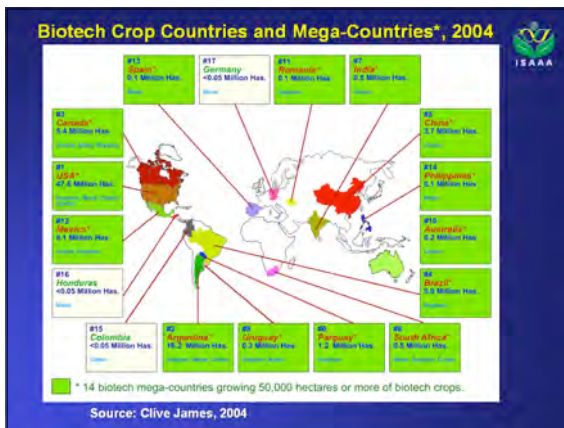
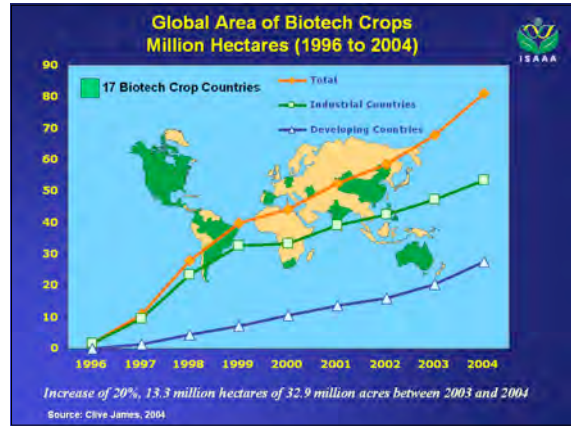


WASHINGTON STATE UNIVERSITY  
Allan Felsot  
Washington State University  
Dep't. of Entomology  
Food & Environmental Quality Lab

## Update on Agricultural Biotechnology Controversies

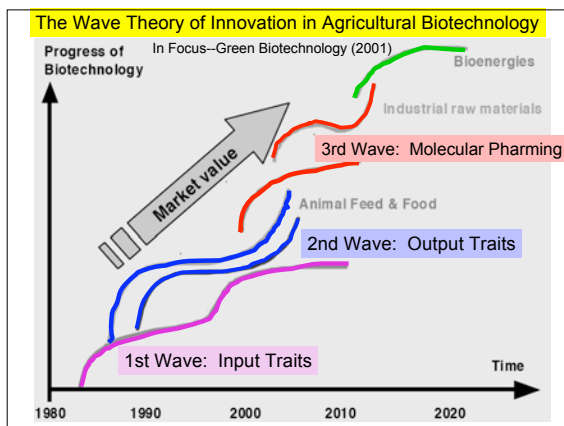
### Pharmaceutical Crops



### Dominant Biotech Crops, 2004

Crop	Million Hectares	% Transgenic
Herbicide Tolerant Soybean	48.4	60
Bt Maize	11.2	14
Bt Cotton	4.5	6
Herbicide Tolerant Maize	4.3	5
Herbicide Tolerant Canola	4.3	5
Bt/Herbicide Tolerant Maize	3.8	4
Bt/Herbicide Tolerant Cotton	3.0	4
Herbicide Tolerant Cotton	1.5	2
<b>Total</b>	<b>81.0</b>	<b>100</b>

Source: Clive James, 2004





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 Campaigning for Food Safety, Organic Agriculture, Fair Trade & Sustainability

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## Biopharmaceutical Crops Are a Disaster Waiting to Happen

From: <http://carmeloruiz.blogspot.com>  
 March 28, 2005


THE BIOPHARMACEUTICAL HARVEST

Carmelo Ruiz-Marrero

Just when the worldwide controversy over genetically modified (GM) foods and crops is growing larger and more heated, the biotechnology industry is getting ready to introduce a whole new class of GM plants whose very properties promise to make the biotech issue even more complicated and thorny than it already is.

## All About PMPs (Plant- Manufactured Pharmaceuticals)

- What is it?
- Why do it?
- How do you do it?
- Is it safe?



## Plant-Manufactured Pharmaceuticals

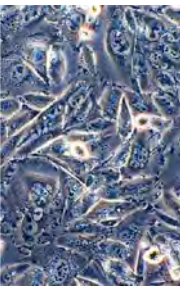
- Specifically, “growing” pharmaceuticals or therapeutic proteins in plants transformed using modern biotechnological techniques
  - a.k.a. “biopharming”
- “Molecular Farming” has been coined as a generic description for use of genetically transformed plants to grow other chemicals of commercial interest

## Traditional Pharmaceutical Manufacturing

- Chemical synthesis in factories
- Fermentation cultures
  - Proteins manufactured in various cell cultures
  - For ex., the Chinese hamster ovary cell line (CHO cells)
    - Clone of an original ovary cell collected from an adult Chinese hamster ~1957

## Chinese Hamster Ovary Cells

- Transgenic
- Contain human genes for synthesizing naturally occurring antibodies and other proteins
- Maintained in cell cultures grown in fermentation vats
  - “Practically immortal”



## Complexity of Modern Pharmaceutical Manufacturing

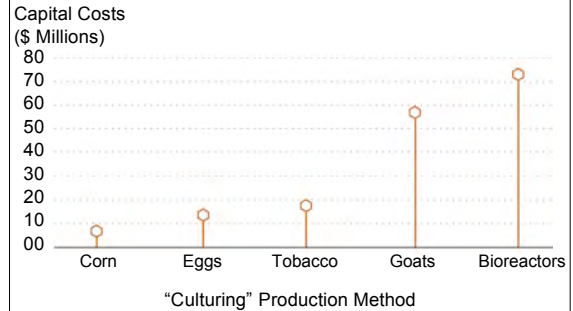
- Cell cultures required large stainless steel vats
- Highly controlled temperature and pressure
- Production is slow
- Cultures must be “babied”
  - Free of contaminating material & pathogens




## Problems with “Traditional” Biotech Manufacturing

- Limited production capacity
  - Cell growth rate & unit production limited
  - Production in animal cells makes separation of pharmaceutical protein more difficult
  - Possible viral and prion contamination
- Space for more vats limited
- Energy is expensive
- Plant expansion is very expensive
- Demand for product is increasing

## Comparative Capital Costs Per Year for Producing 300 kg of Monoclonal Antibodies (MAbs)



Pharming the Field (2002)

## Plants to the Rescue

- Plants can do it cheaper & “cleaner”

SFGate [www.sfgate.com](http://www.sfgate.com)

Future pharmers

Biotech firms using plants in attempt to produce proteins faster, cheaper

Tom Algate, Chronicle Staff Writer  
Monday, August 12, 2002  
©2002 San Francisco Chronicle



## For Example...



- CROP TECH has a patented process for producing a therapeutic protein in tobacco;
  - Protein production triggered only after plant is wounded
    - Plants cut at 2 feet tall before flowering
    - Protein production initiated
    - Allow re-growth of non-protein producing stalk for continuous harvest
  - Protein extracted from the leaves at a \$40 million dollar facility
  - To achieve the same capacity (600 kg product) with a fermentation-based plant using CHO cells would cost ~\$400 million

## Synergy...More With Less

- Epicyte Company projects that 200 acres of corn can produce the same quantity of therapeutic protein that would take a \$400 million dollar fermentation facility to produce
- Thousands of kilograms of product would be needed to keep pace with demand
- Solution is to increase crop acreage



## Long Tradition of Medicinal Plant Production

- Ancient records indicate that in all parts of the world native peoples discovered and developed medicinal uses of local plants
- Herbal medicine of ancient Greece laid the foundations of Western medicine



Illustrations from *De Materia Medica*, a pharmacopoeia used from 2nd - 16th C

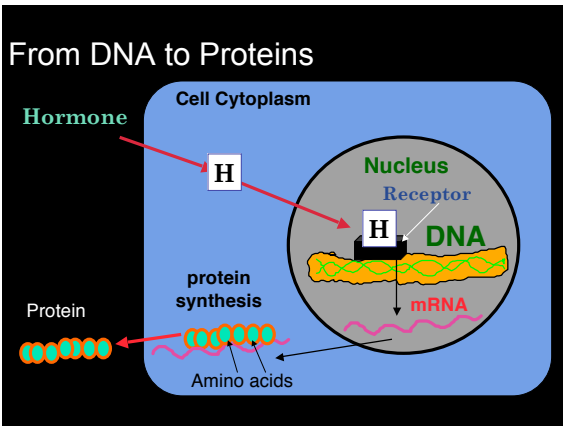
## 19th Century Breakthrough

- Scientists began purifying the active extracts from medicinal plants
- 1806: Breakthrough in pharmaceutical chemistry came when morphine was isolated from opium poppy
- First synthetic drugs were developed in the middle of the 19th century based on natural products

## Candidate Technologies

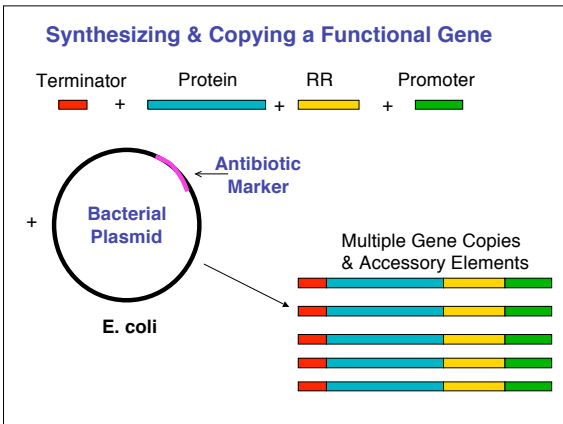
Primary Products	Derived Products
Antibodies (immunoglobulins)	Bio-plastics
Enzymes (industrial, therapeutic, diagnostic, cosmetic)	Vitamins, co-factors
Structural Proteins (peptides, hormones)	Nutraceuticals
Antigens (vaccines)	Fibers
Anti-disease agents, drugs	Secondary Plant Metabolites (phenolics, glucosinolates, tannins, starches, sugars, fragrances, flavors, alkaloids)
Enzyme inhibitors	

## How's It Done?

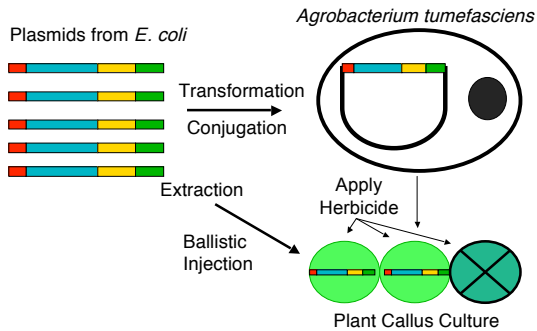


## Engineering the Gene

- Discovery
  - Gene id & function
- Cloning
  - Making multiple identical copies
- Transfer to plant cells
- Selection of desired plant cells
- Growth of whole plants



## Transferring the Gene



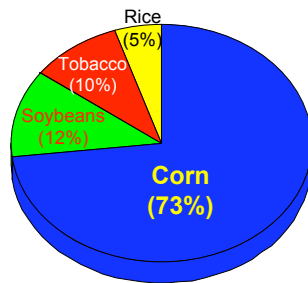
## Tricky Antibody Production

- Antibodies are actually two chains of proteins
- Code for each protein in separate plants
- Cross fertilize them



## Candidate Plants

- Tobacco
- Corn
- Canola
- Potato
- Alfalfa
- Rice
- Safflower
- Soybean



## Advantages of Production in Seeds

- Protein "concentrated" in seed relative to total weight
- Seeds easier and more economical to transport to extraction plant than whole leaves
- Can be stored for long periods without tissue deterioration



## The Players

Company	Plant	Company	Plant
AltaGen Bioscience	Potato (Leaves)	MPB Cologne GmbH	Potato (tuber) Canola (seed)
Crop Tech	Tobacco (Leaves)	Phytomedics	Tobacco; Tomato
Epicyte	Corn; Rice (seeds)	Ventria Bioscience	Rice
Large Scale Biology	Tobacco (leaves)	ProdiGene	Corn (seeds)
Medicago	Alfalfa (leaves)	SemBioSys Genetics	Safflower (value-added protein)
Meristem Therapeutics	Corn (seeds) Tobacco (leaves)		

## Is It Safe?

USA TODAY - THURSDAY, NOVEMBER 25, 2004

**Gene-altered DNA may be 'polluting' corn**

Cross-pollination is found in native varieties in Mexico

**New corn endangers Monarch butterfly**

**FDA to test for biotech corn allergy**

WASHINGTON — The Food and Drug Administration soon will begin blood-testing people who say they may have been sickened by eating a variety of genetically engineered corn.





- ### Background: What PMP's Are
- Regulated drugs subject to mandatory conditions
  - High value, high purity pharmaceuticals
  - Controlled exclusively by registrant at all stages
  - Presently small acreage, confined research plots
  - In commercial production, acreage comparatively small (~1000 acres)

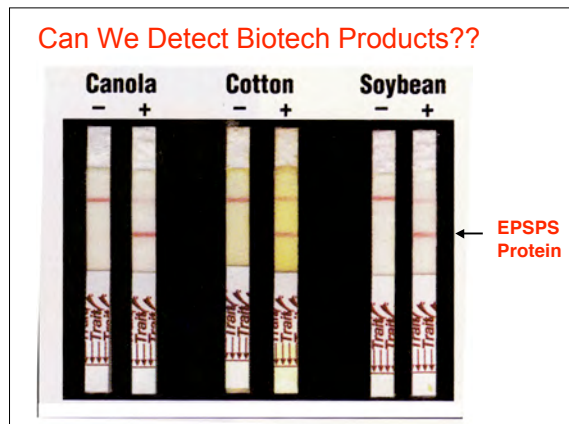
- ### Background: What PMP's Are Not
- Value added opportunities for agriculture or farmers
  - Sold as seed to farmers
  - Exclusive to commodity crops
  - Analogous to Starlink or commodity ag biotech (regulatory oversight, scale)
  - Widespread commercial production

- ### Is It Safe? Human Health Issues
- Concern over pollination of food crops by transgenic pharm crops
    - Many proteins slated for production are naturally produced by our own bodies
    - Oral exposure would probably inactivate protein
    - Many therapeutic proteins will be given intravenously or injected

### Humans 'Naturally' Exposed to 'Foreign' Pharm Proteins

Immunoglobulins	Colostrum (mg/mL)	Milk (mg/mL)
IgG1	46.4	0.60
IgG2	2.9	0.06
IgM	6.8	0.09
IgA	5.4	0.08

*Korhonen 2000*

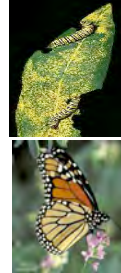


## Is It Safe? Ecological Issues

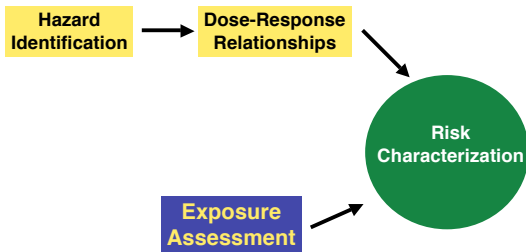
- Will bioactive proteins harm soil biota?
  - When proteins hit the soil, they are rapidly biodegraded
  - If not degraded can be rapidly immobilized on clays or sorbed to organic matter
    - Thus, bioavailability is limited
    - Whole proteins not likely to diffuse directly across bacterial membranes

## New Products & Old Issues

- Human therapeutic proteins will not be biologically functional in an invertebrate or other vertebrates unless appropriate biochemical receptors are present



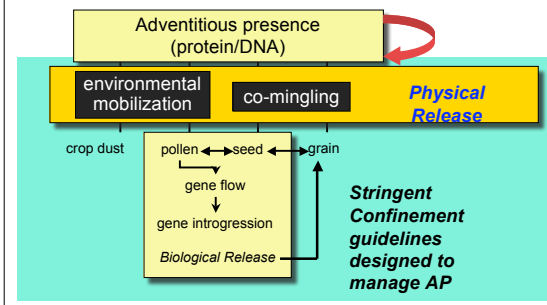
## Risk Assessment-- Testing the Probability of Harm



## Regulatory Responsibilities

- USDA-APHIS
  - Issues permits for growing PMPs during research, development, and manufacture phase
  - Development permits already issued
- FDA
  - Regulatory oversight of entire product lifecycle, from production to waste
  - Ensure integrity, safety and efficacy of product
  - Good Manufacturing Practice Stds. (GMPs)

## Regulatory Oversight Primary Focus on Control and Purity



## Principles of Confinement

- Developed by the Biotechnology Industry Organization (BIO)
- Keeping the crop and its products on the land where grown until removed for processing
- No inadvertent exposure to the public
- Minimal exposure of products to workers and the environment

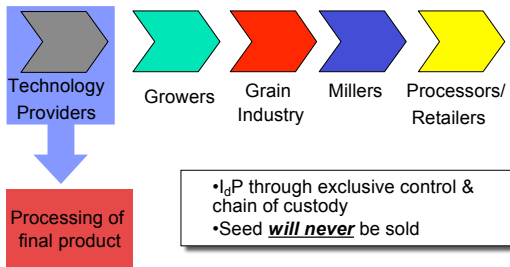
## Principles of Confinement

- Prevention of inadvertent human exposure through food & feed
- Minimized occupational and environmental exposure during all phases of production
- Rigorous compliance with confinement measures
- Analytical methods for detection of products
- Full cooperation with regulatory reviews of confinement measures & on-site inspections
- All confinement systems & procedures based on sound scientific principles

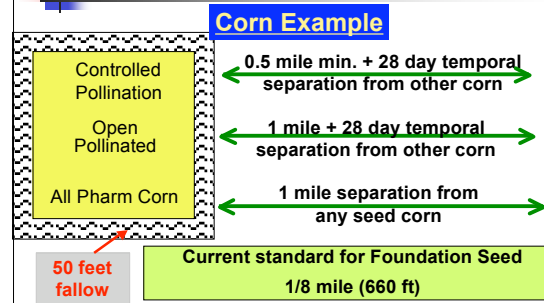
## Standard Operating Procedures for Confinement

- Training
- Contracts and Channeling
- Site Selection & Security
- Crop Production
- Identification
- Containers
- Equipment
- Disposition of Plant Material
- Verification
- Compliance Assessment
- Monitoring
- Remediation

## Identity Preservation De-link from Commodity Agriculture



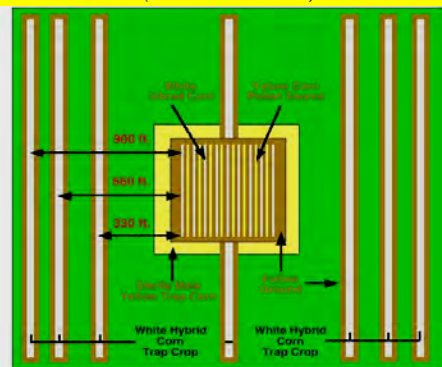
## Temporal and Spatial Isolation for Biopharmaceutical Crops



## Pollen Control Practices

- Alternate 4-row blocks of females with males
  - Female corn plant created by detasseling
  - Female line contains the pharm gene
  - Male line does not contain the gene
  - Male line flowers and mates with female lines
- Need to study detasseling error rate
  - Commercial seed certification inspectors allow less than 1% detasseling error

## Testing Detasseling Efficiency & Gene Flow (Stevens et al. 2002)





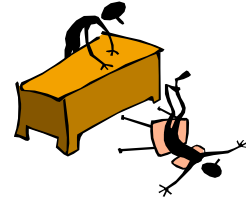
## Gene Flow Study Results

Detasseling Rate	Incidence of Hybridization	# seeds out of 10,000 seeds
0%	0.0301	3
80%	0.0043	0.4
90%	0.0013	0.1
100%	0.0001	0.01

Data from Stevens et al. 2002

## Significance of Gene Flow

- If average ear of corn has 500 seeds, than a hybridization incidence of 0.0013% (i.e., 1.3 seeds out of 100,000 seeds had the 'transgenic' character) is equivalent to
  - One 'pharm' protein-containing seed in every 150 ears of corn



Business 11/13/2002  
Des Moines Register.com

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Agriculture

**Biotech corn may have tainted soybeans**

The USDA has impounded 500,000 bushels and is holding them in Nebraska.

By PHILIP BRASHER  
Register Washington Bureau

11/13

Wash bush was

**APHIS News**

United States Department of Agriculture  
Animal and Plant Health Inspection Service

Jim Rogers (301) 734-8563  
Beth Jones (202) 720-6959

**USDA INVESTIGATES BIOTECH COMPANY FOR POSSIBLE PERMIT VIOLATIONS**

WASHINGTON, Nov. 13, 2002--The U.S. Department of Agriculture's Animal and Plant Health Inspection Service, in close coordination with the Food and Drug Administration is investigating ProdiGene, Inc., of College Station, Texas, for violations of the Plant Protection Act.

## The Prodigene Fiasco

- During routine inspection, USDA-APHIS found tasseled volunteer corn plants with a PMP trait were not completely removed from a soybean field
- Soybeans were already harvested and comingled so whole lot was treated as potentially contaminated and embargoed
- Error caught & beans destroyed
- Not a gene flow problem
- System of inspection worked
- Company did not follow its SOPs

## Learning from Mistakes

- Regulations are dynamic
  - Increased separation distances
  - Buffer & border rows of corn will not be allowed around 'pharm' corn
  - Dedicated machinery
- Follow SOPs



PRODIGENE Home

About ProdiGene Technology, Process & IP Product Development Partnering with ProdiGene News & Articles

Home page

- Oral vaccines made in plants
- Pathogen free therapeutics
- Eco-friendly products

Better, safer products for human health.

ProdiGene is...

The first to commercialize a recombinant protein made from plants (1998)

Currently producing multiple large volume, pathogen free protein products in plants


What's new at ProdiGene?  
ProdiGene brings plant-produced recombinant trypsin to market

PRODIGENE  
Producing Non-animal Sources of Biologics

TrypZean™  
RECOMBINANT TRYPSIN FROM MAIZE

**California edges towards farming drug-producing rice**


Ben Dalton, San Diego  
 Plans to step up cultivation of rice that is genetically modified to yield pharmaceuticals are sparking fierce opposition from some environmental scientists and farmers in California. On 29 March, the California Rice



**Pharmaceutical Rice in California**

... may undermine the market for their conventional crops.

Ventri Bioscience had worked out the production of lactoferrin & lysozyme in rice



*Potential Risks to Consumers, the Environment and the California Rice Industry*

**Modified rice won't be planted -- for now State halts planting of rice for pharmaceutical use**

**Public to have say before state rules on bioengineered crop**

Charlie Goodyear, Chronicle Staff Writer  
 Saturday, April 10, 2004  
 ©2004 San Francisco Chronicle Feedback | FAQ


**SACRAMENTO Business Journal**

**LATEST NEWS**  
 April 9, 2004

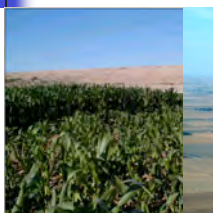
**Regulators block plans for genetically altered rice**

Celia Lamb  
 Staff writer

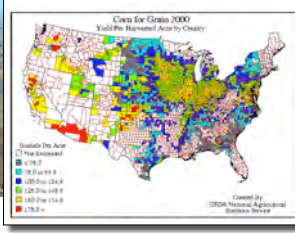
Ventria Bioscience decided to move production of the "pharm" rice to Missouri



**Keeping the Gene 'in the Bottle'--Managing Pollen Flow**



Isolation in the desert away from commodity production



**The Future's So Bright, I Got to Wear Shades**

- Opportunities for "elite" growers & crop consultants
  - Must abide by strict SOPs for confinement
  - Everything tracked & signed off
- Small acreage for any one product
- But there could be a lot of products
- Opportunity will depend on everybody paying attention and managing the whole technology from cradle to grave

**For More Information**

- <http://feql.wsu.edu>
  - Food and Environmental Quality Lab
- <http://wsprs.wsu.edu>
  - Washington State Pest Management Resource Center
- <http://aenews.wsu.edu>
  - Agrichemical & Environmental News
- [afelsot@tricity.wsu.edu](mailto:afelsot@tricity.wsu.edu)