Dr Robert
Lambkin-Williams
BSc, PhD, MRPharmS

Executive Scientific Adviser

The Human Viral Challenge Model – Accelerating Drug and Vaccine Development. Choice of Virus is Critical

International Conference on Flu
June 9, 2015

hVIVO at a Glance

hVIVO- pioneering our **technology platform** of human disease models to accelerate drug development and discovery in respiratory and infectious diseases

- Founded 1989 at University of London, roots in virology research
- Formerly Retroscreen Virology



40+
Clinical Studies



1970+
volunteers

Market-leading human challenge models (HCM) provider

- 15+ years designing HCM and working with regulatory authorities/safety boards
- Clients- leading industry, governmental and academic organizations

Unique capabilities to support rational disease biomarker and drug target selection

- Clinical quality human sample databank
- Cutting-edge omics capabilities

Effective Vaccine

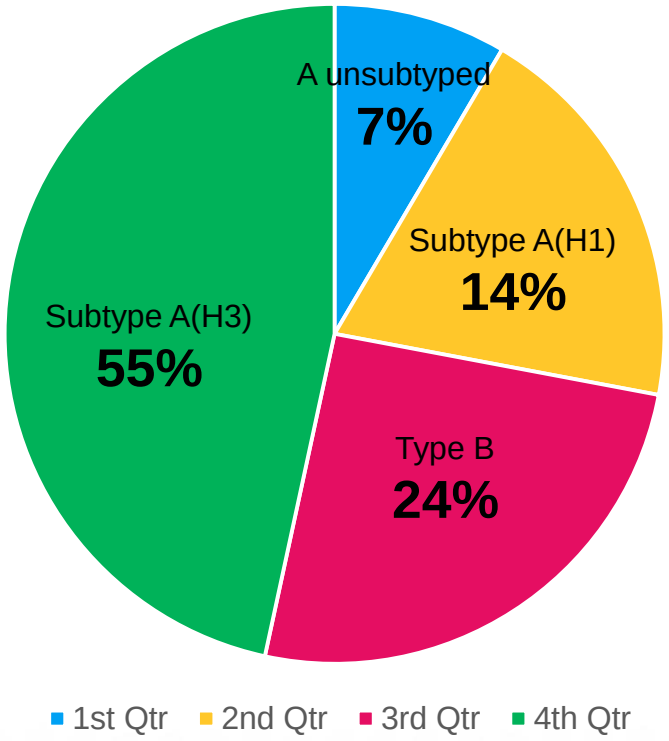
H3N2: High Prevalence Virus

*"..H3N2-predominant seasons have been **associated with more severe illness and higher mortality, especially in older people and young children, relative to H1N1- or B**-predominant seasons…"*

CDC 2015

Influenza viruses circulating in 2014 – 2015

Only sentinel specimens are included



ECDC 2015

http://www.cdc.gov/flu/news/flu-activity-expands.htm
http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/PublishingImages/influenza-europe-weekly-infographic.jpg

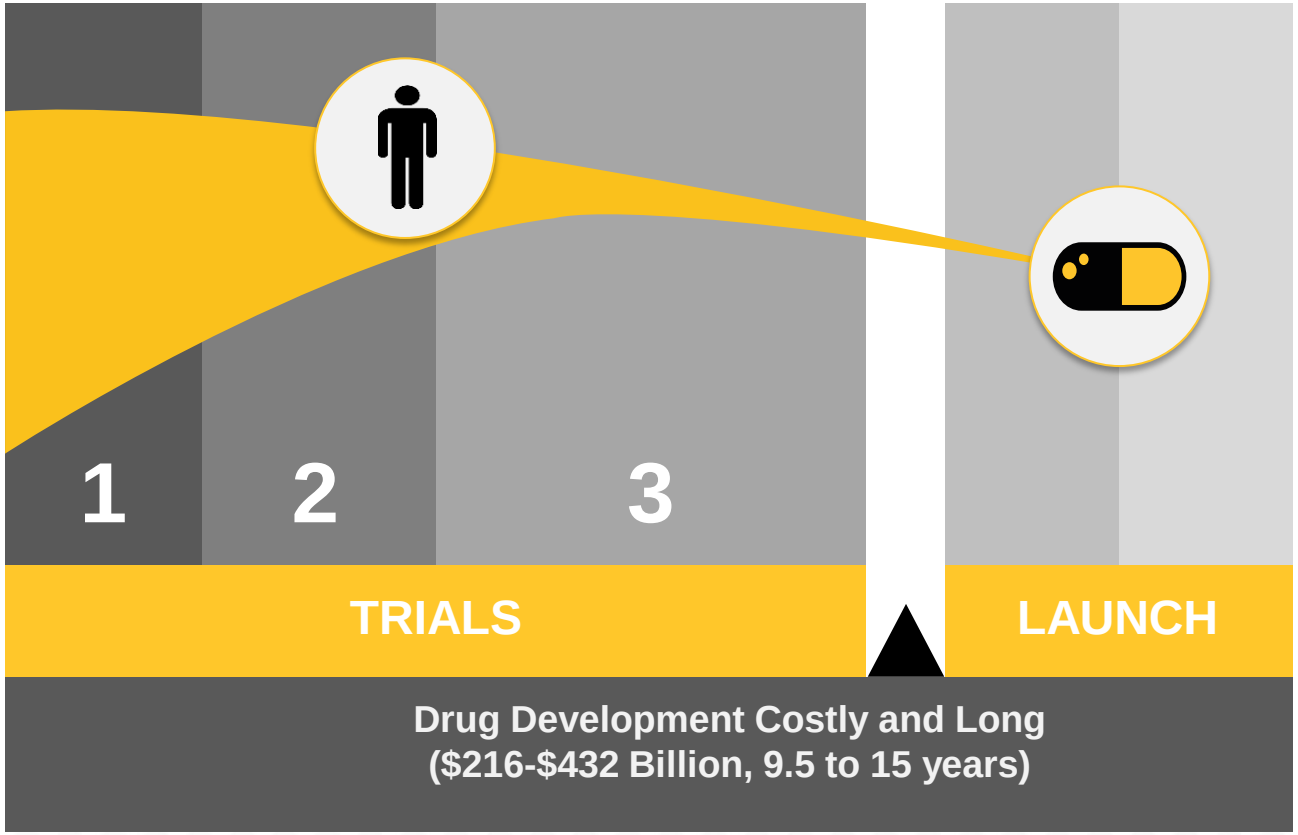
What We Do

Accelerate Drug Development

Challenge Studies = Streamline Processes, Reduce Costs, Move Forward Faster

Traditional



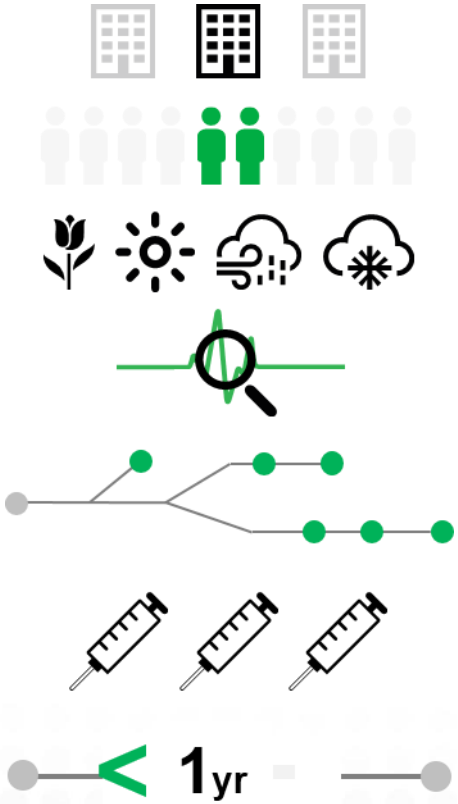


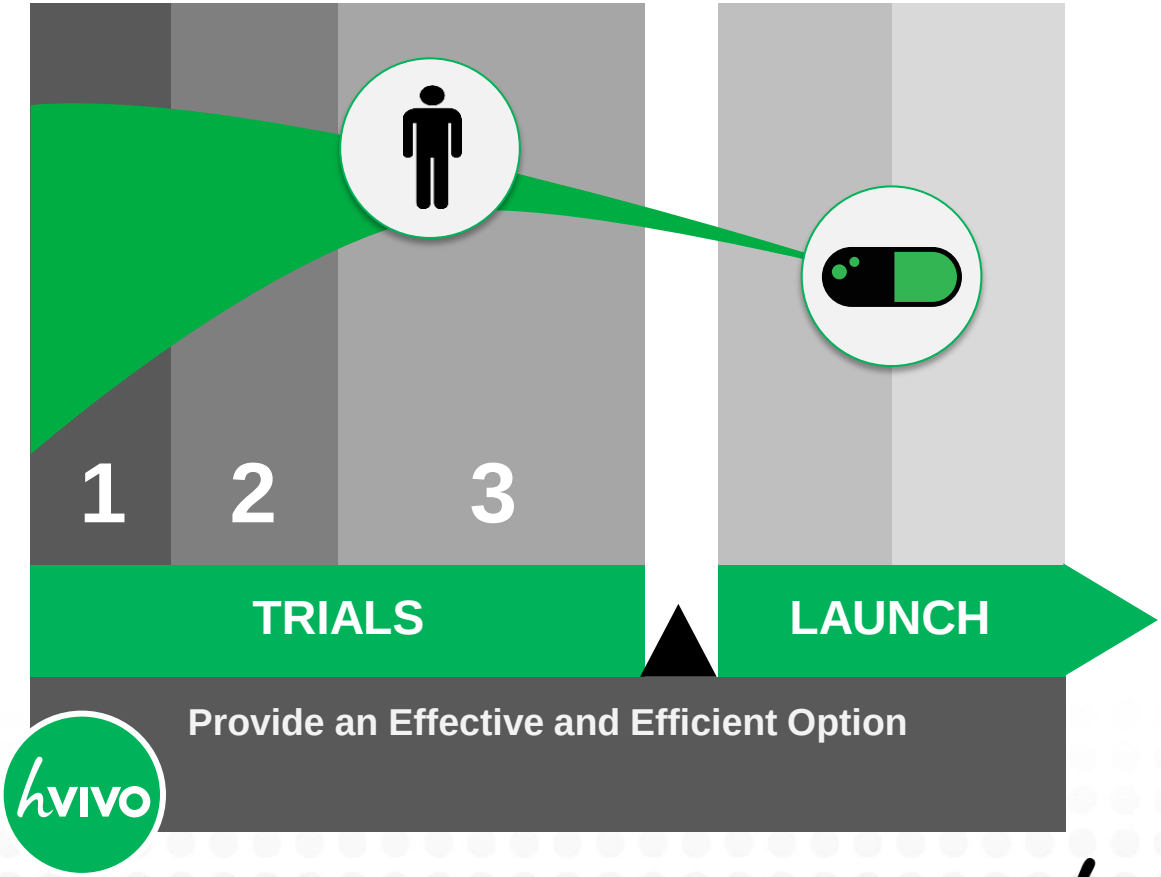
What We Do

Accelerate Drug Development

Challenge Studies = Streamline Processes, Reduce Costs, Move Forward Faster

Challenge





hVIVO

What We Do

Accelerate Drug Development

Regulatory Support: WHO Vaccines 2004

".. Human challenge studies… can provide valuable information on the pathophysiology, clinical manifestations, diagnosis, immunology, treatment response and most importantly **protective efficacy of vaccines**…"

Regulatory Oversight: EC Legislation/Guidance

Clinical Trial Regulations (i.e., SI 2004/1031)

GCP (i.e., SI 2006/1928)

GCP for Laboratories

UK Human Tissue Act (HTA)

Regulatory Support: FDA Guidance 2011

"..**Challenge trials can provide useful exposure-response and safety information**, as well as an opportunity to demonstrate pharmacological antiviral activity in humans under controlled conditions outside the influenza season.

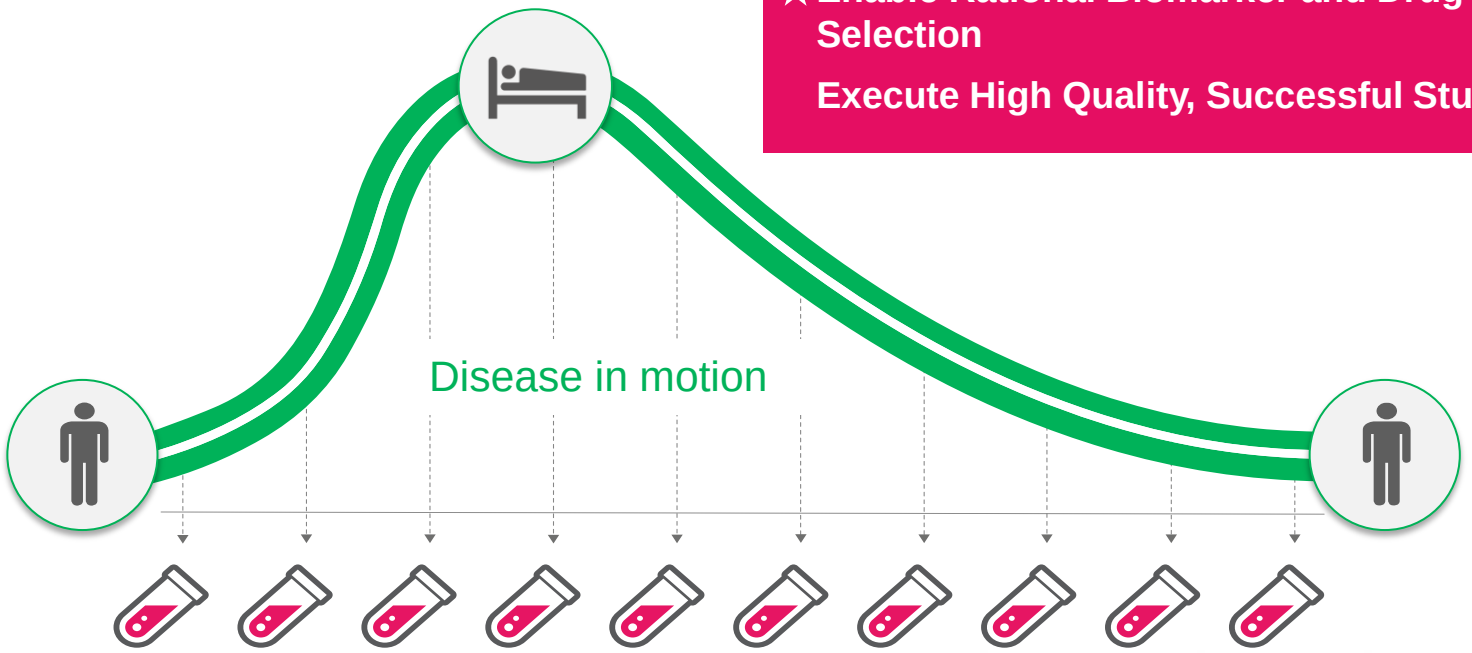
Data from challenge trials can contribute to dose selection for phase 2B and phase 3 trials, and provide the opportunity to explore the effects of different times of drug initiation relative to virus exposure….."

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm091219.pdf

What We Do

Putting Humans at the Heart of Disease Modelling

- Deliver Superior Clinical Results
- Identify Promising Drugs, Faster
- ★Enable Rational Biomarker and Drug Target Selection
- Execute High Quality, Successful Studies



How We Do It

Disease Models: Viral Infection/Viral Exacerbation

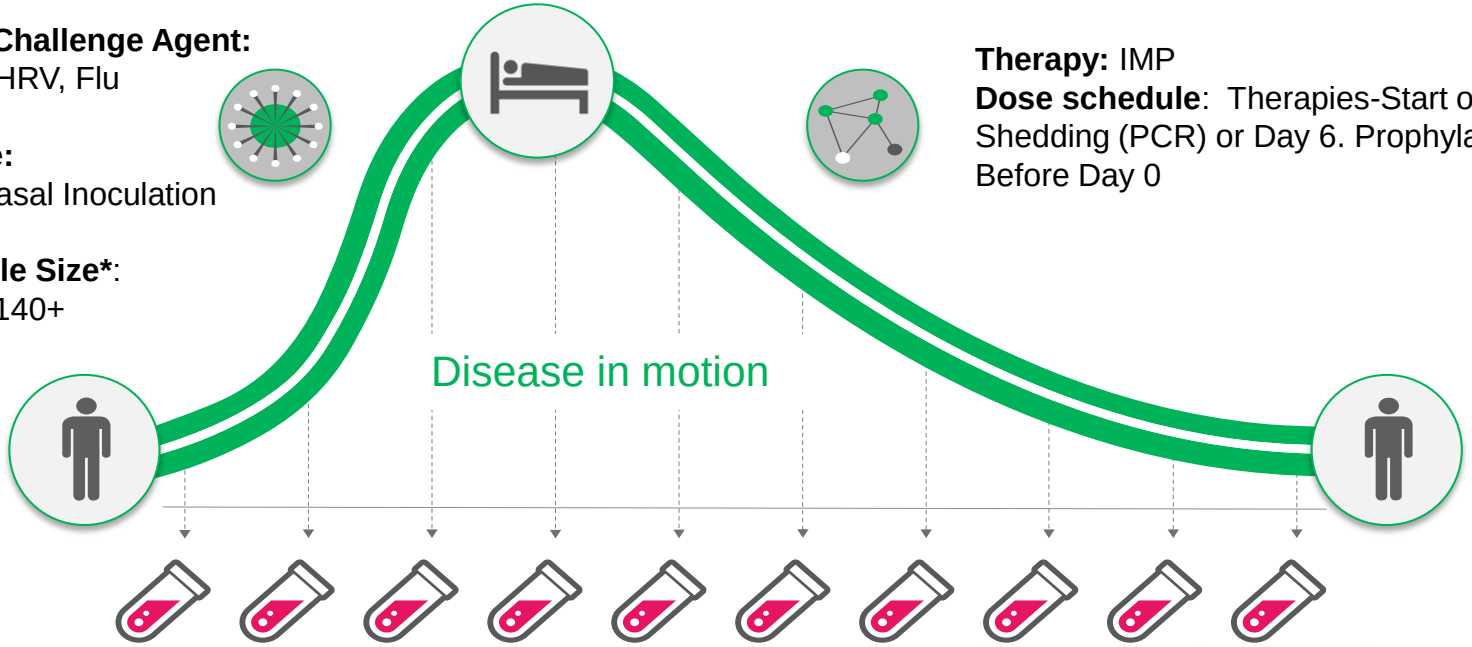
Study design: Dependent upon client requirements, typically are randomised double-blind placebo controlled studies that evaluate IMP antiviral activity, safety and efficacy. Duration: 6 -12 months.

Study Population: Healthy aged 18 to 45 years, Over 45+ years old, Diseased (i.e. asthma)

Viral Challenge Agent:
RSV, HRV, Flu

Route:
Intranasal Inoculation

Sample Size*:
20 to 140+



Therapy: IMP
Dose schedule: Therapies-Start of Viral Shedding (PCR) or Day 6. Prophylaxis- Start Before Day 0

Duration of Quarantine: 12 - 15 days
(10 - 12 days post-Challenge)

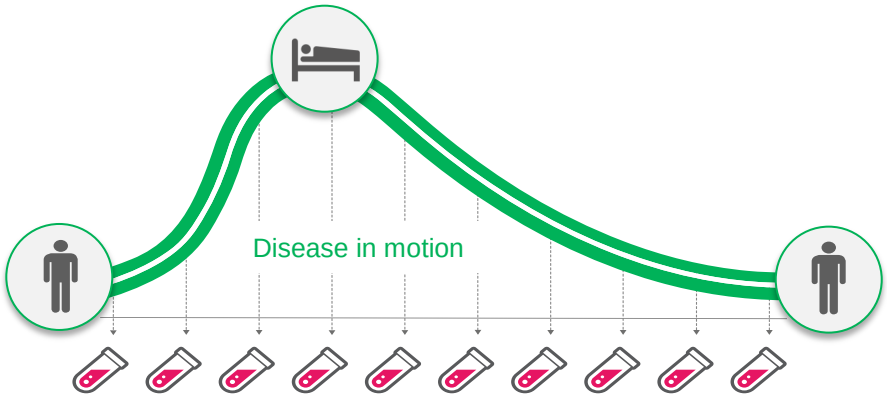
Primary Objective: IMP Antiviral effect vs placebo

Primary Endpoint: Reduction AUC viral load (qPCR)

**Sample size is customised on a per client basis*

Using a Challenge Model

Improve Your Field-Based Studies Success



Challenge study enables you to refine your clinical development plan

- Determine safety profile and identify potential safety biomarkers for field studies
- Confirm efficacy and identify primary endpoints (i.e. ACQ/PEF)
- Identify dose range in humans for field studies

Move forward with confidence to field based studies

How We Do It

Extensive Studies and Virus Library

Virus	# Clinical Studies	# Inoculated
Influenza	25	1098
RSV	12	6791
HRV	4	181
TOTAL	**40**	**1970**

Virus Library
✓ **Influenza A:** H1N1 (2) H3N2 (3) H5N1 (1) ✓ **Influenza B** ✓ **RSV-A (Memphis 37b)** ✓ **HRV-39** ✓ **HRV-16**

How We Do It

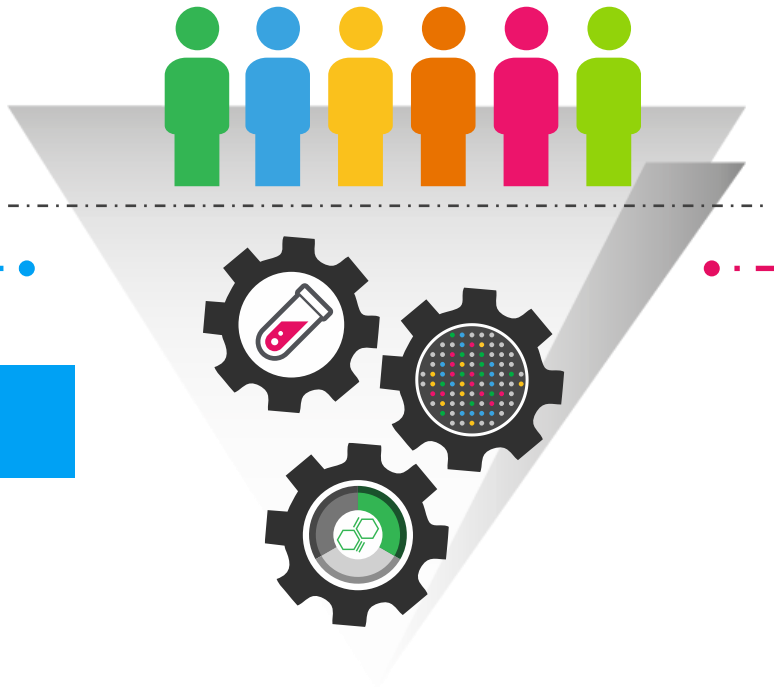
DISEASE MODELS

How We Do It

hVIVO Disease Models

Patient Populations

- Healthy
- Diseased (i.e., Asthma)
- Over 45



Models

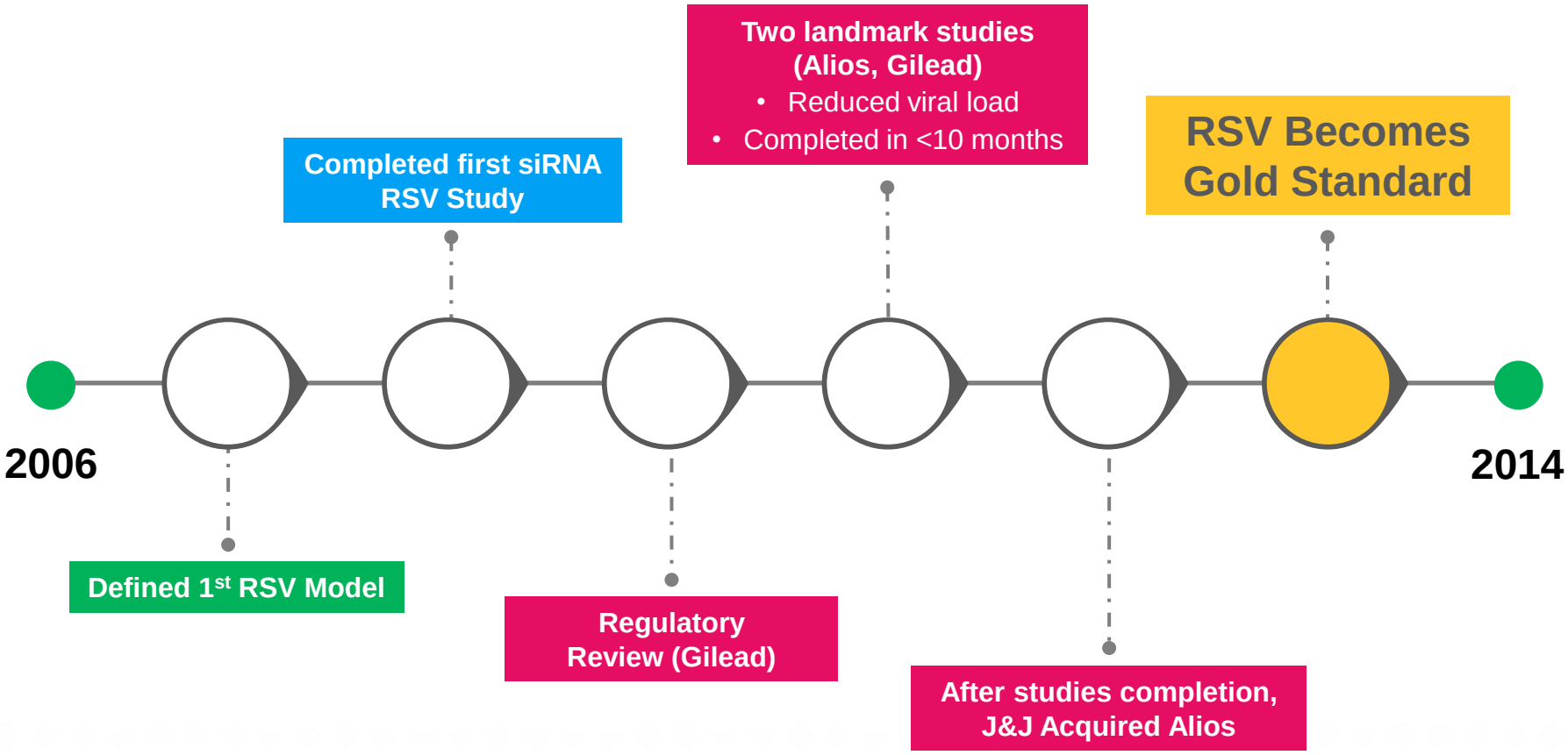
- RSV
- Flu
- HRV
- Asthma

Operations

- Recruitment
- Study Process
- Facilities
- Labs
- Viruses

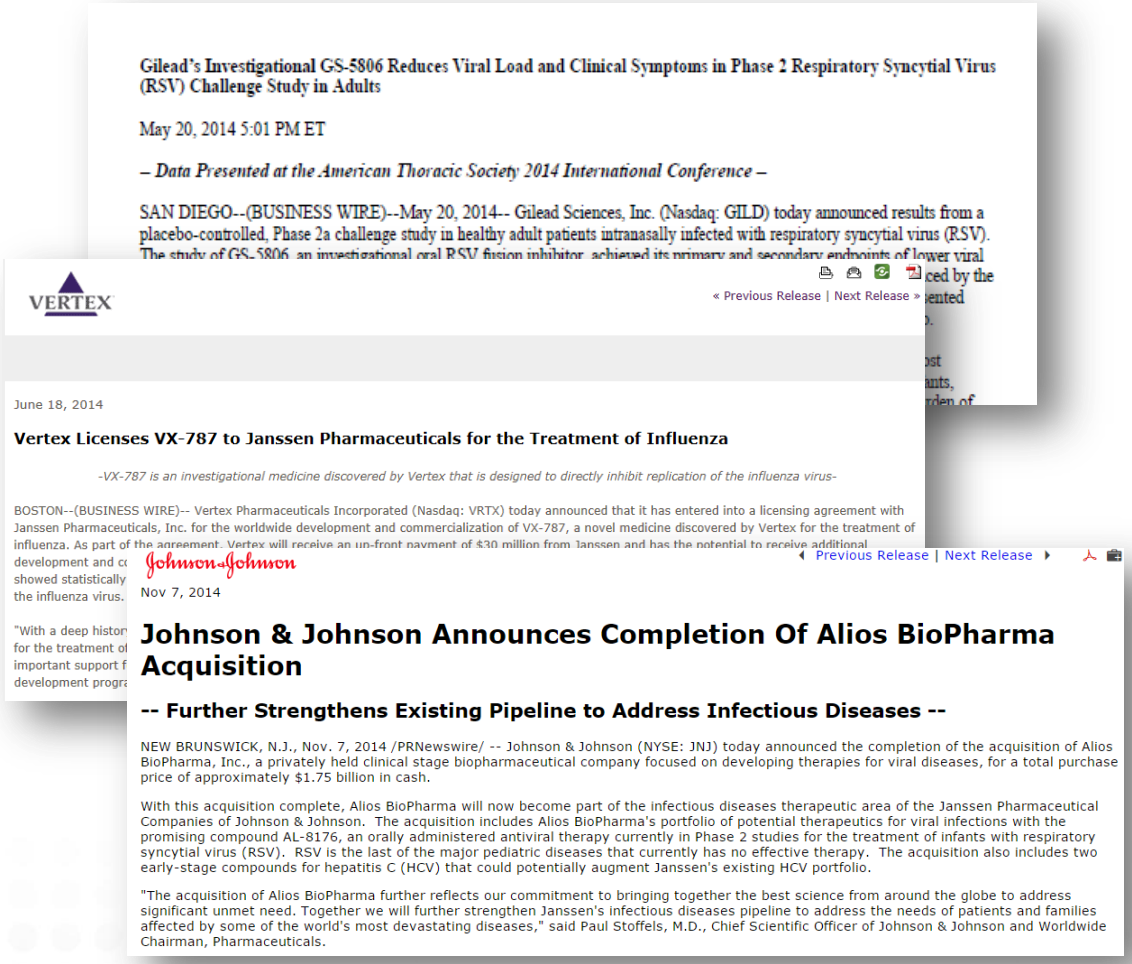
How We Do It

RSV: Path to Gold Standard



hVIVO: Case Studies

Landmark RSV and Flu Challenge Studies



Gilead's Investigational GS-5806 Reduces Viral Load and Clinical Symptoms in Phase 2 Respiratory Syncytial Virus (RSV) Challenge Study in Adults

May 20, 2014 5:01 PM ET

– Data Presented at the American Thoracic Society 2014 International Conference –

SAN DIEGO--(BUSINESS WIRE)--May 20, 2014-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced results from a placebo-controlled, Phase 2a challenge study in healthy adult patients intranasally infected with respiratory syncytial virus (RSV).

VERTEX

« Previous Release | Next Release »

June 18, 2014

Vertex Licenses VX-787 to Janssen Pharmaceuticals for the Treatment of Influenza

-VX-787 is an investigational medicine discovered by Vertex that is designed to directly inhibit replication of the influenza virus-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that it has entered into a licensing agreement with Janssen Pharmaceuticals, Inc. for the worldwide development and commercialization of VX-787, a novel medicine discovered by Vertex for the treatment of influenza.

Johnson & Johnson

Previous Release | Next Release

Nov 7, 2014

Johnson & Johnson Announces Completion Of Alios BioPharma Acquisition

-- Further Strengthens Existing Pipeline to Address Infectious Diseases --

NEW BRUNSWICK, N.J., Nov. 7, 2014 /PRNewswire/ -- Johnson & Johnson (NYSE: JNJ) today announced the completion of the acquisition of Alios BioPharma, Inc., a privately held clinical stage biopharmaceutical company focused on developing therapies for viral diseases, for a total purchase price of approximately $1.75 billion in cash.

With this acquisition complete, Alios BioPharma will now become part of the infectious diseases therapeutic area of the Janssen Pharmaceutical Companies of Johnson & Johnson. The acquisition includes Alios BioPharma's portfolio of potential therapeutics for viral infections with the promising compound AL-8176, an orally administered antiviral therapy currently in Phase 2 studies for the treatment of infants with respiratory syncytial virus (RSV). RSV is the last of the major pediatric diseases that currently has no effective therapy. The acquisition also includes two early-stage compounds for hepatitis C (HCV) that could potentially augment Janssen's existing HCV portfolio.

"The acquisition of Alios BioPharma further reflects our commitment to bringing together the best science from around the globe to address significant unmet need. Together we will further strengthen Janssen's infectious diseases pipeline to address the needs of patients and families affected by some of the world's most devastating diseases," said Paul Stoffels, M.D., Chief Scientific Officer of Johnson & Johnson and Worldwide Chairman, Pharmaceuticals.

VERTEX

GILEAD

Alios BioPharma

"It is an evolving field. We benefitted hugely from this (Retroscreen challenge study) and I think our programme has moved at a faster pace than if we had gone out and tried to do a field-based study."

John Fry
Assoc Director, Clinical Operations
Alios BioPharma

hVIVO

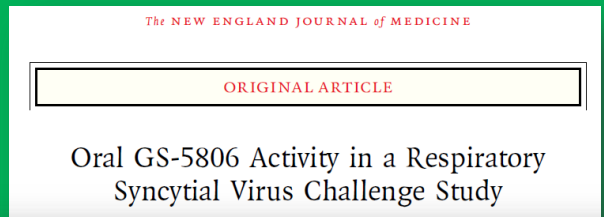
hVIVO: RSV as Gold Standard

Industry Adoption of the hVIVO Model

Evaluation of Therapeutics for RSV: Breakthrough Results

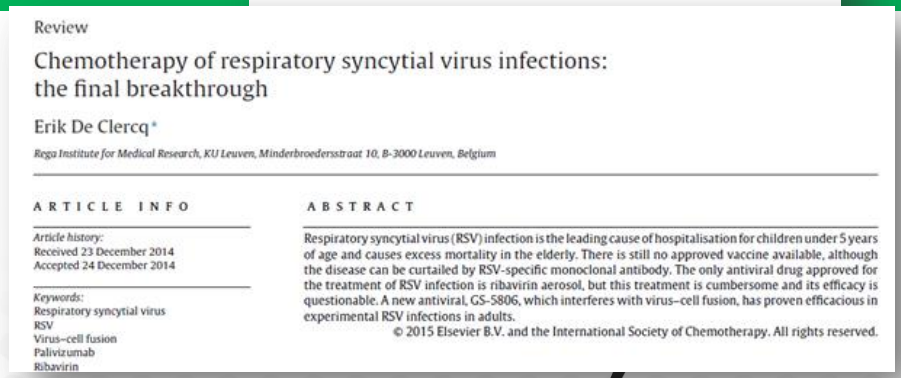
"Since I reviewed the perspectives for the chemotherapy of respiratory syncytial virus (RSV) infections ….almost 2 decades ago, little progress has been made in the prophylaxis or therapy of RSV infection…The recent report of DeVincenzo et al. that GS-5806, which inhibits RSV fusion with the host cell, suppresses clinical disease in healthy adults experimentally infected with RSV[4] ***may have a significant impact on the prevention and treatment of RSV infection….****"*

Eric De Clercq
Rega Institute for Medical Research
2015


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study


Review

Chemotherapy of respiratory syncytial virus infections: the final breakthrough

Erik De Clercq*

Rega Institute for Medical Research, KU Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 23 December 2014
Accepted 24 December 2014

Keywords:
Respiratory syncytial virus
RSV
Virus–cell fusion
Palivizumab
Ribavirin

ABSTRACT

Respiratory syncytial virus (RSV) infection is the leading cause of hospitalisation for children under 5 years of age and causes excess mortality in the elderly. There is still no approved vaccine available, although the disease can be curtailed by RSV-specific monoclonal antibody. The only antiviral drug approved for the treatment of RSV infection is ribavirin aerosol, but this treatment is cumbersome and its efficacy is questionable. A new antiviral, GS-5806, which interferes with virus–cell fusion, has proven efficacious in experimental RSV infections in adults.

© 2015 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.

GS-5806= Gilead compound, study conducted by hVIVO

Source: http://dx.doi.org/10.1016/j.ijantimicag.2014.12.025

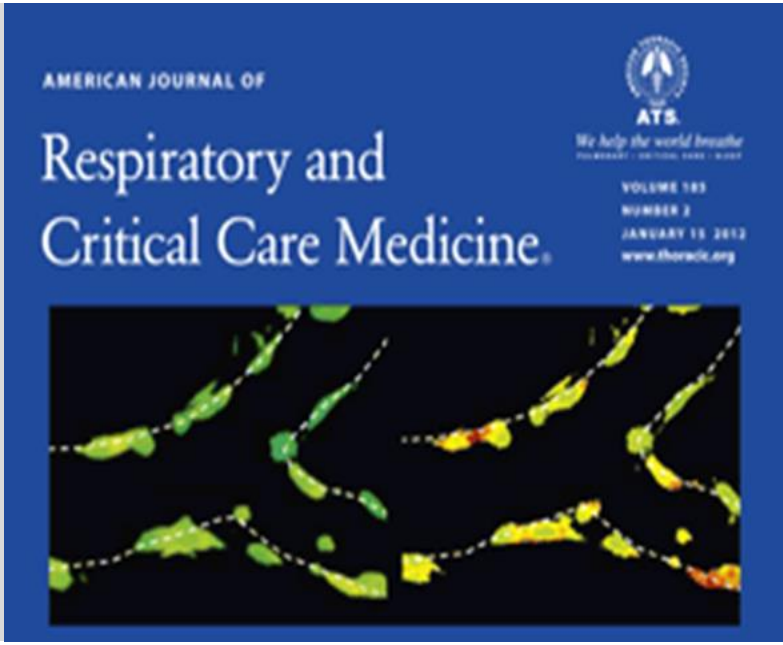
How We Do It

Setting the Standard

Industry Adoption

Evaluation of Therapeutics for RSV: An important step forward

"The advantages of a **safe, reproducible human model are incalculable. This model permits the relatively quick and efficient study of new therapeutics in humans** and assists in making critical decisions whether to advance a product into costly human trials in populations at highest risk for disease; children, elderly or immunocompromised patients. This constitutes a major and welcome advance in the field of RSV."



Client X

"We saw the CLIENT Y challenge data and are pleased to see the RVL model can work so well. We are looking forward to beating the results that CLIENT Y got. Keep up the good work!"

How We Do It

Ongoing Recruitment

97%

Volunteer enrollment success rate

industry norm 15%



How We Do It

Controlled Settings and Processes



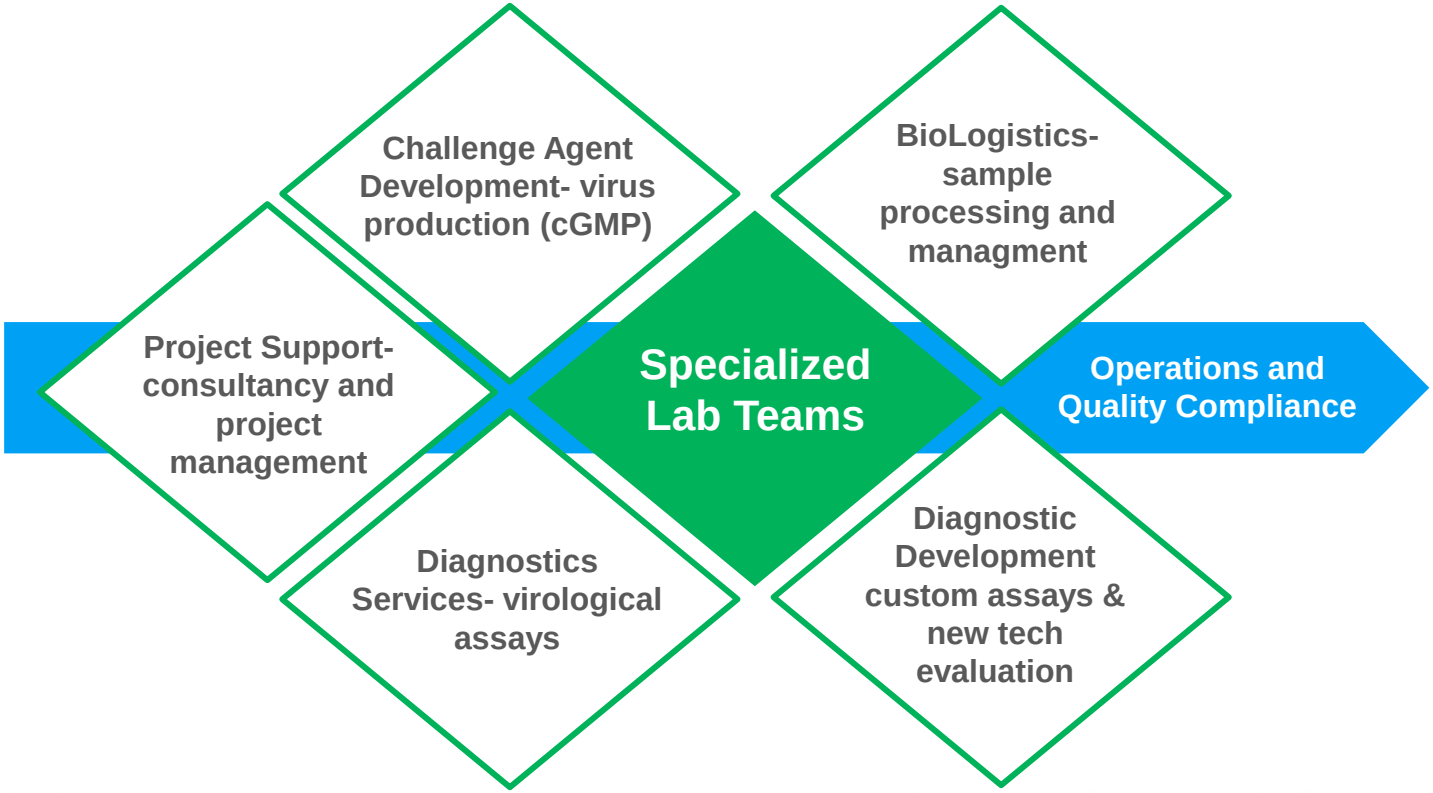






How We Do It

Clean Data: Virology Laboratory Operations



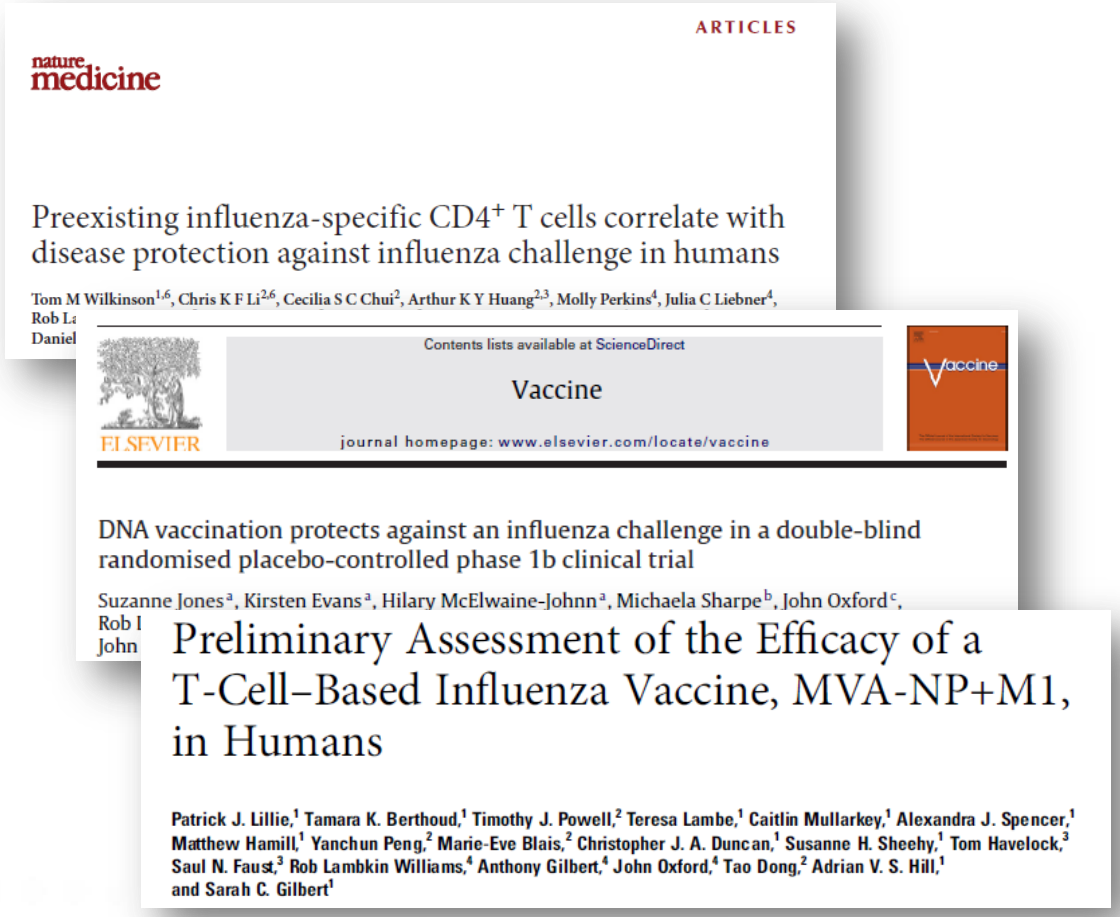
Fast processing- Highly co-ordinated with Screening and Quarantine



hVIVO

hVIVO: Case Studies

Vaccine Proof of Concepts



ARTICLES

nature medicine

Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans

Tom M Wilkinson[1,6], Chris K F Li[2,6], Cecilia S C Chui[2], Arthur K Y Huang[2,3], Molly Perkins[4], Julia C Liebner[4], Rob La... Daniel...

Contents lists available at ScienceDirect

Vaccine

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

ELSEVIER

DNA vaccination protects against an influenza challenge in a double-blind randomised placebo-controlled phase 1b clinical trial

Suzanne Jones[a], Kirsten Evans[a], Hilary McElwaine-Johnn[a], Michaela Sharpe[b], John Oxford[c], Rob I... John...

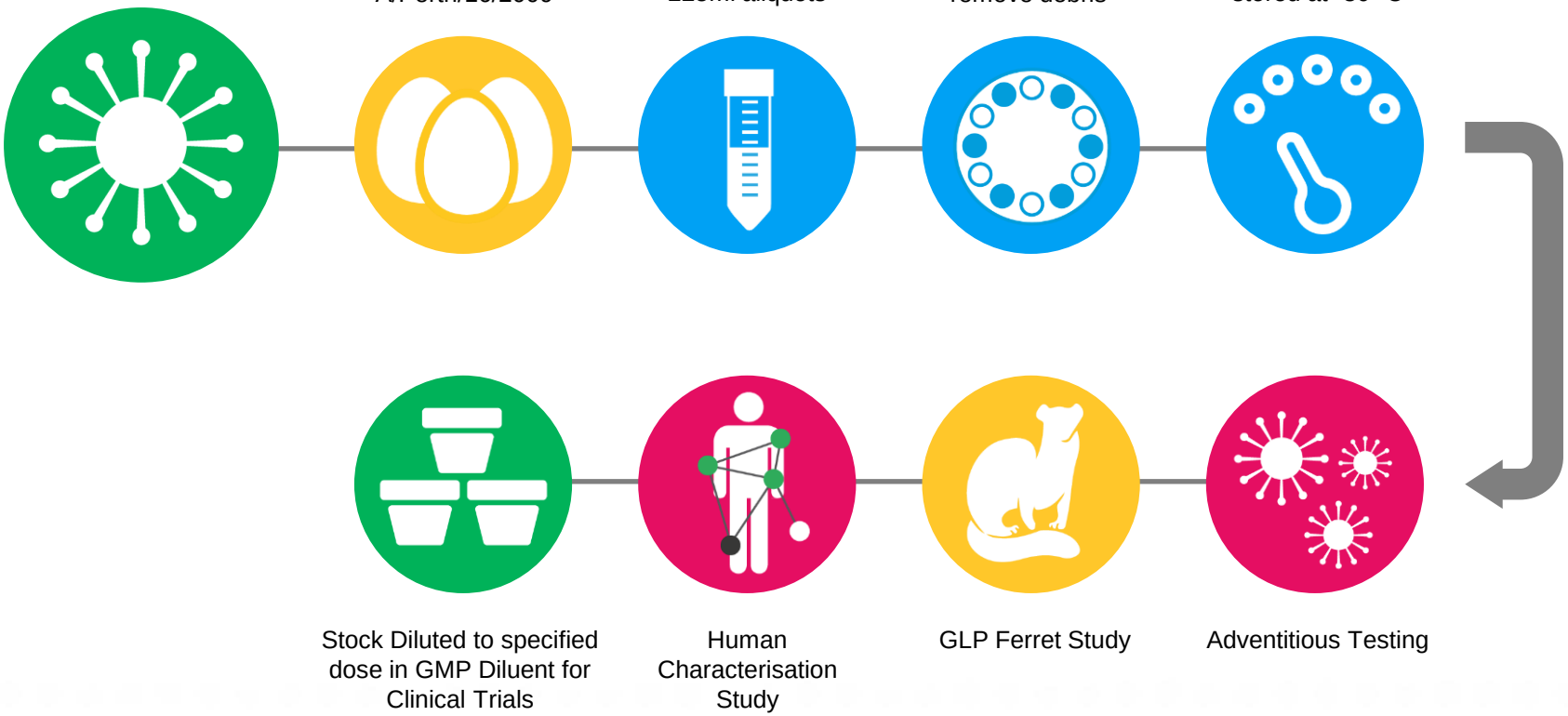
Preliminary Assessment of the Efficacy of a T-Cell–Based Influenza Vaccine, MVA-NP+M1, in Humans

Patrick J. Lillie,[1] Tamara K. Berthoud,[1] Timothy J. Powell,[2] Teresa Lambe,[1] Caitlin Mullarkey,[1] Alexandra J. Spencer,[1] Matthew Hamill,[1] Yanchun Peng,[2] Marie-Eve Blais,[2] Christopher J. A. Duncan,[1] Susanne H. Sheehy,[1] Tom Havelock,[3] Saul N. Faust,[3] Rob Lambkin Williams,[4] Anthony Gilbert,[4] John Oxford,[4] Tao Dong,[2] Adrian V. S. Hill,[1] and Sarah C. Gilbert[1]

- First proof of concept of a DNA vaccine against an infectious disease
- First proof of concept of a T-cell influenza vaccine
- Intranasal vaccine study provided insights on correlates of protection
  - Found IgG and IgA played role in symptom severity
  - Further studies showed importance T-cell immunity
  - Efficacy data assisted in field study design

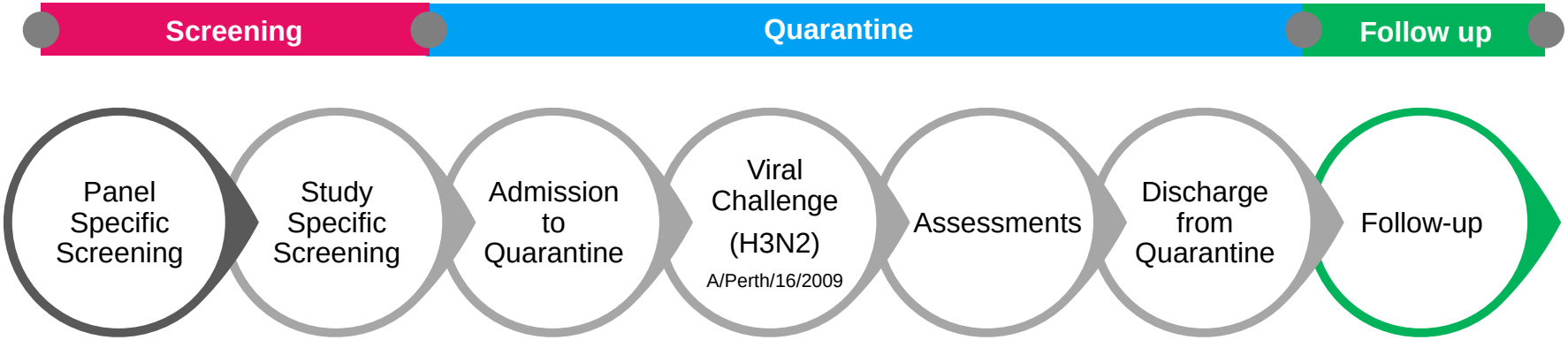
How We Do It

New Challenge Agent Production: H3N2



How We Do It

New Challenge Agent: Study Design



- Serology sample
- GP letters
- Study Consent
- Medical History
- Assessments

- Admission D-2

- Inoculation Day 0

- Assessments
- Symptoms
- Start IMP Administration

- Assessments
- Symptoms
- Continue IMP administration (as needed)

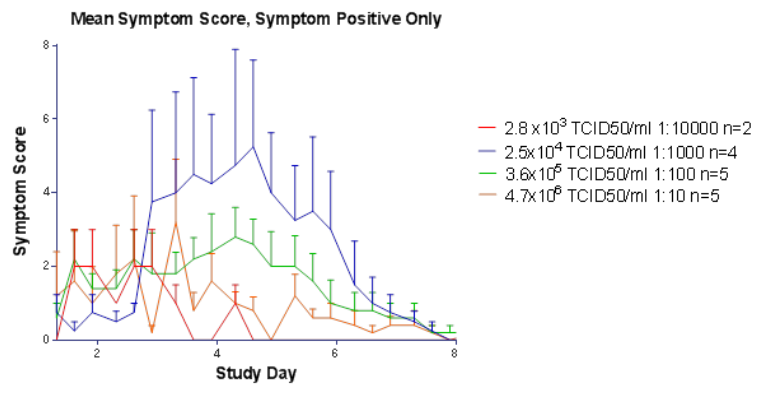
- Leave Unit

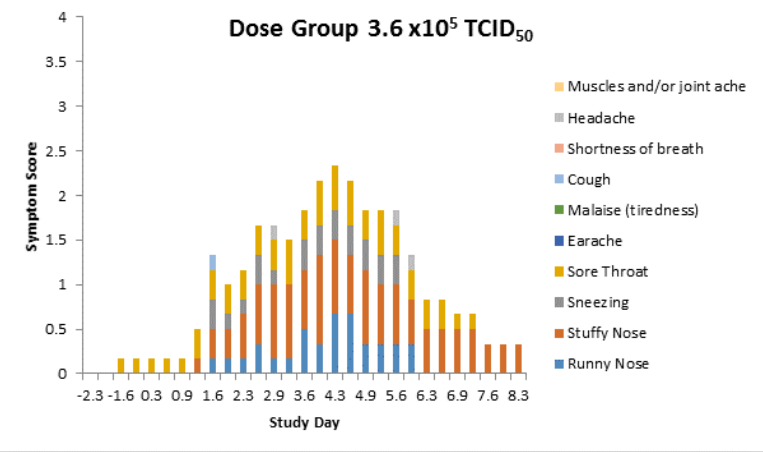
- Assessments

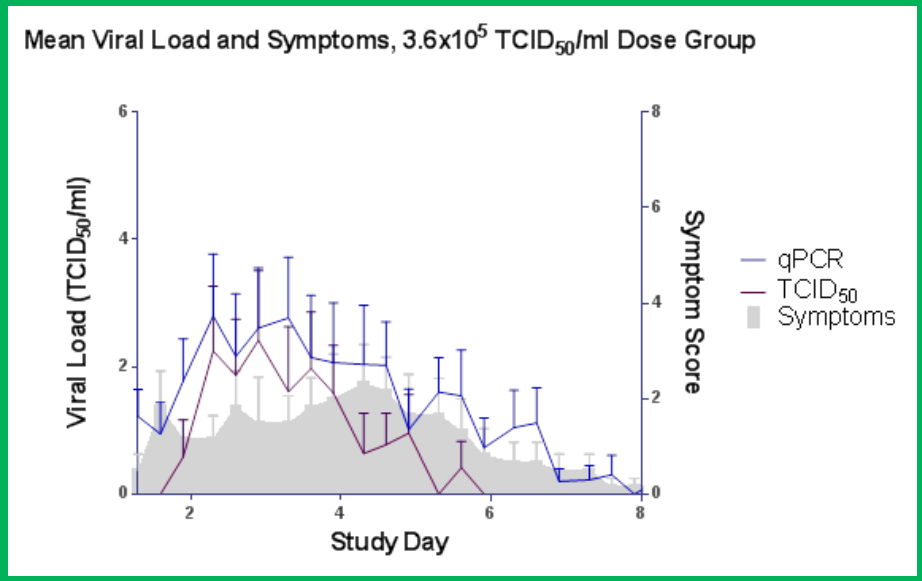
Day (-80) to Day (-3) → Day (-56) to Day (-3) → Day (-2) → Day 0 → Day 1 to Day 7 → Day 8 → Day 28 (+3 days)

How We Do It

H3N2: Symptomology Characteristics







Symptomology is a vital consideration

Balance: Dose, Severity, Safety

Goal: Mimic natural disease

How We Do It

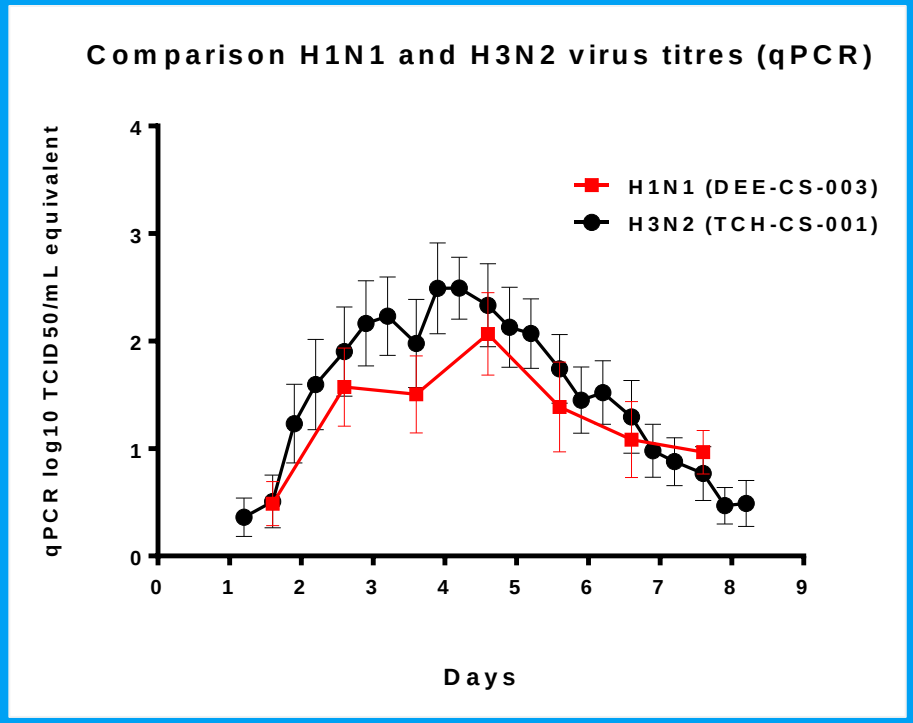
H3N2: High Infection Rate

Inoculum ($TCID_{50}$)	Culture Virus Positive (%)	qPCR Virus Positive (%)	Serocon' (%)	Lab Confirmed Infection (%)
2.8 x10^3	0	17	17	0 (0/6)
2.5x10^4	68	68	50	77 (4/6)
3.6X10^5	51	100	33	77 (4/6)
4.7X10^6	68	100	77	83 (5/6)

Lowest inoculum level + Best infection rate + Symptoms Consistency =
Closest to natural infection and Minimizes artifacts

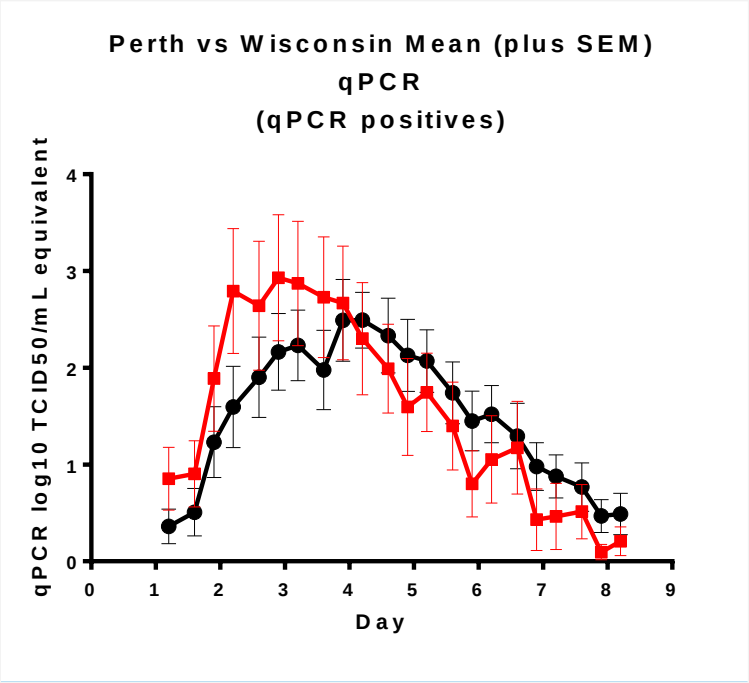
How We Do It

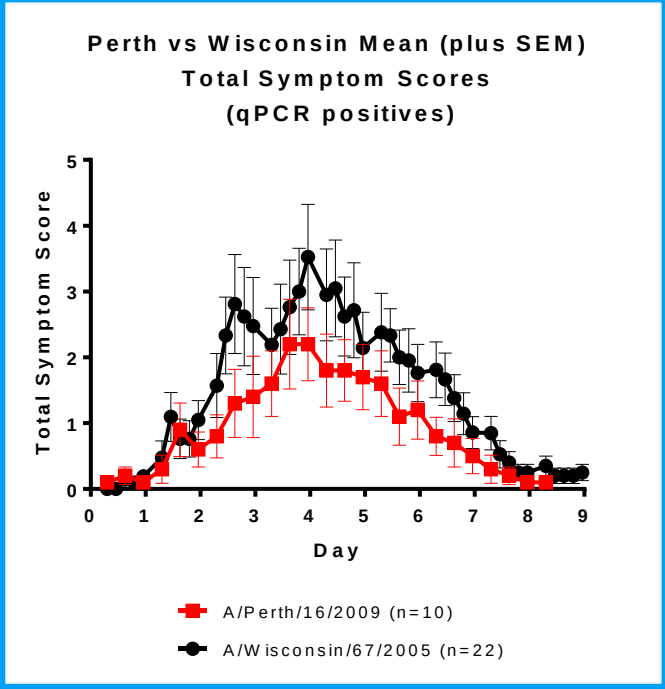
Virus Characterization: H3N2 vs H1N1 (hVIVO)



How We Do It

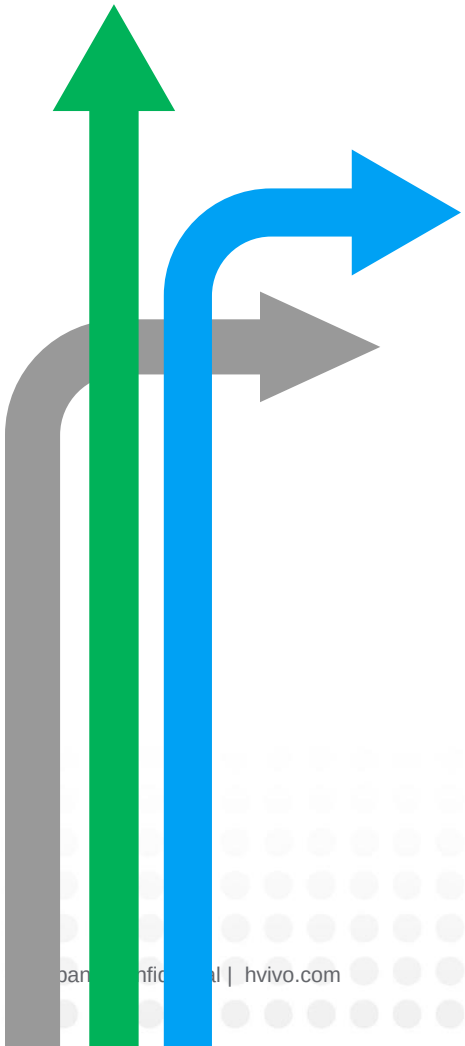
Virus Characterization: Comparability of Historical vs Current





hVIVO Summary

Human challenge models provide an effective option for testing drugs safety and efficacy



hVIVO is the market leader in challenge studies

- Experienced: 40+ Studies, 1970+ Volunteers
- Multiple models (RSV, Influenza, HRV, Asthma, Elderly)
- Rigorously characterized cGMP viruses (H3N2 and H1N1)

The hVIVO platform enables organizations to accelerate their time to market

- Product Validation
- Rational Selection of Biomarkers and Drug Targets

Contact Information

Rob Lambkin-Williams, BSc, PhD, MRPharmS
Executive Scientific Adviser
Email: rlw@hvivo.com
Phone: 011 44 (0) 7710577019

Rich Niemi
Senior Director Business Development
Email: r.niemi@hvivo.com
Phone: 1 609- 841-1504

THANK YOU



better treatments, faster

hVIVO