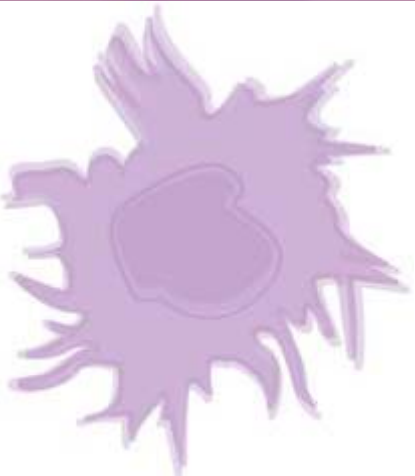


IPH 3102
TLR3 agonist

Targeted Oncology Therapeutic Agent






IPH 3102 Presentation

- Overview
- Scientific Rationale
- IPH3102 Pharmacology
- Expression Profile of TLR3 in Different Cancers
- Summary



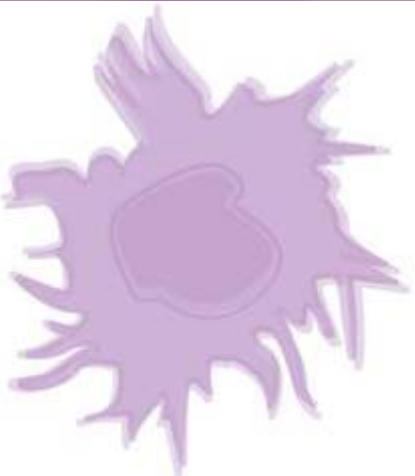
IPH 3102: Overview

- Synthetic high MW dsRNA
- Targets a unique receptor: Toll-like Receptor 3 (TLR3)
- Dual mechanism of action in oncology
 - immunostimulation through dendritic cells activation
 - direct cytotoxicity and pro-inflammatory effect on TLR3 expressing tumors (TLR3 being expressed by a broad spectrum of tumor cells including breast cancer, melanoma, etc...)
- Well characterized oncology drug candidate (validated by a pre-IND meeting with FDA)
- Proprietary anti-TLR3 mAb for companion IVD assay
- Intellectual property protection on the compound, on the anti-TLR3 mAb for diagnostic and on TLR3 as a target for the diagnosis and treatment of cancer
- Development supported by an R&D team with significant expertise in the field and the capability to conduct relevant preclinical and translational research to support clinical development programs
- Worldwide rights available



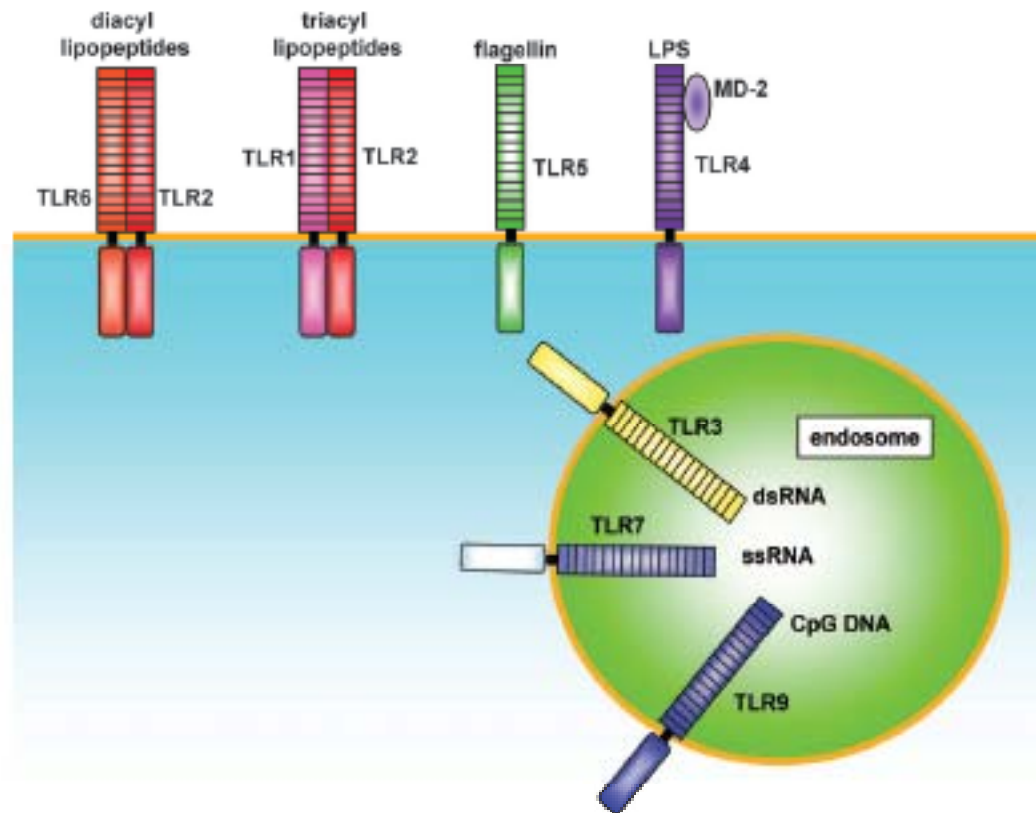
IPH 3102
TLR3 agonist

Scientific Rationale



TLR Family

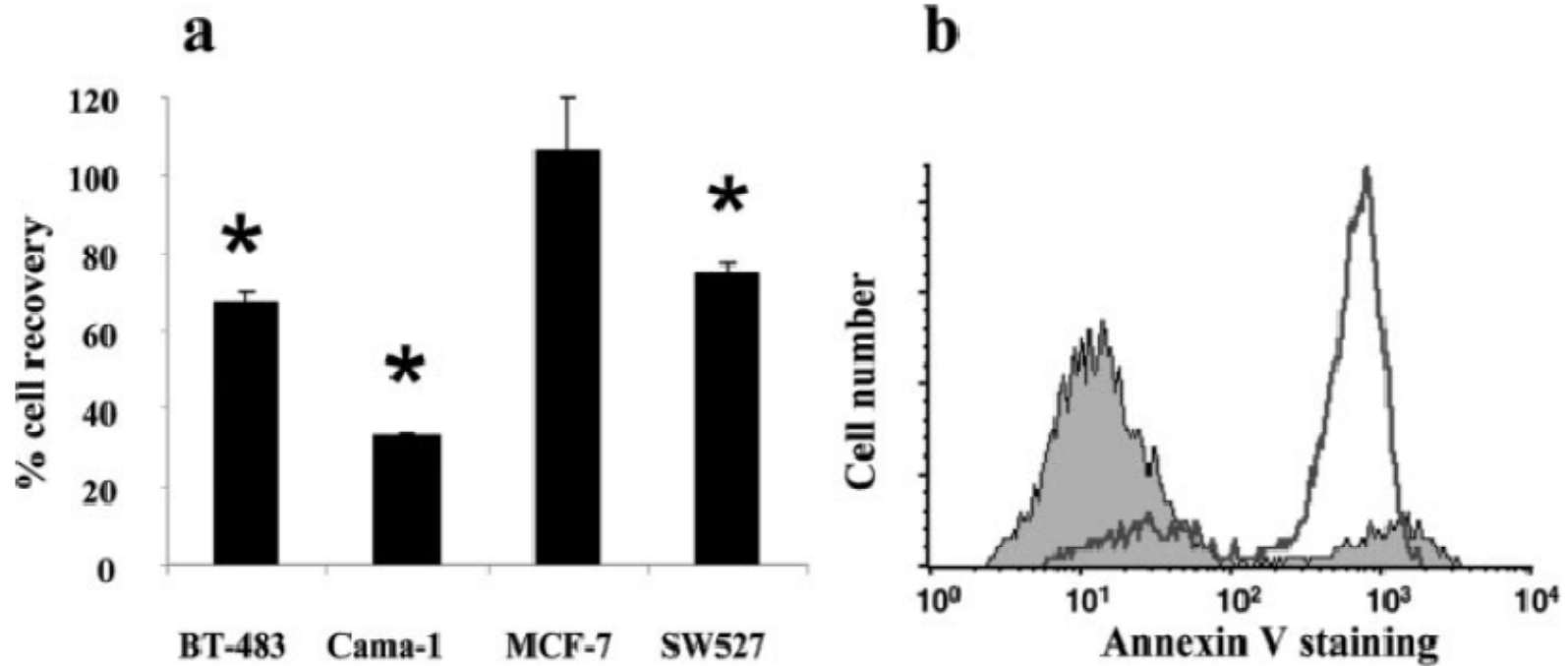
- Toll-like receptors (TLR) are a family comprising **10 members** and are part of Pattern Recognition Receptors used by innate immune system
- TLR3 recognizes double-stranded RNA (dsRNA)



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



dsRNA Induces Tumor Cells Apoptosis *in vitro*

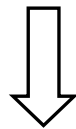


From Salaun, *J. Immunol.*, **176**, 4894 (2006)



Historical Clinical Trials with dsRNA

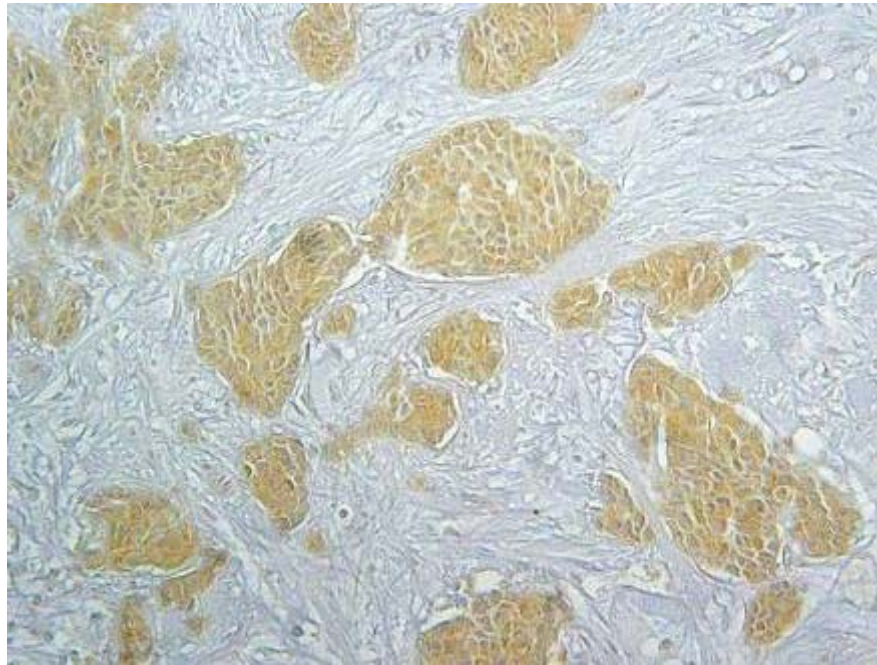
- Synthetic dsRNA immunostimulatory properties known since 60's but the mechanism of action was unknown
- Synthetic dsRNA of poorly defined composition have been tested in the clinic since the 70's
- poly(I:C) and derivatives tested in few clinical trials in cancer and non-cancer indications with some safety issues
- poly(A:U) tested in two Phase II breast cancer clinical trials at Institut Gustave Roussy (IGR, France) in 1972 and 1982 respectively
 - no safety issues
 - slight effect on RFS and OS in N+ patients



- Retrospective analysis of TLR3 expression, the receptor for poly(A:U), on patients tumor samples from IGR Phase II breast cancer clinical trials



Retrospective Analysis of IGR Poly(A:U) Clinical Trial in Breast Cancer



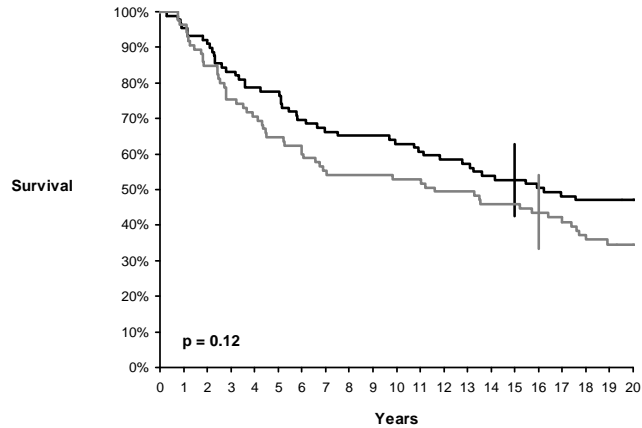
- TLR3 is over-expressed in the tumor cells for ~10% of breast cancer patients
- TLR3 expression monitored in IHC with pAb

« Targeting Toll like receptor 3 by double stranded RNA in breast cancer: results from in vitro studies and randomized trial. » Andre et al, *ASCO 2004*

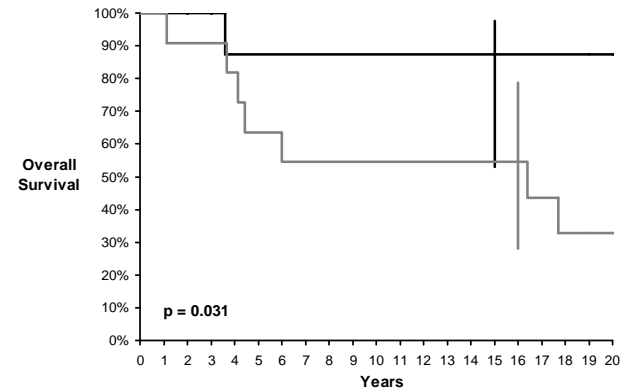


Retrospective Analysis of IGR Clinical Trial #1

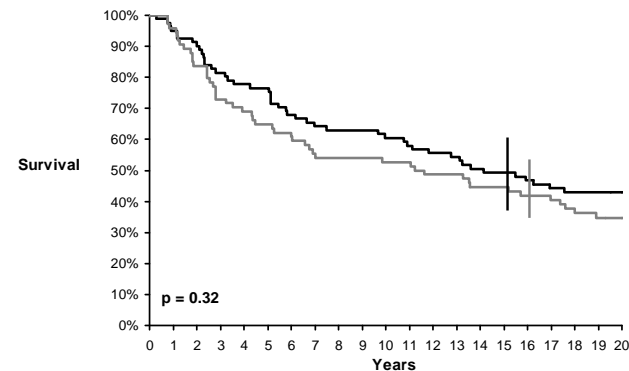
174 patients N+



19 patients TLR3+ (11%)



155 patients TLR3-



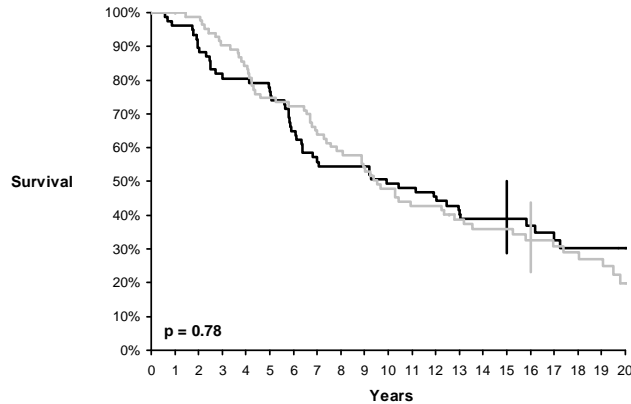
— Poly(A:U)
— Placebo

« Targeting Toll like receptor 3 by double stranded RNA in breast cancer: results from in vitro studies and randomized trial. » Andre et al, ASCO 2004

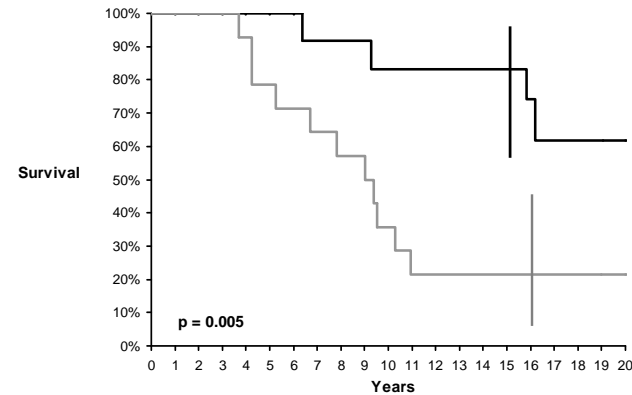


Retrospective Analysis of IGR Clinical Trial #2

162 patients N+



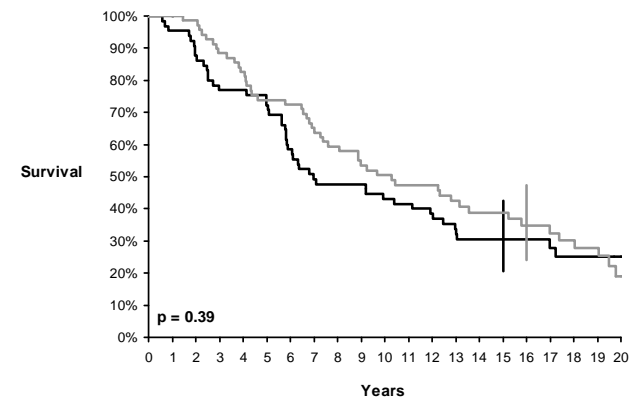
26 patients TLR3+ (16%)



— Poly (A:U) + RT
— Chemotherapy

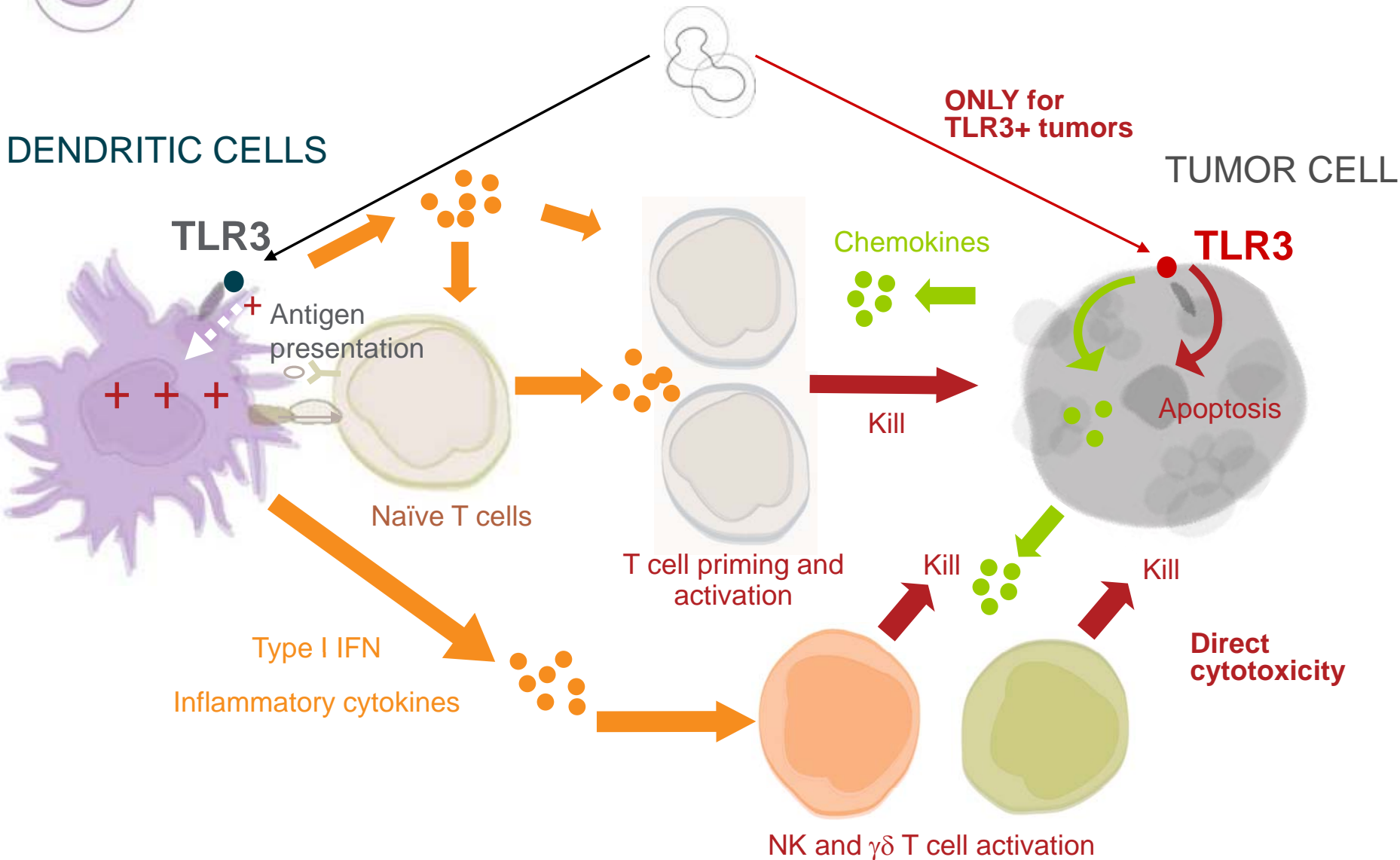
Two retrospective studies showed clear survival benefits in TLR3+ breast cancer 15 years after poly(A:U) treatment

136 patients TLR3-



Andre et al, ASCO 2006

Dual Mechanism of Action for TLR3 Agonists in Oncology





IPH 3102
TLR3 agonist



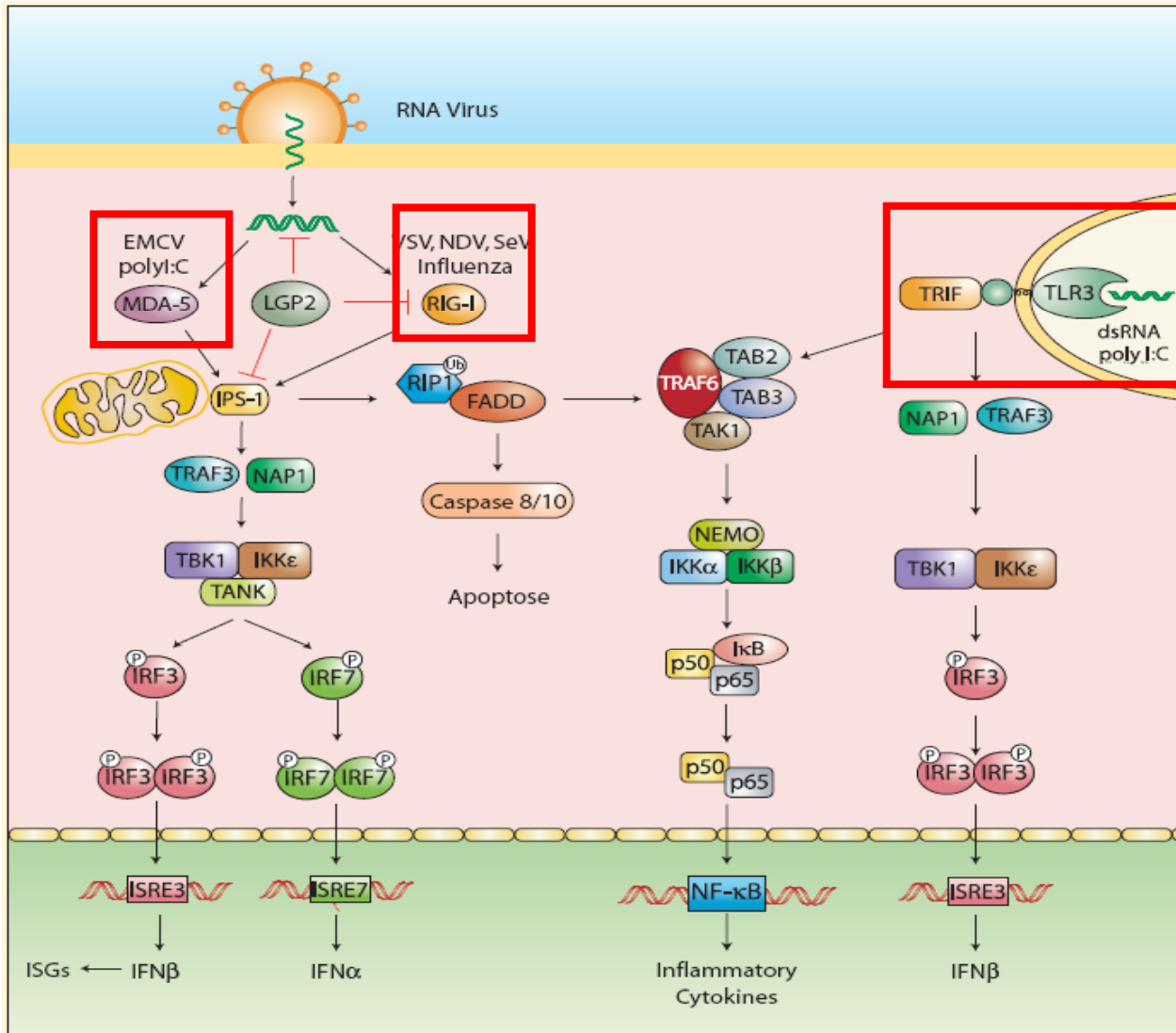
IPH 3102 Pharmacology



IPH 3102 Pharmacology

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

Multiple dsRNA Receptors

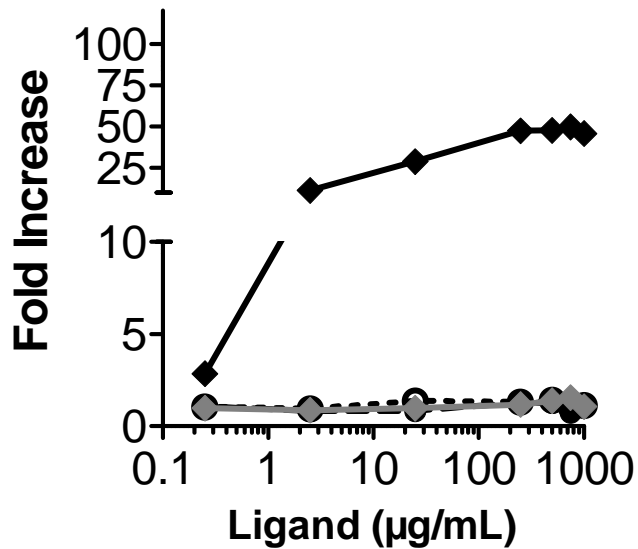


From Invivogen

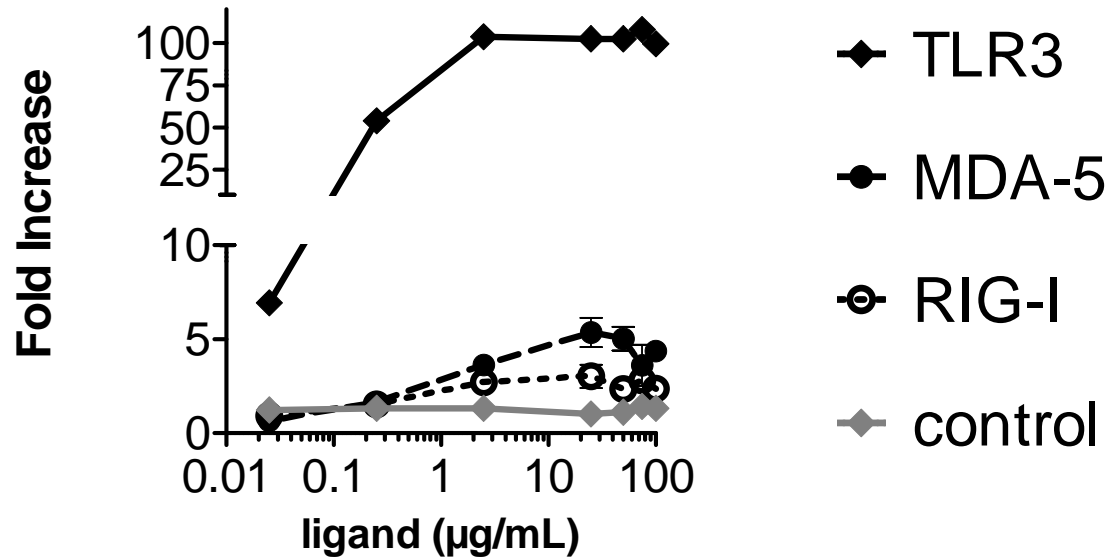


IPH 3102 is a TLR3-specific Agonist in Humans

IPH 3102



poly(I:C)



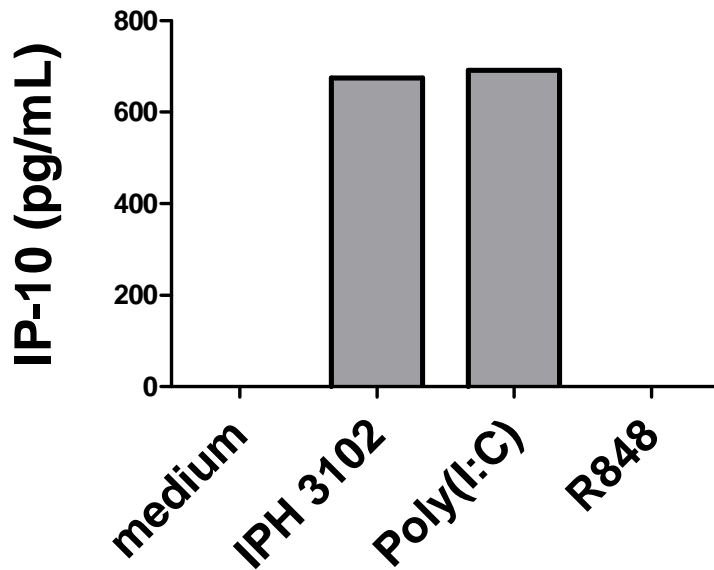
- ◆ TLR3
- MDA-5
- RIG-I
- ◆ control

- 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

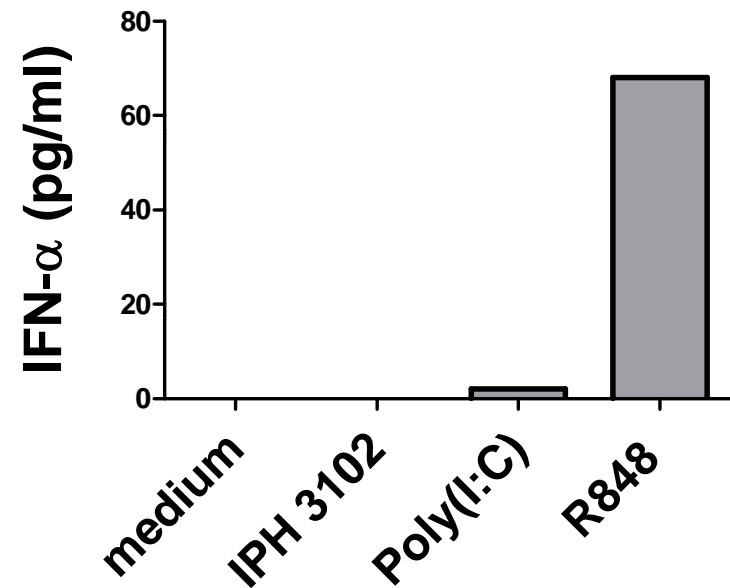


IPH 3102 Activates Specifically Myeloid DC Subset (myDC) in Humans

Human myDC
(TLR3+ TLR7-)



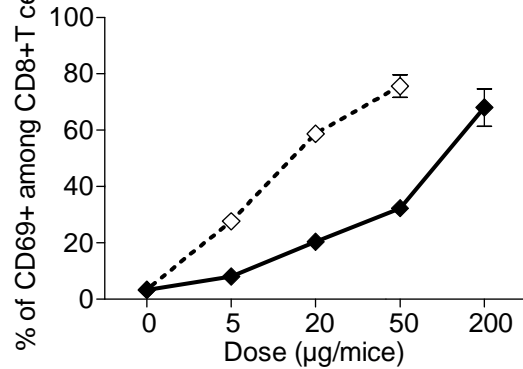
Human pDC
(TLR3- TLR7+)



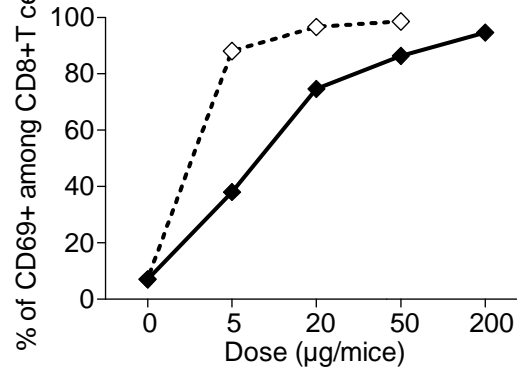


IPH 3102 is a Potent Immunostimulator *in vivo* in Mice

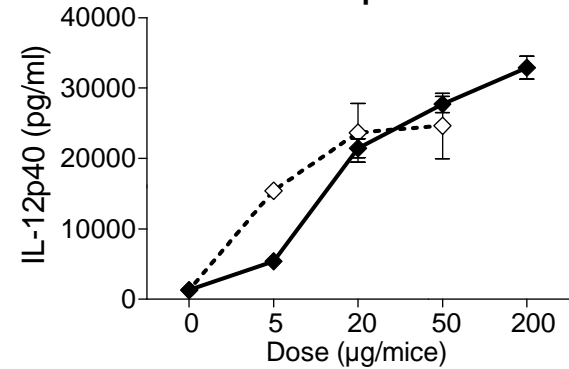
CD8 T cells activation



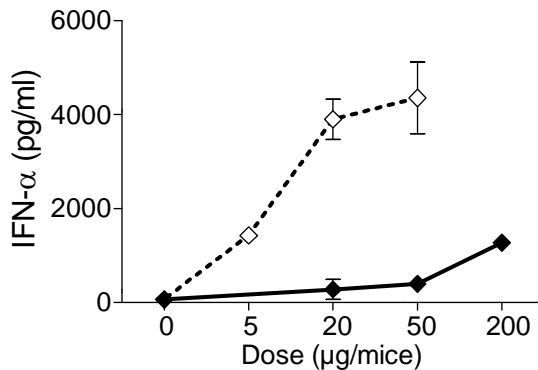
NK cells activation



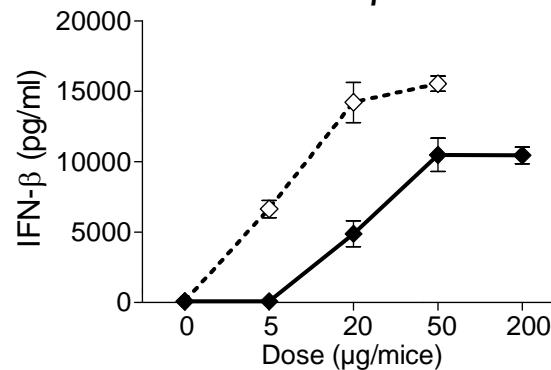
IL-12p40



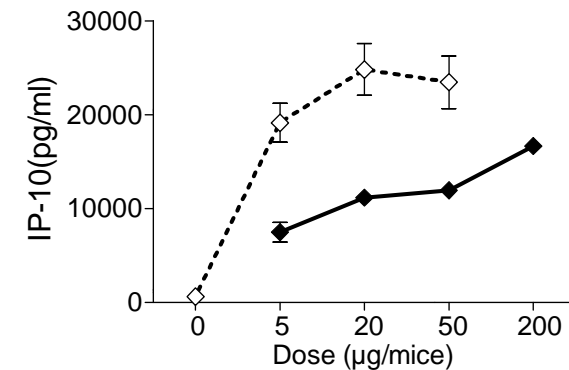
IFN-α



IFN-β



IP-10



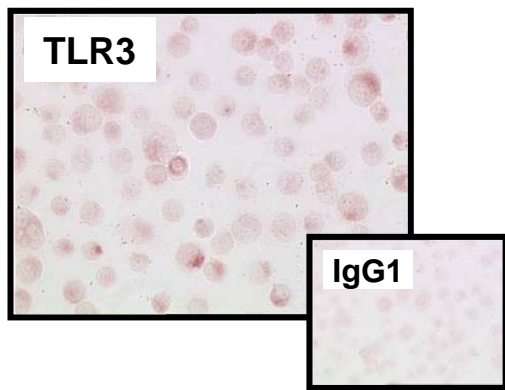
- At higher dose than 50µg, poly(I:C) but not IPH 3102 showed some signs of toxicity presumably related to MDA-5/RIG-I stimulation

◆ IPH 3102
◇ poly(I:C)

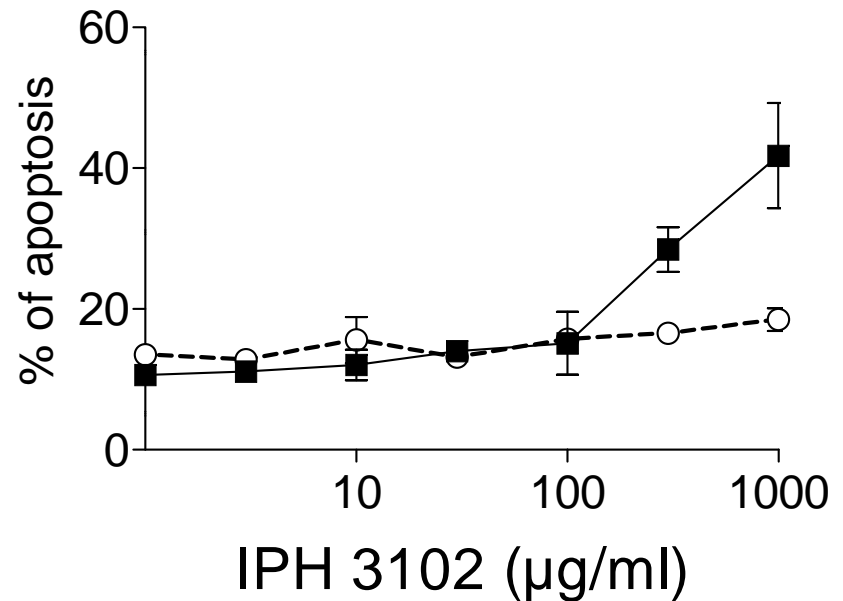


IPH 3102 Induces TLR3-dependant Apoptosis *in vitro* in Breast Cancer Cell Lines

HCC 1806



Apoptosis



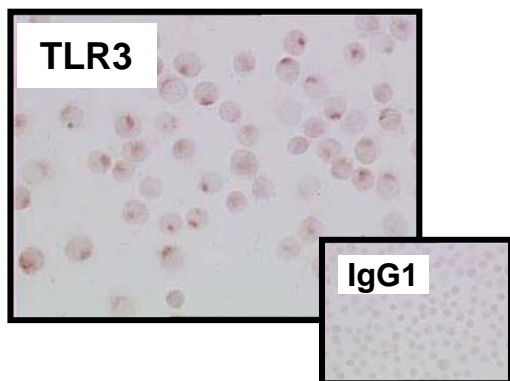
■ HCC1806-shLamin

○ HCC1806-shTRIF

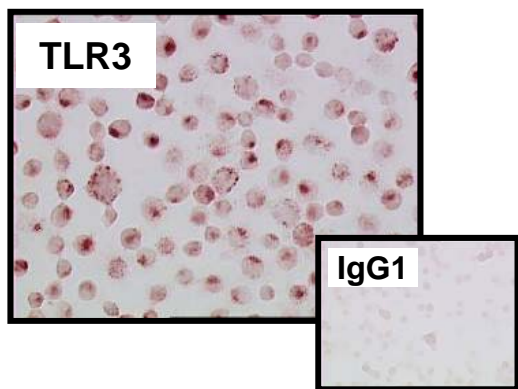


IPH 3102 Induces TLR3-dependant Apoptosis *in vitro* in Melanoma Cell Lines

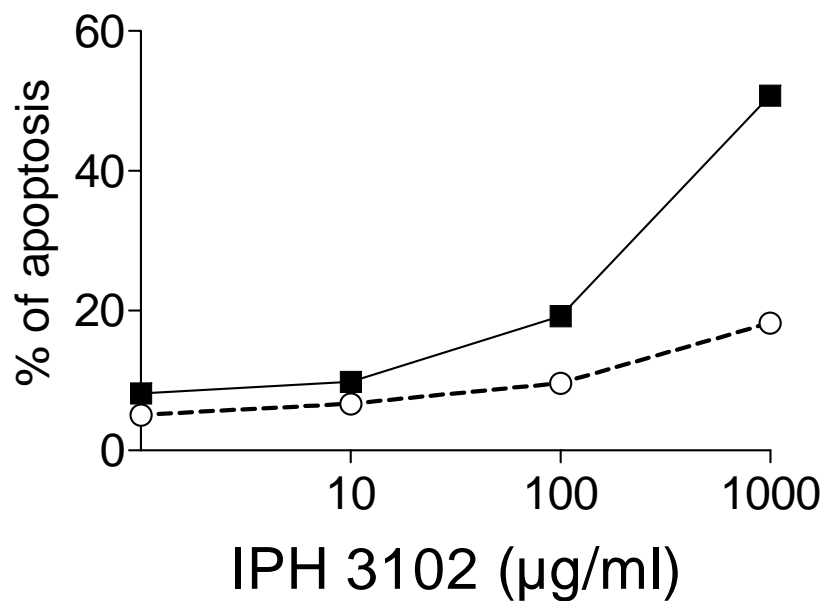
A375



A375 + IFN- α



Apoptosis

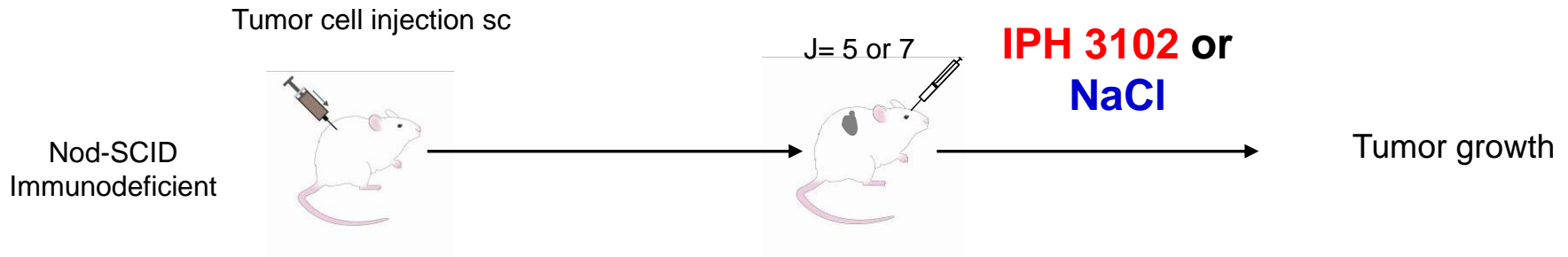


■ A375-shLamin

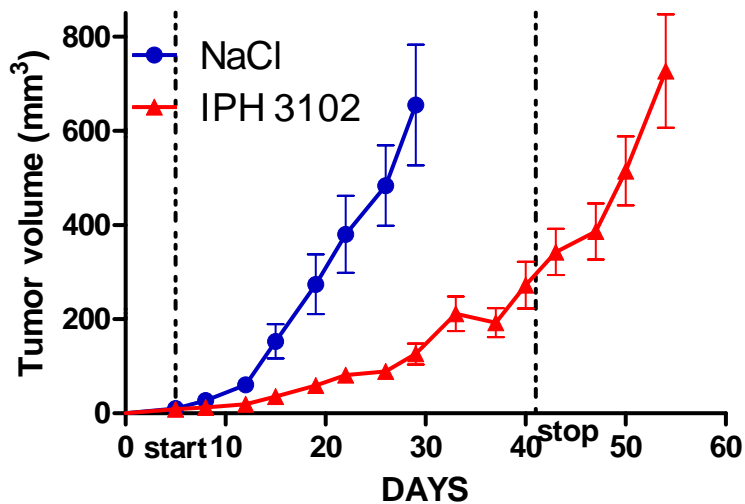
○ A375-shTRIF



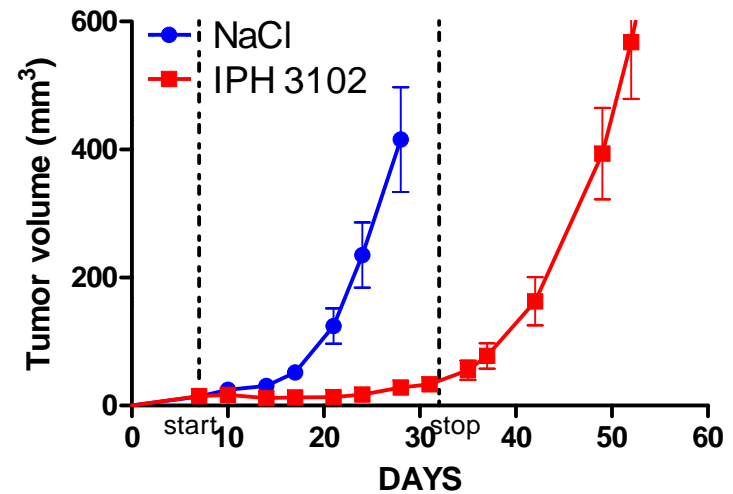
In vivo Anti-tumoral Efficacy of IPH 3102 in Xenogeneic TLR3+ Breast and Melanoma Tumor Models



HCC1806 breast tumor cells



A375 melanoma tumor cells





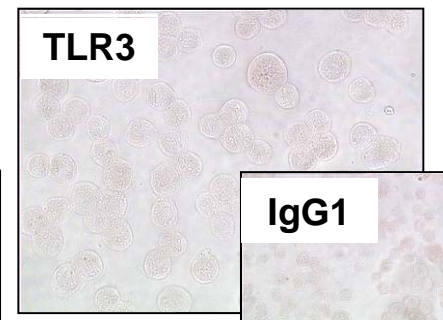
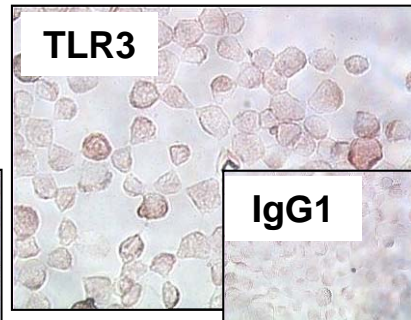
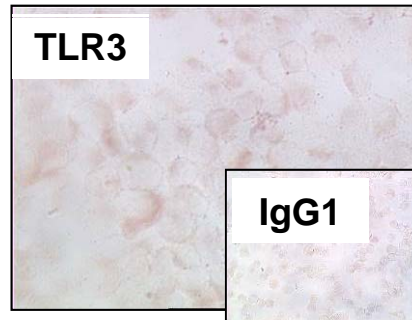
In vivo Anti-tumoral Efficacy of IPH 3102 in Syngeneic Tumor Models (1)

GL26

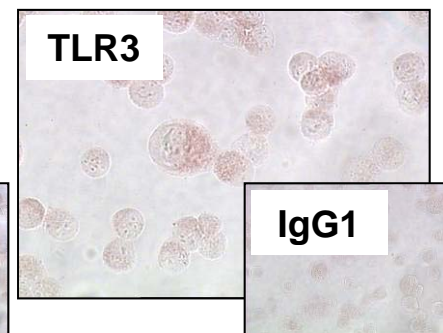
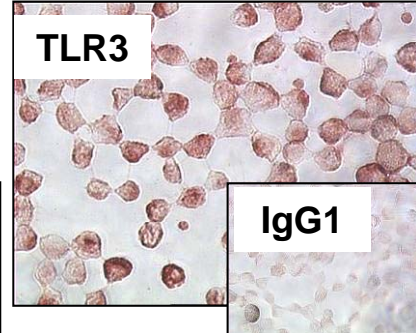
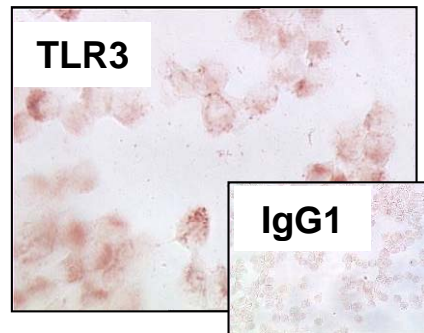
B16-F10

LL2

Medium



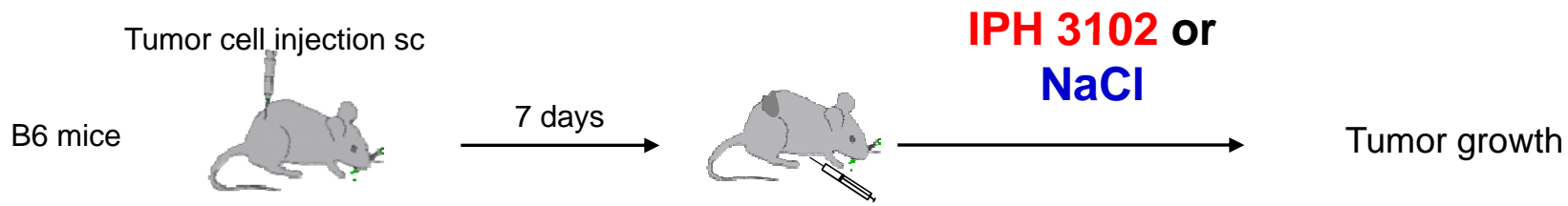
IFN α/β



In vitro		TLR3 expression		Apoptosis		RANTES		IL-6	
Cell Lines	Origin	not pre treated	IFN	not pre treated	IFN	not pre treated	IFN	not pre treated	IFN
GL26	Glioma	-	+/-	+/-	+	+/-	+	-	+
B16-F10	Melanoma	+/-	+	-	+/-	++	++	-	+
LL/2	Lung	-	-	-	-	-	+/-	-	-



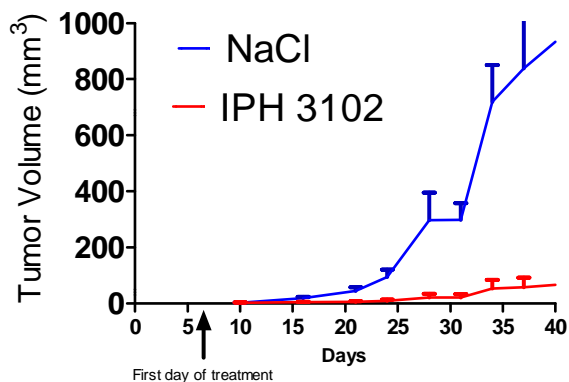
In vivo Anti-tumoral Efficacy of IPH 3102 in Syngeneic Tumor Models (2)



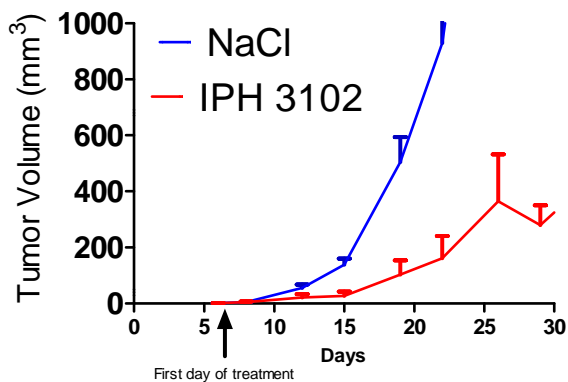
Responsive *in vitro*

Resistant *in vitro*

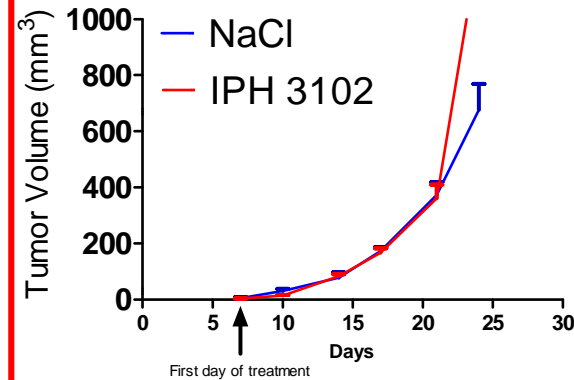
GL26




B16-F10



LL2





IPH 3102
TLR3 agonist

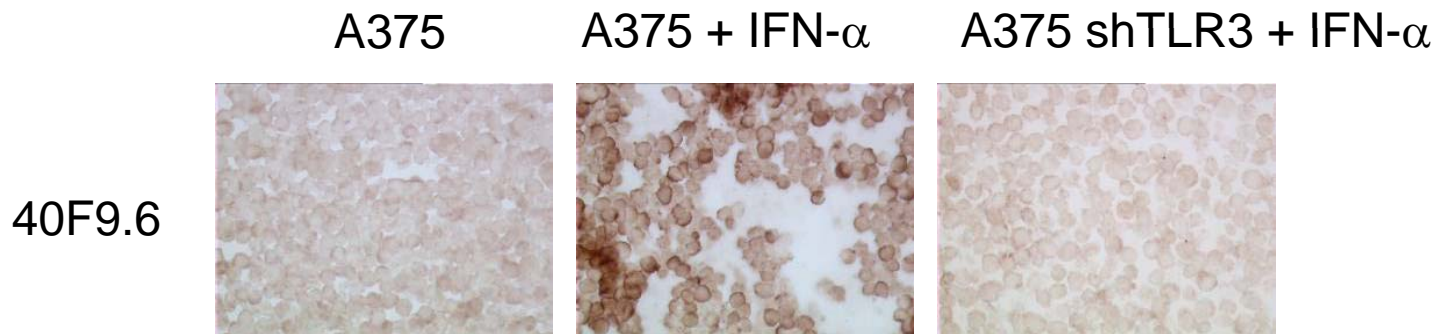
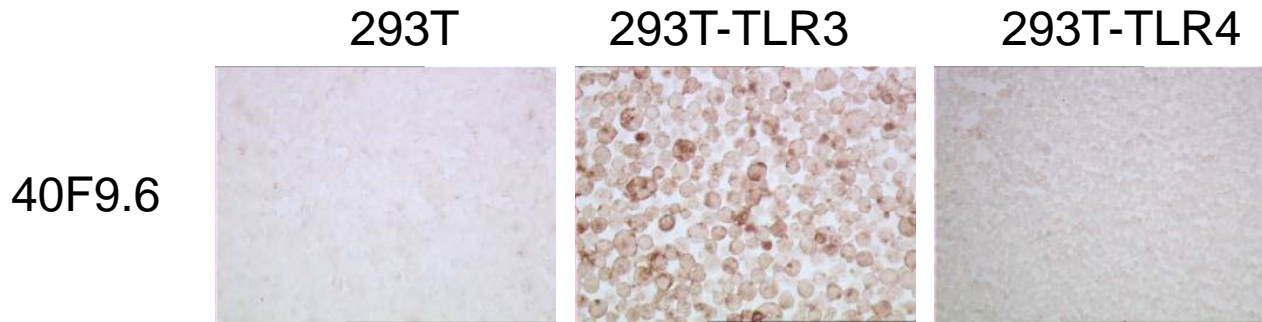


Expression Profile of TLR3 in Different Cancers



Proprietary mAb (40F9.6) for Paraffin-embedded Tissues

TLR3 Staining





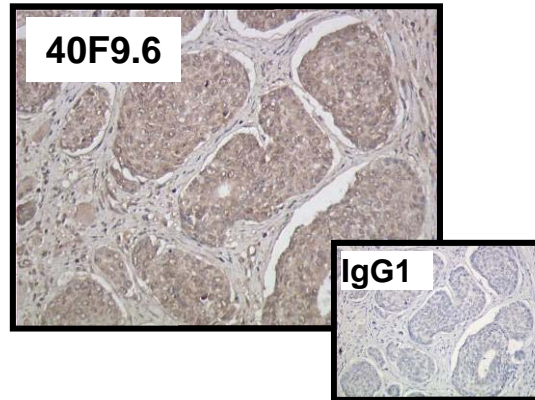
TLR3 Expression in Tumor Types

Tissues	TLR3 expression		
	Normal	Tumor	
		Positive cases/ Total cases	Percentage
Cervix	(+)	8/10	80%
Lung (NSCLC)	(+)	27/48	57%
Esophagus	(+)	7/9	78%
Skin (SCC)	(+)	72/97	74%
Skin (melanoma)	(+)	35/82	43%
Thyroid	(+)	5/9	56%
Larynx	(+)	5/9	55%
Liver	(-)	5/10	50%
Kidney	(+)	2/6	33%
Pancreas	(+)	2/9	22%
Ovary	(-)	2/10	20%
Bladder	(-)	1/9	11%
Uterus	(+)	1/10	10%
Breast	(+)	13 / 112	10%
Stomach	(+)	0/10	0%
Colon (3)	(+)	0/3	0%
Rectum (7)	(-)	0/7	0%

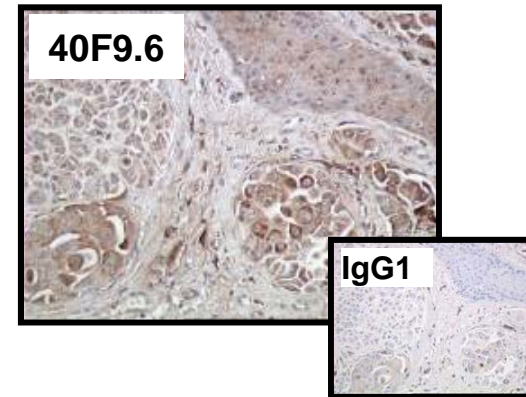


Examples of TLR3 Positive Cases for in Different Tumors

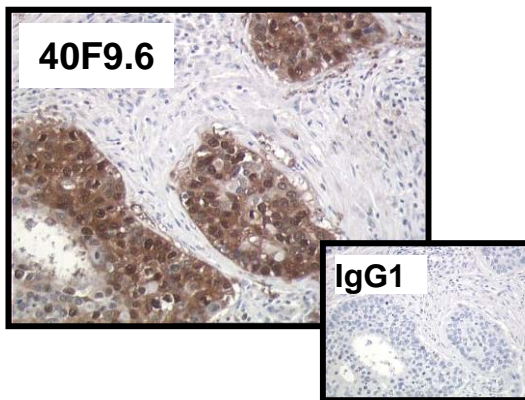
Breast Cancer



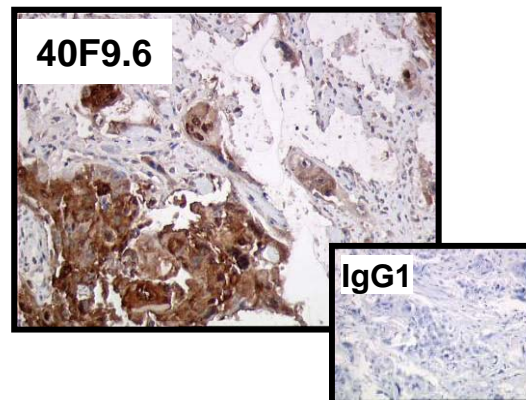
Melanoma



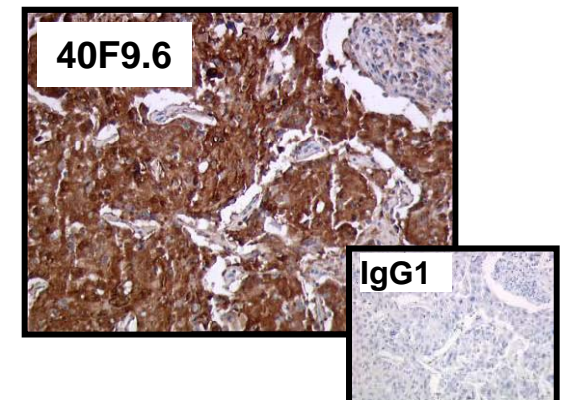
Cervix



Lung adenocarcinoma

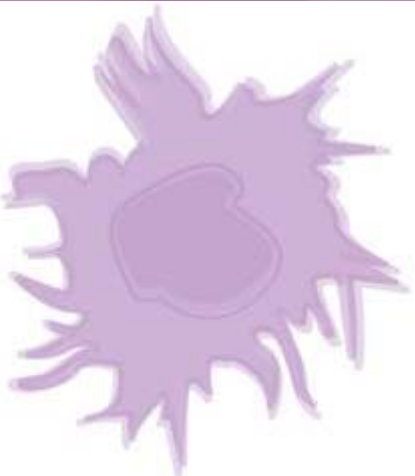


Squamous Cell Lung Carcinoma





Summary



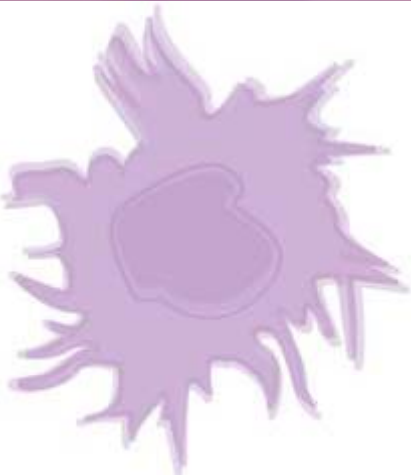


IPH 3102 Summary

- IPH 3102 is a potent TLR3-specific agonist in humans
- IPH 3102 is a potent immunostimulator through myeloid dendritic cells activation *in vitro* and *in vivo*
- IPH 3102 induces apoptosis of TLR3 expressing tumor cell lines
- IPH 3102 shows anti-tumoral efficacy *in vivo* against TLR3-expressing tumors
- TLR3 is expressed by large subsets of patients in multiple cancer indications
- Proprietary anti-TLR3 mAb (40F9.6) for companion IVD assay
- Next steps
 - development of IPH 3102 GMP manufacturing process
 - IND toxicology studies



Exhibits





Innate Pharma 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