Moving Products into the Clinic:
The Next Milestone for Plant Made Pharmaceuticals

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USDA

Ag Outlook Forum

2004

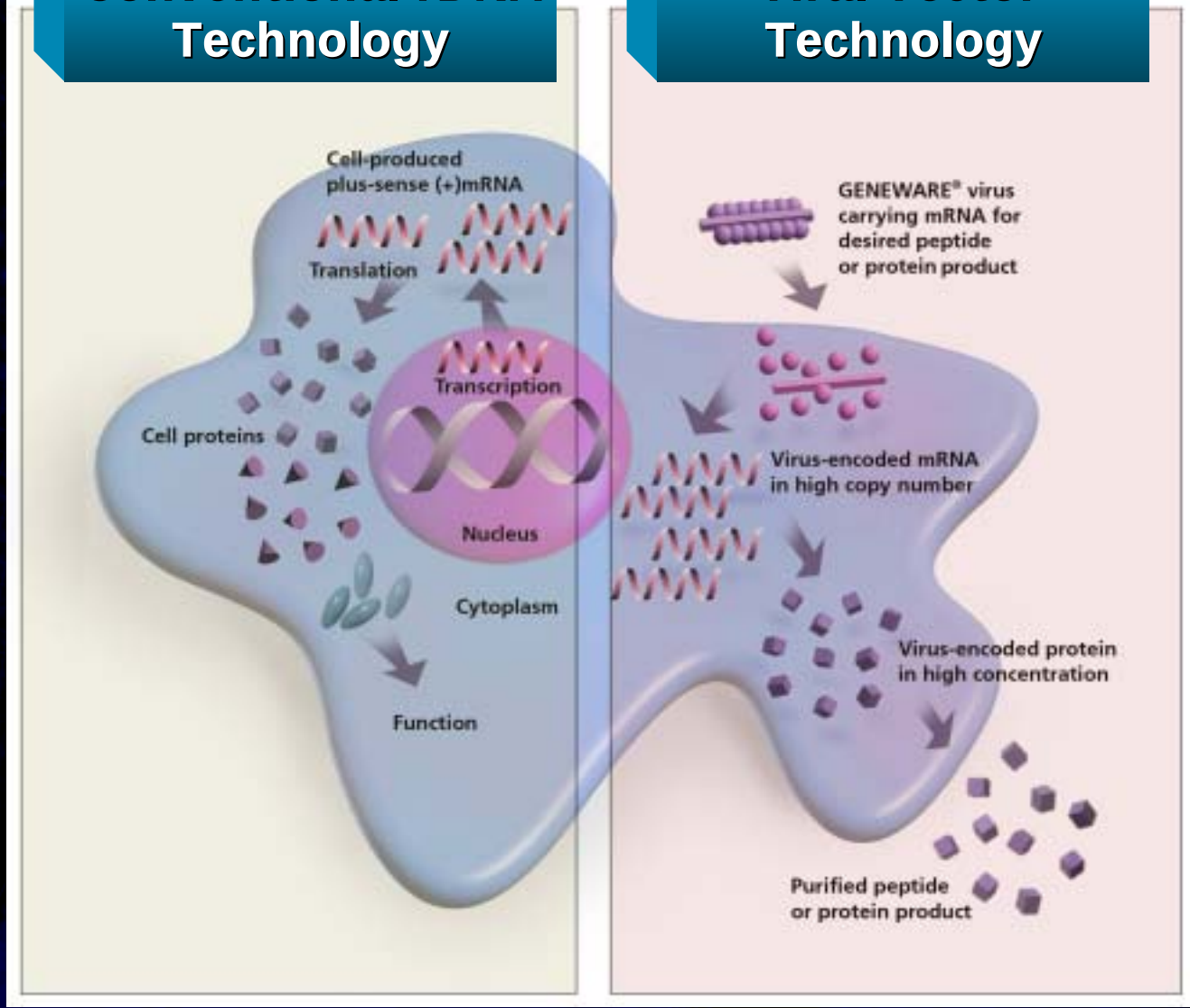
Evolution of a New Method for Biologics Manufacture

- New manufacturing paradigms do not come easy
- 15 years from concept to products in the clinic
- Plant made products as a platform
- The proof is in the products

Bioreactors

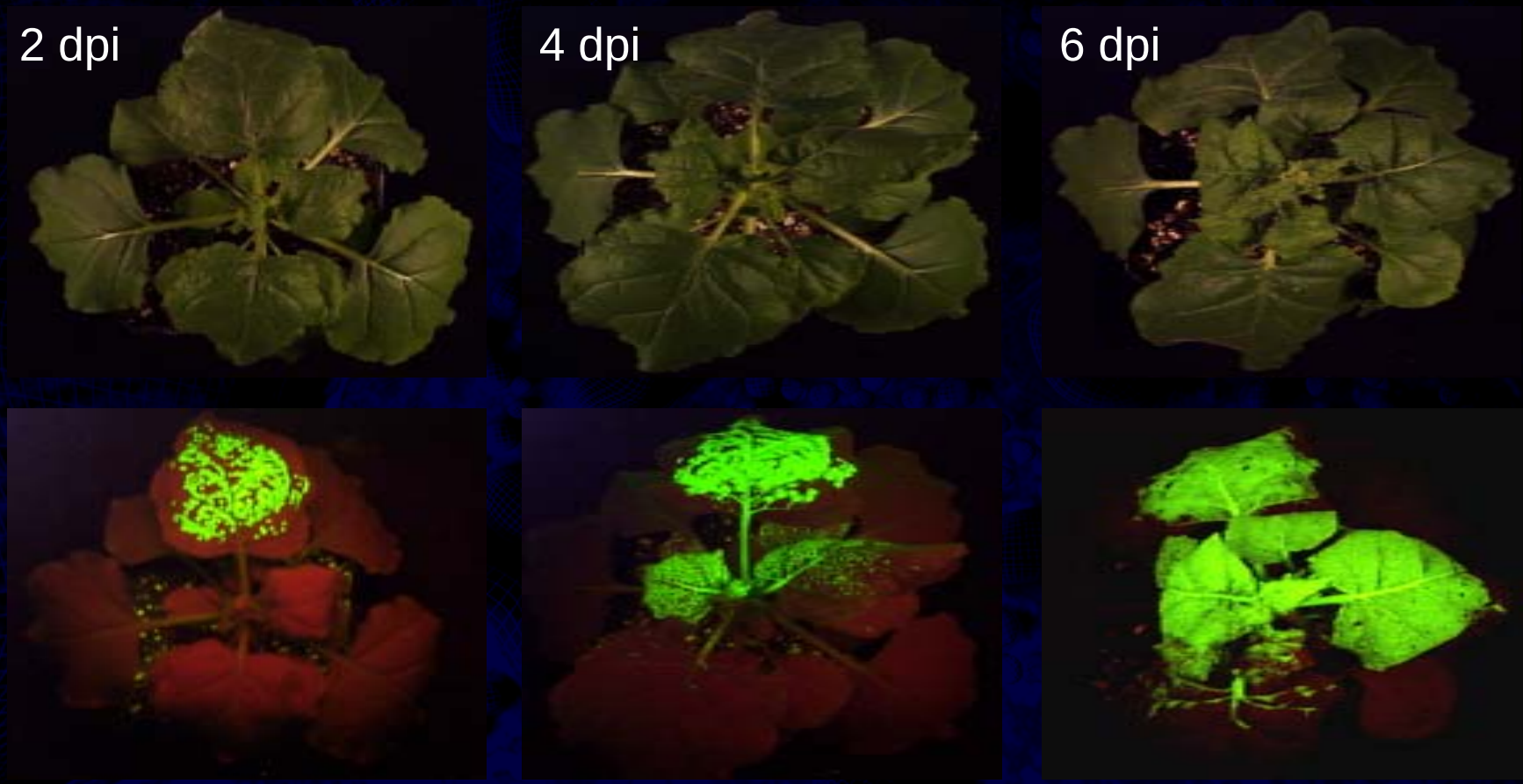
Conventional rDNA Technology

Viral Vector Technology



Plants are Excellent Protein Production Factories

VIRAL VECTOR GFP EXPRESSION



Advantages of Plant Expression

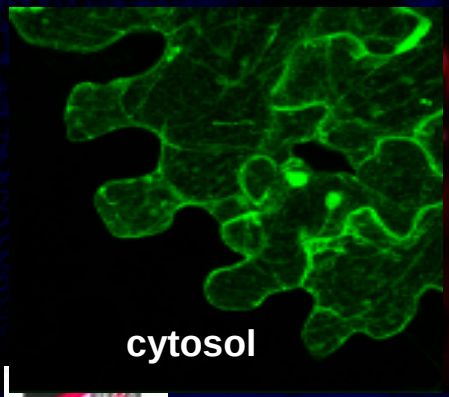
- **Proteins are produced in Eukaryotic cells**
  - Proper production of the protein,
  - Post translational protein modifications (disulfide bonds, glycosylation, etc).

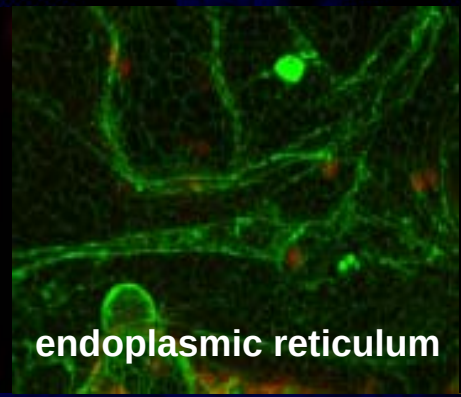
- **High expression levels**
  - Expression levels of 20-1000 mg/Kg fresh weight;
  - Adaptable to various manufacturing scales with rapid scale up capabilities;
  - Economies of scale through agriculture-based bioreactor.
- **Products suitable for this technology**
  - Therapeutic proteins; monoclonal antibodies
  - Subunit vaccine components

Distribution and Targeted Localization of Recombinant Protein in Plants

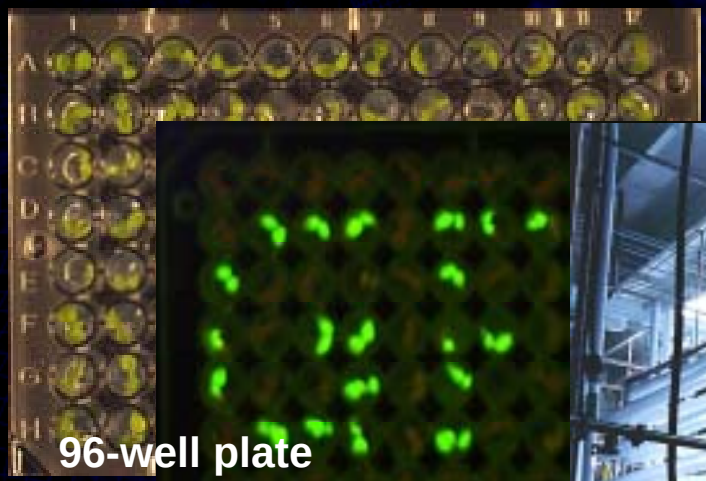
Distribution of expressed RNA and protein in infected plant

Targeted localization of proteins in infected plant cells.





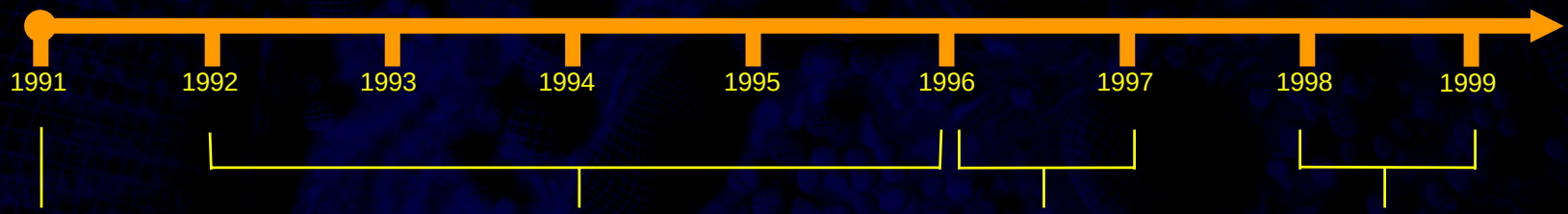
Plant Made Therapeutics
Allows Scale-Adaptable Protein Production



There are Few Well Developed Manufacturing Facilities

Large Scale Biology
USDA / APHIS-APPROVED OUTDOOR FIELD RELEASES

Recombinant Viral Vector Field Releases



First release of recombinant viral vector system

Multiple small-plot releases

Full-scale field release (12-15 acres)

Full-scale field release (35 acres) Policy clearance to 1000 acres

The FDA/USDA Guidance Document on Bioengineered Plants: History and Highlights

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History of the the Guidance Document

- 1999
  - White paper from industry group presented to FDA
  - FDA establishes topic as a priority
  - Working Group formed at FDA
  - USDA invited to join the Working Group
- 2000
  - FDA/USDA joint meeting in Ames, Iowa
    - Included open public hearing

History of the Guidance Document - 2

- 2000-2001
  - Guidance document drafted by Working Group
- 2001-2002
  - Review of Guidance document by counsel for FDA and USDA and input from EPA
- September 6, 2002
  - Guidance Document issued

The Main Principles of the Guidance

- Based on existing law
- Relies on USDA/APHIS/Biotechnology Regulatory Services Division
- Regulates the products the same way as similar products made by different technology
- Considers the field as part of the manufacturing facility
- Concentrates on issues unique to plant production systems

Considers the field as part of the manufacturing facility

“All fields used to grow source bioengineered pharmaceutical plants are subject to inspection by the USDA (7 CFR 340.4; 9 CFR 101-108) and/or by the FDA (42 U.S.C. 262; 21 U.S.C. 374).”

Concentrates on issues unique to plant production systems

- Host and source plant characterization
- Expression systems
- Seed banks
- Genetic stability
- Tissue Distribution
- Environmental considerations
- Confinement measures
- Special issues for unpurified products

Host plant characterization

Should include:

- **the potential for the plant to express an allergenic or toxic compound**
- **the method of plant propagation**
- **the measures necessary to ensure confinement**
- **if it is a food crop species, the measures to ensure that non-food (or non-feed) material will not get into food or feed**

Regulations Are Adequate and Effective

- Execution is the key
- Agriculture is as important as bioprocess
- Training of personnel and contractors
- Well developed protocols
- Long term land use planning

cGMP IS SOMETHING YOU DO, NOT SOMETHING YOU HAVE

Very Few Products have made it to the Clinic

- Monsanto/NeoRx - mAb for cancer therapy
- Meristem Therapeutcs - gastric lipase cystic fibrosis
- Large Scale Biology - patient specific cancer vaccine

Choice of Platform to Develop Pharmaceuticals in Plant

Target : Low cost monoclonal antibody for passive antibody therapy for drug abuse- PCP and methamphetamine acute and chronic treatment

Customer: Public healthcare system

Plants: Have the potential to meet cost, purity, and efficacy requirements

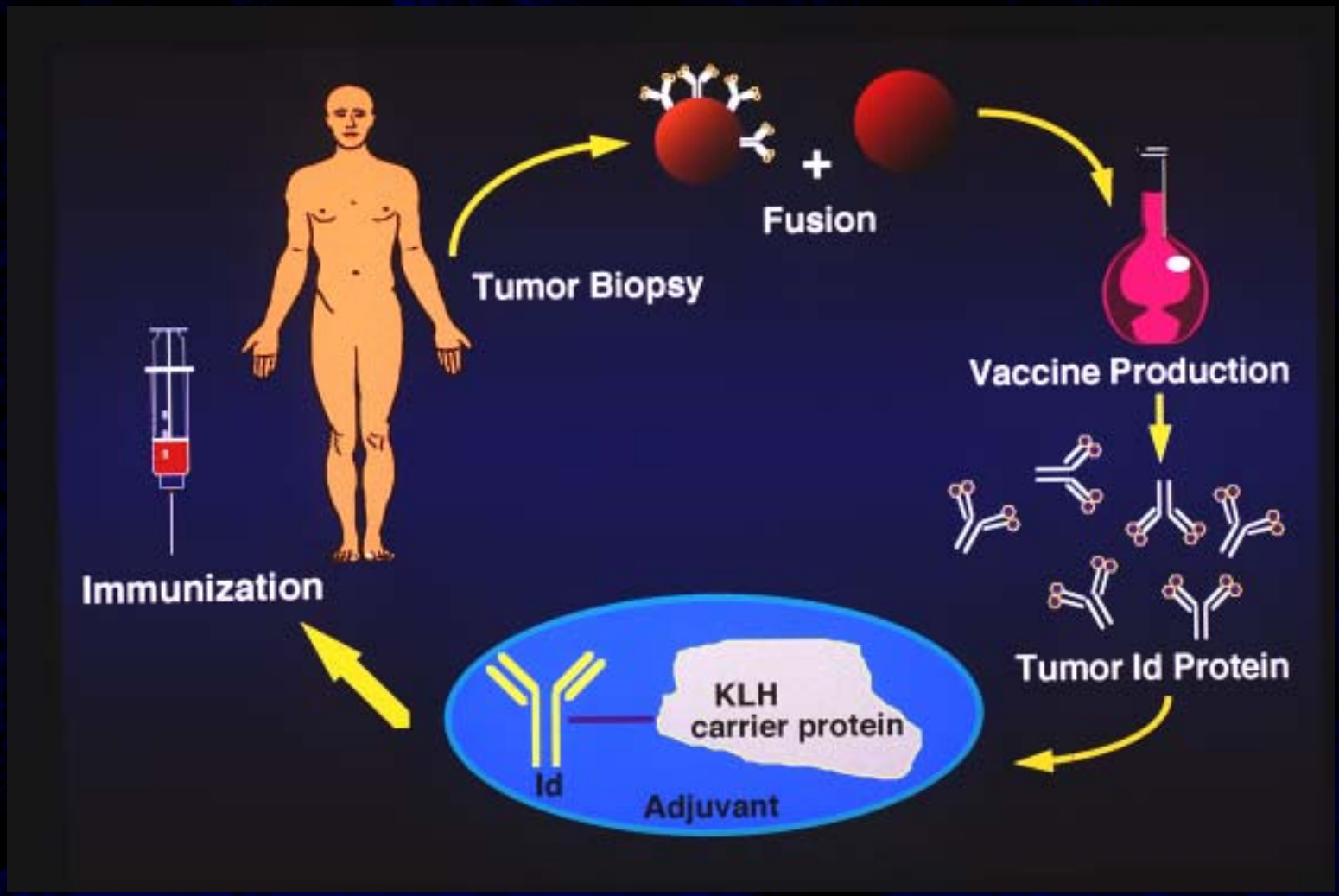
Scalable Process without large capital expense and time

Personalized Medicine with Plant Made Pharmaceuticals

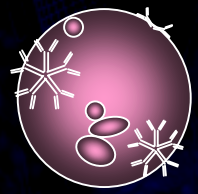
Patient Specific Vaccine for

Non-Hodgkins Lymphoma

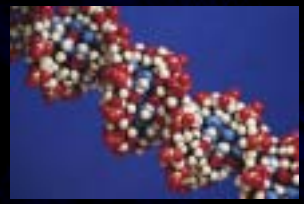
Hybridoma Produced Full Ig Vaccine



NHL Vaccine Process Overview



STAGE 1: Biopsy Processing



GENEWARE® vector

Identify tumor Ig genes

STAGE 2: Cloning the Variable Region Ig Sequences

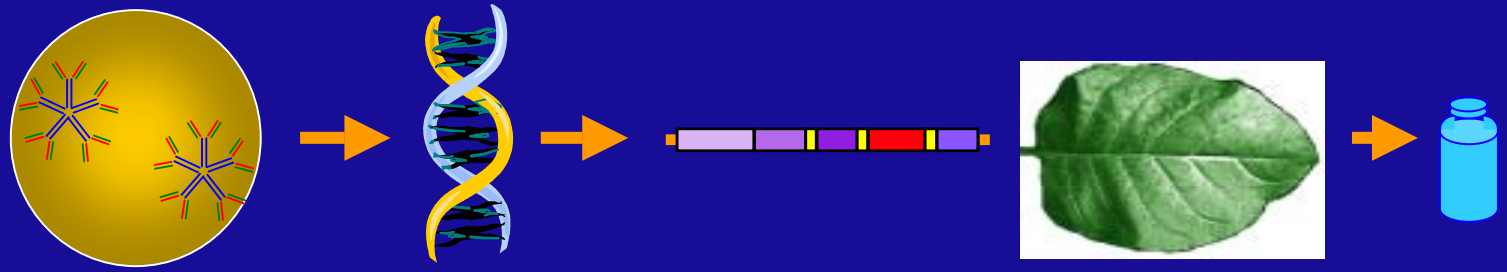
STAGE 3: Cloning and Selection

STAGE 4: Downstream Purification

STAGE 5: Finish and Fill

Distribute to pharmacies of clinical centers

Patient-Specific Vaccine for Treatment of Non-Hodgkins Lymphoma

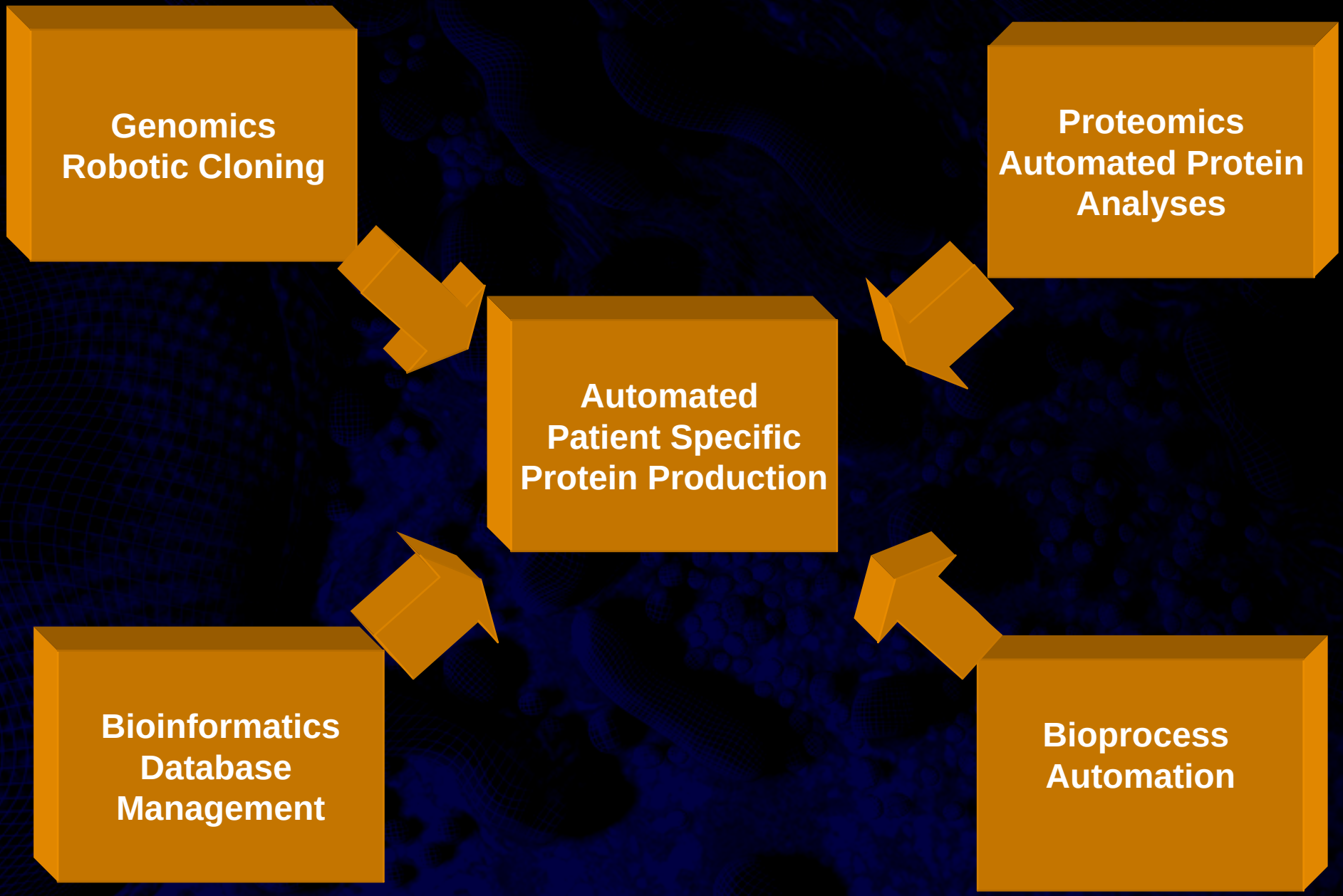


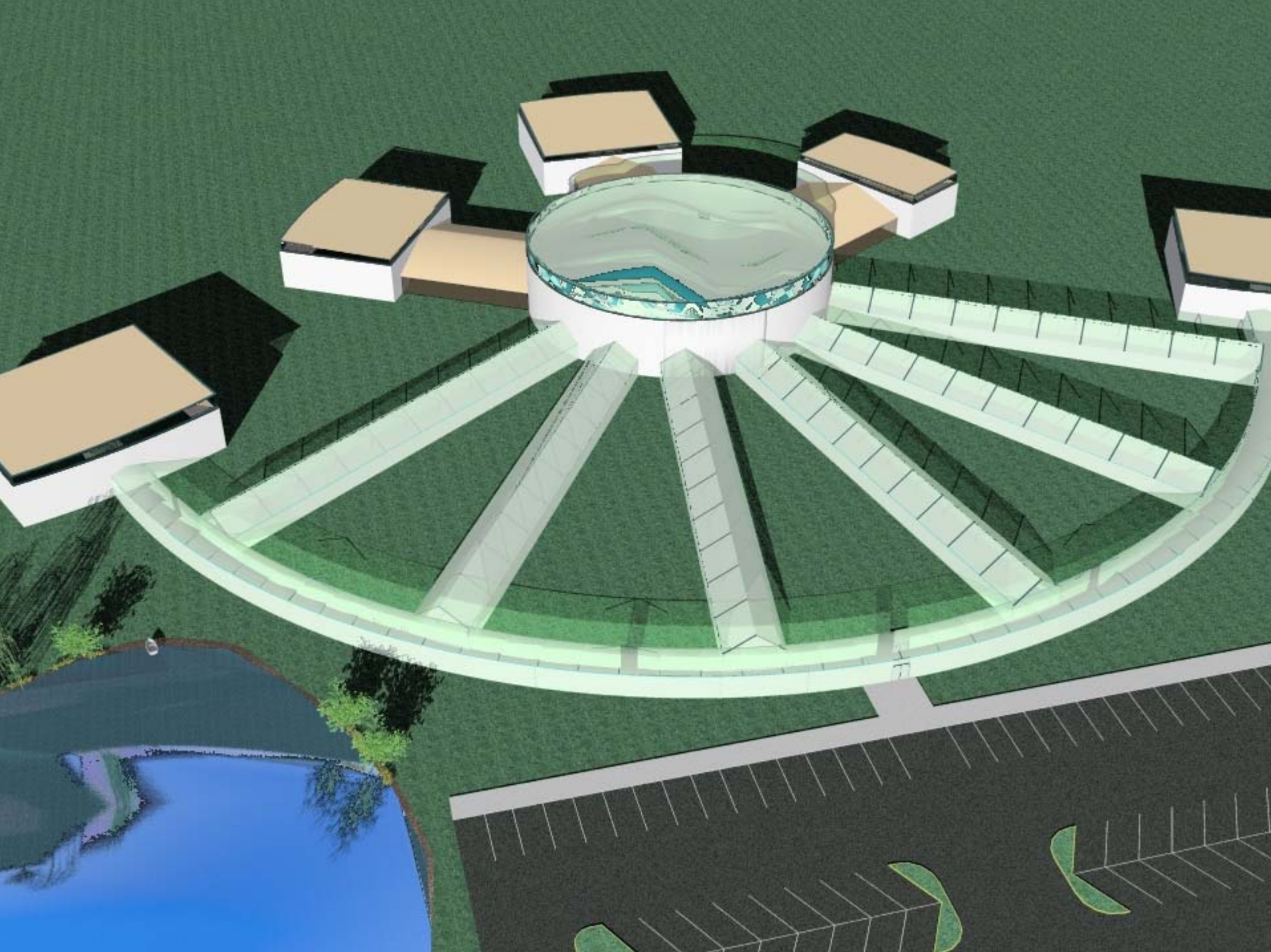
LSB's production process: 6-10 weeks

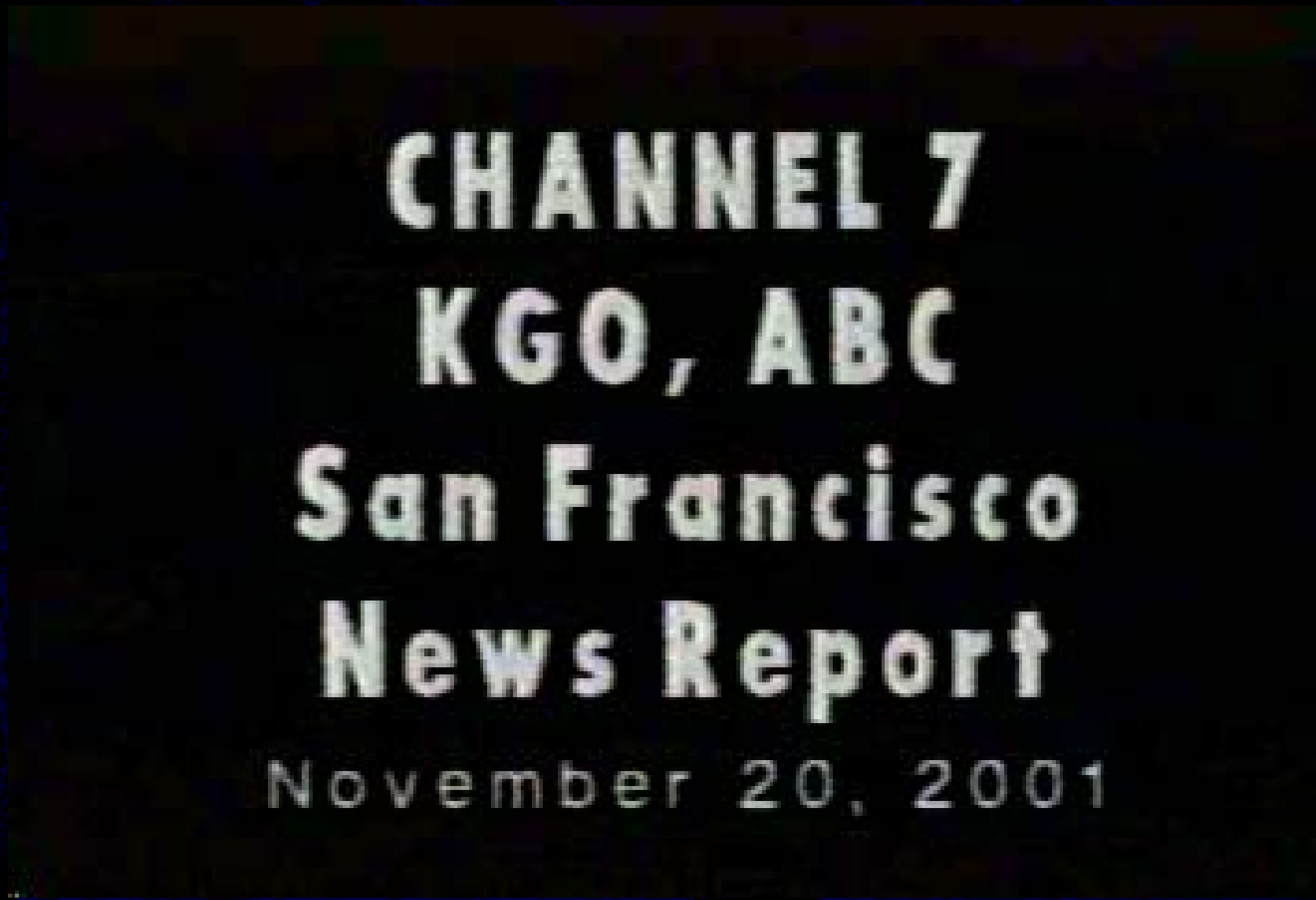
Traditional process: 1 year

NHL Clinical Development

- Completion of the Phase I clinical study
  - No adverse events in 16 individual drug products
    - 15 glycosylated vaccines
  - Good immunogenic response – indication of efficacy
    - Large percentage of patients made cellular or humoral responses
  - Demonstration cGMP manufacturing capability
  - Demonstration of ability to administer a clinical trial
  - Excellent communication and review by FDA
- Request for review for Phase III trial in to FDA
  - Special Assessment Protocol preparation


Genomics
Robotic Cloning
Proteomics
Automated Protein
Analyses
Automated
Patient Specific
Protein Production
Bioinformatics
Database
Management
Bioprocess
Automation

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