

LAG-3: Validation Of Next Generation Checkpoint Pathways



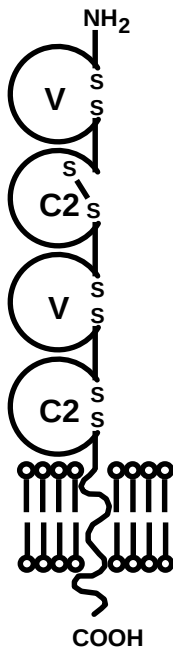
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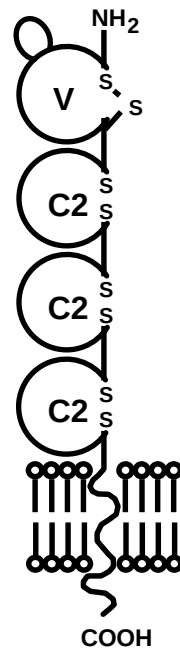
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Lymphocyte Activation Gene-3 (LAG-3 or CD223)

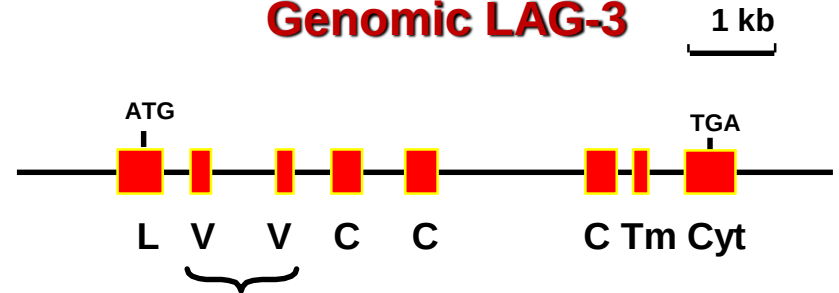
CD4



LAG-3

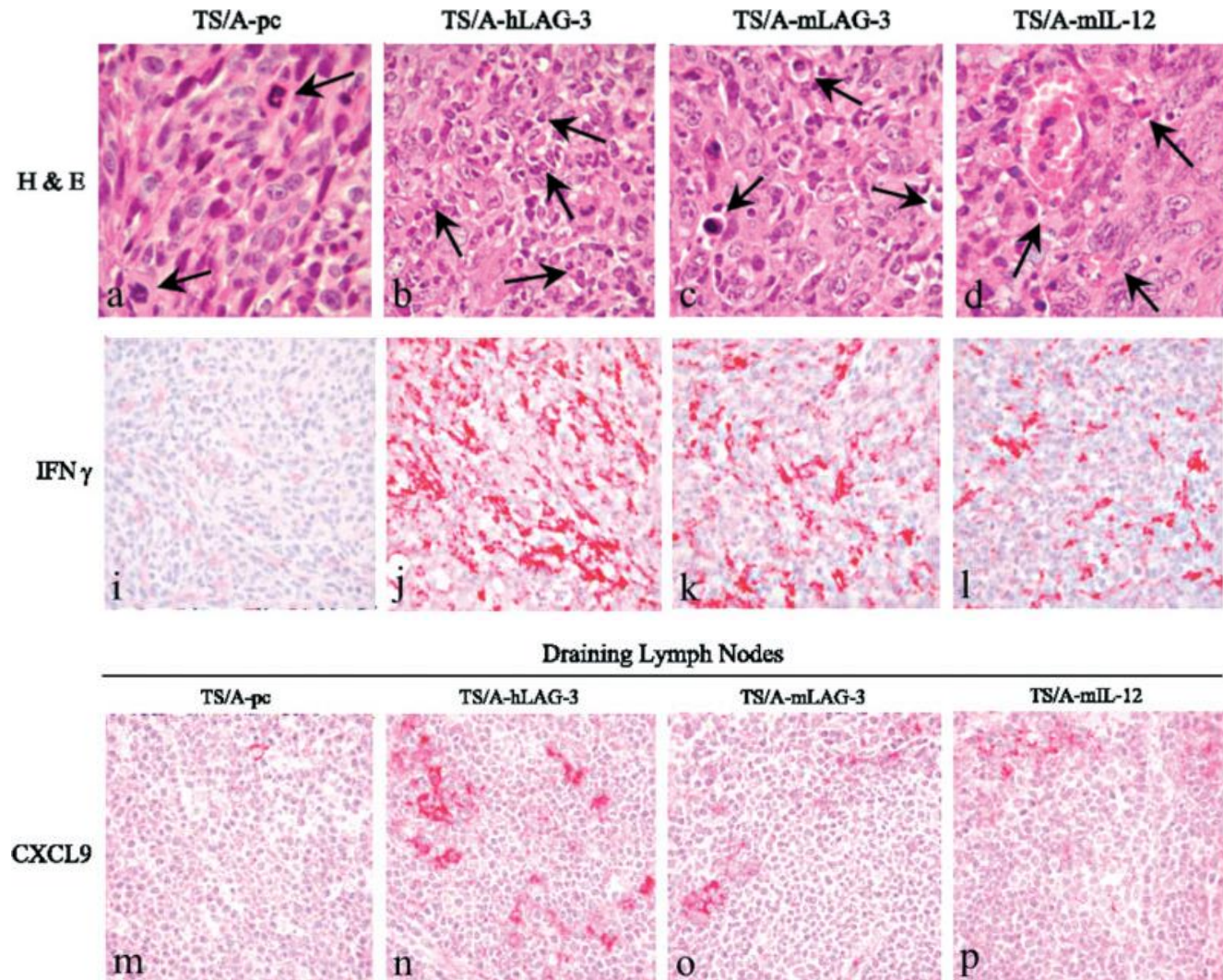


Genomic LAG-3

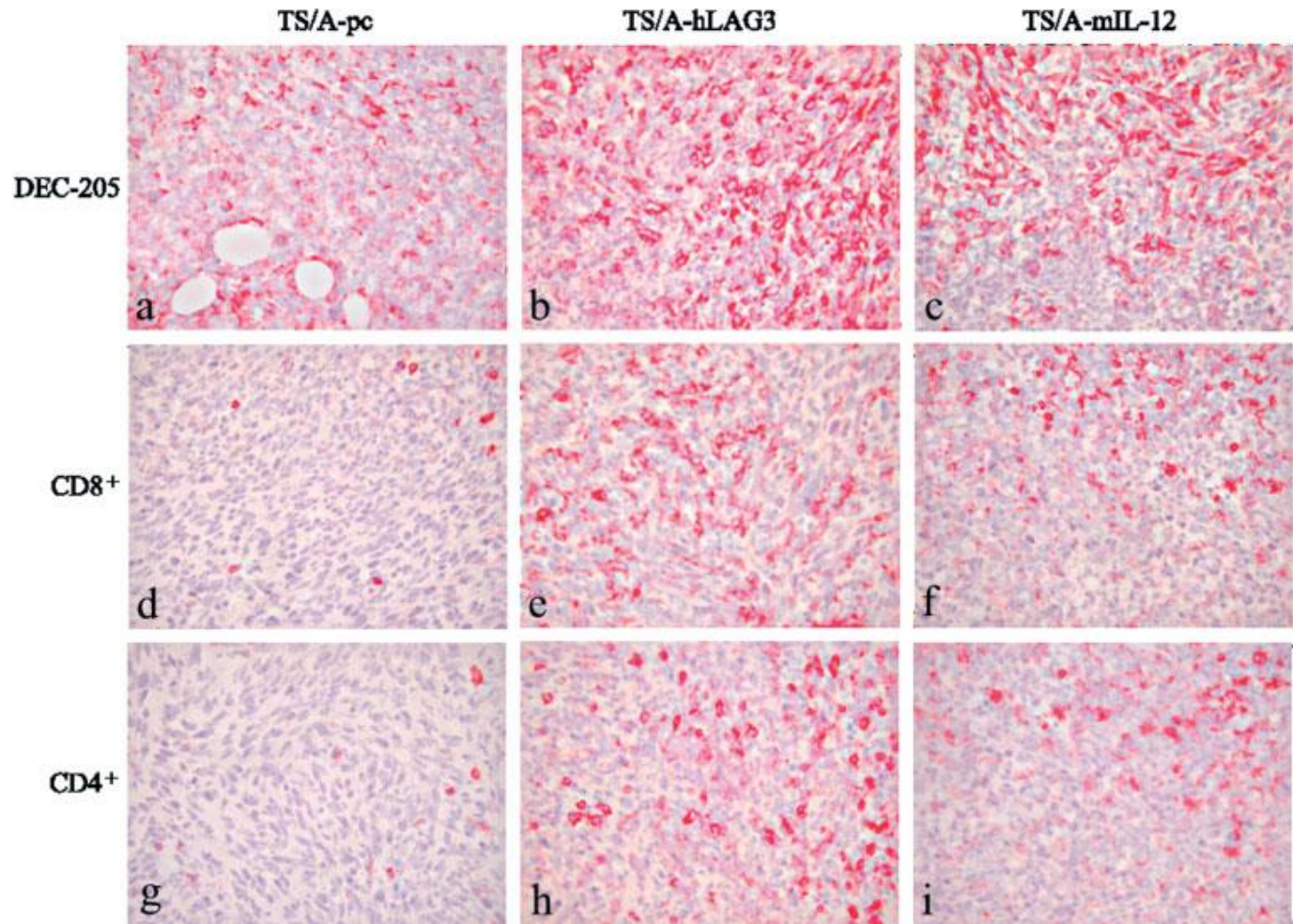


- 4-IgSF domain transmembrane proteins.
- Same genomic organization (intron in D1, duplication event D1D2 vs D3D4)
- Close proximity on 12p13.

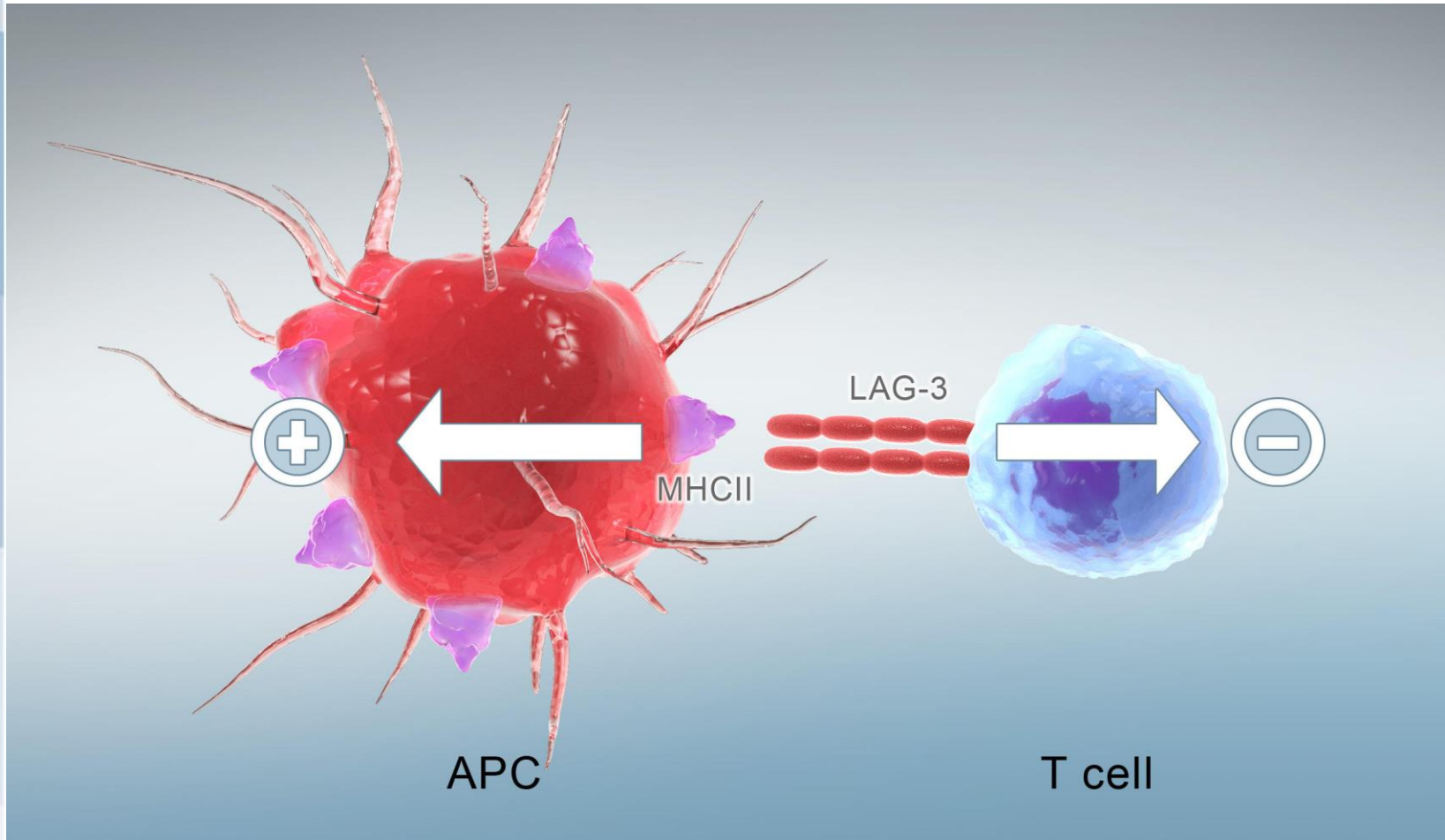
Immunological mechanisms elicited at the tumour site by LAG-3 versus IL-12: sharing a common Th1 anti-tumour immune pathway

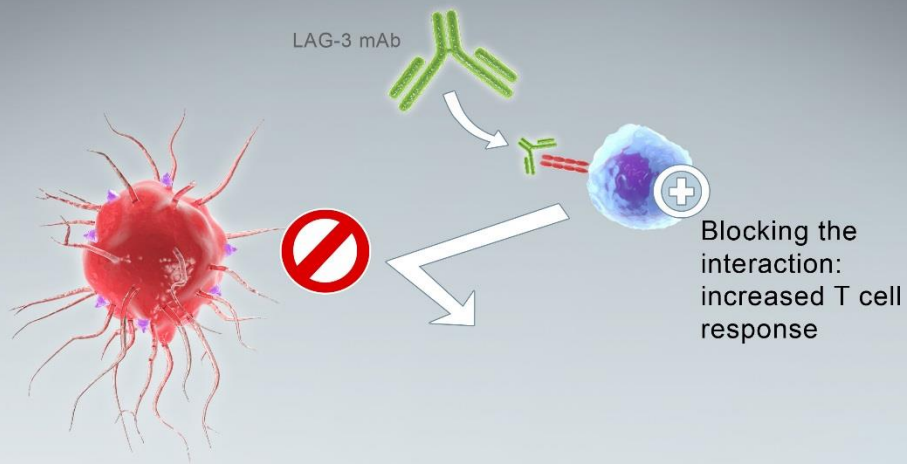


**Immunological mechanisms elicited at the tumour site
by LAG-3 versus IL-12:
sharing a common Th1 anti-tumour immune pathway**

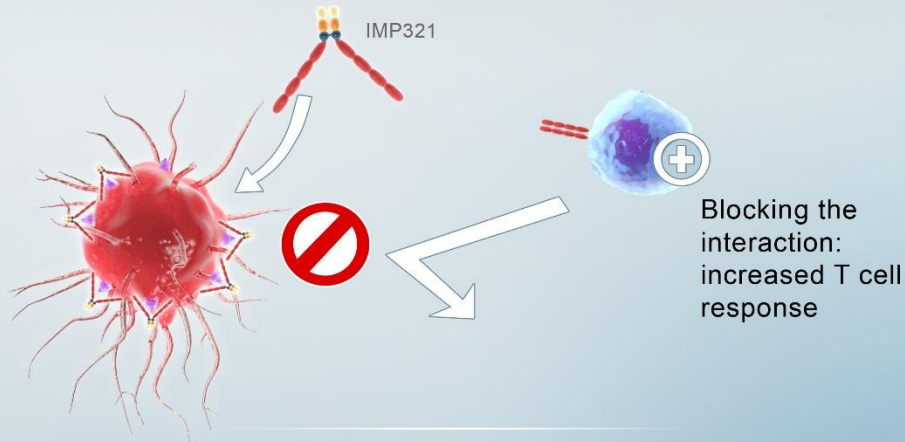


LAG-3/MHC class II interaction

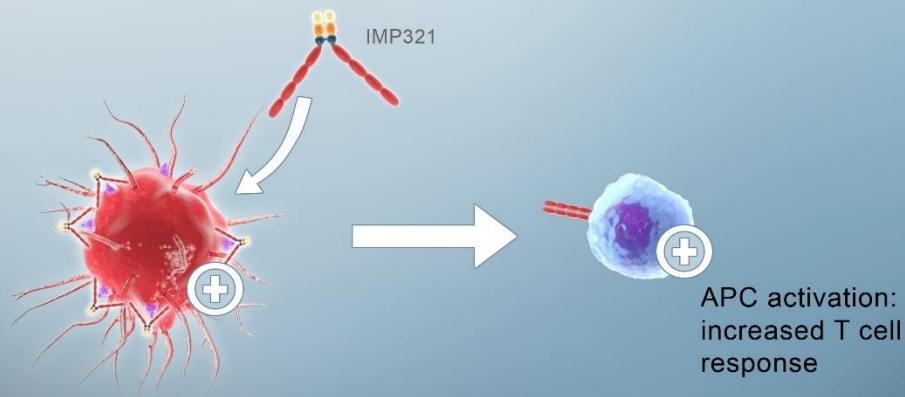




LAG-3 blocking mAb:
an immune checkpoint
inhibitor



LAG-3Ig fusion protein (IMP321):
an immune checkpoint
inhibitor



LAG-3Ig fusion protein (IMP321):
an APC activator
(primary MoA)

First-in class APC Activator

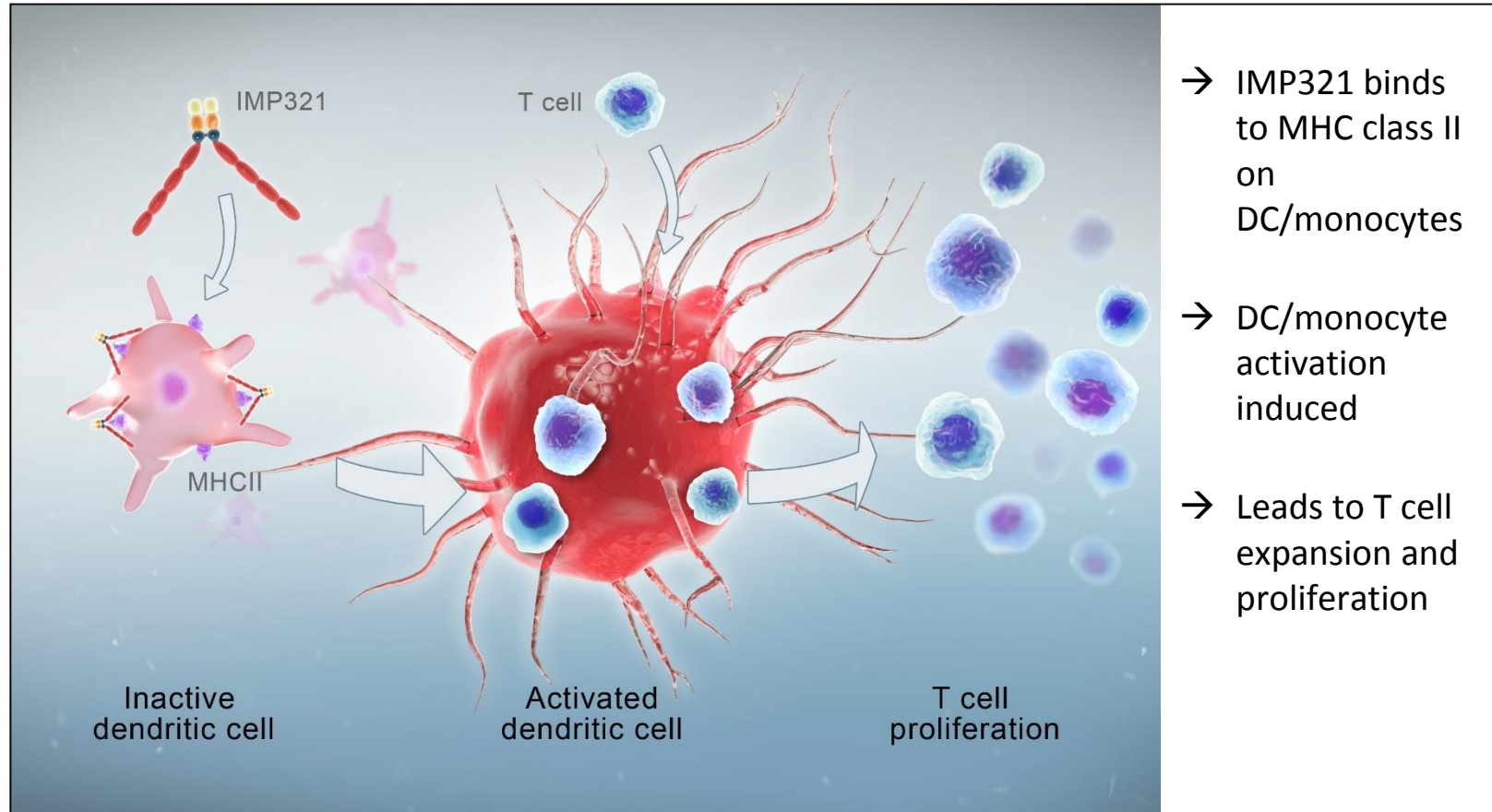
IMP321 (LAG-3Ig)

IMP321

- A soluble dimeric recombinant form of LAG-3 for the **activation of the APC* network in the body**
- Very stable human protein with **high affinity for dendritic cells/monocytes (i.e. APC)**
- Effectively tested as **chemoimmunotherapy** in several indications
- Extension to other indications possible by coupling with other first-line chemotherapy
- Can also be used at low doses as an **adjuvant to cancer vaccines**

IMP321

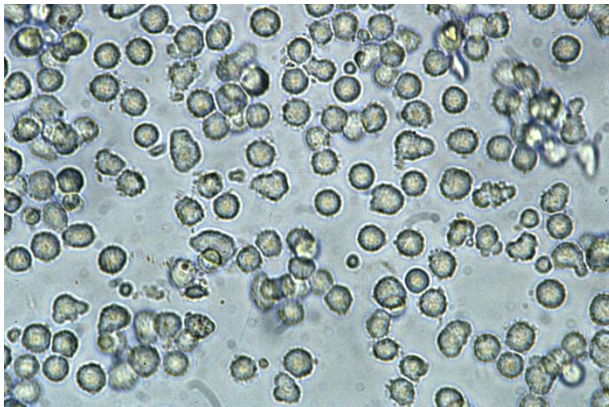
Soluble dimeric recombinant form of LAG-3Ig (fusion protein)



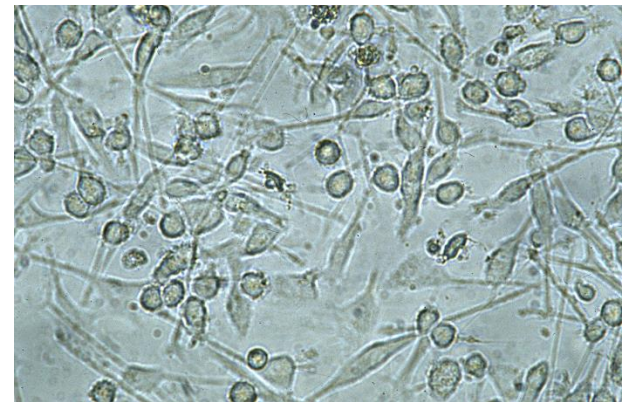
- Highly efficacious in multiple animal models of cancer and infectious disease
- Shown to be safe, non-immunogenic and efficacious in humans
- At low doses can be used as a T cell adjuvant for cancer vaccines

IMP321 (LAG-3Ig) as an MHC class II agonist (primary MoA)

mDC + hlgG1 (negative control), 4 hrs



mDC + 1 µg/ml LAG-3Ig, 4 hrs



Monocyte-derived DC (mDC): human blood monocytes are cultured with GM-CSF + IL-4 for 5 days and are differentiated into immature DC

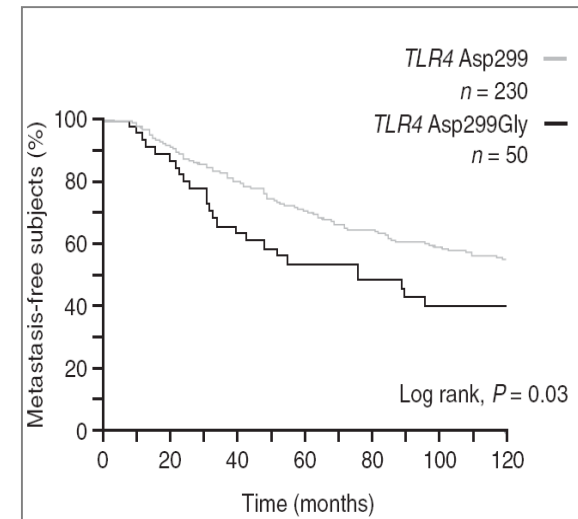
IMP321 Clinical Trials Overview

Protocol	Patient Population	Compound	Status
P001 Phase I	healthy males	IMP321 (adjuvant)	Completed
P002 Phase I	healthy males	IMP321 (adjuvant)	Completed
P003 Phase I	metastatic renal cell carcinoma	IMP321 (monotherapy)	Completed
P005 Phase I	metastatic breast carcinoma	IMP321 (chemo-immunotherapy)	Completed
P006 Phase I/IIa	disease free melanoma	IMP321 (adjuvant)	Completed
P007 Phase I/IIa	metastatic melanoma	IMP321 (adjuvant)	Completed
P008 Phase I/II	advanced pancreatic cancer	IMP321 (chemo-immunotherapy)	Completed
P009 Phase I/IIa	melanoma	IMP321 (adjuvant)	Completed
P010 Phase II	prostate carcinoma	IMP321 (adjuvant)	Completed

Rationale for combining chemotherapy with IMP321 (LAG-3Ig) in breast cancer

A defect on APC function induces a lower response to chemo

TLR4 dictates the efficacy of anti-tumor chemotherapy in humans. Kaplan-Meier estimates of time to metastasis between two groups of patients bearing the normal or mutated TLR4 alleles. The time to progression was analyzed in 280 women with nonmetastatic breast cancer with lymph node involvement who were treated by surgery followed by anthracycline-based chemotherapy and local irradiation.

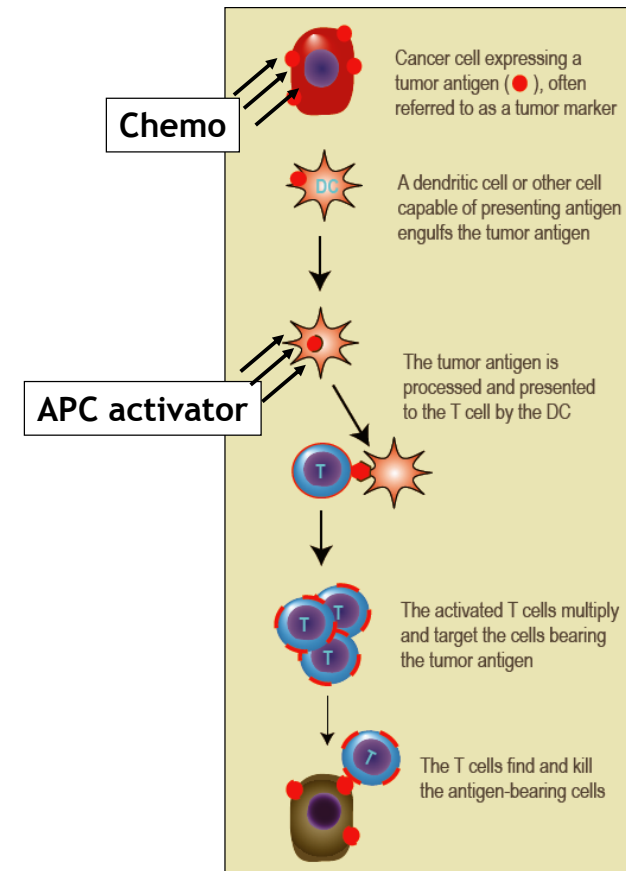


(Nature Medicine 2007, 13:1050-1059)

In breast cancer patients who receive adjuvant chemotherapy, the analysis of metastasis-free survival showed an overall significantly lower percentage of metastasis-free patients in the group with *mutated* TLR4. The effect of the TLR4 mutation is to reduce antigen-presenting cell function. Such patients could not benefit fully from the immunological component of chemotherapy, i.e. the induction of cytotoxic CD8 T cell responses to tumor antigens released by the dying tumor cells.

A new field: combination of chemo with a non-specific (i.e. not a vaccine) active immunotherapy

An APC activator like IMP321 given after chemotherapy induces the APCs to mature and transport the apoptotic cell death tumor antigenic debris to the lymph nodes for presentation to the T cells. Importantly, a concentration of only a few ng/mL of IMP321 has been shown to be active *in vitro* on APCs, showing the great potency of IMP321 as an agonist of the immune system.

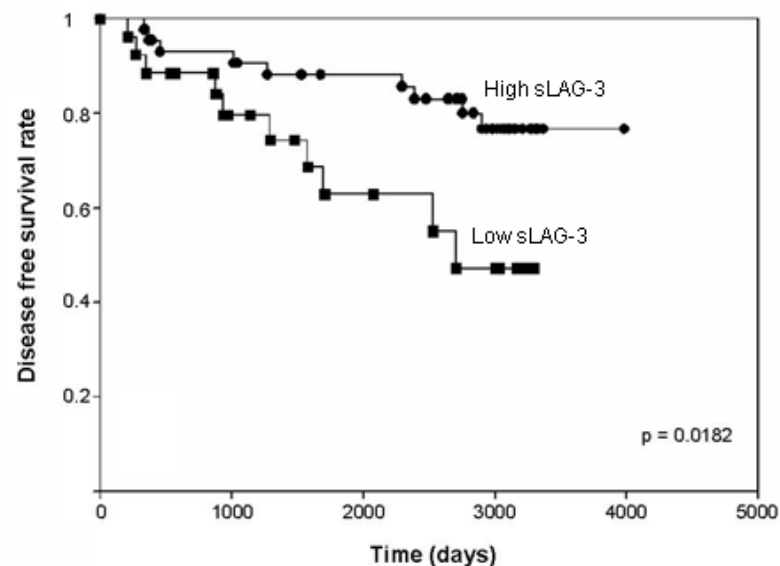


Pre-treatment serum sLAG-3 concentration predicts survival in breast cancer

Survival analysis of patients with breast carcinoma according to pre-treatment serum sLAG-3 concentration. The Kaplan–Meier curves for the duration of disease-free survival according to the concentration level of natural sLAG-3 found in the serum at time of first diagnosis are shown for progesterone receptor positive tumor patients.

Low sLAG-3 (<120 pg/ml), n=26;

High sLAG-3(> 120 pg/ml), n=43.

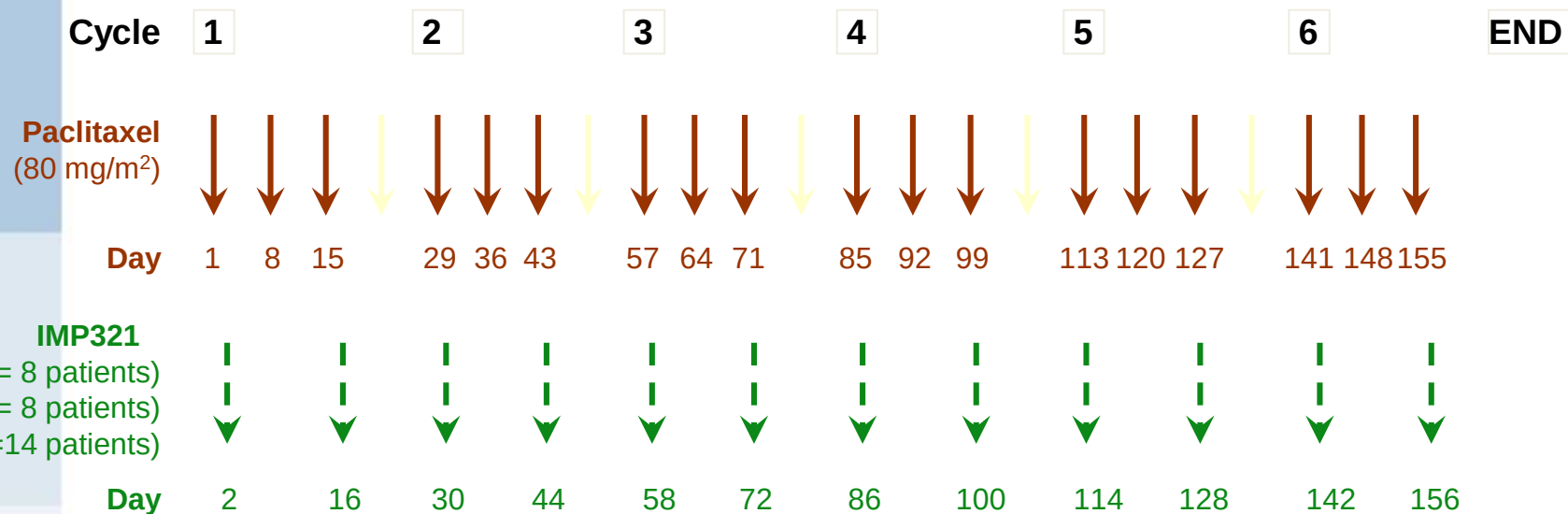


(Cancer Letters 2006, 235:147-153)

Chemo-immunotherapy in MBC

Administration Schedule

- Weekly paclitaxel, 3 weeks out of 4, combined with IMP321 every two weeks, the day after paclitaxel.
- Blood samples drawn before paclitaxel on Days 1 and 85 and at the final visit - testing the *residual effect* of IMP321 13 days after injection.



Blood samples

1

85

170

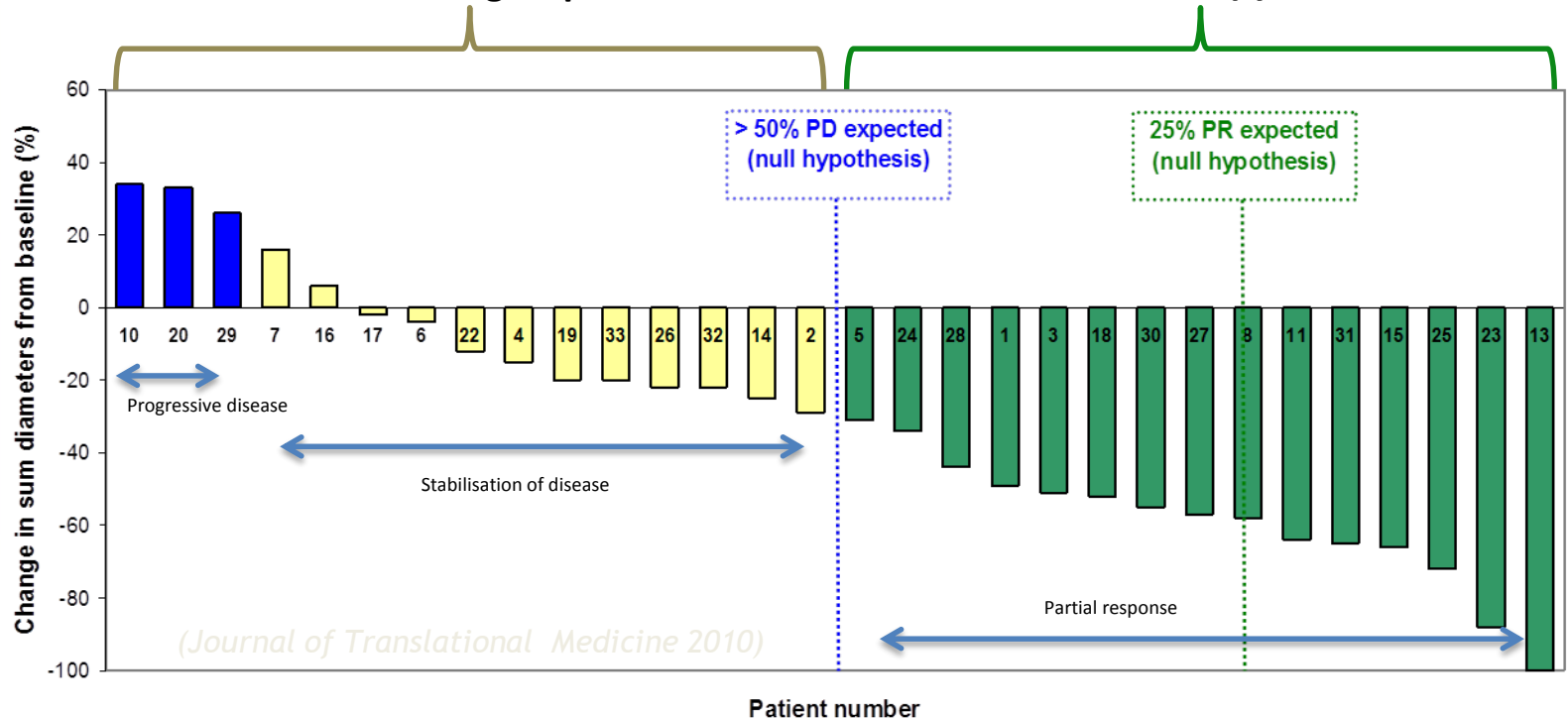
IMP321 Phase IIa Data in Metastatic Breast Cancer (MBC)

Compared to the historical control group

(254 patients with measurable disease at baseline on weekly, 3 weeks out of 4, paclitaxel (ECOG 2100 study)*)

Clinical benefit: Only 10 % of IMP321 patients progressed in contrast to more than 50% of patients in the historical control group

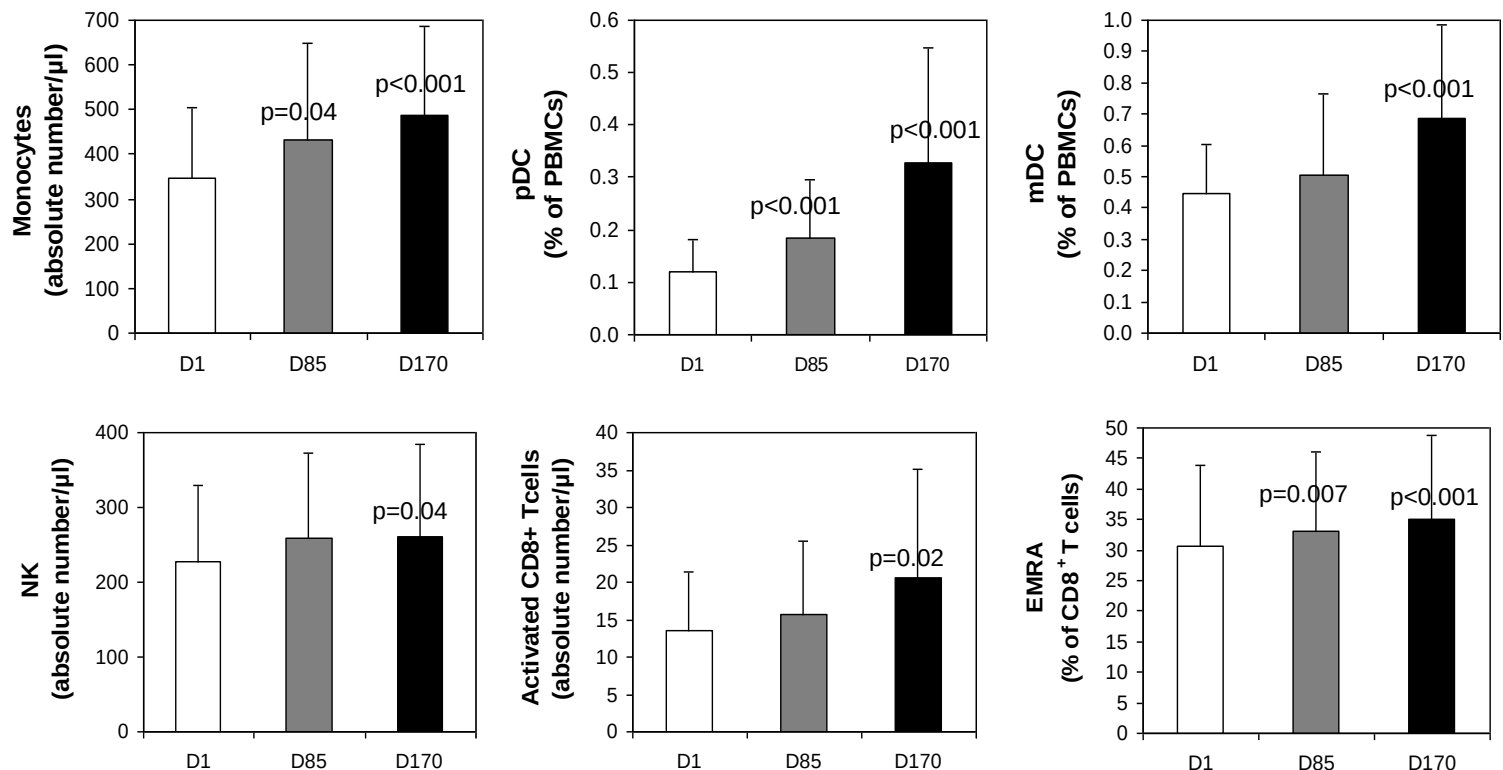
A 50% response rate was observed in IMP321 patients versus 25% in the historical control group receiving chemotherapy alone



*J Clin Oncol. 2009 Oct 20;27(30):4966-72.

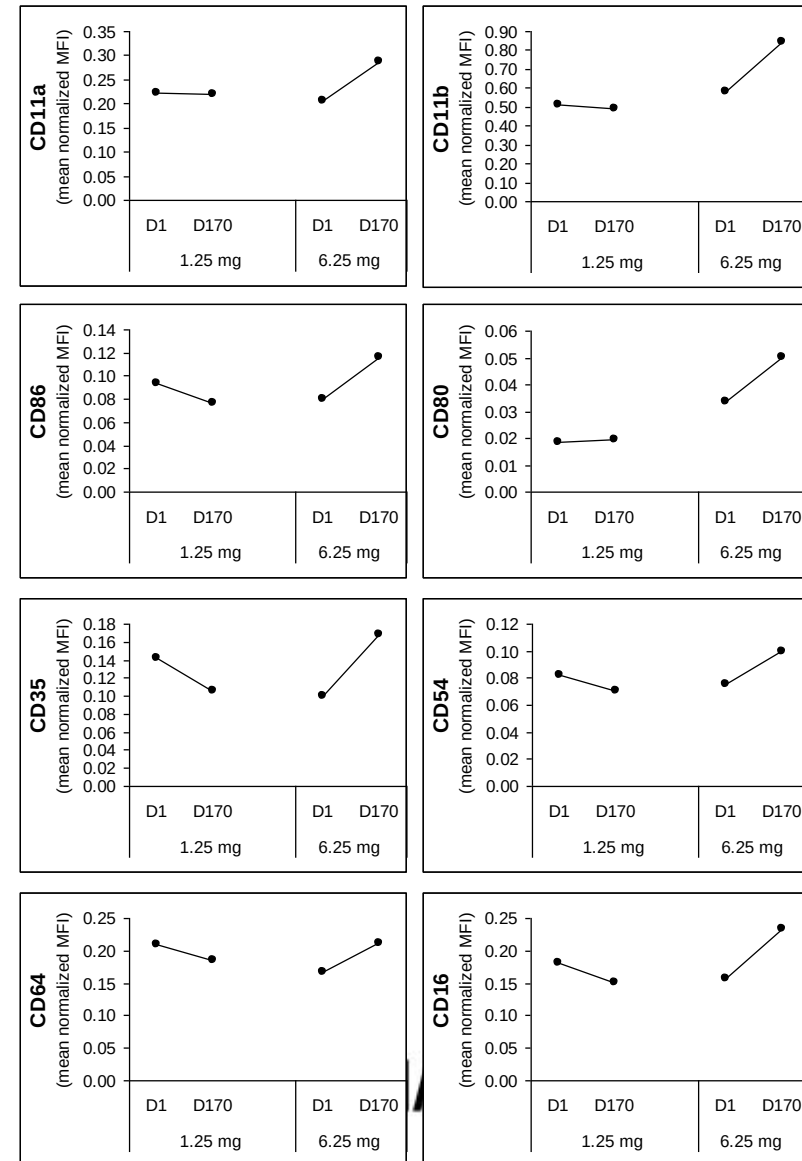
IMP321 induces a sustained increase in primary target cells (MHC class II⁺ monocytes and DC) and secondary target cells (NK and CD8 T cells)

- Increased monocyte, dendritic cell, NK and memory CD8 T cell counts
- Sustained for at least six months as samples are analyzed 13 days after the last injection (i.e. just before the next IMP321 injection)



Activation of monocytes by IMP321: all markers are up

- 8 activation markers analyzed on fresh CD14⁺ whole blood cells: CD11a, CD11b, CD16, CD35, CD54, CD64, CD80 and CD86
- IMP321 dose-response activation of residual monocyte responses at day 13 post-injection in all 8 cases (D170 versus D1)
- Activation sustained for months as samples are analyzed 13 days after the last injection (i.e. just before the next IMP321 injection)



AIPAC

Active Immunotherapy PAClitaxel

AIPAC – Overall Study Design

Title

AIPAC (Active Immunotherapy PAClitaxel): A multicentre, Phase IIb, randomised, double blind, placebo-controlled study in hormone receptor-positive metastatic breast carcinoma patients receiving IMP321 (LAG-3Ig fusion protein) or placebo as adjunctive to a standard chemotherapy treatment regimen of paclitaxel.

Design

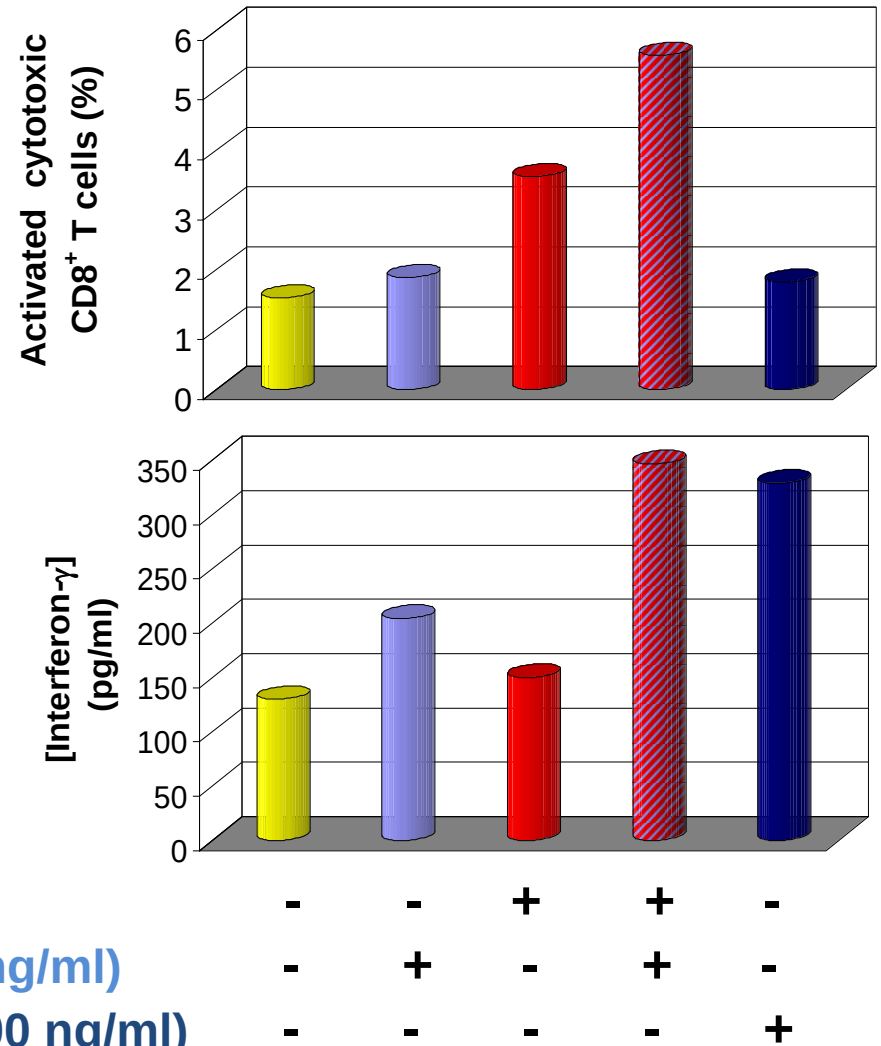
- Open label, dose escalation (run-in stage)
- Randomized, double-blind, placebo-controlled (Phase IIb stage)
- 211 breast cancer patients (stage IV, hormone receptor-positive)
- Paclitaxel + IMP321 vs. paclitaxel + placebo

Rationale for combining IMP321 (LAG-3Ig) with an anti-PD1 blocking mAb

Combining IMP321 with a PD-1 blocking mAb increases CD8⁺ T cells response *in vitro*

Synergy of IMP321 and neutralizing anti-PD-1 antibody on T cell response

PBMCs were stimulated with antigenic peptides in the presence or in the absence of low dose of IMP321 (30 ng/ml) with or without a neutralizing anti-PD-1 antibody at low dose (30 ng/ml) or high dose (1,000 ng/ml). The CD8⁺ T cell response was analyzed by monitoring the expression of activation marker on cell surface or measuring the release of cytokine in the cell supernatant.



IMP321 (30 ng/ml)

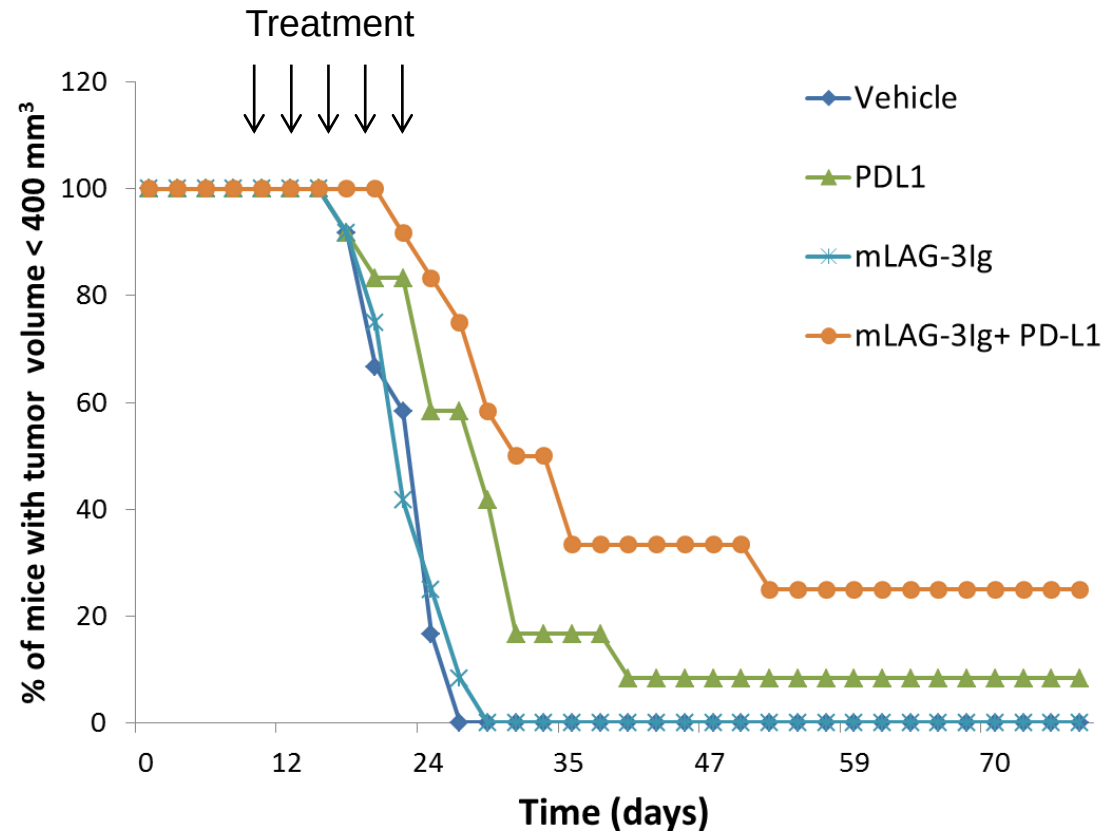
Anti-PD-1 Ab (30 ng/ml)

Anti-PD-1 Ab (1,000 ng/ml)

Combining LAG-3Ig with a PDL-1 blocking mAb helps controlling tumor growth

BALB/c mice were injected s.c. with the CT26 colon carcinoma cell line.

Ten days post tumor implantation, groups of 12 mice were injected with PBS, 10 mg/kg anti-PDL-1 and/or 1 mg/kg mLAG-3Ig, i.p.



TACTI-mel

Two ACTive Immunotherapeutics in melanoma

TACTI-mel – Overall Study Design

- **Title**
- TACTI-mel (Two ACTIVE Immunotherapeutics in melanoma): A multicentre, open label, dose escalation, Phase 1 study in patients with unresectable or metastatic melanoma receiving IMP321 (LAG-3Ig fusion protein) as an adjunctive therapy to anti-PD-1 therapy with pembrolizumab
- **Design**
- Open label, dose escalation
- 24 melanoma patients (unresectable stage III or stage IV)
- Keytruda® + IMP321 at 1, 6 or 30 mg

THANK YOU

A decorative graphic consisting of a grid of colored squares. The top row has five squares: red, red, light gray, light gray, and dark gray. The second row has three squares: red, light gray, and dark gray. The third row has one square: light gray.

Frédéric Triebel, CSO/CMO
Immune Checkpoint Modulation & Combination
Therapies
April 13, 2016
London, UK.