



September, 2017



Translational Biomedical Research at NIDVD/XMU-SPH



School of Public Health



SPH on Xiang'an Campus



Introduction of SPH

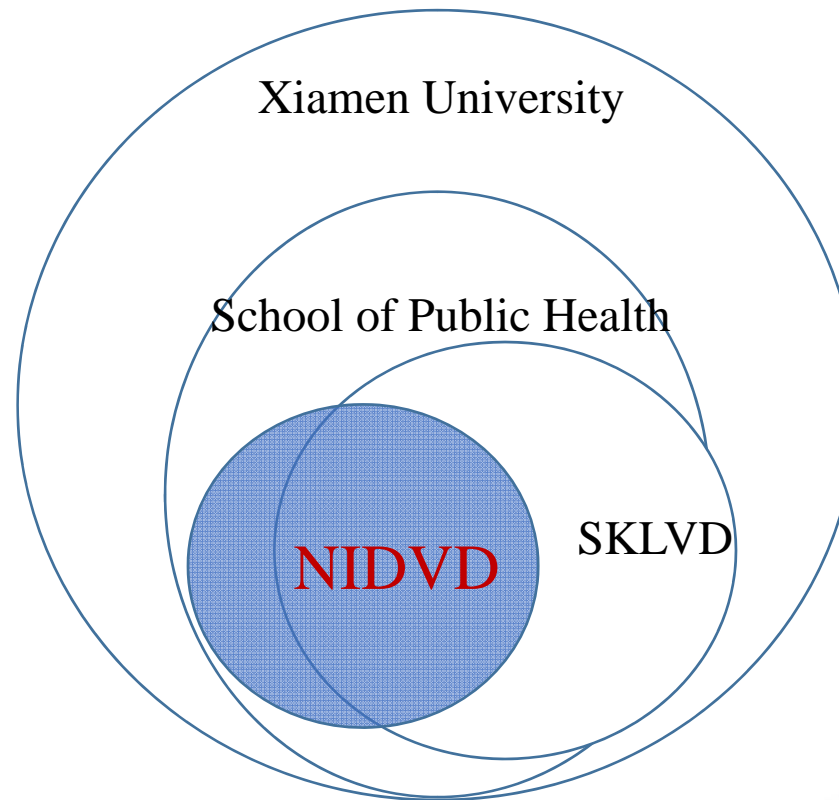
- **Newly established since 2011**, by merging the Department of Preventive Medicine (**DPM**) and National Institute of Diagnostics and Vaccine Development in infectious diseases (**NIDVD**).
- There are **76** full-time faculty members, including **19** professors, **18** associate professors. And there are **37** adjunct professors from all over the world.
- Currently have **415** undergraduate students , **150** graduate students and **46** PhD students.
- The total area of School of Public Health is about 25,000 m²,



NIDVD

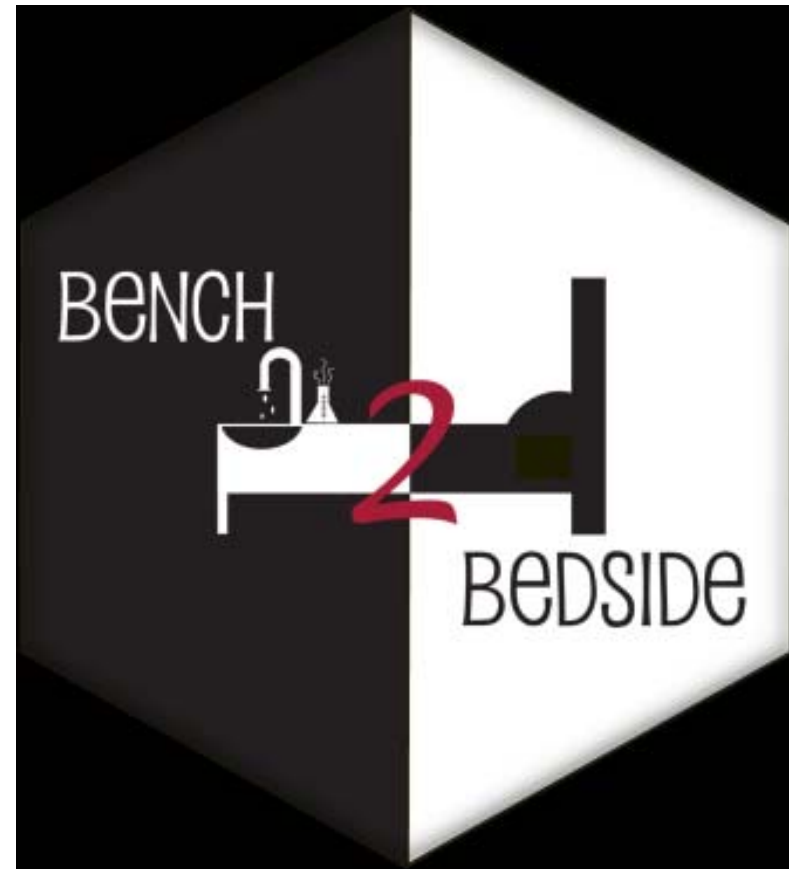
National Institute of Diagnostics and Vaccine Development in infectious diseases

- Xiamen University (1921-)
- **NIDVD** (2005-)
- SKLVD (2013-)
State Key Laboratory of
Mol. **Vaccinology** and Mol.
Diagnostics



What do we do?

- Bridging the gap – B2B

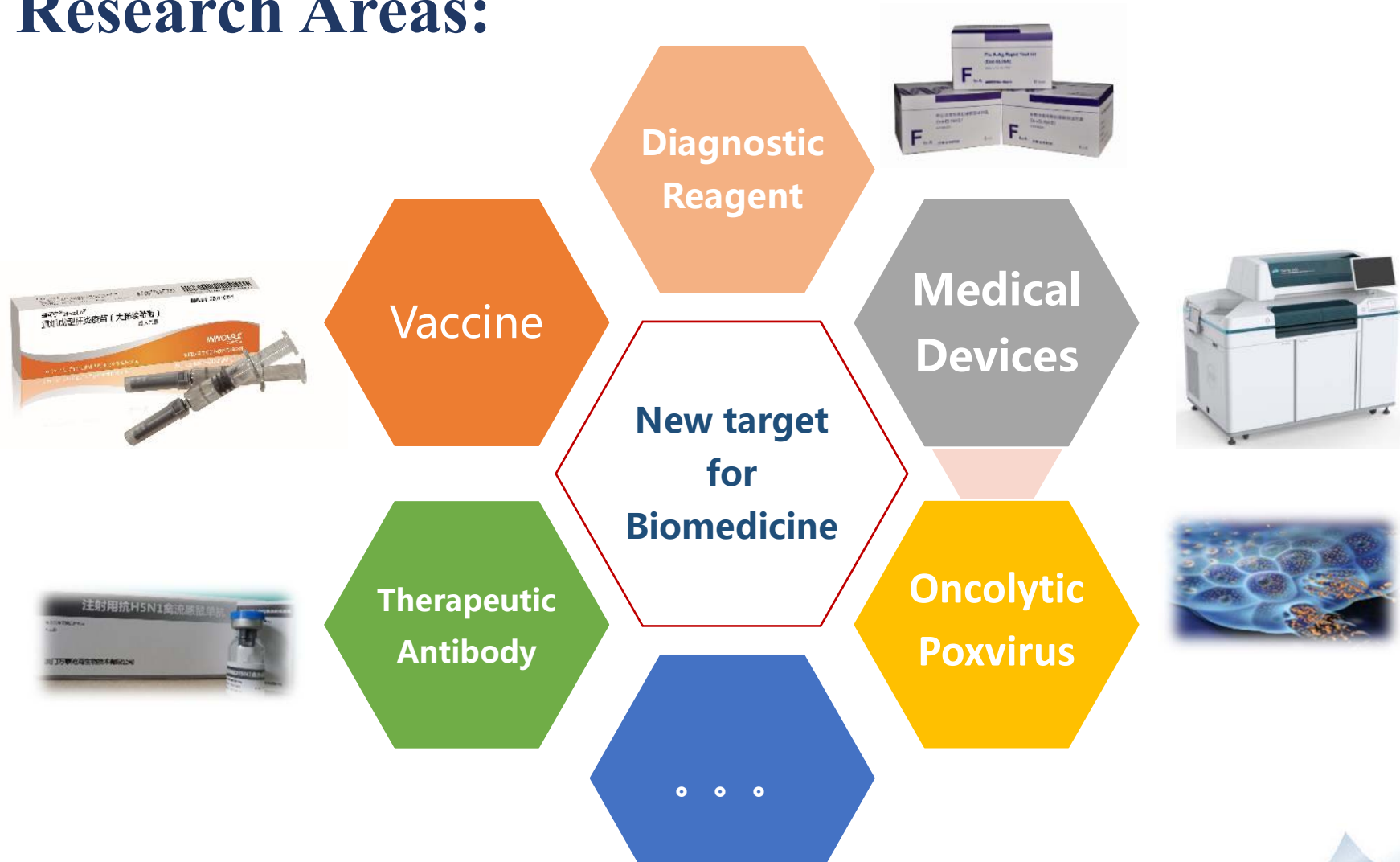


Research Areas:

~90% in infectious Diseases

~10% in Oncology

Research Areas:



- ✓ 1 First-class new medicine
- ✓ >100 diagnostic reagents
- ✓ 1 automated diagnostic device
- ✓ 2 portable diagnostic devices

- ✓ 14 received CE marked
- ✓ 2 WHO PQ'ed
- ✓ 1 approved in Taiwan
- ✓ 2 clinical test license of vaccine

Projects completed or ongoing (2012-2017)

Project sources	Number
National Level Projects	79
Ministry Level and Provincial Level Projects	45



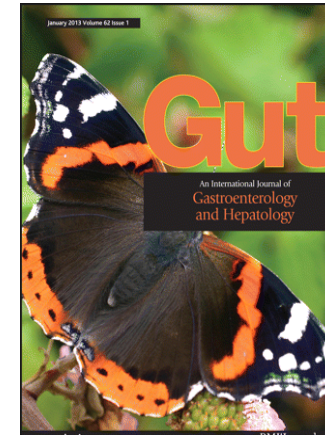
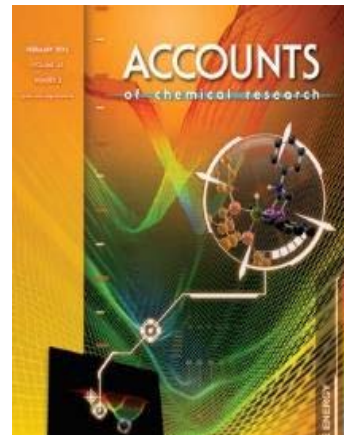
Publications (2012-2016)

SCI indexed Papers, 388 in total, 2012-2016

272 (Published as first author or corresponding author)

35 (IF>10)

108 (IF>5)



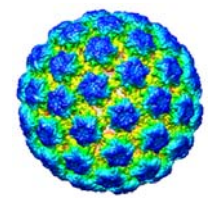
Pathogenic Microorganisms Being Studied

Category	Pathogens
Digestive system infectious disease	HEV, HBV, HCV, HDV, EV71, CA16, RV
Sexually transmitted diseases	HIV, HPV, TP
Respiratory disease	Flu A, Flu B, RSV, MTB
Others	HSV, VZV, EBV, HCMV, Zika



Product pipelines of XMU-SPH

Products	Pre-clinical	Clinical Trials			Market
		Phase 1	Phase 2	Phase 3	
HIV Ab ELISA					
HEV IgM/IgG ELISAs					
HIV/HBsAg/Flu... POCTs					
... ~40 Immunoassays					
...~60-90 CLIAs					
Hep E vaccine					
HPV 16/18 vaccine					
HPV 6/11 vaccine					
HPV 11-valent vaccine					
VZV-7D vaccine					
Therapeutic H5N1 mAb					
Therapeutic HBV mAb					



Sample Achievements at XMU-SPH



1. Diagnostic kits

- >100 licensed diagnosis kits (14 CE marked, 2 WHO PQ'ed)
 - HIV, TB, HAV, HBV, HCV, HDV, HEV, Flu-A, EV71, CA16, 2009-H1N1,
 - Leading products in Chinese market:
 - HIV (~40%); HCV (~25%); TP (~20%); HEV (~80%)

- WHO PQ certificates:

HIV Antibody Enzyme-linked Immunoassay Kit (Double Antigen Sandwich Assay)

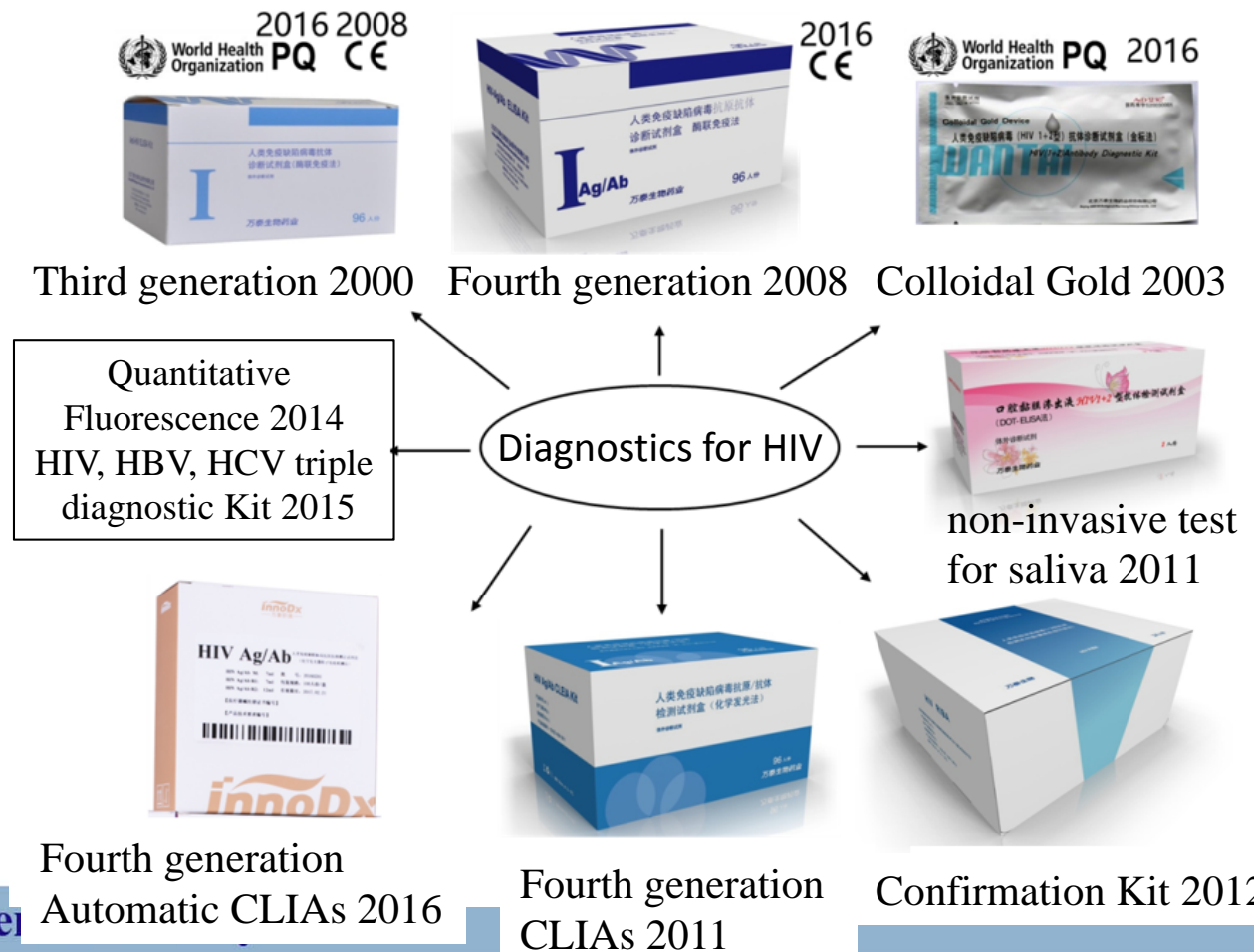
HIV Antibody Enzyme-linked Immunoassay Kit (Colloidal Gold Assay)



Diagnostic Kits for HIV

The third generation HIV diagnostic kit was developed in 2000.
Hold 40% of Chinese market for 15 years.

- Received CE certificate in 2008
- Received WHO PQ certificate in 2016



Diagnostic Kits for HIV

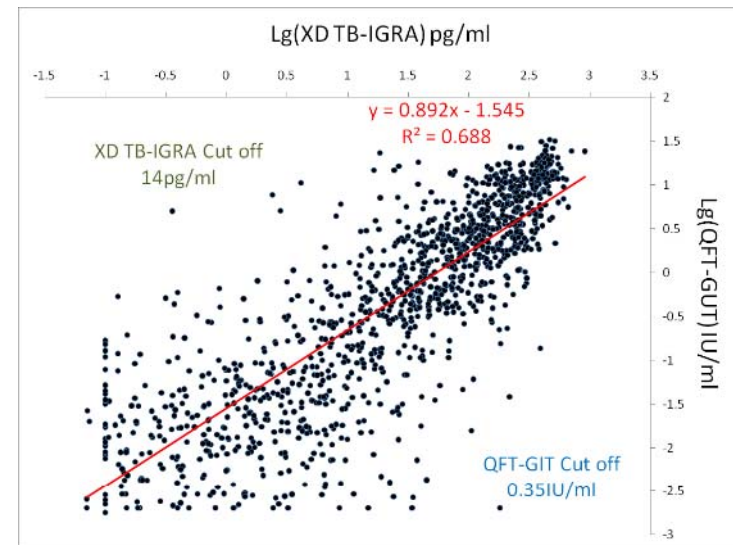
Diagnostic and Confirmation Kits

HIV (Type 1+2) Antibody Enzyme-linked Immunoassay Kit (Double Antigen Sandwich Assay)	CFDA 、 PQ 、 CE
HIV Antigen/Antibody Diagnostic Kit (Enzyme-linked Assay)	CFDA、 CE
HIV (Type 1+2) Antibody Diagnostic Kit (Colloidal Gold Assay)	CFDA、 PQ
Oral mucosal exudate HIV (Type 1+2) Antibody Diagnostic Kit (DOT-ELISA Assay)	CFDA
HIV Antigen/Antibody Diagnostic Kit (Chemiluminescence Assay)	CFDA
HIV Antigen/Antibody Diagnostic Kit (Chemiluminescence Microparticle Immunoassay)	CFDA
HIV (Type 1+2) Antibody Confirmation Kit (Recombinant Immunoblotting Assay)	CFDA
HIV (Type 1+2) Antibody Diagnostic Kit (Immunofiltration Assay)	CFDA



M. Tuberculosis γ - Interferon Diagnostic Kit (Interferon Gamma Release Assay)

- Major infectious disease prevention and control program:
TB-IGRA diagnostic kit



Compare with imported product,
total consistent rate: 94%

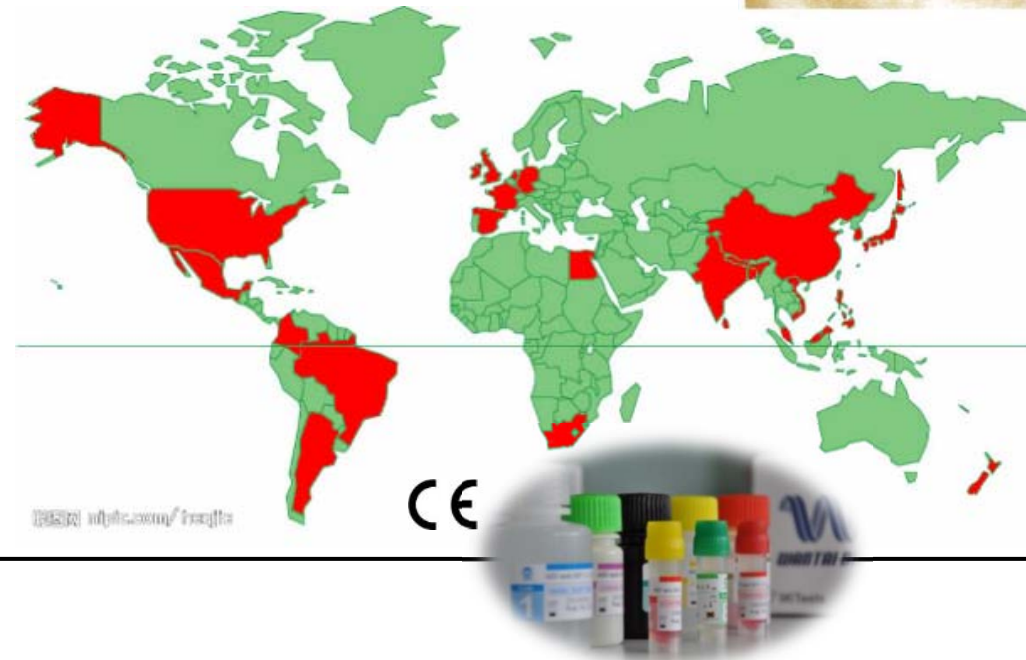
CE Certificate: Tuberculosis IgG Antibody Diagnostic Kit (Enzyme-linked Assay)



Diagnostic Kits for HEV: Golden Standard

4 CE certificates, Golden Award of Chinese Patent

- ✓ Improved the accuracy from 60% to 95%
- ✓ 80% of Chinese market, exported to 24 countries



Am. J. Trop. Med. Hyg., 93(4), 2015, pp. 714–717
doi:10.4269/ajtmh.15-0159
Copyright © 2015 by The American Society of Tropical Medicine and Hygiene

Two Generations of “Gold Standards”: The Impact of a Decade in Hepatitis E Virus Testing Innovation on Population Seroprevalence

Brittany L. Kmush, Alain B. Labrique,* Harry R. Dalton, Zabed B. Ahmed, John R. Ticehurst, Christopher D. Heaney, Kenrad E. Nelson, and Khalequ Zaman

Diagnostic Kits for HCV

Products	Certificate
Hepatitis C Virus Antibody Diagnostic Kit (Enzyme-linked Assay)	CFDA、CE
Hepatitis C Virus Antibody Confirmation Kit (Recombinant Immunoblotting Assay)	CFDA
Hepatitis C Virus Antibody Diagnostic Kit (Double Antigen Sandwich Assay)	CFDA
Hepatitis C Virus Antibody Diagnostic Kit (Chemiluminescence Microparticle Immunoassay)	CFDA

Most of the confirmation Kit are using Western Blotting assay

- **Less sample needed: 20ul**
- **Easy to operate**
- **Accurate**
- **Reliable**



New Type of HBV Diagnostic Reagent



北京大学第一医院
PEKING UNIVERSITY FIRST HOSPITAL

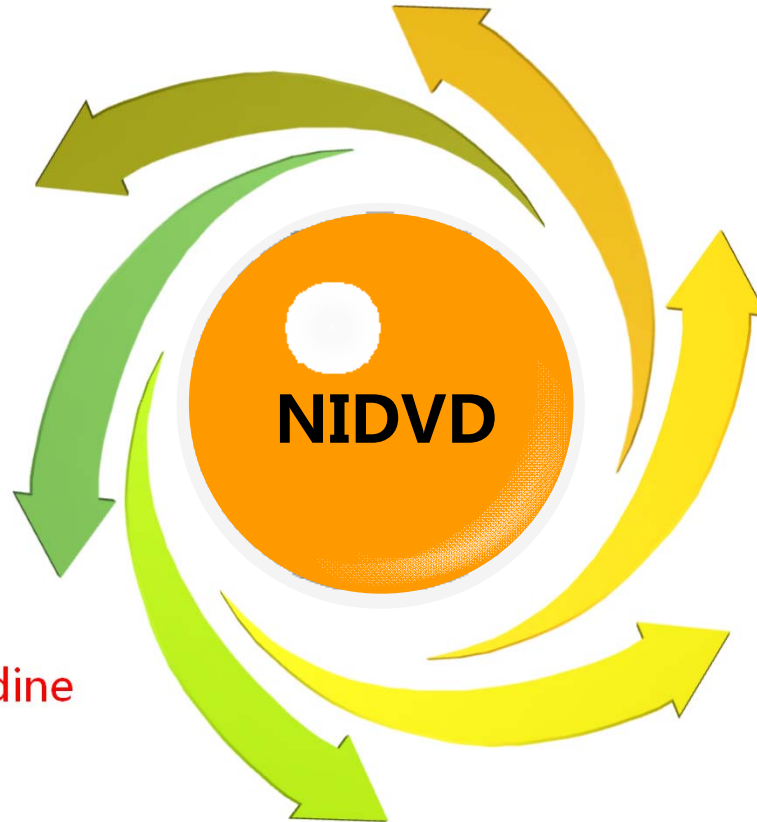
Interferon\Entecavir
treatment
Theranostics. 2014
Medicine. 2014



Interferon\Telbivudine
Therapy
Gut. 2014



Immune mechanism
of qAnti-HBc.
Gut. 2013



UNIVERSITÀ DI PISA

Superinfection of HDV.
Plos One. 2015



REVEAL Cohort
Research of Natural
History



Rapid response for emerging infectious diseases

- ✓ **H5N1**, outbreak since 2003, NIDVD developed 1st Rapid Diagnostic assay in 2004, received venture capital from **KPCB, San Francisco**.
- ✓ **EV71**, epidemic in Mar. 2008, NIDVD developed 1st IgM assay in Nov. 2008, commercialized since 2011
- ✓ **H1N1(2009)**, outbreak since Apr. 2009, NIDVD developed high quality rapid assay for Flu A on Jul. 2009, commercialized H1N1(2009) specified assay in 2010
- ✓ **MERS (2015)**, cooperation with Hong Kong University, developed rapid diagnosis reagent for MERS. Only takes 15 mins, faster than previous assay (3 hours)
- ✓ **NEXT.....**

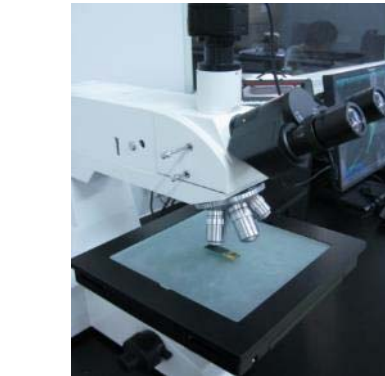


2. Diagnostic instruments

Automated Chemiluminescent Immunoassay System



CCPCR



Infrared microscope



Instrument testing system



Immune fluorescence quantitative analyser

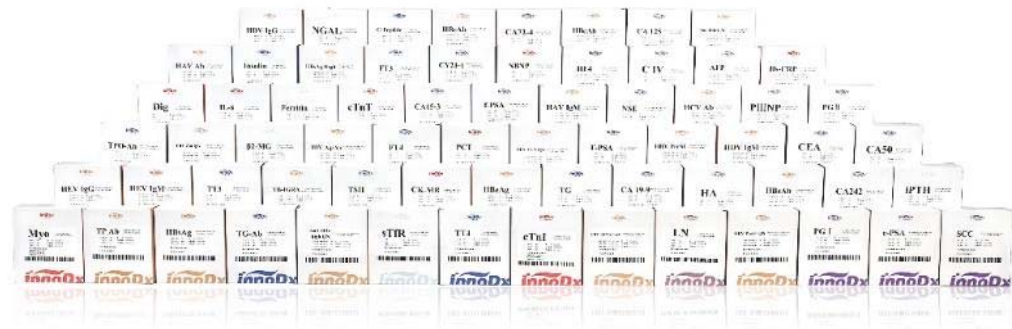


Immune-Gold Labeller



Automatic Chemiluminescent Immunoassay System

Key Research Program of China



Diagnostic Reagents

Initiation

Prototype

Received Certificate

Launched



2011

2012

July, 2014

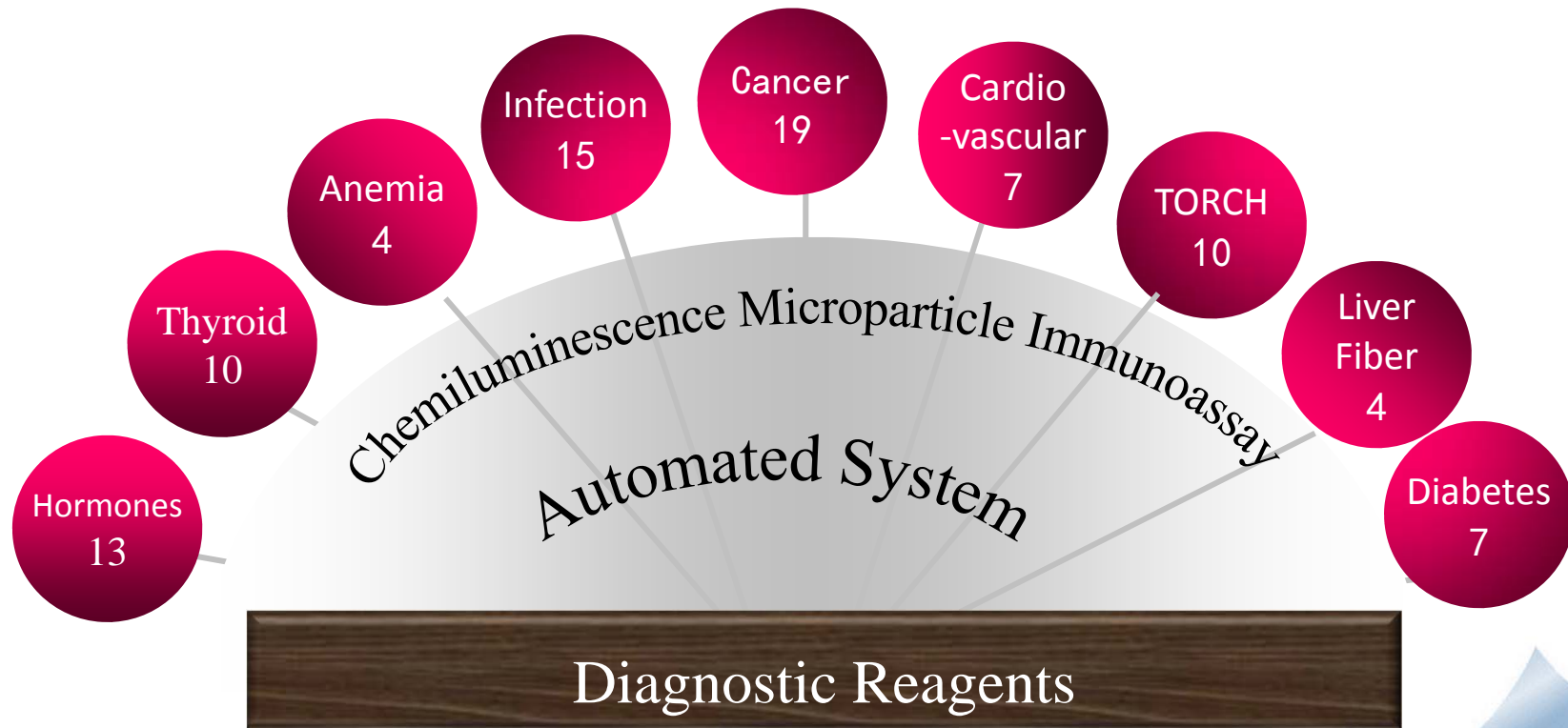
April, 2016

October, 2016



Automated Chemiluminescent Immunoassay System

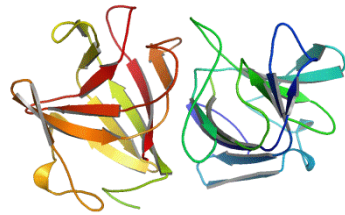
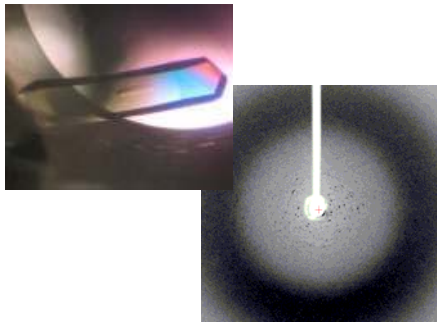
Supporting Reagent:



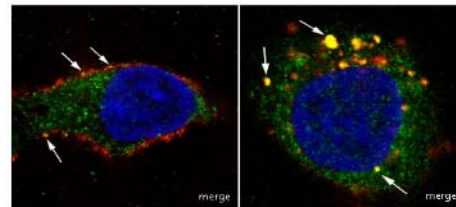
3. Vaccines

3.1 Recombinant Hepatitis E Vaccine

— from molecule to population



	239	ConA	BSA
Total			
CD8 ⁺			
CD4 ⁺			
Total			



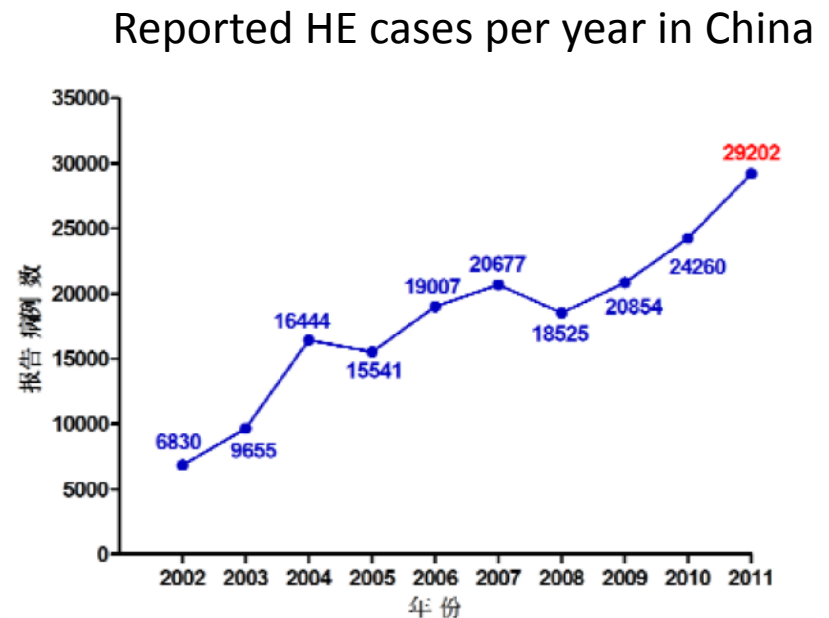
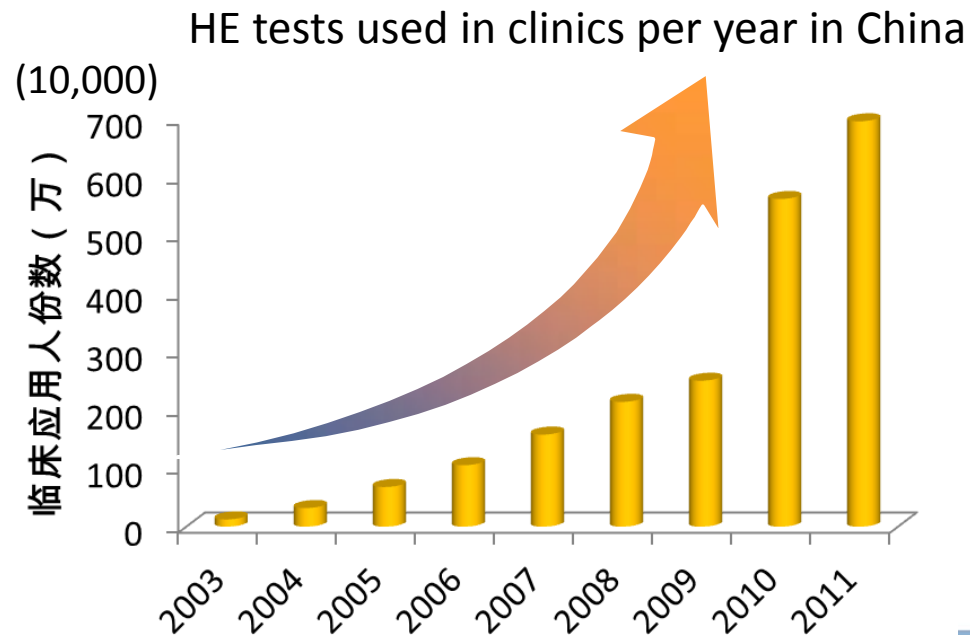
0h

6h



Un-expected much higher incidence of HEV

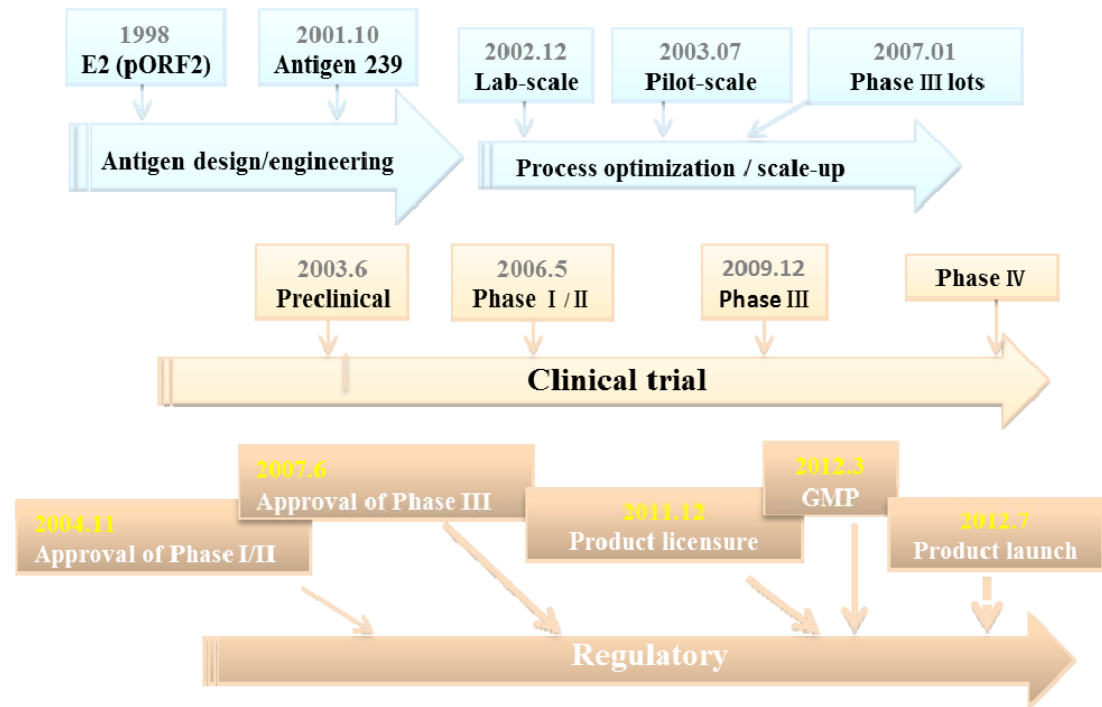
- > Of clinic non-A-D hepatitis, **20~30% is** hepatitis E
- > HEV reagent market increases. HEV becomes the most observed acute viral hepatitis in clinics, replacing HAV with more disease cases.



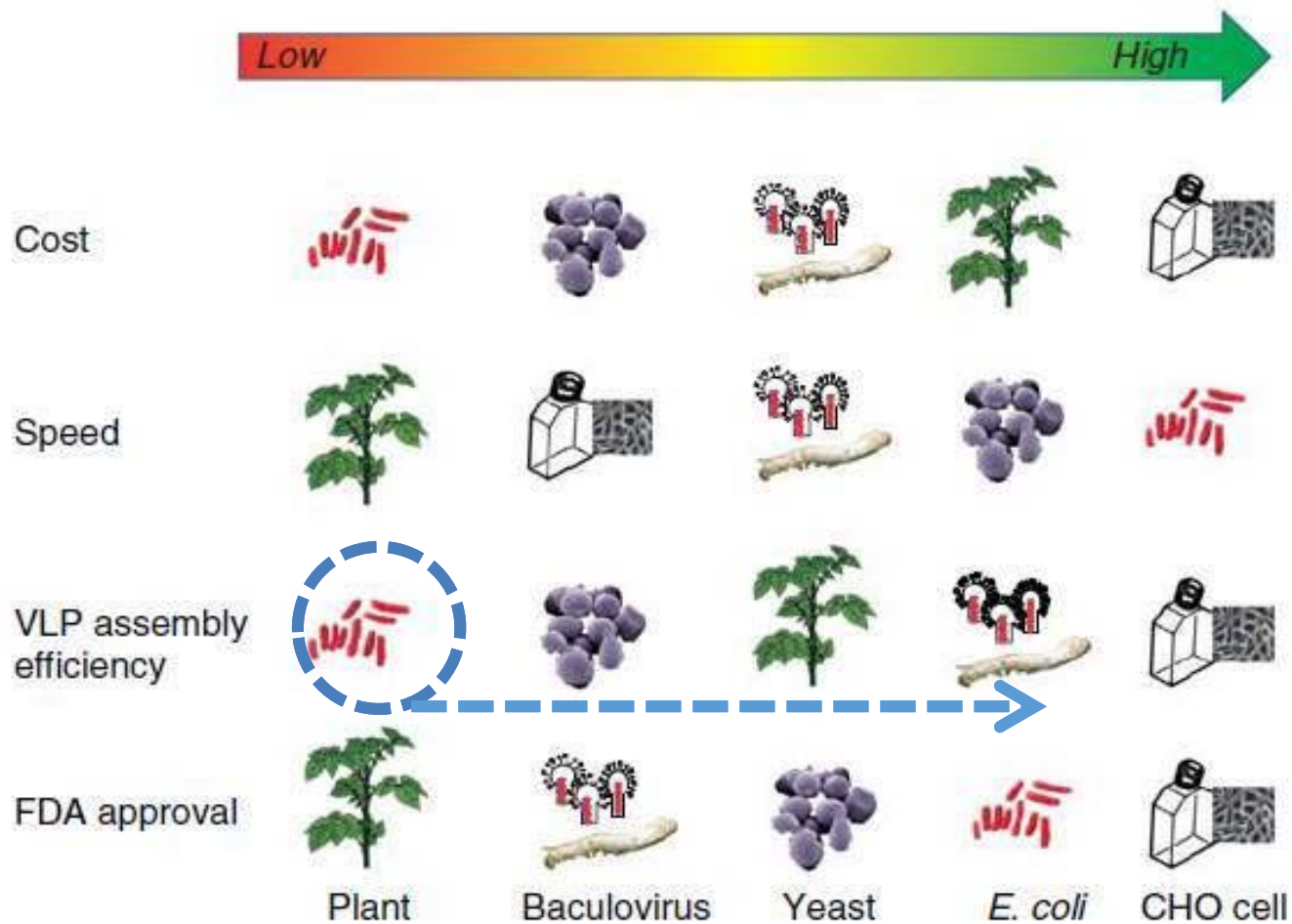
The first HEV vaccine launched

2012.10.27

- ✓ 14 years
- ✓ 200 researchers
- ✓ 0.5 billion funding
- ✓ Original innovation



Recombinant VLP based vaccine (E coli platform)



Cho, H. J., Y. K. Oh, et al. (2011). "Advances in human papilloma virus vaccines: a patent review." Expert Opin Ther Pat.



Comments from peer-reviewed journals

THE LANCET



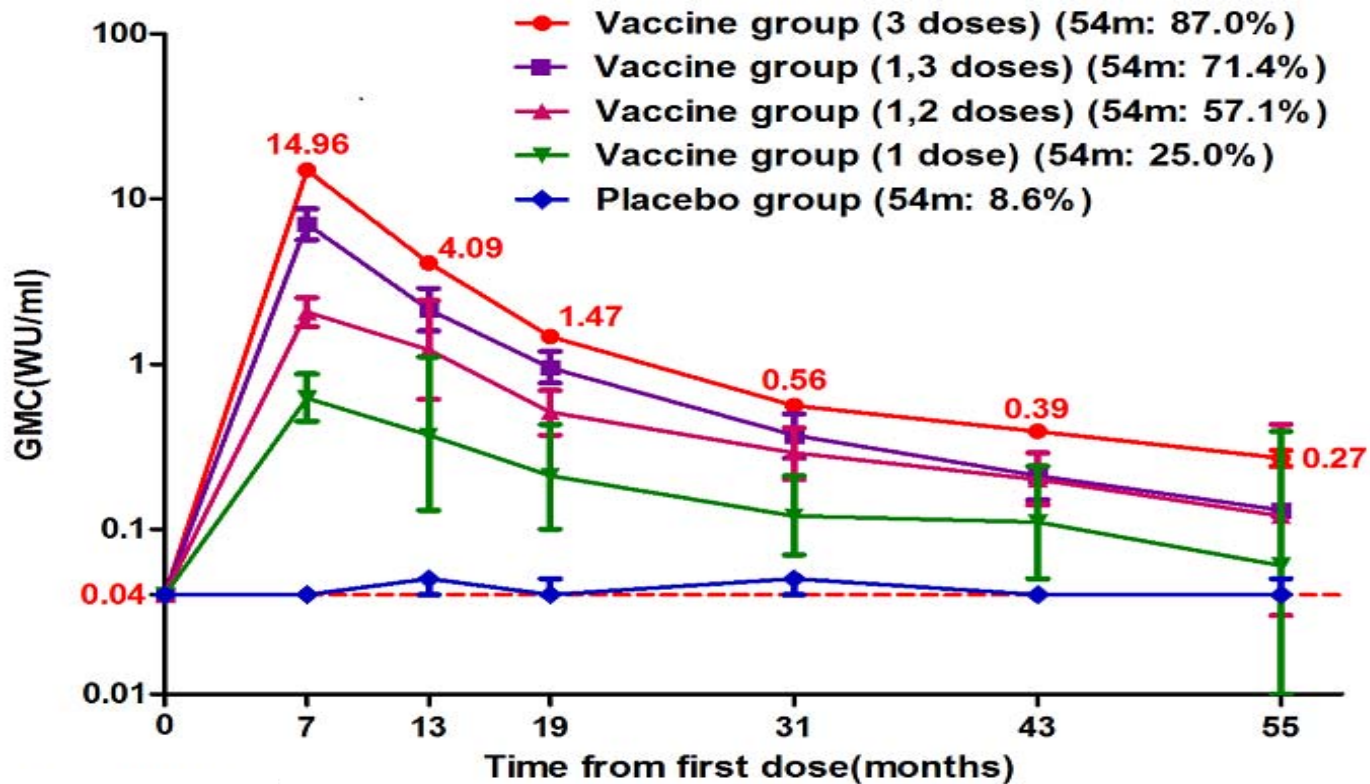
The Lancet, Early Online Publication, 23 August 2010
 doi:10.1016/S0140-6736(10)61030-6 [Cite or Link Using DOI](#)

Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial

Feng-Cai Zhu MSc a, Prof Jun Zhang MD b, Xue-Feng Zhang MSc a, Cheng Zhou MD c, Zhong-Ze Wang MD d, Shou-Jie Huang MD b, Hua Wang MD a, Chang-Lin Yang BSc d, Han-Min Jiang BSc d, Jia-Ping Cai BSc d, Yi-Jun Wang BSc d, Xing Ai MSc a, Yue-Mei Hu MD a, Quan Tang MD a, Xin Yao MSc e, Qiang Yan MSc b, Yang-Ling Xian BSc e, Prof Ting Wu PhD b, Yi-Min Li MD e, Prof Ji Miao PhD b, Prof Mun-Hon Ng PhD b, Prof James Wai-Kuo Shih PhD b, Prof, Dr Ning-Shao Xia MD b



Durability of Protective Immunity

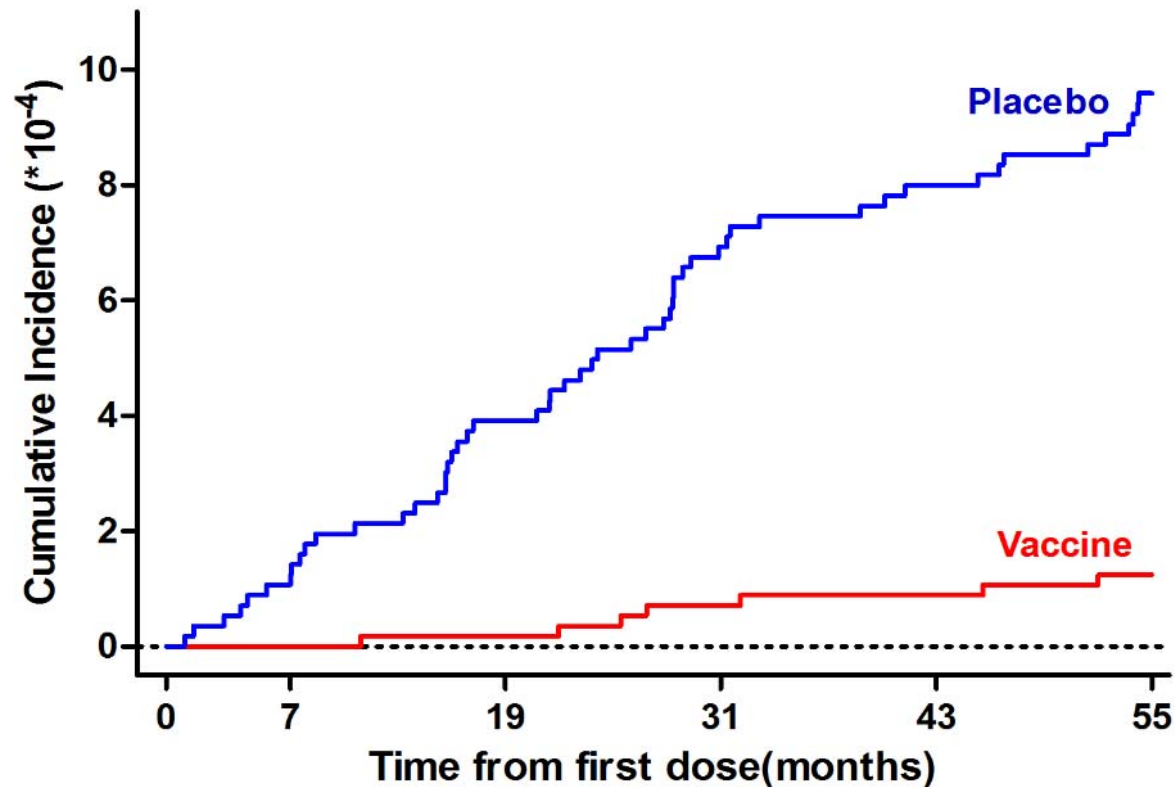


Zhang J, et al. *New Engl J Med.* 2015, 372: 914-22



Accumulated number of Hepatitis E cases

Intention-to-treat analysis for subjects received >1 dose



Zhang J, et al. *New Engl J Med.* 2015, 372: 914-22



Long-term efficacy research

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Efficacy of a Hepatitis E Vaccine

Jun Zhang, M.Sc., Xue-Feng Zhang, M.Sc., Shou-Jie Huang, M.Sc., Ting Wu, Ph.D., Yue-Mei Hu, M.Sc., Zhong-Ze Wang, B.Sc., Hua Wang, M.D., Han-Min Jiang, B.Sc., Yi-Jun Wang, M.Sc., Qiang Yan, M.Sc., Meng Guo, B.Sc., Xiao-Hui Liu, B.Sc., Jing-Xin Li, M.Sc., Chang-Lin Yang, B.Sc., Quan Tang, B.Sc., Ren-Jie Jiang, M.Sc., Hui-Rong Pan, Ph.D., Yi-Min Li, M.D., J. Wai-Kuo Shih, Ph.D., Mun-Hon Ng, Ph.D., Feng-Cai Zhu, M.Sc., and Ning-Shao Xia

ABSTRACT

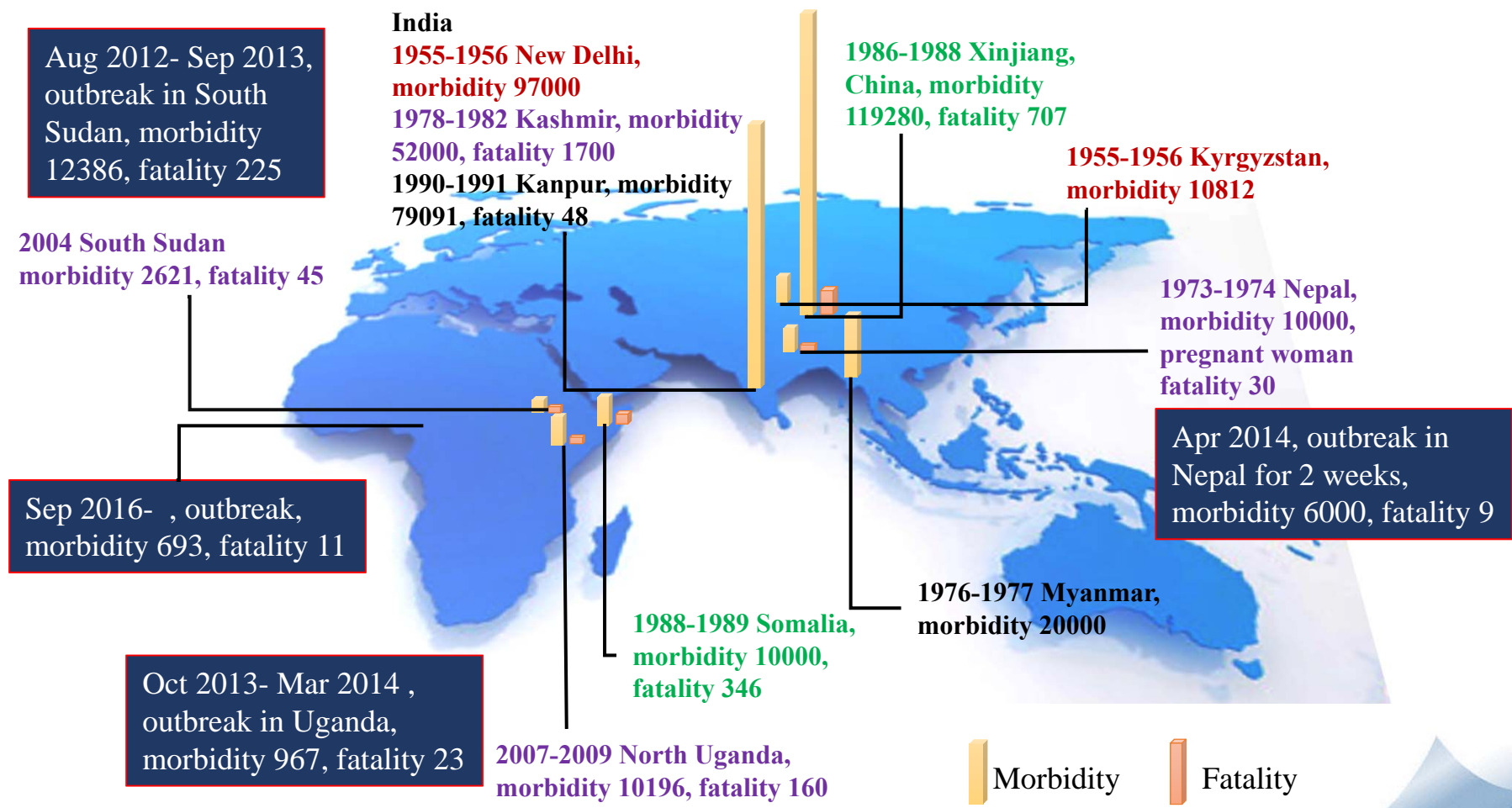
BACKGROUND

Hepatitis E virus (HEV) is a leading cause of acute hepatitis. The long-term efficacy of a hepatitis E vaccine needs to be determined.



Promotion of the application of HEV vaccine in the world

Many countries along “the Belt and Road” have high prevalence of hepatitis E



3 million hospitalizations, **70,000** casualties and **3,000** abortions/stillbirths occurs on an annual basis



HEV vaccine beyond China

- ✓ **2013-** : Discussion of HEV vaccination in refuge camps with Médecins Sans Frontières (MSF)
- ✓ **2014:** HEV Working Group of WHO recommended HEV vaccine for humanitarian crisis
- ✓ **2015.5:** WHO released position paper of HEV vaccine
- ✓ **2017.5:** Working Group Meeting To Develop WHO Recommendations To Assure The Quality, Safety And Efficacy Of Hepatitis E Vaccine. To promote WHO prequalification of HEV vaccine.



World Health
Organization

Organisation mondiale de la Santé

**Safety profile of a recombinant hepatitis E
vaccine**

2015, 90, 185-200



World Health
Organization

Weekly epidemiol
Relevé épidém

Organisation mondiale de la Santé

1ST MAY 2015, 90th YEAR / 1^{er} MAI 2015

No. 18, 2015, 90, 185-200

<http://www.who.int/wer>

Contents

185 Hepatitis E vaccine:
WHO position paper, May 2015

**Hepatitis E vaccine: WHO
position paper, May 2015**

Global Registry of HEV vaccine

- ✓ Explore the possibility of global registry for HEV vaccine with John Hopkins University, ICDDR, IVI, NIH, PATH, etc.
- ✓ Signed agreement with ICDDR Bangladesh for clinical trial in Bangladesh on gestational age women. Temporarily stopped in 2016.
- ✓ 2016, Funded by Gates Foundation, IVI started global verification on manufacturing facilities, to promote the application of HEV vaccine.
- ✓ Applied for registry in Nepal and Pakistan.



IND Filing in United States

- August 2016, IND filed for HEV vaccine in United States through NIH

This is the first Chinese vaccine applied clinical trial in United States, and was funded by NIH (5 million USD)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

MEMORANDUM

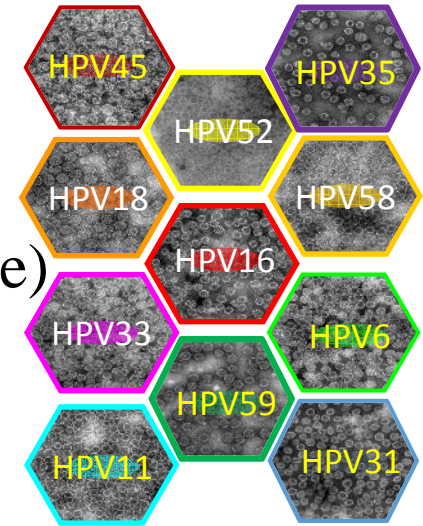
DATE: August 16, 2016
FROM: Office of Regulatory Affairs (ORA), DMID, NIAID, NIH
SUBJECT: **Pre-Investigational New Drug (IND) Type B Meeting Request for Recombinant Hepatitis E Vaccine (*Escherichia coli*)/Hecolin®**
TO: Director, Division of Vaccines and Related Products, OVRR, CBER, FDA

In accordance with 21 CFR 312.82(a), the Division of Microbiology and Infectious Diseases (DMID) is requesting a Type B (pre-IND) meeting with representatives of the Office of Vaccines Research and Review (OVRR), CBER, FDA, to discuss CMC, preclinical, and clinical trial designs to evaluate Recombinant Hepatitis E Vaccine (*Escherichia coli*)/Hecolin® as a vaccine for active immunization against hepatitis E virus (HEV) infection.



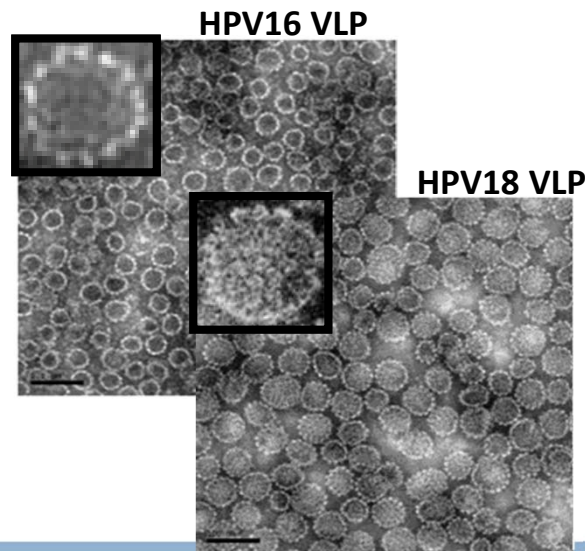
3.2 HPV Vaccine

HPV 16/18 Bivalent Vaccine (Cervical Cancer Vaccine)

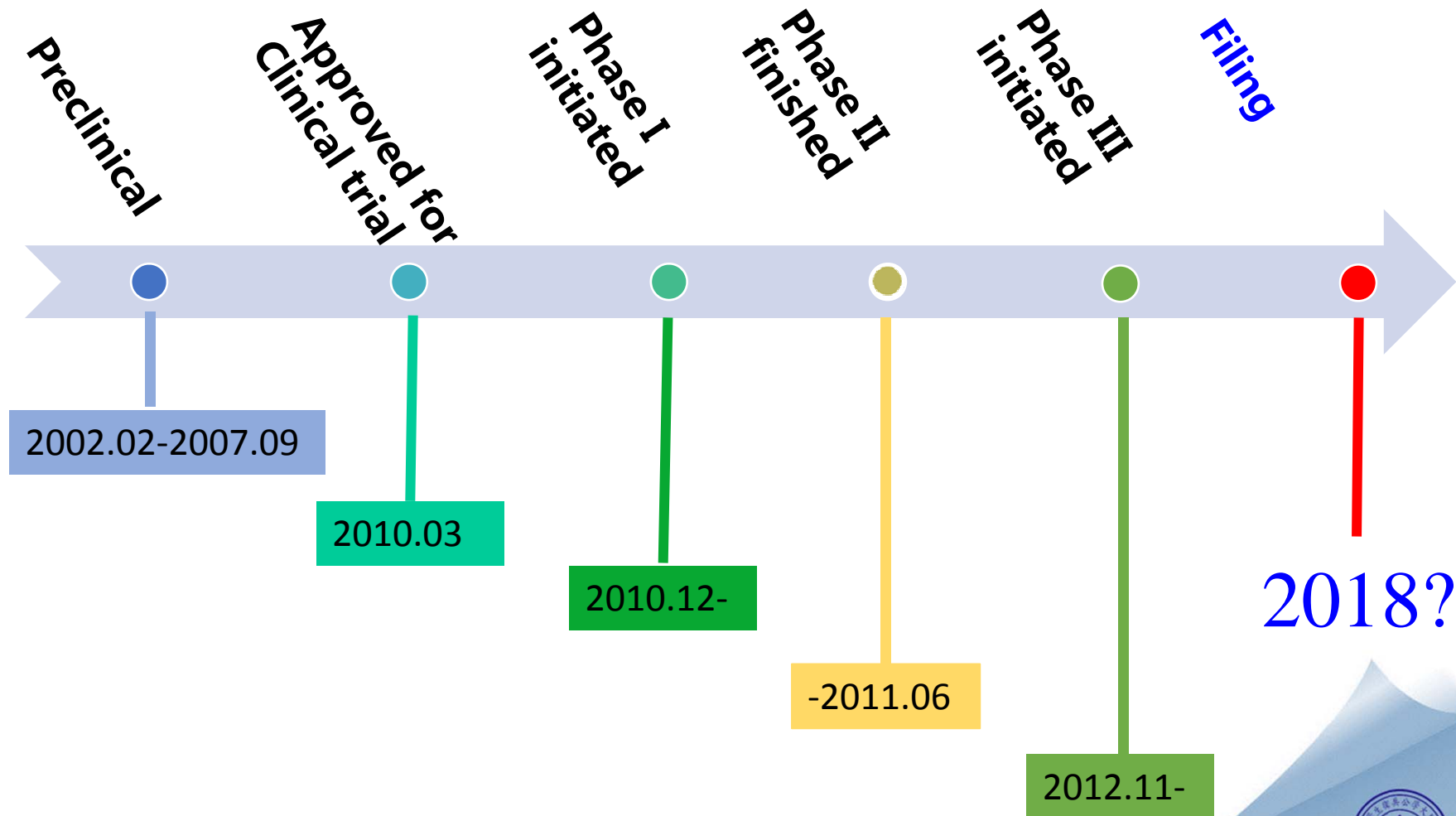


- **Top priority project on the national level**
- First in China, third in the world, goes in Phase III clinical test.

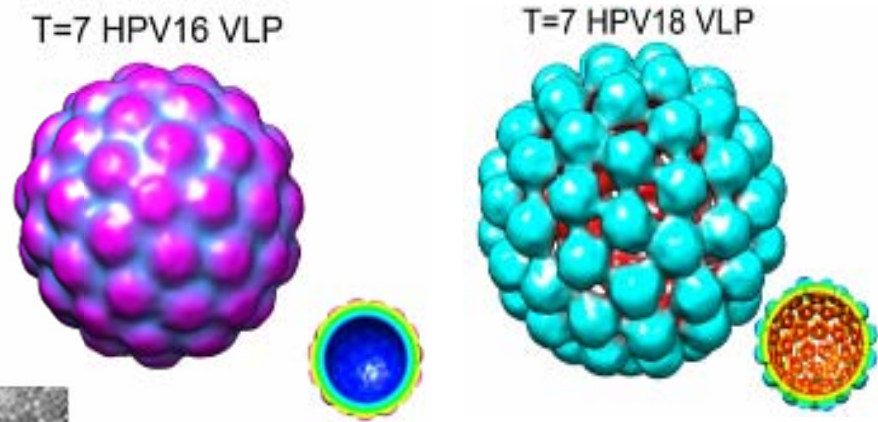
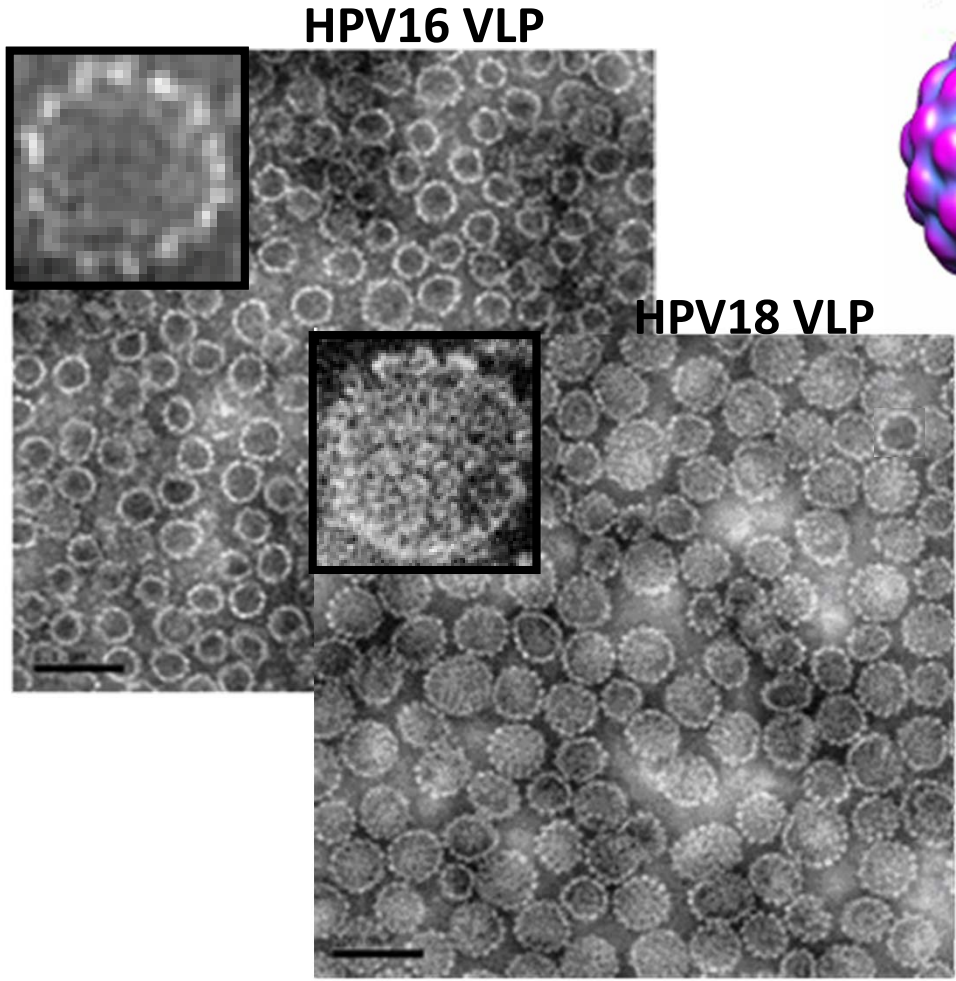
Unique process using *E. coli*, 6 international and domestic patents



First HPV Vaccine of China



Recombinant HPV16/18 bivalent vaccine



**HPV 16/18
bivalent vaccine**



Development and Clinical trial of HPV16/18 vaccine

Visit	1	2	3	4	5	6	7	8	9	10	11
Visit time point	0d*	1m	6m	7m*	12m	18m*	24m	30m*	42m*	54m*	66m*
No. of visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11

Rate of vaccination for 3 shots >95%

↑
2012.11-2013.05
7372
inoculators

↑
2013.12
After 3 shots

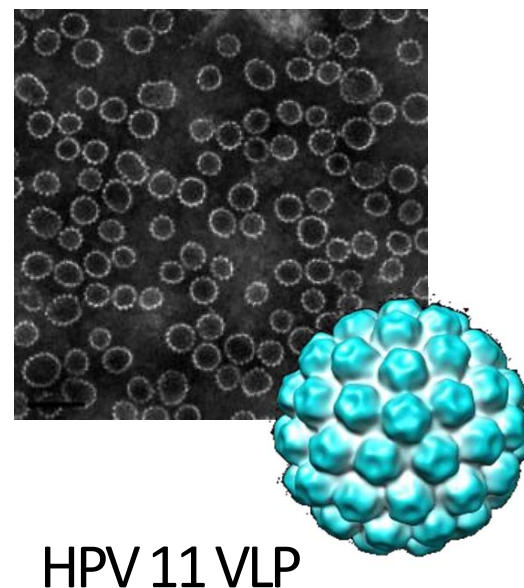
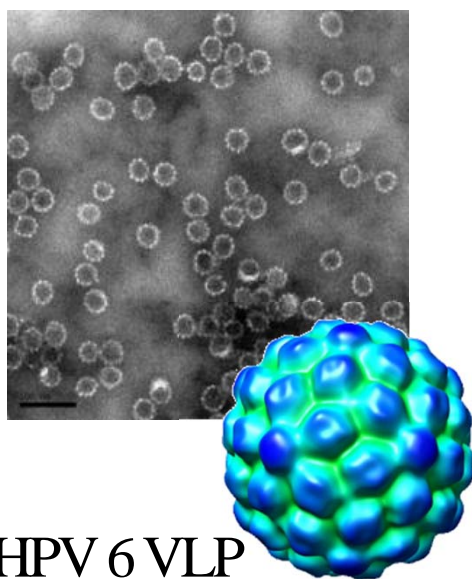
↑
2015.12
Infection endpoint

↑
2018
Pathological endpoint



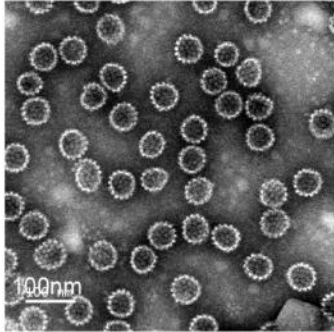
Recombinant HPV6/11 bivalent vaccine

- ✓ Clinical trial approved in 2013
- ✓ Funded by central government (2015ZX09101034)
- ✓ Phase I clinical trial started in March, 2015.
- ✓ Phase II clinical trial

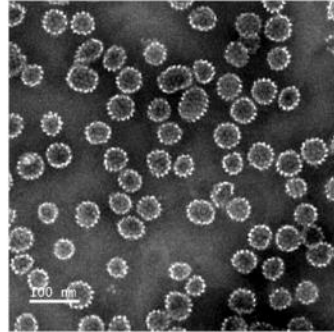


HPV 9-valent vaccine *(follow on of Gardasil-9)*

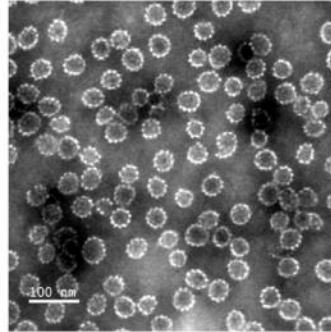
HPV6 VLP



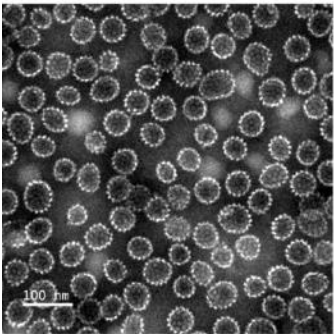
HPV11 VLP



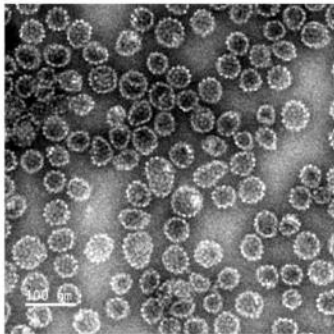
HPV16 VLP



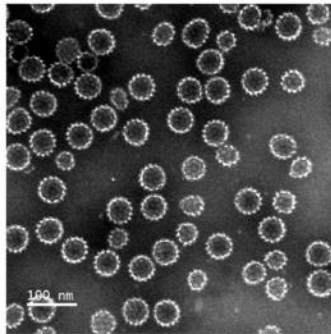
HPV18 VLP



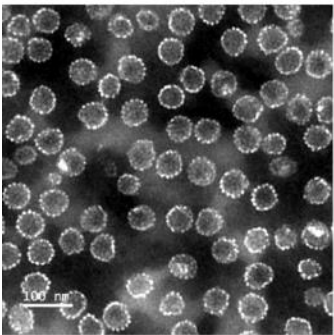
HPV31 VLP



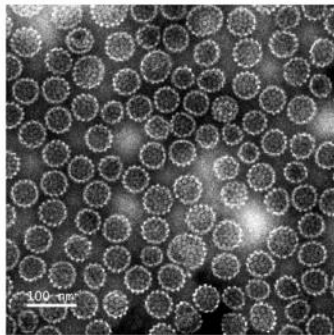
HPV33 VLP



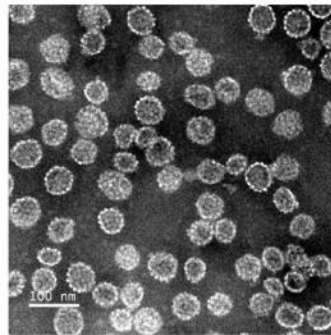
HPV45 VLP



HPV52 VLP



HPV58 VLP

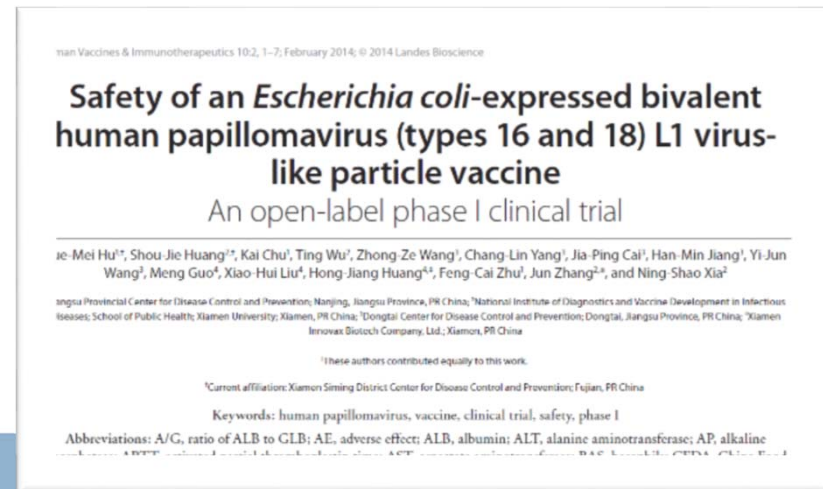


◆ June 2015, applied
for clinical trial.



Promotion of Chinese HPV vaccines into global markets

- ✓ 2008- : Participated the amendment of WHO guideline on HPV vaccine.
- ✓ 2010- : Discussions with Gate Foundation, PATH, DCVMN, etc.
- ✓ 2014- : Instructed by WHO prequalification experts.
- ✓ 2014 : Published the data of phase I clinical trial.
- ✓ 2015 : Published the data of phase II clinical trial.
- ✓ 2016- : Seeking funding from non-profit organizations.
- ✓ 2016 : Second WHO Workshop on Implementation of Recommendations to assure the quality, safety and efficacy of recombinant human Papillomavirus virus-like particle vaccines.



3.3 Attenuated VZV vaccine

Preclinical

Developing a new generation of VZV vaccine

- skin and neuro-attenuated
- genetically defined
- easily manipulated
- high yield



RUTGERS
UNIVERSITY

Patent: PCT/CN2010/001139

Publication: *PLoS Pathog.* 2010 Jul 1;6:e1000971. IF=9.3; *J Virol.* 2012. IF=5.189



Comments and Qiu Shi Award



William J. Rutter

Rutter, William J.
Chairman and CEO
Synergenics, LLC

Email: bill@synergenics.net

Comment from Dr. William Rutter:

E. coli platform provides a way to produce genetic engineering vaccines with low cost.

September 2015, NIDVD received

Qiu Shi Outstanding Scientific Research Team Award

For:

Opens a new way of developing genetic engineering vaccines



School of Public Health,



求是科技基金會
Qiu Shi Science & Technologies Foundation

科学精神 人文情怀

Overview

Our Founder

Our Chairman

Our Advisors

Qiu Shi Awards

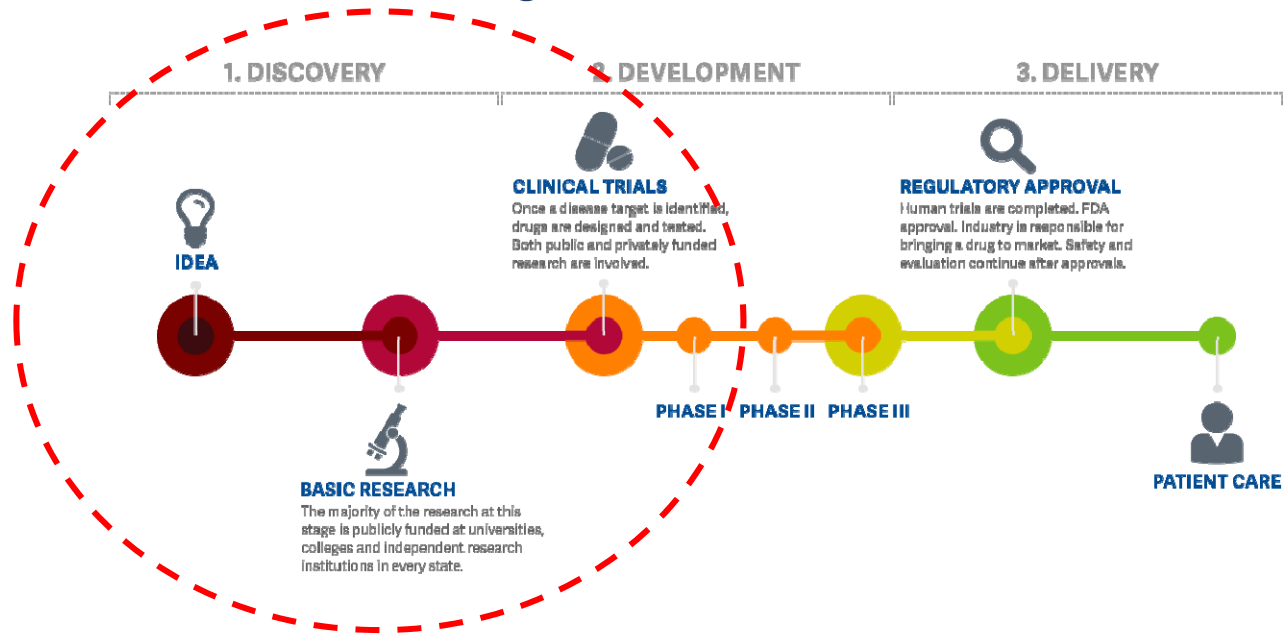
List of Qiu Shi Laureates

Overview

The Qiu Shi Science & Technologies Foundation was established by Mr. CHA Chi Ming (1914-2007) and his family in Hong Kong in 1994. It was named after the present Zhejiang University in Hangzhou, formerly known as Qiu Shi Academy. In Chinese, "Qiu Shi" means the pursuit of truth. The primary mission of the Foundation is to promote scientific and technological progress in China by recognizing and rewarding successful Chinese scientists and scholars.

The Foundation's advisory board consists of a group of distinguished and internationally acclaimed scientists, namely, Professors Chen Ning YANG, ZHOU Guangzhao, Yuet Wai KAN, David HO, HAN Qide, SUN Jiadong, and SHI Yigong. The late Professor Shiing-Shen CHERN, an acclaimed mathematician, and Professors Yuan Tseh LEE and Andrew Chi-Chih YAO were also our former advisors. Our advisors are solely responsible for the selection and evaluation of candidates for the various Qiu Shi Awards.

“Benchside” Projects -



- Hepatitis B virus – *virus clearance?*
- Oncolytic virus – *treating tumors*
- Influenza virus – *universal vaccine?*
- Respiratory syncytial virus – *vaccine?*
- Novel assay platforms – *integrated assays. ccPCR*

International Cooperation of SPH



International Cooperation



Vaccine Research Center of NIH: **RSV antibody**
Science 2013 May; Science 2013 Nov; Patent 201310082338.1



Taiwan University: **Therapeutic antibody of HBV**, Diagnostic of HDV
Gastroenterol 2013; Gut 2013; J Hep 2012;



National University of Singapore: **Structural Biology**
PNAS 2011; Cell Res 2015; PLoS Pathogens 2009



Health Protection Agency: **International standard of HPV**



RUTGERS
UNIVERSITY

Rutgers University: **Attenuated varicella vaccine**
PLOS Pathogens 2010; J Virol 2012; PCT/CN2010/001139



Cooperation with NIH:

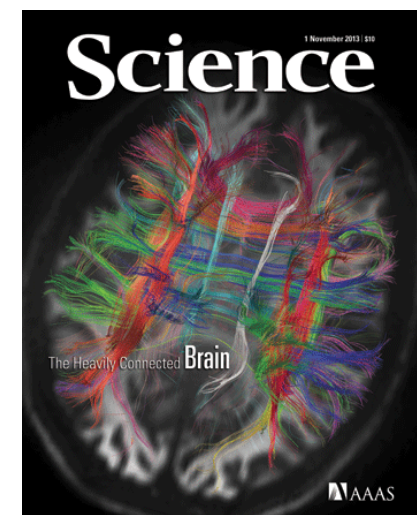
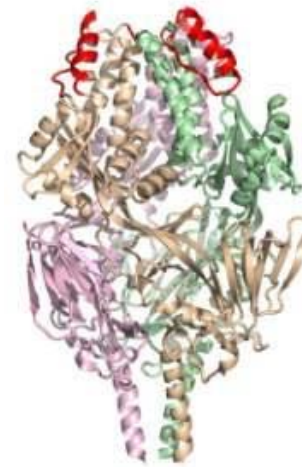
Discovery: New target for treating and preventing RSV

- 2010: NIH seeking collaboration
- 2012, 2014 received NSFC-NIH joint funding
- Analyzed structure of the RSV protein *Science*, 2013 May
- Designed new antigen for vaccine *Science*, 2013 Nov

Science's Top 10 Break through of 2013



The screenshot shows the Science magazine website interface. At the top, there are navigation links for 'Home', 'News', 'Journals', 'Topics', and 'Careers'. Below this, a search bar is visible. The main content area features the article 'Science's Top 10 Breakthroughs of 2013' by Robert Coontz, dated Dec 19, 2013, at 2:00 PM. The article text begins with 'Every year, the editors of Science huddle together and pick an outstanding scientific achievement as the Breakthrough of the Year. This year's winner is CANCER IMMUNOTHERAPY: harnessing the immune system to battle tumors. Scientists have thought for decades that such an approach to cancer therapy should be possible, but it has been incredibly difficult to make it work. Now, many oncologists say we have turned a corner, because two different techniques are helping a subset of patients. One involves...'. To the right of the article, there are sections for 'Got a tip?' with a link to 'How to contact the news team', and 'ScienceInsider' with a link to 'How science fares in the U.S. budget deal' by Science News Staff, dated May 1, 2017. There is also a link to a 'Paper about how microplastics harm fish should be retracted.'



Joint Patent
201310082338.1

Cooperation with Taiwan University



"I realized the impact of our research would be bigger if it extended to the mainland."



—CHEN PEI-JER,
NATIONAL TAIWAN
UNIVERSITY

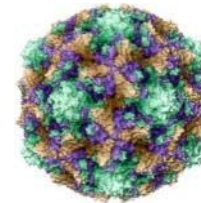
Science 2009

INTERNATIONAL COLLABORATION

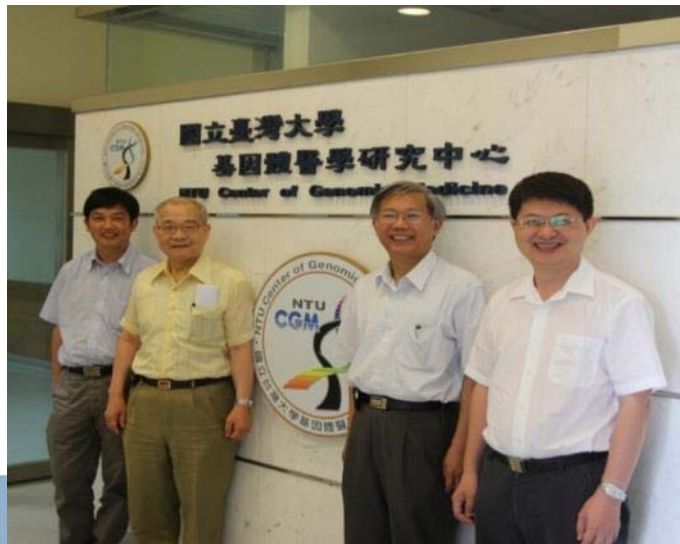
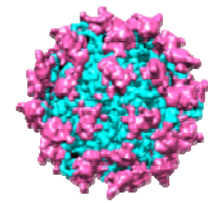
**Bioscientists Slowly Bridge
The Taiwan Strait**

Chinese National
Cooperation Site for
Science and Technology
Exchange with Taiwan

EV71



HBV



Cooperation with WHO

SAGE meeting Hepatitis E working group report in 2014

Global Advisory Committee on Vaccine Safety meeting in 2014

WHO Working Group Meeting on RSV vaccine standardization and clinical evaluation in 2016

WHO Informal Consultation on Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) in 2016.

Second WHO Workshop on Implementation of Recommendations to assure the quality, safety and efficacy of recombinant human Papillomavirus virus-like particle vaccines in 2016.

Dr. Qinjian Zhao became a member of SAGE Decade of Vaccines Working Group in 2016.

Working Group Meeting To Develop WHO Recommendations To Assure The Quality, Safety And Efficacy Of Hepatitis E Vaccine in May, 2017



Co-organized WHO meetings

April, 2016

- WHO Informal Consultation on Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) and Working Group Meeting



November, 2016

- Second WHO Workshop on Implementation of Recommendations to assure the quality, safety and efficacy of recombinant human Papillomavirus virus-like particle vaccines



ибо
hvala
mauruuru
danke 謝謝
ngiyabonga
teşekkür ederim
dank je
thank you
gracias
moichakl
dziękuje
sagolun
sukriya
kop khun krap
go raibh maith a
jado
terima kasih
grazie
arigato
takk
dakujem
me
ευχαριστώ
merci

