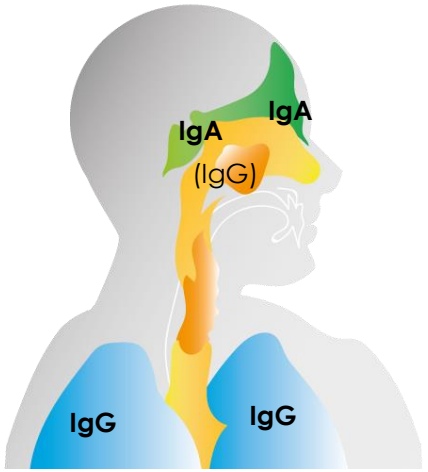
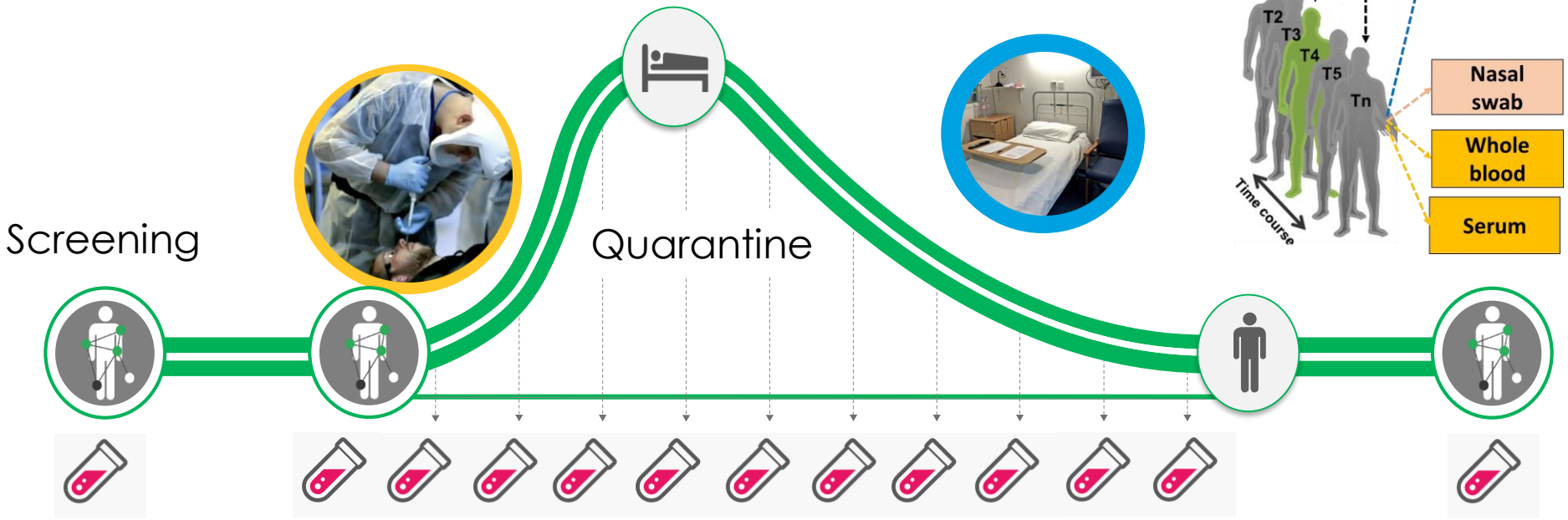
Pre-existing NP specific T-cell response correlates with reduction of symptoms in a human influenza challenge model

31 August 2019

Nicolas Noulin – hVIVO – n.noulin@hvivo.com
Delphine Guyon-Gellin – Osivax – dguyongellin@osivax.com

Human Viral Challenge Model

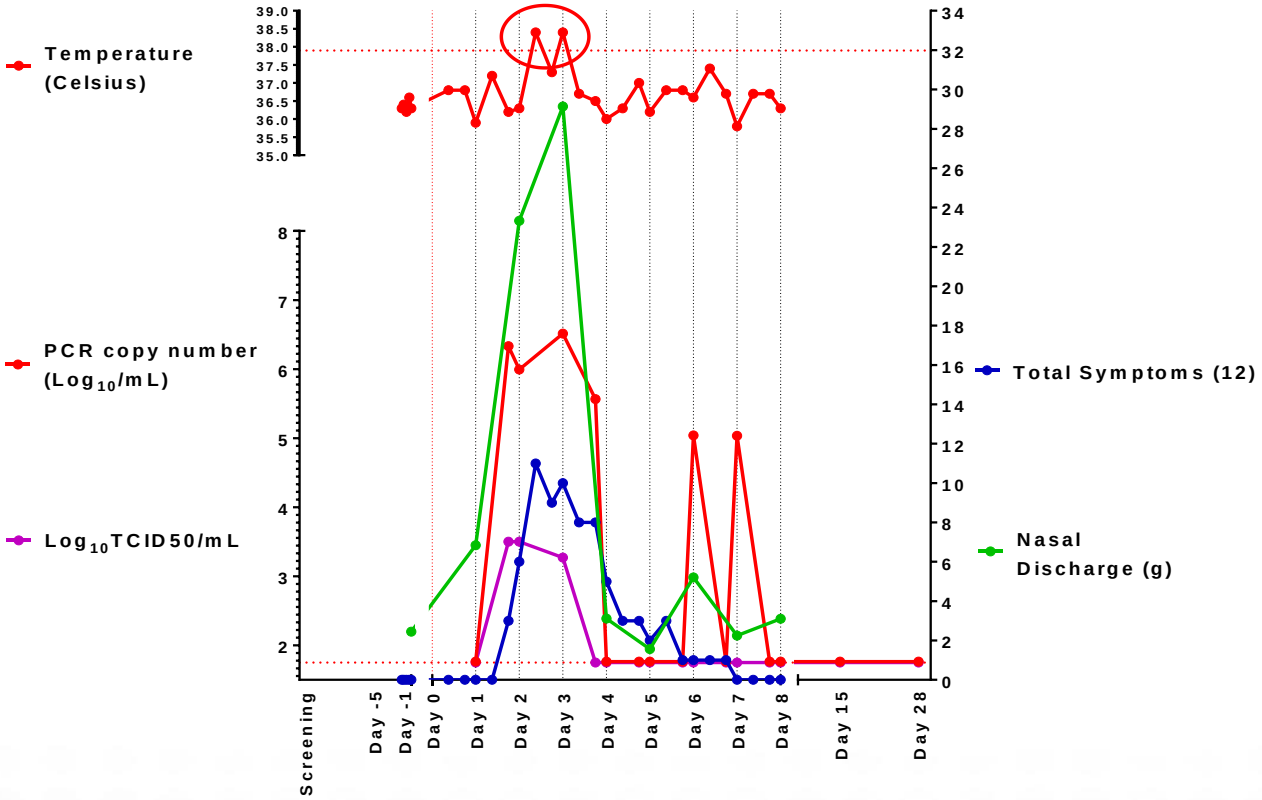


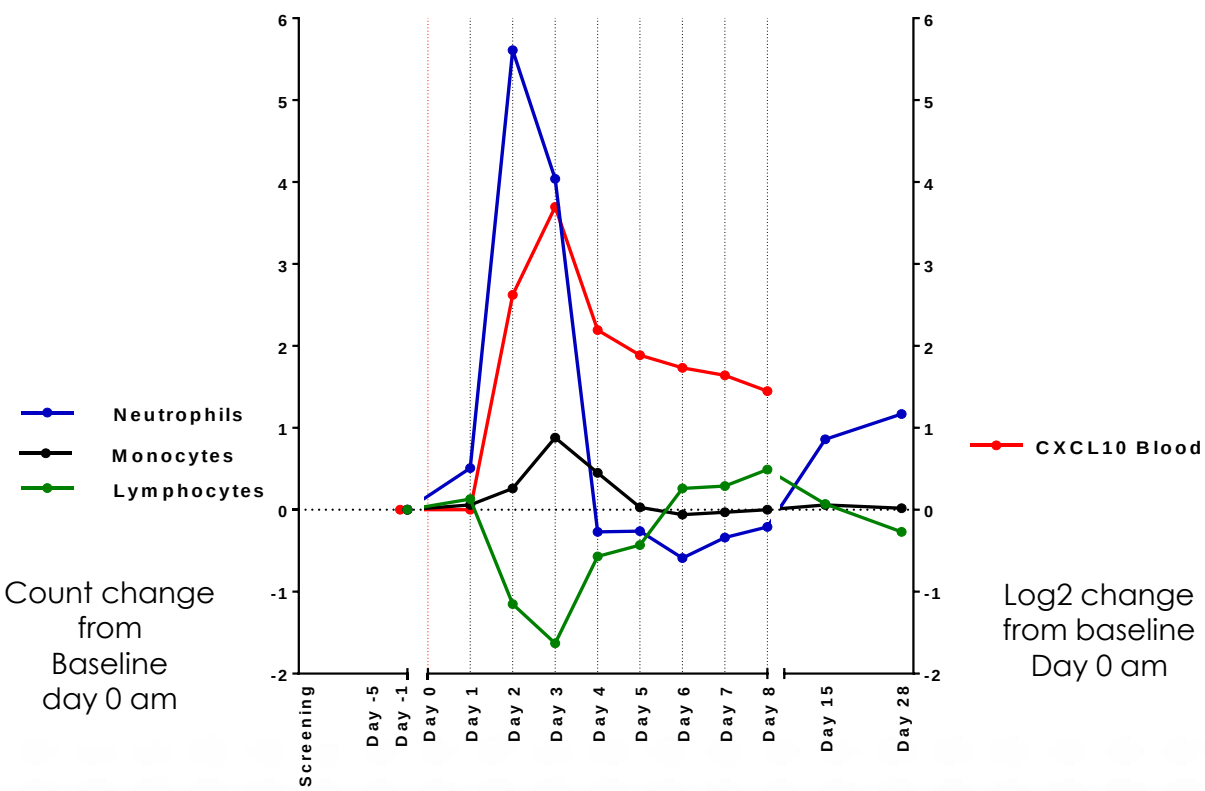


Volunteers	
Healthy Subjects	71 Volunteers: 22 ♀ and 49 ♂ Age 18-64, Mean 30y, Median 27y Mainly Caucasian (79%)
HAI Titre	≤ 10 at screening

Virus	
Strain	A/Perth/16/2009 H3N2 (wild type)
Form	Allantoic Fluid in Sucrose PBS 1X
Status	cGMP & Free of adventitious agents
Dose	$3.6x10^5$ $TCID_{50}$ (Optimal)
Inoculation	1 mL (IN)

Multi-parameter analysis is key to study design and selection of secondary endpoints





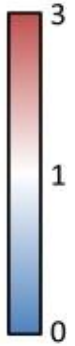
Example of a profile of infection
A/Perth/16/2009 H3N2

Changes in circulating cytokine levels over time

Symptomatic subjects

Hours post-inoculation

	5	12	21	29	36	45	53	60	69	84	93	108	117	132	141	165
IP-10	0.7	0.7	0.8	1.2	1.7	7.2	9.6	7.5	5.9	6.3	8.0	4.2	3.6	3.5	3.4	2.8
IL-6	1.7	3.9	2.2	2.2	4.6	3.5	3.6	6.2	5.1	2.1	1.9	2.8	2.2	1.4	1.1	0.8
IL-15	0.4	0.7	1.1	0.9	1.1	3.2	4.1	4.3	4.0	2.9	4.4	1.5	1.7	1.6	1.4	1.2
MCP-1	1.2	1.3	1.0	1.4	1.9	2.7	4.3	3.4	0.9	1.9	1.7	1.7	1.7	1.9	1.1	1.3
IL-8	1.4	1.2	1.2	1.3	1.5	1.6	1.0	2.5	1.4	1.0	1.3	3.1	2.2	1.6	1.1	1.0
IL-1RA	0.9	0.9	0.9	0.9	1.4	1.1	3.1	1.8	1.4	1.0	1.2	1.0	1.0	1.5	1.0	1.1
Eotaxin	1.3	1.3	1.0	1.5	1.3	1.3	1.6	1.5	0.6	1.3	0.7	1.4	1.3	1.5	1.0	1.3
MIG	1.0	0.9	0.8	1.0	1.1	1.1	1.0	1.2	1.6	1.4	1.7	1.5	1.4	1.7	1.3	1.3
MIP-1α	1.0	0.9	0.8	1.3	1.1	1.0	1.1	1.1	1.5	1.1	1.5	1.3	1.1	1.7	1.2	1.3
IL-12	1.1	1.2	1.4	0.9	1.2	1.1	1.0	1.7	1.3	1.2	1.5	1.0	1.2	1.0	0.8	0.9
IL-2R	1.0	0.9	0.8	1.1	1.1	0.9	1.1	1.1	1.5	1.1	1.4	1.2	1.3	1.6	1.2	1.3
MIP-1β	0.9	0.8	0.9	1.0	1.3	0.9	0.9	1.4	1.4	1.2	1.3	1.1	1.0	1.5	1.1	1.2
IL-10	1.1	1.0	1.2	1.0	1.0	1.3	1.0	1.6	1.2	0.8	1.5	0.7	0.9	0.7	0.5	0.7
IFN-α	1.0	1.0	1.2	1.0	1.2	1.0	1.1	1.5	1.4	0.9	1.1	0.6	0.9	0.7	0.5	0.6
IL-13	1.2	1.0	1.2	1.1	1.4	0.9	0.8	1.2	1.2	0.7	0.9	0.7	1.0	0.8	0.6	0.6
IFN-γ	1.1	0.9	1.0	1.0	1.5	1.2	0.9	1.6	1.4	0.7	0.9	0.5	1.0	0.8	0.5	0.5
TNF-α	1.0	0.8	1.0	1.0	1.2	0.8	0.9	1.5	1.2	0.6	0.8	0.6	1.0	1.2	0.7	0.8
RANTES	0.8	0.9	0.8	1.0	0.7	1.1	1.1	0.7	0.7	0.8	1.3	1.3	1.1	1.2	0.7	0.9
IL-4	1.1	0.9	1.0	1.0	1.3	0.8	0.7	1.7	1.0	0.6	0.8	0.6	1.0	0.9	0.6	0.7
IL-17	1.2	0.9	1.0	1.1	1.1	0.8	1.0	1.4	1.0	0.5	0.7	0.5	1.0	0.9	0.5	0.6
IL-7	1.3	0.7	1.0	1.0	1.2	1.0	1.0	1.9	1.2	0.4	0.7	0.4	0.9	0.6	0.4	0.4
GM-CSF	1.0	0.9	1.1	0.9	1.1	1.0	0.7	1.2	0.8	0.6	1.1	0.6	0.8	0.7	0.5	0.8
IL-2	0.9	0.7	1.0	0.7	1.1	0.6	0.7	1.1	1.2	0.6	1.0	0.6	0.8	1.0	0.8	0.8
IL-5	1.0	0.7	1.0	0.9	1.1	0.8	0.7	1.1	1.7	0.7	1.1	0.4	0.6	0.8	0.5	0.5
IL-1b	1.0	0.6	1.2	1.0	1.0	0.8	0.2	0.5	1.4	0.5	0.8	0.4	0.6	0.7	0.9	0.9



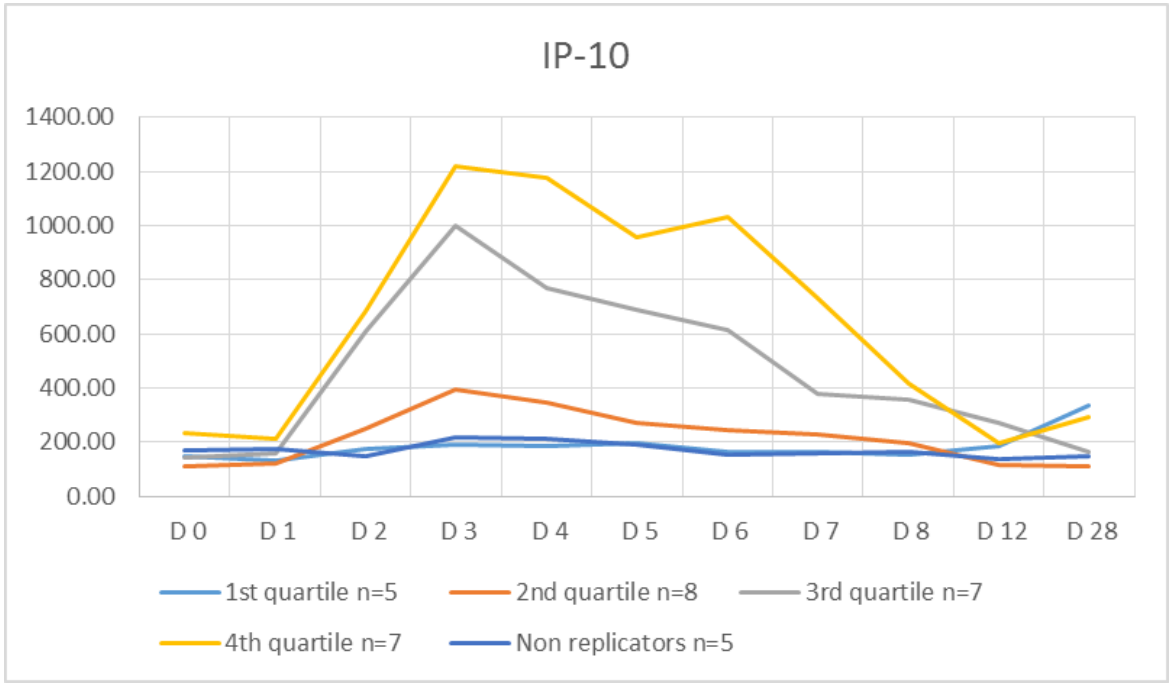
Asymptomatic subjects

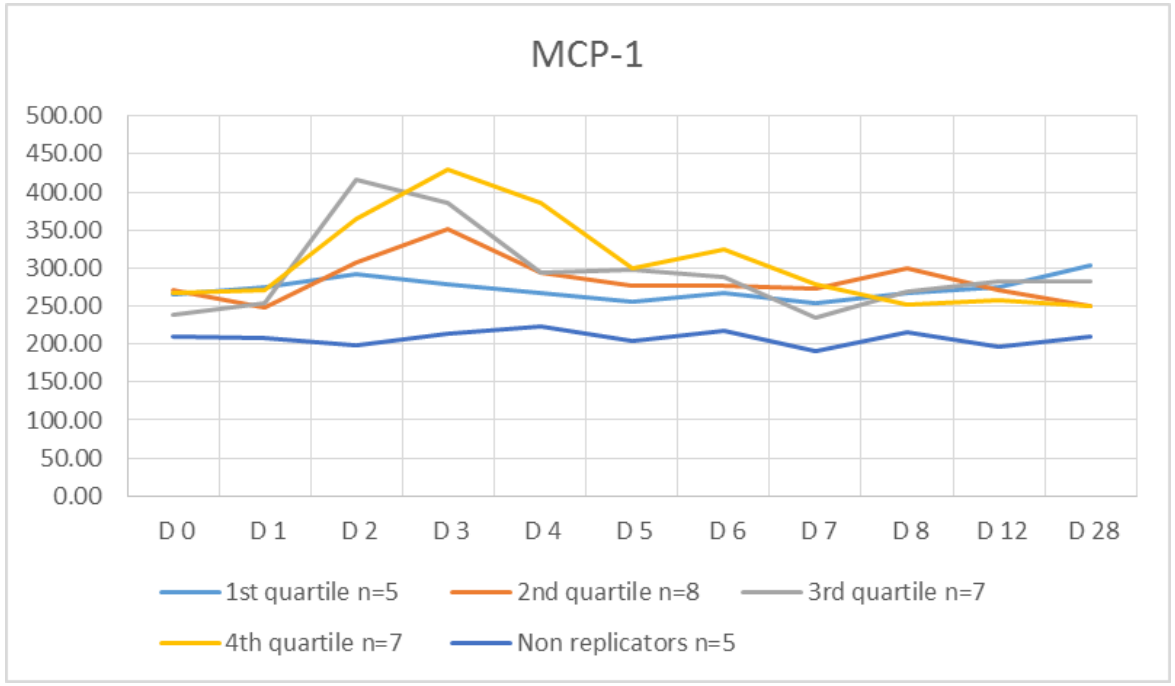
Hours post-inoculation

	5	12	21	29	36	45	53	60	69	84	93	108	117	132	141	165
IP-10	0.6	1.0	1.1	0.8	1.3	0.9	1.2	1.4	2.1	1.1	1.7	1.1	1.7	1.7	2.6	3.1
IL-6	1.2	1.4	1.2	1.8	1.3	1.2	1.1	1.0	1.2	1.4	1.1	1.8	2.0	0.8	0.7	0.8
IL-15	0.6	0.7	0.6	0.5	0.8	1.4	0.8	1.5	0.9	0.8	0.7	0.6	0.9	0.7	0.8	0.8
MCP-1	0.7	1.5	0.9	0.8	1.1	1.3	0.9	1.5	1.1	1.2	1.0	1.4	1.4	1.5	1.4	1.2
IL-8	0.7	1.6	0.9	1.2	1.3	0.8	0.7	0.9	1.0	1.4	1.0	1.2	1.2	1.2	1.0	1.1
IL-1RA	0.9	1.5	0.9	0.9	0.9	3.3	0.8	3.3	0.8	1.0	1.0	0.7	1.2	1.1	1.3	0.9
Eotaxin	0.9	1.5	0.9	0.8	1.3	1.1	1.1	1.3	1.1	1.2	1.1	1.4	1.3	1.5	1.3	1.2
MIG	0.9	1.2	0.9	0.8	1.1	0.9	0.9	1.2	1.0	1.1	1.2	1.0	1.3	1.5	1.8	2.5
MIP-1α	0.8	1.2	0.7	0.7	1.2	1.3	1.3	1.7	1.3	1.0	1.1	1.0	1.4	1.2	1.3	1.1
IL-12	0.9	0.9	0.9	1.1	0.6	1.0	0.7	0.9	0.5	0.8	0.6	0.6	0.8	0.6	0.6	0.6
IL-2R	0.8	1.2	0.8	0.9	1.1	0.9	1.1	1.2	1.0	1.1	1.0	1.0	1.2	1.2	1.2	1.0
MIP-1β	0.9	1.3	0.9	0.7	1.1	1.8	1.0	2.1	1.0	1.5	1.3	1.0	1.5	1.6	1.7	1.4
IL-10	1.0	1.0	0.8	0.8	0.7	0.5	0.7	0.6	0.7	0.6	0.7	0.6	0.7	0.5	0.6	0.6
IFN-α	0.9	0.8	0.8	0.8	0.6	0.9	0.6	0.7	0.5	0.7	0.4	0.4	0.7	0.5	0.5	0.4
IL-13	0.9	1.0	0.7	0.9	0.7	0.7	0.6	0.7	0.5	0.7	0.5	0.3	0.6	0.5	0.6	0.4
IFN-γ	0.7	0.9	0.6	0.7	0.4	0.5	0.4	0.5	0.3	0.5	0.3	0.2	0.5	0.4	0.4	0.3
TNF-α	0.8	1.1	0.7	0.7	0.5	0.7	0.4	0.9	0.4	0.7	0.7	0.3	0.9	0.7	0.8	0.6
RANTES	0.8	1.1	1.2	1.0	1.3	1.3	1.4	1.5	1.4	1.3	1.4	1.4	1.4	1.2	1.1	0.9
IL-4	0.7	0.9	0.6	0.7	0.3	0.5	0.2	0.5	0.2	0.5	0.3	0.3	0.6	0.4	0.5	0.4
IL-17	0.7	1.0	0.6	0.6	0.5	0.5	0.5	0.7	0.5	0.6	0.5	0.3	0.7	0.5	0.6	0.4
IL-7	0.7	1.0	0.4	0.7	0.5	0.7	0.4	0.6	0.3	0.6	0.3	0.2	0.6	0.3	0.3	0.2
GM-CSF	1.0	1.1	0.9	0.9	0.7	0.7	0.6	0.7	0.6	0.7	0.7	0.6	0.8	0.7	0.8	0.7
IL-2	0.8	0.9	0.7	0.8	0.5	1.2	0.4	1.2	0.4	0.7	0.5	0.5	0.8	0.7	0.6	0.6
IL-5	0.7	0.7	0.5	0.6	0.5	0.6	0.6	0.6	0.5	0.6	0.3	0.4	0.6	0.4	0.4	0.3
IL-1b	0.7	0.8	0.6	0.8	0.4	1.5	0.3	1.3	0.2	0.6	0.4	0.4	0.6	0.5	0.5	0.5

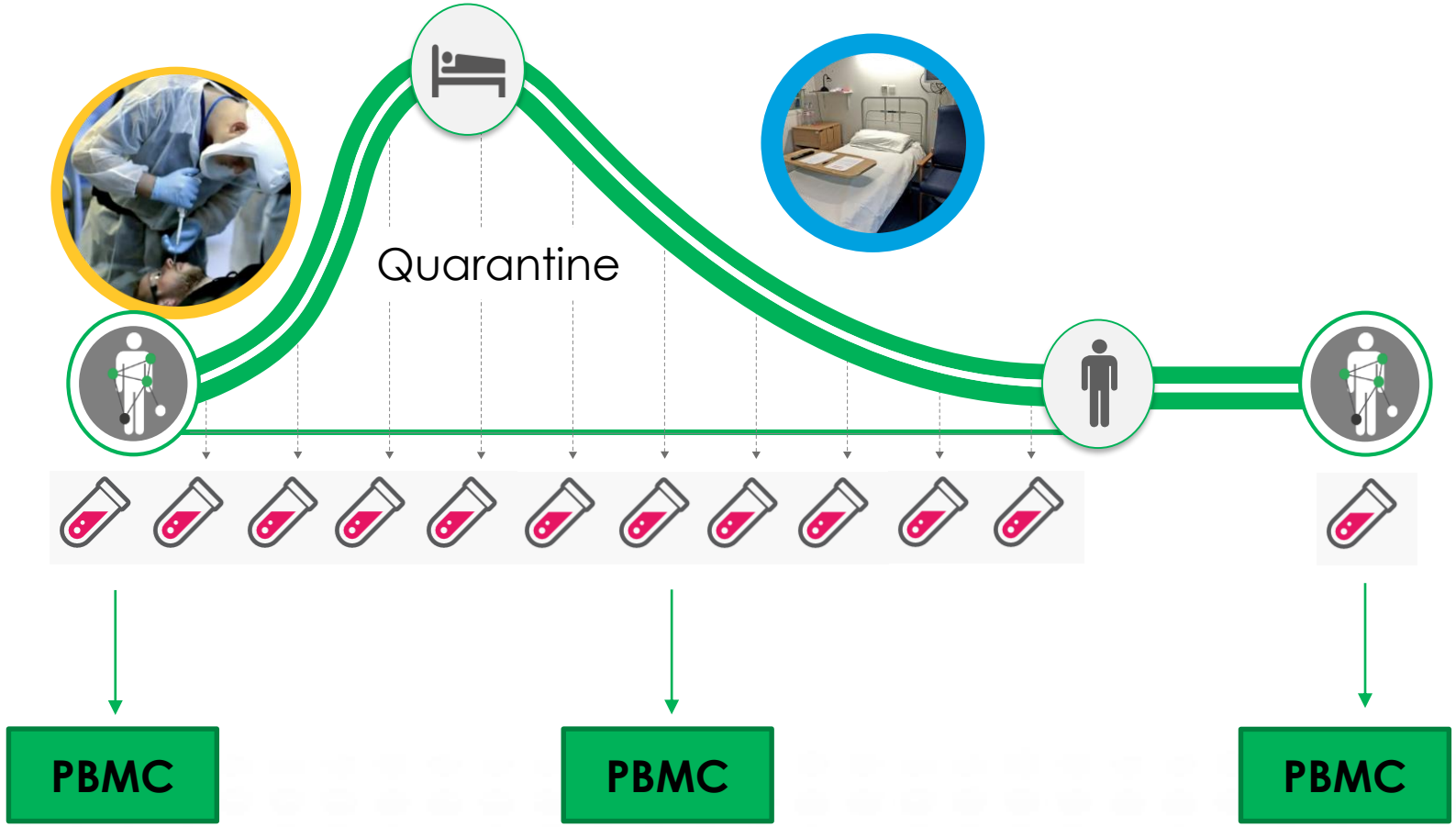
McClain, Clin Exp Immunol. 2016, A/Wisconsin/67/2005 H3N2

CXCL10 (IP-10) and CCL2 (MCP-1) in serum, groups based on AUC viral load (PCR)





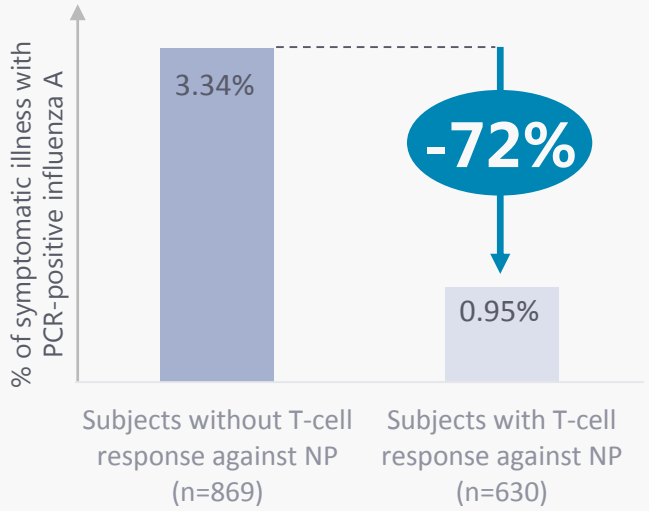
A/Perth/16/2009 H3N2


Quarantine
PBMC
PBMC
PBMC

Context and Objective

Context: In recent **epidemiological studies,** cellular immunity to the well-conserved influenza nucleoprotein (NP) has been correlated with reduction of symptomatic PCR-confirmed cases of influenza

Pre-existing T-cell response against NP correlates with 72% reduction in disease

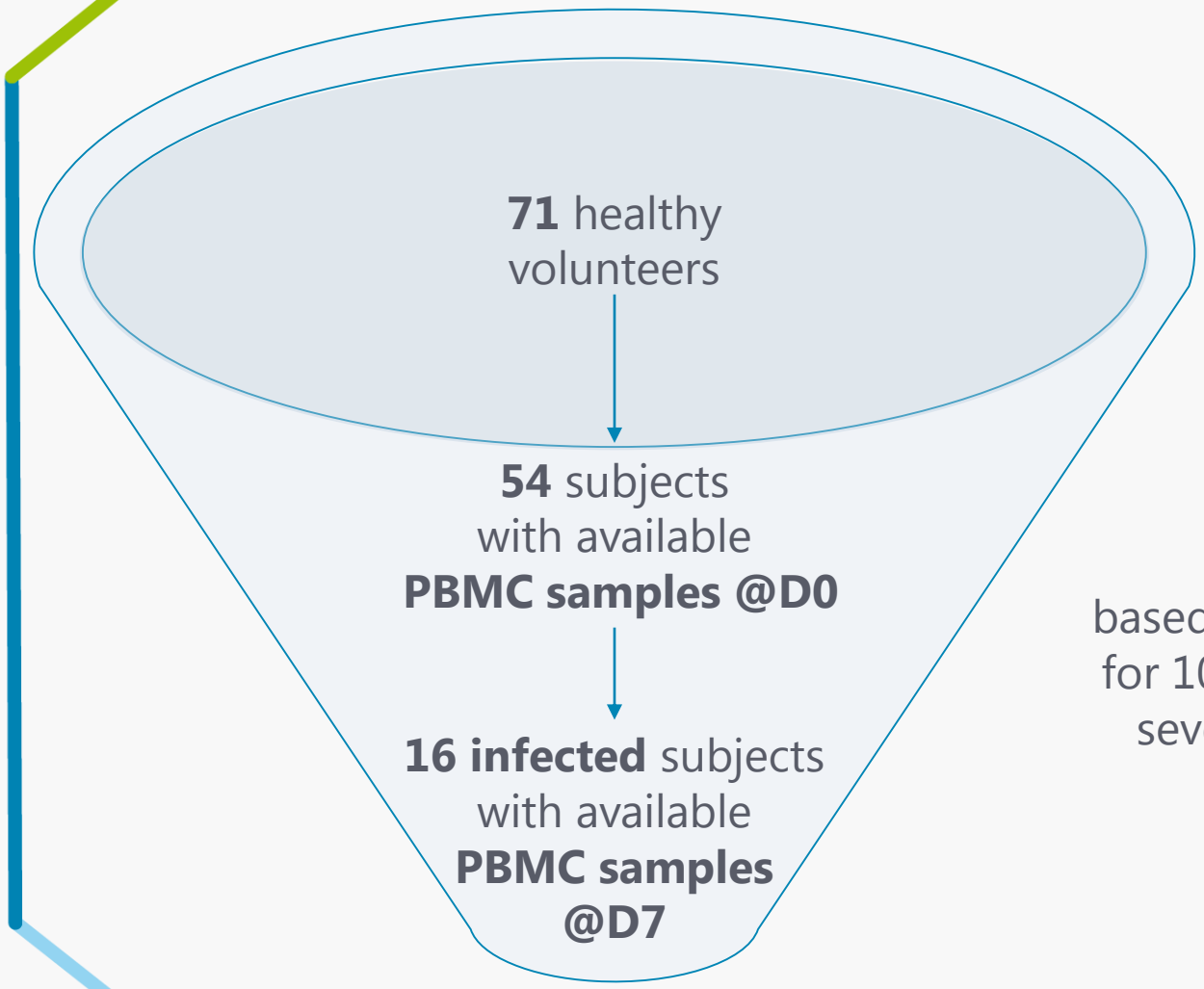


Source: Hayward et al, 2015

Objective: Investigate, in a **human challenge study**, the impact of pre-existing NP-specific T-cell response on influenza infection outcomes including symptom scores, viral loads and infection rates

OSIVAX hVIVO

Method



Total T-cell response against NucleoProtein (NP)
measured by IFNγ ELISPOT assay

assessed for correlation with

Symptoms
based on **self-assessment** for 10 parameters using a severity scale of 0 to 6

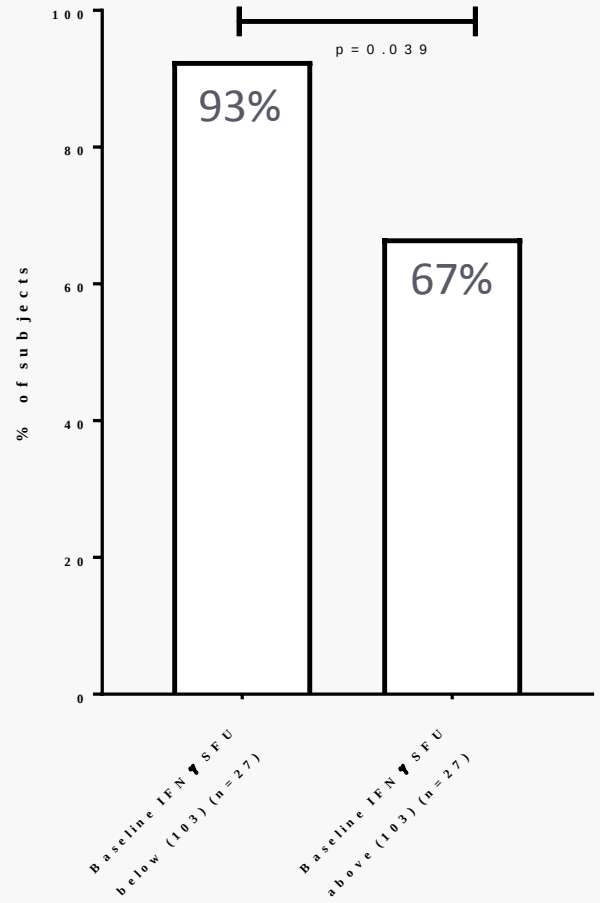
Infection rate

Viral load
in nasopharyngeal swabs assessed using a RT-qPCR assay

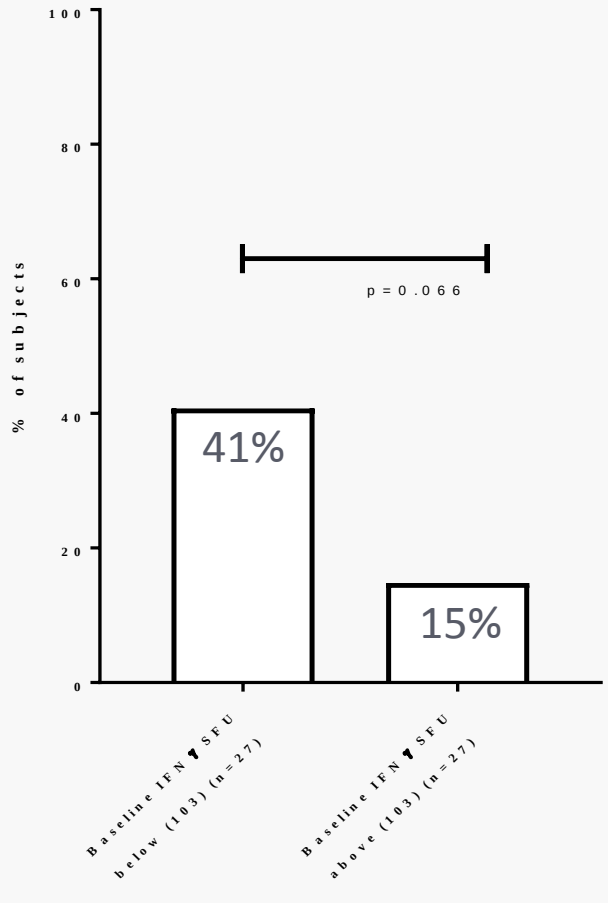
OSIVAX hVIVO

Subjects with a pre-existing NP-specific T-cell response at baseline above the median had a reduction in incidence of symptoms

Incidence of any symptoms



Incidence of ≥ grade 2 symptoms on multiple occasions

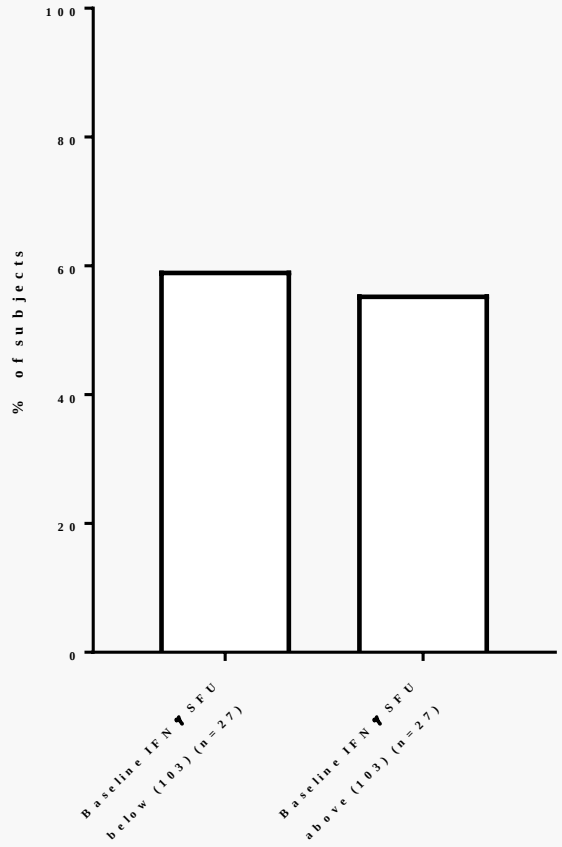


OSIVAX

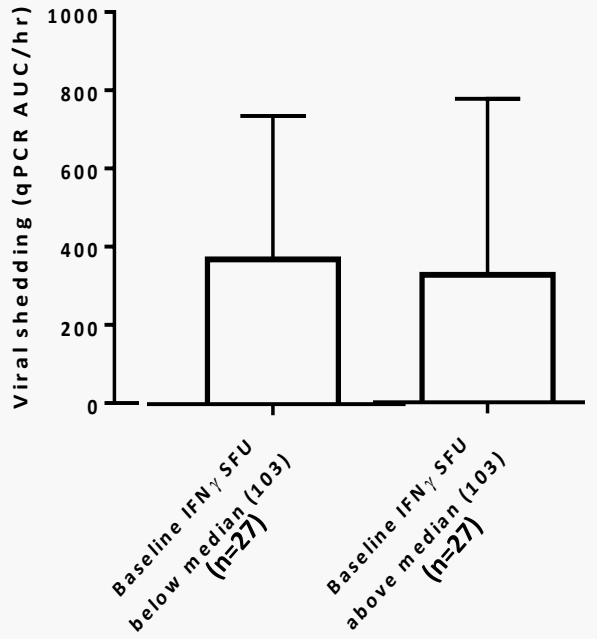
hVIVO

However a pre-existing NP-specific T-cell response at baseline above the median was not associated with infection rate or viral load reduction

Infection rate

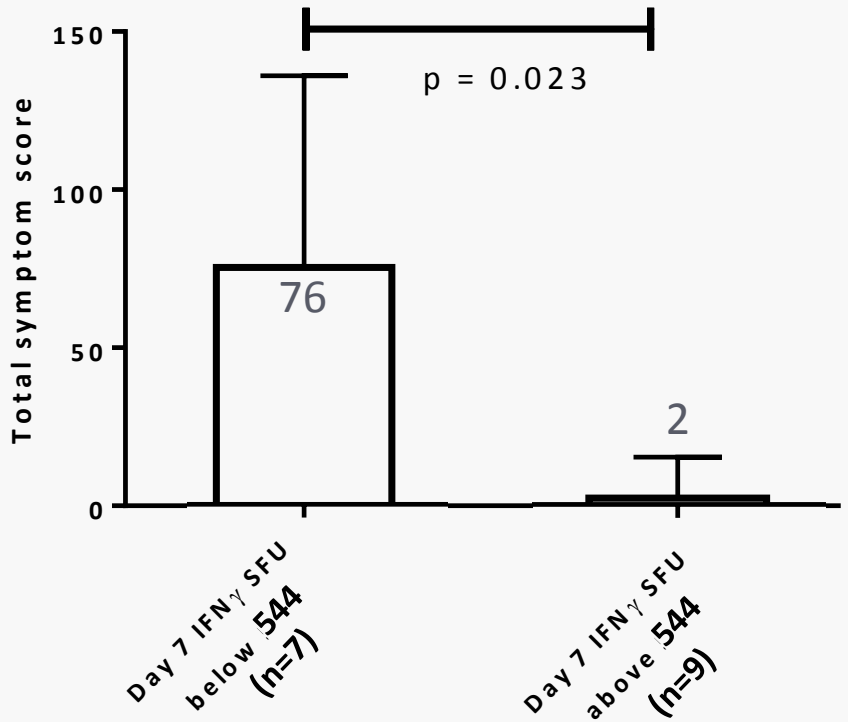


Viral load



At Day 7 post-challenge, infected subjects generating high NP specific T-cell response (>mean) had significantly lower symptom scores

Total symptom score in infected subjects for whom the response was tested on day 7 (n=16)



OSIVAX

hVIVO

Conclusions

- Previous epidemiology studies (Hayward et al., 2015) showed that a pre-existing NP specific T-cell response correlates with reduction of symptomatic PCR-confirmed cases of influenza
- These results in human influenza challenge model settings reinforce previous findings by demonstrating pre-existing or rapidly developing NP specific T-cell immunity is associated with lower levels of symptoms
- Vaccines triggering NP specific T-cell responses may establish broadly protective immunity across multiple influenza strains and represent an attractive approach to improve influenza prevention

OSIVAX hVIVO

Acknowledgements

– Kate Carney
– Michael Ghebre
– Alex Mann
– Anthony Gilbert

– Judith Del Campo
– Florence Nicolas
– Imène Turki
– Alexandre Le Vert

For any questions

– Nicolas Noulin – hVIVO – n.noulin@hvivo.com
– Delphine Guyon-Gellin – Osivax – dguyongellin@osivax.com