# Questions

- Thank You!

