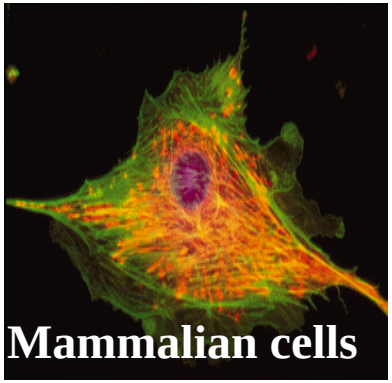
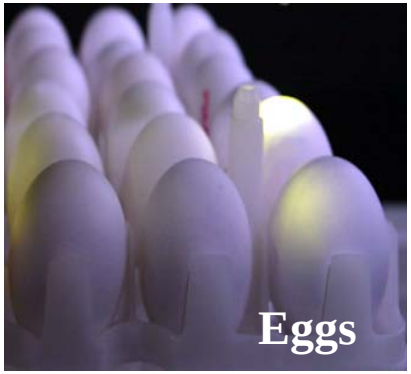
Plants for Better Health: Plant Biotechnology in the Generation of New Vaccines and Therapeutics

Jukka Kervinen, July 16th 2013

Many Expression Hosts Are Available but How to Choose the Most Suitable for Production?





Interest in New Biopharmaceutical Production Technologies

Some concerns with current systems:

- Safety: potential to harbor mammalian viruses
- Capacity: limited facilities for worldwide demand
- Response time: clone selection, line development and scale up
- Cost: expensive infrastructure and facility overhead
- Complexity: intricate systems with multiple points for failure

Recombinant Protein Production in Plants

Benefits & Challenges:

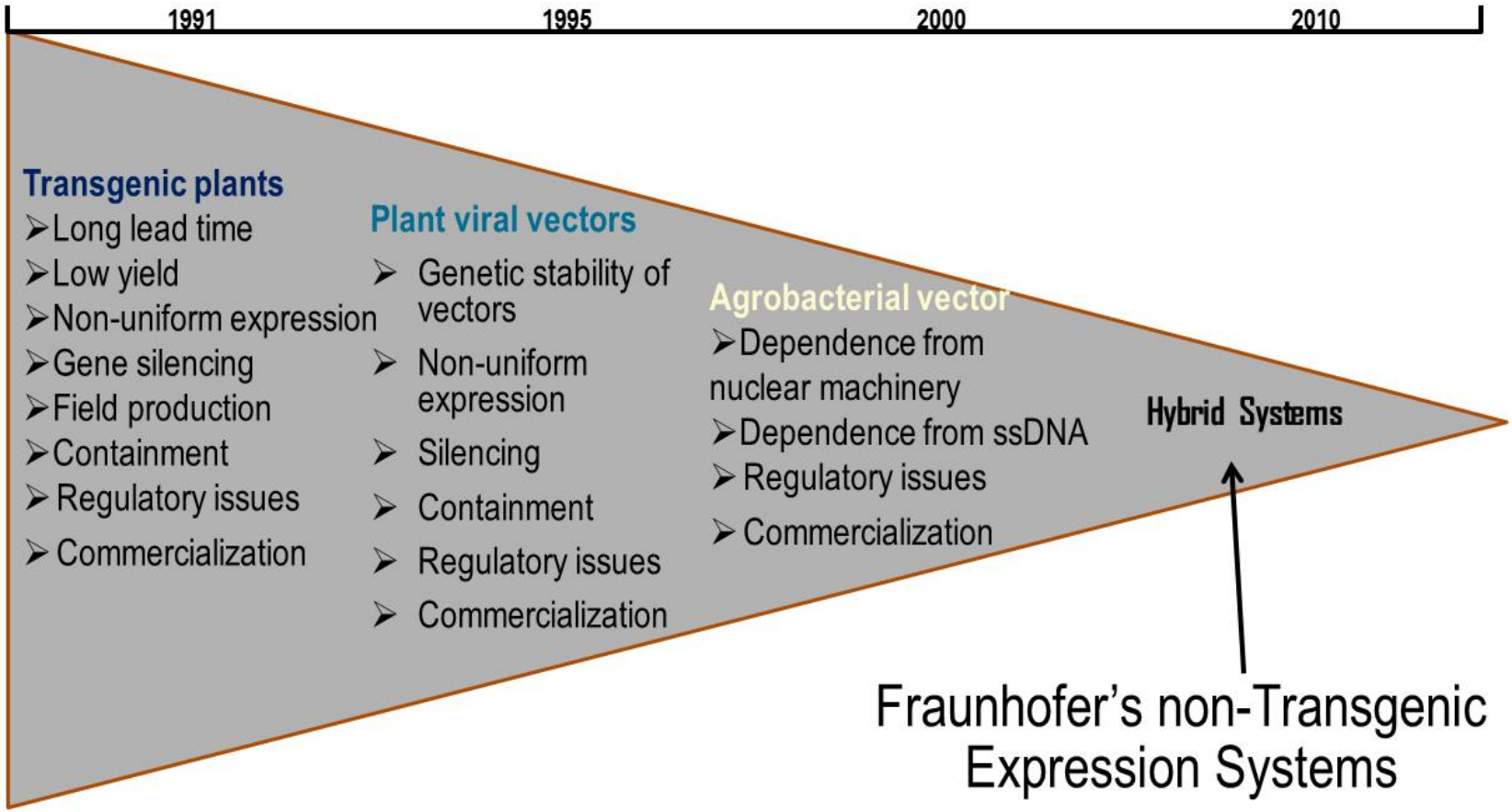
- Lack of human or animal pathogens
- High scalability
- Low upstream costs
- Production with desired structure and biological function
- Post-translational modifications (glycosylation, phosphorylation, proteolytic cleavages, etc.) can be beneficial or detrimental
- Level of expression and yield
- Response time
- Uniformity of expression

Field production

Confined production

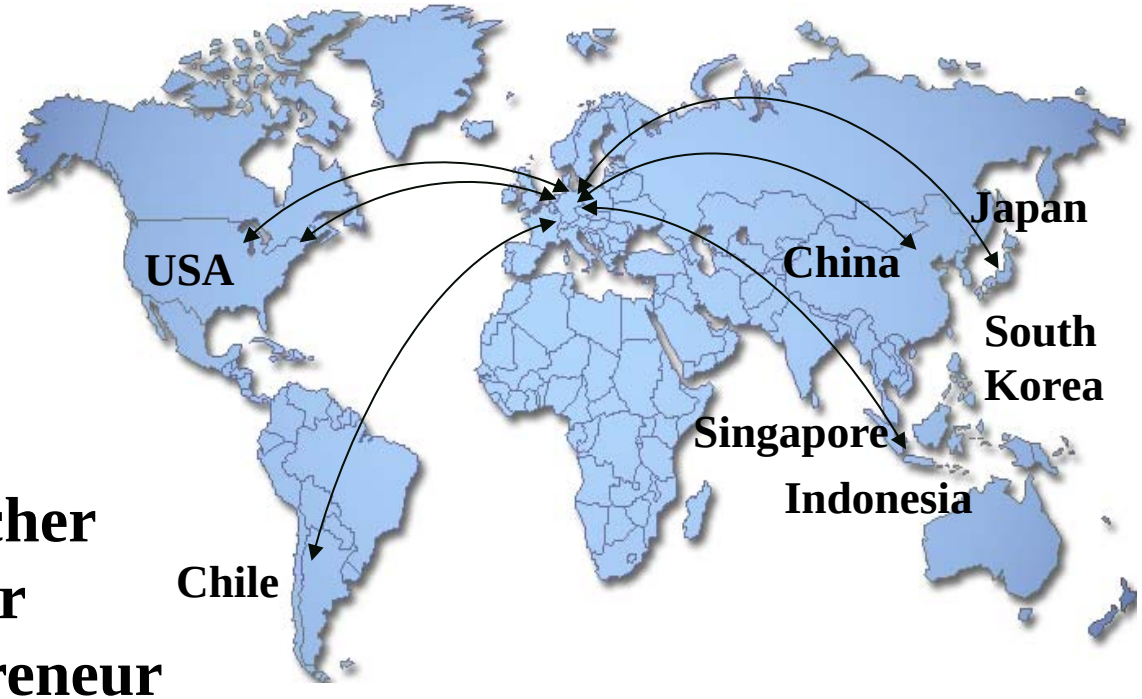
Contained production

Recombinant Protein Production in Plants



Fraunhofer Institutes and Centers

Researcher
Inventor
Entrepreneur



- Nonprofit applied research organization: focused on industry partnerships and the commercialization of technology through licensing and spin offs
- ~1.6 billion Euro annual budget & ~17,000 staff
- 59 German Institutes: spanning many fields of science and technology
- 7 US Centers: CMB focused on plant-based production of biopharmaceuticals

Fraunhofer Center for Molecular Biotechnology

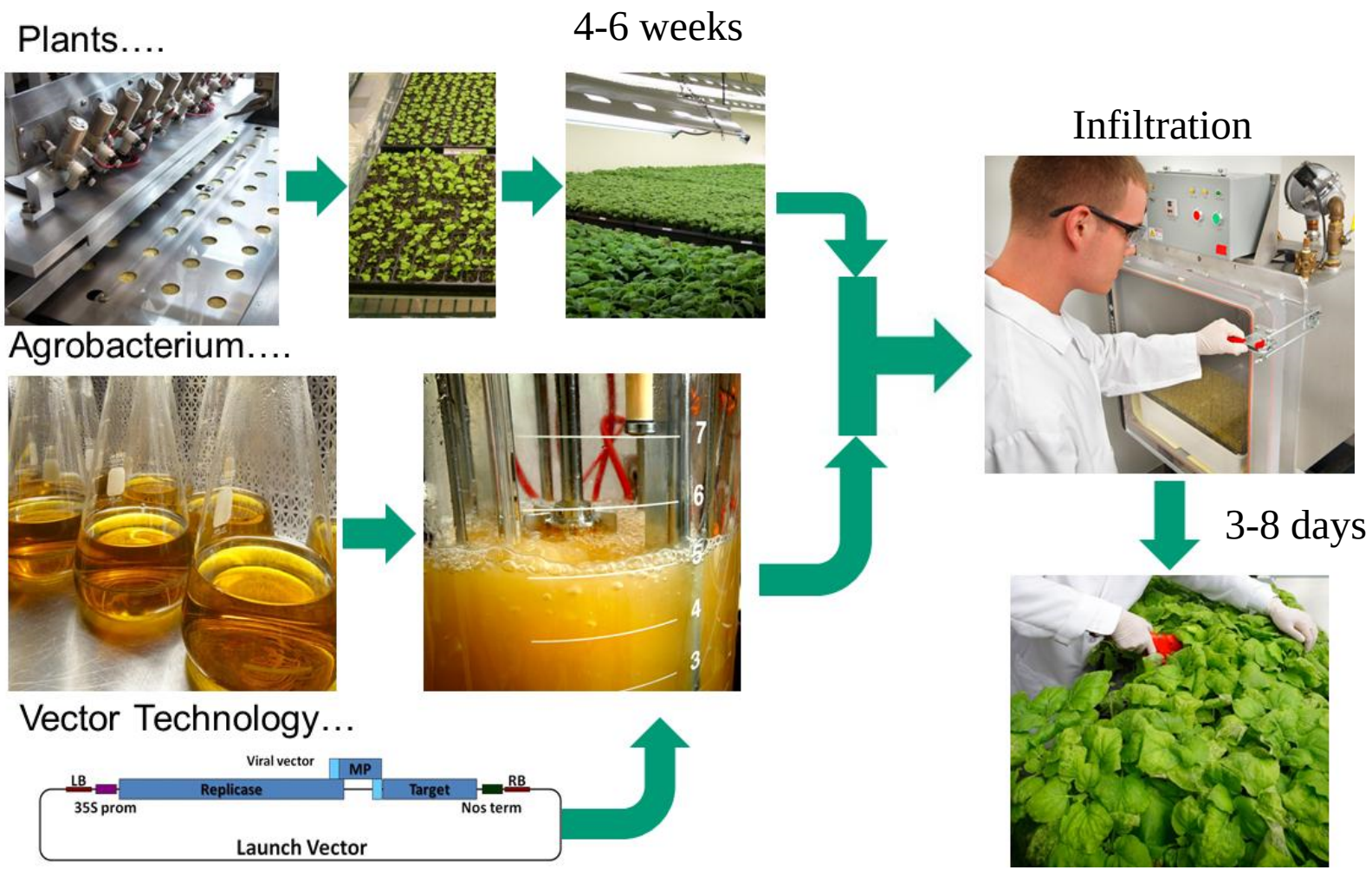
The Center was established as a Partnership between Fraunhofer Germany and the State of Delaware in 2001. Today ~100 employees.

Newark, DE

Purified Proteins for Pharmaceuticals

- FhCMB's approach is based on transient expression using virus-based vectors introduced into plant tissues by vacuum infiltration
  - Launch vectors for high level target expression
  - Vacuum infiltration of *Agrobacteria* for synchronized vector delivery to non-transgenic plants
  - Hydroponic system for confined, soil free and uniform biomass generation

Plant Growth, Infiltration & Harvesting

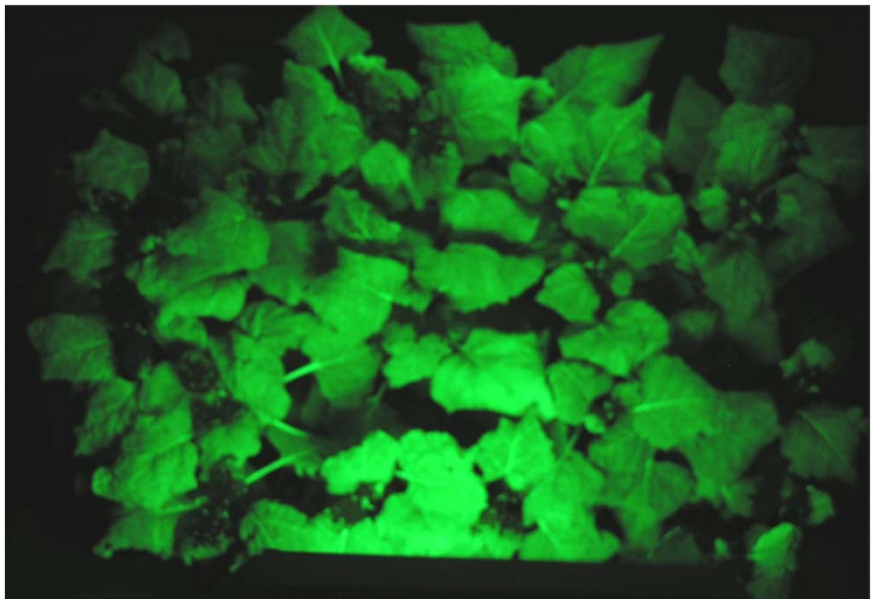


Plant Growth, Infiltration & Harvesting

Film

Plant Growth, Infiltration & Harvesting

Not Infiltrated

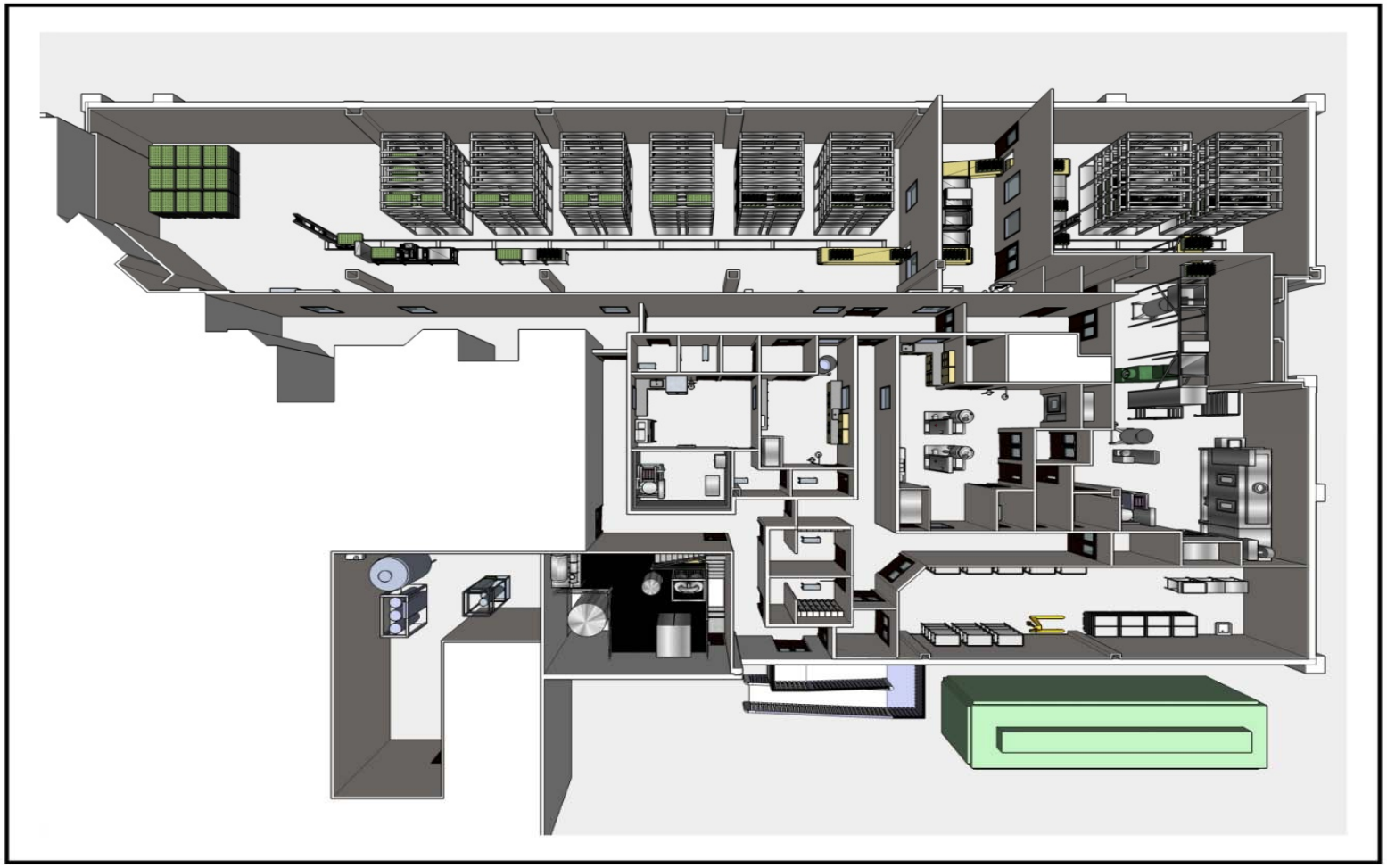


Infiltrated with GFP

From Laboratory to a Pilot Plant Facility

- Process development is carried out in the R&D laboratory for up to 5 kg of plant biomass
- Technology is transferred to a Pilot Plant Facility for up to 50-100 kg of plant biomass

cGMP Pilot Plant Production Facility



Equipment design and work was carried out in collaboration with
the Fraunhofer Center for Manufacturing Innovation

cGMP Pilot Plant Production Facility

Film

cGMP Pilot Plant Production Facility

Production host: *Nicotiana benthamiana*
Seed used per batch: ~1 g (10,000 seed)
Growth period: 4-6 weeks
Average aerial biomass: ~50 kg
Biomass increase: ~50,000 fold
Seed per plant: ~15 g

One plant provides enough seed for ~0.75 metric tons of biomass

cGMP Pilot Plant Production Facility:

Pre-Infiltration Plant Growth

cGMP Pilot Plant Production Facility:

Vacuum Infiltration

cGMP Pilot Plant Production Facility:

Post-Infiltration Plant Growth

cGMP Pilot Plant Production Facility:

Harvest

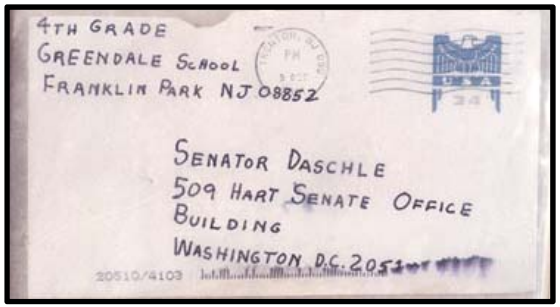
FhCMB Pilot Facility – Process Chromatography for Purification

How can we use this technology?

Bacillus anthracis, a bug with attitude!

Anthrax is a top choice for use as a biological warfare agent.

- Bacteria spores can be processed to become airborne
- Spores remain dangerous for decades
- Can be produced in large quantities with basic technology

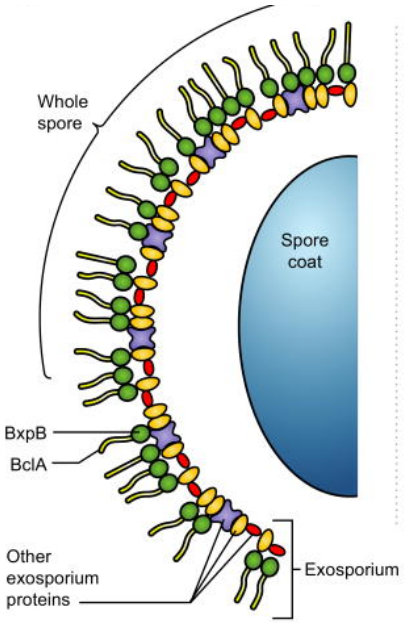


A letter sent to Senator Tom Daschle containing anthrax powder killed two postal workers in 2001.

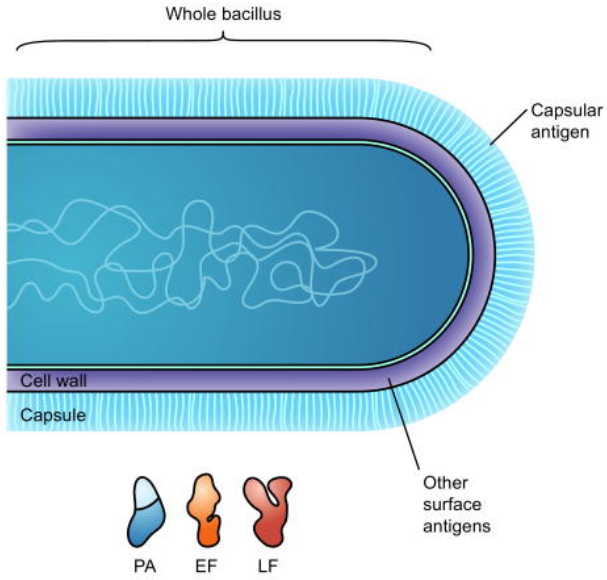
Anthrax was used as a biological weapon in the United States.

- Post 9/11 terror attacks, US citizens contracted cutaneous and inhalational anthrax
- Delivering weaponized anthrax was as simple as putting it in an envelope and mailing.

Anthrax Vaccination Strategies



Spore



Vegetative basilli

Potenitial vaccination targets

- Live attenuated spores
- Spore components (BclA, BxpB)

- Live attenuated bacilli
- Protective antigen (PA)
- Edema factor (EF)
- Lethal factor (LF)
- Capsular antigen

Mol Aspects Med 30, 490-502, 2009

Examples of Industrially Produced Plant-Based Biologics

Plant Expression Systems and Recombinant Protein Products

Manufacturer	System	Product	Stage
Protalix	Carrot (root cell suspension)	Elelyso™ (taliglucerase alfa) (Gaucher Disease)	FDA Cleared
InVitria	Rice (seed)	Cell Culture Products (rh-albumin, rh-lysozyme, rh-transferrin, rh-lactoferrin)	Marketed
Medicago	Tobacco (whole plant)	Influenza Vaccines	Phase II
Planet Biotechnology	Tobacco (whole plant)	Dental Caries	Phase II
Ventria Bioscience	Rice (seed)	VEN100 (rh-lactoferrin) VEN200 (rh-albumin)	Phase II Phase I
Synthon	Duckweed (whole plant)	Interferon Alpha (Hepatitis C)	Unknown*

*Synthon acquired intellectual property related to this and other products during the June 2012 liquidation of Biolex Therapeutics. The terms of the acquisition were not published and the status of these products is not currently available.

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Fraunhofer-CMB, Newark, DE

Thank you!