

Development of a Rapid Production System for Pandemic Influenza Vaccines

medicAGO

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Forward Looking Statements

All statements, other than statements of historical facts, included in this presentation regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The words "believe", "anticipate", "estimate", "plan", "expect", "intend", "may", "project", "will", "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements, including the factors discussed under "Risk Factors" and in other sections of the prospectus. These factors and the other cautionary statements made in the prospectus should be read as being applicable to all related forward-looking statements wherever they appear in this presentation.

Our statements of "belief" in respect of our product and partner product candidates are based primarily upon our results derived to date from our research and development program. We believe that we have a reasonable scientific basis upon which we have made such statements. It is not possible, however, to predict, based upon studies in vitro and animal studies whether a new therapeutic agent or technology will be proved to be safe and/or effective in humans. We cannot assure that the particular results expected by us will occur.

Any forward-looking statements and statements of "belief" represent our estimates only as of the date of the prospectus and should not be relied upon as representing our estimates as of any subsequent date. Except as required by law, we do not assume any obligation to update any forward looking statements or statements of "belief". We disclaim any intention or obligation to update or revise any forward-looking statements or statements of "belief", whether as a result of new information, future events or otherwise.

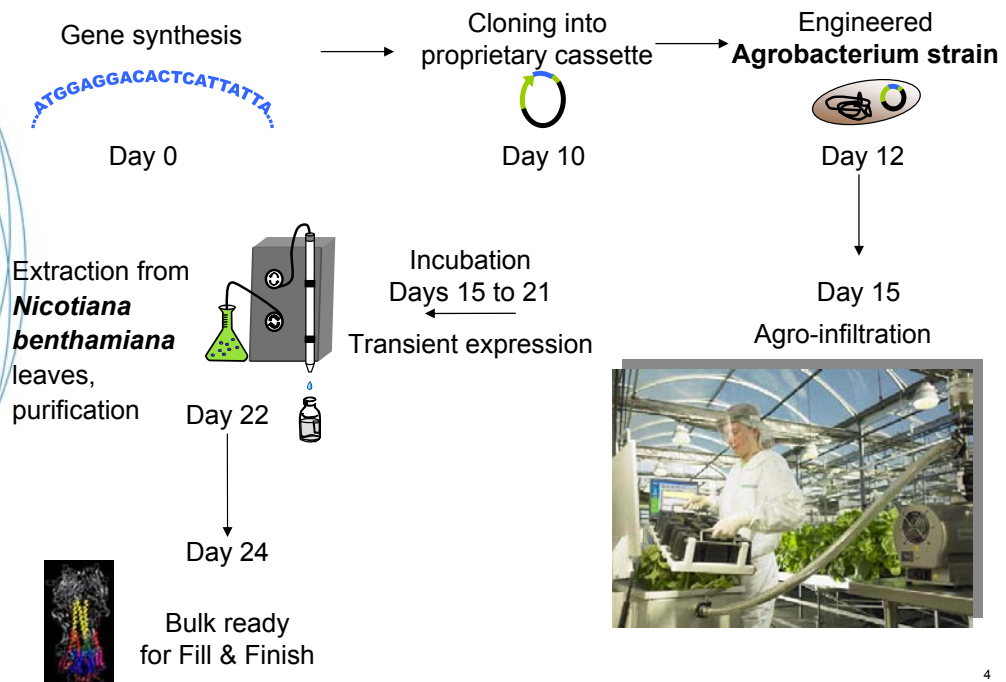
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Medicago at a glance

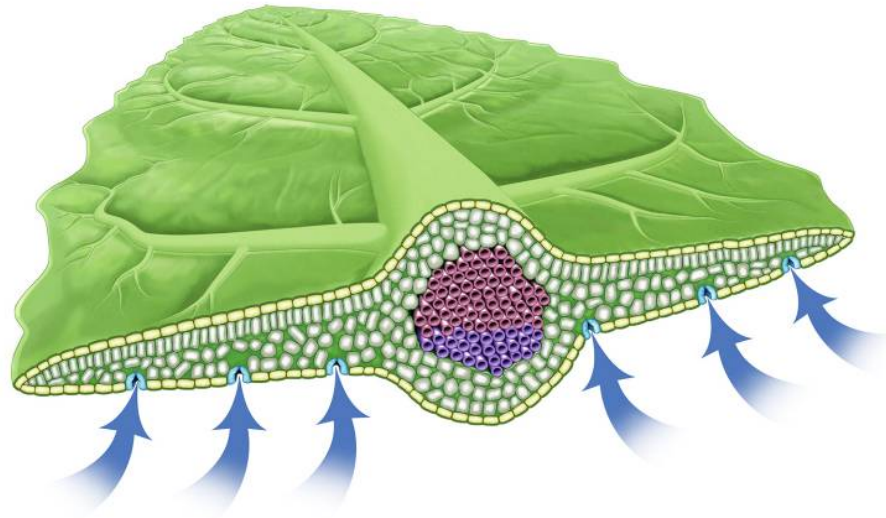
| | |
|---------------------------|--|
| Focus | Influenza Vaccines |
| Technology | VLP technology in plants |
| Principle | Transient expression in plants to produce recombinant proteins |
| Headquarters | Quebec City, QC |
| Employees | 50 |
| Public company since 2006 | TSX-V : MDG |



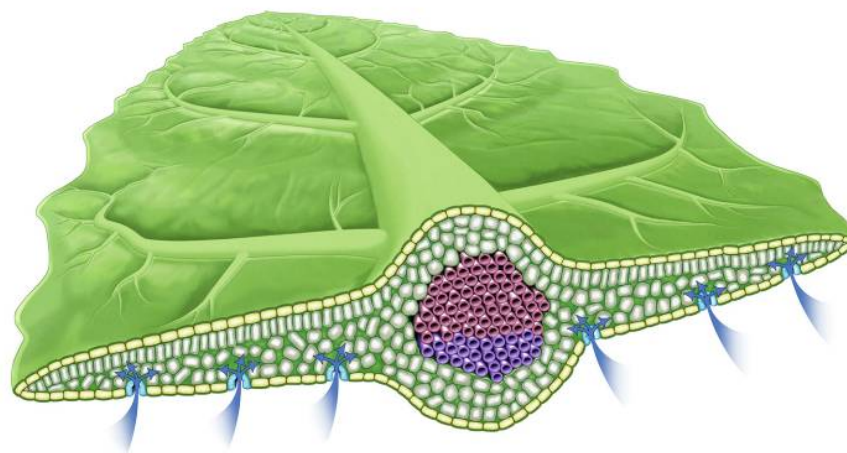
Production by transient expression



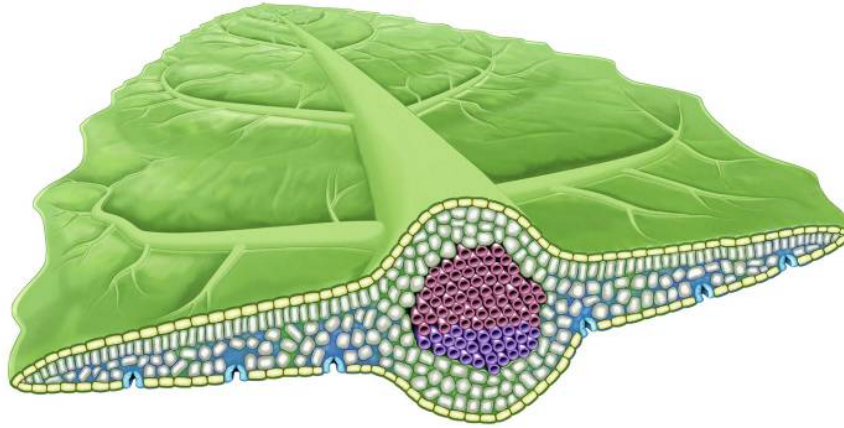
Agroinfiltration, the principle



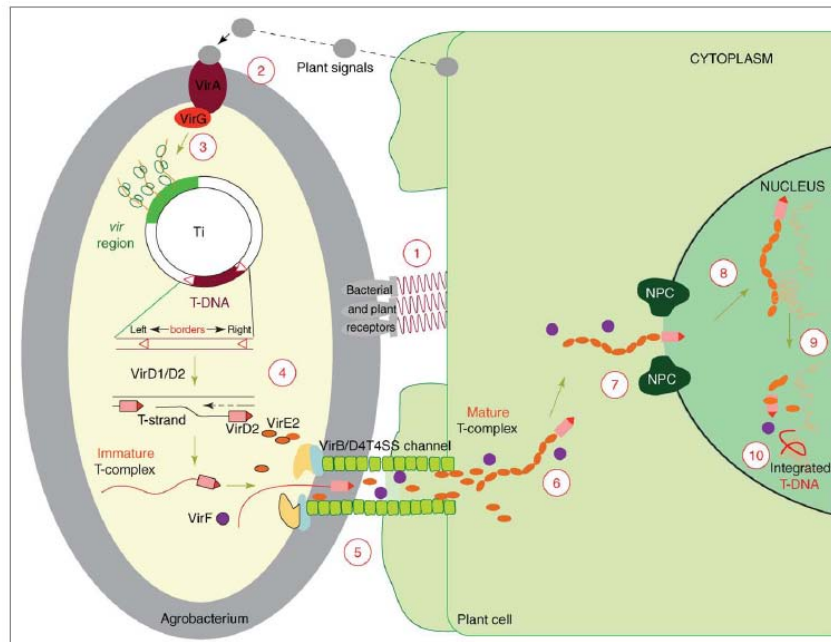
Agroinfiltration, the principle



Agroinfiltration, the principle



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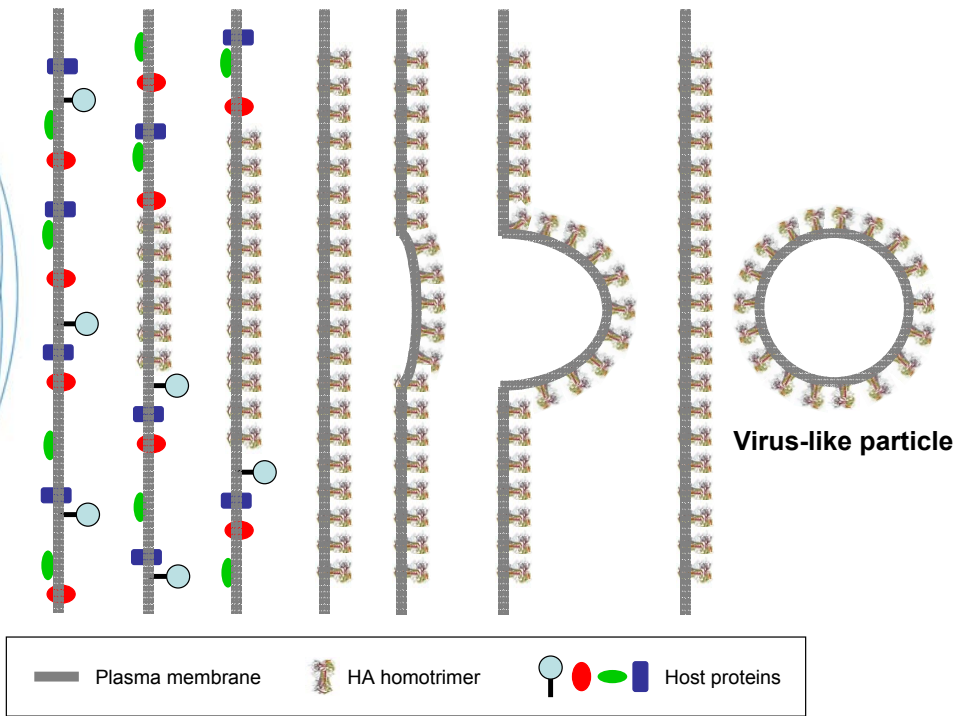


A model for the *Agrobacterium*-mediated genetic transformation. The transformation process comprises 10 major steps and begins with recognition and attachment of the *Agrobacterium* to the host cells (1) and the sensing of specific plant signals by the *Agrobacterium* VirA/VirG two-component signal-transduction system (2). Following activation of the *vir* gene region (3), a mobile copy of the T-DNA is generated by the VirD1/D2 protein complex (4) and delivered as a VirD2-DNA complex (immature T-complex), together with several other Vir proteins, into the host-cell cytoplasm (5). Following the association of VirE2 with the T-strand, the mature T-complex forms, travels through the host-cell cytoplasm (6) and is actively imported into the host-cell nucleus (7). Once inside the nucleus, the T-DNA is recruited to the point of integration (8), stripped of its escorting proteins (9) and integrated into the host genome (10). A detailed model of the host cellular mechanisms and the role of plant-specific factors in the transformation process are given in Figure 2. (This illustration was reproduced, with modifications, from [28] with permission.).

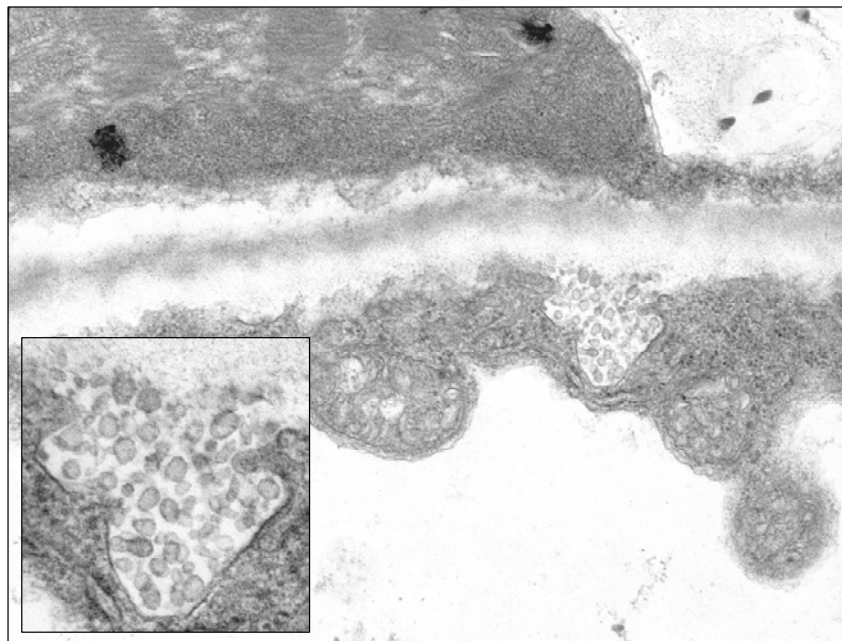
Figure 3. Illustration of *Agrobacterium* infection of a plant cell. From Tzfira and Cytovsky, *Current Opinion in Biotechnology* 2006, 17:147-154.

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HA accumulation and VLP formation

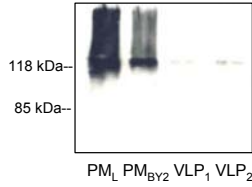


Influenza VLP accumulation site

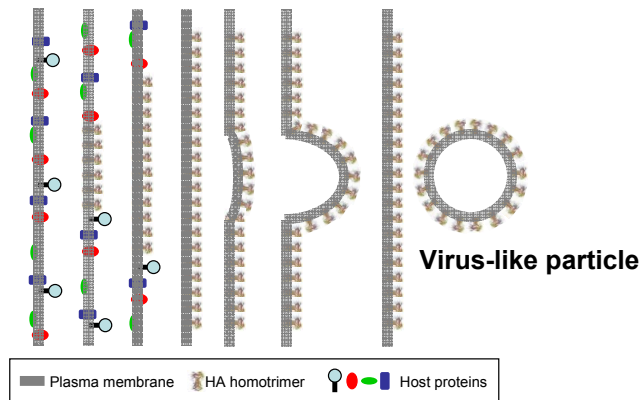


Host membrane proteins are excluded from VLPs

Western blot: antibodies to PMA

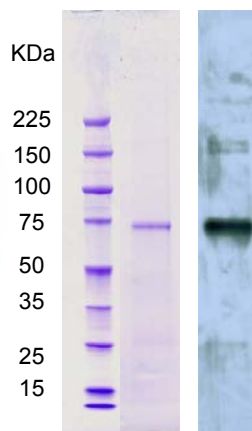


Immunodetection of plasma membrane marker, Proton pump ATPase (PMA) in purified VLP (two independent samples, VLP1, VLP2) and highly-purified PM from tobacco leaves (PML) and BY2 tobacco cells (PMBY2).



Certificate of Analysis of GMP H5/VLP material

Identity: rHA5, confirmed by Coomassie-stained SDS-PAGE & by Western blot analysis



| | |
|-----------------------|---|
| Concentration in rHA: | 105 µg/ml ± 2% |
| Purity of rHA: | 95% |
| Microbial count: | None |
| DNA: | < 10 ng/dose (Below spec. for human use) |
| Endotoxins: | < 100 EU/dose (Below spec. for human use) |

The production of enveloped VLPs in Nicotiana

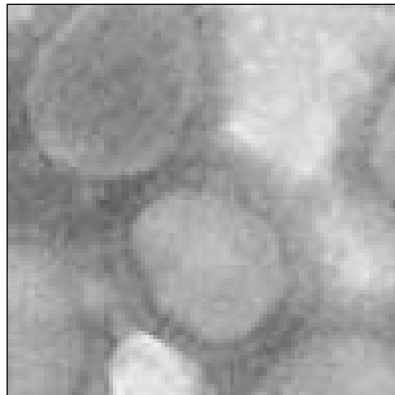
- In mammalian species, Influenza particles bud from lipid rafts of the plasma membrane and require NA for release
- It is now possible to produce enveloped VLPs formed in plants without the need of NA to be released
- M1 protein is not required for VLP assembly
- Structure needs to be conserved in the extraction and purification steps
- Plant lipids are part of the VLP
 - Potential adjuvant effect
 - Stimulation of immune effector cells

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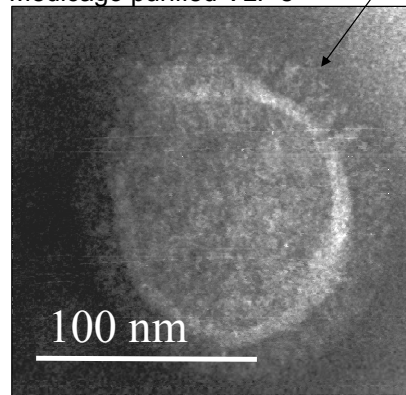
VLP vaccine technology

Lead product: H5N1

Influenza Virus



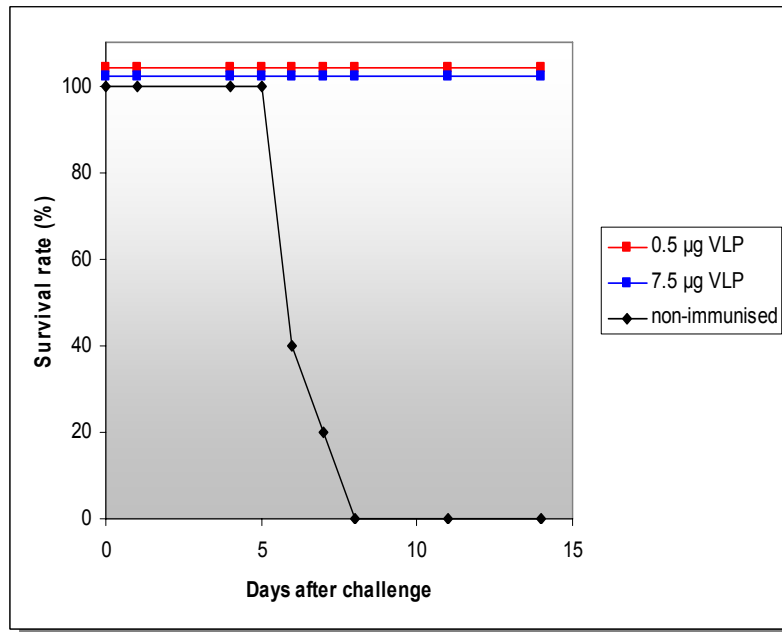
Medicago purified VLP's



- Morphology and size similar to Influenza virus
- Reproducible system
- Not infectious and highly immunogenic

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Mice: VLPs induce protection against an influenza strain of a different clade (A/Vietnam/1194/04, clade 1)



- Challenge with 10 LD₅₀

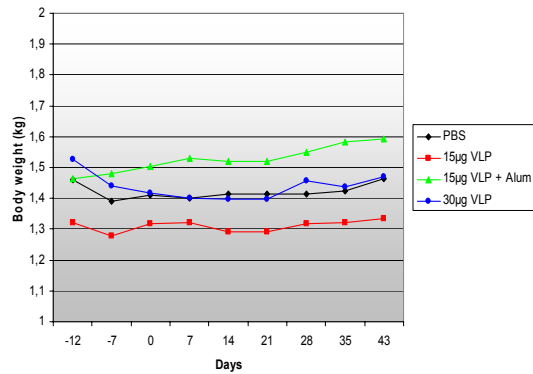
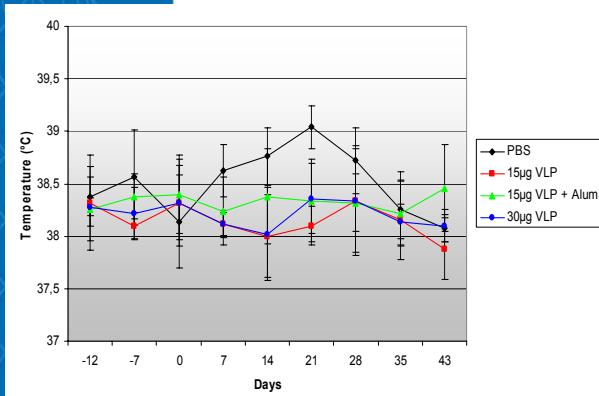
Ferrets: VLP vaccine meets 3/3 of the CHMP* criteria for candidate pandemic vaccines after a single dose

- Two groups met the 3 CHMP criteria after the first dose
 - 5 µg & 15 µg
- All groups were adjuvanted with alum

| Day | Criteria | Study group | | |
|--------------------|---------------------------------------|-------------|------|-------|
| | | 1 µg | 5 µg | 15 µg |
| 14 (post 1st inj.) | >40% with 4-fold increase in HI titer | 100% | 100% | 80% |
| | Mean geometric increase of 2.5 | 7.6 | 15.6 | 11.2 |
| | >70 % with HI titer of 1/40 | 60% | 100% | 80% |
| | Mean HI titer | 38 | 78 | 56 |

* European Committee of Medicinal Products for Human Use (CHMP) criteria for licensure of influenza vaccines
 1. Number of seroconversion or significant increase in HI titers (4-fold) >40%
 2. Mean geometric increase of 2.5
 3. The proportion of subjects achieving an HI titer of 1/40 should be >70%

Ferrets: Safety of the VLP vaccine



- Immunisations on days 0 and 21
- No statistical difference in body temperature (except for PBS)
- No statistical difference in body weight
- No local reaction observed
- Injection site looked normal at necropsy

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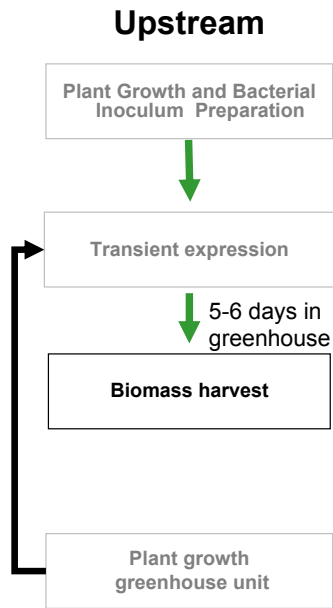
Pilot cGMP facility

- Current setting: 1400 sq meters
 - ① 1000 sq. meters BL2+ greenhouses (850 m2: growth of non-transgenic plant -130 m2: incubation after *Agrobacterium* vacuum-infiltration)
 - ② 30 sq. meters purification (2 Control rooms)
 - 20-25 people (development + production)
 - One batch a week (25kg)



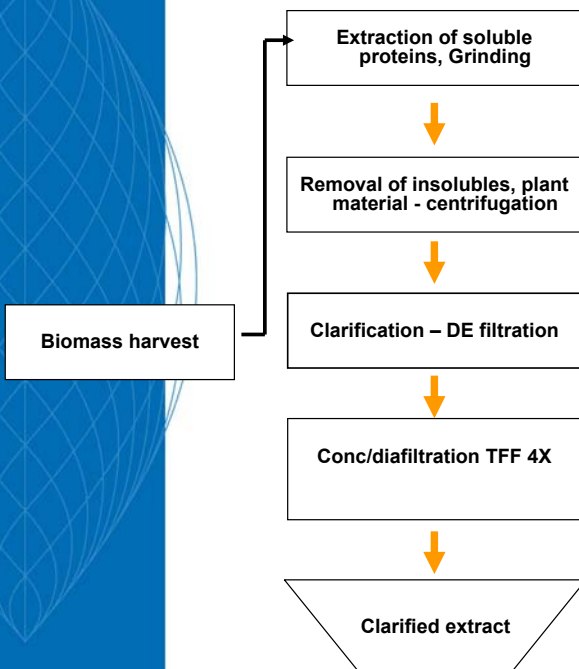
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Process development for cGMP production



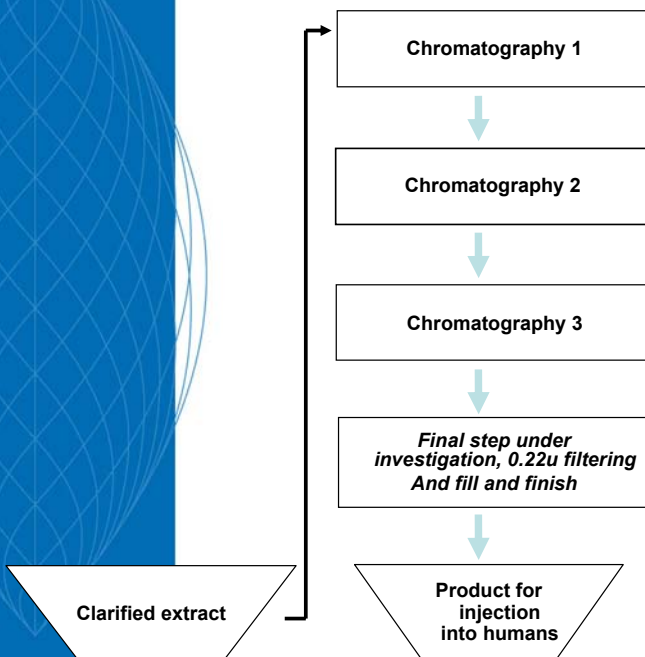
Process development for cGMP production

Primary Recovery



Process development for cGMP production

Purification



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cGMP Production

- Medicago's manufacturing operations are driven by simplicity to best answer the need for fast response to pandemic issue.
- This contributes to:
 - Effective and Efficient Manufacturing
 - Efficient Process Control
 - Easier Product Lifecycle Management
 - Lower Costs
 - Easier Technology Transfer

All quality improvement comes via simplification of design, manufacturing layout, processes and procedures

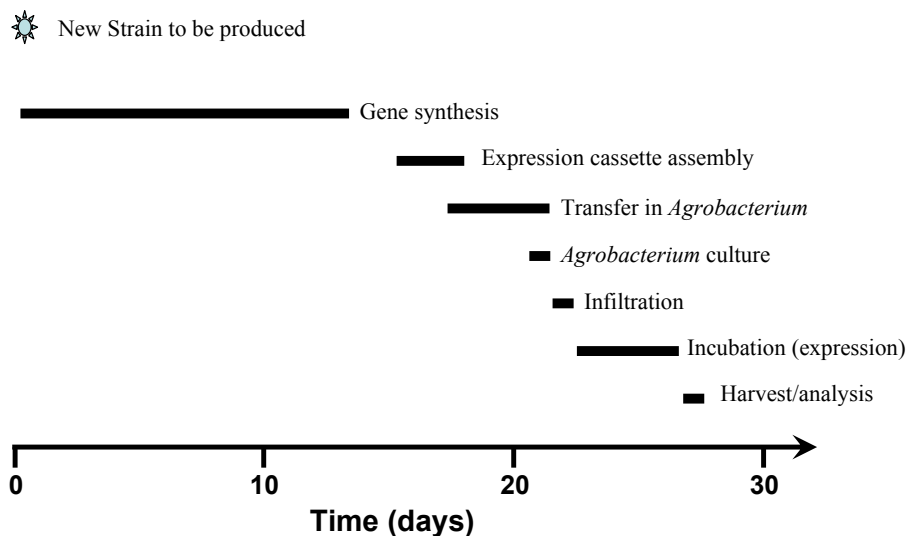
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Production of Pandemic Influenza Vaccines

| Limitations of current technology | Medicago's technology |
|---|---|
| Limited egg supply | Plants are already grown (standby) |
| Unknown yield for pandemic strain | Production of a recombinant protein/Not dependent on viral replication |
| Limited number of facilities worldwide | Easy technology to transfer |
| Current technologies are costly | Lower costs of capital and operational expenses |
| Vaccine dosage-2 dose regime with highly concentrated product | Low dose was demonstrated in mice/ferrets 5 mcg |
| Current technologies too slow to be ahead of pandemic wave | Rapid production systems that can deliver final product ahead of a pandemic wave |

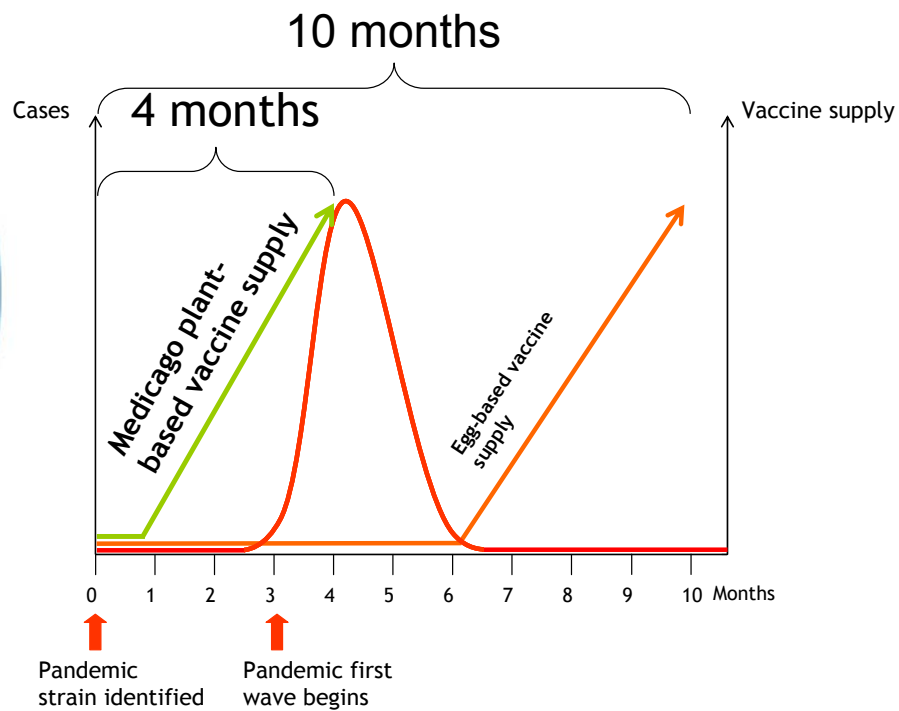
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Reaction time



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Pandemic - Medicago solution = First responder



Challenges for plant-based products

New substrate – standardization & control procedures

Some new Analytical tools

Data are required to prove:

- *Quality*
- *Safety*
- *Efficacy*
- *Process control*
- *Stability*

Same as for all other regulated products

Medicago's approach

It is a known fact that biological products are influenced by their process and that for regulatory agencies:

“the process is the product”

So understanding the process and the product is the key element for success ⇒ Quality by Design

Knowledge is the a key element to Quality

Rafael Aguayo, Author on Quality

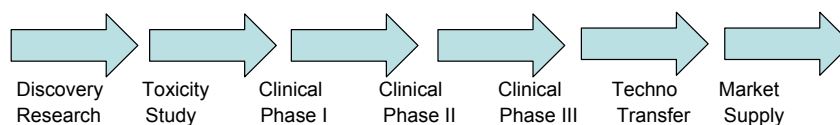
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Quality by Design at Medicago

Categories being used with the Quality by Design approach

Two categories throughout the product phases of development

1. Product/Process design and performance
2. Product Lifecycle Management



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Approach with Quality by Design

| Quality by Design | | |
|--|-----------------|--|
| Understand the product | Desired product | Product Performance Product Specifications |
| | Product design | Dosage form Stability Formulation Product Quality Attributes |
| Understand the process | Desired process | Process Performance Process Capability Process Control Process Robustness |
| | Process design | Process Parameters |
| Product Lifecycle Management: Continuous improvement | | |

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Quality by Design at Medicago

Product/Process

- Product development is from organized systems and methods
- Science-based understanding of the process and the product, using adaptable parameters according to verified design range
- Product and process specifications based on understanding the items that affect product performance

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Quality by Design at Medicago

Product Lifecycle Management

- Quality Assurance is present from the discovery phase with effective understanding of appropriate regulations from the start
- Control Strategy consists of risk-based approaches based on:
 - Risk assessment with scientific understanding
 - Relation between capability of process and product quality and performance
 - Plan for risk mitigation

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It is not a question of how well each process works, but the question is how well they all work together

Lloyd Dobens and Clare Crawford, Thinking on Quality

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