FLU 2016
San Francisco

The Human Viral Challenge Model: Accelerating Drug and Vaccine Development

Dr Anthony Gilbert
Medical Director

hVIVO at a Glance

hVIVO, a specialty biopharma company with clinical testing capabilities, is pioneering a human-based analytical platform to accelerate drug discovery and development in respiratory and infectious diseases.

- Founded 1988
- Based in the U.K.



45+
Clinical Studies



2200+
volunteers

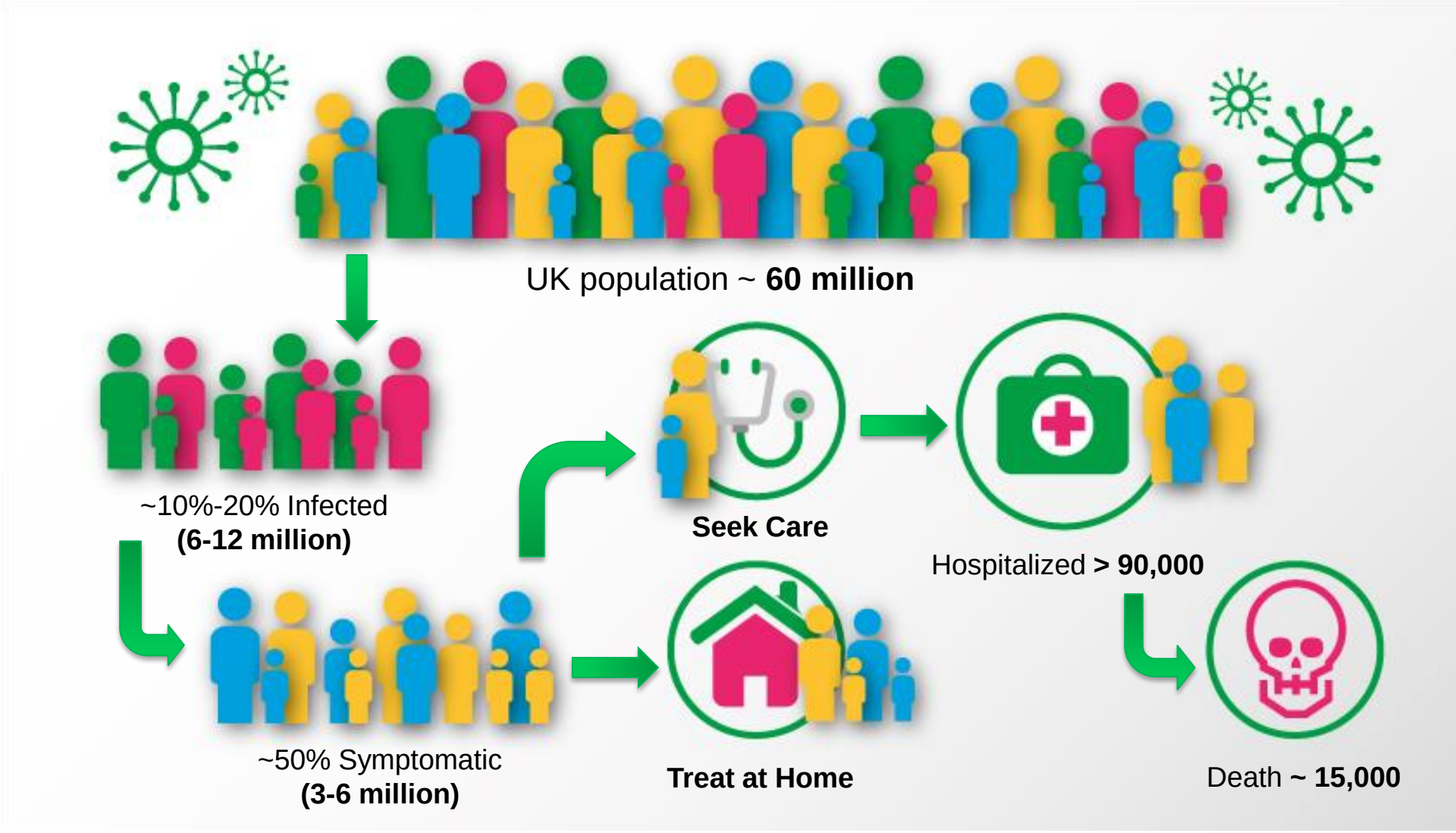
hVIVO platform: leveraging human disease models to illuminate disease in motion

- Market-leader with **4 Models (Flu, Common Cold, RSV, Asthma)**
- 15+ years designing HCM with pharma and regulatory authorities/safety boards

Unique capabilities to support rational disease biomarker and drug target selection

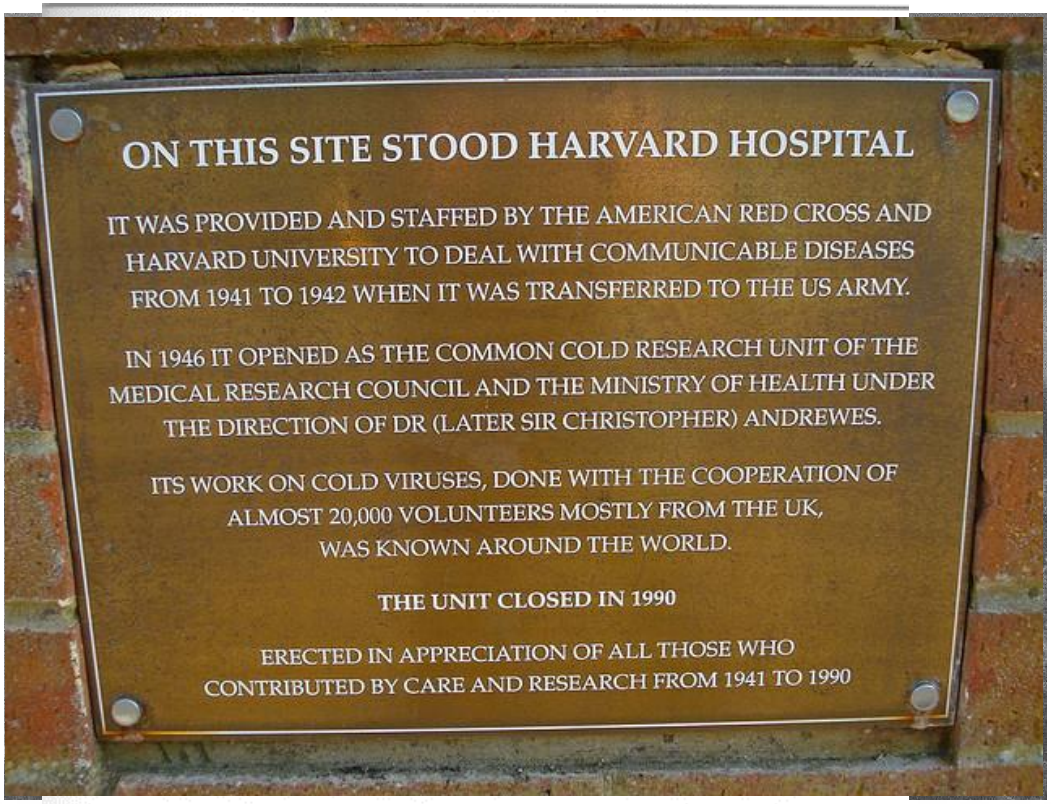
- Clinical quality human sample databank
- Cutting-edge omics capabilities

Influenza: Annual Impact



Common Cold Unit

Salisbury, United Kingdom



Drug Development

Changing the paradigm

What if you could run your trial regardless of season?

What if you could utilise adaptive designs to determine the drug dosing range and safety profile in your early phase study studies

What if you could monitor patients throughout the disease cycle (before, during, after)?

What if you could run your study in one site and under 12 months?

What if you could have the data and insights to rationally select drug targets and biomarkers?

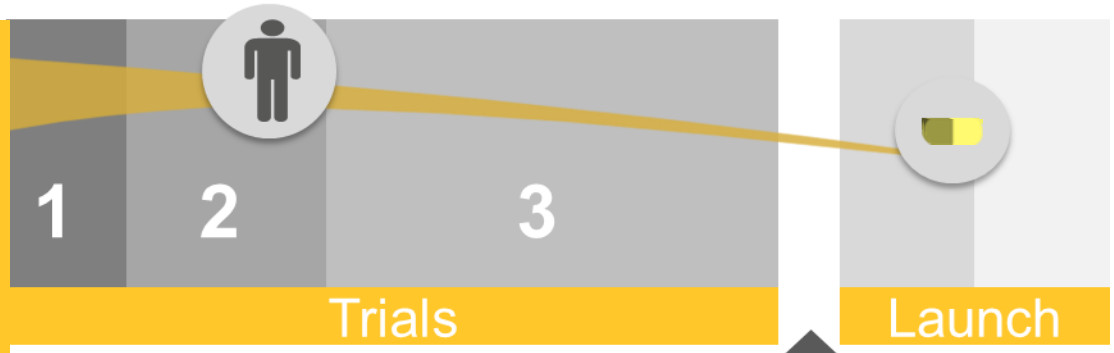
Challenge Studies

Get Answers Sooner

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

Traditional

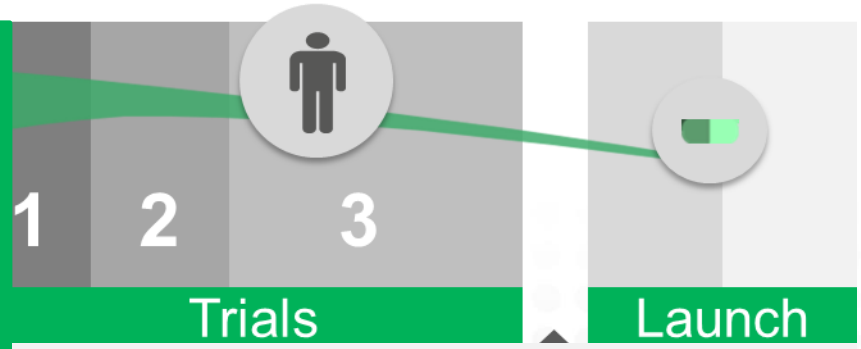
Many Sites
Many Subjects (300+)
Seasonality Constraints
Delayed Monitoring (48hrs)
Few End Points
Limited Dose Ranges
Long (1+ Yrs)



Drug Development Costly and Long

Challenge

1 Site
Few Subjects (~40-140)
All Seasons
Real-Time Monitoring
Flexible End-Points
Multiple Dose Ranges
Short (<1 Yr)



Provide an Effective and Efficient Option

How We Do It

Disease Models: Viral Infection/Viral Exacerbation

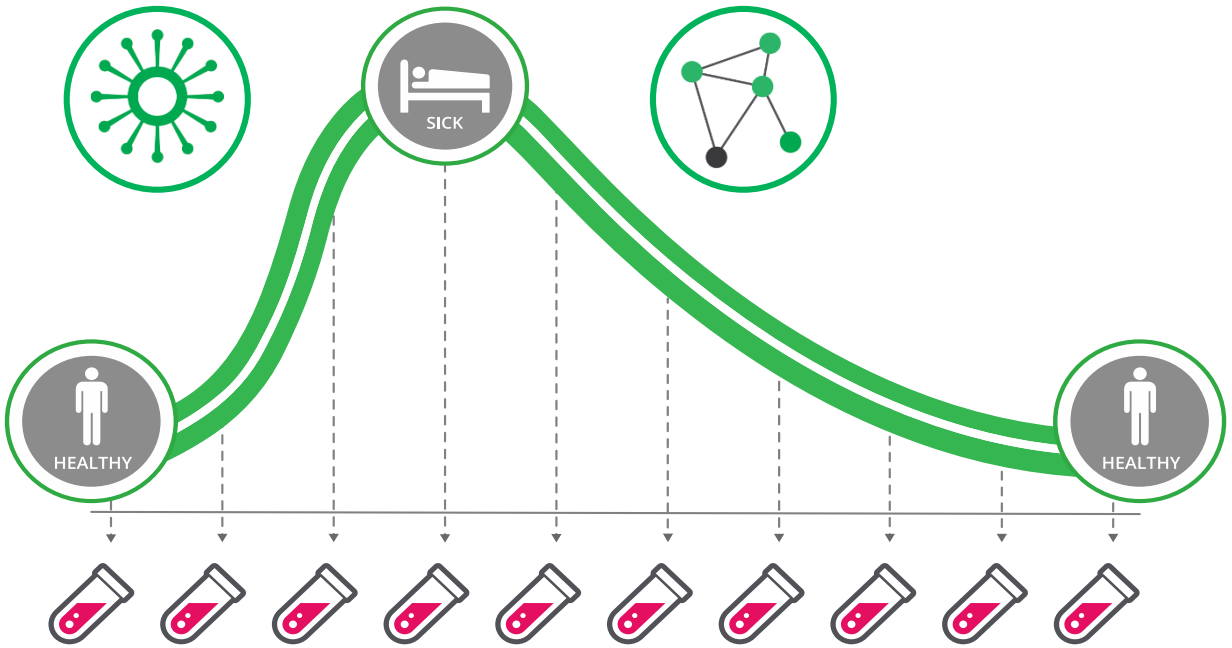
Models: Influenza, Respiratory Syncytial Virus, Human Rhinovirus, Asthma

Applications: Proof of Concept, Animal Model Validation and Mechanism of Action

Study Population: Healthy, Diseased subjects **Ages:** 18- 45 years, Over 45 years

Viral Agent:
Flu, HRV, RSV,

Therapy: Treatment, Vaccine, Prophylaxis



Sample Size: est.
40-140*

Duration of Quarantine: 11-15 days (follow up visits)*

Duration of Study: < 12 months

Examples Primary Objective:
Reduced viral load compared to placebo
Reduced exacerbations compared to placebo

** Sample size varies based on application/study*

Why We Do It

Accelerate Vaccine / Drug Development

Regulatory Guidance: EMA 2014

"…Human challenge studies could provide useful information for establishing correlates of protection…"

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

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….."

FDA

hVIVO

Why We Do It

Accelerate Vaccine / Drug Development

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: 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**…"

World Health Organization

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

http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/035-101.pdf?ua=1

hVIVO

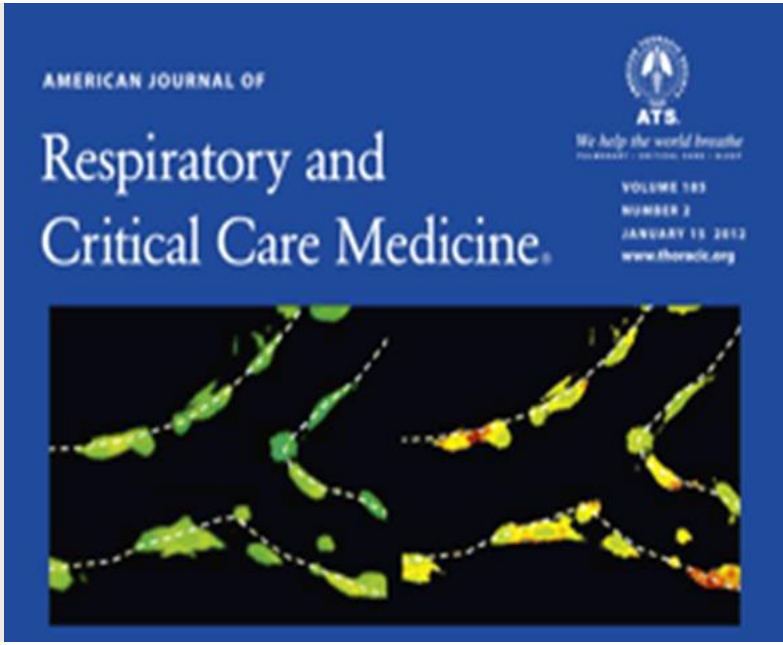
Why We Do It

Accelerate Vaccine / Drug Development

Industry Adoption

Evaluation of Therapeutics for RSV:
An important step forward

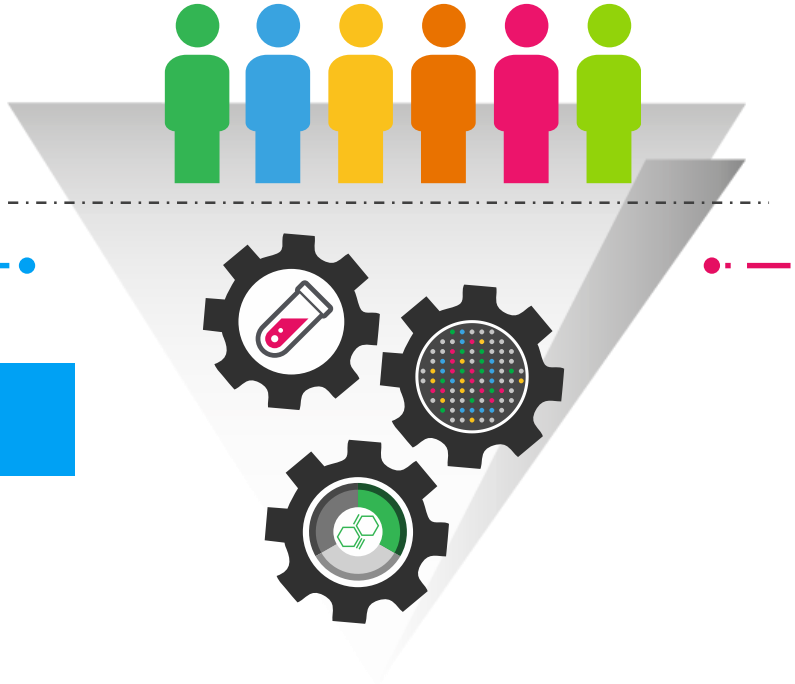
"The advantages of a **safe, reproducible human model are incalculable. This model permits the relatively quick and efficient study of new therapeutics in humans** and assists in making critical decisions whether to advance a product into costly human trials in populations at highest risk for disease;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



HOW WE DO IT

How We Do It

hVIVO Disease Models



Patient Populations

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

Models

- Influenza
- RSV
- HRV
- Asthma

Operations

- Recruitment
- Study Process
- Facilities
- Labs
- Viruses

How We Do It

Ongoing Recruitment

97%

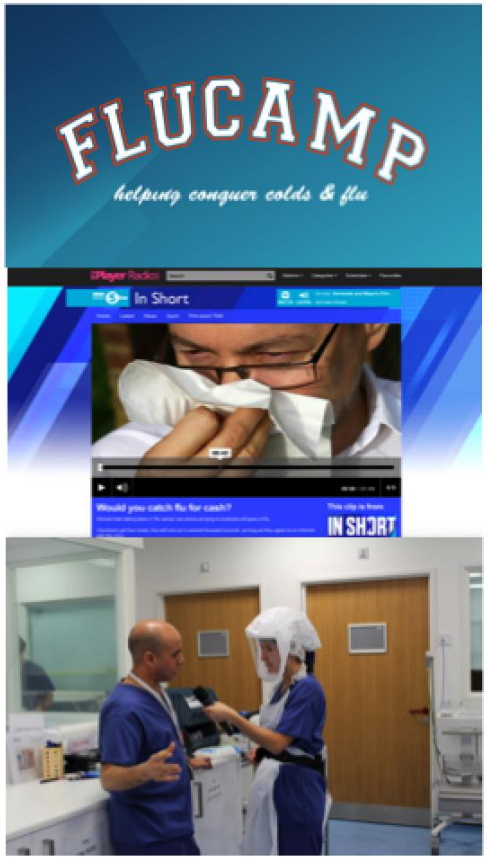
Volunteer enrollment success rate

70%

Industry norm of delayed trials due to patient enrollment problems



FluCamp – Media Coverage



BBC Radio 5 live



BBC – Bang Goes The Theory



BBC – The Truth about your medicine cabinet

hVIVO

How We Do It

Clean Data: Controlled Settings and Processes

- **Managing infection control methods and quarantine units**
- **En-suite design keeps each volunteer isolated throughout study.**
- **Proven inoculation processes close to natural infection with strong safety profile**
- **Each subject supplies their own baseline, reducing variability**
- **Resulting in cleaner data**









hVIVO

How We Do It

Symptom Diary Card

Subject Number	Subject Initials	Date	Time (24 hour clock)	Time of Day (mark with an X)		
	F M L	D D M M M Y Y Y Y	H H : M M	Morning	Afternoon	Evening

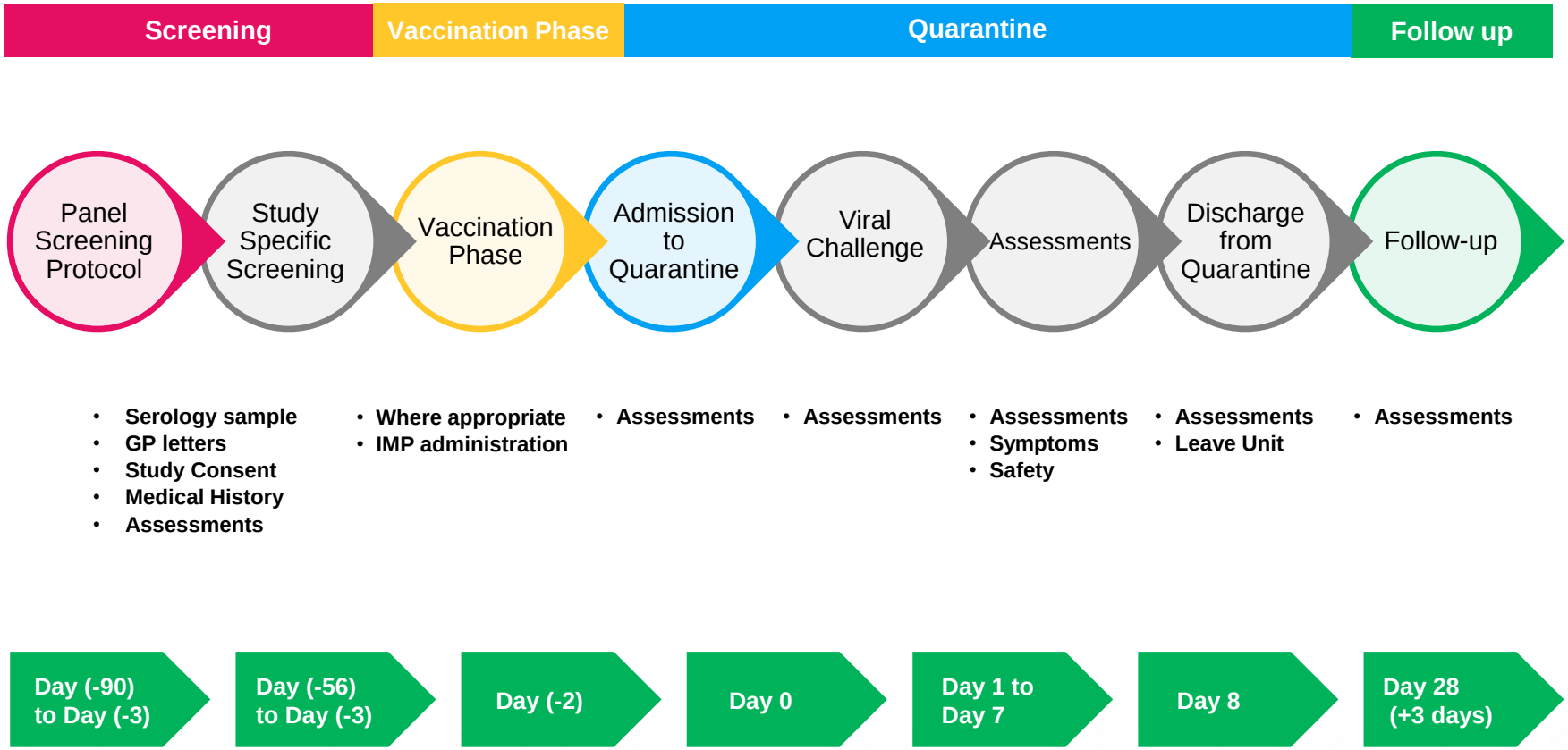
Level	0	1	2	3
Symptoms Please report the symptoms you are experiencing at the moment (Mark with an ×)	I have NO symptoms	Just noticeable	It's clearly bothersome from time to time, but it doesn't stop me from participating in activities	It's quite bothersome most or all of the time, and it stops me from participating in activities
Runny Nose	☐ 0	☐ 1	☐ 2	☐ 3
Stuffy Nose	☐ 0	☐ 1	☐ 2	☐ 3
Sneezing	☐ 0	☐ 1	☐ 2	☐ 3
Sore Throat	☐ 0	☐ 1	☐ 2	☐ 3
Earache	☐ 0	☐ 1	☐ 2	☐ 3
Malaise (tiredness)	☐ 0	☐ 1	☐ 2	☐ 3
Cough	☐ 0	☐ 1	☐ 2	☐ 3
Shortness of breath	☐ 0	☐ 1	☐ 2	☐ 3
Headache	☐ 0	☐ 1	☐ 2	☐ 3
Muscle and/or joint ache	☐ 0	☐ 1	☐ 2	☐ 3

Subject's initials	Doctor's Initials	Date	Time (24 hour clock)
		D D M M M Y Y Y Y	H H : M M

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How We Do It

Study Design



How We Do It

Extensive Studies and Virus Library

Virus	# Clinical Studies	# Inoculated
FLU	27	1222
RSV	13	775
HRV	7	289
TOTAL	**47**	**2286**

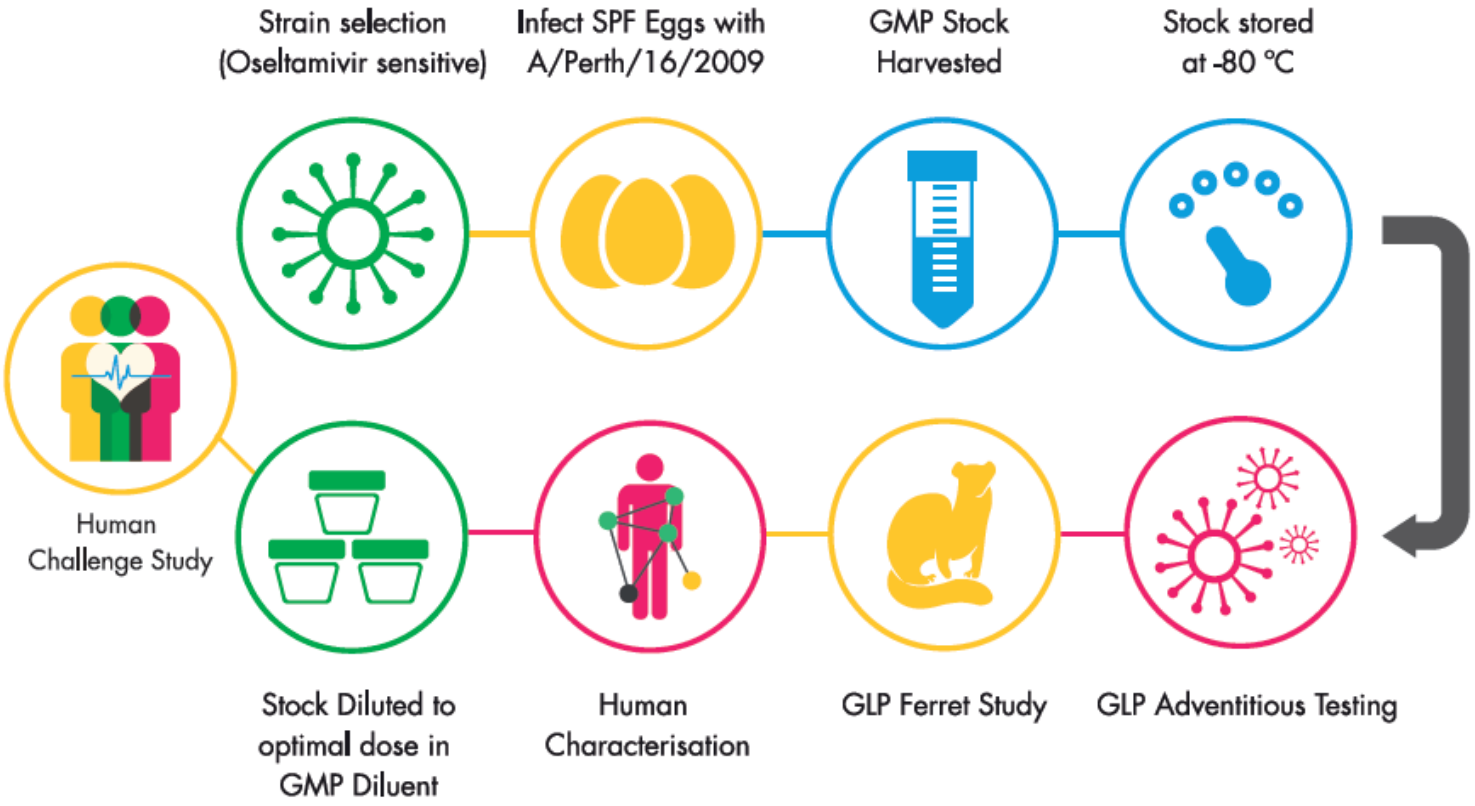
Virus Library

Experience with a broad range of viruses. Those currently available include:

- ✓ **Influenza A:**
  - H1N1 (2)
  - H3N2 (3)
  - H5N1 (1)
- ✓ **RSV-A (Memphis 37b)**
- ✓ **HRV-16**
- ✓ **HRV-14**

How We Do It

Challenge Agent Production



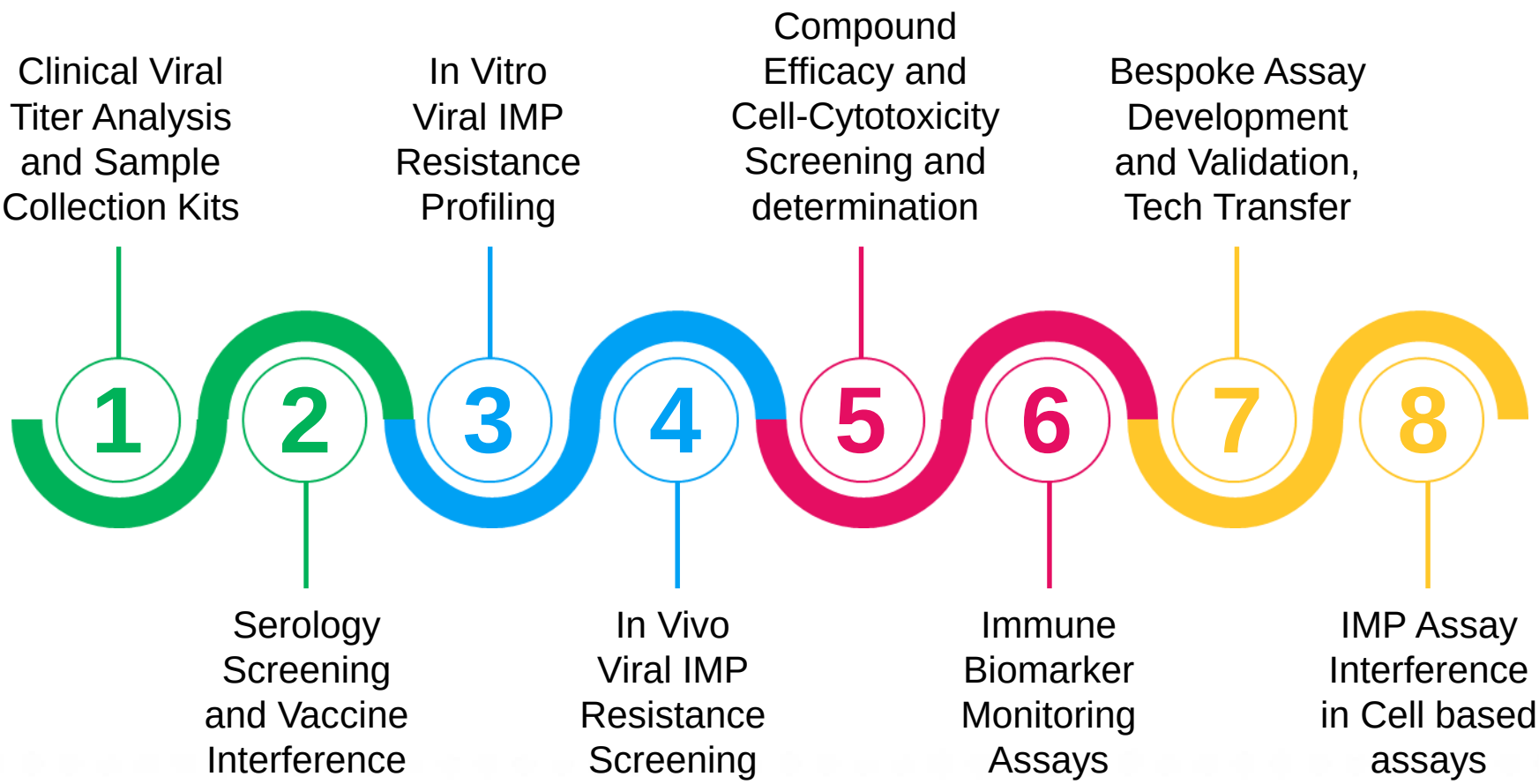
Our Labs - Overview





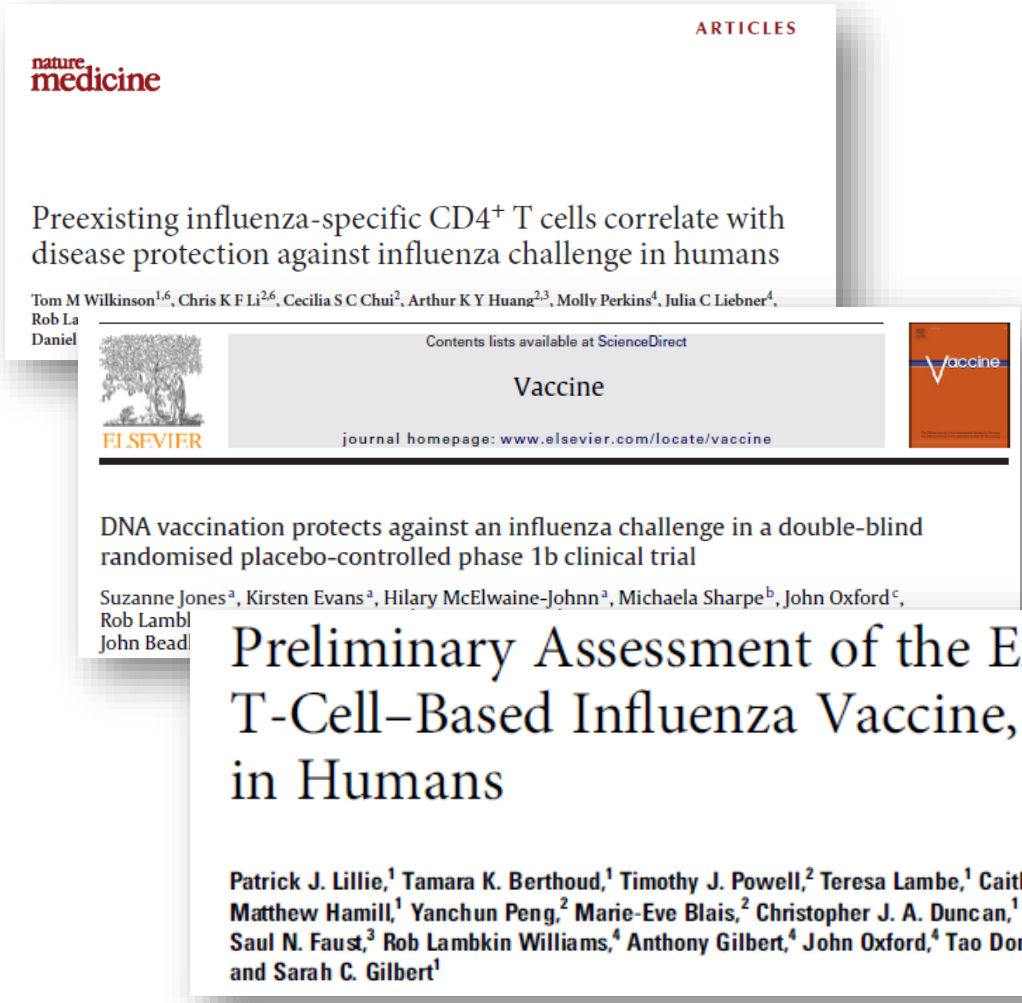
- Virological and Immunological focused analysis using cell-based, molecular and proteomic platforms.
- Therapeutic Area coverage- Respiratory Virus Pathogens; Vaccines, Antivirals, Prophylactics and Immuno-modulators.
- Analysis of biomarkers from a broad spectrum of sample matrices (e.g. serum, plasma, PBMC, nasal swabs, nasal washes). Sample stabilization solutions and field-trial sample collection kits.
- Comprehensive menu- Flu, RSV, HRV
- Global clinical trial capabilities

Lab Services Summary



CASE STUDIES

Influenza Challenge Studies - Proof of Concept



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

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 Lambl... John Beadl...

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]

Answering key questions

- CD4+ T cells correlate with disease protection against influenza
- DNA vaccine against an infectious disease
- First proof of concept of a T-cell influenza vaccine

Utilising the Human Challenge Model:
Novel T-Cell-Based Vaccine

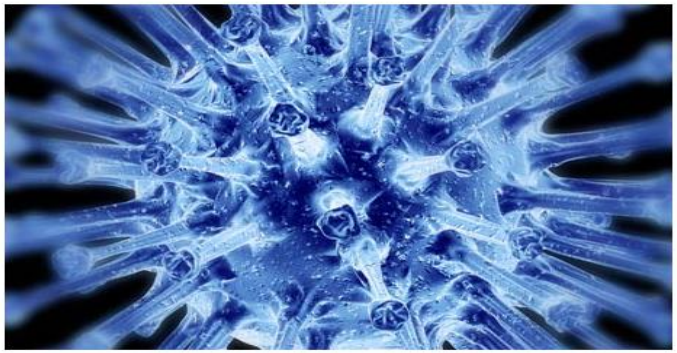
guardian.co.uk

Flu breakthrough promises a vaccine to kill all strains

British team's success with jab that targets proteins common to every type of flu virus

Alok Jha, science correspondent
guardian.co.uk, Sunday 6 February 2011 21.50 GMT

A larger | smaller



A team at Oxford University has had success testing a vaccine that can neuter any strain of flu virus. Photograph: Science Photo Library

Scientists at Oxford University have successfully tested a universal flu vaccine that could work against all known strains of the illness, taking a significant step in the fight against a disease that affects billions of people each year.

hVIVO: Case Studies

Multiple Landmark Challenge Studies

VERTEX

GILEAD

Alios BioPharma

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

SAN DIEGO--(B
placebo-controlled
The study of GS-5
load (the amount o
nose) and also sym
today during a post

RSV is a pathogen
otherwise healthy p
individuals with ce

Johnson & Johnson

Previous Release | Next Release

Nov 7, 2014

Johnson & Johnson Announces Completion Of Alios BioPharma Acquisition

-- Further Stre

NEW BRUNSWICK, N.J.
BioPharma, Inc., a priv
price of approximately

With this acquisition co
Companies of Johnson
promising compound A
syncytial virus (RSV).
early-stage compounds

"The acquisition of Alio
significant unmet need.
affected by some of the
Chairman, Pharmaceuti

VERTEX

« Previous Release | Next Release »

June 18, 2014

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

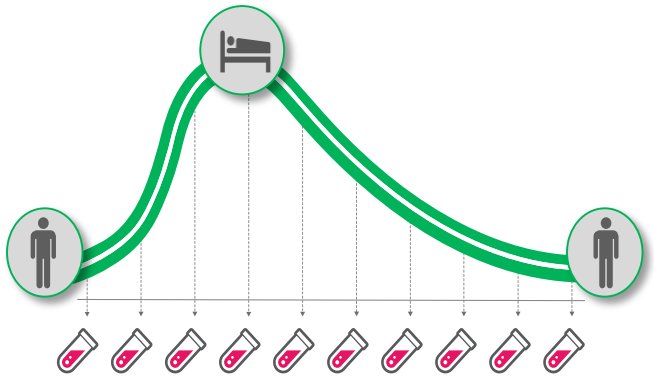
-VX-787 is an investigational medicine discovered by Vertex that is designed to directly inhibit replication of the influenza virus-

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. As part of the agreement, Vertex will receive an up-front payment of $30 million from Janssen and has the potential to receive additional development and commercial milestone payments as well as royalties on future product sales. Vertex completed a Phase 2a study of VX-787 in 2013 that showed statistically significant improvements in viral and clinical measurements of influenza infection. VX-787 is designed to directly inhibit replication of the influenza virus.

"With a deep history in developing new medicines for viral infections and diseases, Janssen is well-positioned to advance the global development of VX-787 for the treatment of influenza," said Jeffrey Leiden, M.D., Ph.D., Chairman, President and Chief Executive Officer of Vertex. "This collaboration provides important support for the continued development of VX-787 in influenza and contributes to our financial strength to enable continued investment in our key development programs for cystic fibrosis and in research aimed at discovering new medicines."

At Risk Populations

Young vs Old

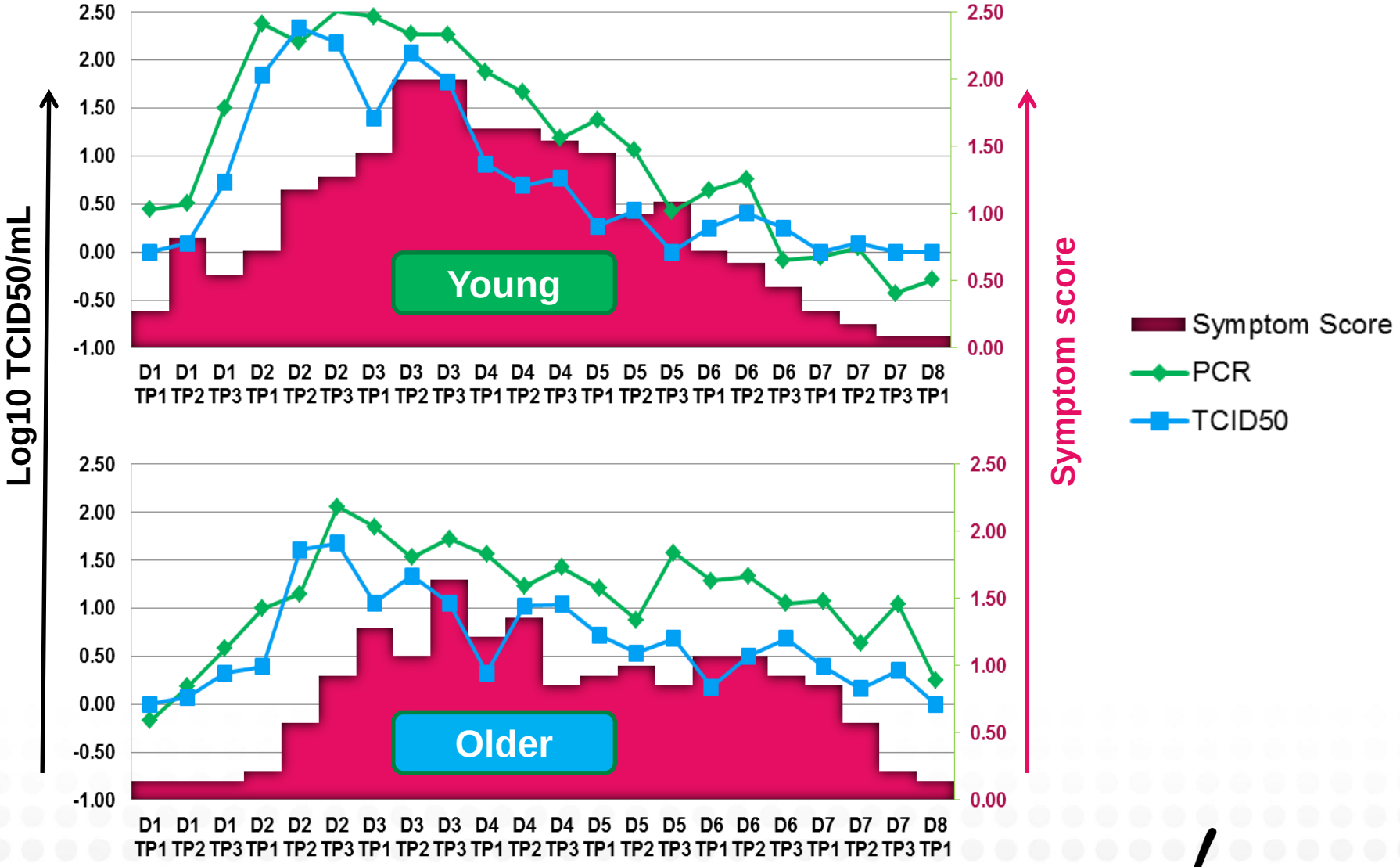


- Enter Quarantine unit Day -2
- Inoculation Day 0
- Assessments
  - Symptoms (SDC t.i.d)
  - Virology (NPS t.i.d)
  - Serology
  - Safety (24/7)
- Leave unit Day 8
- Follow up visit 28 days

Virus	
Subtype	H3N2
Strain	A/Perth/16/2009 (wild-type)
Form	Allantoic Fluid in Sucrose (PBS 1X)
Status	cGMP & Free of Adventitious Agents
Dose	$3.6x10^5$ TCID50 (Optimal)
Inoculation (IN)	1 mL
Volunteers	
Healthy Subjects	18-45: 12 Volunteers (4F, 8M) Mean age 24.9 Median age 21.5 46-65: 16 Volunteers (5F, 11M) Mean age 48.9 Median age 48.0
HAI titre	≤ 10

At Risk Populations

Correlation: Virus Shedding / Symptoms



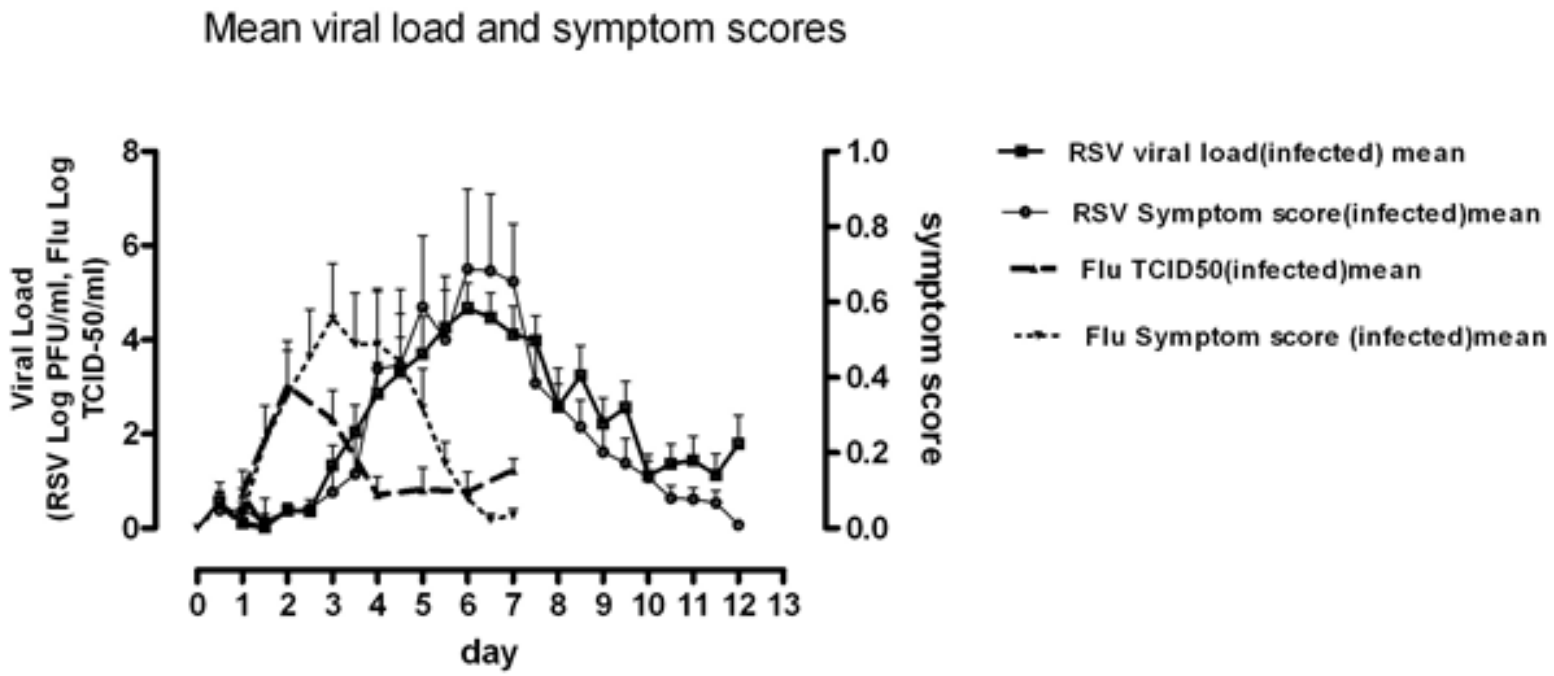
Development of Diagnostics

Cell Host & Microbe
Article

Gene Expression Signatures Diagnose Influenza and Other Symptomatic Respiratory Viral Infections in Humans

Aimee K. Zaas,[1,3,9] Minhua Chen,[2,9] Jay Varkey,[1] Timothy Veldman,[3] Alfred O. Hero III,[4] Joseph Lucas,[3] Yongsheng Huang,[4] Ronald Turner,[5] Anthony Gilbert,[6] Robert Lambkin-Williams,[6] N. Christine Øien,[3] Bradly Nicholson,[7] Stephen Kingsmore,[8] Lawrence Carin,[2] Christopher W. Woods,[1,3,7] and Geoffrey S. Ginsburg[3,*]
[1]Division of Infectious Diseases and International Health, Department of Medicine, Duke University School of Medicine
[2]Department of Electrical and Computer Engineering
[3]Institute for Genome Sciences & Policy
Duke University, Durham, NC 27710, USA
[4]Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, MI 48109, USA
[5]University of Virginia School of Medicine, Charlottesville, VA 22904, USA
[6]Retroscreen Virology Ltd., London EC4N 6EU, UK
[7]Division of Infectious Diseases, Durham Veteran's Affairs Medical Center, Durham, NC 27705, USA
[8]National Center for Genome Resources, Santa Fe, NM 87505, USA
[9]These authors contributed equally to this work
*Correspondence: geoffrey.ginsburg@duke.edu
DOI 10.1016/j.chom.2009.07.006

Disease Dynamics: Comparison of RSV and Flu

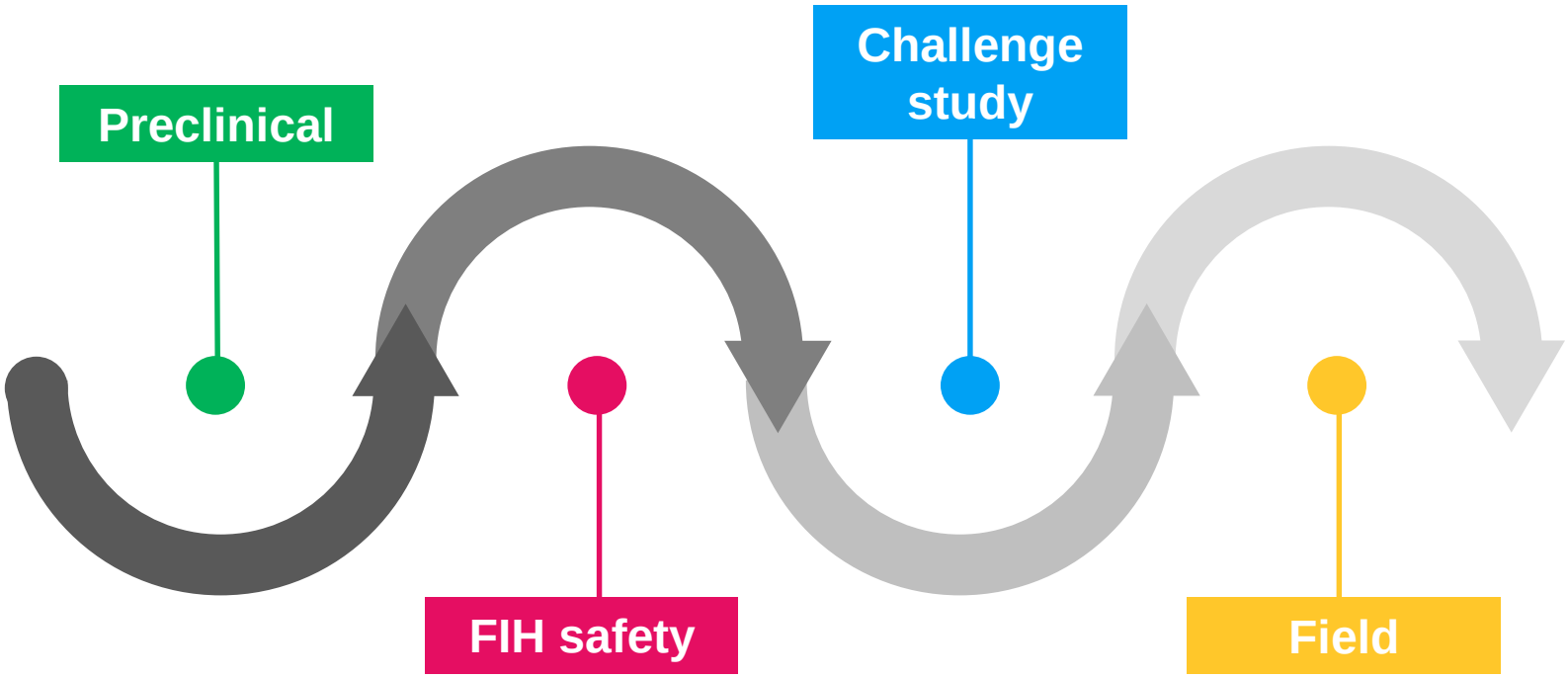


Bagga B, Woods CW, Veldman TH, Gilbert A, Mann A, et al. (2013) Comparing influenza and RSV viral and disease dynamics in experimentally infected adults predicts clinical effectiveness of RSV antivirals. Antivir Ther.

CONCLUSION

Clinical Development Pathway

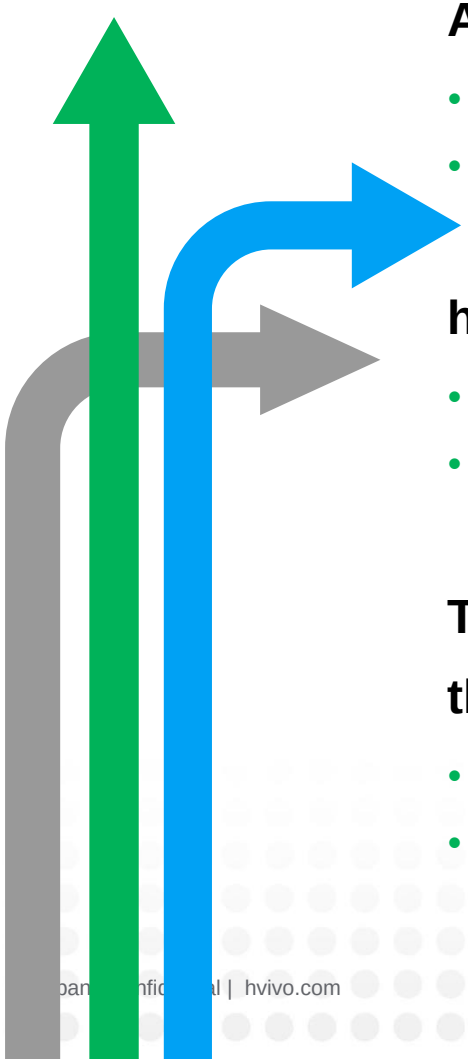
Accelerating Drug Development



Incorporate challenge studies to address key questions sooner and improve future studies

hVIVO Summary

Human disease models provide an effective option for testing drug and vaccine safety and efficacy



Address key questions in drug and vaccine development

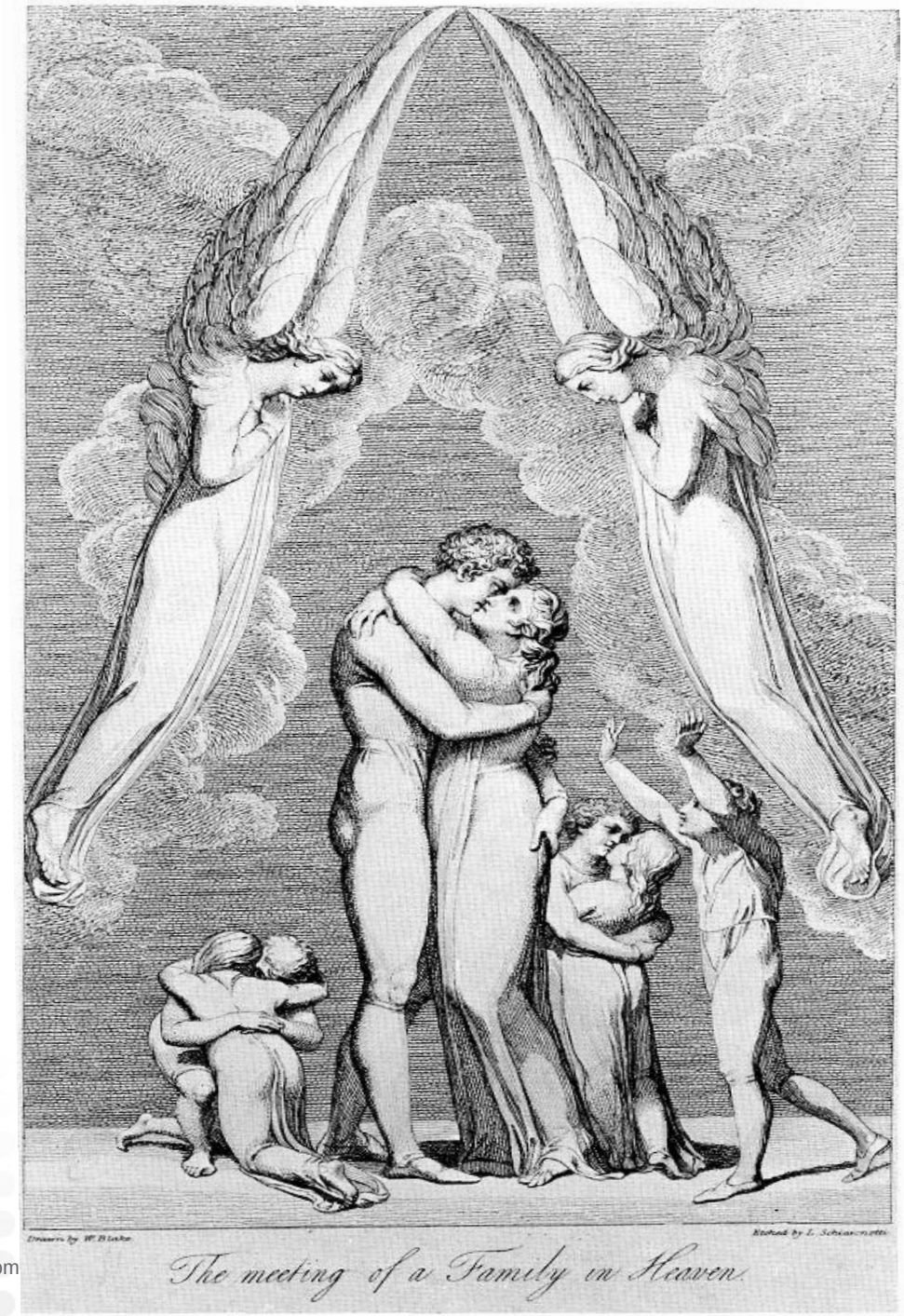
- Correlates of Protection
- At Risk Patients

hVIVO is the market leader in challenge studies

- Experienced: 45+ Studies, 2200+ Volunteers
- Multiple Models (Influenza, RSV, HRV, Asthma, Elderly)

The hVIVO platform enables organisations to accelerate their time to market

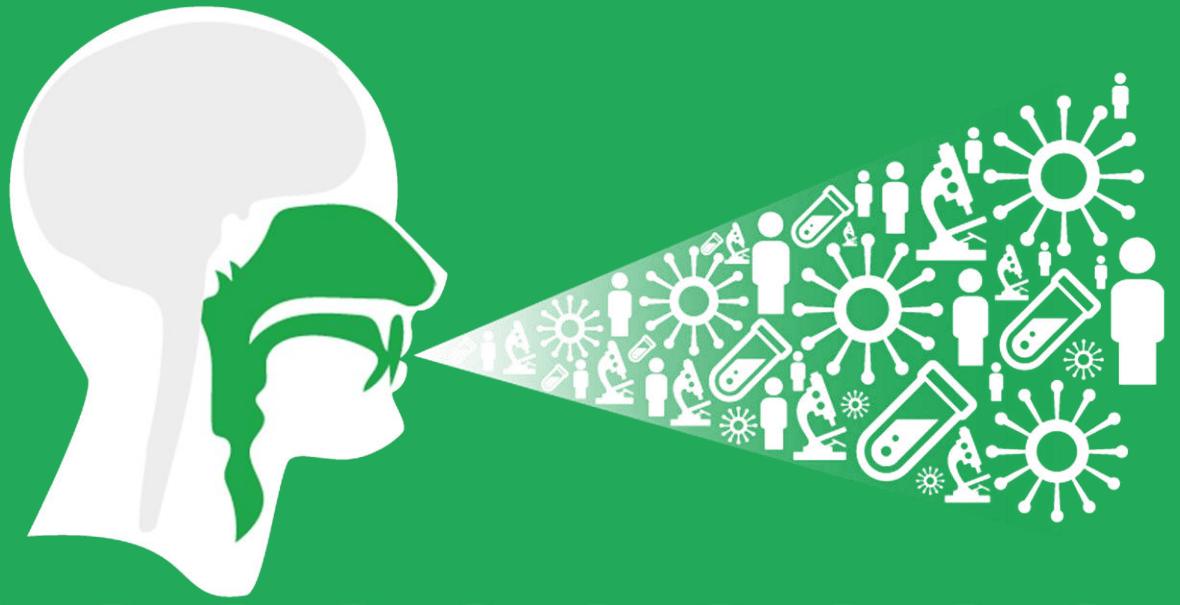
- Product Validation
- Rational Selection of Biomarkers and Drug Targets


The meeting of a Family in Heaven

Contact Information:

Dr Anthony Gilbert
Email: a.gilbert@hvivo.com
Phone: 011 44 (0) 7984 845832

Rich Niemi
Email: r.niemi@hvivo.com
Phone: 01 609 841 1504



Better Treatments, Faster

hVIVO