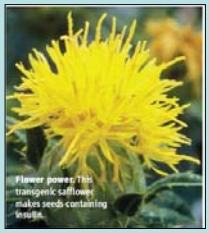
Biopharma and bioindustrial crops



Steve Strauss, BI/FS 435/535 (H)

Spring 2009

www.sciencemag.org SCIENCE VOL 320 25 APRIL 2008
Published by AAAS

Definitions

- PMP and PMIP – Plant made pharmaceutical and plant made industrial proteins from GE plants
- Plant is a bioreactor, not the product – materials are extracted and processed to some degree, not consumed directly
  - Native or foreign products
  - Leftover tissue may be used, e.g. for energy
- Contrast to nutritionally enhanced food like Golden Rice – meant to be consumed as a food
  - Concept of vaccine tomato, -banana discussed earlier….unlikely uses?

Definitions

- Some PMPs may also be considered PMIPs
  - Ventria disease-fighting enzymes
- Commercial scale can vary widely (one greenhouse to millions of acres)

Three biological types of GMO crops?

- Bioreactor crops
- Crops with novel traits due to novel genes
  - Bt pest tolerant
  - Herbicide tolerant
  - Virus tolerant
- Crop with novel traits due to modified gene expression and thus physiology
  - Salt and drought tolerant, nutritional efficiency
- Vs. cisgenic, intragenic, famogenic, transgenic, xenogenic, etc — that emphasize source and degree of modification
  - Cisgenic = unaltered, sexually compatible species
  - Intragenic = altered, sexually compatible species
  - Others = incompatible species sources

What types of molecules are included in "biopharm"

- Although many "small molecule" drugs come from plants (opium, theophylline, codeine, Metamucil, anti-cancer drug Taxol)…
- PMP largely refers to the production of large proteins in plants, i.e. things like:
  - Protein hormones (insulin, growth hormone)
  - Antibodies for diagnostic or therapeutic use
  - Immune regulators

Why use plants?

Advantages

- Cost reduction
  - low/no inputs
  - low capital cost
  - scalability
- Addresses greater diversity of products?

Why use plants?

Advantages

- Stability
  - storage in natural dormant tissues like seed, tubers
- Safety
  - eukaroytic production system with normal protein processing, folding, post-translational modifications (e.g., addition of sugars)
  - free of animal viruses

Why not use plants?

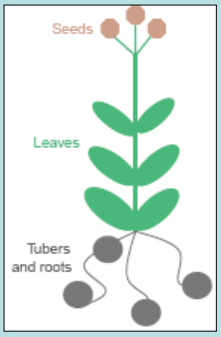
Disadvantages

- Mixing/contamination
  - Environment
    - gene flow and wildlife exposure
  - Food supply
    - contamination
- Health safety concerns
  - allergens
  - toxicity
  - dosage
  - exposure

Why use food crops?

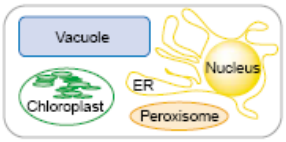
- Agricultural crops are bred for large seeds, high protein production, and reduced dispersal (shattering) of seed
- Often highly stable, chemically stable protein reserves (dessicated, dormant)
  - Thus storability, uniformity
- Existing methods and equipment for harvesting and extraction and processing
  - BUT – use of PMP-dedicated units
- *Not conventional agriculture production systems (for foreseeable future)*

Where and how product is expressed is critical to yield, stability, quality and safety



Subcellular location important

- Ubiquitous expression and expression of transgenic proteins in storage organs (e.g. tubers, seeds)
- Accumulation in 'optimal' compartments (e.g. ER, chloroplast)
- Production of plastic-like biomaterials in chloroplasts and peroxisomes



Chemical inducible expression another option to avoid impacts on plant growth and health from high production

Three major types of PMPs

- Vaccines (possibly edible vaccine forms)
- Antibodies
- Therapeutic proteins and intermediates

Plant-made vaccines

- Low antigen cost - traditional method uses fermentation vats
- High yield - oral vaccines require high yields – hard to produce using traditional vats
- Low capital cost
- Ease of scale up
  - 200 acres – HPV for world
  - 40 acres – HPV required annually for China (2006 BioDesign Institute, Az State)
- Readily produced in developing countries
- Oral: No syringes & assoc. costs and safety

Examples of plant-made vaccines

- Pig vaccine in corn
- HIV-suppressing protein in spinach
- Human vaccine for hepatitis B in potato and tobacco
- Pneumonia vaccine in plant chloroplasts

Plant-made monoclonal antibodies

- Plants first shown capable of producing active MAbs in 1989
- Plants used include tobacco, corn, potatoes, soy, alfalfa, and rice
- Free from potential contamination of mammalian viruses
- GE corn can produce up to 1 kg antibody/acre and can be stored at room temperature for up to 5 years
  - Humphreys DP et al. Curr Opin Drug Discover Dev 2001; 4:172-85

Examples of plant-made MAbs

- Respiratory syncytial virus
- Dental Caries MAb
- Genital herpes MAb

Plant made “other pharmaceuticals”

- Therapeutic proteins and intermediates
- Blood substitutes – human hemoglobin
- Proteins to treat diseases such as cystic fibrosis (CF), HIV, hypertension, hepatitis B…..many others

Diverse antibodies can be produced in plants

Goldstein, QJ Med 2004

Table 2 Recombinant antibodies expressed in transgenic plants

Year	Format	Antibody/Antigen	Plant organ	Cellular location	Transformed species
1989	IgG1	Phosphonate ester	Leaf	ER	Tobacco
1990	IgM	NP hapten	Leaf	ER chloroplast	Tobacco
1991	VH domain	Substance P (neuropeptide)	Leaf	Intra- & extra-cellular	*N. benthamiana*
1992	scFv	Phytochrome	Leaf	Cytosol	Tobacco
1993	IgG1 Fab	Human creatine kinase	Leaf	Nucleolus	Tobacco
1993	scFv	Phytochrome	Leaf	Apoplast	Tobacco
1993	scFv	AMCV	Leaf	Cytosol	*N. benthamiana*
1994	IgG	Fungal cutinase	Root	Apoplast	Tobacco
1994	IgG1	*Streptococcus mutans* adhesin	Leaf	Apoplast	Tobacco
1995	IgA/G	*Streptococcus mutans* adhesin	Leaf	Apoplast	Tobacco
1995	IgG	TMV	Leaf	Apoplast	Tobacco
1996	scFv	Cutinase	Leaf	ER	Tobacco
1996	IgM	RKN secretion	Leaf root	Apoplast	Tobacco
1996	scFv	BNYVV	Leaf	Apoplast	*N. benthamiana*
1996	scFv	Human creatine kinase	Leaf	Cytoplasm ER	Tobacco
1996	IgG/Fab	Human creatine kinase	Leaf	Apoplast	*A. thaliana*
1997	scFv	β-1,4-endoglucanase	Root	Cytosol	*S. tuberosum*
1997	scFv	Ouazulene	Leaf	ER	Tobacco
1997	scFv	Abscisic acid	Leaf	ER	Tobacco
1997	scFv	Abscisic acid	Seed	ER	Tobacco
1997	scFv-Fc	CD-40	Plant	Apoplast	Tobacco tissue culture
1998	scFv	Ouazulene	Tuber	ER	Potato
1998	Humanized IgG	HSV-2	Plant	Secretory pathway	Soybean
1998	scFv	Dihydro-flavonol 4-reductase	Leaf	Stroma	*P. hybrida*
1999	IgG	Human IgG	Plant	Apoplast	Alfalfa
1999	scFv	CEA	Leaf	Transient expression	Tobacco
1999	scFv	Topoisomers	Plant	ER, apoplast	*N. benthamiana*
1999	Ia-scFv	TMV	Leaf	ER, apoplast	Tobacco cell susp.
1999	scFv	TMV	Plant	Cytosol	Tobacco
1999	scFv	CEA	Cell	Er, apoplast	Rice suspension cells
1999	scFv	18C11 mouse B-cell lymphoma	Leaf	Apoplast	*N. benthamiana*
2000	scFv	CEA	Plant	ER, apoplast	Rice, Wheat
2000	scFv	TMV	Leaf	Apoplast, membrin	Tobacco

CEA, carcinoembryonic antigen; ER, endoplasmic reticulum; AMCV, artichoke mottle crinkle virus; TMV, tobacco mosaic virus; RKN, root knot nematode; BNYVV, beet necrotic yellow vein virus; HSV-2, herpes simplex virus-2; scFv-Fc, scFv-Fc-radio-immunotoxin. *N. benthamiana*, tobacco (Nicotiana-related species. *A. thaliana*, Arabidopsis, an experimental species. Table modified from Fischer & Emans.[7]

Diversity of vaccines can be produced in plants

Goldstein, QJ Med 2004

Table 3 Recombinant vaccines expressed in plants

Year	Vaccine-antigen	Species
1992	Hepatitis virus B surface antigen	Tobacco
1995	Malaria parasite antigen	Virus particle*
1995	Rabies virus glycoproteins	Tomato
1995	*Escherichia coli* heat-labile enterotoxin	Tobacco Potato
1996	Human rhinovirus 14 (HRV-14) and human immunodeficiency virus type (HIV-1) epitopes	Virus particle*
1996	Norwalk virus capsid protein	Tobacco Potato
1997	Diabetes-associated autoantigen	Tobacco Potato
1997	Hepatitis B surface proteins	Potato
1997	Mink Enteritis Virus epitope	Virus particle*
1997	Rabies and HIV epitopes	Virus particle*
1998	Foot and mouth disease virus VP1 structural protein	Arabidopsis
1998	*Escherichia coli* heat-labile enterotoxin	Potato
1998	*Escherichia coli* heat-labile enterotoxin	Potato
1998	Rabies virus	Virus particle*
1998	Cholera toxin B subunit	Potato
1998	Human insulin-Cholera toxin B subunit fusion protein	Potato
1999	Foot and mouth disease virus VP1 structural protein	Alfalfa
1999	Hepatitis B virus surface antigen	Yellow lupin, lettuce
1999	Human cytomegalovirus glycoprotein B	Tobacco
1999	Dental caries (*S. mutans*)	Tobacco
1999	Diabetes-associated autoantigen	Tobacco Carrot
2002	Respiratory syncytial virus	Tomato

*Plant virus—can be expressed in multiple plant species. Modified from Fischer & Emans[8], Giddings et al.[12] and Kofman et al.[10]

Diversity of other therapeutics can be produced in plants

Goldstein, QJ Med 2004

Table 4 Biopharmaceuticals derived from transgenic plants

Potential application/indication	Plant	Protein	Method
Anticoagulants			
Protein C pathway	Tobacco	Human protein C (serum protease)	AMT
Indirect thrombin inhibitors	Ethiopian mustard	Human hirudin variant 2	AMT
Recombinant hormones/proteins			
Neutropenia	Tobacco	Human granulocyte-macrophage colony-stimulating factor	AMT
Anaemia	Tobacco	Human erythropoietin	AMT
Antihyperanalgesic by opiate activity	Tobacco	Human erythropoietin	AMT
Wound repair/control of cell proliferation	Thale cress, oilseed	Human enkephalins	AMT
Hepatitis B and C treatment	Rice, turnip	Human interferon-α	AMT
Liver cirrhosis	Potato, tobacco	Human serum albumin	AMT
Blood substitute	Tobacco	Human haemoglobin	AMT
Collagen	Tobacco	Human homotrimeric collagen	AMT
Protein/peptide inhibitors			
Cystic fibrosis, liver disease and haemorrhage	Rice	Human α-1-antitrypsin	PB
Trypsin inhibitor for transplantation surgery	Maize	Human aprotinin	PB
Hypertension	Tobacco/tomato	Antiotensin-1-converting enzyme	AMT
HIV therapies	*Nicotiana benthamiana*	α -Trichosanthin from TMV-U1 subgenomic coat protein	AMT
Recombinant enzymes			
Gaucher's disease	Tobacco	Glucocerebrosidase	AMT

AMT, *Agrobacterium*-mediated transformation. PB, particle bombardment. Modified from Giddings *et al.*[32] Fischer & Emans.[2] See also Thomas.[9]

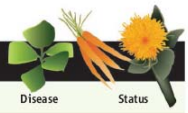
Some PMP/PMIP companies

Company name	Location	Species for production
Meristem Therapeutics	Clermont-Ferrand, France	Maize
CropTech	Charleston, S.C.	Tobacco
PlantGenix	Philadelphia, Pa.	Various
Large Scale Biology	Vacaville, Calif.	Tobacco
Monsanto Protein Tech	St. Louis Mo.	Maize
SemBioSys	Calgary, Alberta, Canada	Safflower
Medicago	Quebec City, Quebec, Canada	Alfalfa
Ventria	Sacramento, Calif.	Rice
Epicyte Pharmaceutical	San Diego, Calif.	Maize
Planet Biotechnology	Hayward, Calif.	Tobacco
ProdiGene	College Station, Tex.	Maize

Out of business companies circled!

Drugs in pipeline 2008

Plant Genomes



Selected Plant-Made Pharmaceuticals

Company	Plant	Grown in	Drug or product	Disease	Status
Human drugs					
Protalix Biotherapeutics	carrot	cell culture	glucocerebrosidase	Gaucher disease	Phase III trial*
Biolex Therapeutics	duckweed	indoor chambers	alpha interferon	hepatitis C	Phase II trial*
SemBioSys Genetics	safflower	field	insulin	diabetes	Phase VIII trial †
Meristem Therapeutics	corn	field	lipase	cystic fibrosis	Phase III trial †
Other products					
Ventria Bioscience	rice	field	lactoferrin, lysozyme	diarrhea	Efficacy trial §
Cobento	*Arabidopsis*	greenhouse	human intrinsic factor	Vitamin B-12 deficiency	Approved ††
Planet Biotechnology	tobacco	field	secretory antibody vaccine	tooth decay	E.U. approved
Dow AgroSciences	tobacco	cell culture	poultry vaccine	Newcastle disease	USDA approved
CIGB, Cuba	tobacco	greenhouse	vaccine purification antibody	hepatitis B	On market

* Ongoing; † Projected late 2008; § Completed; †† In Ukraine.

Steps along the way. No plant-made human drug has made it through final clinical trials, but several "pharmed" proteins are close to or on the market as supplements, a vaccine reagent, and a medical device.

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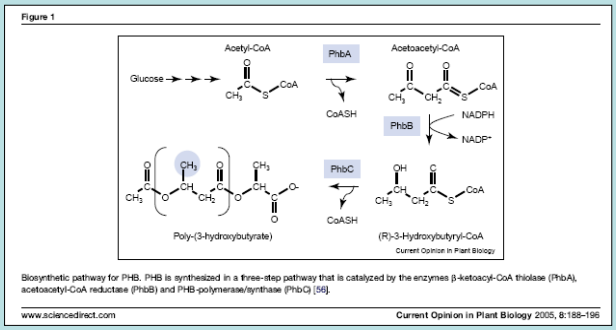
Proposed PMIPs

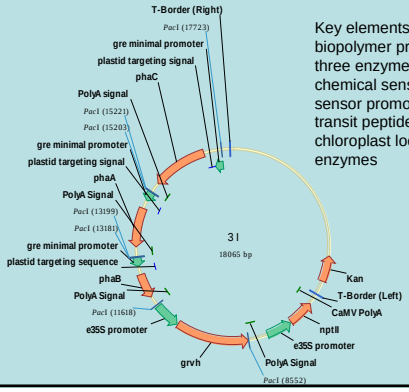
- Current Opinion in Plant Biology 2005, 8:188–196
  - Biodegradable plastics
  - Silk proteins from spiders – very high tensile strength
  - Elastins, collagen - strong elastic fibers present in ligaments/arterial walls, connective tissues
  - Industrial enzymes (e.g., used in pulping, food treatment, hygiene applications)

PHB: Example of a PMIP

Three enzyme pathway for polyhydroxy-butyrate production
A precursor for many types of plastics



Inducible construct for synthesis of PHB in transgenic plants



Key elements for biopolymer production = three enzymes, inducer chemical sensor protein, sensor promoter elements, transit peptide for chloroplast localization of enzymes

Field regulatory oversight

- Expectation of permanent regulation, unless considered GRAS
- USDA/APHIS existing regulations stringent
  - Frequent inspections, severe penalties,
- Closed loop management system
  - Use of dedicated equipment
  - Defined isolation distances and timing of production (spatial/temporal)
  - Inbreeders vs. outcrossers
  - Visual genetic markers
  - Male/female sterile lines
  - Food vs. non-food crops

Health / exposure issues

- Does the production of human proteins in plants raise new allergy issues?
  - Changed glycosylation of proteins made in plants may affect allergenicity?
    - Already common for bacterially produced human proteins, but an issue to be seriously considered
    - Could it produce autoimmune disease?
    - How to define safe thresholds for exposure?

Health / exposure issues

- Do some of the industrial proteins raise significant issues for non-target exposures, or fitness of wild plants with relatives?
  - Toxins, avidin, Ventria antimicrobial proteins?
- Variation in quality/quantity, small molecule contaminants, due to environmental stresses, variation in crop physiology, a safety and efficacy issue?

Risks of co-mingling with food supply depends…

- Potential for co-mingling with subsistence or wholly eaten foods the major safety risk
  - Eg., tomato, banana, potato
  - Limited control in developing world

Commodity Chain (highly diluted)

Subsistence

Statement from BIO regarding plants that produce pharmaceutical and industrial products (2009)

http://www.bio.org/healthcare/pmp/statement.asp

- We support strong regulatory oversight for all products of crop biotechnology.
- We encourage and invite alternative approaches to this issue that would deliver at least equivalent assurances for the integrity of the food supply and export markets.
- We believe that permits should continue to be required by USDA/APHIS for the interstate movement, field testing, and commercial planting of all regulated articles that are not intended to be used for human food or animal feed.

Statement from BIO regarding plants that produce pharmaceutical and industrial products (2009)

http://www.bio.org/healthcare/pmp/statement.asp

- We encourage all BIO members to submit detailed confinement and handling plans and standard operating procedures with each of their mandatory permit applications to USDA/APHIS.
- We strongly encourage the USDA to treat these plans and procedures as mandatory permit conditions, subject to mandatory audit and inspection.

Oregon Biopharm Committee Policy Recommendation to Governor

http://www.oregon.gov/ODA/PLANT/biopharm.shtml#Policy_Final_Statement
October 2006

- The committee chose “endorsement, moderate scope” to indicate that it supports wisely chosen and carefully studied applications of biopharm technology in Oregon.
- The “moderate scope” choice option, however, reflected the committee’s interest in substantial State of Oregon involvement in federal regulatory decisions about where and how biopharm crops may be grown in Oregon

Oregon Biopharm Committee Policy Recommendation to Governor

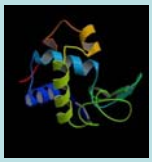
http://www.oregon.gov/ODA/PLANT/biopharm.shtml#Policy_Final_Statement
October 2006

- The committee also identified as a key issue the lack of federal standards with respect to the requirement for, and scope of early food safety evaluations that address the risk of unintended spread. These are critical to help characterize the public health and legal risks during field research and commercial production.
- The committee strongly recommends that the state require demonstration of adequate insurance to cover potential damages.
- Establish a science-based and health protective public communications plan for biopharmaceuticals and related biotechnologies

Ventria example

- *Slides after this one provided by Ventria*
- Goal to produce pharmaceutical enzymes from humans in rice
- They were forced to leave California, then Missouri, then North Carolina due to fears over contamination of commercial crops
- Rice is a predominant inbreeder
  - Very low levels of gene flow expected
- Now appear to be producing in a rice-free state, Kansas

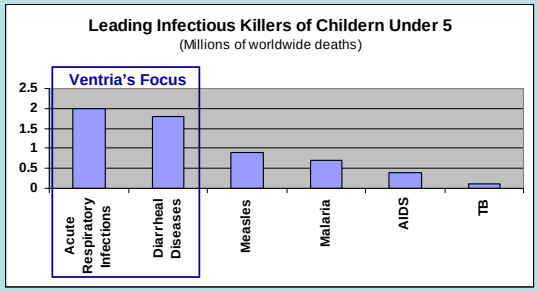
Lactoferrin & Lysozyme



- **Human proteins found in mother’s milk, saliva, and tears.**
- **Multi-functional:**
  - **Source of Iron (LF)**
  - **Cell Growth Factor (LF)**
  - **Anti-microbial (LF & LZ)**
  - **Anti-Inflammatory (LF)**
  - **Immunomodulatory (LF & LZ)**

Provided by Ventria Inc.

Global Health Problems



Source: *World Health Organization*

Provided by Ventria Inc.

Global Health Problems

Ventria's Solution

- **Orally delivered Lactoferrin and Lysozyme produced using ExpressTec™, plant-made pharmaceutical production system**
- **Able to produce 1,000's of kilograms with minimal capital investment**
- **Biologic yield is very high, and the processing is efficient, reducing the cost of production.**

Provided by Ventria Inc.

Global Health Problems

Why solutions to these problems have not been developed?

Problem

- **Inability to produce therapeutic solutions in sufficient quantities**
- **High cost of products produced in traditional systems**

Provided by Ventria Inc.

Pediatric & Adult Diarrhea

Lactiva & Lysomin

Problem: 1.9 million children die per year from acute diarrhea

Product –

- A **rice-based** ORS containing Lactiva™ and Lysomin™

Benefits

- Similar rehydration benefits to ORS
- Reduction of volume and duration of diarrhea
- Action against causative pathogen(s)
- Protective effects on intestinal permeability
- Rebalance gastrointestinal cytokines (colitis)
- Not an antibiotic

Provided by Ventria Inc.

Gastrointestinal Disorders

Lactiva & Lysomin

Problem: Gastrointestinal disorders afflict over four million people in the United States and many more worldwide.

Product – Lactoferrin & Lysozyme

- A functional ingredient formulated into drinks, medical foods and supplements

Benefits

- Rebalance gastrointestinal cytokines (colitis)
- Protective effects on intestinal permeability
- Reduced occurrence of inflammation episodes (diarrhea)
- Reduce incidence of antibiotic-induced C. difficile attack in geriatric populations
- Not an antibiotic

Provided by Ventria Inc.

Inhibition of Biofilm Formation

LACUREX

Problem: Biofilm formation and its resistance to antibiotic treatment is a major concern in persistant infections because bacteria that is protected by biofilm shows a 100 to 1000 fold increase in resistance to antibiotic treatment. It is estimated that biofilm formation affects 10 million people per year in the United States.

Product –

- A topical to prevent formation of biofilm on wounds.

Benefits

- Natural antimicrobial to inhibit biofilm formation and prevent serious infection.
- Speeds healing
- Not an antibiotic

Provided by Ventria Inc.

Real-Life Example: Enbrel

- Enbrel
  - Introduced by Immunex in 1997
  - Treats rheumatoid arthritis (1 million patients in the U.S.)
  - Biopharmaceutical produced by mammalian cell culture
- Enbrel shortage due to limited manufacturing capacity
  - In March 2002: 13,000 patients on waiting list
  - Manufacturers forced to ration Enbrel to prevent hoarding
  - Patients participate in lottery-type system to gain access to treatment

Provided by Ventria Inc.

Real-Life Example: Enbrel

"Immunex didn't have the money to build a large enough scale facility to manufacture Enbrel in large enough quantities. This is where transgenic plants could have a huge advantage. If Enbrel were produced in corn, they could have just planted more acres, which would have been much less expensive than building new, larger facilities."

Kent Iverson
Biopharmaceutical Consultant
Former Enbrel Development Team

Provided by Ventria Inc.

Monoclonals against HIV in maize

- ***Science* 28 March 2008:Vol. 319. no. 5871, p. 1735 Editors' Choice: Highlights of the recent literature**
- *Plant Biotechnol. J*. **6**, 189 (2008); *Proc. Natl. Acad. Sci. U.S.A*. **105**, 3727 (2008).
- Monoclonal antibodies that block the binding of HIV to cellular receptors have been shown to neutralize the virus in vitro, to protect monkeys from HIV challenge, and to prevent viral transmission through mucosal tissue.
- But such antibodies can be produced only at high cost and low capacity through expression in mammalian cells and are therefore not optimal for commercial manufacture.
- Two studies describe the purification of the anti-HIV antibody 2G12 from genetically engineered maize on a large and cost-effective scale.

Monoclonals against HIV in maize

- Rademacher *et al*. used a fluorescent marker protein to identify and breed transgenic plants that accumulated a high amount of 2G12 in the seed endosperm, the plant's specialized storage tissue.
- Ramessar *et al*. purified the antibody from 2G12-expressing maize without using protein A-affinity chromatography, a step typically used for antibody isolation, but toxic if protein A leaches into the final product.

Monoclonals against HIV in maize

- Despite differences between mammalian and plant-specific processing of protein-linked carbohydrate, both studies found that glycan modification of maize-produced 2G12 antibodies did not alter antibody binding to the gp120 subunit of the envelope protein of HIV.
- The HIV-neutralizing properties of mammalian cell- and maize-produced 2G12 were comparable, with the latter being somewhat more potent.

Monoclonals against HIV in maize

- Maize-produced 2G12 could be an effective prophylactic mucosal microbicide, and large-scale plant cultivation and prolonged seed storage in the absence of cold temperatures make this method of antibody production economically attractive.

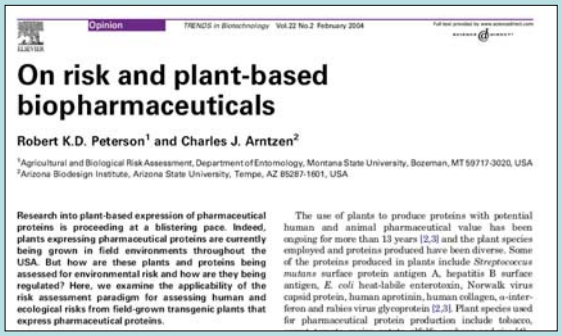
Summary and key issues

- Plants can be grown under a wide range of containment levels (field, greenhouse, ponds, caves, indoors, plastic bags)
- Many types of plants and tissues possible, many types of products with distinct safety profiles
  - No biological generalities re. safety useful, despite social lumping as "biopharma" and controversy thereof
  - Plants are full of thousands of medicinal, allergenic, and industrial compounds, often quite toxic – context is critical
- PMPs aimed at a very small section of the total medical products market
  - The perception of "medicines in plants" misleading
- Net economic value unclear given high costs of marketing pharmaceuticals, research patent monopolies, contamination risks

Summary and key issues

- Many of the products are expected to have little or no activity if accidentally ingested, esp. at low levels
  - Most proteins rapidly broken down in gut
- The biological safety vs. legal safety, regulatory, and market/perception dimensions are distinct but very important
  - Fusion of medicine, industrial chemistry, metabolic engineering, and agriculture at limits of knowledge and social capacity to assess risk – many possibilities, many questions, and socially and biologically difficult to deal with

Regulatory and market paradigms and inertia a major obstacle?



Opinion TRENDS in Biotechnology Vol.22 No.2 February 2004

On risk and plant-based biopharmaceuticals

Robert K.D. Peterson[1] and Charles J. Arntzen[2]

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[2]Arizona Biodesign Institute, Arizona State University, Tempe, AZ 85287-1601, USA

Research into plant-based expression of pharmaceutical proteins is proceeding at a blistering pace. Indeed, plants expressing pharmaceutical proteins are currently being grown in field environments throughout the USA. But how are these plants and proteins being assessed for environmental risk and how are they being regulated? Here, we examine the applicability of the risk assessment paradigm for assessing human and ecological risks from field-grown transgenic plants that express pharmaceutical proteins.

The use of plants to produce proteins with potential human and animal pharmaceutical value has been ongoing for more than 13 years [2,3] and the plant species employed and proteins produced have been diverse. Some of the proteins produced in plants include *Streptococcus mutans* surface protein antigen A, hepatitis B surface antigen, *E. coli* heat-labile enterotoxin, Norwalk virus capsid protein, human aprotinin, human collagen, α-interferon and rabies virus glycoprotein [2,3]. Plant species used for pharmaceutical protein production include tobacco,

Discussion questions

- Should all uses, or all field uses, of biopharma food or feed crops be banned? If any exceptions, which and why?
- Do you think tolerances can be established so that small accidental releases into food are acceptable? How to establish them?
- Do the benefits of biopharma crops justify taking some risks inherent to their use? Which ones?
- Do you expect the non-target effects of biopharma proteins on wild animals that feed on crops to be significant and require careful study before uses are allowed? How to compare to new conventional crop species and varieties?