

Mitsubishi Tanabe Pharma Corporation



R&D Meeting 2017

Vaccine Business Strategy

September 27, 2017 (Wed.)

Seiichi Murakami

**Managing Executive Officer,
Division Manager of Ikuyaku. Integrated Value Development Division**

Today's Agenda

- 1** What is Vaccine?
- 2** The External Environment in the Vaccine Business
- 3** MTPC's Vaccine Business Strategy
 - ▶ Aiming to Strengthen Domestic Business
 - ▶ Overseas Business Strategy
- 4** Medicago's VLP* Technologies
(Medicago President Bruce Clark)

* VLP: Virus Like Particle

What is Vaccine?

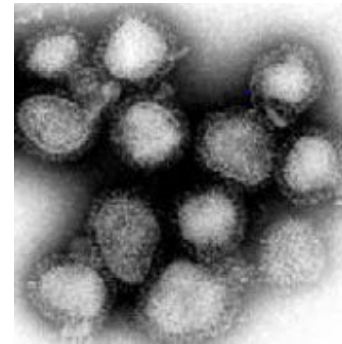


Pathogens that Cause Infectious Diseases

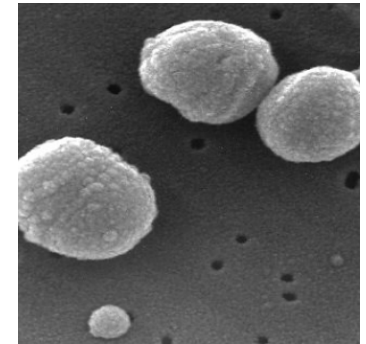
Viruses (30–300nm)

Influenza, Rabies, Varicella, Polio, etc.

➡ Antiviral agents, vaccines



Influenza



Streptococcus pneumoniae

Bacteria (3 μm)

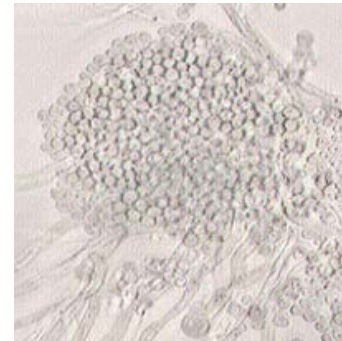
Streptococcus pneumoniae, Pertussis, Diphtheria, Tetanus, etc.

➡ Antibiotics, vaccines

Fungi (Several μm–several dozen μm)

Candida, Cryptococcus, etc.

➡ Antifungal agents



Candida



Malaria

Protozoa / parasites (Several μm–several hundred μm)

Malaria, Amebic dysentery, etc.

➡ Antiprotozoal agents

Viral Diseases Since Ancient Times



Pockmarks

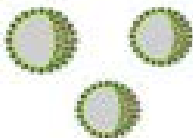
The Pharaoh Ramses V mummy
Died of smallpox, 1196 BC
<http://www.tulane.edu/>



Paralysis sequelae

Priest with polio,
lithograph from circa 1400 BC
Found at Memphis, capital of ancient Egypt

Types and Features of Vaccines

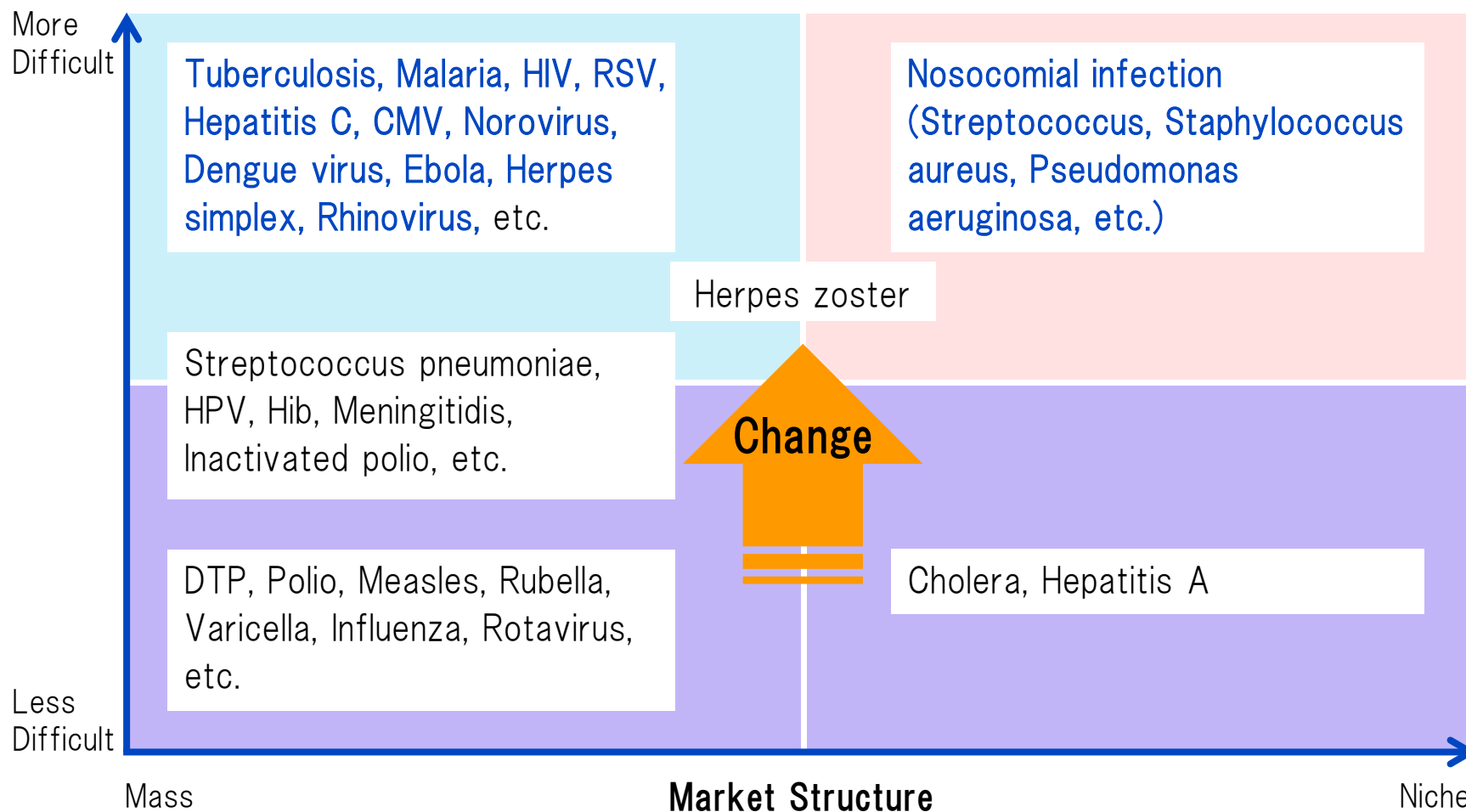
		Antibodies	Adverse effects
Live Attenuated Vaccines 	Measles, Rubella, Mumps, Varicella, Rotavirus, Yellow fever, BCG	+++	+++
Inactivated Vaccines 	Influenza, Japanese encephalitis, Hepatitis A, Hepatitis B, Polio, Streptococcus pneumoniae, Hib, DPT	+	+ ~ ++
New Vaccines 	VLP vaccines, etc. (HPV, Influenza)	+ ~ +++	—

Existing Vaccines (Periodic Vaccinations)

		U.S.	Germany	Japan
Pediatric	DTaP: diphtheria, tetanus, pertussis	○	○	○
	Polio	○	○	○
	MR: measles-rubella	○	○	○
	Hib	○	○	○
	Streptococcus pneumoniae	○	○	○
	HPV: human papilloma virus	○ (Male/female)	○	Temporary halt
	Meningitidis (ACYW) (B)	○	○	
	Mumps	○	○	
	Hepatitis A	○		
	Hepatitis B	○	○	○
	Rotavirus	○	○	
	Chickenpox	○	○	○
	Influenza	○		
	Tuberculosis			○
	Japanese encephalitis			○
Adult	Influenza	○		
	Td/Tdap*	○		
	MR: measles-rubella	○	○ (Measles only)	
	Mumps	○		
	HPV: human papilloma virus	○		
	Chickenpox	○		
Seniors	Streptococcus pneumoniae	○	○	○
	Herpes zoster	○		
	Influenza	○	○	○
	Td/Tdap*	○		

* Td: diphtheria (half dose), tetanus; Tdap: diphtheria (half dose), tetanus, pertussis

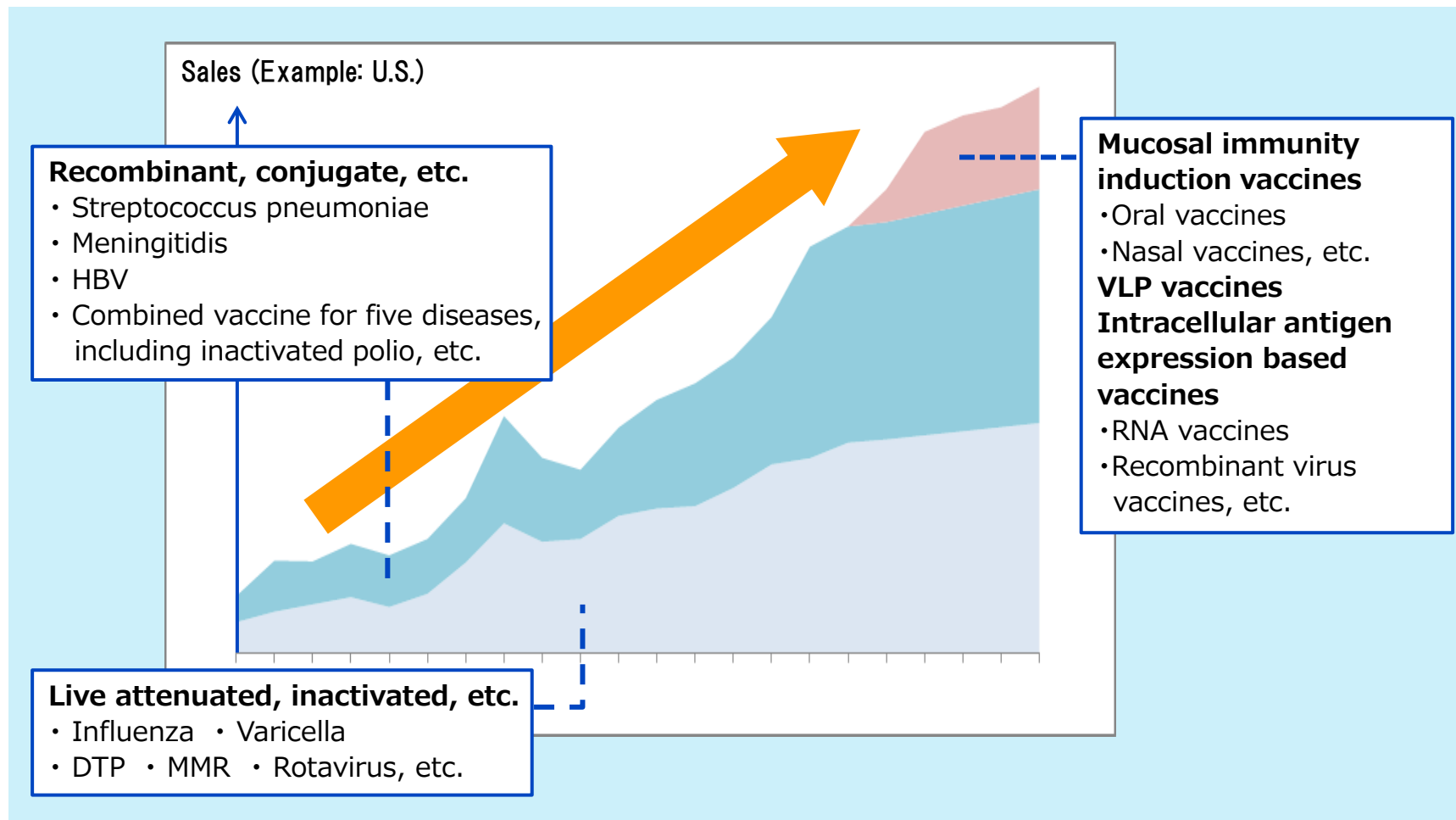
Vaccine Target Diseases (Current-Future)



HIV; human immunodeficiency virus, RSV; respiratory syncytial virus, CMV; cytomegalovirus, HPV; human papilloma virus, DTP; Diphtheria, Tetanus, Pertussis

Progress in Vaccine Technologies

Technical innovation has led to increases in types of vaccines and in improved vaccines



The External Environment in the Vaccine Business



Operating Environment in the Vaccine Business

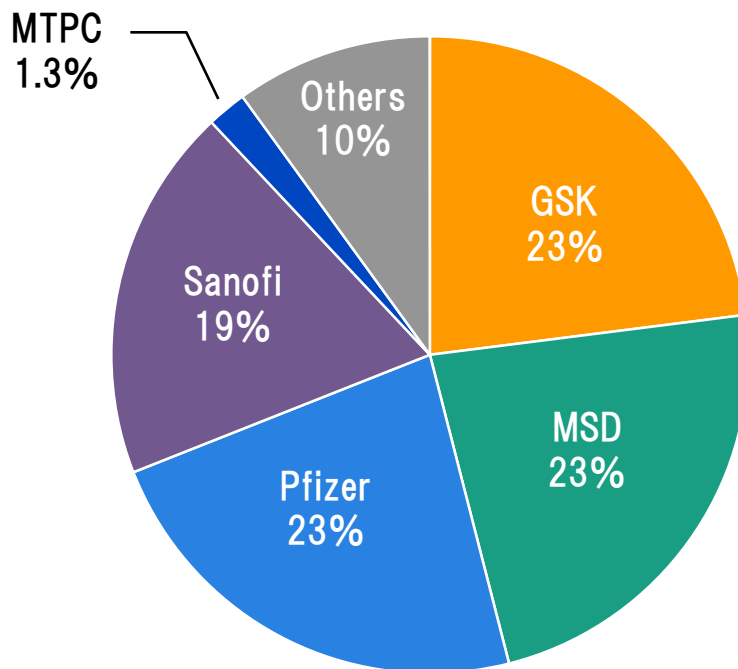
- ▶ Vaccination and vaccines are an indispensable health care service for the protection of human life and safety. With a basic philosophy that vaccine-preventable diseases should be prevented, the Japanese government has declared that vaccines are not just a countermeasure to infectious diseases but a foundation of national security.
- ▶ Vaccines are difficult to develop. In addition, from the pre-approval stage, vaccine developers must face the risks involved in building facilities capable of mass production. In this setting, barriers to entry are high, and a few large companies have an oligopoly.
- ▶ On the other hand, in recent years, a *Streptococcus pneumoniae* vaccine, HPV vaccine, and other vaccines have been launched, and the market has expanded. In addition, the 2009 pandemic vaccine issues reconfirmed the necessity of stockpiling vaccines and developing new technologies, and this field has become the focus of attention.
- ▶ Moving forward, new and improved vaccines will be needed, and with new technologies, it will be possible to enter this field.

Global Vaccine Market

Vaccine market share (2016)

Market scale: \$26,000 million

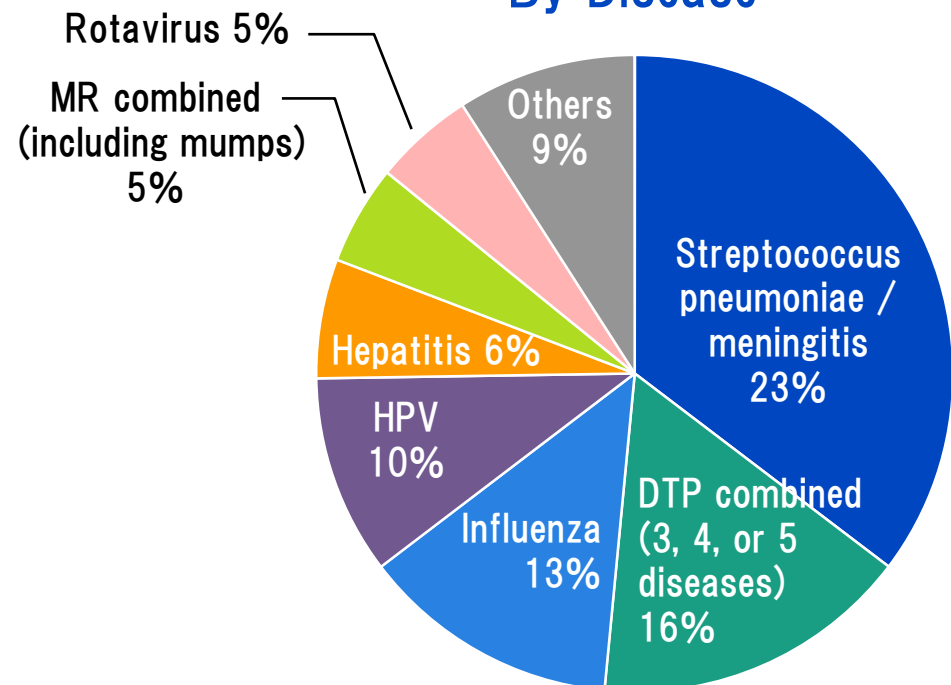
By Company



Four large companies (GSK, MSD, Pfizer, Sanofi) have the majority of the market (88%)

Source: Prepared from Evaluate pharma

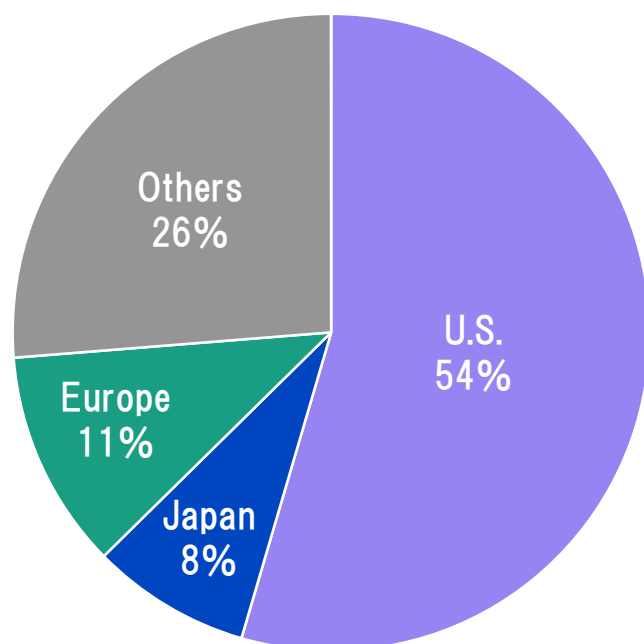
By Disease



No. 1: Streptococcus pneumoniae;
No. 2: pediatric combined,
No. 3: influenza

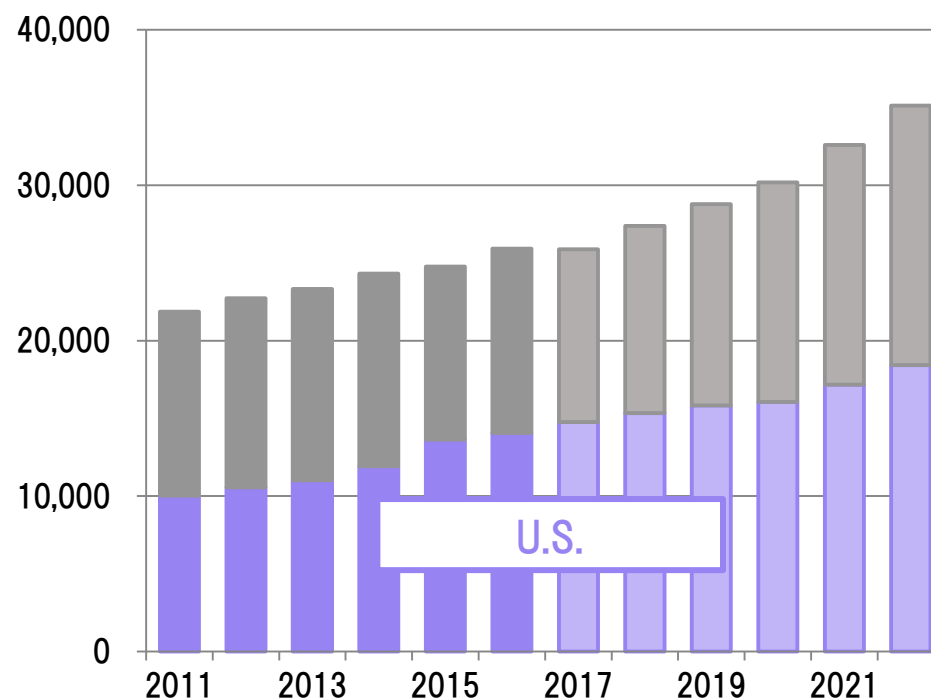
Vaccine Market by Region

Market share by country (2016)



Market forecasts (2011-2022)

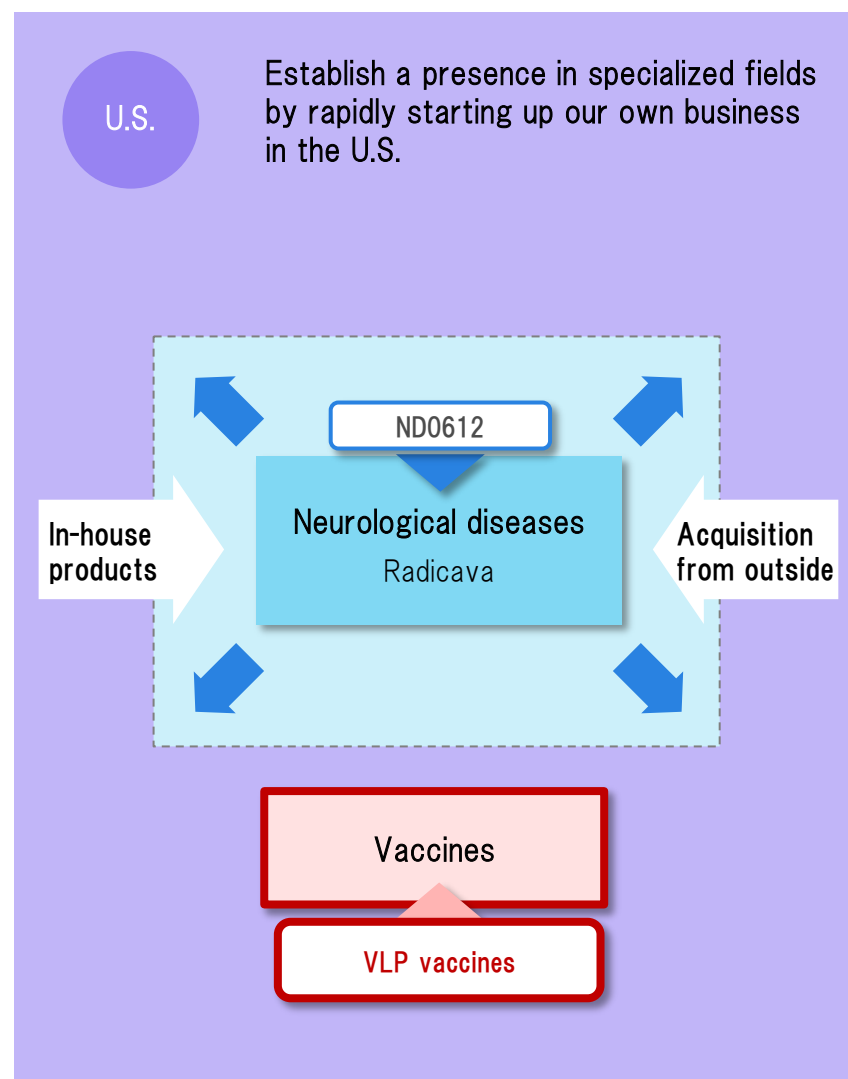
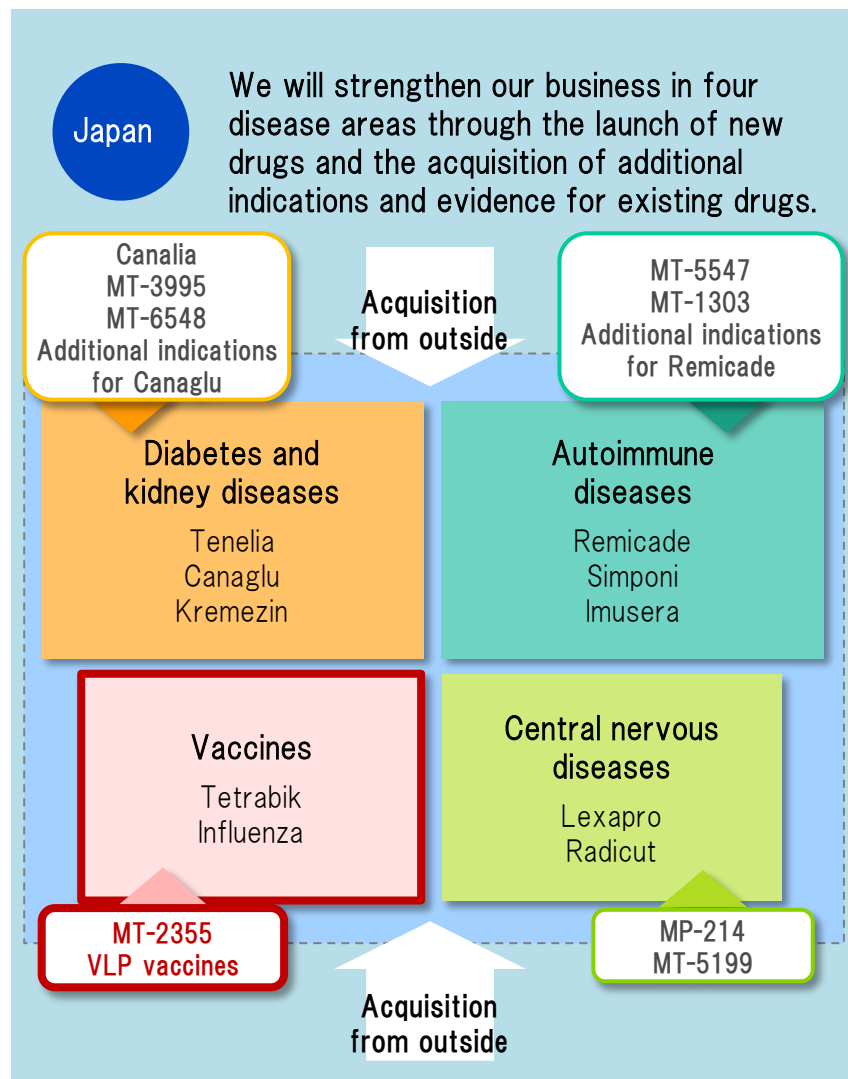
(Millions of U.S. dollars)



Source: Prepared from Evaluate pharma

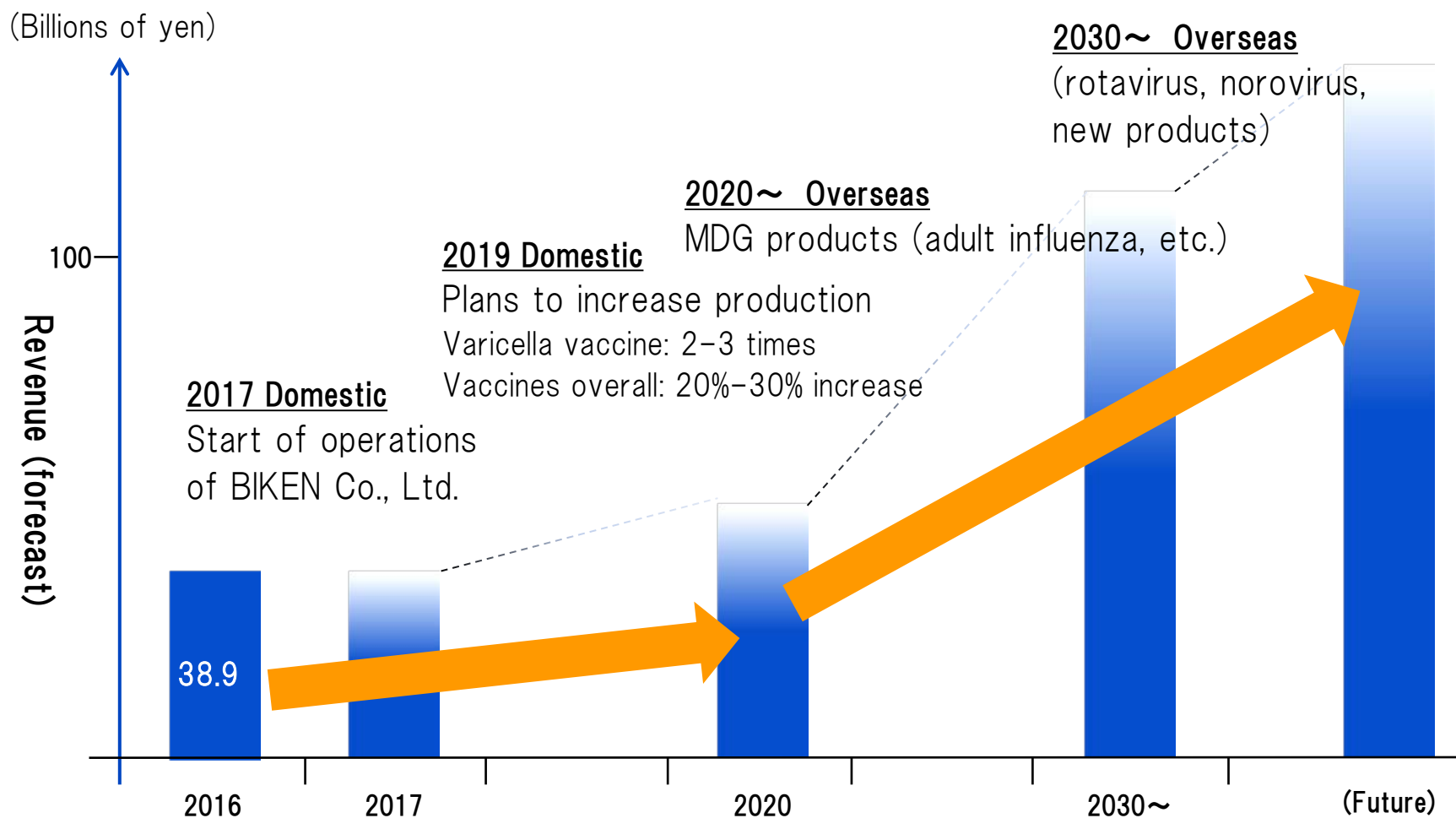
MTPC's Vaccine Business Strategy

Business Strategies for 2020





Numerical Targets (sales of more than ¥100.0 billion)



Aiming to Strengthen Domestic Business



History of Alliance between the BIKEN Foundation and MTPC



Varicella vaccine



Influenza vaccine



Measles-rubella vaccine



Japanese encephalitis vaccine



Tetrabik (DPV-IPV)

1934

Establishment of BIKEN Foundation*

1961

Mitsubishi Tanabe Pharma (former Tanabe Seiyaku Co., Ltd.) starts sales of BIKEN Foundation products

1990 ~

Alliance for overseas exports of BIKEN Foundation products

2010 ~

Joint development of Tetrabik, combined vaccine for five diseases, etc.

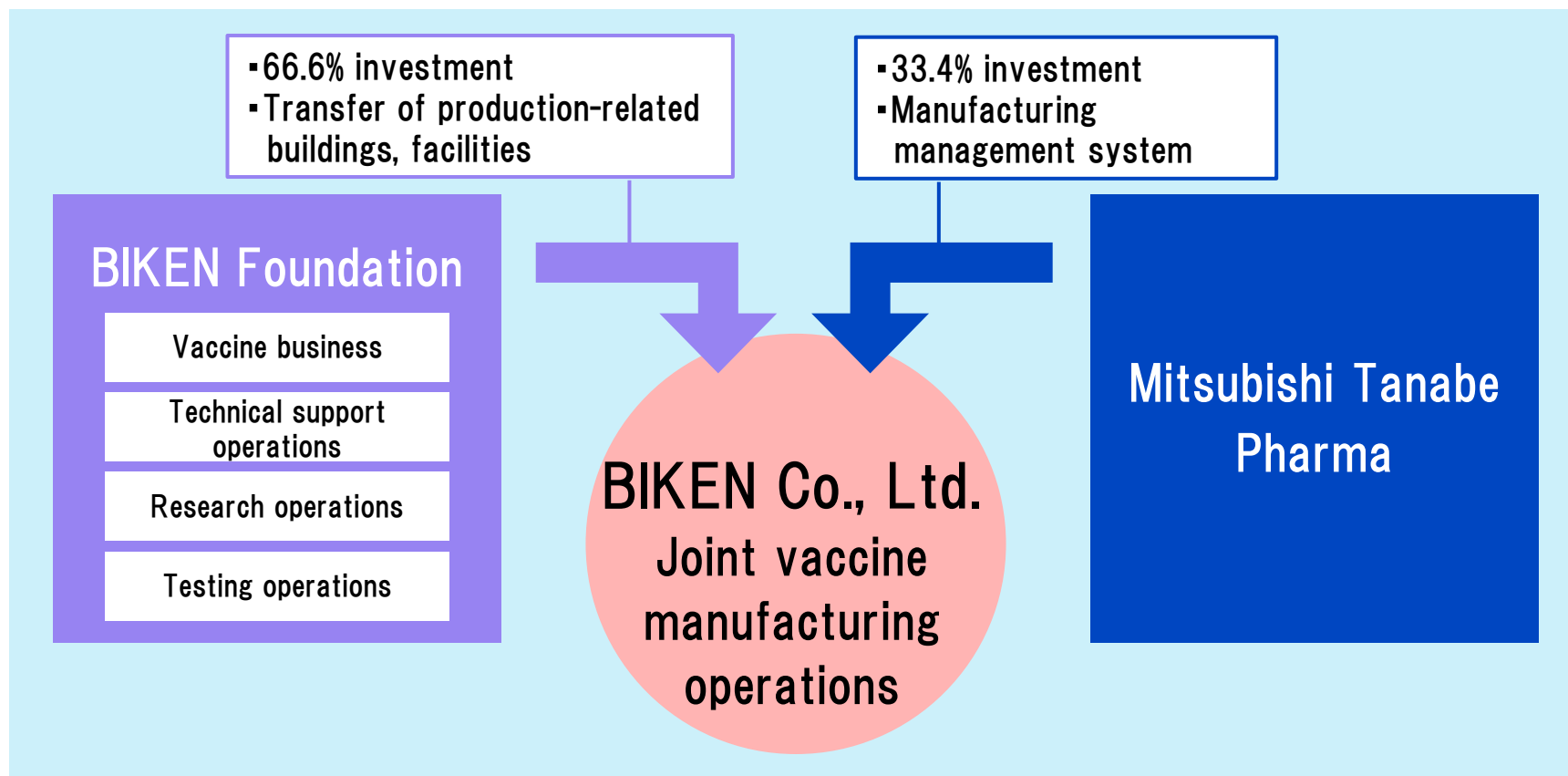
May 2017

Final agreement regarding establishment of joint venture

September 1, 2017
Start of operations of joint venture

* The Research Foundation for Microbial Diseases of Osaka University

Strengthening Our Alliance through the Establishment of BIKEN Co., Ltd.



Accelerate reinforcement of manufacturing foundation, provide stable supply of vaccines that are competitive in Japan and overseas



Targeting Expansion in the Scale of Production



Kannonji Institute(Yahata)
51,842m², established in 1946



Seto Center
165,165m² Established in 2011

- ▶ September 2017: Start of operations of BIKEN Co, Ltd.
- ▶ Start of full-scale operations at Seto Office (planned)
- ▶ Plan for 2019:
 - Varicella vaccine – 2 to 3 times; vaccines overall - 20% to 30% increase
- ▶ Products to be manufactured:
 - Influenza vaccine ▪ Varicella vaccine ▪ Measles-rubella vaccine
 - Japanese encephalitis vaccine ▪ Pertussis, Diphtheria, Tetanus vaccine, etc.

Vaccine Development Projects (domestic / joint development products)

As of September 2017

Project	Stage	Features
TRIBIK	Approved	- Joint development with BIKEN Foundation* - Preparation for restart of sales for use in Stage 2
MT-2355	Phase 3 (Japan)	- Joint development with BIKEN Foundation* - Vaccine combining Tetrabik and Hib vaccine - One dosage form simplifies vaccination process

* The Research Foundation for Microbial Diseases of Osaka University

Vaccines with a High Development Priority in Japan

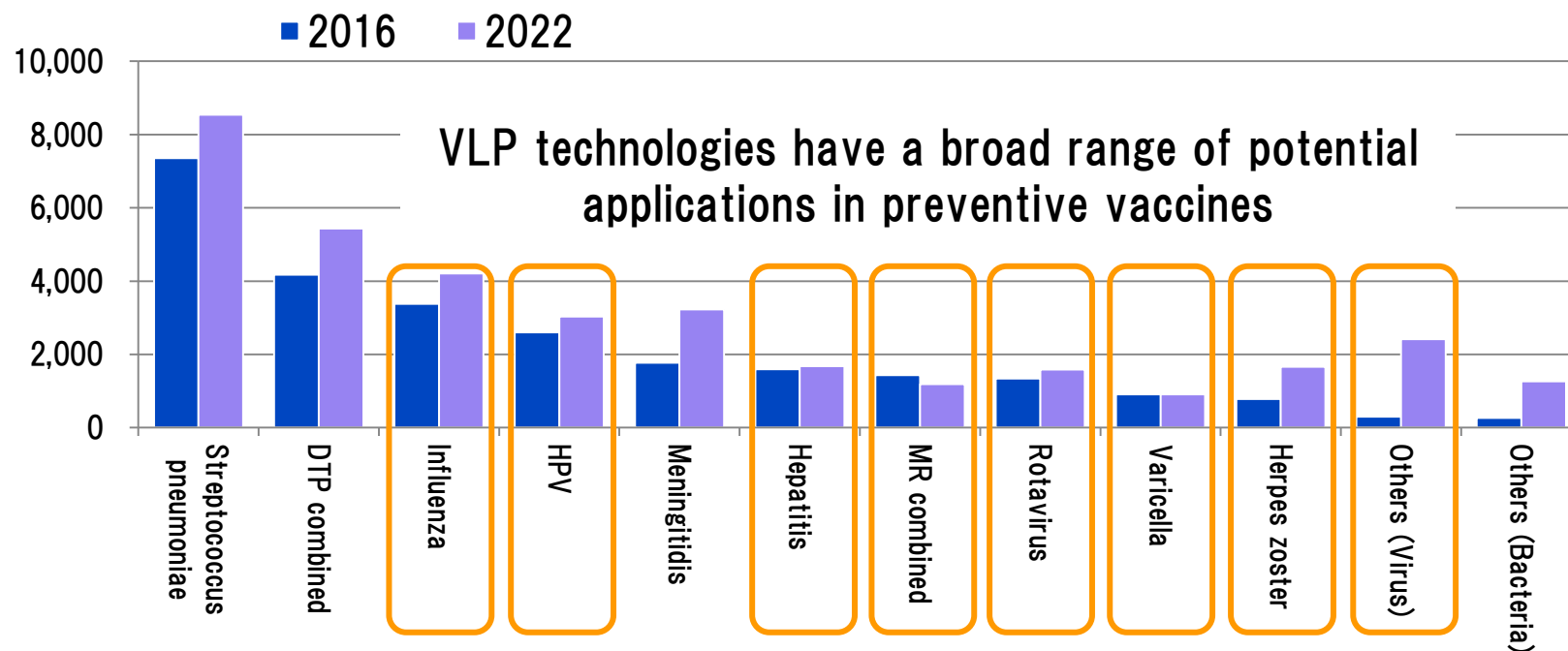
- ▶ Combination vaccine including measles-rubella: MMR, MRV, MMRV
- ▶ Combined vaccines including pertussis, diphtheria, tetanus, and inactivated polio (DPT-IPV): 5- and 6-disease combined vaccines
- ▶ Nasal vaccines and other improved influenza vaccines
- ▶ RS virus vaccine
- ▶ Herpes zoster

Source: Prepared from Ministry of Health, Labour and Welfare's basic plan regarding vaccines

Overseas Business Strategy

Potential of VLP Technology

(Millions of U.S. dollars)



* Among the components of the DTP combined vaccines, there is potential for the application of MDG technologies for polio and hepatitis B
DTP combined: Combined vaccines including diphtheria, tetanus, and pertussis (including products that also combine polio, hepatitis B, Hib)
HPV: Human papillomavirus; MR combined: Combined vaccines including measles and rubella (including products that also combine mumps)
Other (viruses): Smallpox, Japanese encephalitis, tick-borne disease, dengue fever, norovirus, CMV, RSV. Other (bacteria): tuberculosis, anthrax, cholera, Clostridium difficile, Staphylococcus

Source: Prepared from Evaluate pharma

Vaccine Development Projects

(overseas / new vaccines and improved vaccines)

As of September 2017

Project	Stage	Features
Seasonal Influenza VLP Vaccine	Phase 3 (U.S., Canada) • Start of phase 3 for adults (August) • Aiming to start sales in North America in 2020	• Using plant-based vaccine manufacturing technologies • Expected to offer high levels of effectiveness due to the fact that they have the same structure as viruses, as well as safety due to the fact that they do not include virus genes
H5N1 VLP Influenza Vaccine	Phase 2 (Canada)	
Rotavirus VLP Vaccine	Pre-clinical	
Norovirus VLP Vaccine	Pre-clinical	
Other VLP Vaccine	Discovery research	

Cautionary Statement

The statements contained in this presentation is based on a number of assumptions and belief in light of the information currently available to management of the company and is subject to significant risks and uncertainties.



**Medicago: transforming the approach
to vaccines and protein-based
therapeutics**

Bruce D. Clark PhD
President & CEO
September 27, 2017

Medicago Overview

Focus	Vaccines & Therapeutic Proteins
Manufacturing technology	Transient expression in plants
Vaccine technology	Virus-like particles
Employees	~300+
Success story	Innovative Canadian Vaccine Technology Potential advantages over current vaccine technologies (efficacy, cross protection) Pandemic Supply advantages
Headquarters, laboratories & cGMP facilities	HQ in Quebec City, CANADA Research Triangle Park, NC, USA



Medicago Overview: Global activities



Canada

- Head office in Quebec City
- 215+ employees
- R&D laboratory
- Pilot facility



USA

- Research Triangle Park, Durham, NC
- 110+ employees
- Commercial cGMP facility



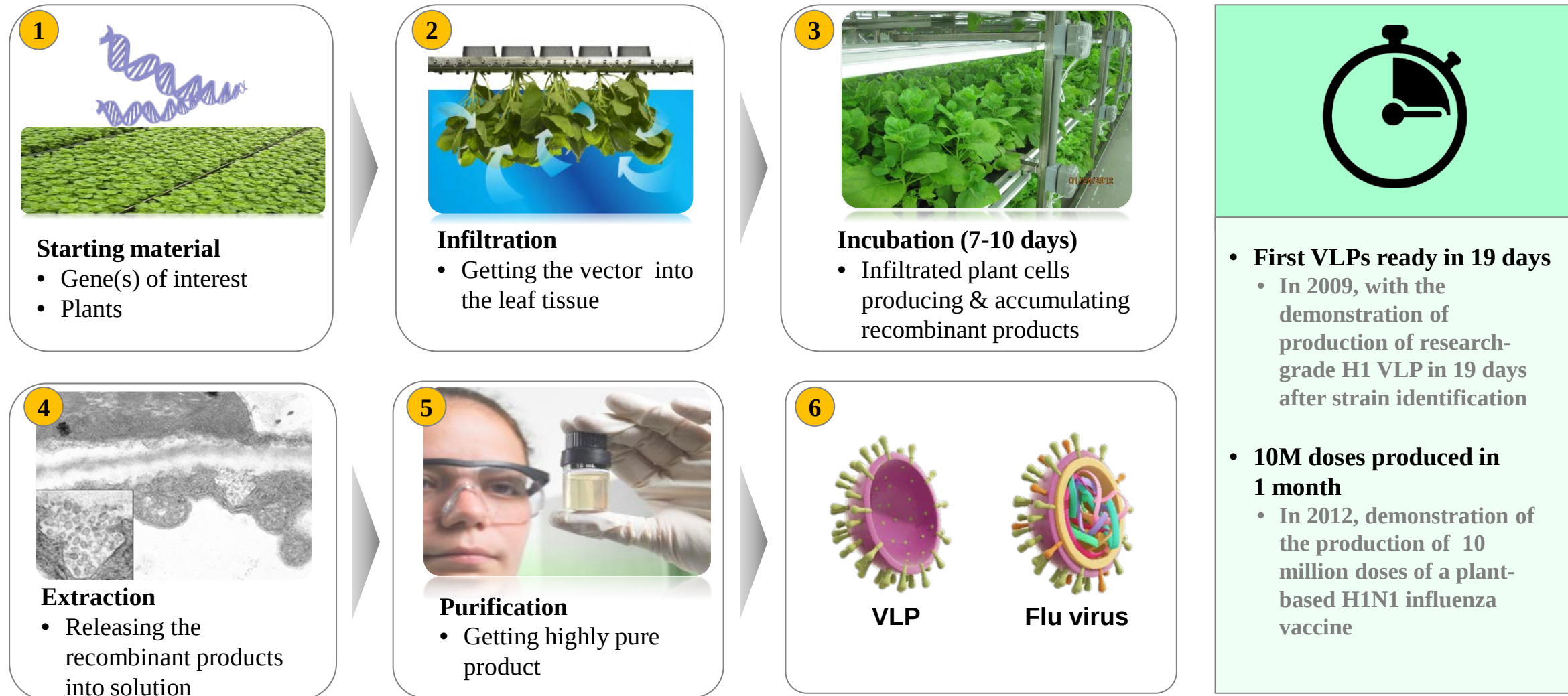
France

Research Lab

South Africa

Research Lab

Technology: Transient Plant-based Expression System



(1) D'Aoust et al, Plant Biotechnology Journal (2010) 8, pp. 607–619

(2) <http://globalbiodefense.com/2012/07/28/darpa-program-hits-milestone-in-plant-based-vaccines-for-pandemics/>

Manufacturing advantages

LEAD TIME

- Clinical grade material in 5-6 weeks
- Rapid monovalent manufacturing + dose-sparing = surge capacity
- 10M doses in 30 days (DARPA 2012)

SIMPLE

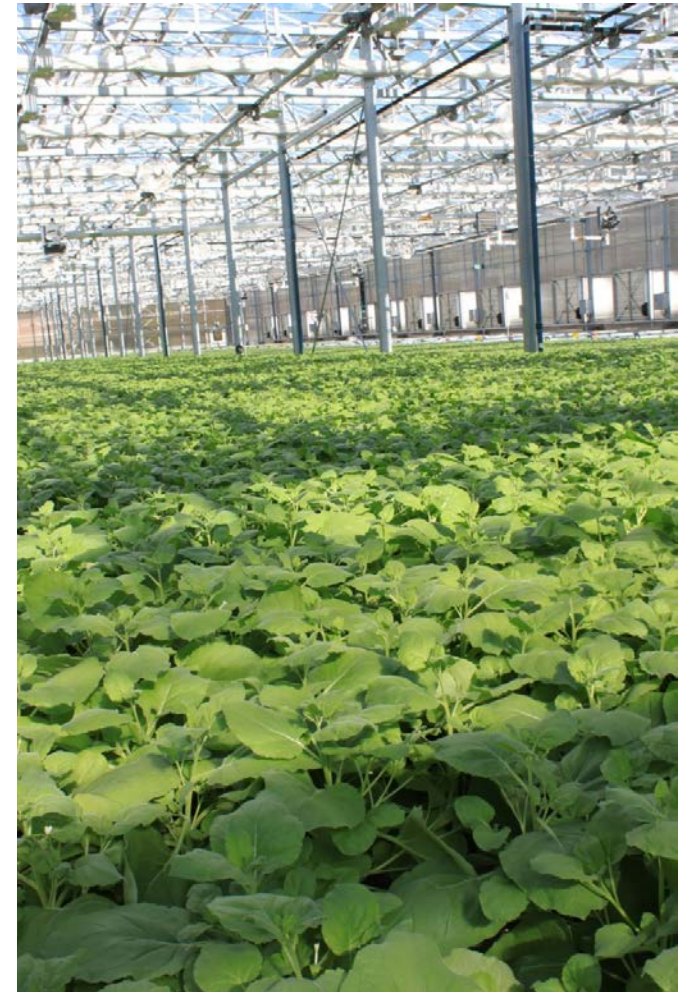
- Does not use transgenic plants
- No need for stable integration
- High yields (multiple transformation events per cell)

SCALABLE

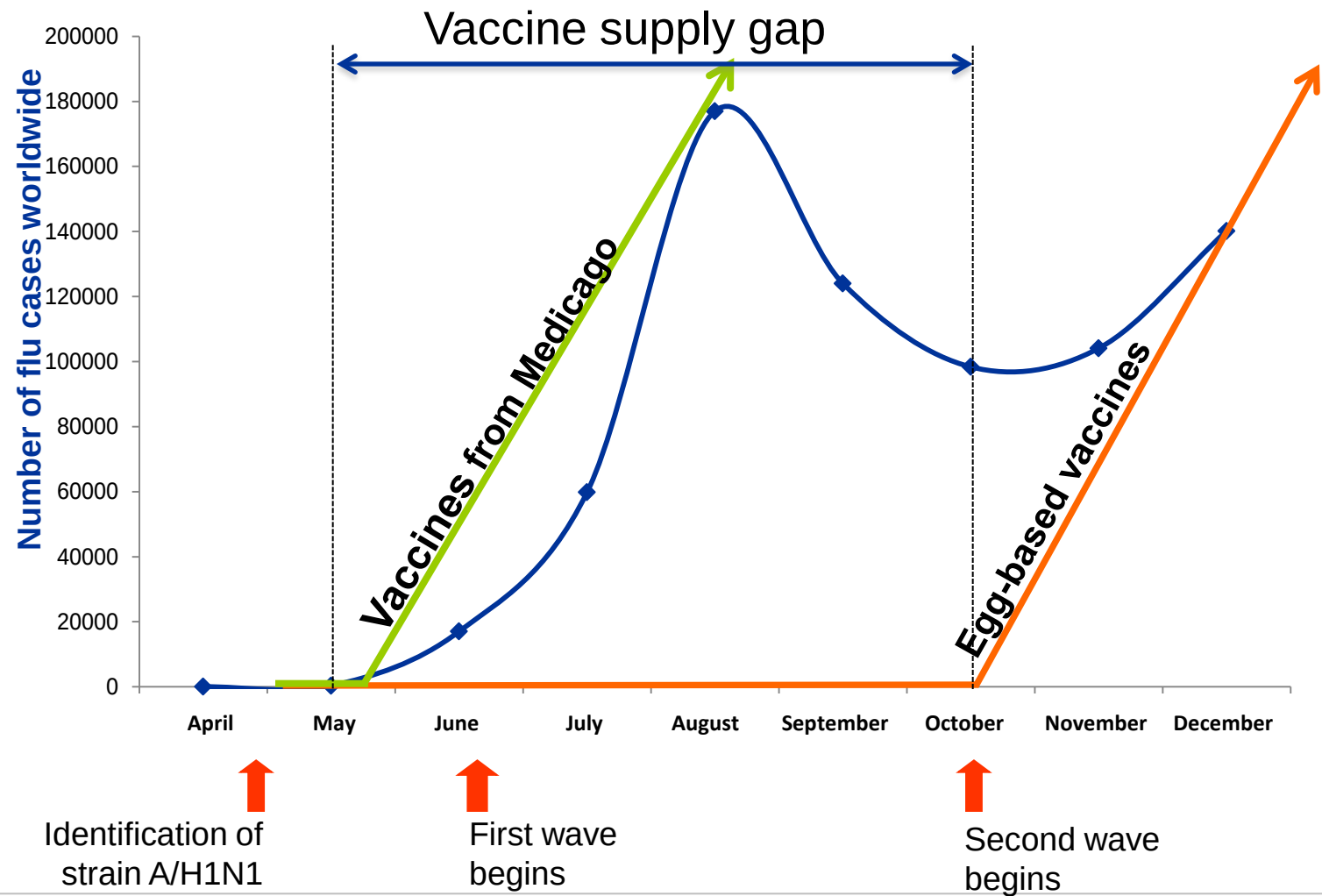
- No risk at scale-up vs. fermenters
 - One plant or 10,000 plants require the same growth conditions
- Low cost compared to fermenters
- Capacity adjustable to market needs

VERSATILE

- Co-expression of different proteins or subunits
- From vaccines to antibodies



First Responder Capability during Outbreaks (H1N1 Pandemic)



Medicago VLPs are industry-leading technology and the first plant-based flu vaccine available

Evolution of Vaccines Technologies, illustration with Flu vaccines:

Live attenuated



First live attenuated flu vaccine developed in the 1930s

- Mimic natural infection
- Strong antibodies response (T cells & B cells)
- Risk: can revert towards virulent form
- Difficult to produce in scalable setting

• **Flumist** (AZ), licensed in 2003

Split (Inactivated)



First split flu vaccine licensed in 1968

- Less reactogenic than whole virus vaccines but low immunogenicity: need to use adjuvant
- No Cell-Mediated Immune response
- Long production process

• **Fluzone** (Sanofi Pasteur)
• **Fluarix, Flulaval** (GSK)
• **Afluria** (Seqirus)

Subunit vaccine

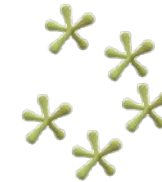


First subunit flu vaccine licensed in the 1980s

- Safe: lacking core genetic material
- Need adjuvant

• **Fluad, Fluvirin**, **Flucelvax** (Seqirus)

Recombinant vaccine

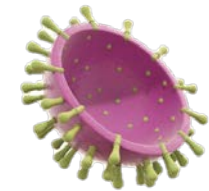


First recombinant flu vaccine licensed in 2013

- Safe: lacking core genetic material
- Strong immune response
- Expensive to develop
- No Cell-Mediated response documented

• **Flublok** (Protein Sciences, acquired by Sanofi Pasteur)

Virus-Like Particles (VLP)



First VLP quadrivalent flu vaccine candidate entered Phase III in 2017

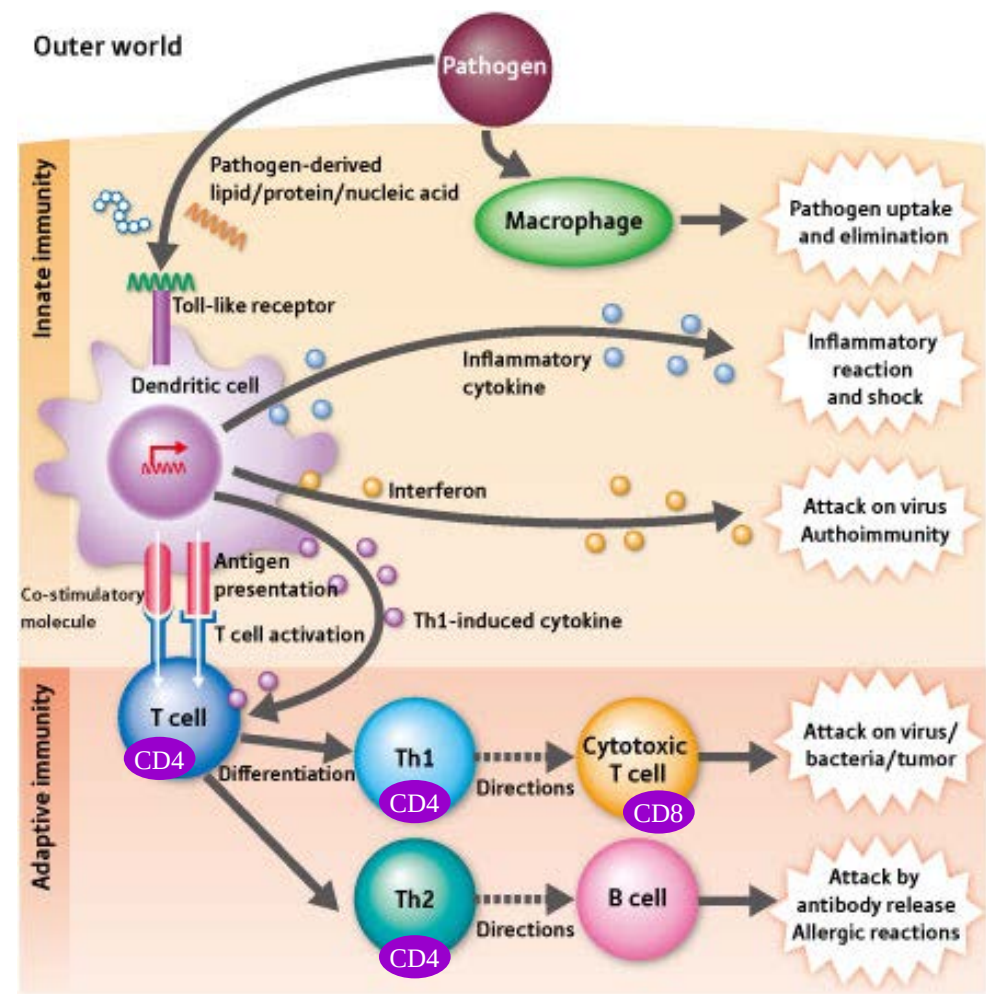
- Medicago's VLP is similar to a wild-type virus
- Lacking core genetic material (non-infectious)
- Highly efficient way to present antigens to the immune system

• **Medicago vaccine candidate**

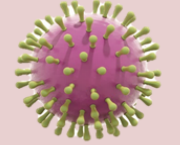
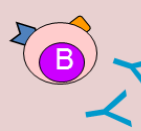
Egg-based vaccines
Cell-based vaccines
Plant-based vaccines

Plant-based VLP vaccine have common features with infection-induced immune response

Different immune responses:

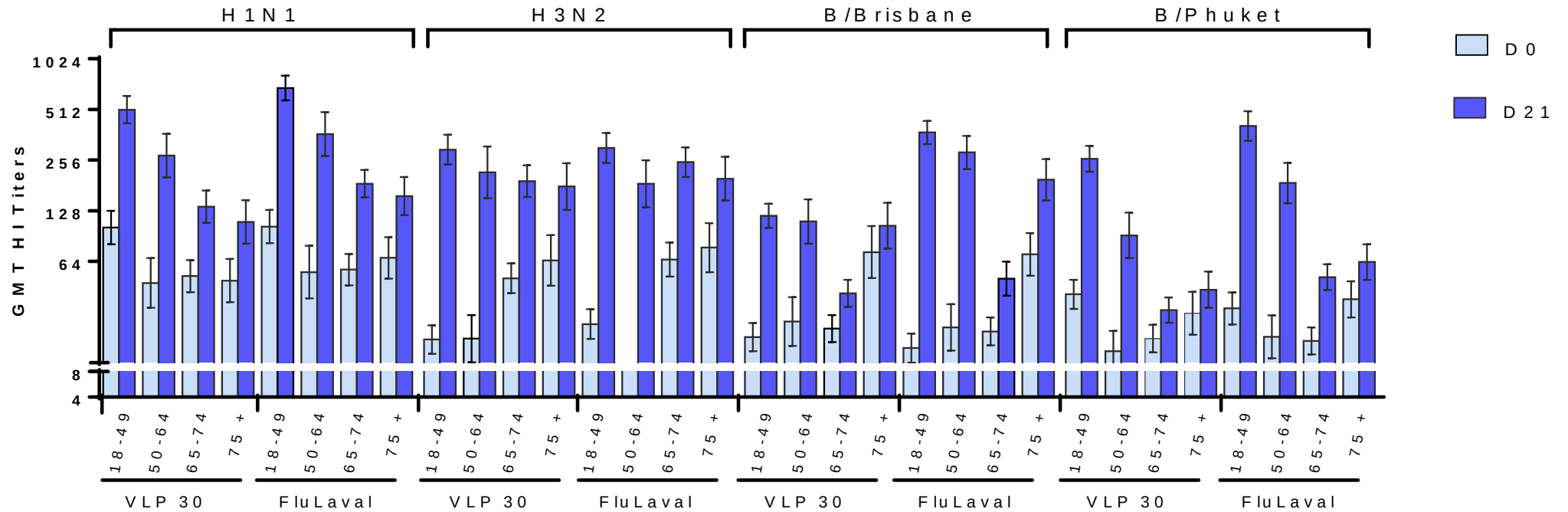


Immune responses in case of flu infection & flu vaccination:

Immune Effectors	Infection	Vaccines	
		Split Vaccines (egg-based)	VLP
			
Innate Immunity (Macrophages, NK cells, Dendritic Cells) 	+++	+	+++
Humoral Immunity (Antibodies) 	++ in young +/- in the elderly	+++	++
T Cell Immunity (T helper) 	++	+/-	++
T Cell Immunity (CTL) 	++	- (literature)	+ (demonstrated in mice)

HAI antibody levels in 2016 comparative studies

(2016 P2 trial NCT02768805 and NCT02831751)



- Important Note: Virus reagents used are biased towards egg-based vaccines
 - Lower reactivity to VLP than FluLaval and other egg-based vaccines
- Comparable Antibody response to licensed vaccine when no reagent bias in the HAI test

Observations from Pre-clinical studies

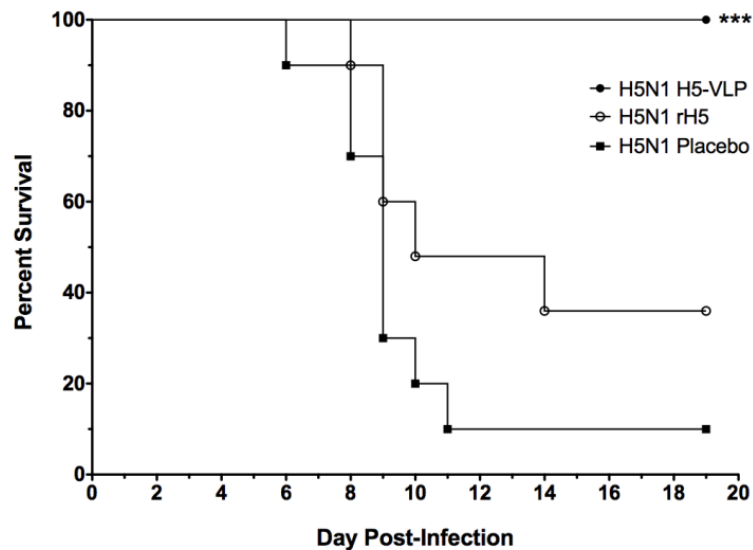
NIAID sponsored study



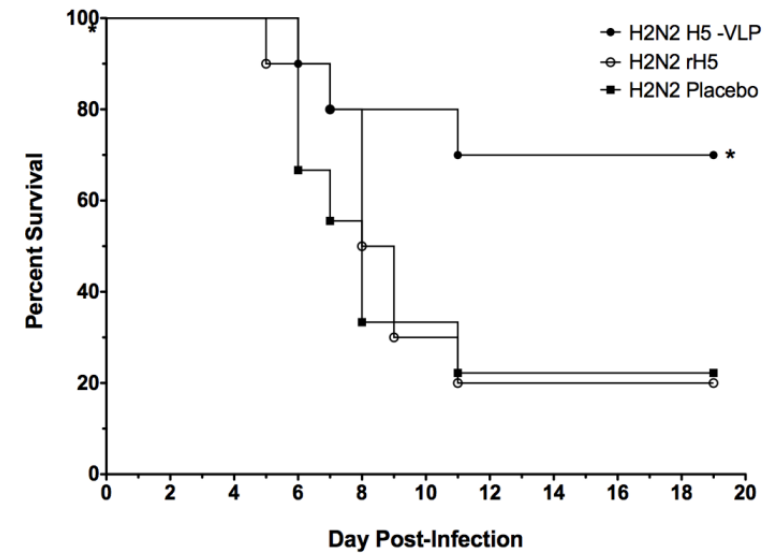
Cross-Protection in animals after a single dose of H5 VLP vaccine

- Protection against H5N1 Vietnam (100%) and H2N2 Japan (70%)

Challenge against heterologous H5N1 Vietnam



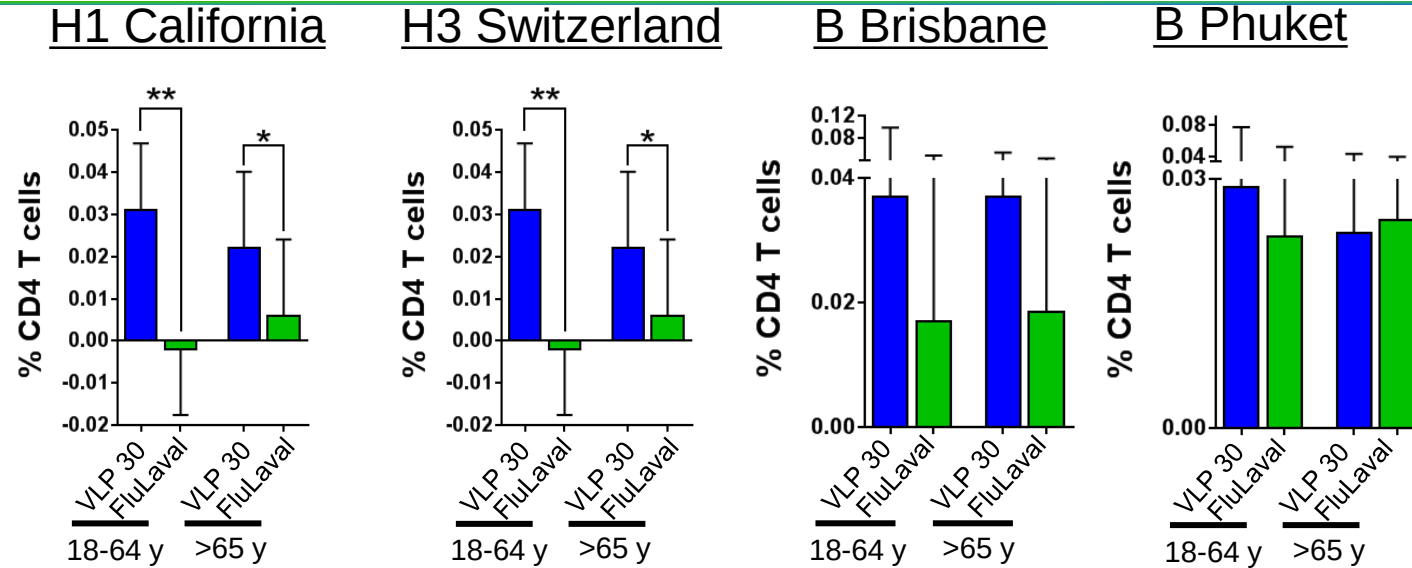
Challenge against heterosubtypic H2N2 Japan



VLPs elicit cell-based Immune response in all groups: 2016 study

measuring CD4+ T cell response (D21-D0) (2016 P2 trial NCT02768805 and NCT02831751)

Vaccine matched strains



No significant increase between D0 and D21 with FluLaval T in healthy adults

No significant increase between D0 and D21 with FluLaval T in healthy adults

P<0.05*, P<0.01**, P<0.001*** Pairwise comparison of treatment groups uses Tukey-Kramer test after fitting a fixed effect model, or non-parametric Wilcoxon rank-sum test. 30 subjects per group for 18-64y, 45 subjects per group for >65y.

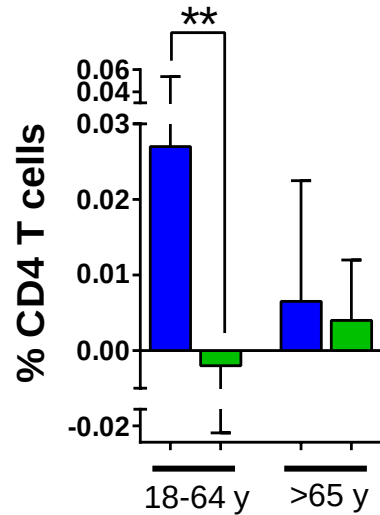
The VLP vaccine induces a significant CD4+ T cell response against all vaccine strains in both adults and elderly

- FluLaval showed specific CD4+ T cells against B strains only

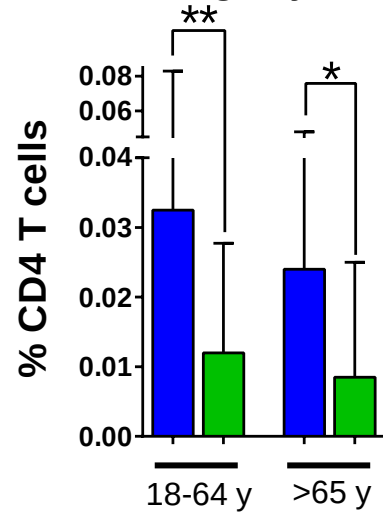
VLPs elicit cell-based Immune response in all groups: 2016 study measuring CD4+ T cell response (D21-D0) (2016 P2 trial NCT02768805 and NCT02831751)

Non-vaccine strains

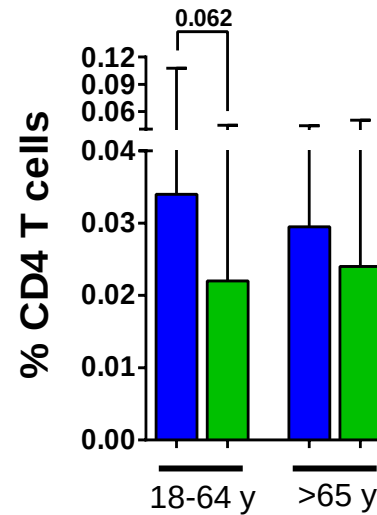
H1 Brisbane/2007



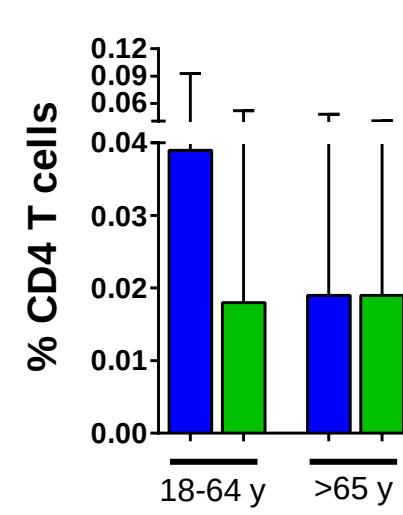
H3 Uruguay/2007



B Florida/2006



B Malaysia/2004



P<0.05*, P<0.01**, P<0.001*** Pairwise comparison of treatment groups uses Tukey-Kramer test after fitting a fixed effect model, or non-parametric Wilcoxon rank-sum test. 30 subjects per group for 18-64y, 45 subjects per group for >65y.

The VLP induces significant CD4+ Tcell response against non-vaccine strains

Seasonal influenza vaccine (Quadrivalent) – Phase II Clinical results

5 clinical trials completed to date

■ Highlights:

- 5 trials completed in 2820 subjects (ages 18-64 & 65 and above) – safety established

■ Phase II Results:

- 30 µg per strain is the optimal dose that:
 - » Meets licensure criteria in healthy adults
 - » Offer the optimal antibody and cell-mediated responses
- The antibody response compares to that of licensed vaccines
- Cell-mediated responses are higher than a standard dose comparator vaccine
- VLP vaccine induces broader immune responses than licensed vaccines that can give cross-protection in case of vaccine mismatch
- End of Phase II meeting with FDA: support Phase 3 trials in both adults and elderly (ages 65+)

■ Pivotal Phase 3 in 10,000 healthy adults is ongoing in 7 countries



Medicago platform and VLP technology addresses unmet needs and challenges of previous vaccines technologies

Current vaccines technologies face some challenges:

- Reduced immunogenicity from methods of inactivation - and splitting, in the case of influenza
- Limited capacity to produce viruses for vaccine development (Norovirus)
- Lack of protection to native virus (Dengue and other flaviviruses)
- Risks associated with attenuated viruses as vaccine
- Time line of production for egg-based vaccines
- Cost of production for cell-based vaccines

Recombinant vaccines offer the potential to design and produce safer vaccine with targeted antigens but subunit vaccines suffer from weak immunogenicity and incapacity to stimulate cell-mediated immunity

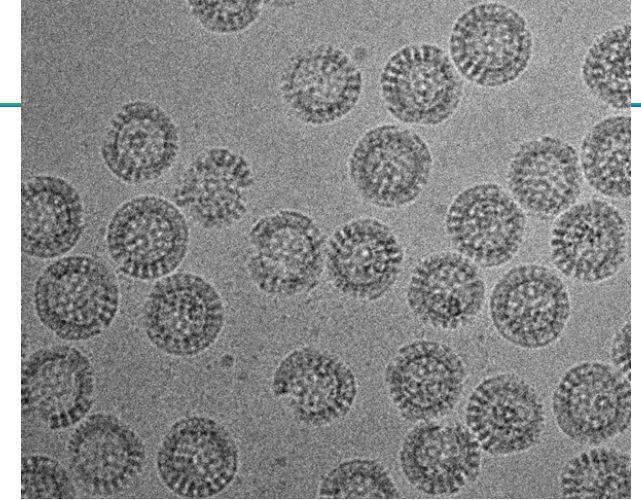
Competitive advantage of Medicago:

- Virus-like particles offer the best combination of safety and immunogenicity as they are not infectious but still can trigger a strong and balanced immune response
- Our proprietary VLPEXpress™ discovery platform provides unsurpassed capacity for the development of self-assembling VLPs
- Our manufacturing platform, based on transient expression in plants, assures production speed and surge capacity in face of urgent need for new vaccine supply

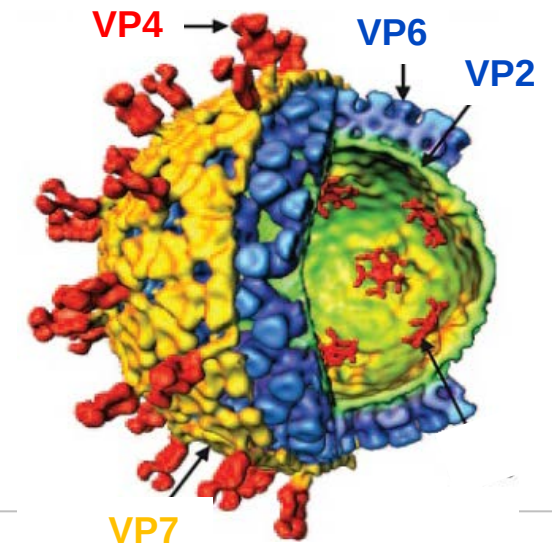
Leveraging the benefits of VLPs

Other indications in development – Rotavirus (MTPC)

- Induces severe diarrhea in children < 3 years
- Current vaccines are live-attenuated viruses
 - Risk of intussusception
- Recommended for routine vaccination of < 3 years in USA, Canada, TBC
- Market of TBC
- First demonstration of triple layer VLP made by a plant system
 - Protected by patents
- Plant-made RLPs show no risk of intussusception

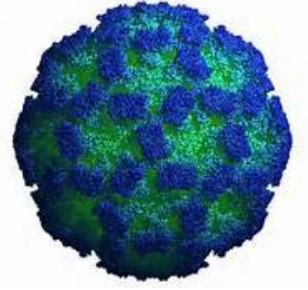


Plant-produced rotavirus-like particles containing VP2, VP6, VP7, VP4 from G1 genotype

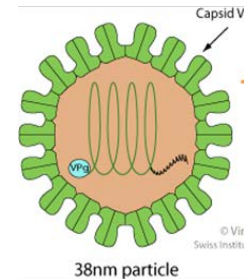


Leveraging the benefits of VLPs

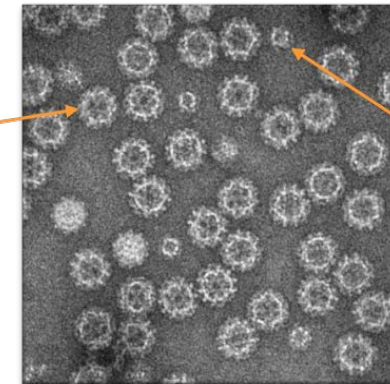
Other indications in development – Norovirus



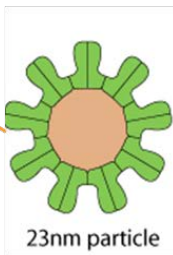
- Induces severe diarrhea in children, adults and elderly
- Unmet medical need, no existing vaccines
 - Takeda in phase 2 in adults
- Market similar to rotavirus
- Medicago has expressed 15 genotypes at high yields
- First target indication is pediatrics
 - Could get an ACIP recommendation and fast track status
- Two routes of administration, intramuscular and oral evaluated in animal models



credit: © ViralZone



credit: Medicago



Plant-produced norovirus-like particles

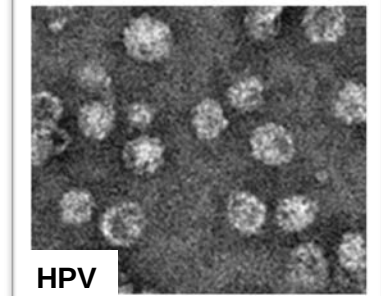
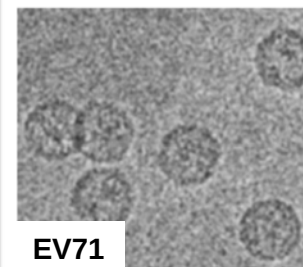
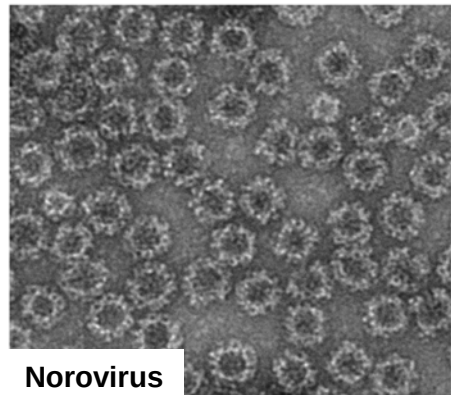
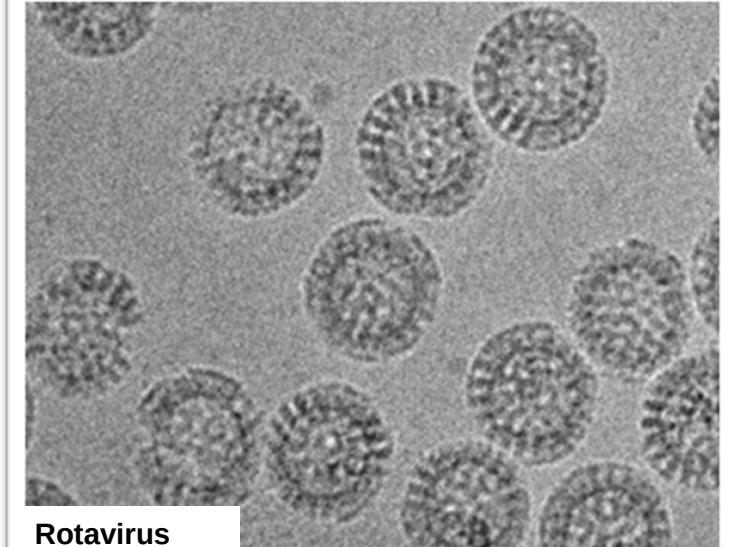
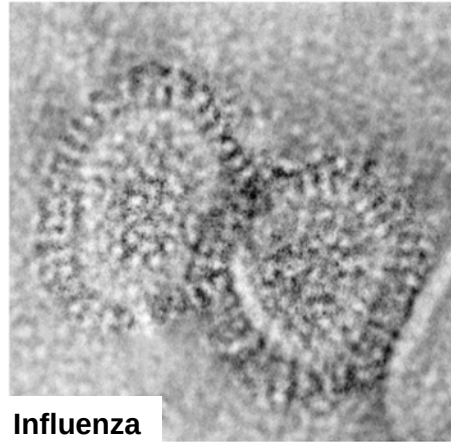
Medicago has worked on over 20 different vaccine targets, developing potential VLP vaccines

- **Enveloped viruses**

- o Influenza
- o West-Nile virus
- o Hepatitis B
- o HIV
- o SARS
- o Rabies

- **Non-enveloped viruses**

- o Rotavirus
- o Norovirus
- o EV71
- o HPV



Our platform is also versatile supporting development of antibodies

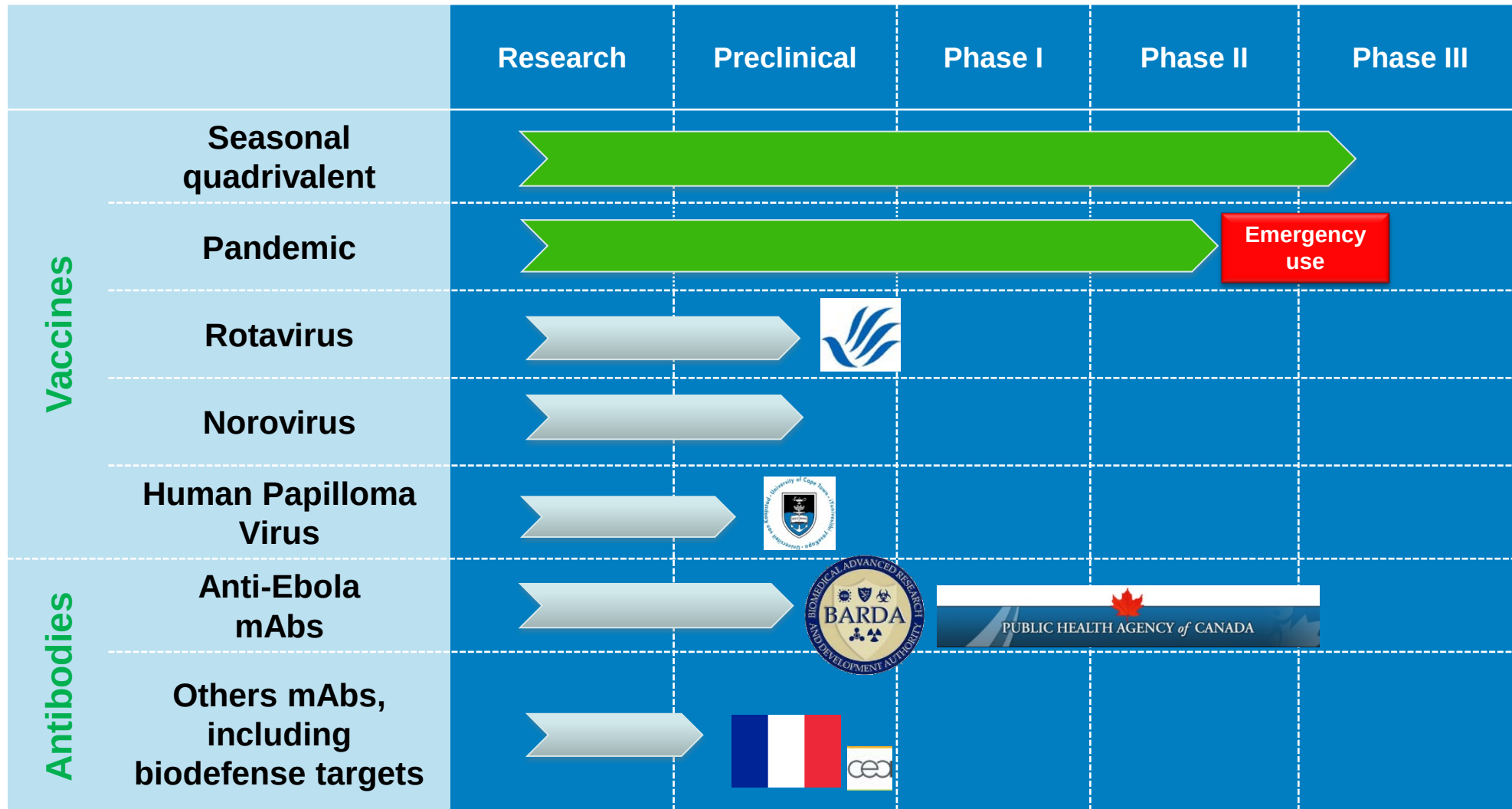
Antibody development is long, costly and suffers from flexibility

- In mammalian cell culture systems, the transient expression technologies used for discovery cannot be brought to manufacturing scale
- Stable mammalian cell lines used for production are the result of a long screening process
- Scaling-up cell culture production is costly and risky as several culture parameters (culture movements, gas exchange...) differ with the change of scale

Competitive advantage of Medicago:

- Our transient expression technology has been developed so that the **process is integrated from discovery to manufacturing**
 - o Our proprietary VLPEXpress™ discovery platform provides unsurpassed capacity for the discovery and screening of antibody candidates
 - o Production approaches identified at small scale are directly transferable to pilot and large scale production (Same *Agrobacterium* line used, same plants)
- Medicago has developed proprietary antibody engineering technologies to improve the bioactivity of antibodies (Glycoengineering)

Development Pipeline



We are protecting our assets with 779 patents & patents applications and 11 trademarks across 42 countries

Patents and patent application: 779

- 404 granted patents
- 375 pending applications
- Technologies: 49 patent families
- Geographical coverage: 48 countries
- In-licenses: 20 technologies
- Out-licenses: 2 technologies
2 products (country-specific)

Trademarks: 11

- Corporate marks: 6 marks
- Product marks: 4 marks
- Geographical coverage: 6 countries