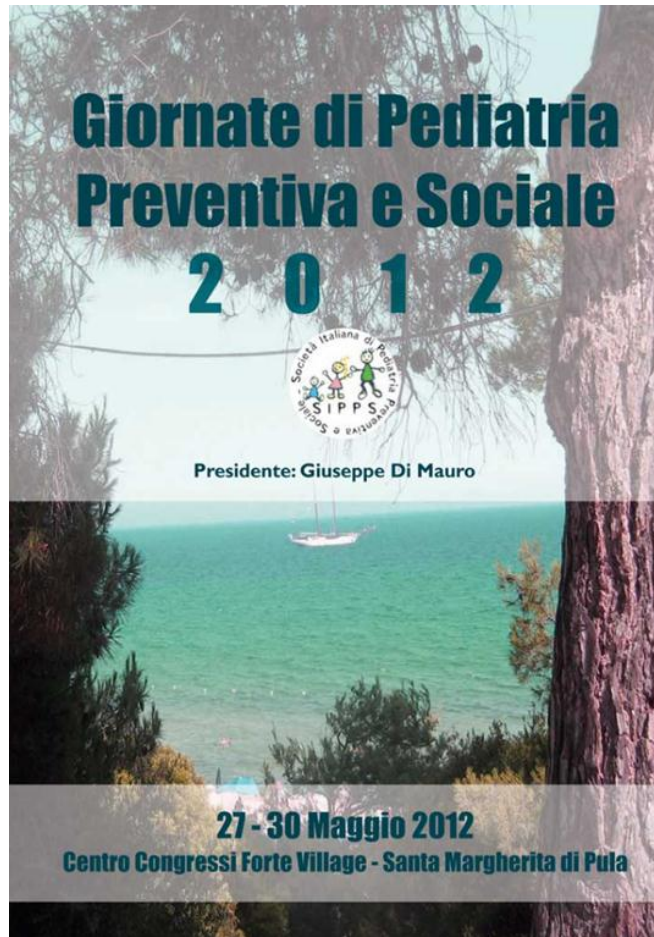


Gli immunomodulanti: il meccanismo d'azione



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*Istituto
Giannina
Gaslini*



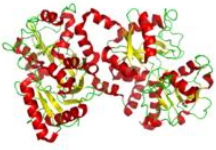
*Fondazione
Gerolamo
Gaslini*



Biological Response Modifiers

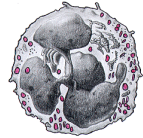
- Prodotti dall'organismo: **Lattoferrina**
- Di derivazione vegetale: **Echinacea, Propoli e Resveratrolo**
- Di derivazione batterica: **Lisati batterici, Frazioni antigeniche, Frazioni ribosomiali e Glicoproteine**
- Di produzione sintetica: **Levamisolo, Isoprinosina e Pidotimod**



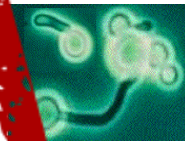


Lattoferrina

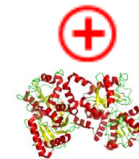
- E' una **proteina** presente nel latte, nel colostro, nelle lacrime e nella saliva ma anche nei **granuli specifici dei neutrofili**



- La sua attività antimicrobica è correlata alla **affinità per il Fe³⁺**: sottraendo Fe³⁺ presente nelle secrezioni mucose, **impedisce la proliferazione** di virus, batteri e funghi



- L'affinità dei suoi domini cationici **(+)** per la superficie cellulare batterica, che ha una carica **(-)**, determina la morte del microrganismo per **citólisi**

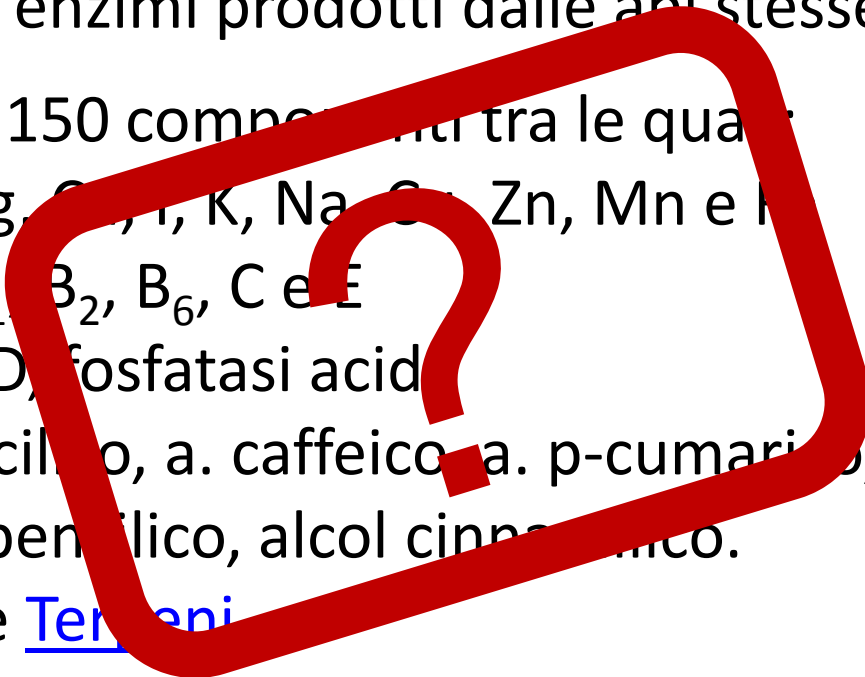


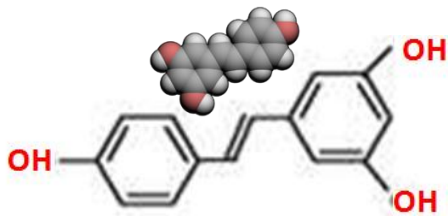


Propoli

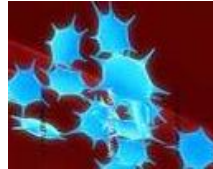


- E' una **sostanza resinosa** che le api raccolgono dalle gemme e dalla corteccia delle piante ed elaborano aggiungendo pollini, cera ed enzimi prodotti dalle api stesse
- Contiene oltre 150 componenti tra le quali:
 - a) **Minerali**: Mg, Ca, P, K, Na, Cu, Zn, Mn e Fe
 - b) **Vitamine**: B₁, B₂, B₆, C e E
 - c) **Enzimi**: G6PD, fosfatasi acide
 - d) **Acidi**: a. salicilico, a. caffeico, a. p-cumarico, a. grassi
 - e) **Alcoli**: alcol benilico, alcol cinnamico
 - f) **Flavonoidi** e **Terpeni**
- La **composizione** della propoli è **variabile** a seconda della zona di origine, della stagione, dell'annata, etc ...





Resveratrolo



- Rinvenuto nella **buccia dell'acino d'uva**, è una delle **fitoalessine** prodotte naturalmente da parecchie piante, in difesa da agenti patogeni quali batteri o funghi
- Possiede proprietà **antiossidanti**, **antinfiammatorie** e **antiaggreganti**, legate alla capacità di bloccare la produzione del **cicloossigenasi-2 (COX-2)**
- Nel corpo umano il resveratrolo viene **eliminato** in brevissimo tempo ma si ha una scarsa conoscenza degli **effetti collaterali** della **somministrazione prolungata** di tale sostanza



Echinacea o “Cone flower”



- L'Echineea è una **pianta** utilizzata anticamente dagli Indiani del Nord America per medicare molte **malattie cutanee** e le **reazioni locali da morso di serpente**
- **La radice** contiene numerose sostanze attive:
 - a) **poliacetileni** e un **glucoside** (l'echinacoside), dotati di un marcato **effetto antibiotico e fungicida**
 - b) **oli essenziali** ad **azione immunostimolante**
- **Le indicazioni cliniche** sono: a) **uso topico** nelle infiammazioni **cutanee** e nelle ferite torpide
b) **uso sistemico** nella profilassi e il trattamento delle **malattie da raffreddamento**



Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children

A Randomized Controlled Trial

James A. Taylor, MD *JAMA*. 2003;290:2824-2830



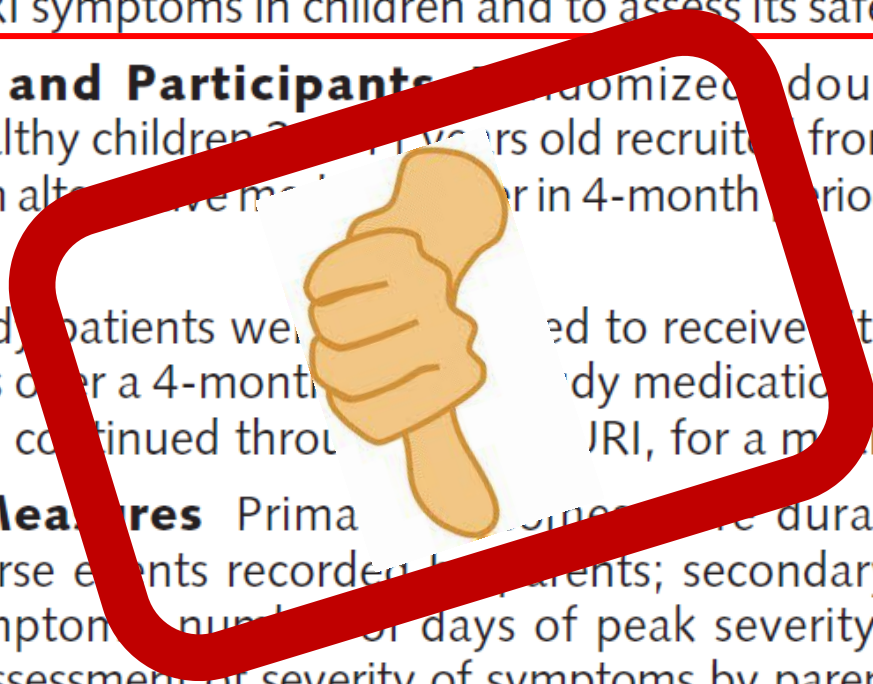
Objectives To determine if *Echinacea purpurea* is effective in reducing the duration and/or severity of URI symptoms in children and to assess its safety in this population.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled trial of healthy children 2 to 11 years old recruited from a regional practice-based network and an alternative medicine center in 4-month periods from 2000 through 2002.

Interventions Study patients were randomized to receive either echinacea or placebo for up to 3 URIs over a 4-month period. No other medication was begun at the onset of symptoms and continued throughout the duration of the URI, for a maximum of 10 days.

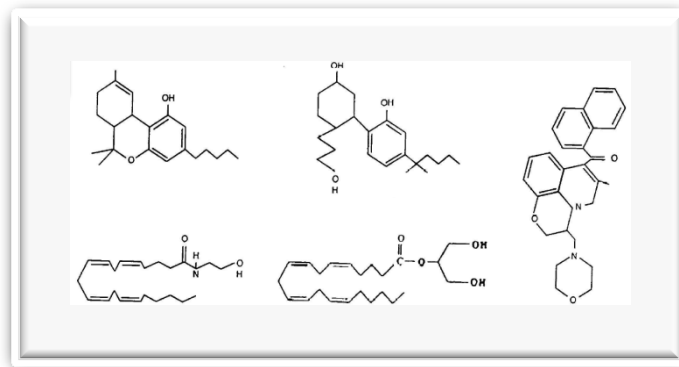
Main Outcome Measures Primary outcomes were the duration and severity of symptoms and adverse events recorded by parents; secondary outcomes included peak severity of symptoms, number of days of peak severity, number of days of fever, and a global assessment of severity of symptoms by parents of study children.

Conclusions *Echinacea purpurea*, as dosed in this study, was not effective in treating URI symptoms in patients 2 to 11 years old, and its use was associated with an increased risk of rash.



Major immunostimulant categories commonly used in childhood recurrent respiratory infections

- Bacterial extracts



- Synthetic chemical compounds

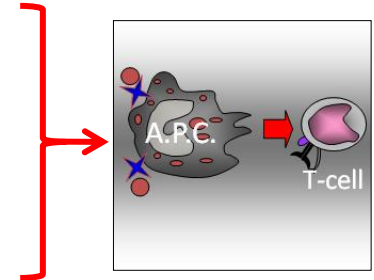
Oral bacterial extracts: mechanisms of action

Bacterial extracts

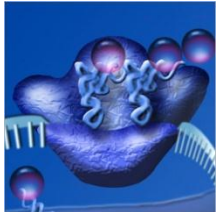


LW50029
IRS-19
OM-85 BV
Bronchovaxom
Lantigen B

Induces **lymphocyte proliferation** in MALT
Increases **IFN synthesis**
Enhances **Th1 immune response**
Increases **secretory IgA synthesis**
Activates **macrophages and NK cells**

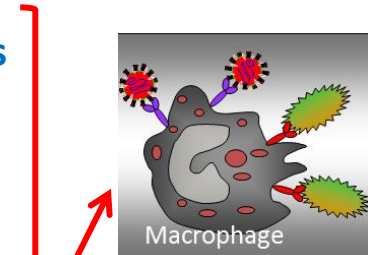


Ribosomal extract

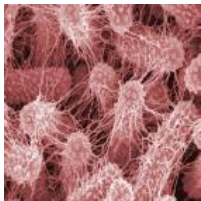


D53
Immucyral

Increases Fc- receptor dependent **phagocytosis**
Enhances the **oxidative metabolism**
Inhibits of **PMN migration**

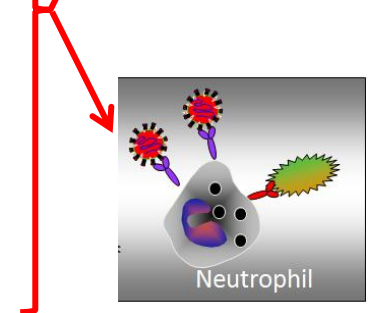


Glycoprotein

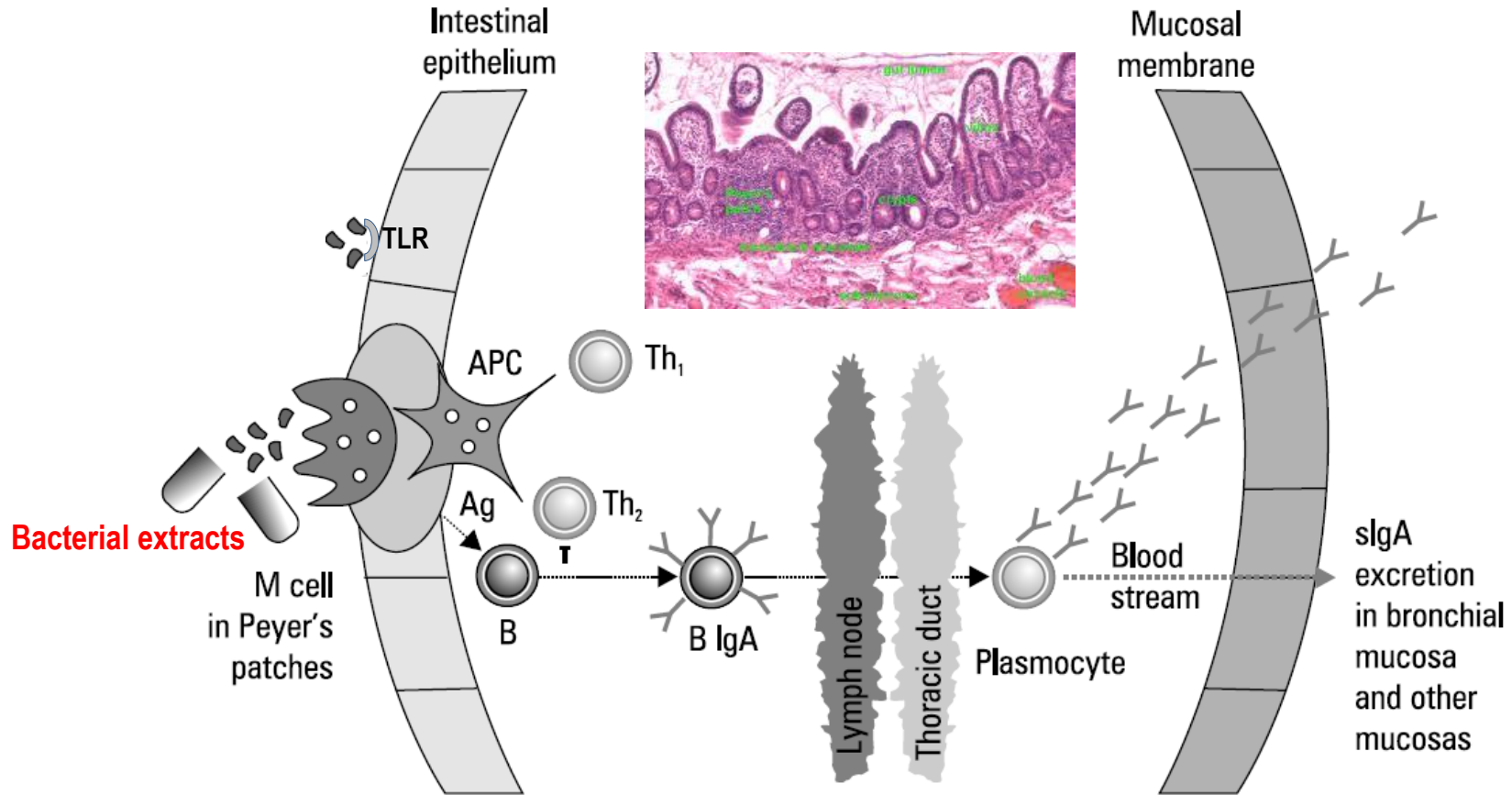


RU41740
K. pneumoniae
Biostim

Increases complement- and Fc receptor-
dependent **phagocytosis**
Enhances the **oxidative metabolism**
Does not affect neutrophil migration



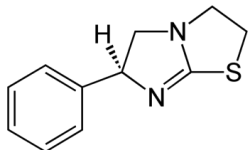
Activity of the oral bacterial extracts



Synthetic immunostimulants: mechanisms of action

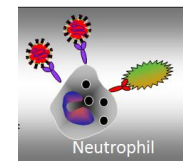
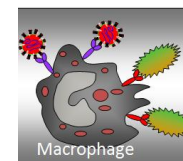
Levamisole

A compound belonging to imidazothiazole derivatives



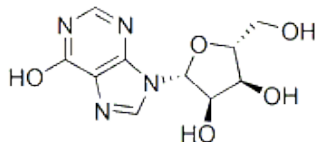
Stimulates T-lymphocytes
Restores the phagocytic activity of macrophages and PMNs

Withdrawn from the market due to the risk of serious side effects



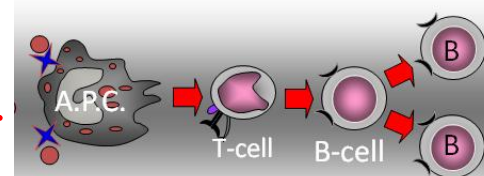
Isoprinosine

A nucleoside precursor to adenosine



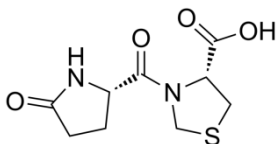
An **energy** molecule, participating in O_2 metabolism and protein synthesis

Stimulates **macrophage** activity
Stimulates **T- and B-cell** proliferation and maturation

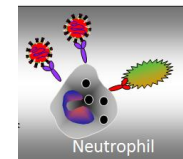
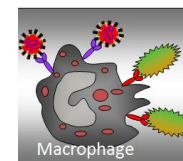


Pidotimod

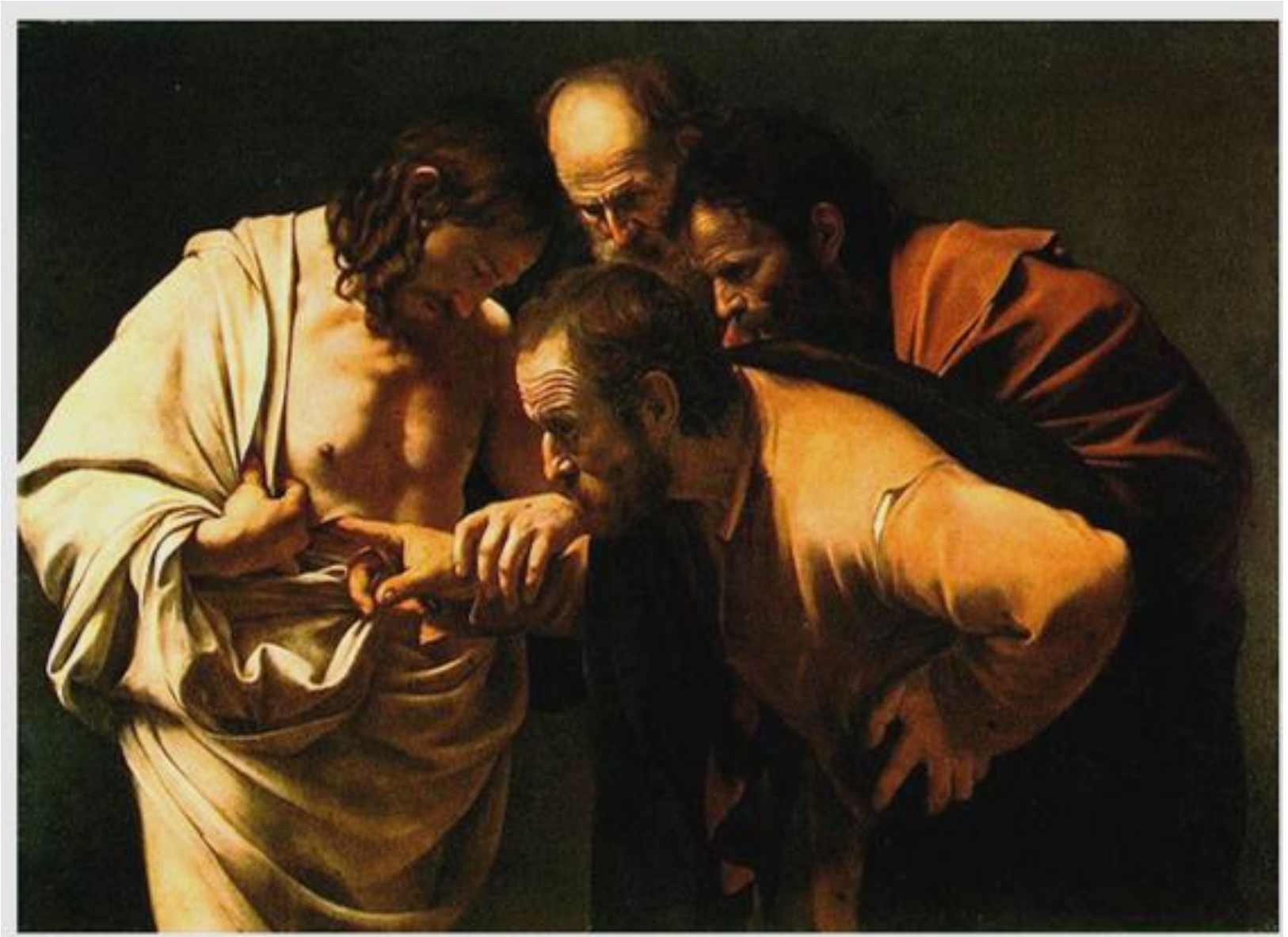
1,3-thiazolidine-4-carboxylic acid



Synthetic dipeptide active on both the **adaptive** and the **innate** immune responses



Biological response modifiers



Caravaggio. L'incredulità di San Tommaso



Immunostimulants for preventing respiratory tract infection in children

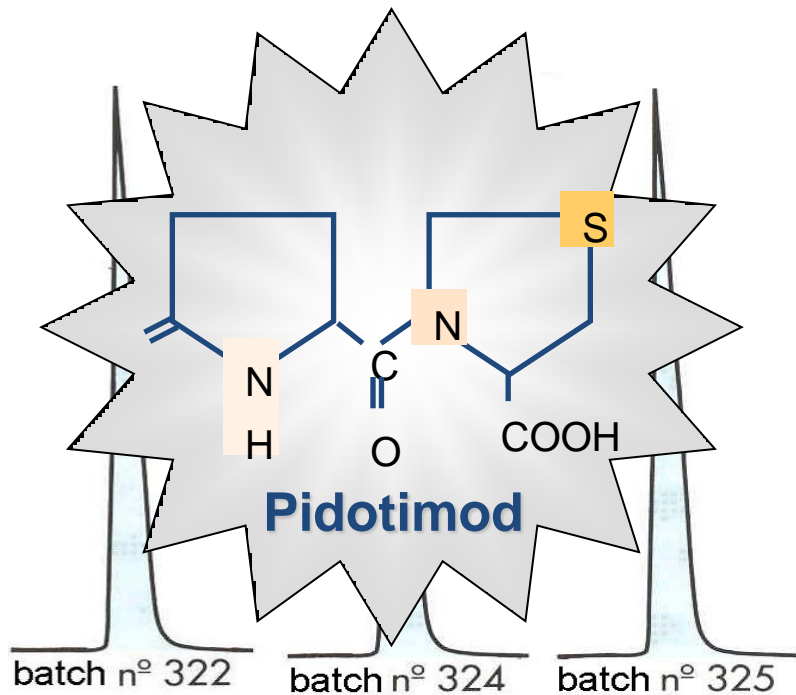
Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JLL
The Cochrane Library 2008, Issue 4, 1-65

- **Objectives.** To determine the **efficacy** and **safety** of **immunostimulants** in preventing *acute respiratory tract infections* (ARTIs) **in children**
- **Conclusions.** This review showed that **immunostimulants** *reduce* the incidence of *ARTIs* in children, *by 40%* on average
- The safety profile of **immunostimulants** appears to be good
- This positive result should be interpreted *with caution* due to the **heterogeneity** and the **poor quality** of the trials

Immunos-timulant	n	n analysis data	Duration < 6 months	Duration 6 months	Duration > 6 months	Quality A	Quality B	Quality C	Quality D
D53	16	11	7	9	-	-	16	-	-
IRS19	1	0	-	1	-	-	-	1	-
Lantigen B	2	0	-	2	-	-	2	-	-
LW50020	2	0	2	-	-	-	2	-	-
<u>OM-85 BV</u>	12	8	-	10	2	4	8	-	-
RU41740	5	5	-	3	2	-	5	-	-
Total bacterial	38	24	9	25	4	4	33	1	-

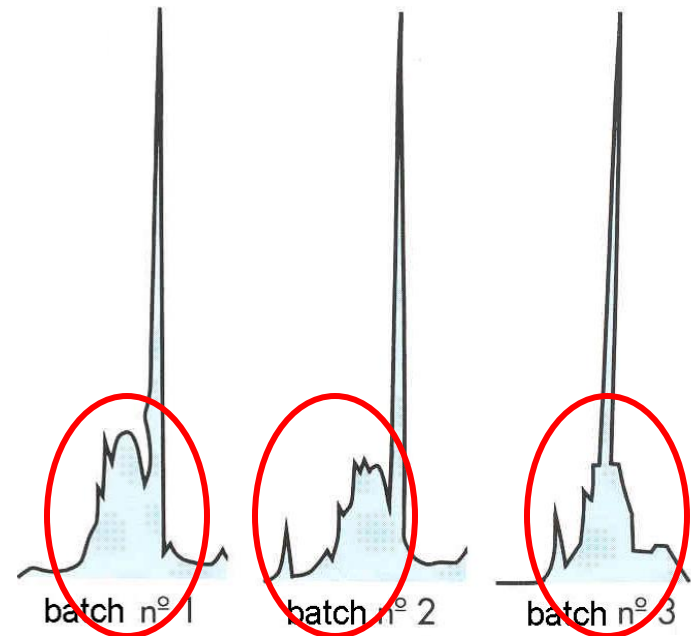
The synthetic route assures **purity** and **reproducibility** of production process

Pidotimod



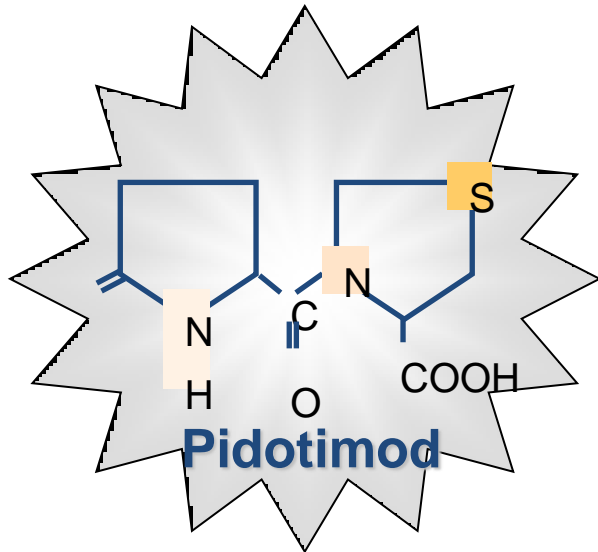
The spectrum of the different batches looks always the same

Bacterial extracts

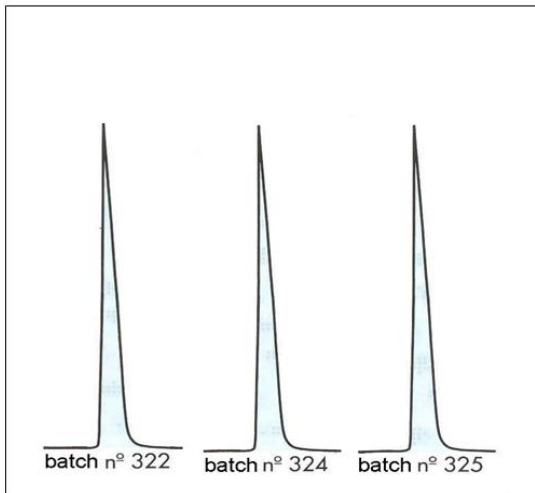


The same does not occur with bacterial extracts

Questions

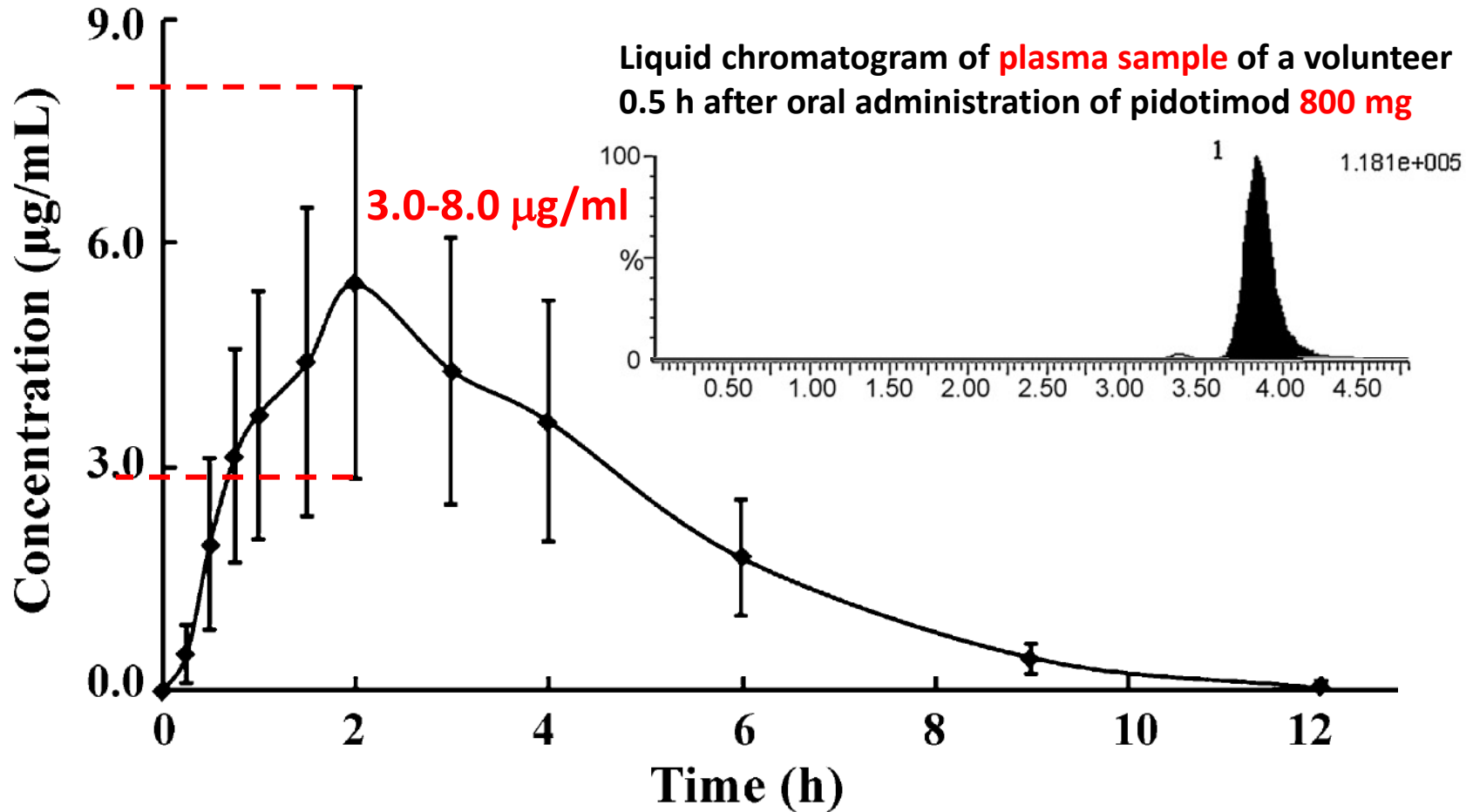


- Is biodegradation occurring in GE tract?
- Do we have convincing *in vitro* and experimental animal studies
- Which new studies are needed?



The spectrum of the different batches looks always the same

Mean plasma concentration–time curve of pidotimod in 20 male volunteers after a single 800 mg oral dose of pidotimod

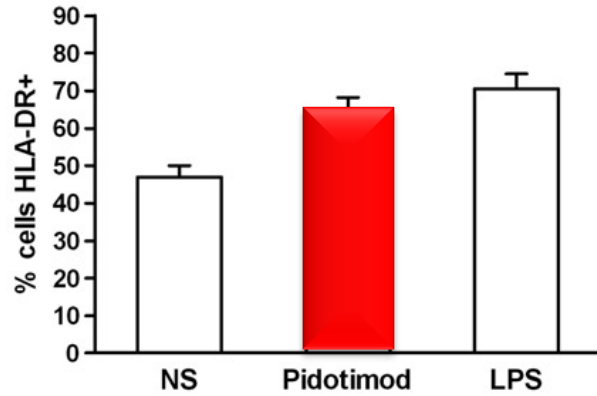


Human dendritic cell activation induced by exposure to Pidotimod (1 $\mu\text{g}/\text{ml}$)

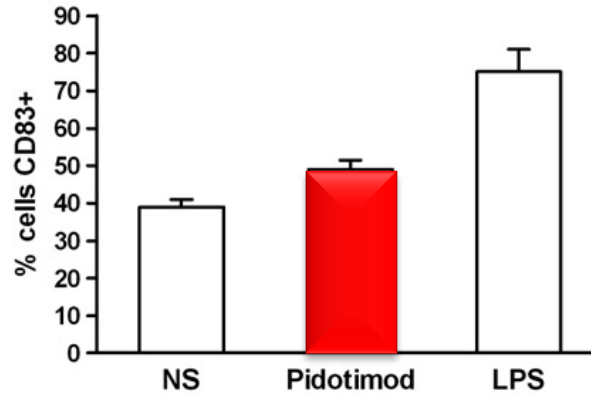


A.P.C.

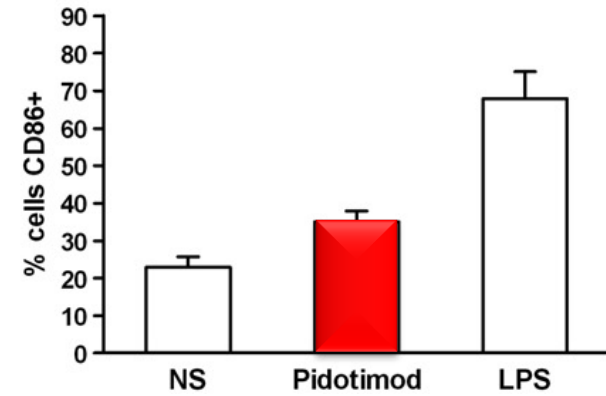
HLA-DR



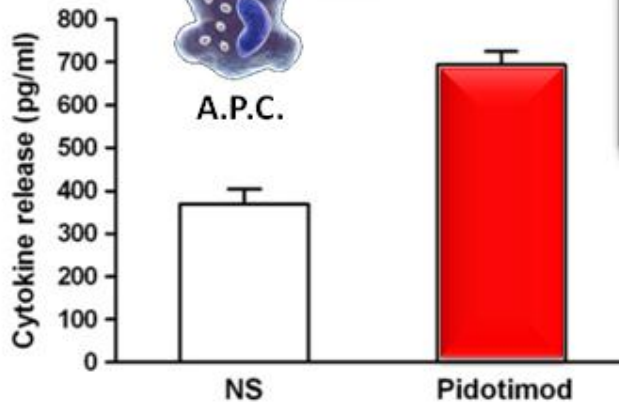
CD83



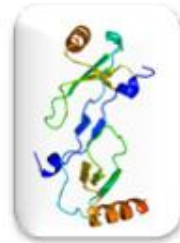
CD86



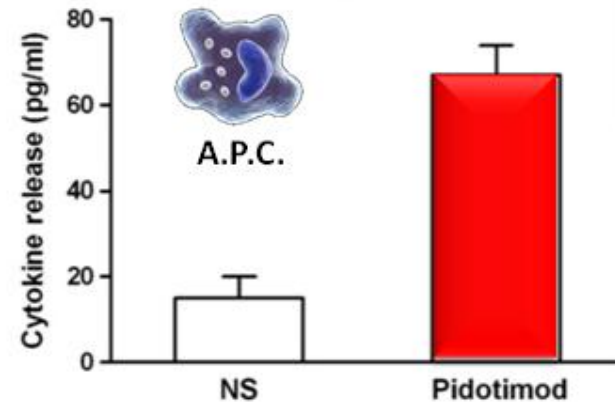
MCP-1



A.P.C.



TNF- α



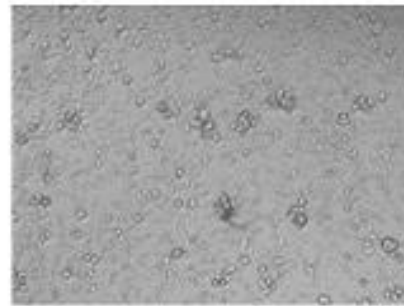
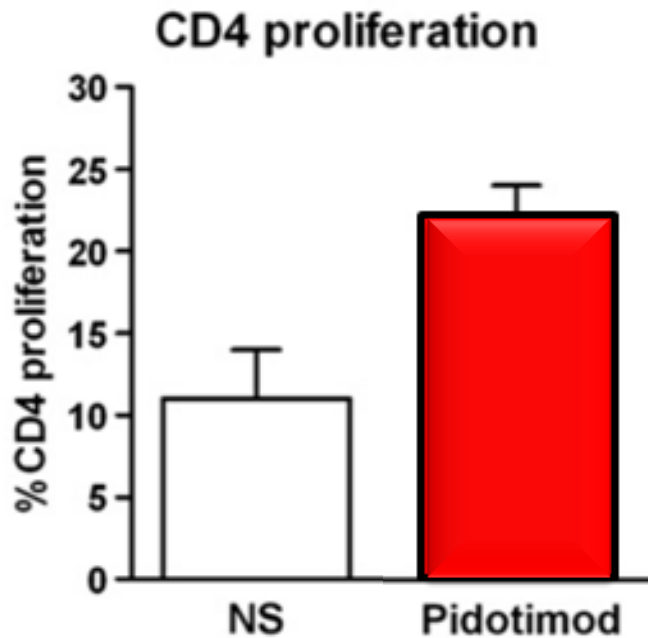
A.P.C.



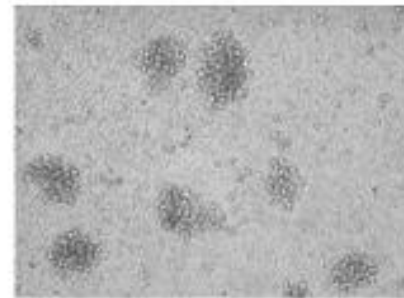
Human CD4 T-cell activation induced by exposure to Pidotimod (1 $\mu\text{g}/\text{ml}$)



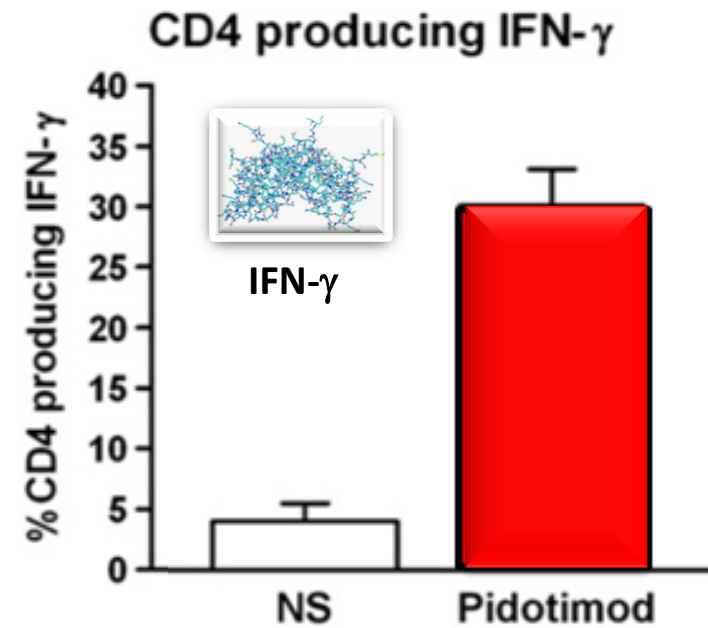
T-cells



NS



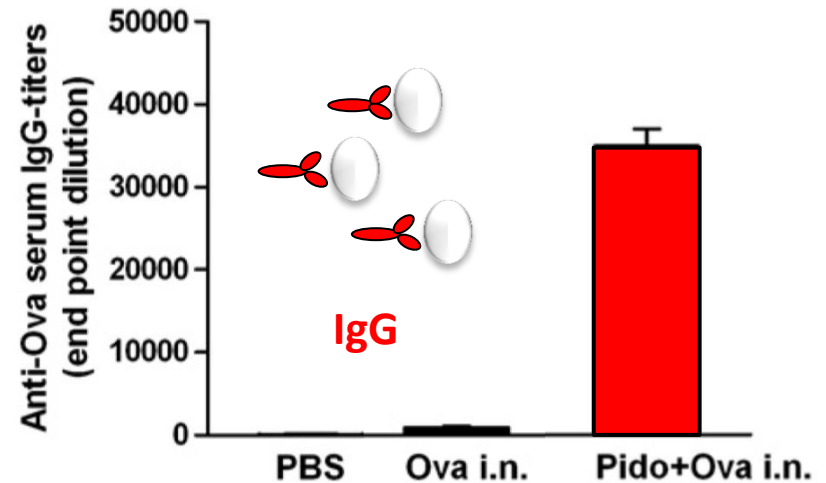
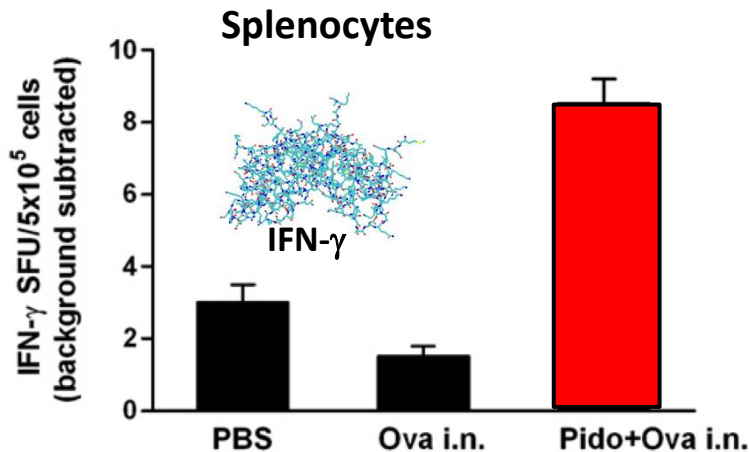
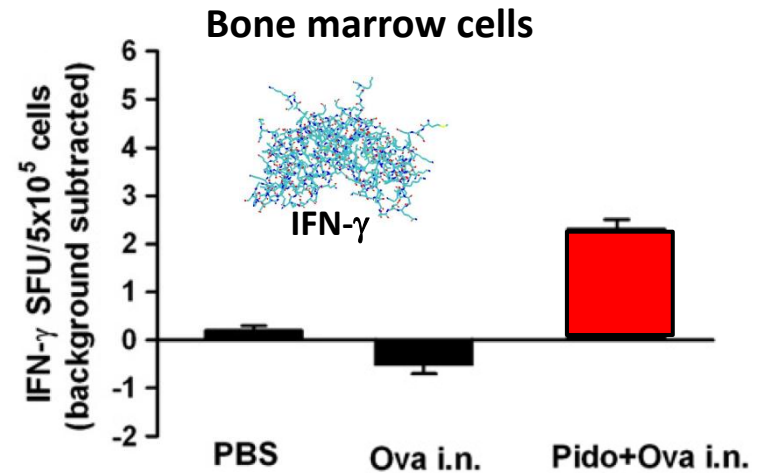
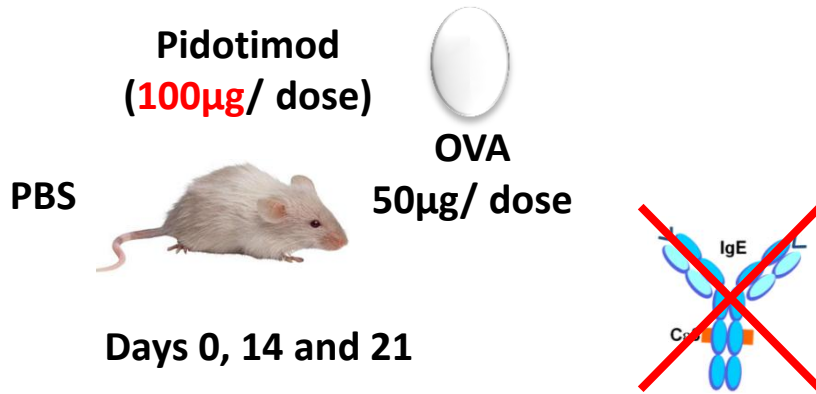
Pidotimod



IFN- γ



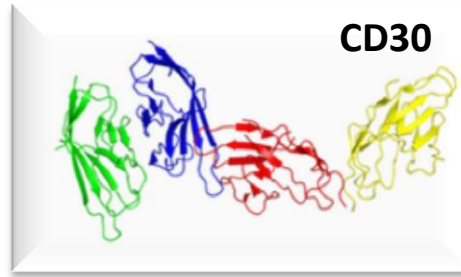
Intranasal immunization with Pidotimod increases IFN- γ production by splenocytes and bone marrow B-cells and OVA-specific IgG production



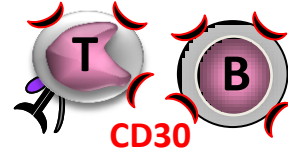
Critical role of the CD30 co-stimulatory molecule in the development of allergic asthma



OVA

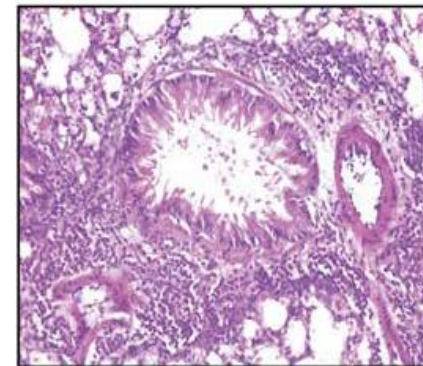
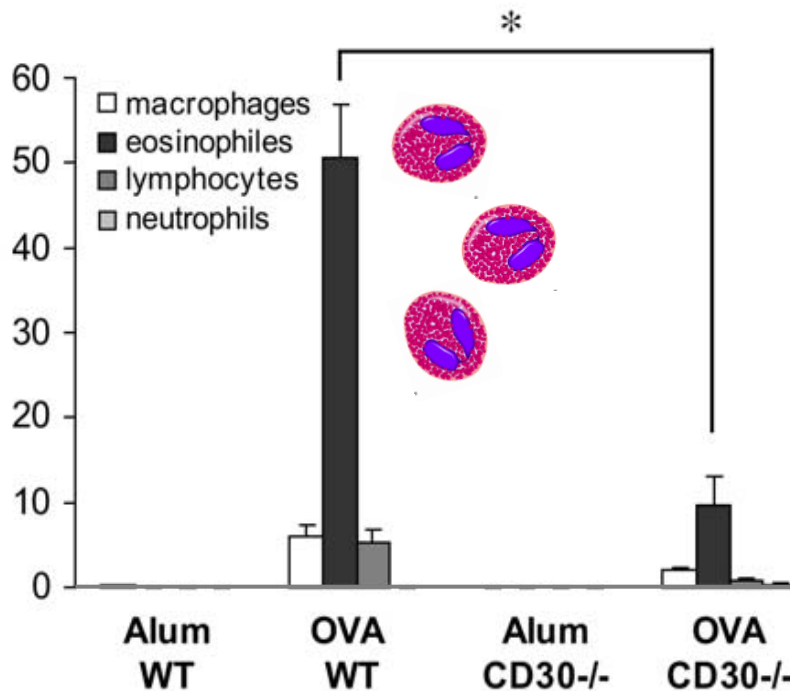


CD30

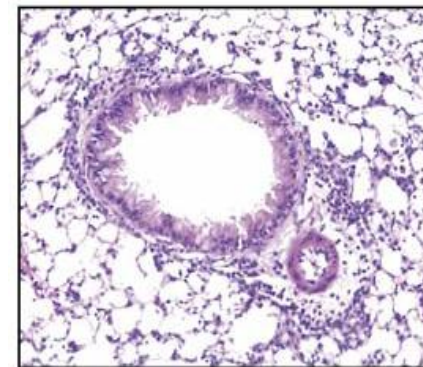


CD30

total cells/ml in BAL fluid ($\times 10^4$)



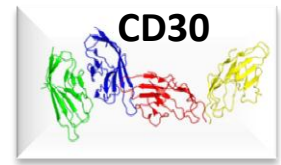
OVA WT



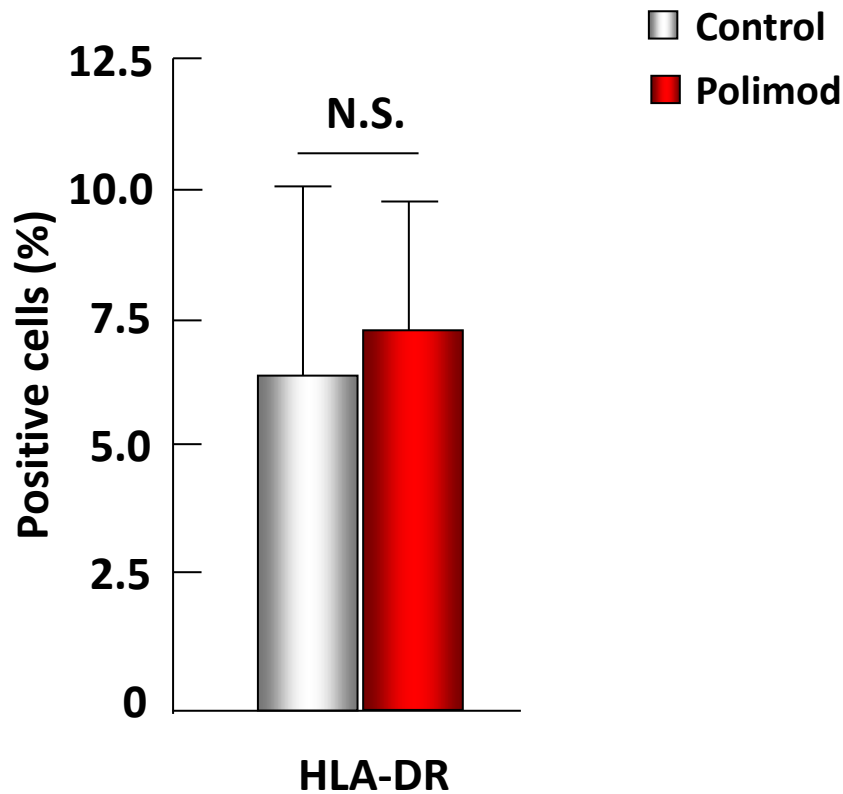
OVA CD30^{-/-}



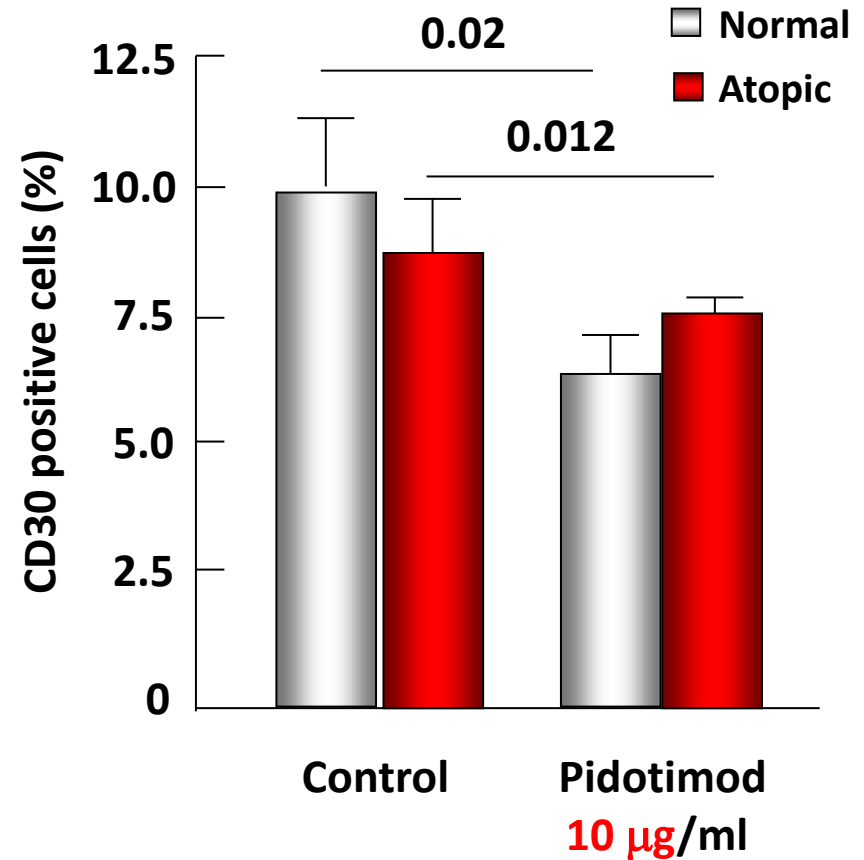
Pidotimod ($10 \mu\text{g/ml}$) decreases the *in vitro* the PHA-induced expression of CD30 in peripheral blood mononuclear cells of atopic asthmatic and normal children



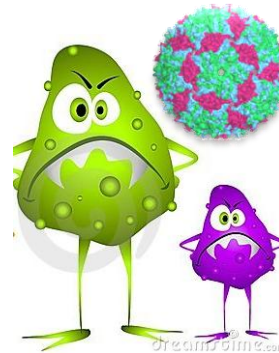
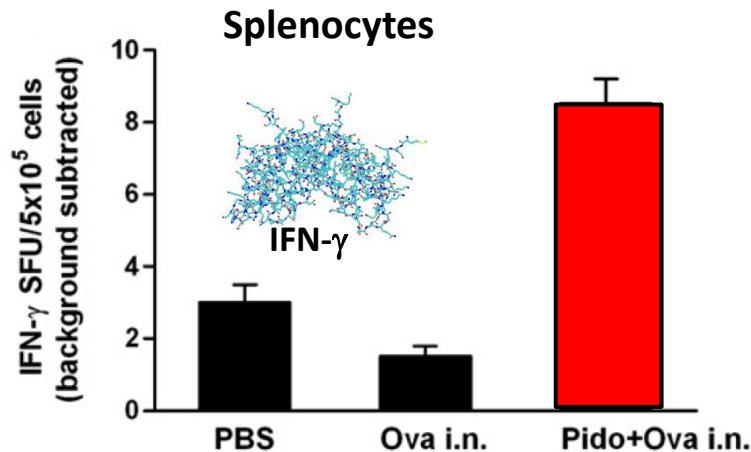
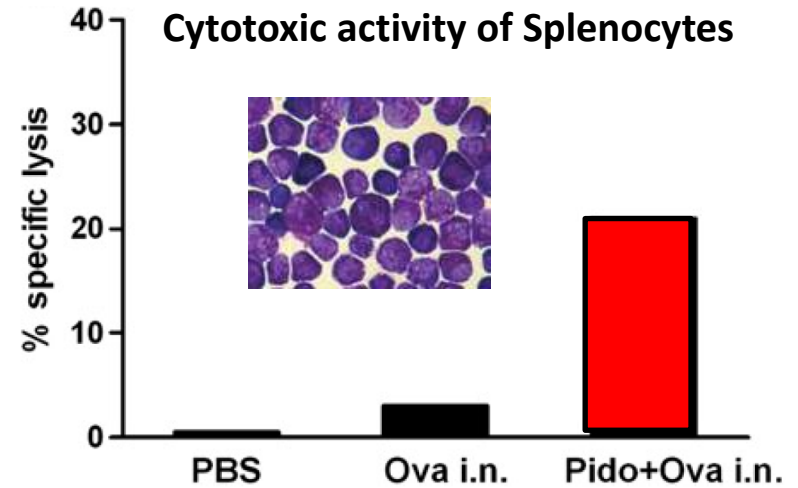
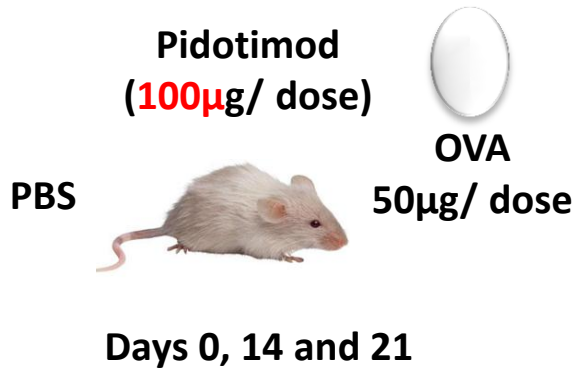
A. HLA-DR+ & CD-30+ cells



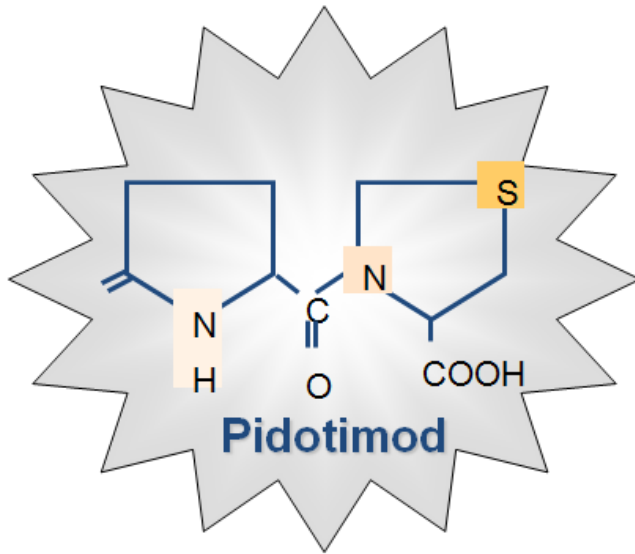
B. CD-30+ cells



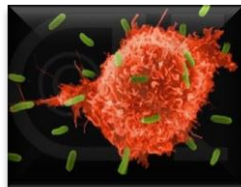
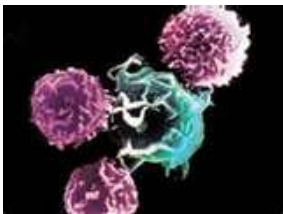
The enhanced IFN- γ production induced by intranasal immunization with Pidotimod increases the cytotoxic activity of splenocytes



Which kind of new information is needed ?



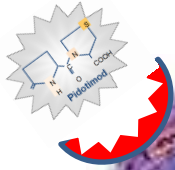
**Innate - Adaptive
Immune System**



**Intracellular pathways
involved**

Possible intracellular signaling pathways involved in pidotimod actions

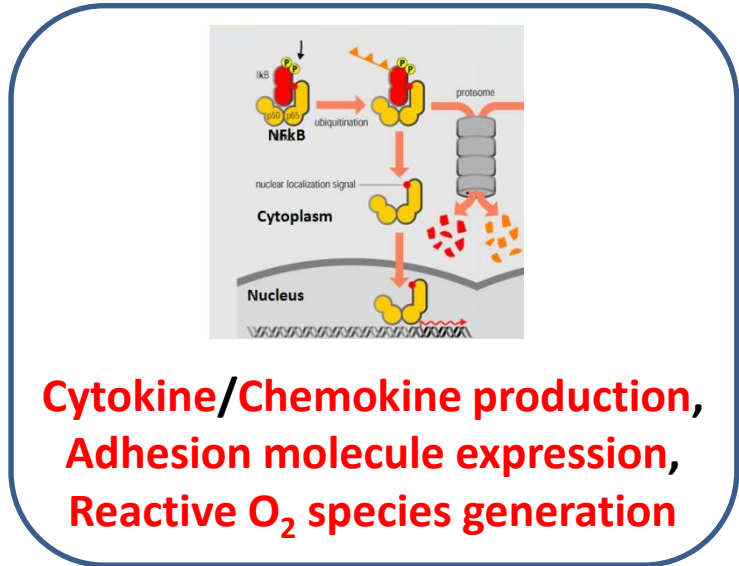
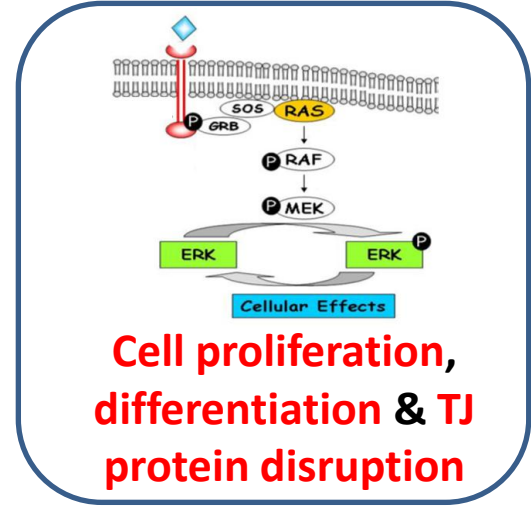
Surface or Cytoplasmic Receptor



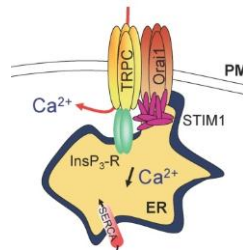
MAPK extracellular signal-regulated kinase (ERK)-1/2 phosphorylation

Nuclear Factor- κ B activation

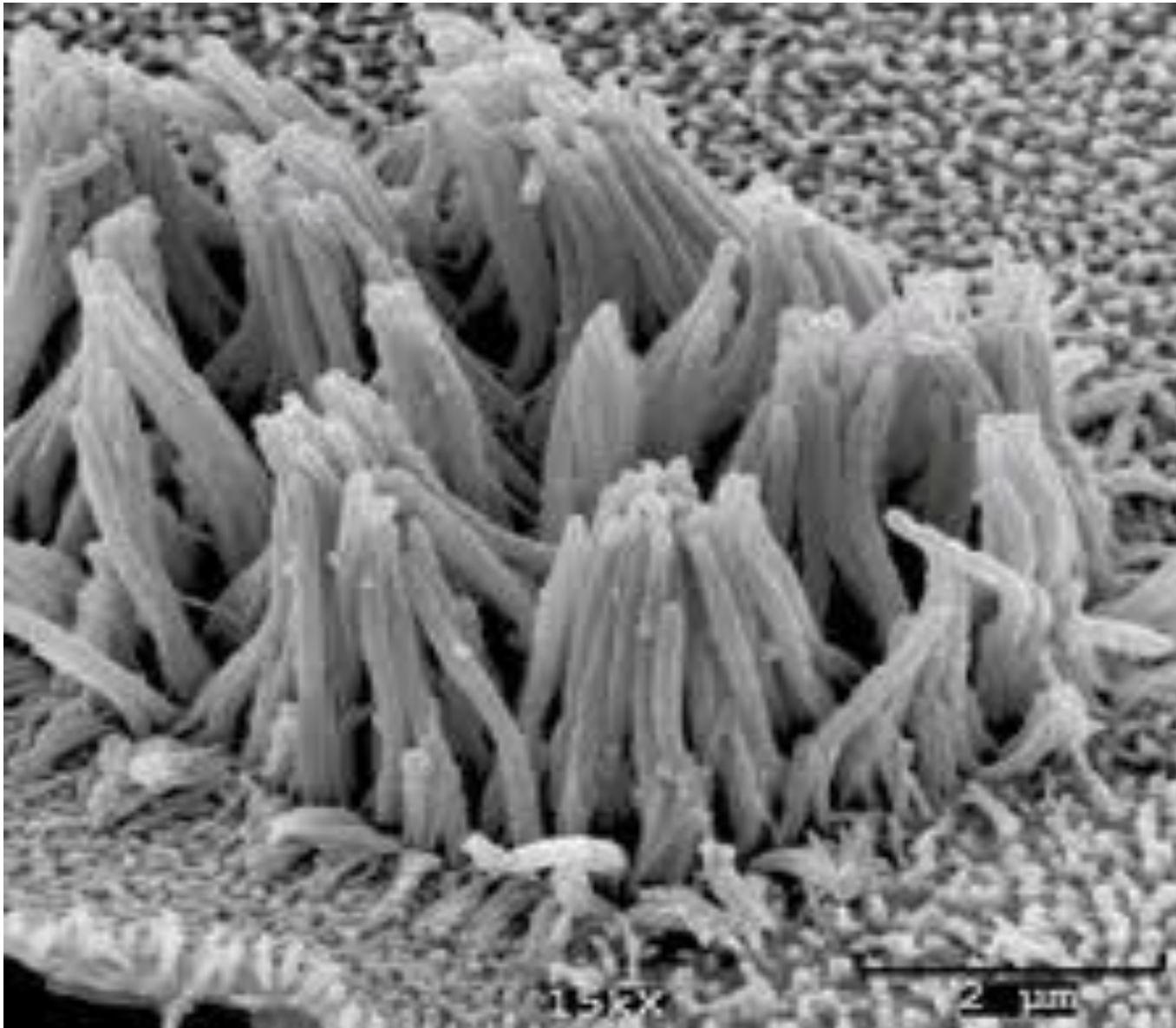
Calcium (Ca^{2+}) mobilization



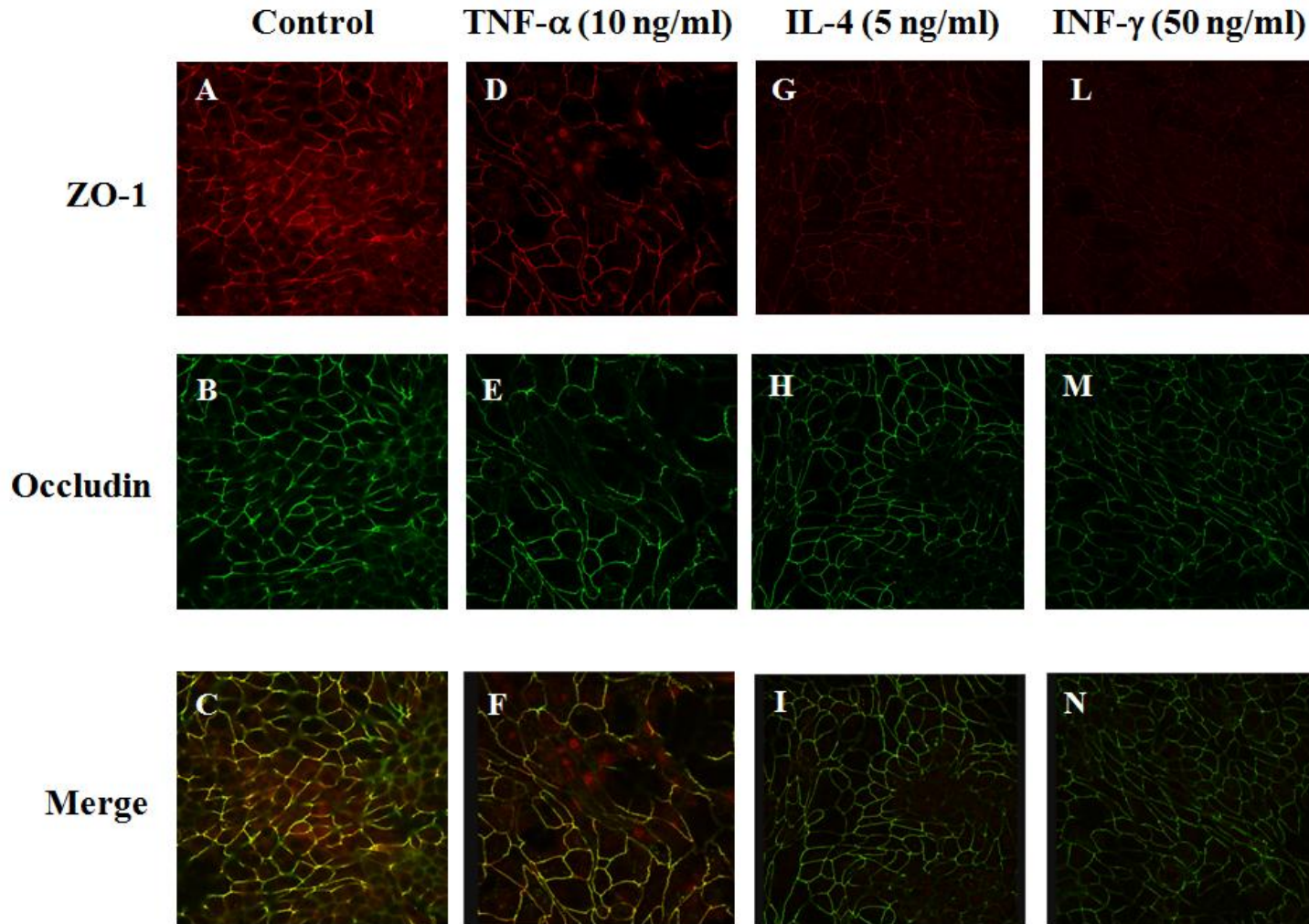
Proliferation, Differentiation, Activation & Reactive O_2 species generation



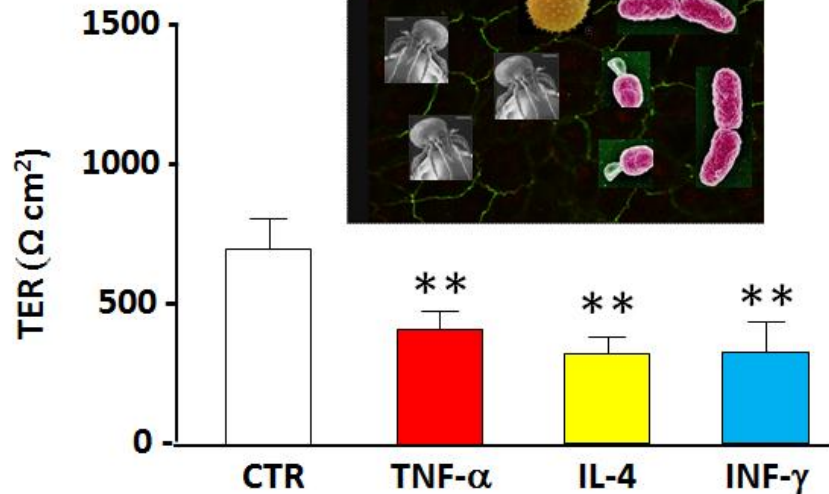
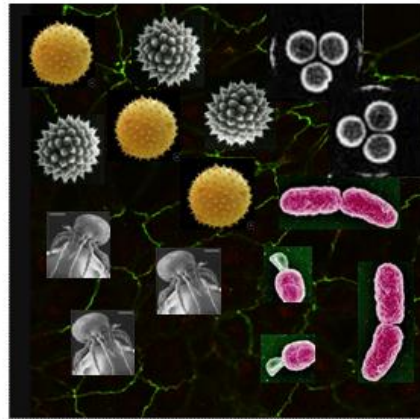
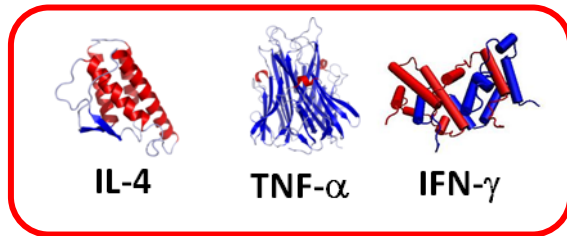
The first preliminary answer from HBECs ?



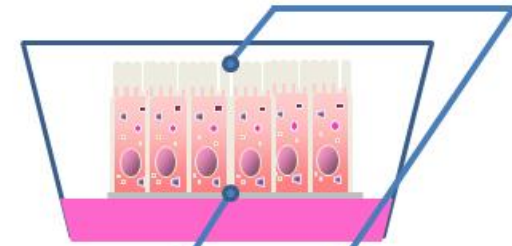
Pro-inflammatory cytokines disrupt airway epithelial tight junctions Occludin and ZO-1



Cytokine-induced T. J. disruption is associated with reduction of airway epithelial barrier integrity



Transmembrane electrical resistance (TER)

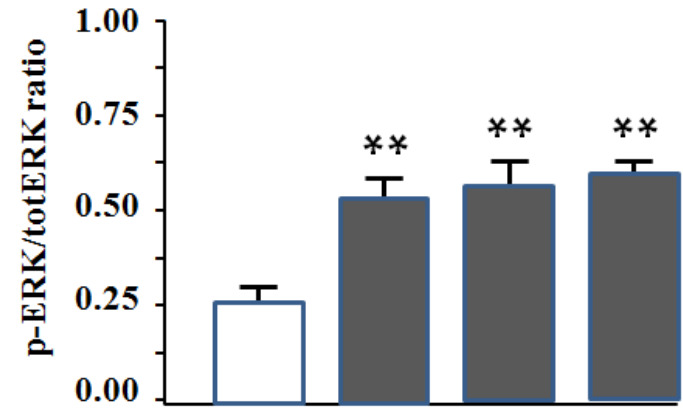
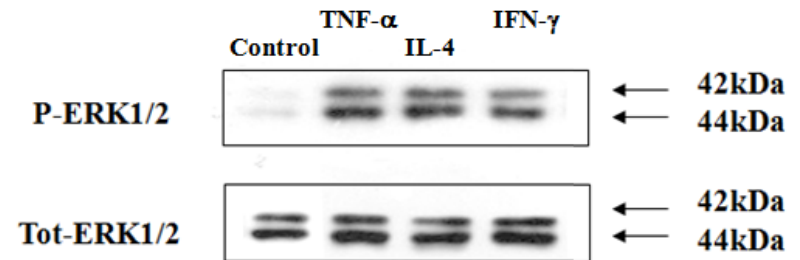
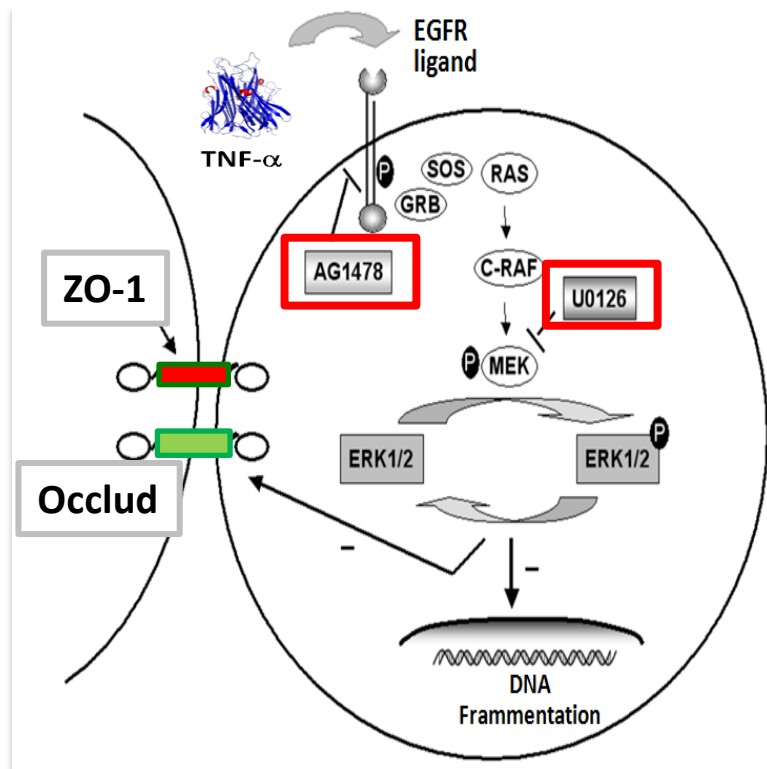


Voltmeter

Used for measuring the differences in electrical potential between two points in an electric circuit



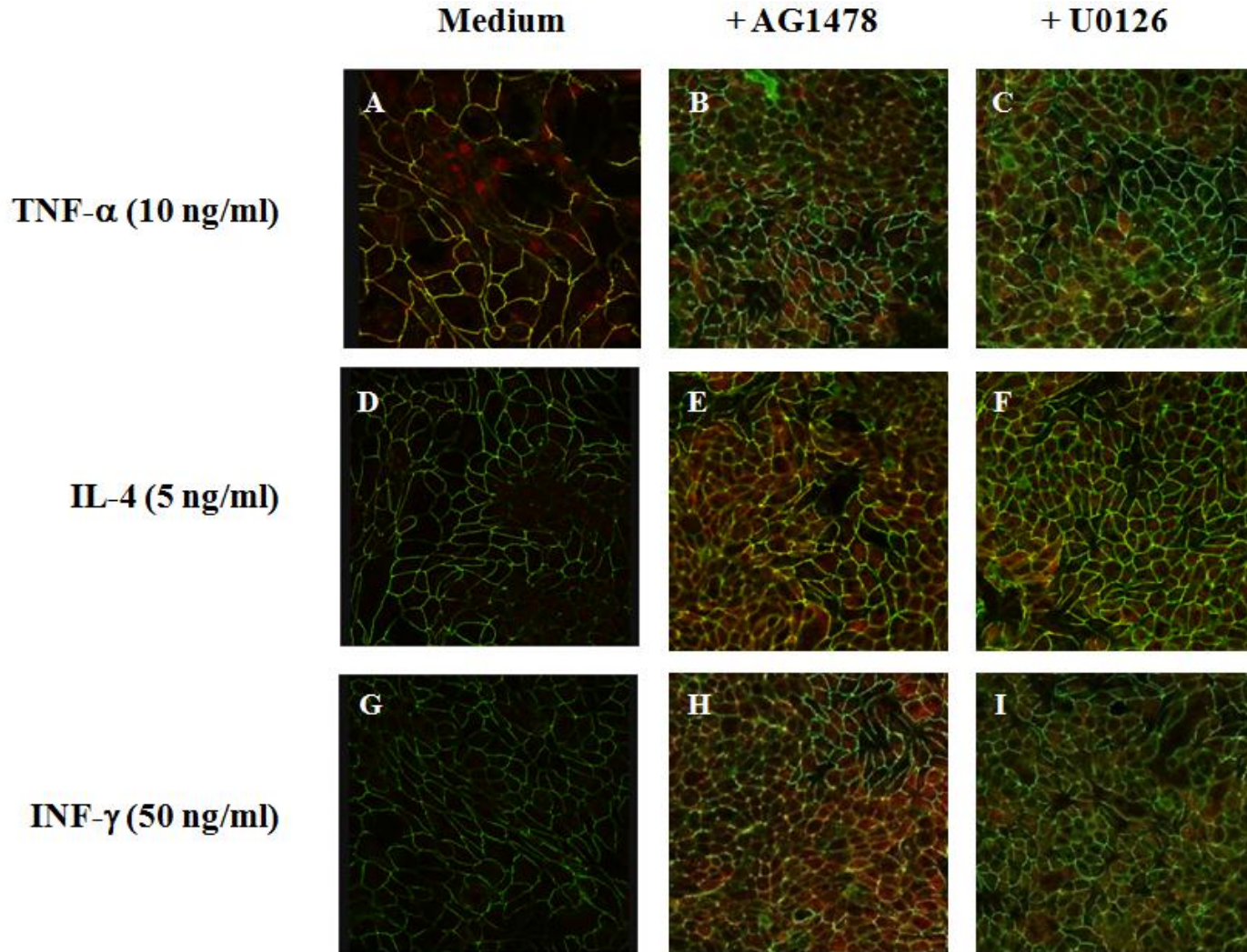
Inhibition of ERK-1 phosphorylation prevents cytokine-induced T. J. disruption



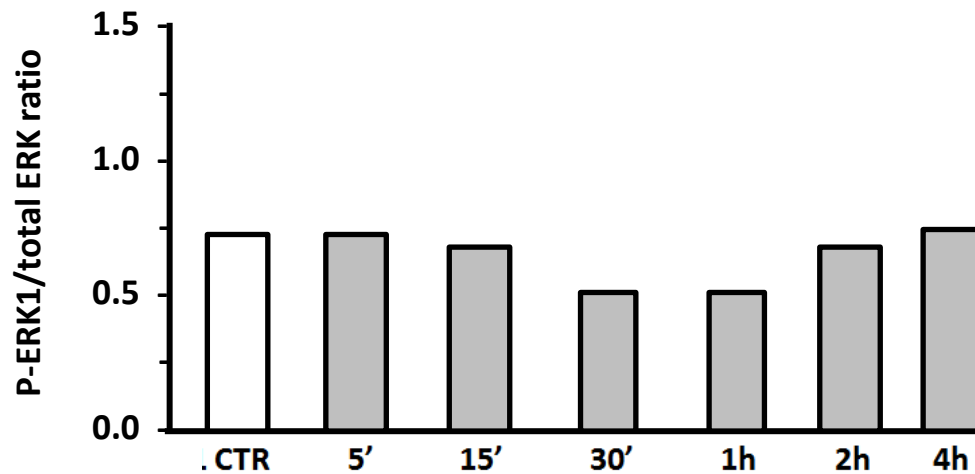
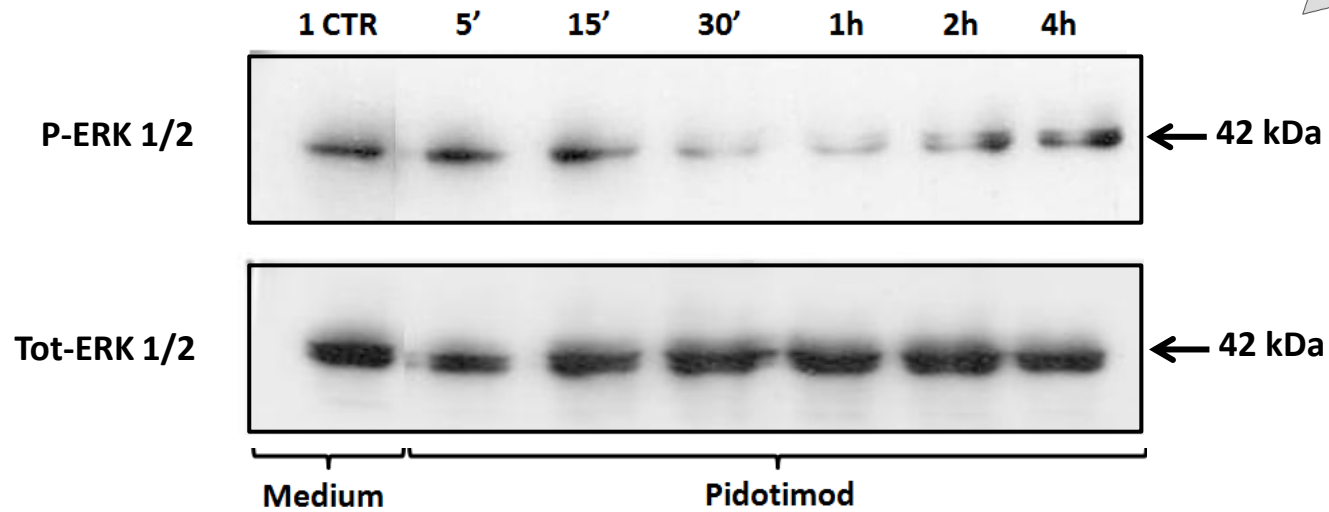
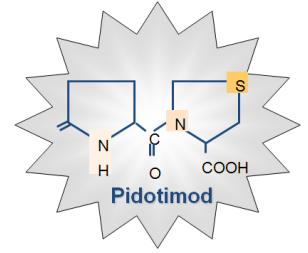
TNF- α (10 ng/ml)	-	+	-	-
IL-4 (5 ng/ml)	-	-	+	-
INF- γ (50 ng/ml)	-	-	-	+



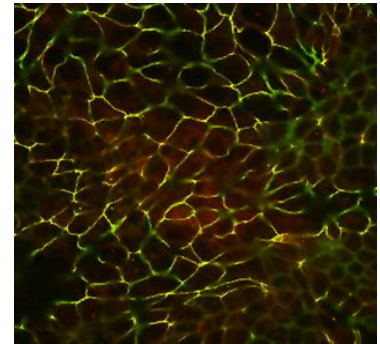
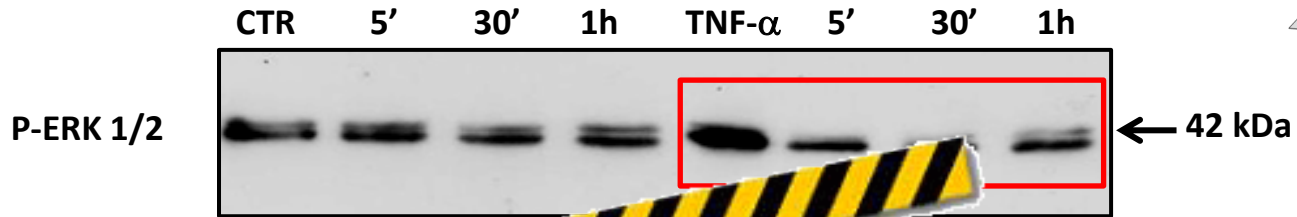
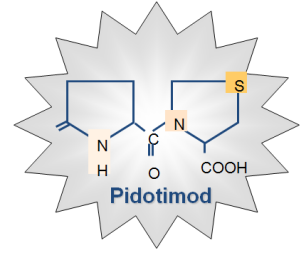
Inhibition of ERK-1 phosphorylation prevents cytokine-induced T. J. disruption



Pidotimod and “constitutive” ERK 1/2 phosphorylation in airway epithelial cells



Pidotimod and TNF- α -induced ERK 1/2 phosphorylation in airway epithelial cells



WORK IN PROGRESS
CHECK BACK SOON!

Grazie per l'attenzione e
... non mancate il 21-23 Giugno!



21 • 23 Giugno 2012

XVI Congresso Nazionale
della Società Italiana per le Malattie Respiratorie Infantili

Centro Congressi Porto Antico Di Genova

Segreteria Organizzativa



Idea congress

Via della Farnesina, 224

00135 Roma

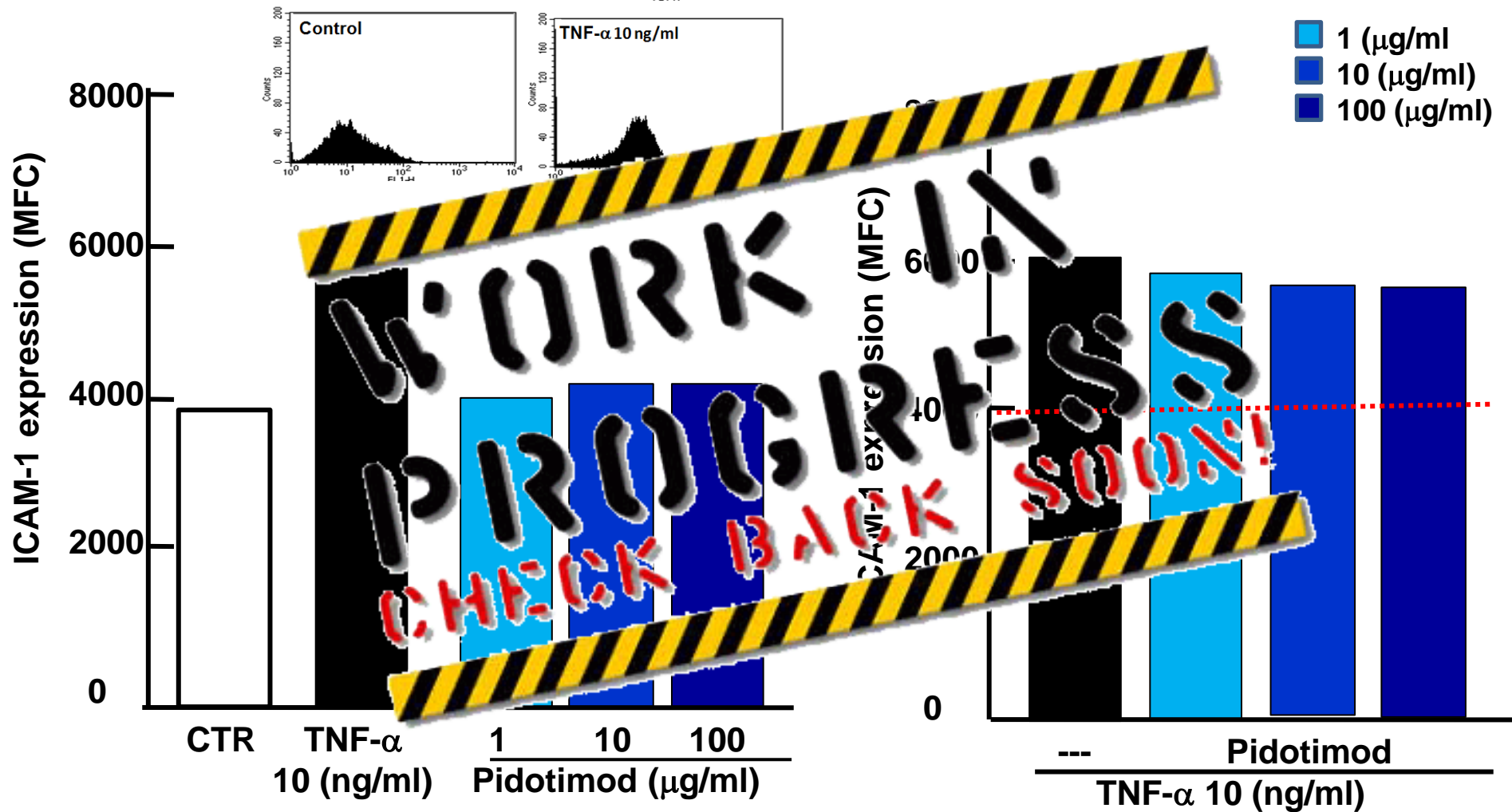
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Pidotimod and “constitutive” and TNF- α -induced ICAM-1 expression by airway epithelial cells



Informazioni Generali

Sede del congresso

Forte Village Resort - Santa Margherita di Pula Cagliari
Tel: +39 070 92171 - Fax +39 070 921246 - forte.village@fortevillage.com

Periodo

27 - 30 Maggio 2012

Quota di Iscrizione

Medici entro il 15/05/2012 € 250,00 + IVA 21%
Dopo tale data si effettueranno iscrizioni esclusivamente in sede congressuale

La quota di iscrizione dà diritto a:

- partecipazione ai lavori - kit congressuale - attestato di partecipazione
- attestati E.C.M.*

* Gli attestati riportanti i crediti E.C.M., dopo attenta verifica della partecipazione e dell'apprendimento, saranno disponibili on-line 45 giorni dopo la chiusura dell'evento, previa attribuzione da parte del Ministero della Salute dei Crediti Formativi. Il partecipante potrà ottenere l'attestato con i crediti consegnato collegandosi al sito internet www.ideacpa.com e seguendo le semplici procedure ivi indicate

Modalità di Pagamento:
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La partecipazione del medico non dà diritto ad alcuna E.C.M.

Pernottamento in pensione completa dal 27 al 30 Maggio 2012

Quota partecipante in camera doppia uso singola € 900,00

Quota accompagnatore € 450,00

in camera doppia con il partecipante

Modalità di Pagamento:
Banca Carli alla BCC - Filiale di Cagliari - IBAN IT 17 02 10 3302 3300 0000 0017 0007 - SWIFT: BCCICRIT 3302000000 - C/c Carli alla BCC
Spett.le la Casella del richiedente/Ademp. Banca Carli con l'Indirizzo postale e C/c Carli alla BCC, da spedire in Via della Felicità, 224 00133 Roma
Assicurazione per la Protezione all'Infortunio:
In caso di annullamento o presenza infortunio, del 10% dell'importo iscritto per l'iscrizione per mezzo del sito www.ideacpa.com
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La partecipazione del medico non dà diritto ad alcuna protezione all'Infortunio.

Per ulteriori richieste si prega di contattare
la Segreteria Organizzativa. Grazie

Il Congresso seguirà le nuove procedure per l'attribuzione, presso il Ministero della Salute, dei Crediti Formativi di "Educazione Continua in Medicina" (E.C.M.) per la professione di Medico Chirurgo

Elenco Presidenti - Moderatori - Relatori

Eugenio Baraldi - Padova
Paolo Becherucci - Firenze
Sergio Bernasconi - Parma
Gianni Bona - Novara
Luciana Biancalani - Firenze
Guido Brusoni - La Spezia
Elena Chiappini - Firenze
Giuseppe Di Mauro - Caserta
Luigi Falco - Caserta
Vassilios Fanos - Cagliari
Pietro Ferrara - Roma
Alessandro Fiocchi - Milano
Ahmad Kantar - Belluno
Gian Luigi Marseglia - Pavia

Teresita Mazzei - Firenze
Giuseppe Mele - Lecce
Emanuele Miraglia del Giudice - Napoli
Michele Miraglia del Giudice - Napoli
Bruno Nobili - Napoli
Andrea Novelli - Firenze
Domenico Perri - Aversa (CA)
Laura Perrone - Napoli
Francesco Rossi - Napoli
Giovanni Arturo Rossi - Genova
Carmelo Salpietro - Messina
Attilio Varricchio - Napoli
Leo Venturelli - Bergamo
Eleonora Zanella - Milano

Segreteria Scientifica

Paolo Becherucci
Sergio Bernasconi
Guido Brusoni
Giuseppe Di Mauro
Leo Venturelli

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Giornate di Pediatria Preventiva e Sociale

2012



Presidente: Giuseppe Di Mauro

27 - 30 Maggio 2012

Centro Congressi Forte Village - Santa Margherita di Pula

Domenica 27 Maggio 2012

17.00 Registrazione dei partecipanti

18.00 Saluto ai partecipanti
Giuseppe Di Mauro, Giuseppe Male

18.30 LETTURE MAGISTRALI
Moderatori: Eugenio Baraldi, Bruno Nobili

Attualità nell'uso del GH in età evolutiva
Laura Perrone

Prevenzione primaria dell'APLV: linee guida e aspetti pratici
Alessandro Flocchi

Il maltrattamento infantile: ... l'isola che ... c'è
Pietro Ferrara

Lunedì 28 Maggio 2012

08.30 I Sessione
SESSIONE INTERATTIVA
Presidente: Emanuele Miraglia del Giudice
Moderatori: Guido Brusoni, Elena Chioppini

Informatizziamo lo studio: rete, salvataggi, stampanti, accessori vari...
Paolo Becherucci

L'infermiere nell'ambulatorio del Pediatra di famiglia
Luciano Biancaloni, Leo Venturini

Il contributo infermieristico della rete dei servizi pediatrici territoriali
Eleonora Zanella

11.30 Discussione

Lunedì 28 Maggio 2012

16.00 II Sessione
IL BAMBINO, LE INFEZIONI RICIDIVANTI E GLI
IMMUNOMODULATORI IN PEDIATRIA
Presidente: Carmelo Salpietro
Moderatori: Giuseppe Di Mauro, Domenico Perri

Le infezioni respiratorie ricorrenti: epidemiologia e diagnosi
Gian Luigi Marsiglio

Il punto di vista dell'otorino
Attilio Varricchio

Le infezioni ricidivanti delle vie urinarie
Vassilios Fanos

Gli immunomodulanti: il meccanismo d'azione
Giovanni A. Rossi

Gli immunomodulanti: dalle evidenze alla clinica
Gianni Bona

20.00 Discussione

Martedì 29 Maggio 2012

08.30 I Sessione
SESSIONE INTERATTIVA
Presidente: Sergio Bernasconi
Moderatori: Guido Brusoni, Laura Perrone

Attualità dalla ricerca: la metabolomica
Eugenio Baraldi

La lettura dell'emocromo: al di là dei numeri
Bruno Nobili

L'approccio al bambino e all'adolescente obeso: veri e falsi problemi
Emanuele Miraglia del Giudice

11.30 Discussione

Martedì 29 Maggio 2012

16.00 II Sessione
APPROPRIATEZZA PRESCRITTIVA: LINEE GUIDA, PROTOCOLLI,
RACCOMANDAZIONI, EVIDENCE BASED IN MEDICINE
E APPLICAZIONI PRATICHE IN TEMA DI:
Presidente: Sergio Bernasconi
Moderatori: Giuseppe Di Mauro, Carmelo Salpietro

Aerosolterapia
Ahmad Kantar

Otite Media Acuta
Michele Miraglia del Giudice

Faringotonsillite
Elena Chioppini

Polmoniti
Giovanni A. Rossi

LETTURA
Introducono: Luigi Falco, Francesco Rossi
Attualità in tema di farmaci equivalenti: luci ed ombre
Teresta Mazzei, Andrea Novelli

20.00 Discussione

Mercoledì 30 Maggio 2012

08.30 SESSIONE MATTUTINA
Conclusioni del Congresso
Giuseppe Di Mauro

09.30 Compilazione questionario E.C.M. e chiusura Congresso

The first preliminary answer from HBECs ?



VALUTAZIONE DI EFFICACIA DEL PIDOTIMOD NELLA PREVENZIONE DELLE IRR IN UNA POPOLAZIONE DI BAMBINI CON S. DI DOWN

18 bambini con sindrome di Down di età compresa fra 3 e 9 anni

T0: tutti i bambini hanno eseguito vaccinazione anti-influenzale (Inflexal V) e prelievo ematico

PARAMETRI IMMUNOLOGICI

Analisi dell'espressione (tramite PCR array) di 84 geni coinvolti nella risposta innata e adattativa

LIVELLI DI ANTICORPI ANTI-FLU

(pre-vaccinazione)

18 bambini randomizzati

9

PIDOTIMOD

400 mg/die per 90 gg

9

NESSUN INTERVENTO



T1: PARAMETRI IMMUNOLOGICI e ANTICORPI ANTI-FLU

T3: PARAMETRI IMMUNOLOGICI



COMPOSTI SINTETICI

Pidotimod

Review e metanalisi

Autore	Titolo	Tipologia	Conclusioni
Riboldi P. Int J Immunopathol Pharmacol 2009.	Pidotimod: a reappraisal	Review	Efficace nel ridurre le IRR delle alte vie e le infezioni delle vie urinarie dei bambini

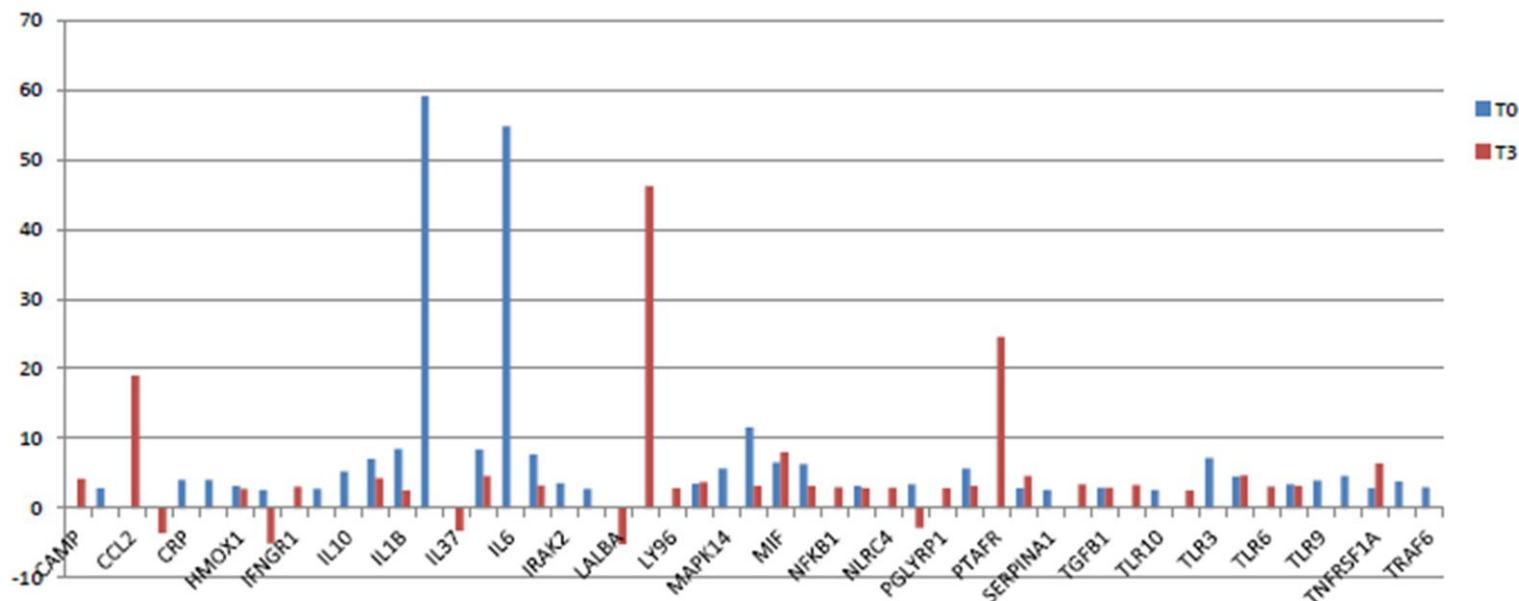
PubMED-Embase



Pidotimod sembra ridurre il numero di IRR



Confronto espressione genica T0 e T3

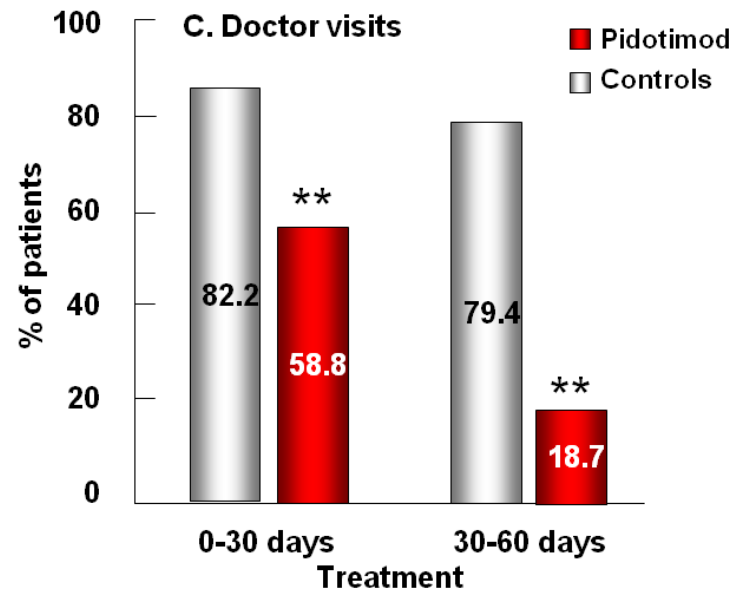
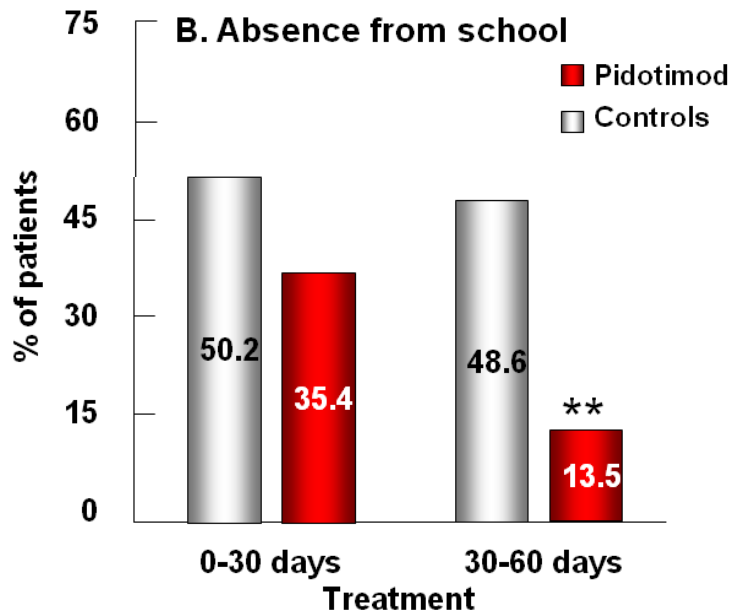
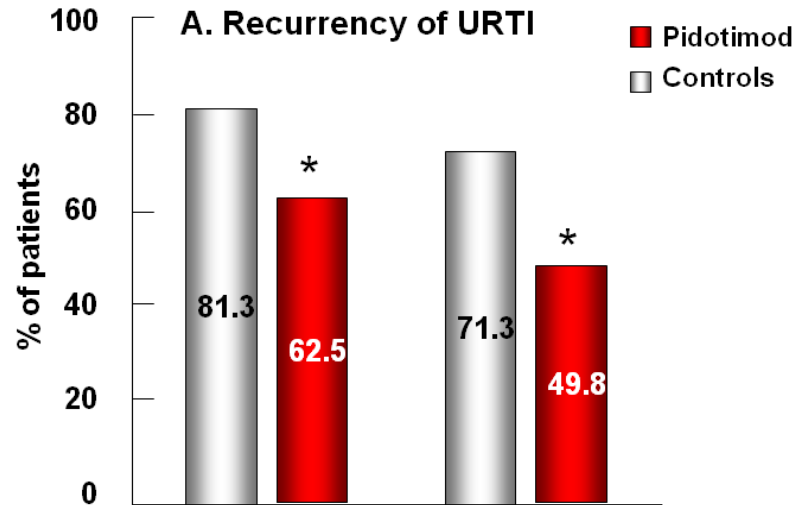


Aumento dell'espressione genica dei geni coinvolti nella risposta innata e adattativa nel gruppo di bambini trattati con Pidotimod

(geni coinvolti nella risposta alle infezioni batteriche e virali)



Pidotimod (400 mg/day x 60 days) or placebo in 101 children (4.7 ± 2.1 years) with *recurrent URTI*



* $p < 0.05$
** $p < 0.01$



Pidotimod in the acute phase and in the follow-up of RTI severe enough to require antibiotic treatment



Evaluation

60 children {
Pidotimod
400 mg b.i.d.
+ antibiotics

• **Pidotimod**
400 mg o.d.

• **Acute phase of the URTI**

15 days

Maintenance period

60 days

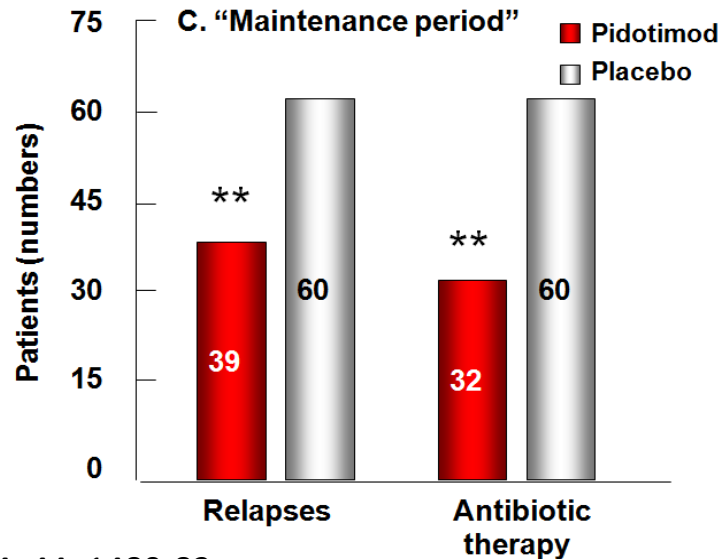
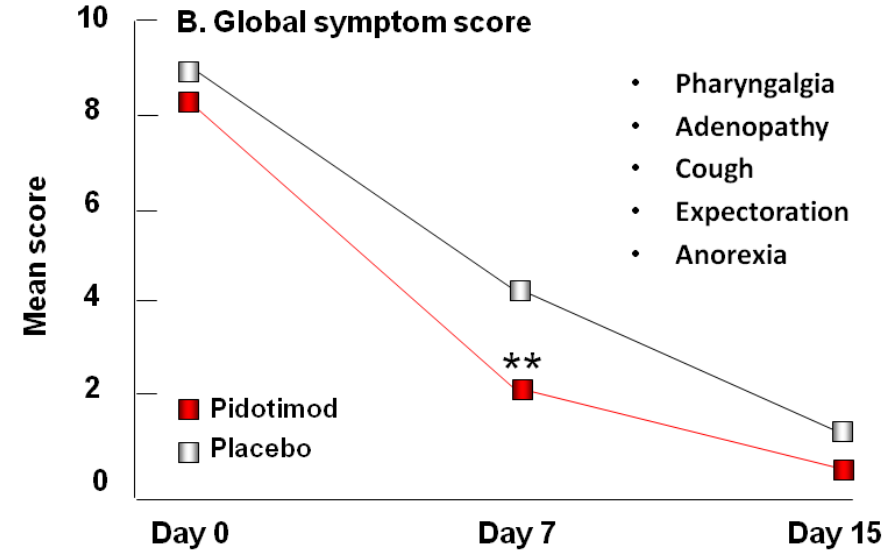
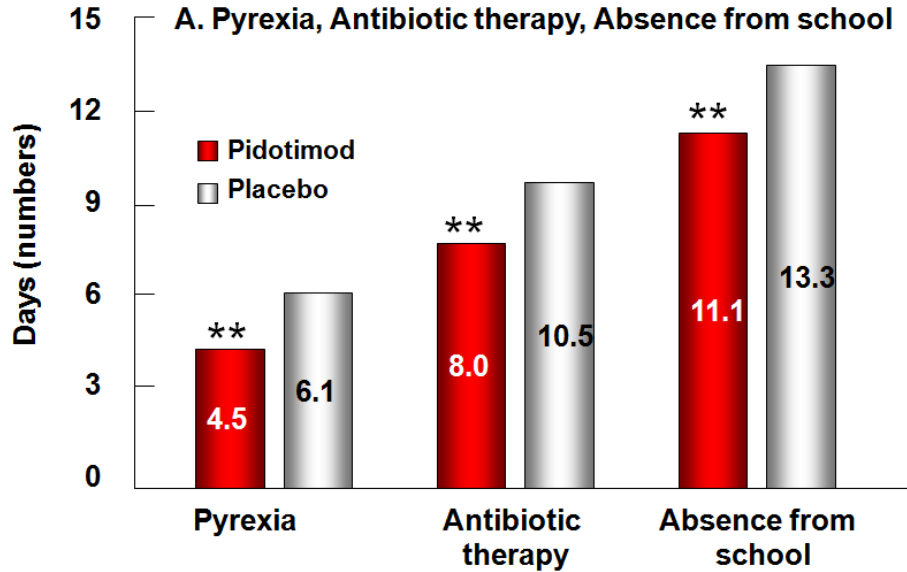
Evaluation

60 children {
Placebo
b.i.d.
+ antibiotics

• Placebo
o.d.



Pidotimod in the acute phase and in the follow-up of URTI severe enough to require antibiotic treatment



** p < 0.01

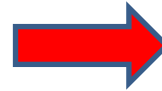
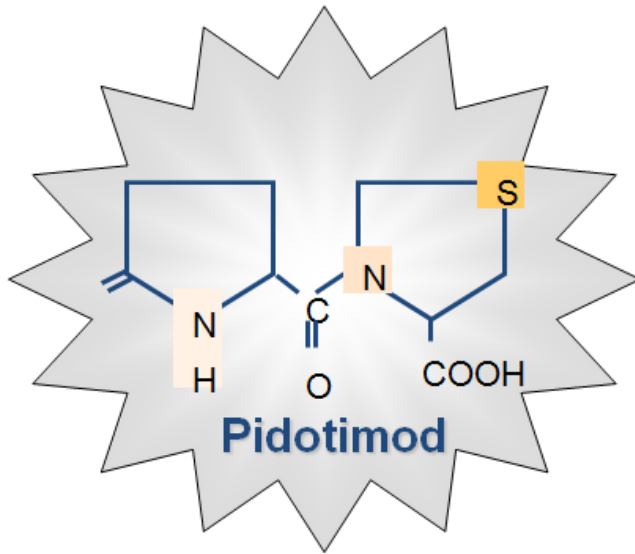


Oral purified bacterial extract (OM-85 BV) in acute respiratory tract infections in childhood: a systematic quantitative review

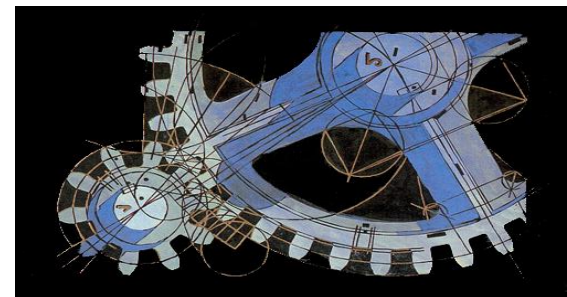
- **Aim.** To summarised the evidence on the effectiveness of the immunomodulator OM-85 BV in the prevention of ARTI in children
- **RESULTS.** 13 studies (2,721 patients) of low to moderate quality tested OM-85 BV, but patients and outcomes differed substantially, which impeded pooling results
- **CONCLUSION.** Evidence in favour of OM-85 BV in the prevention of ARTI in children is weak
- There is a trend for fewer and shorter infections and a reduction of antibiotic use



Which kind of new information is needed ?

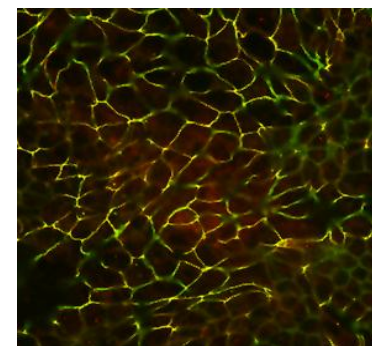
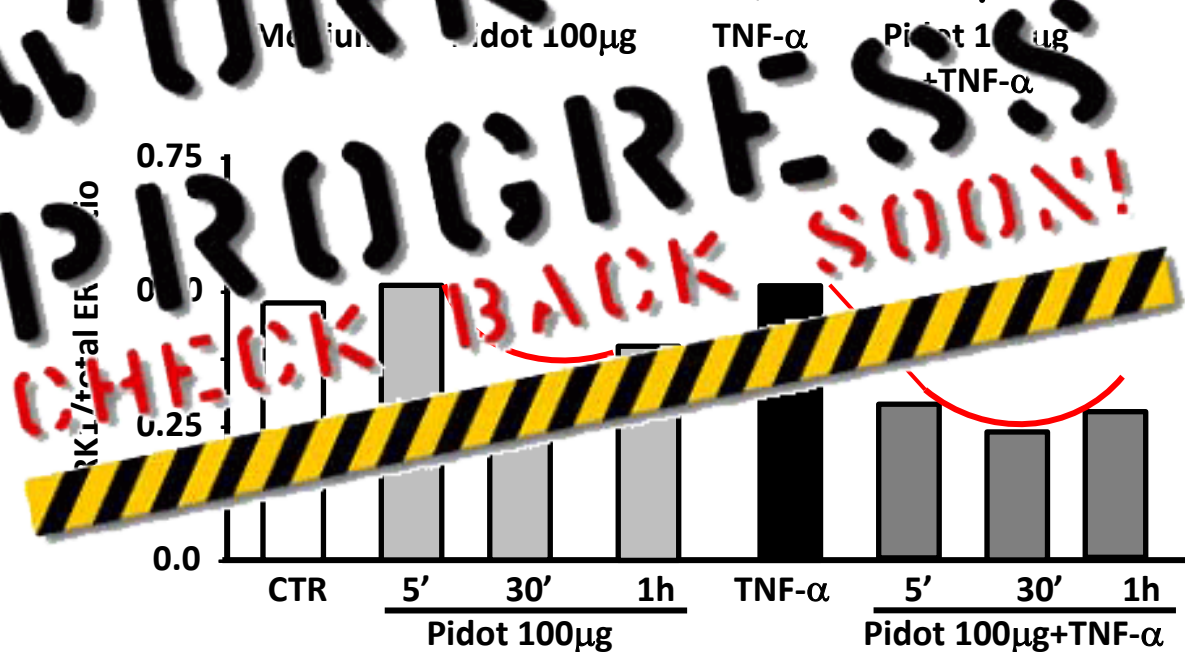
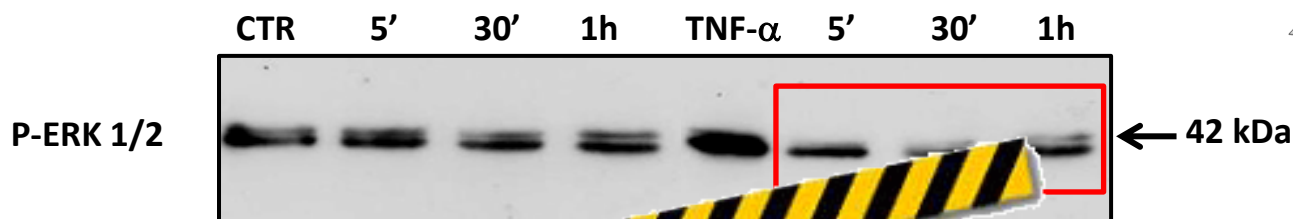
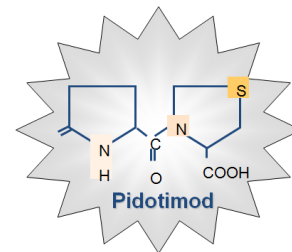


“Modern” clinical studies



Intracellular pathways
involved

Pidotimod and TNF- α -induced ERK 1/2 phosphorylation in airway epithelial cells



WORK IN PROGRESS
CHECK BACK SOON!