Development of Recombinant Pertussis Vaccines

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Pertussis Vaccines

WHO Position Paper – September 2015

Pertussis (whooping cough) is an important cause of death in infants worldwide, and continues to be a public health concern despite high vaccination coverage. In 2013, according to WHO estimates, pertussis was still causing around 63 000 deaths in children aged <5 years. Two types of pertussis vaccines are available: wP vaccines and aP vaccines.

A switch from wP to aP vaccines for the primary schedule should only be considered if additional periodic booster or maternal immunization can be assured and sustained. National programmes currently administering wP vaccination should continue to use wP vaccines for primary vaccination series. National programmes currently using aP vaccine may continue using this vaccine but should consider the need for additional booster doses and additional strategies such as maternal immunization in case of resurgence of pertussis.

Resurgence of Pertussis

An Increasing Concern Worldwide

- Waning immunity
- Genetic shifts of circulating Bp strains

Table 1. Possible Vaccination Strategies to Control the Resurgence of Pertussis

Strategy	Remarks
Return to the use of wcP	Probably unacceptable
Develop less-reactogenic wcP	Not yet done
Maternal vaccination to provide transplacental antibody to protect newborn	Now generally recommended
Vaccination of newborn contacts (cocoon strategy)	Difficult to obtain complete coverage
More frequent boosters with acP	Costly and difficult to put in place
Change antigens in acP to those from currently circulating strains	Uncertain effect
Increase quantities of current antigens	Would require large trials
Inactivate PT by genetic mutation or milder chemical	Probably advisable to increase immunogenicity
Add new virulence factors	Would require large trials
Use stronger adjuvants	May require large trials
Administer live attenuated *Bordetella pertussis* intranasally	Early development Probably best as a boost strategy

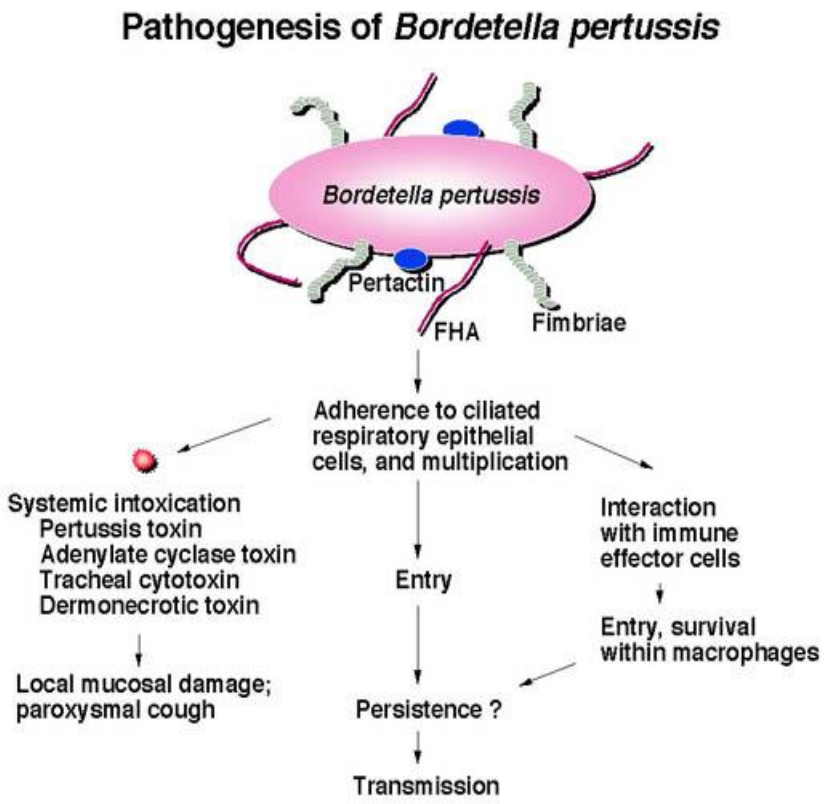
Abbreviations: acP, acellular pertussis vaccine; PT, pertussis toxin; wcP, whole-cell pertussis vaccine.

Source: Plotkin A. (2013) Clinical Infectious Diseases

Bordetella pertussis

Pathogenesis

- **PT**
  - Principal toxin secreted by Bp, 5 subunits, A-B structure
  - Many pathologic effects mediated by ADP ribosylation of G protein effectors
- **FHA**
  - Filamentous adhesion factor
- **PRN ("69K")**
  - Impurity present in Japanese T-type vaccines
  - RGD sequences promoting adhesion to cells
- **Agg 2+3**
  - or Fimbriae



Pertussis Vaccines

Three Types of Vaccines

- **Whole-cell Pertussis vaccines (wP)**
- **Acellular Pertussis vaccines using chemically detoxified Pertussis Toxin (cPT)**
  - Co-purified antigens (Asia)
  - Individually purified antigens (Western countries)
- **Recombinant Pertussis vaccines**
  - Live-attenuated (nasal route)
  - Inactivated
    - Genetically-detoxified Pertussis Toxin
    - Recombinant antigens such as PT, ACT, PRN…

Call for New Pertussis Vaccines

Genetically-Inactivated PT, the Solution ?

The Diphtheria and Pertussis Components of Diphtheria-Tetanus Toxoids–Pertussis Vaccine Should Be Genetically Inactivated Mutant Toxins

John B. Robbins,[1] Rachel Schneerson,[1] Birger Trollfors,[2] Hiroko Sato,[3] Yuji Sato,[3] Rino Rappuoli,[3] and Jerry M. Keith[1]

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Vaccine

Vaccine 25 (2007) 2811–2816

The rise in pertussis cases urges replacement of chemically-inactivated with genetically-inactivated toxoid for DTP

John B. Robbins[a,*], Rachel Schneerson[a], Jerry M. Keith[a], Joseph Shiloach[b], Mark Miller[c], Birger Trollors[d]

Relative Contribution of Th1 and Th17 Cells in Adaptive Immunity to *Bordetella pertussis*: Towards the Rational Design of an Improved Acellular Pertussis Vaccine

Pádraig J. Ross[1], Caroline E. Sutton[1,3], Sarah Higgins[1,3], Aideen C. Allen[1], Kevin Walsh[1], Alicja Misiak[1], Ed C. Lavelle[2], Rachel M. McLoughlin[3], Kingston H. G. Mills[1]*

1 Immune Regulation Research Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland, **2** Adjuvant Research Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland, **3** Host Pathogen Interactions Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland

Genetically Detoxified Pertussis Toxin Induces Th1/Th17 Immune Response through MAPKs and IL-10-Dependent Mechanisms[1]

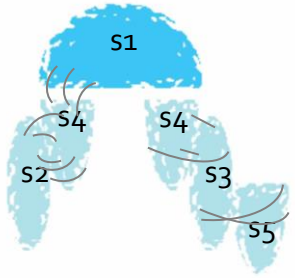
Maria Nasso,[2]* Giorgio Fedele,[2]* Fabiana Spensieri,[3]* Raffaella Palazzo,* Paolo Costantino,[†] Rino Rappuoli,[†] and Clara Maria Ausiello[4]*

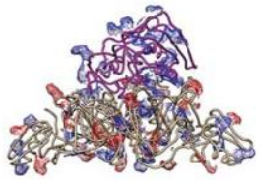
Genetically Detoxified Pertussis Toxin

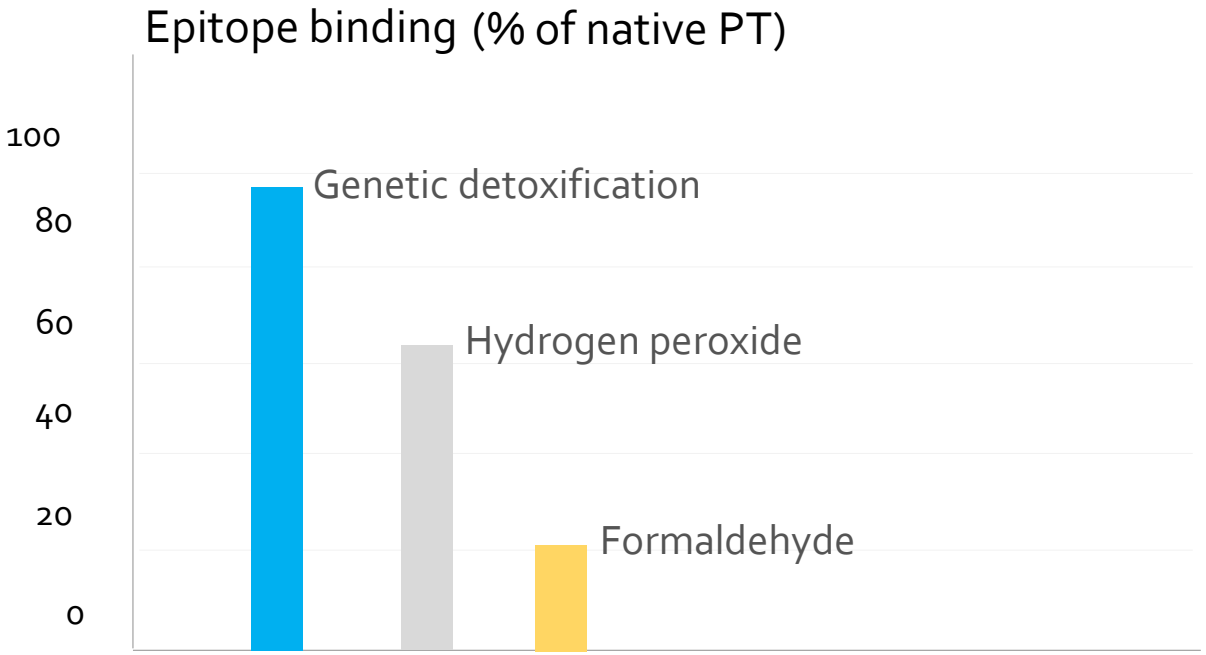
A Non-Toxic and Superior Immunogen

rPT is a PT devoid of toxicity while maintaining the other properties of the native PT.

cPT introduces dramatic changes on the toxin surface.







- Chemical treatment can destroy up to 80% of surface epitopes
- The rPT preserves the epitopes for T-cell binding significantly better than cPT.

Source: Ibsen H, 1996

Chiron Pediatric DTaP containing 5 µg rPT

84% Efficacy in US NIAID-Sponsored Italian Efficacy Trial

Table 1. Efficacy trials of acellular pertussis vaccine

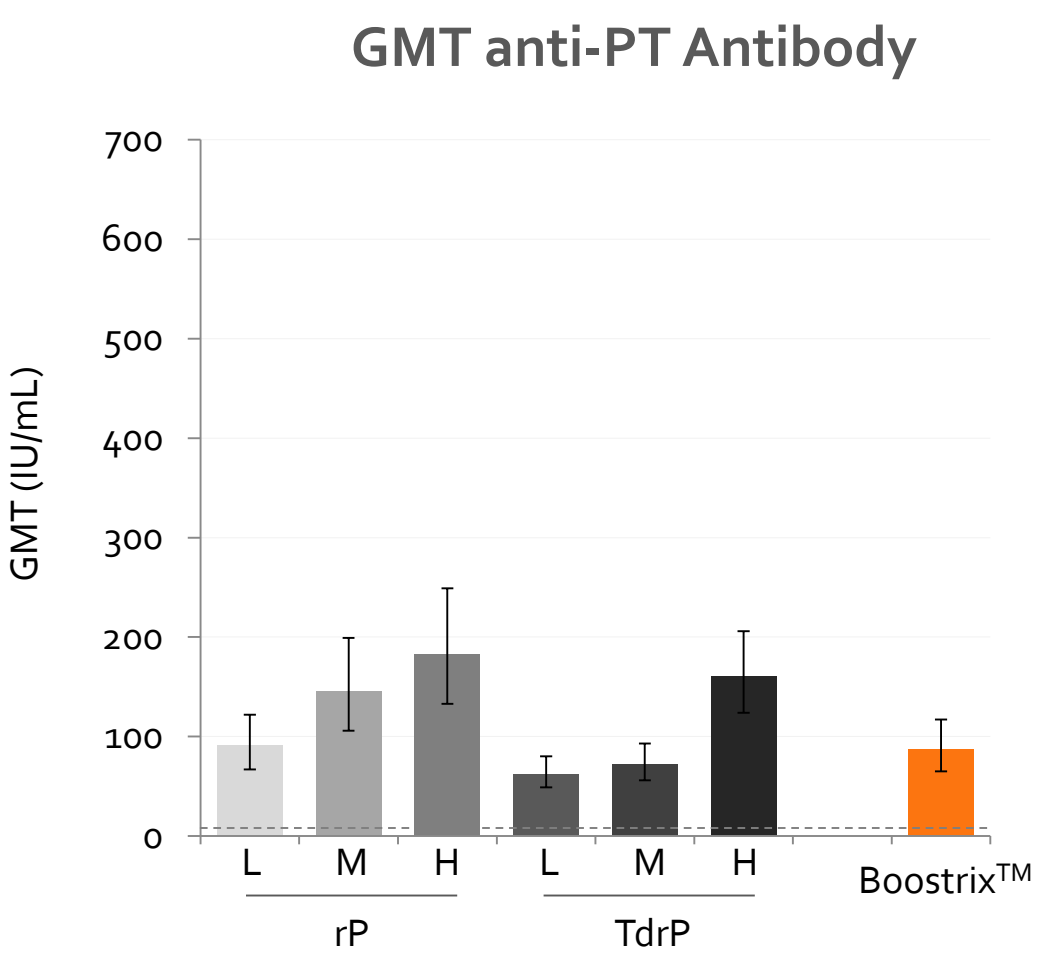
Study site (Period)	Vaccine	Manufacturer	Component (µg P/dose) PT	FHA	PRN	Agg(s)	Dose	VE(95% CI)
Sweden	DTaP(2)	SKB	25	25	0	0	3	59(51–66)
(1992–1995)	DTaP(5)	CLL	10	10	3	5	3	85(81–89)
	DTwP	CLI	—	—	—	—	3	48(37–58)
Sweden	DTaP(1)	NAV	40	0	0	0	3	71(63–78)
(1991–1994)								
Sweden	aP(2)	Biken/JNIH6	23	23	0	0	2	92(83–96)
(1986–1990)	aP(1)	Biken/JNIH7	38	0	0	0	2	79(66–87)
Italy	DTaP(3)	CB	5	2·5	2·5	0	3	84(76–90)
(1992–1993)	DTaP(3)	SKB	25	25	8	0	3	84(76–90)
	DTwP	CLI	—	—	—	—	3	36(14–52)
Germany	DTaP(2)	B/CL	23	23	0	0	3	82(68–90)
(1993–1995)	DTwP	BW	—	—	—	—	3	96(87–99)
Germany	DTaP(3)	SKB	25	25	0	0	4	89(77–95)
(1992–1994)	DTwP	BW	—	—	—	—	4	97(83–99)
Germany	DTaP(4)	L/T	3·2	34·4	1·6	0·8	4	82(75–)
(1991–1994)	DTwP	L	—	—	—	—	4	91(86–)
Senegal	DTaP(2)	PM	25	25	0	0	3	74(52–86)
(1990–1994)	DTwP	PM	—	—	—	—	3	91(79–96)

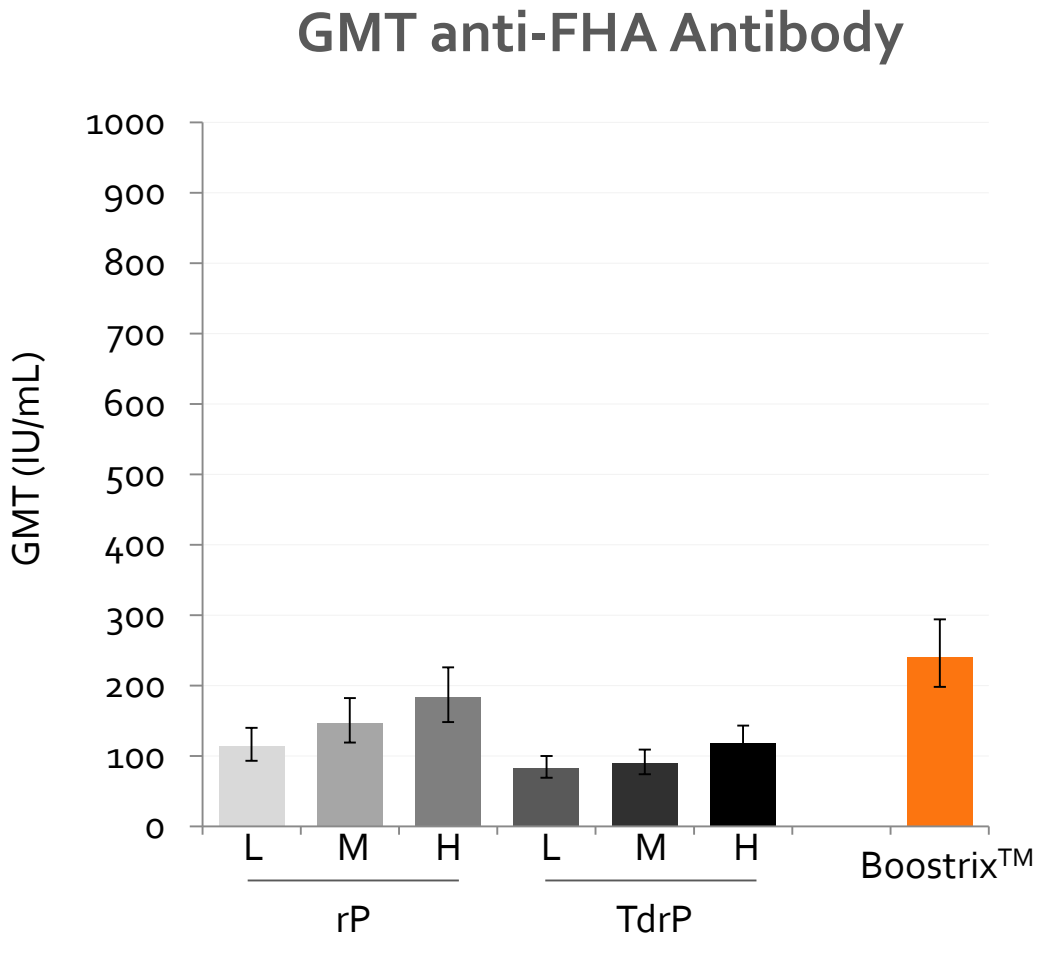
B/CL: Biken/Connaught, BW: Behringwerke, CB: Chiron Biocine, CLI: Connaught Laboratories Inc. (USA), CLL: Connaught Laboratories Limited (Canada), L: Lederle, L/T: Lederle/Takeda, NAV: North American Vaccine, PM: Pasteur Merieux, SKB: SmithKline Beecham.

Source: Y. Sato and H. Sato, Biologicals, 1999

GSK (Novartis) Adult aP/TdaP in Phase I Study

Immunogenicity Results at Day 30 post vaccination



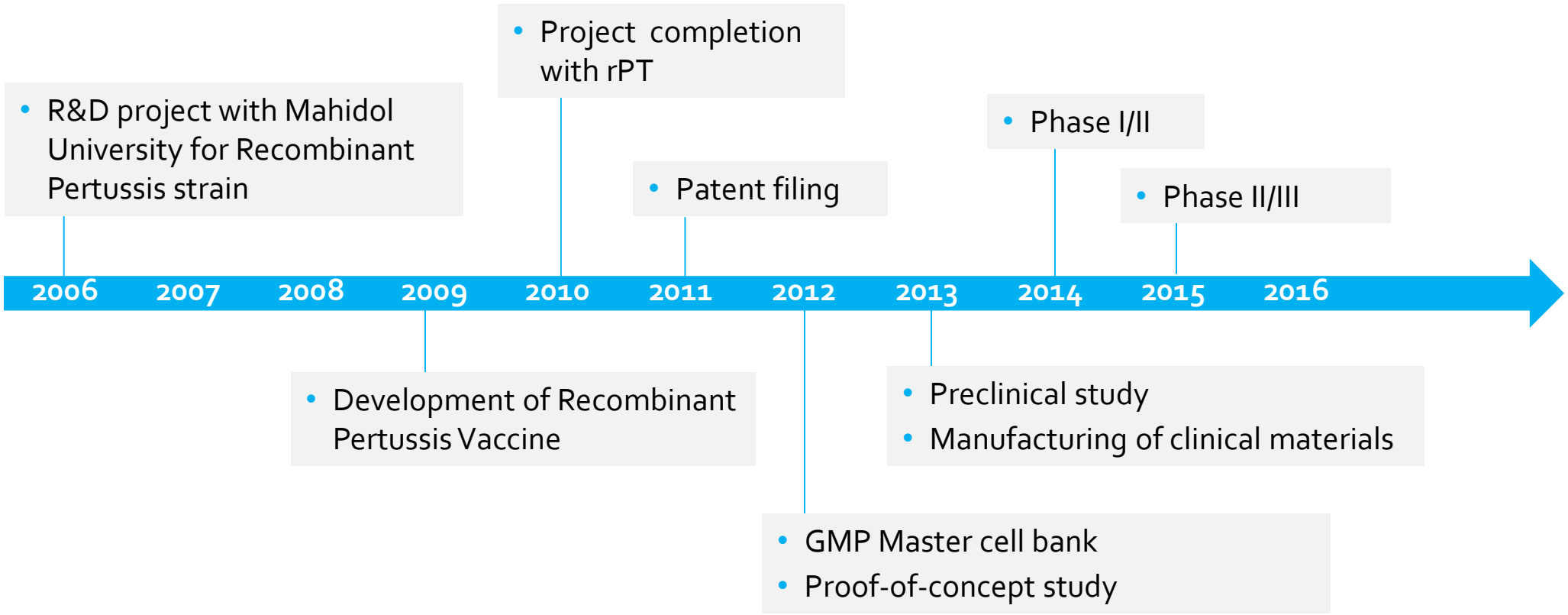


https://clinicaltrials.gov/ct2/show/NCT01529645

BioNet Recombinant Acellular Pertussis Vaccines

BioNet Pertussis Project

Timelines and Status

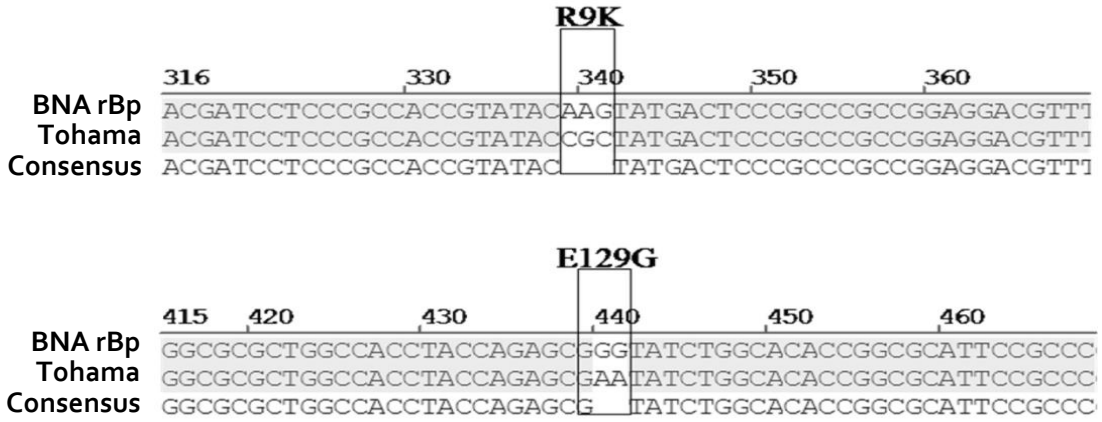


Design of *Bordetella pertussis* Construct

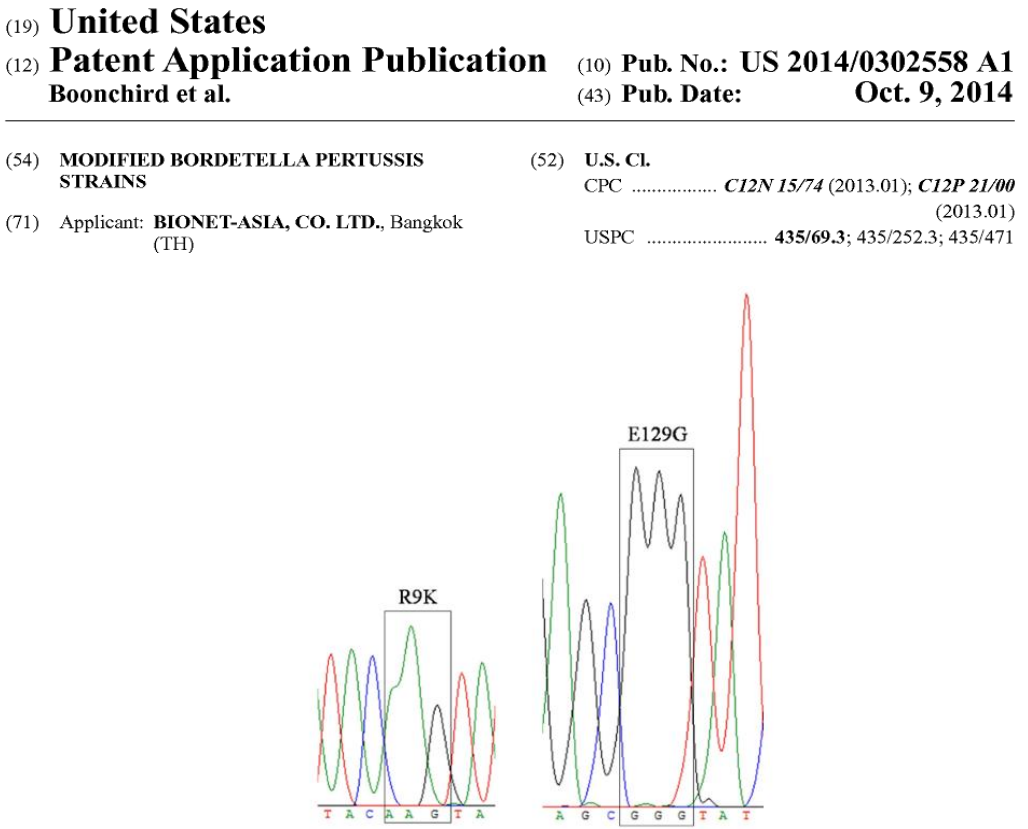
Scar-free Recombinant Pertussis Strain (PCT Publication: WO 2013/141823)

BioNet modified Bp strain

no antibiotic resistance marker remaining after strain construction



- Mutations: ARG9 to LYS9 and GLU129 to GLY129
- Resulting in the loss of its catalytic and toxic effects



(19) **United States**

(12) **Patent Application Publication**

Boonchird et al.

(10) **Pub. No.: US 2014/0302558 A1**

(43) **Pub. Date: Oct. 9, 2014**

(54) **MODIFIED BORDETELLA PERTUSSIS STRAINS**

(71) Applicant: **BIONET-ASIA, CO. LTD.**, Bangkok (TH)

(52) **U.S. Cl.**

CPC ***C12N 15/74*** (2013.01); ***C12P 21/00*** (2013.01)

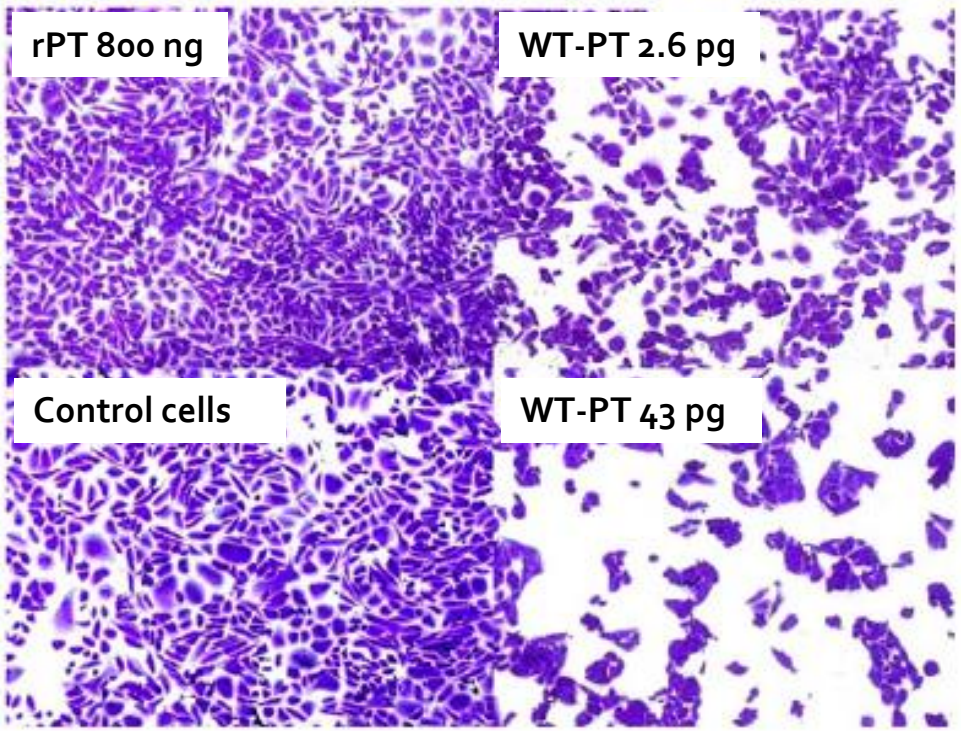
USPC **435/69.3**; 435/252.3; 435/471

Source: Buasri *et al.* (2012) *BMC Microbiology* 12:61

BioNet Recombinant Pertussis Toxin

Loss of Toxicity by Genetic Modification

PT-Specific Toxicity Test in CHO cells



- Toxicity of wild type PT by clustering of CHO cells in dose-dependent manner.
- Reduced toxicity of recombinant PT by a factor of 5×10^5 to 1×10^6
- Purified rPT was successfully inactivated by mutation at 9K/129G at S1 subunit resulting in loss of catalytic toxicity of PT.

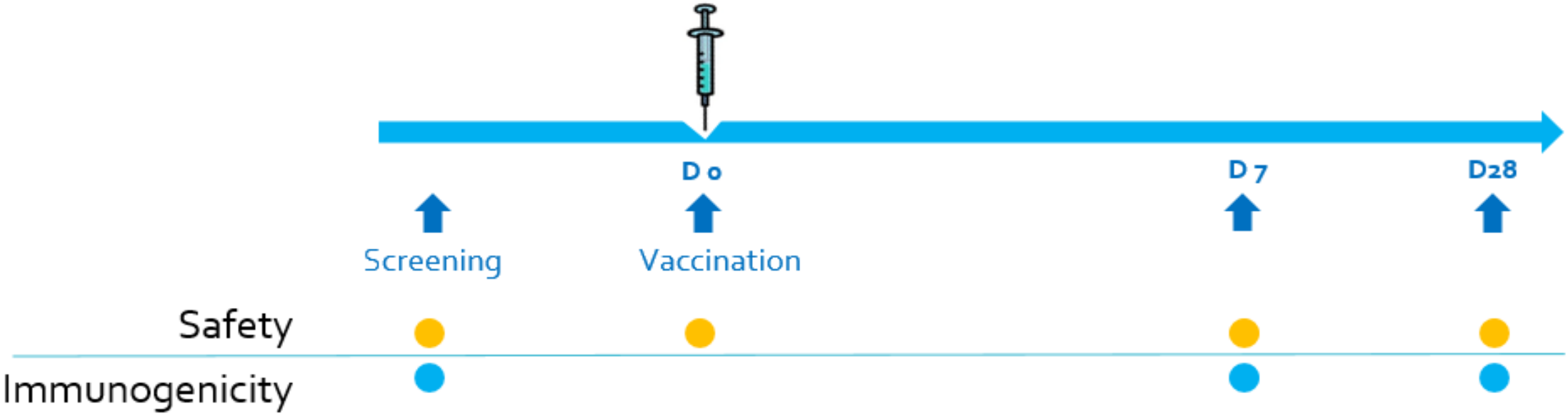
Source: Buasri *et al.* (2012) *BMC Microbiology* 12:61

TDA101

Clinical Study of BioNet rP/TdrP

Phase I/II Study Procedures Overview

- **Objective:** To assess safety and immunogenicity of a single injection of BNA's rP or BNA's TdrP or Adacel® (Sanofi Pasteur) vaccines
- **Study Population:** Healthy adult volunteers (Male & Female), 18-35 years of age
- **Principle Investigator:** Prof. Chukiat Sirivichayakul, Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand



BioNet Clinical Study

Summary

- Overall, subjects in BNA's rP & TdrP vaccine groups had similar local, systemic post-immunization reactions and AEs than subjects in the Adacel® group (data not shown).

- One month after vaccination

  - ELISA anti-PRN GMTs were similar in BNA's rP & TdrP groups and in Adacel® group.

  - ELISA anti-PT and anti-FHA GMTs were statistically significantly higher in BNA's rP & TdrP groups than in Adacel® group.

BioNet rPT in patch soon in Phase I Study

Preclinical Results Published on June 9th, 2015 in Vaccine

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Needle-free and adjuvant-free epicutaneous boosting of pertussis immunity: Preclinical proof of concept

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