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

Open Up the Future
Mitsubishi Tanabe Pharma

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

Open Up the Future
Mitsubishi Tanabe Pharma

Viruses (30-300nm)

Influenza, Rabies, Varicella, Polio, etc.
➡ Antiviral agents, vaccines

Bacteria (3μm)

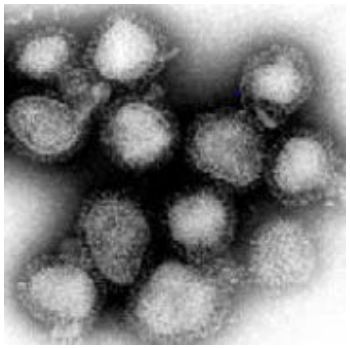
Streptococcus pneumoniae, Pertussis, Diphtheria, Tetanus, etc.
➡ Antibiotics, vaccines

Fungi (Several μm-several dozen μm)

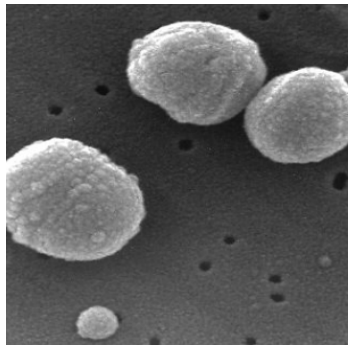
Candida, Cryptococcus, etc.
➡ Antifungal agents

Protozoa / parasites (Several μm-several hundred μm)

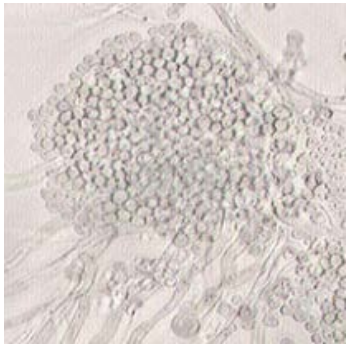
Malaria, Amebic dysentery, etc.
➡ Antiprotozoal agents



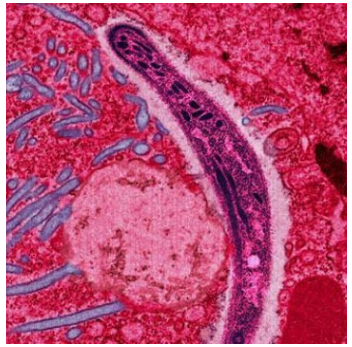
Influenza



Streptococcus pneumoniae

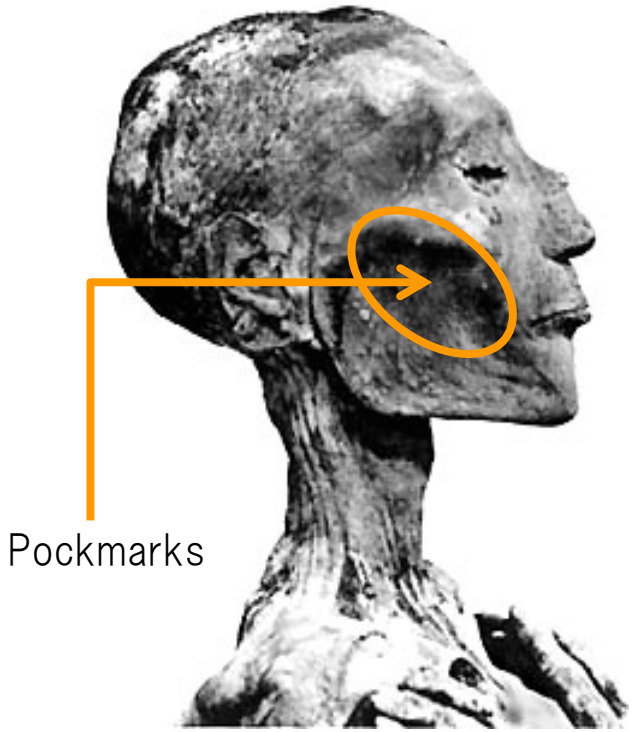


Candida



Malaria

Viral Diseases Since Ancient Times

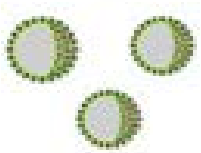


The Pharoh Ramses V mummy
Died of smallpox, 1196 BC
http://www.tulane.edu/

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

Types and Features of Vaccines

Open Up the Future
Mitsubishi Tanabe Pharma

		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)	+～+++	−

DPT; Diphtheria, Pertussis, Tetanus

Existing Vaccines (Periodic Vaccinations)

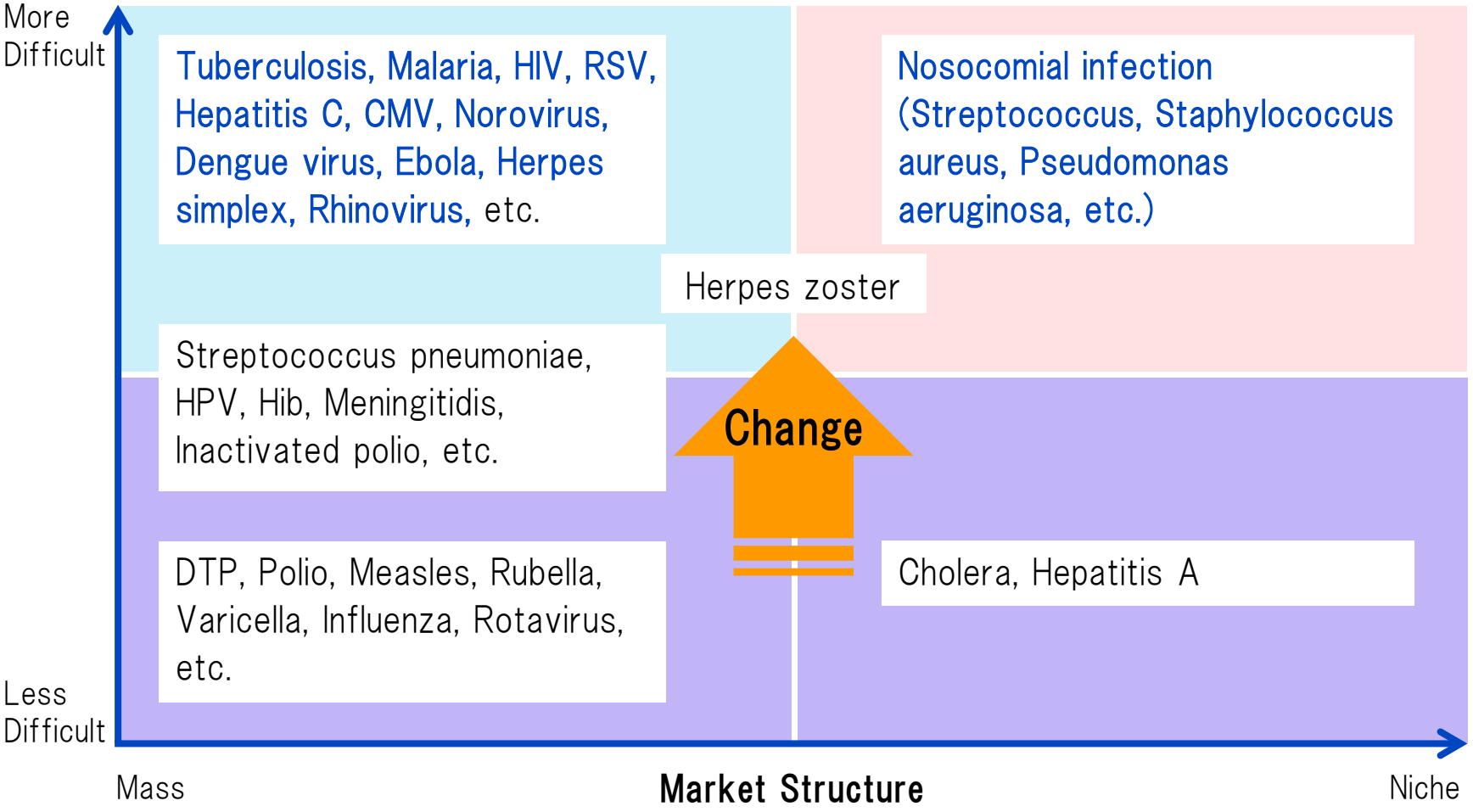
Open Up the Future
Mitsubishi Tanabe Pharma

			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)

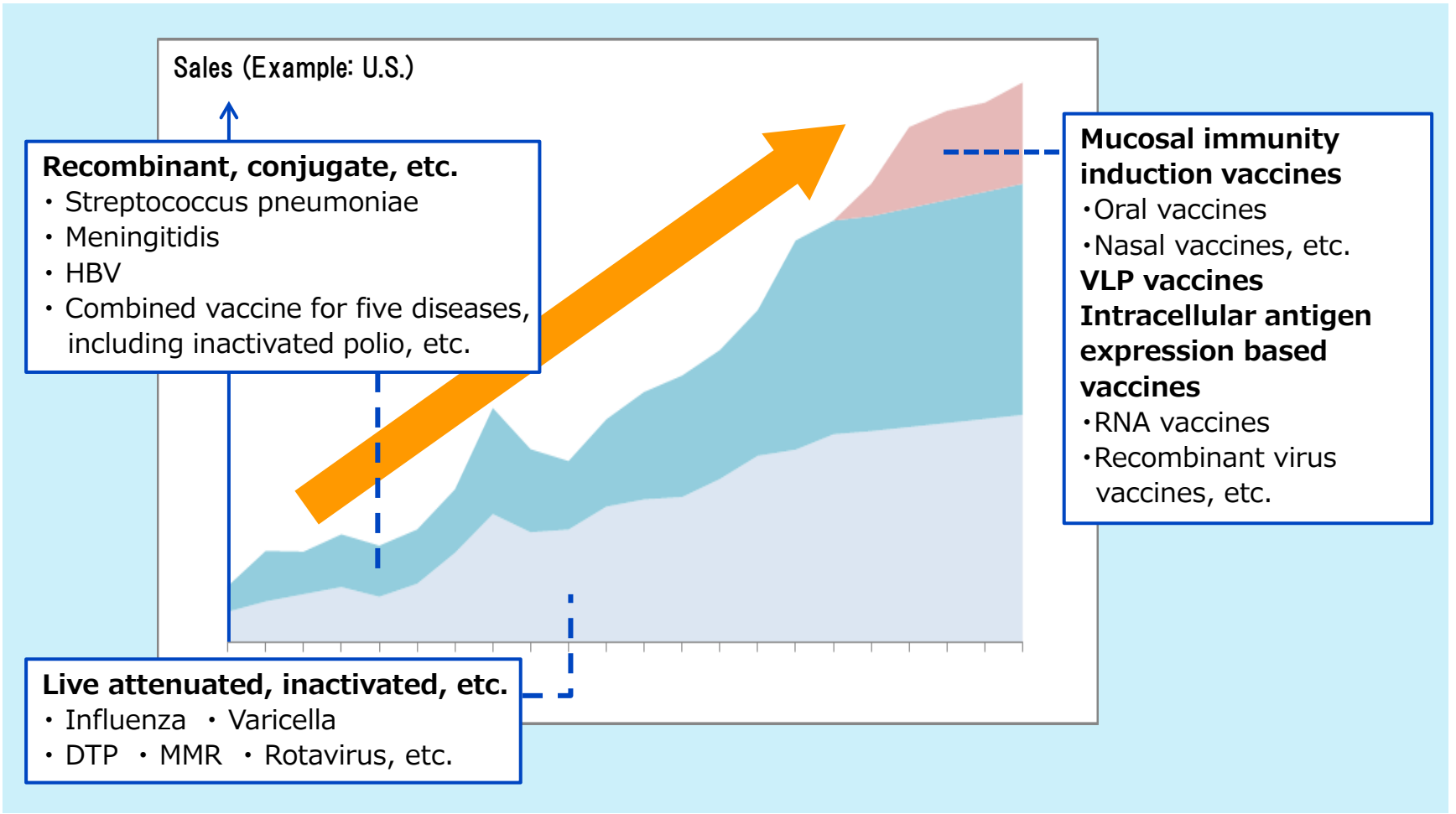
Open Up the Future
Mitsubishi Tanabe Pharma



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



MMR; Measles, Mumps, Rubella

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.

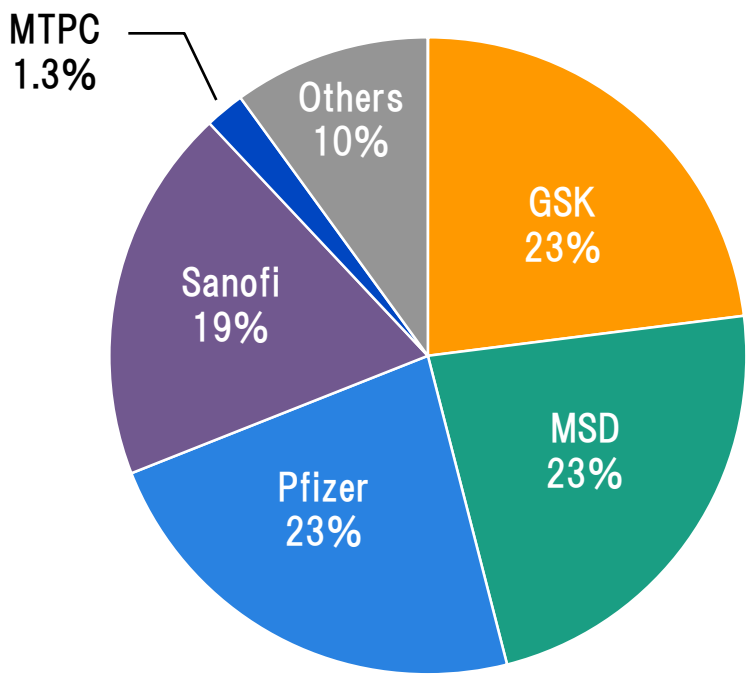
Global Vaccine Market

Open Up the Future
Mitsubishi Tanabe Pharma

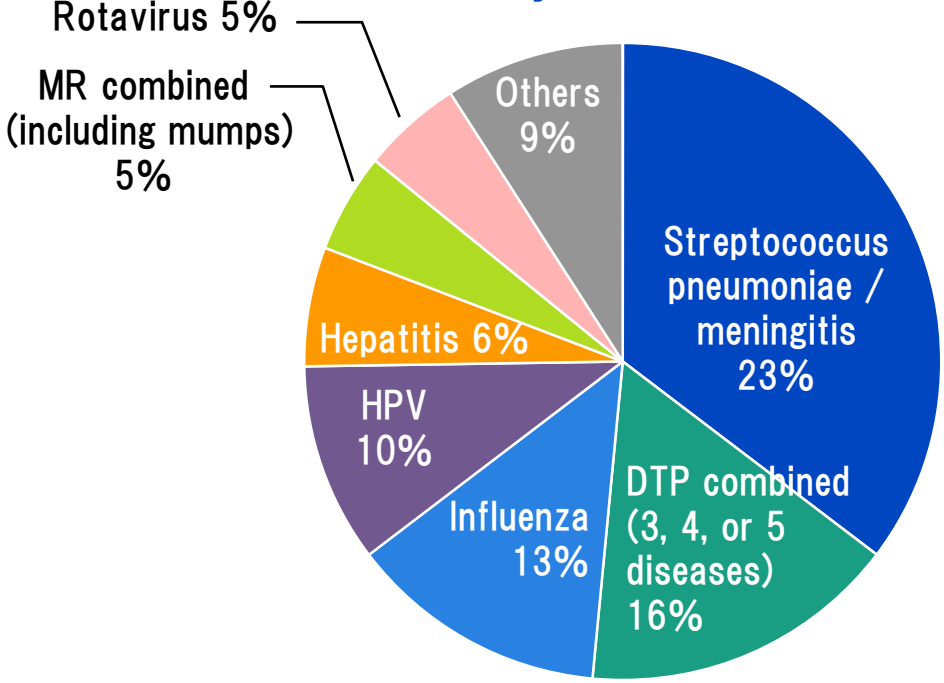
Vaccine market share (2016)

Market scale: $26,000 million

By Company



By Disease



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

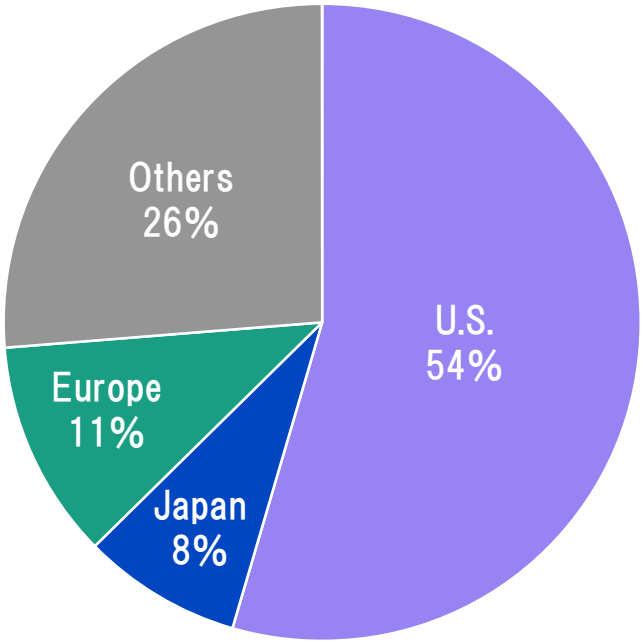
No. 1: Streptococcus pneumoniae;
No. 2: pediatric combined,
No. 3: influenza

Source: Prepared from Evaluate pharma

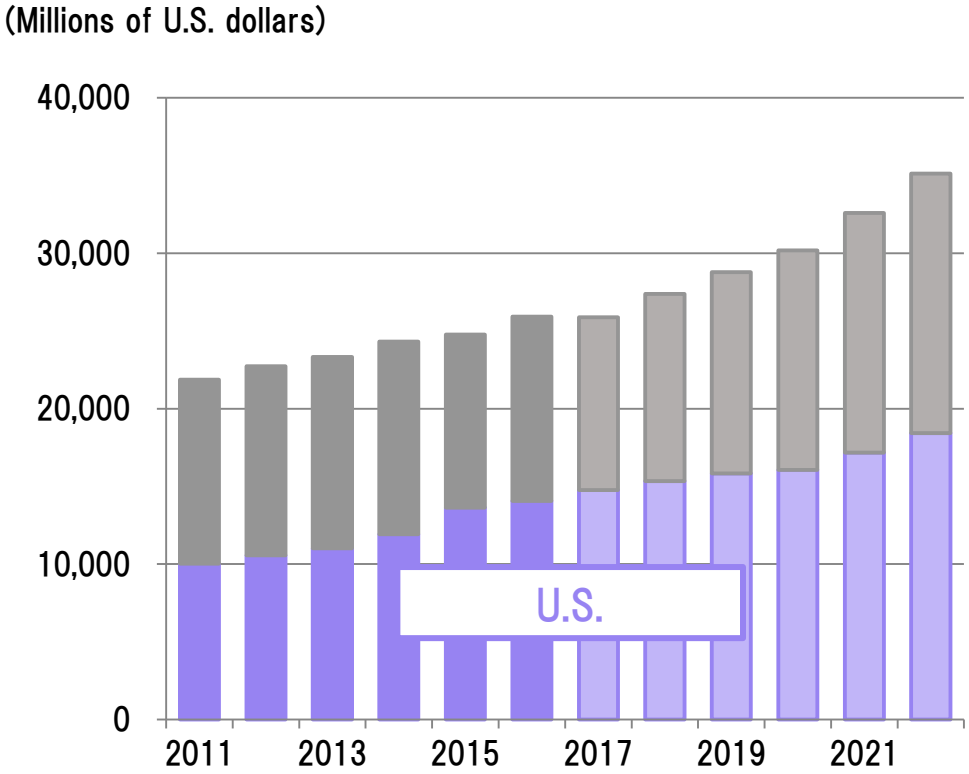
Vaccine Market by Region

Open Up the Future
Mitsubishi Tanabe Pharma

Market share by country (2016)



Market forecasts (2011-2022)



Source: Prepared from Evaluate pharma

MTPC's Vaccine Business Strategy

Business Strategies for 2020

Japan

We will strengthen our business in four disease areas through the launch of new drugs and the acquisition of additional indications and evidence for existing drugs.

Canalia
MT-3995
MT-6548
Additional indications for Canaglu

Acquisition from outside

MT-5547
MT-1303
Additional indications for Remicade

Diabetes and kidney diseases
Tenelia
Canaglu
Kremezin

Autoimmune diseases
Remicade
Simponi
Imusera

Vaccines
Tetrabik
Influenza

Central nervous diseases
Lexapro
Radicut

MT-2355
VLP vaccines

MP-214
MT-5199

Acquisition from outside

U.S.

Establish a presence in specialized fields by rapidly starting up our own business in the U.S.

ND0612

In-house products

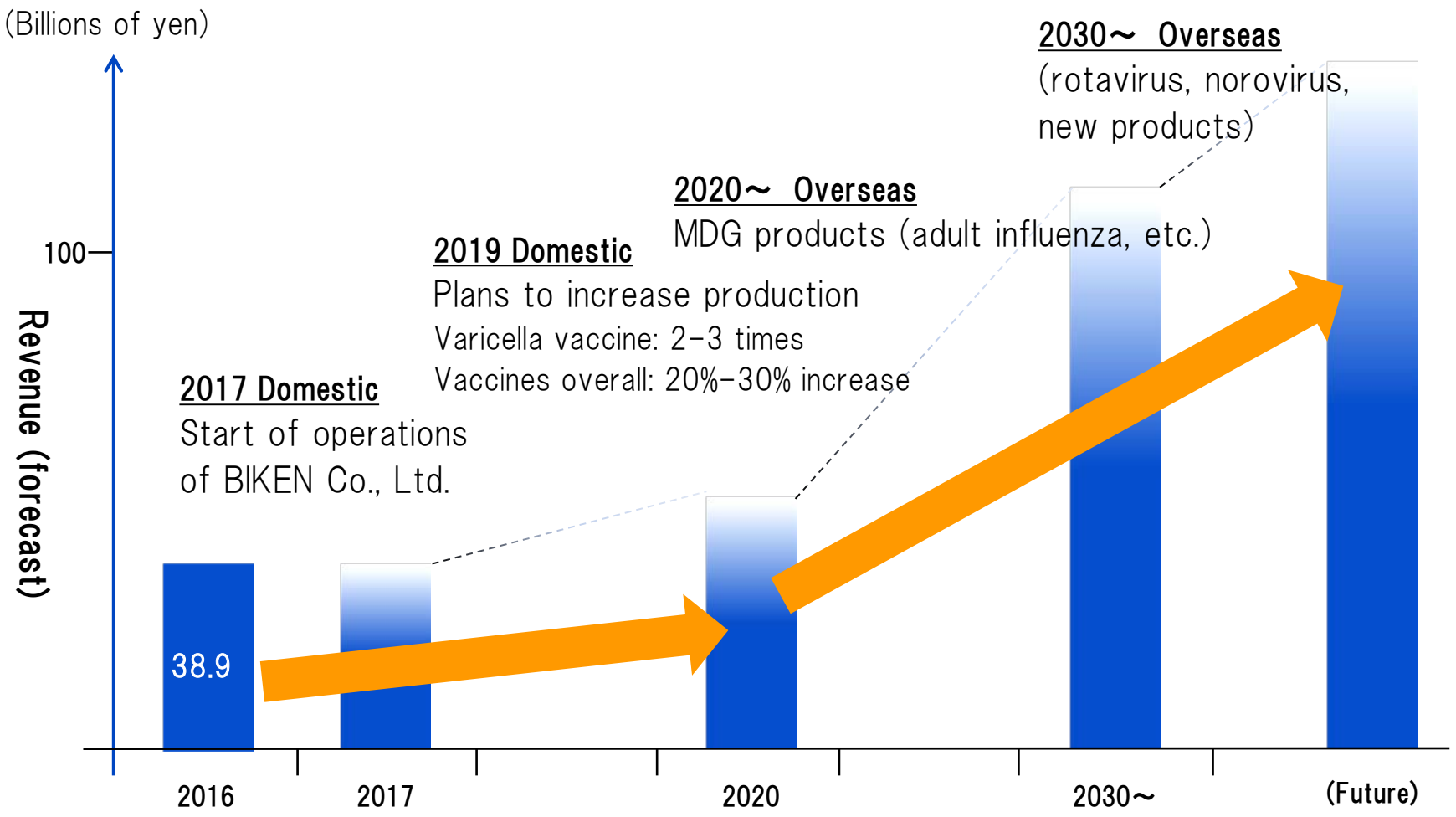
Neurological diseases
Radicava

Acquisition from outside

Vaccines

VLP vaccines

Numerical Targets (sales of more than ¥100.0 billion)



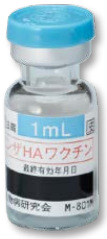
Aiming to Strengthen Domestic Business

History of Alliance between the BIKEN Foundation and MTPC

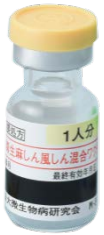
Open Up the Future

Mitsubishi Tanabe Pharma

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.

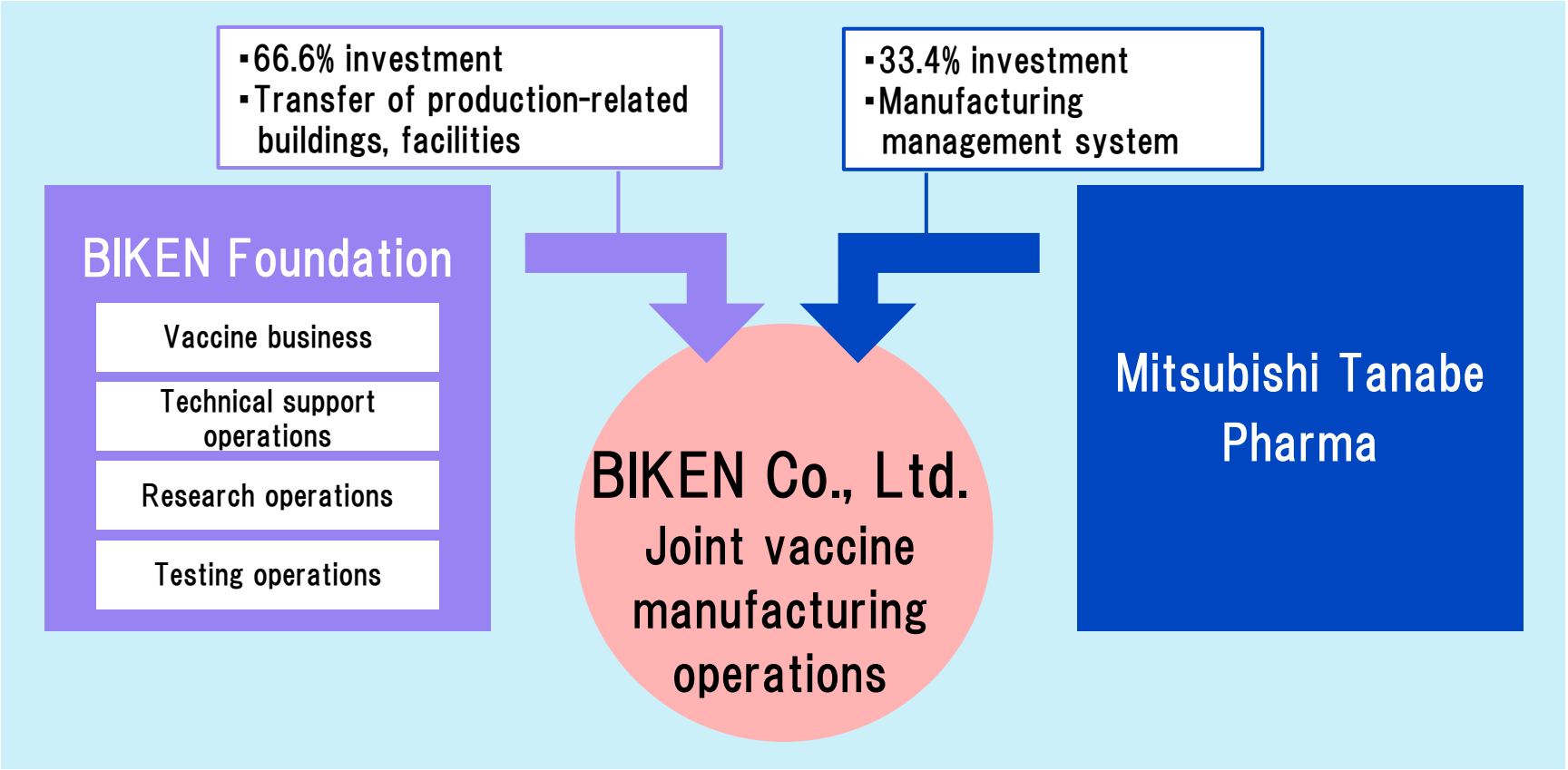
May 2017
Final agreement regarding establishment of joint venture

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.

Open Up the Future
Mitsubishi Tanabe Pharma



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

Targeting Expansion in the Scale of Production

Open Up the Future
Mitsubishi Tanabe Pharma

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

Seto Center
165,165㎡ 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)

Open Up the Future
Mitsubishi Tanabe Pharma

As of September 2017

Project		Stage	Features
TRIBIK	Combined vaccine for three diseases (DPT)	Approved	• Joint development with BIKEN Foundation* • Preparation for restart of sales for use in Stage 2
MT-2355	Combined vaccine for five diseases (DPT-IPV-Hib)	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

Open Up the Future
Mitsubishi Tanabe Pharma

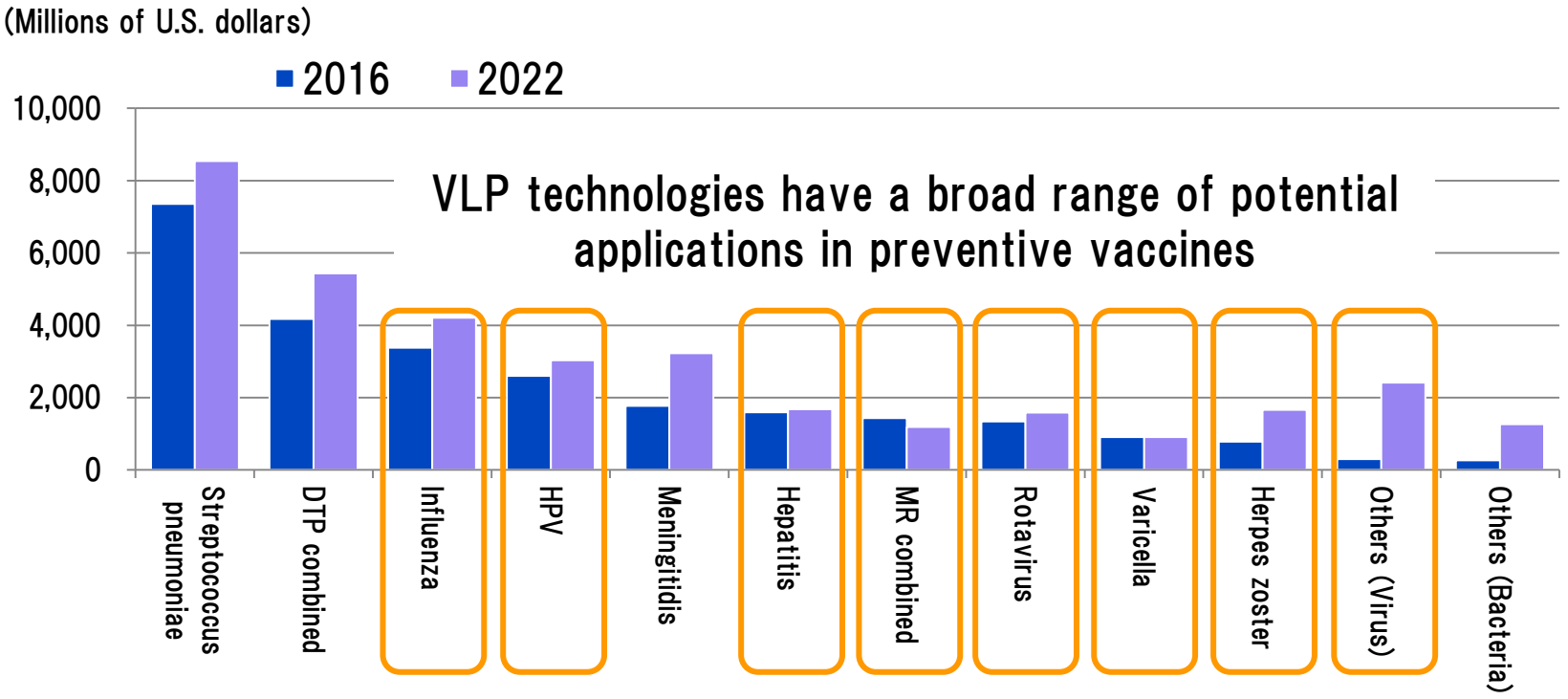
- Combination vaccine including measles-rubella: MMR, MRV, MMRV
- Combined vaccines including pertussis, diphtheria, tetanus, and inactivated polio (DPT-IPV): 5- and 6-disease combined vaccines
- Nasal vaccines and other improved influenza vaccines
- RS virus vaccine
- Herpes zoster

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

Overseas Business Strategy

Potential of VLP Technology

Open Up the Future
Mitsubishi Tanabe Pharma



* Among the components of the DTP combined vaccines, there is potential for the application of MDG technologies for polio and hepatitis
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)

Open Up the Future
Mitsubishi Tanabe Pharma

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

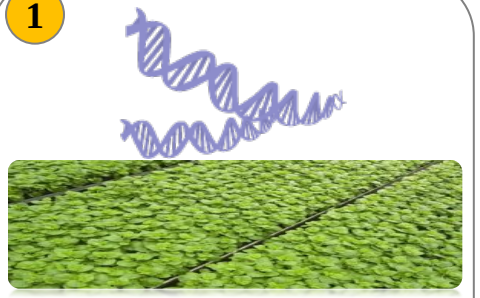
Research Lab

South Africa

Research Lab

Technology: Transient Plant-based Expression System

1



Starting material
- Gene(s) of interest
- Plants

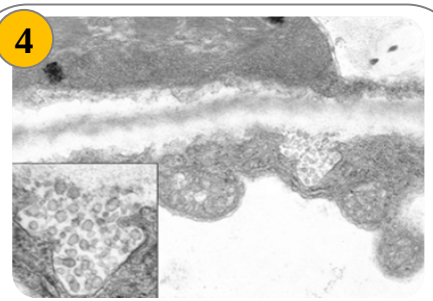
2

Infiltration
- Getting the vector into the leaf tissue

3

Incubation (7-10 days)
- Infiltrated plant cells producing & accumulating recombinant products

4

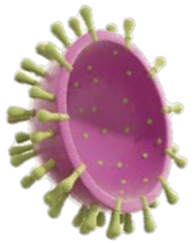


Extraction
- Releasing the recombinant products into solution

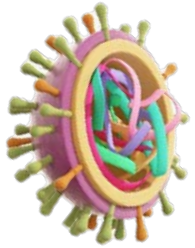
5

Purification
- Getting highly pure product

6



VLP



Flu virus

- **First VLPs ready in 19 days**
  - **In 2009, with the demonstration of production of research-grade H1 VLP in 19 days after strain identification**
- **10M doses produced in 1 month**
  - **In 2012, demonstration of the production of 10 million doses of a plant-based H1N1 influenza vaccine**

(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/)

medicago

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)**

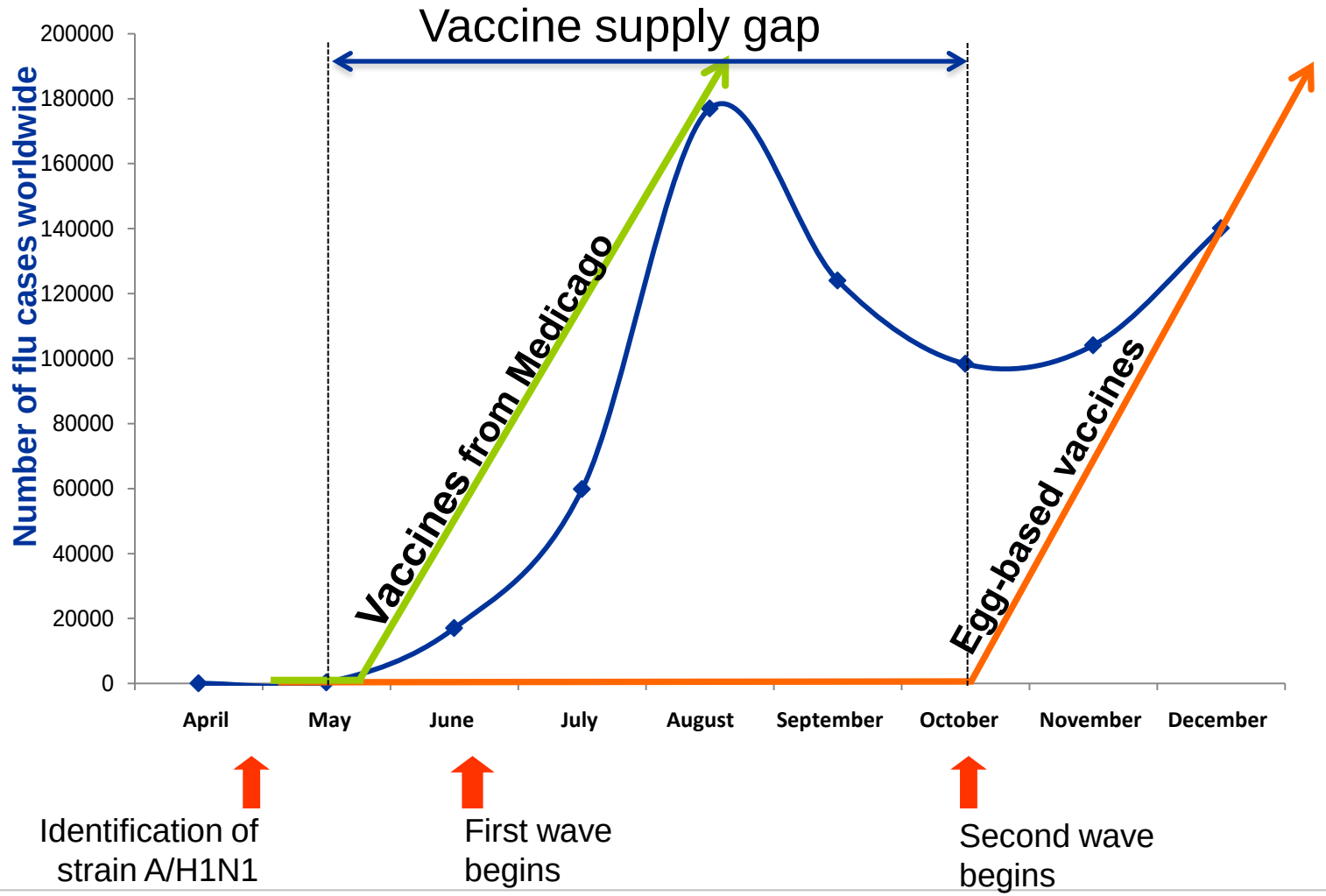
SCALABLE

- **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:

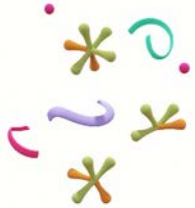
Live attenuated

*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)

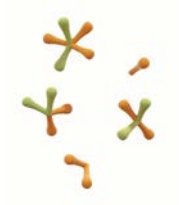


*First split flu vaccine licensed in **1968***

- 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** (Sequirus)

Subunit vaccine

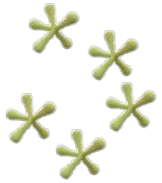


*First subunit flu vaccine licensed in the **1980**s*

- Safe: lacking core genetic material
- Need adjuvant

- **Fluad, Fluvirin , Flucelvax** (Sequirus)

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 Particules (VLP)

*First VLP quadrivalent flu vaccine candidate entered **Phase III in 2017***

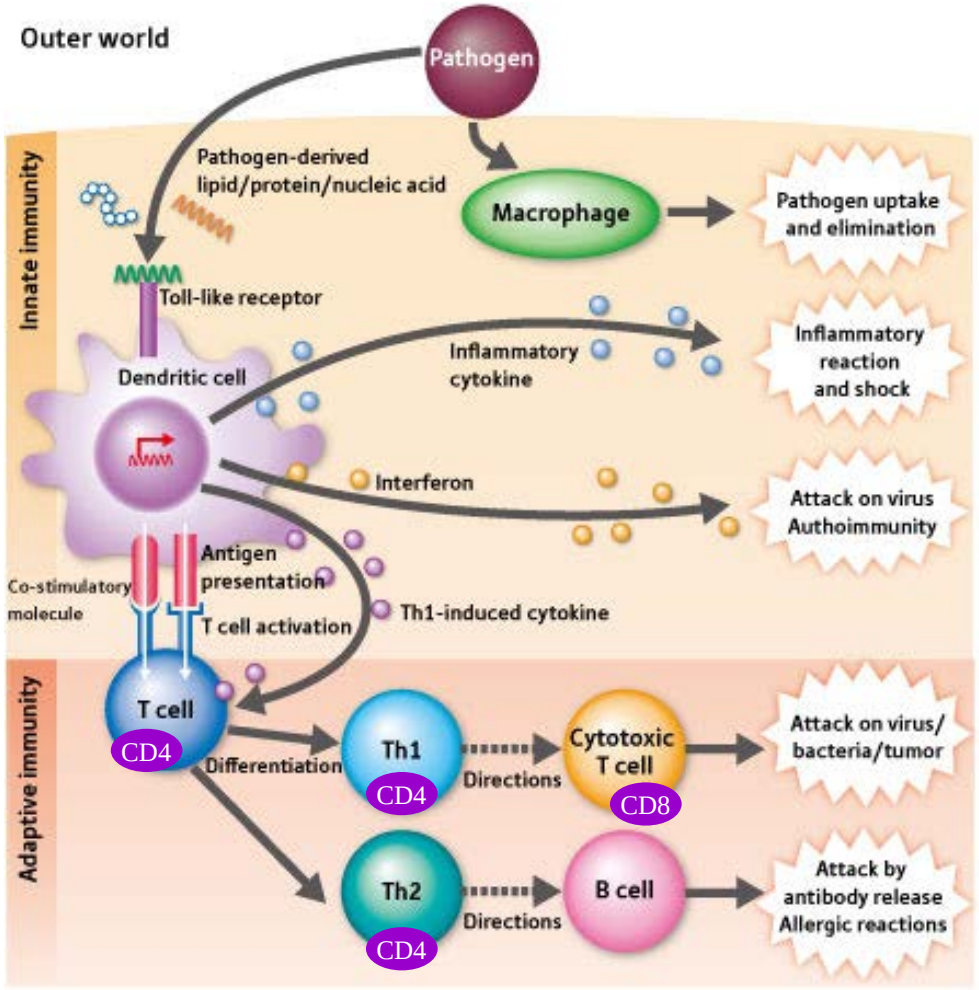
- Medicago's VLP is similar to a wild-type virus
- Lacking core genetic material (non-infectious)
- Highly efficient way to present antigens to the immune system

- **Medicago vaccine candidate**

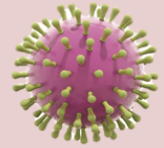
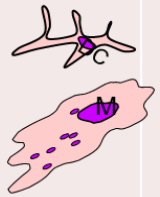
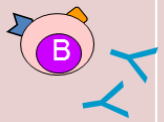
Egg-based vaccines
Cell-based vaccines
Plant- based vaccines

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

Different immune responses:

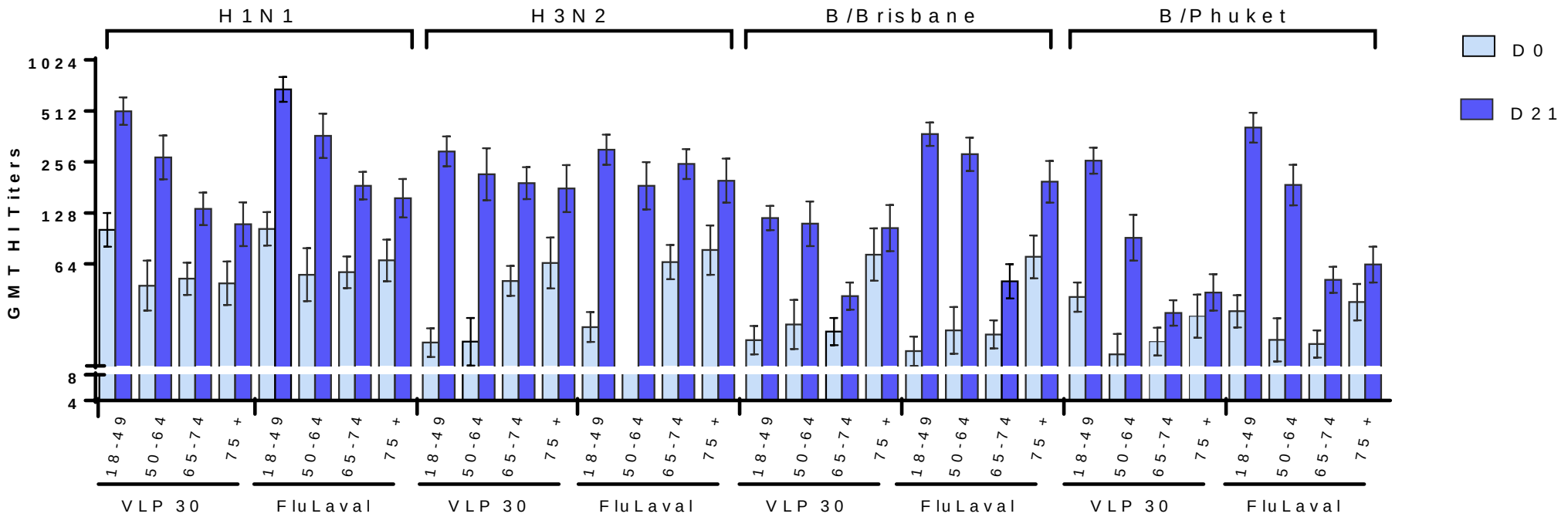


Immune responses in case of flu infection & flu vaccination:

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

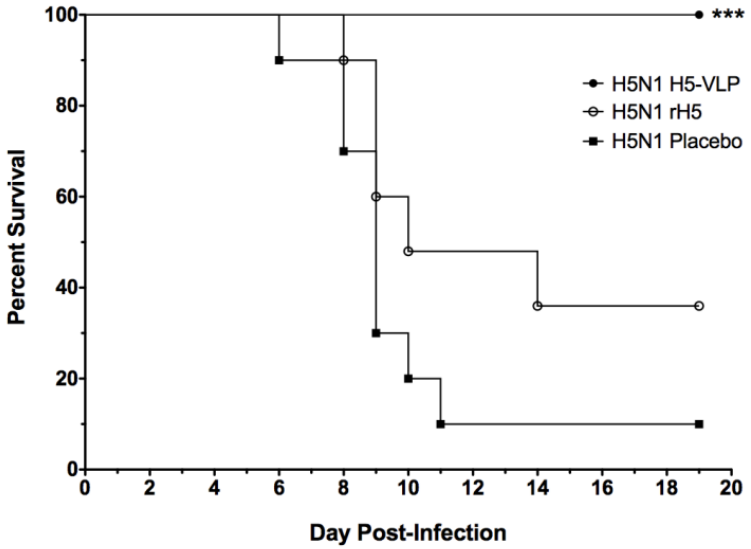
Observations from Pre-clinical studies

NIAID sponsored study

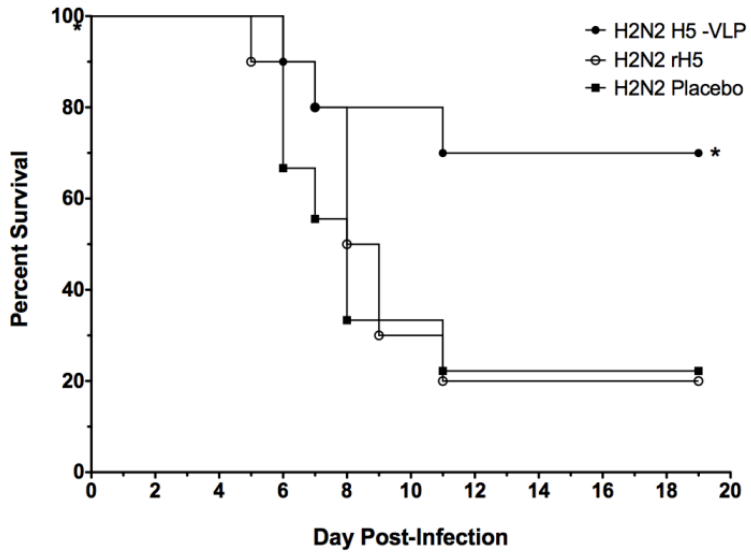
Cross-Protection in animals after a single dose of H5 VLP vaccine

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

Challenge against heterologous H5N1 Vietnam

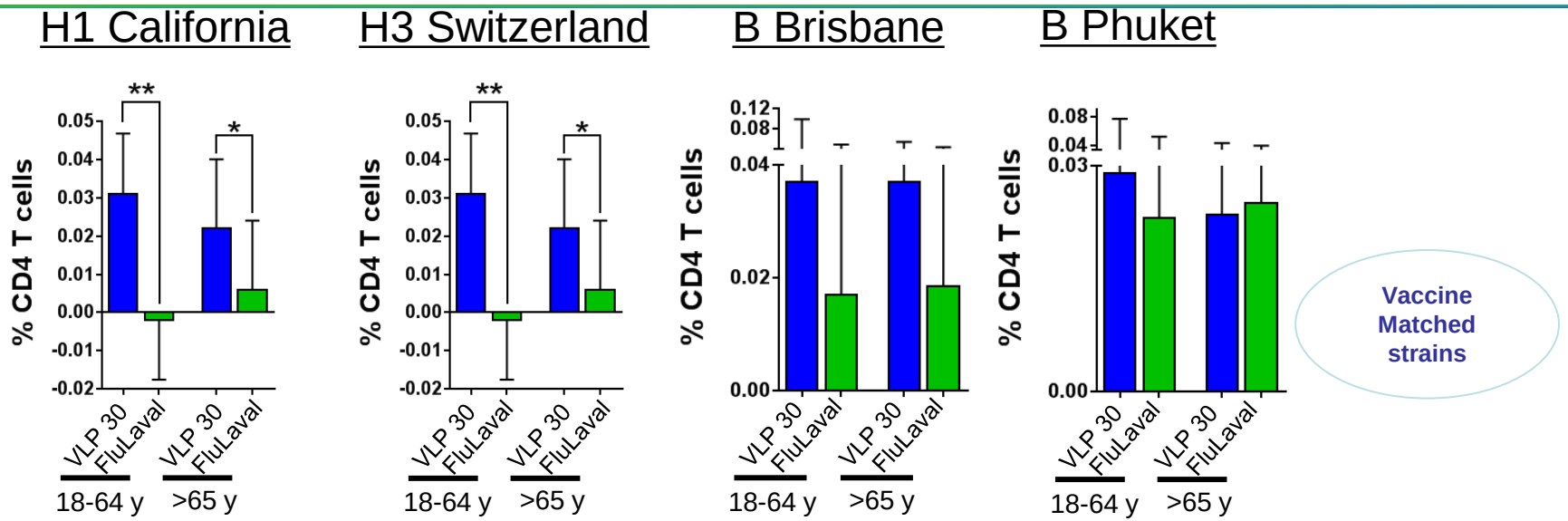


Challenge against heterosubtypic H2N2 Japan



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

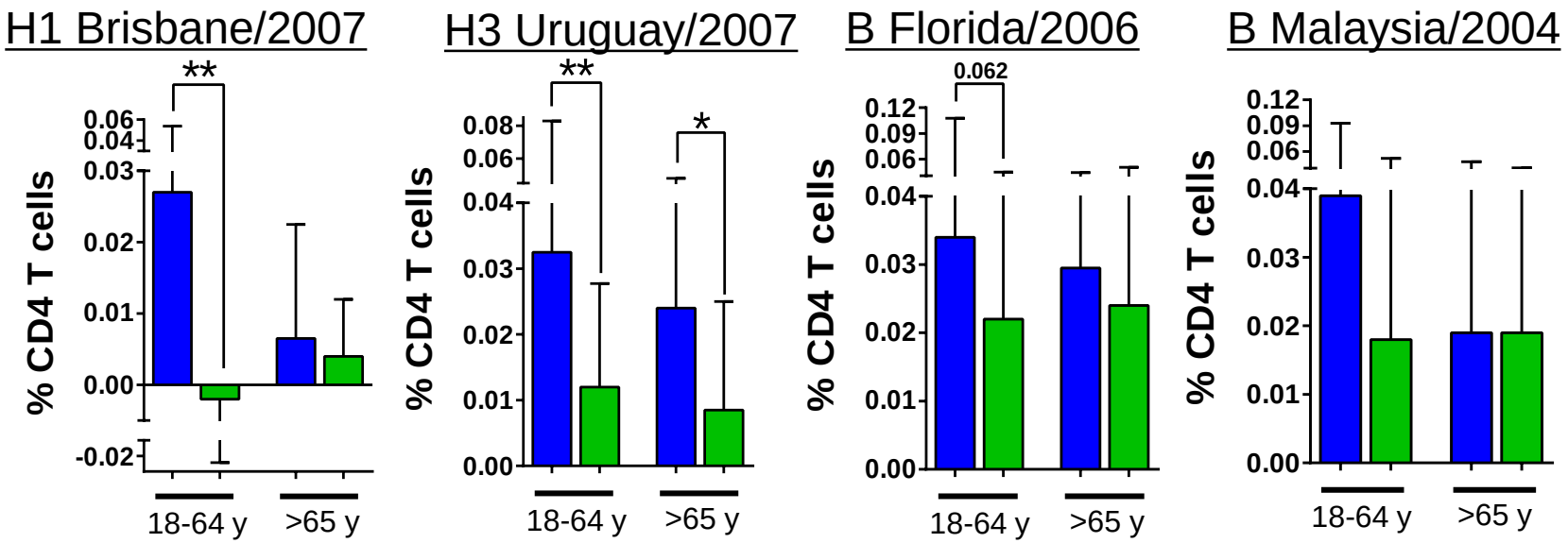
P<0.05*, P<0.01**, P<0.001*** Pairwise comparison of treatment groups uses Tukey-Kramer test after fitting a fixed effect model, or non-parametric Wilcoxon rank-sum test. 30 subjects per group for 18-64y, 45 subjects per group for >65y.

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



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

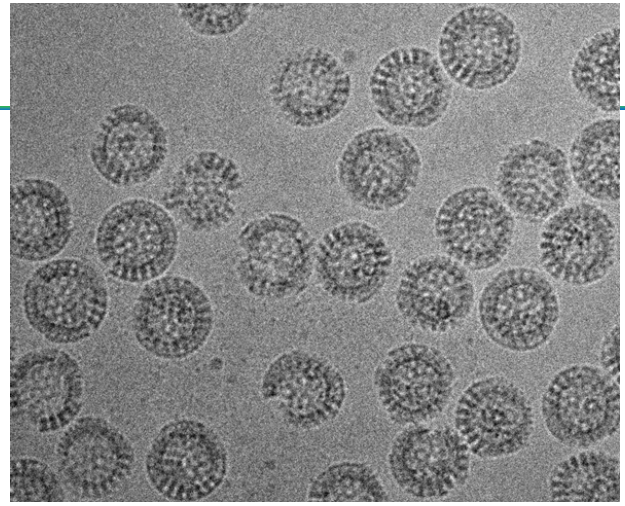
Competitive advantage of Medicago:

- 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

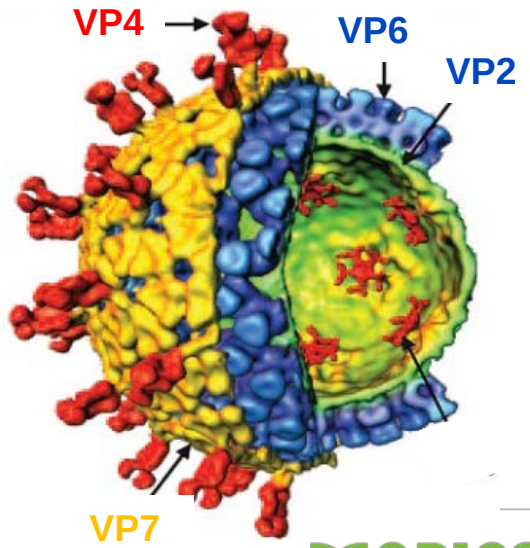
Leveraging the benefits of VLPs
Other indications in development – Rotavirus (MTPC)

- Induces severe diahrrea 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

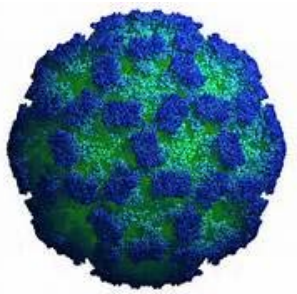
- First demonstration of triple layer VLP made by a plant system
  - Protected by patents
- Plant-made RLPs show no risk of intussusception



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

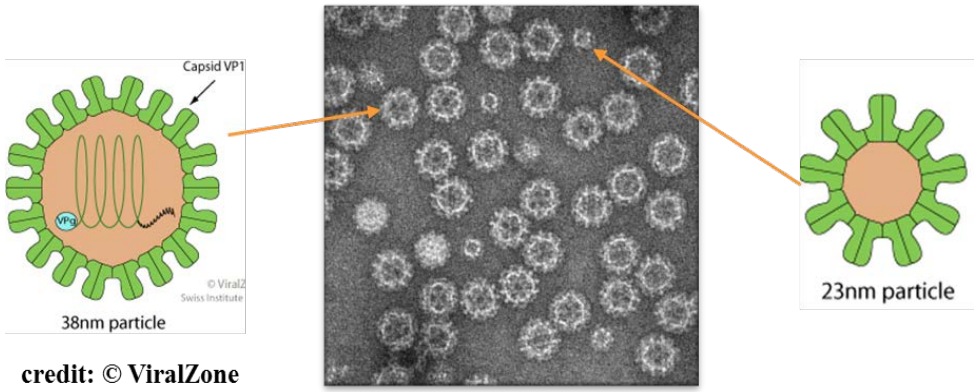


Leveraging the benefits of VLPs
Other indications in development – Norovirus



- Induces severe diahrrea 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



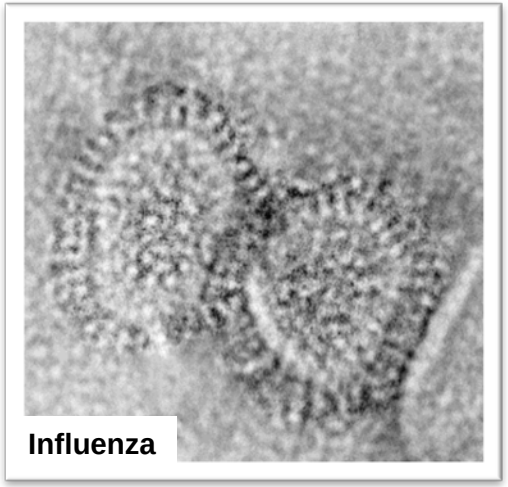
credit: © ViralZone

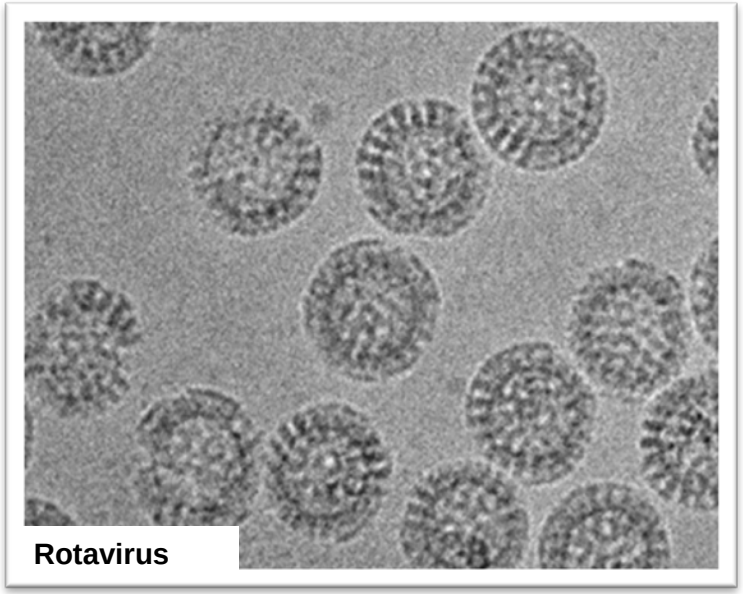
credit: Medicago

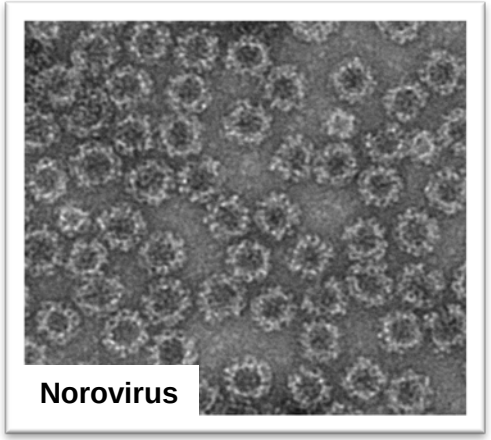
Plant-produced norovirus-like particles

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

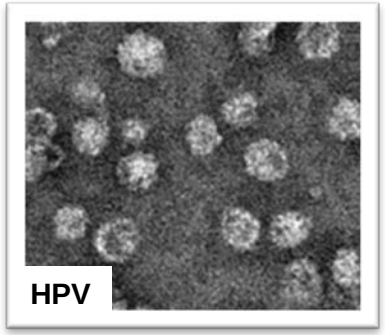
- **Enveloped viruses**
  - o Influenza
  - o West-Nile virus
  - o Hepatitis B
  - o HIV
  - o SARS
  - o Rabies
- **Non-enveloped viruses**
  - o Rotavirus
  - o Norovirus
  - o EV71
  - o HPV


Influenza


Rotavirus


Norovirus


EV71


HPV

Our platform is also versatile supporting development of antibodies

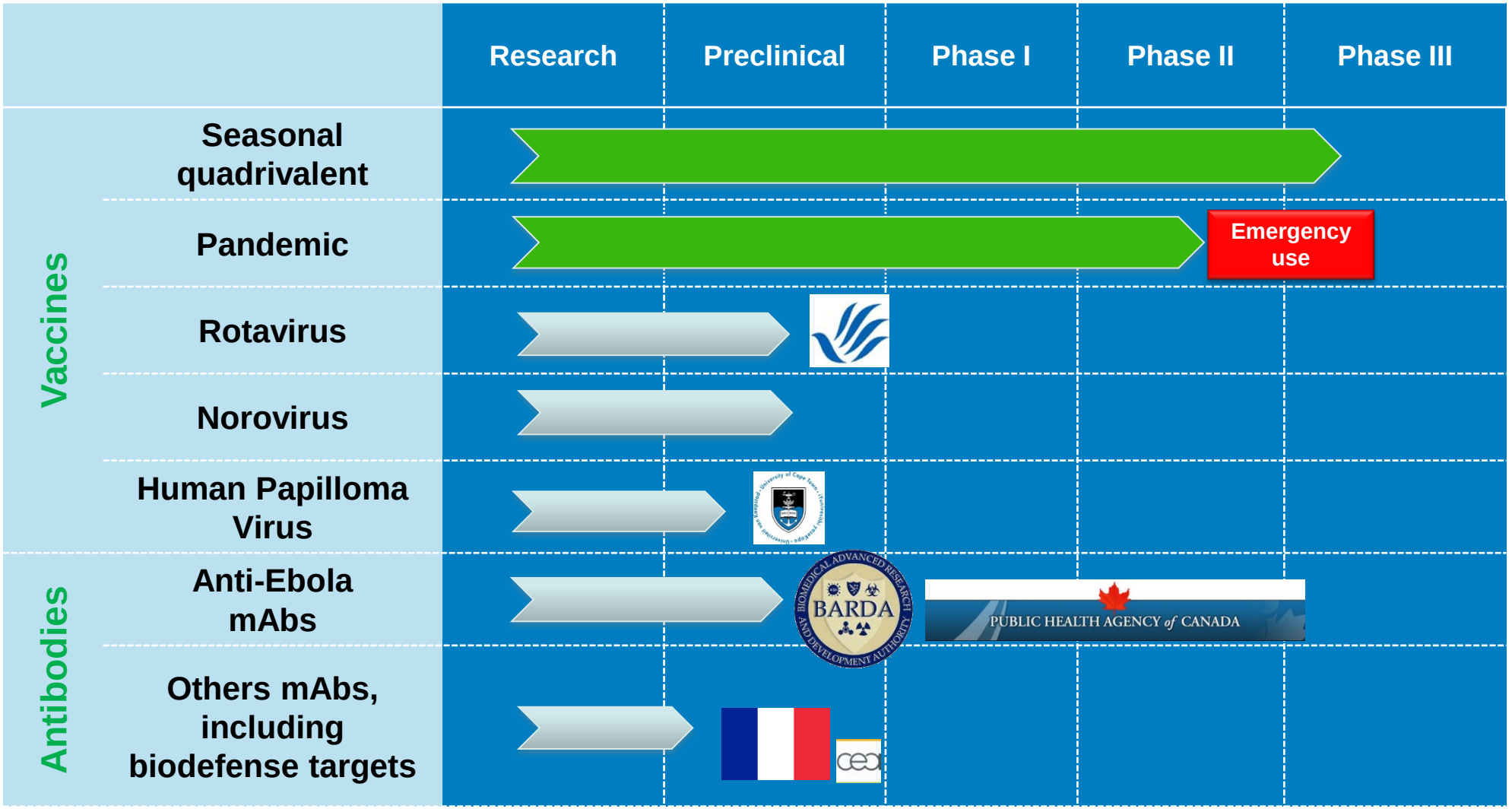
Antibody development is long, costly and suffers from flexibility

- 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**
  - Our proprietary VLP*Express*™ discovery platform provides unsurpassed capacity for the discovery and screening of antibody candidates
  - 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