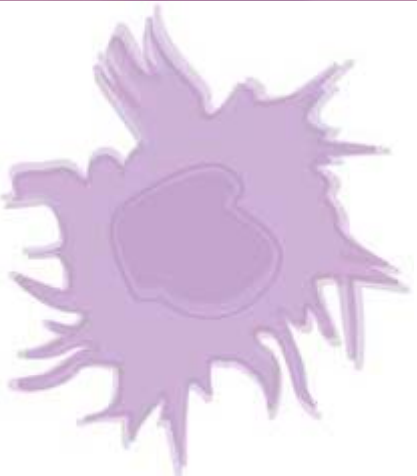


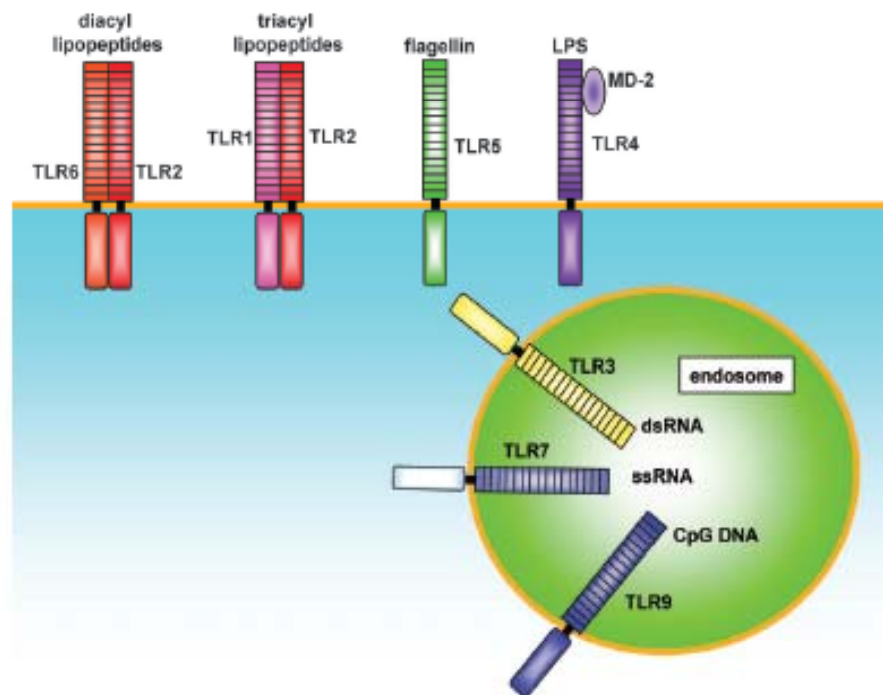


# TLR agonists as vaccine adjuvants



# TLR Family

- Toll-like receptors (TLR) are a family comprising **10 members** and are part of Pattern Recognition Receptors used by innate immune system
- TLR3 recognizes double-stranded RNA (dsRNA)
- TLR7 and TLR8 recognizes single stranded RNA (ssRNA) in a sequence dependant manner



From Takeda and Akira, *Int. Immunol.*, **17**, 1 (2005)




# Innate Pharma TLR Agonists as Vaccine Adjuvants

- Summary of partnership opportunities
  - IPH 3102: TLR3 agonist
  - IPH 3201: TLR7/8 agonist

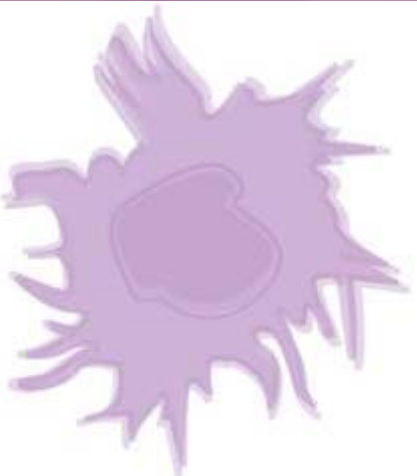


# Overview of Partnership Opportunities

Molecule	Description
<b>IPH 3102</b>	<ul style="list-style-type: none"><li>• Synthetic high MW dsRNA</li><li>• Targets a unique receptor, TLR3</li><li>• Dual mechanism of action in oncology<ul style="list-style-type: none"><li>◦ Immunostimulation through myeloid DC activation</li><li>◦ Direct cytotoxicity and pro-inflammatory effect on TLR3 expressing tumors</li></ul></li><li>• Evidence for potent adjuvant properties</li><li>• Well characterized drug candidate (validated by a pre-IND meeting with FDA) with development potential as vaccine adjuvant</li><li>• Preclinical stage</li></ul>
<b>IPH 3201</b>	<ul style="list-style-type: none"><li>• Synthetic oligoribonucleotide</li><li>• Targets TLR7/8</li><li>• Greater potential for vaccine adjuvant than TLR7/8 agonists NCE</li><li>• Preclinical stage</li></ul>



IPH 3102  
TLR3 agonist

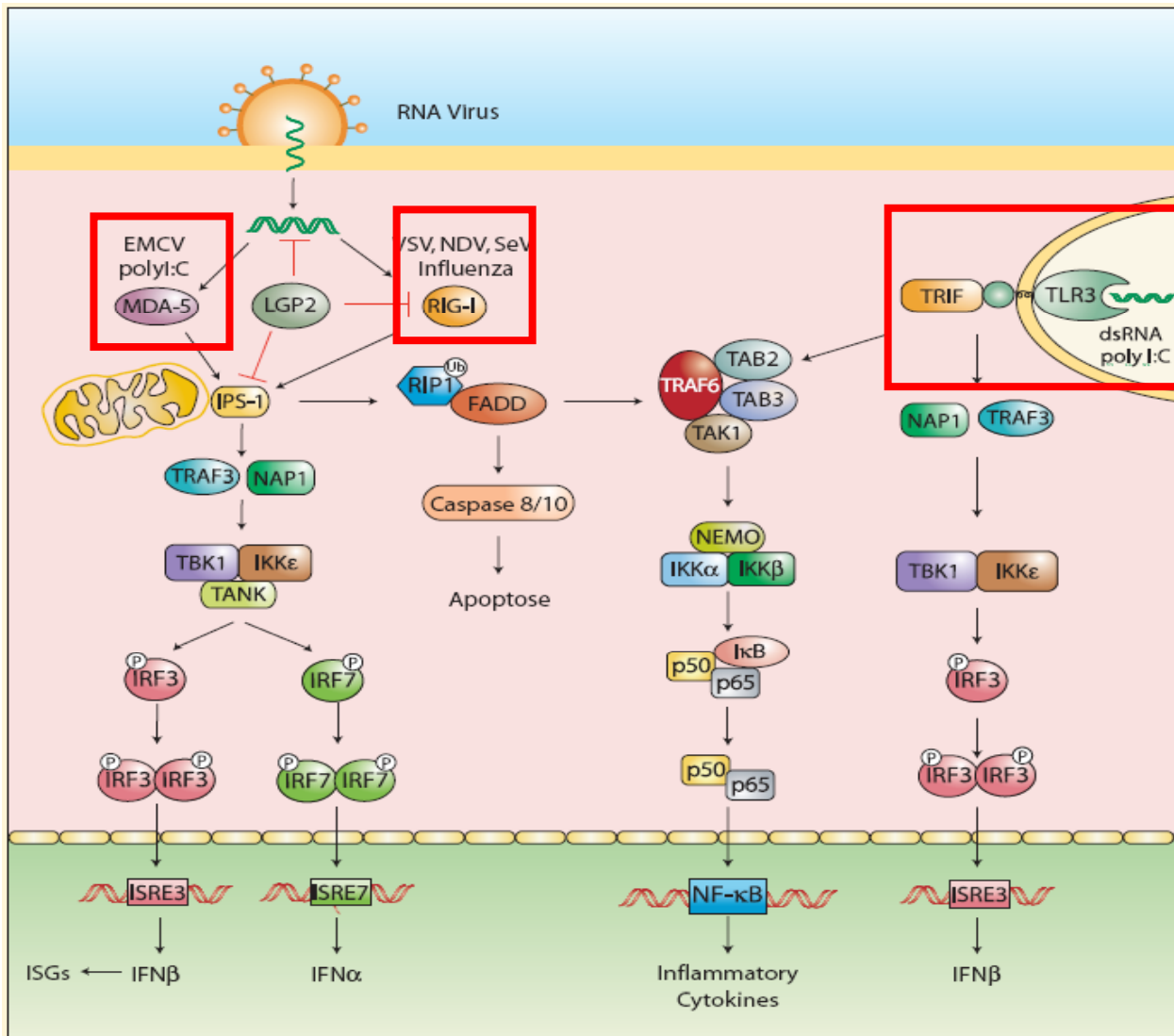




# IPH 3102 Pharmacology

- IPH 3102 is high MW synthetic dsRNA
- IPH 3102 industrial manufacturing process is under development

# Receptors for dsRNA

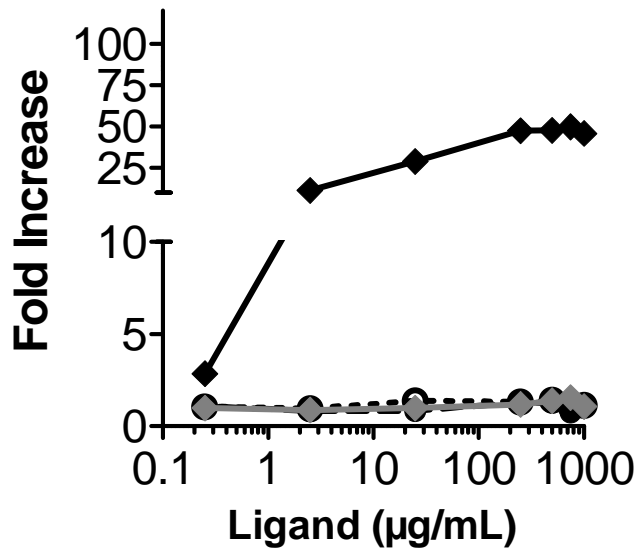


From Invivogen

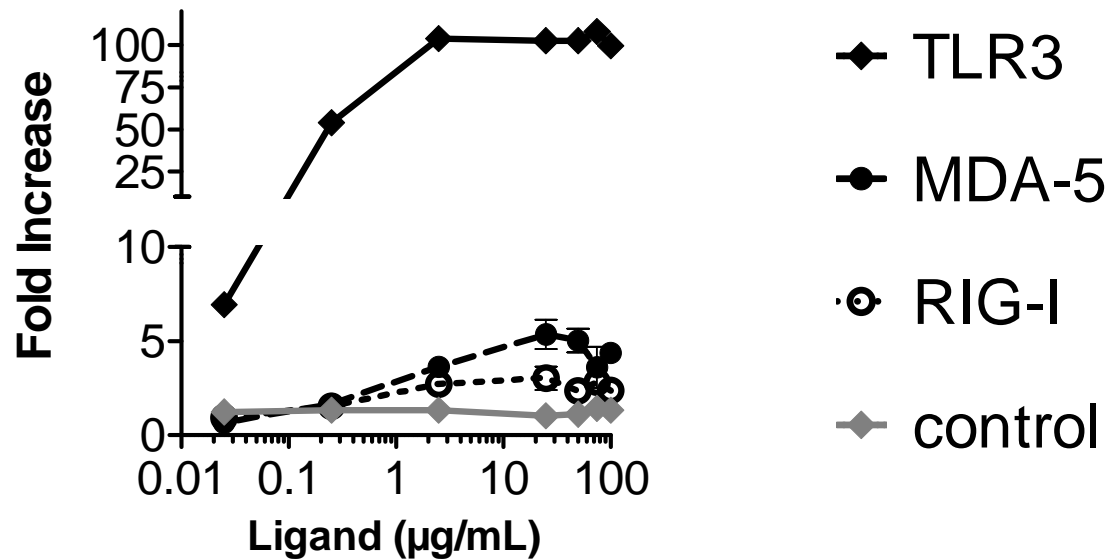


# IPH 3102 is a TLR3-specific Agonist in Humans

## IPH 3102



## poly(I:C)



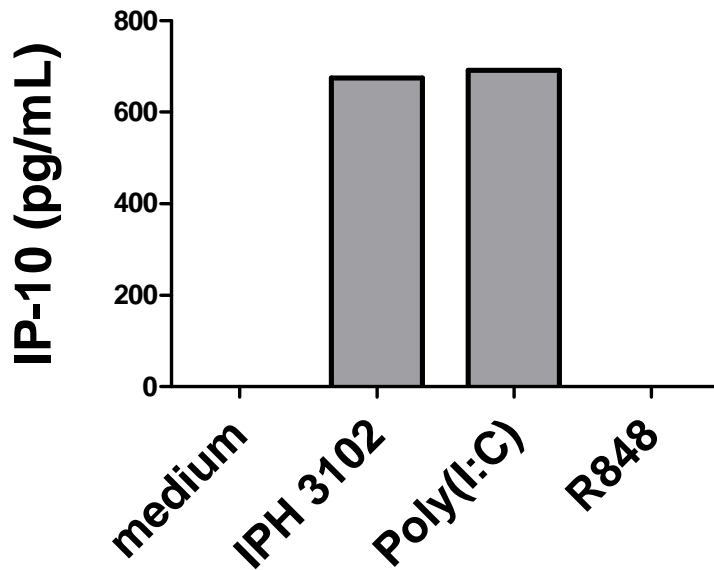
- ◆ TLR3
- MDA-5
- RIG-I
- ◆ control

- IPH 3102 is specific for TLR3 whereas poly(I:C) is not
- Accumulating evidence in the literature suggests that poly(I:C) toxicity *in vivo* in mice is due to MDA-5/RIG-I stimulation

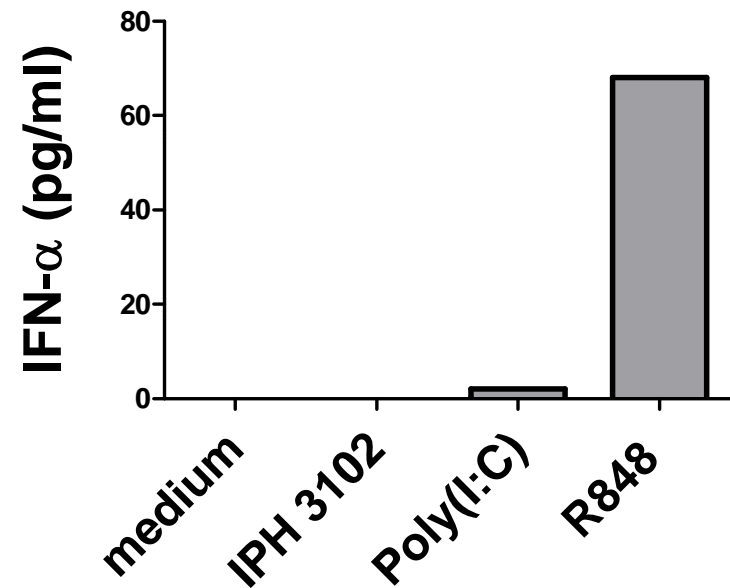


# IPH 3102 Activates Specifically Myeloid DC Subset (myDC) in Humans

Human myDC  
(TLR3+ TLR7-)



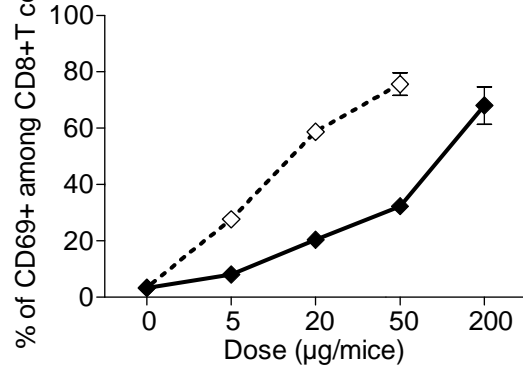
Human pDC  
(TLR3- TLR7+)



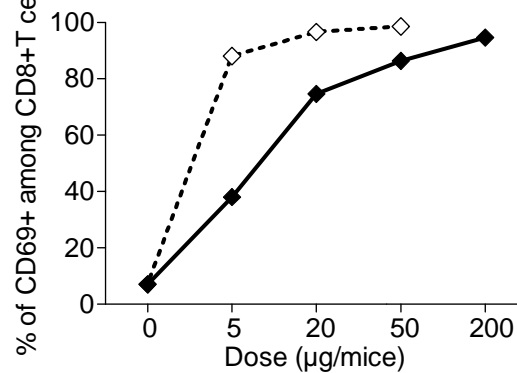


# IPH 3102 is a Potent Immunostimulator *in vivo* in Mice

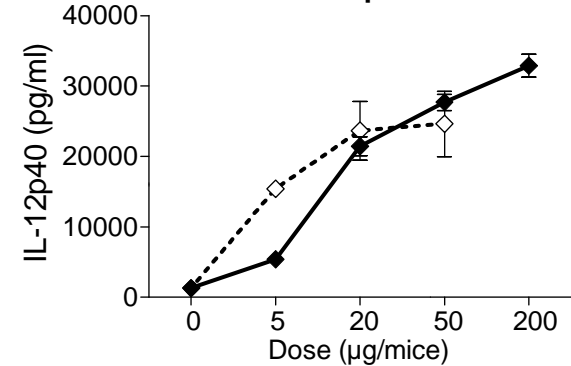
### CD8 T cells activation



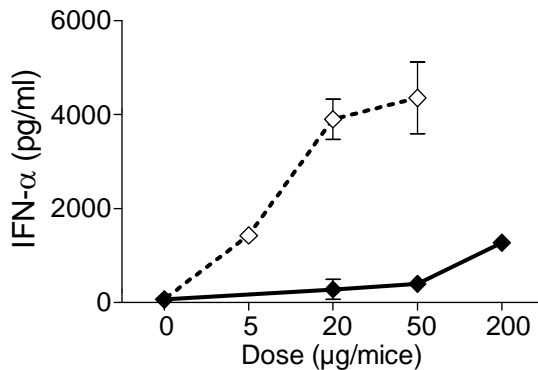
### NK cells activation



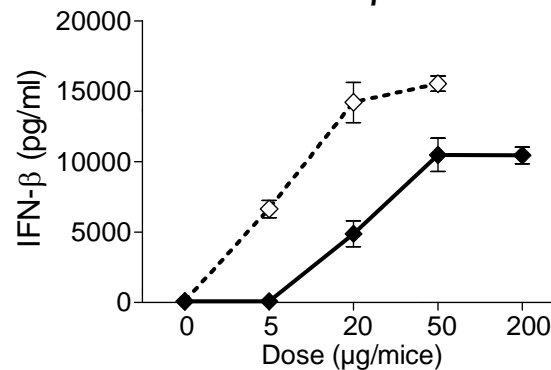
### IL-12p40



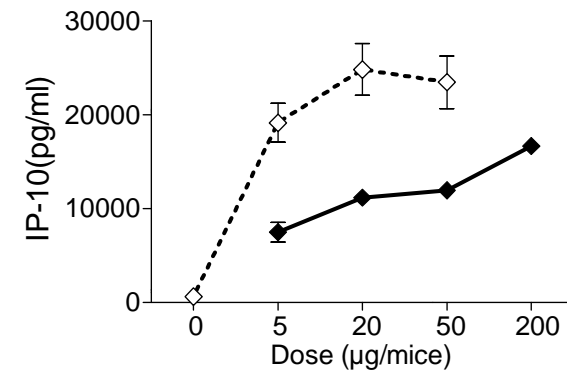
### IFN-α



### IFN-β



### IP-10



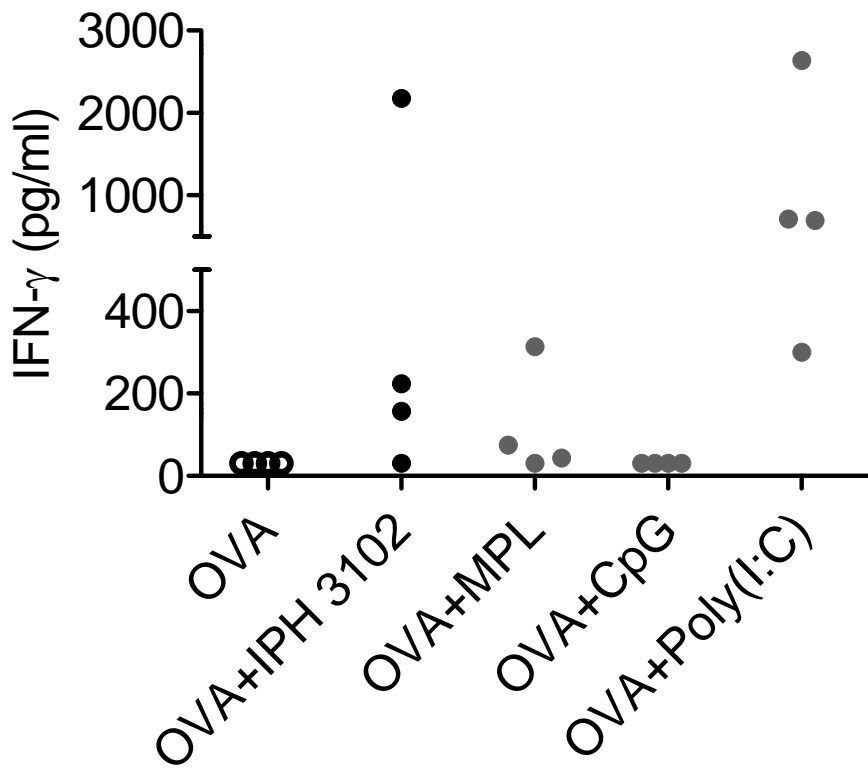
- At higher dose than 50µg, poly(I:C) but not IPH 3102 showed some signs of toxicity presumably related to MDA-5/RIG-I stimulation

◆ IPH 3102  
◇ poly(I:C)



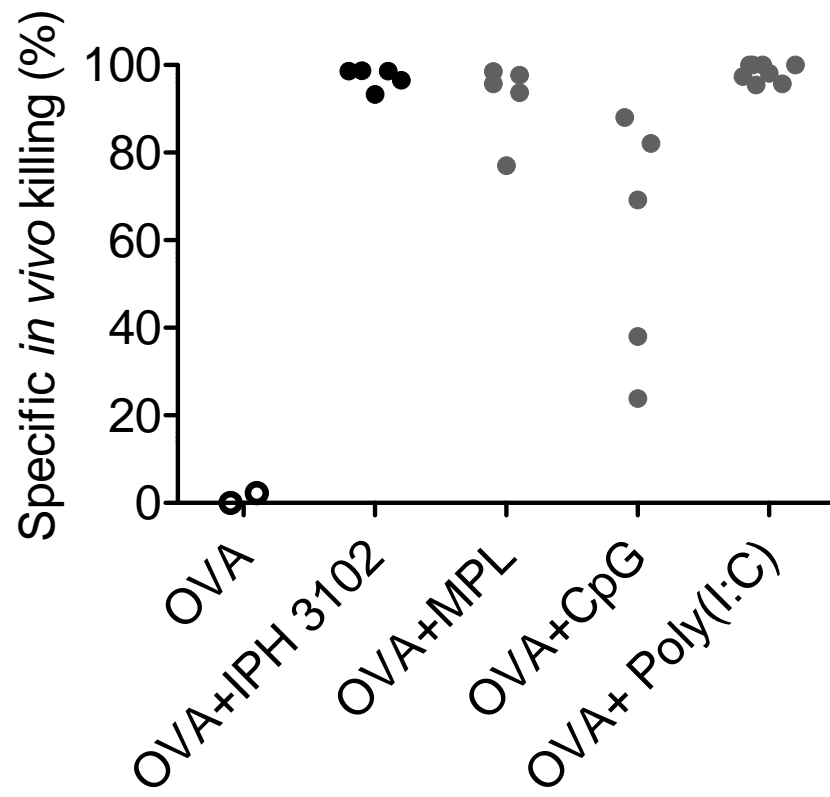
# IPH 3102 Acts as Adjuvant to Induce Ag-specific T cell Response *in vivo*

## CD4 T cell response




Ex vivo OVA-Class II peptide restimulation

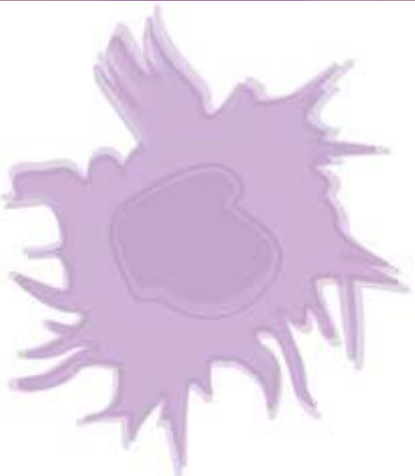
## CD8 T cell response



*In vivo* OVA-specific CTL lysis



IPH 3201  
TLR7/8 agonist





# IPH 3201 Overview

- IPH 3201 is an oligoribonucleotide (ORN) composed of 21 uridine bases with a phosphorothioate backbone
- IPH 3201 is available as a non-cGMP 5g batch



# ssRNA are TLR7/8 Agonists

## Innate Antiviral Responses by Means of TLR7-Mediated Recognition of Single-Stranded RNA

Sandra S. Diebold,<sup>1</sup> Tsuneyasu Kaisho,<sup>2,3</sup> Hiroaki Hemmi,<sup>2</sup> Shizuo Akira,<sup>2,4</sup> Caetano Reis e Sousa<sup>1\*</sup>

SCIENCE VOL 303 5 MARCH 2004

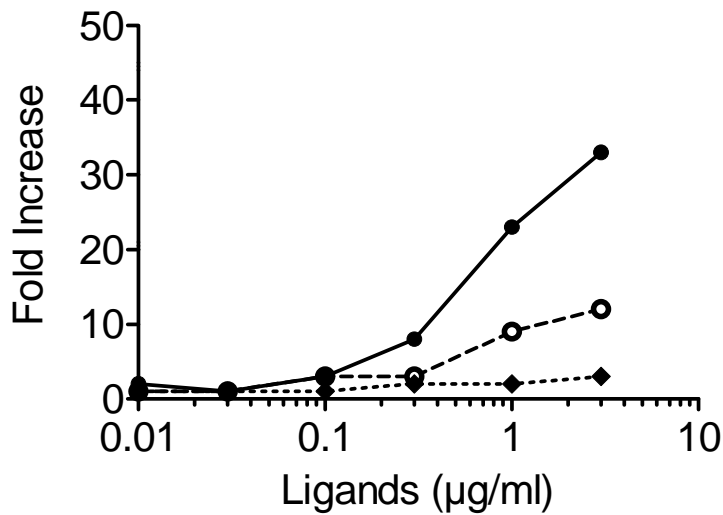
## Species-Specific Recognition of Single-Stranded RNA via Toll-like Receptor 7 and 8

Florian Heil,<sup>1\*</sup> Hiroaki Hemmi,<sup>2\*</sup> Hubertus Hochrein,<sup>1</sup> Franziska Ampenberger,<sup>1</sup> Carsten Kirschning,<sup>1</sup> Shizuo Akira,<sup>2,3</sup> Grayson Lipford,<sup>4</sup> Hermann Wagner,<sup>1</sup> Stefan Bauer<sup>1†</sup>

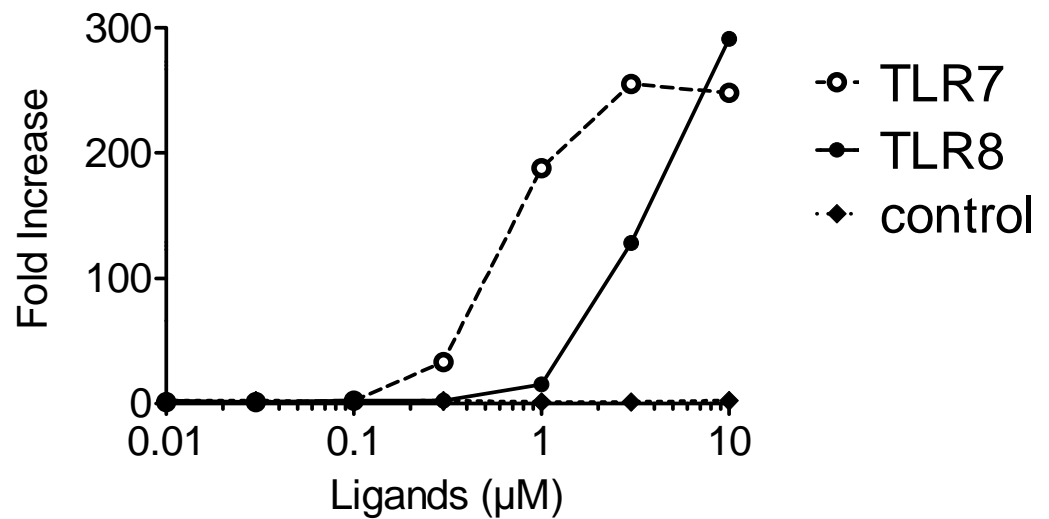


# IPH 3201 is a TLR7 and TLR8 Agonist in Humans

## IPH 3201



## R848

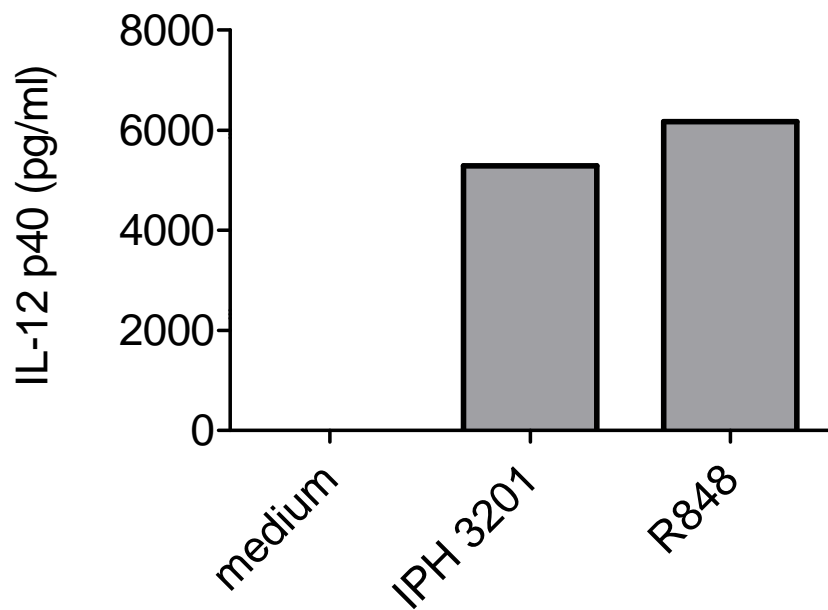


- TLR7
- TLR8
- ◆ control

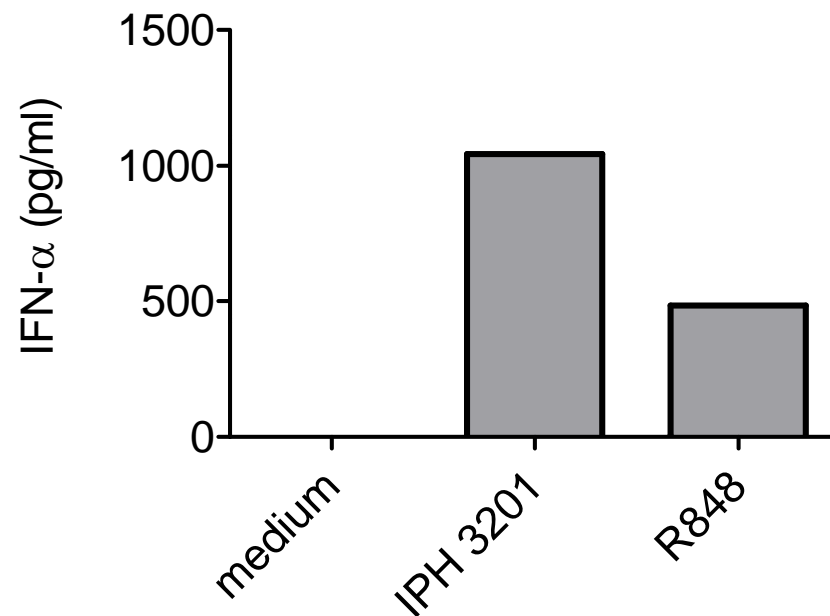


# IPH 3201 Activates both Myeloid DC (myDC) and Plasmacytoid DC (pDC) Subsets in Humans

## Human myDC (TLR7-TLR8+)

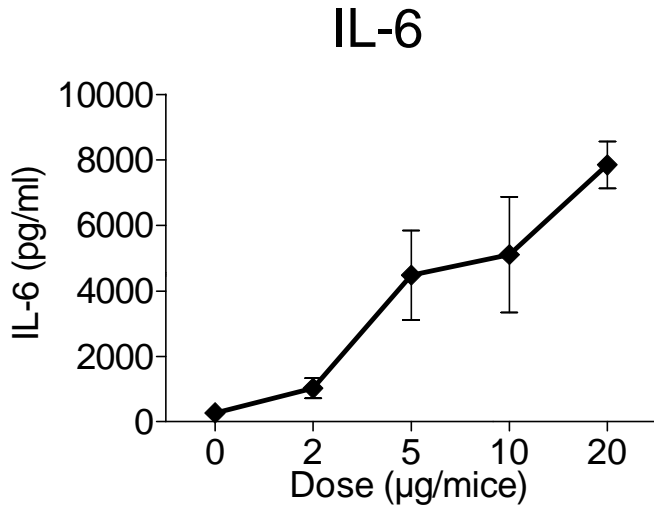
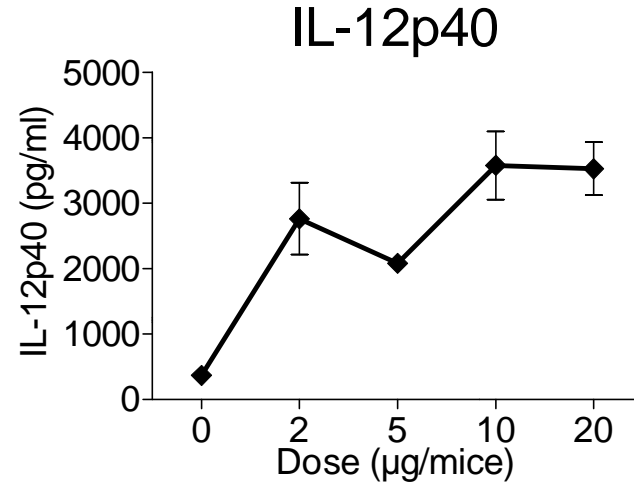
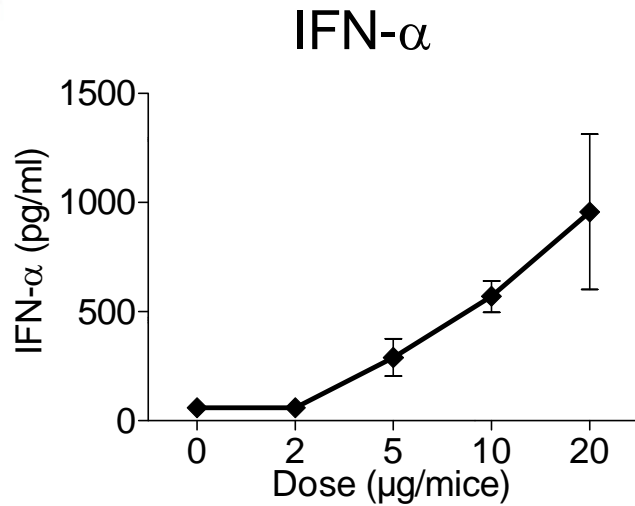


## Human pDC (TLR7+TLR8-)





# IPH 3201 is a Potent Immunostimulator *in vivo* in Mice

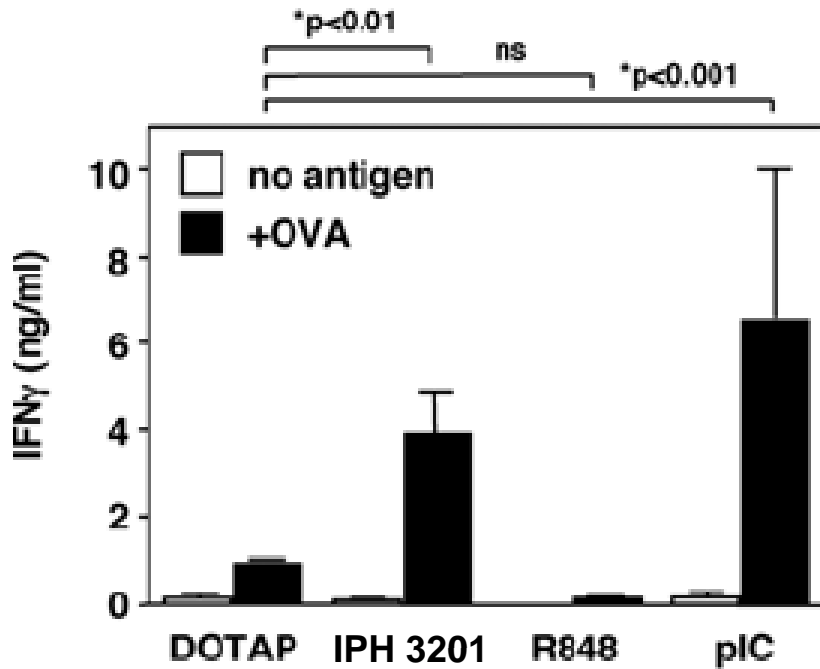


◆ IPH 3201

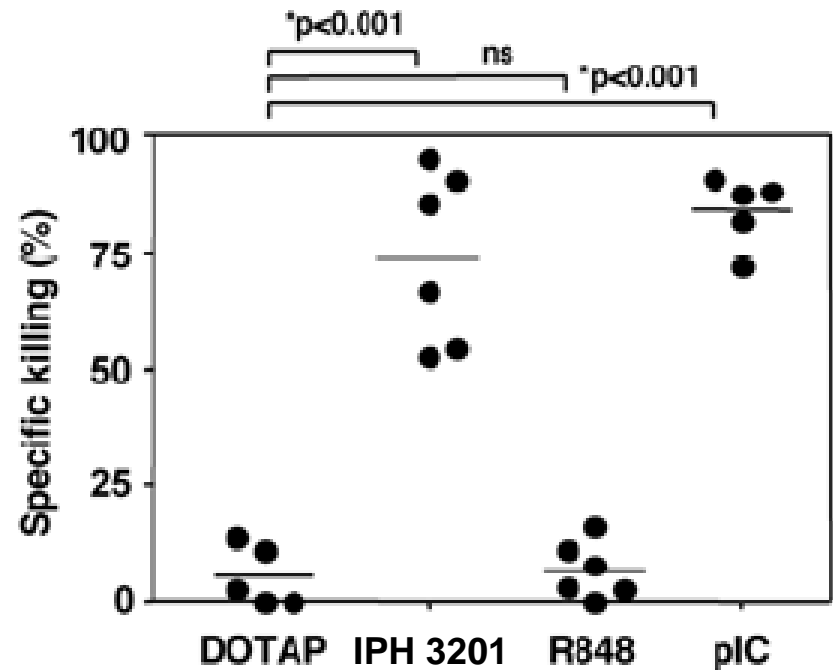


# IPH 3201 Acts as Adjuvant to Induce Ag-specific T cell Response *in vivo*

## CD4 T cell response



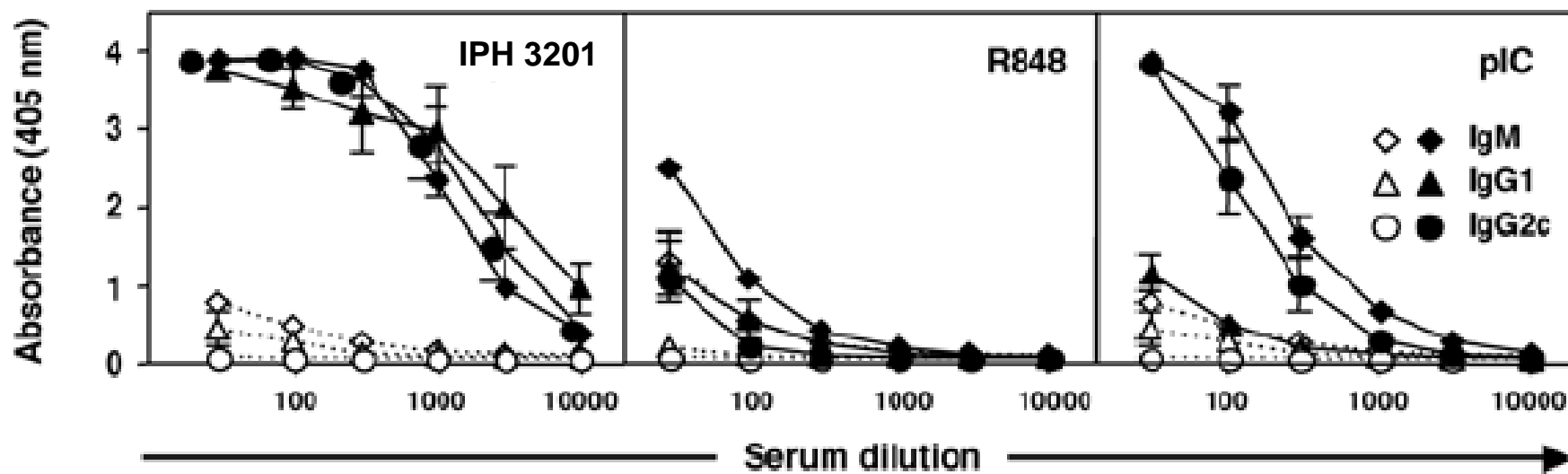
## CD8 T cell response



Adapted from Rajagopal et al., *Blood*, 2010



# IPH 3201 Acts as Adjuvant to Induce Ag-specific B cell Response *in vivo*



Adapted from Rajagopal et al., *Blood*, 2010

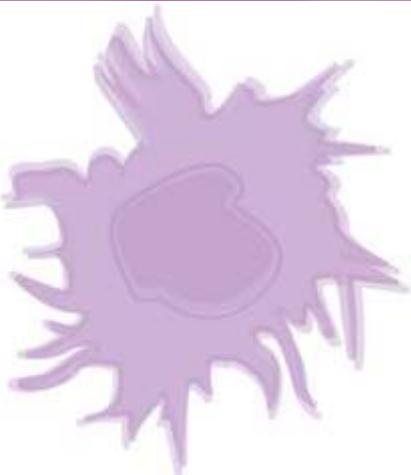


# Summary

- IPH 3102 (TLR3) and IPH 3201 (TLR7/8) are potent vaccine adjuvants against a model Ag in mice
- Due to its TLR3 specificity, IPH 3102 is expected to have a better safety profile than poly(I:C)
- Due to its IFN- $\alpha$  induction capacity, IPH 3201 has greater potential for vaccine adjuvant than TLR7/8 agonists NCE like R848
- Next steps
  - POC for IPH 3102 and IPH 3201 as vaccine adjuvant against a model Ag in Non Human Primate



## Exhibits





# TLR3 Intellectual Property

- **TLR3 cancer diagnostic/treatment patents**

- Schering Plough - WO 06/014653 (Lebecque, Salaun). Induction of apoptosis in TLR expressing tumor cells. Priority date July 2004
- Institut Gustave Roussy - WO 06/054177 (Andre, Zitvogel, Sabourin). Treatment of patients having TLR3 expressing tumor cells with a TLR3 ligand. Priority date November 2004
- Institut Gustave Roussy. Methods for administering TLR3 agonists in [cancer] vaccination. Priority date April 2008

- **TLR protein and antibody patents**

- Schering Plough - WO 98/50547 (Hardiman, Rock, Bazan). Human TLR proteins, related reagents and methods. Includes claims to human TLR3 protein and anti-TLR3 antibodies. Priority date May 1997
- Innate Pharma. Antibodies that specifically bind TLR3 in paraffin embedded tissue sections. Priority date September 2008

- **dsRNA patents**

- Innate Pharma. dsRNA compositions including IPH31xx series, and use thereof in therapy and vaccination. Priority date April 2008



# TLR7/8 Intellectual Property

- TLR7/8 agonist composition of matter and use patent
  - Cancer Research Technologies - WO2007/042554 (Reis e Sousa, Diebold, Paturel). Uridine-rich oligonucleotides and their use at TLR7 agonists in vaccination and therapy. Priority date October 2005



# In vivo CTL Assay for Adjuvant Properties Monitoring

C57 BL/6mice

