



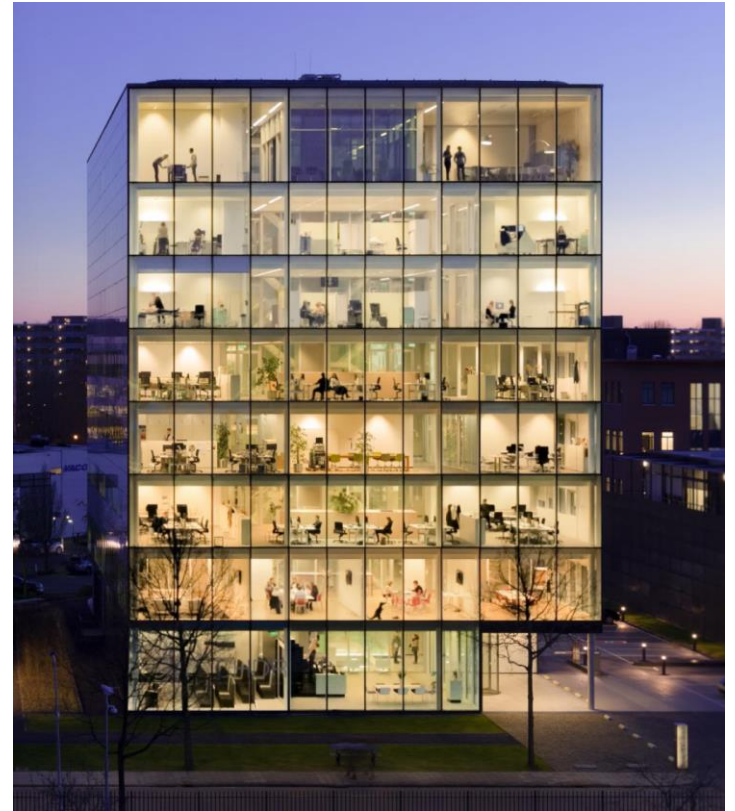
Human immune challenge models

EUFEMED, 24 May 2023

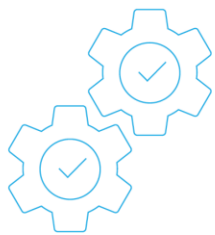
Matthijs Moerland
mmoerland@chdr.nl

Centre for Human Drug Research

- › Full service CRO, established in 1987 as foundation
 - › focus on integrated early phase clin phar programs
 - › healthy volunteers and patients
 - › method development
 - › training site (PhD, clinical pharmacology)
- › Close collaborations with Universities & Medical Centers
- › 50+ early phase clinical trial projects per year for big pharma & biotech



Modern early phase drug development



Method
validation

HEALTHY VOLUNTEERS
(SAFETY / PKPD)



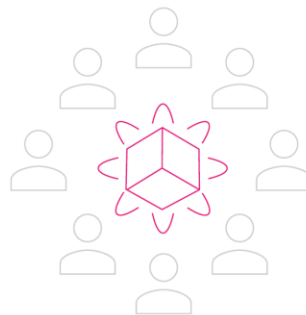
Single ascending dose



Multiple ascending dose

POP: Proof-of-Pharmacology

INTERMEDIATE
POPULATIONS



Pharmacological challenges
Behavioural challenges

POM: Proof-of-Mechanism

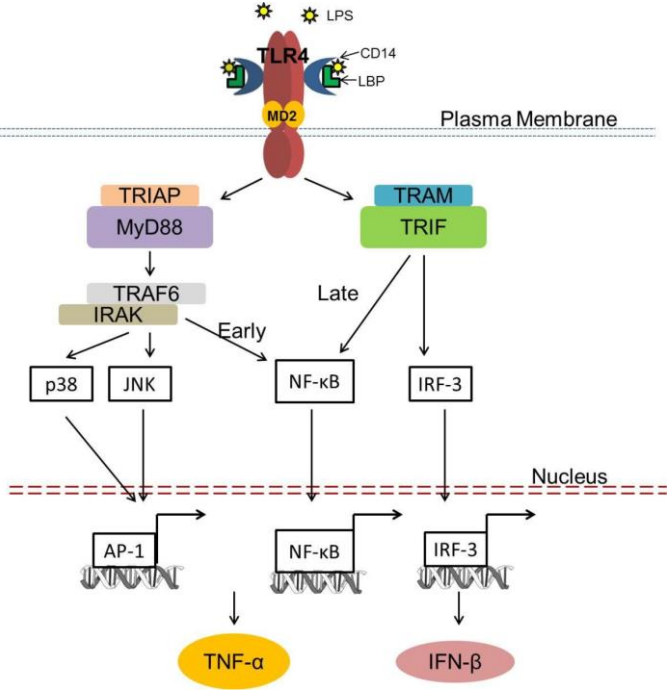
TARGET POPULATIONS
(MONOCENTRE APPROACH)



Surrogate endpoints in patients
Efficacy in patients

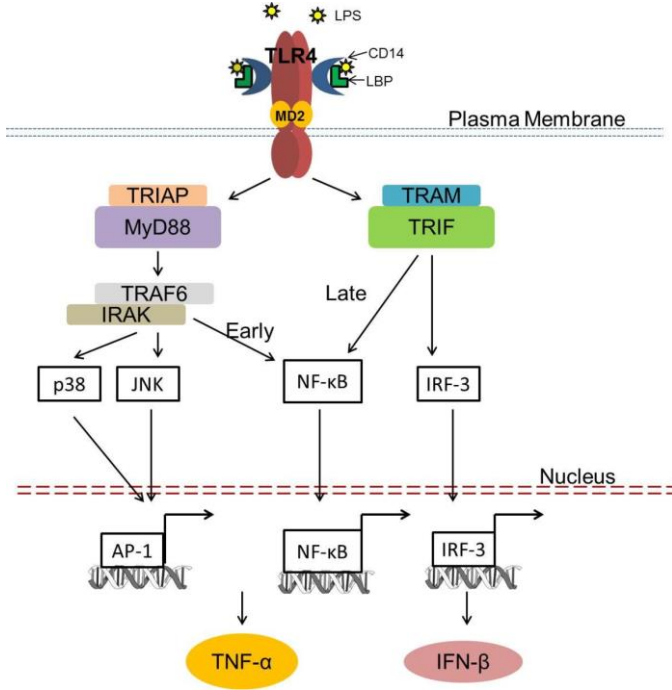
POC: Proof-of-Concept

Intravenous LPS challenge

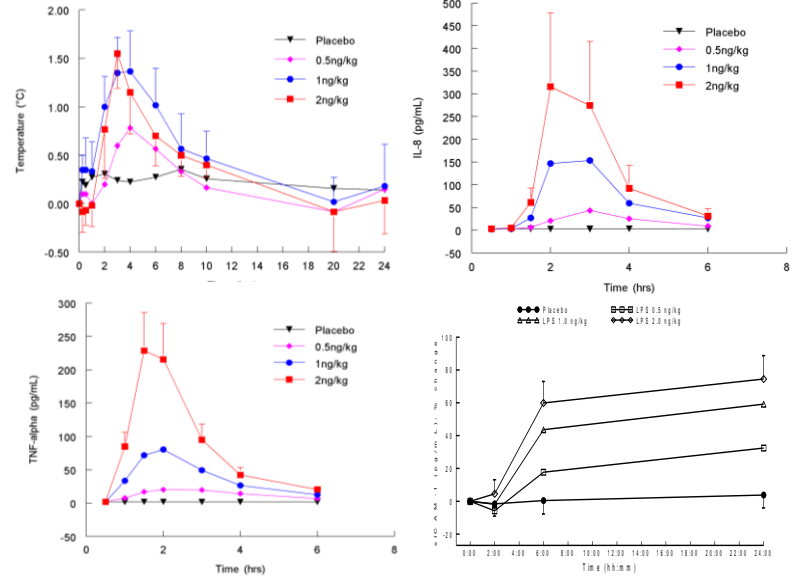


Zhang, Medicine 2015

Intravenous LPS challenge

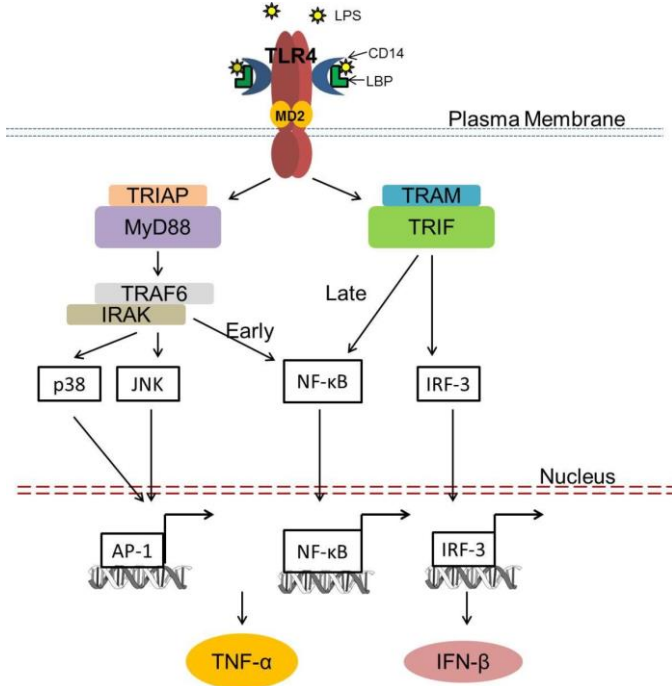


Zhang, Medicine 2015

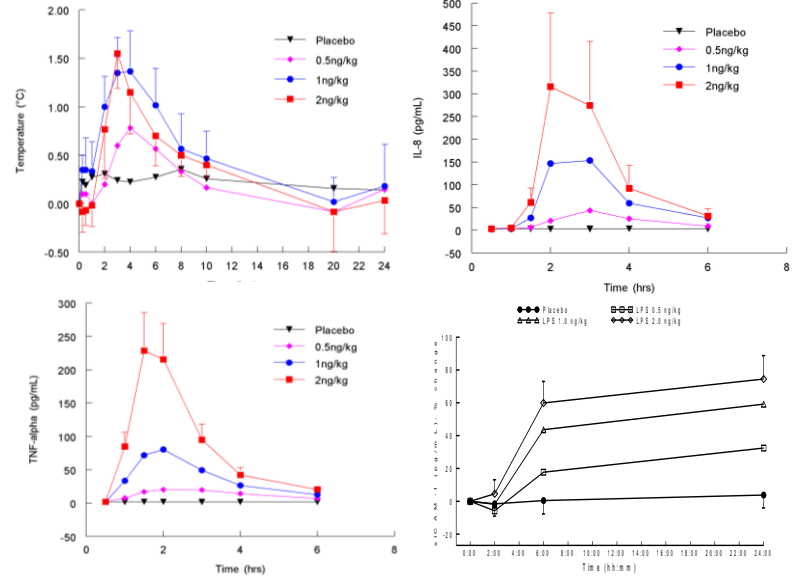


Journal of Inflammation. 2014; 11: 28

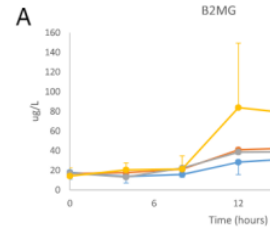
Intravenous LPS challenge



Zhang, Medicine 2015



Journal of Inflammation. 2014; 11: 28



J Pharmacol Toxicol Methods. 2018;89:39-46

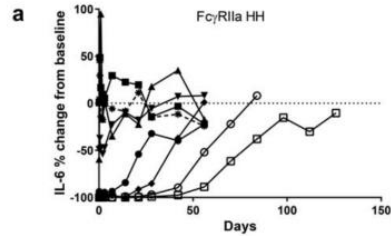
FIH study TLR4 mAb

CLINICAL TRIAL

Evidence of NI-0101 Pharmacological Activity, an Anti-TLR4 Antibody, in a Randomized Phase I Dose Escalation Study in Healthy Volunteers Receiving LPS

E Monnet^{1,4}, G Lapeyre¹, E van Poelgeest², P Jacqmin³, K de Graaf¹, J Reijers², M Moerland², J Burggraaf² and C de Min¹

Ex vivo PD



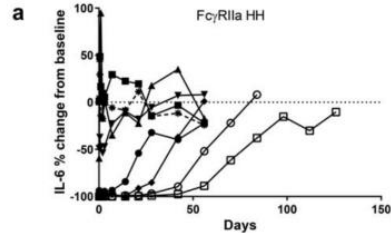
FIH study TLR4 mAb

CLINICAL TRIAL

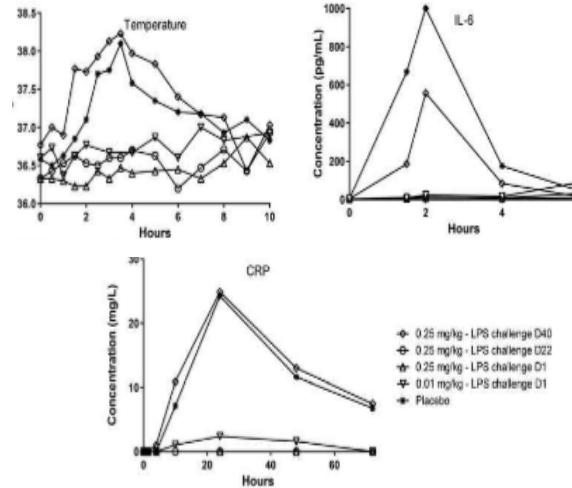
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Ex vivo PD



In vivo PD




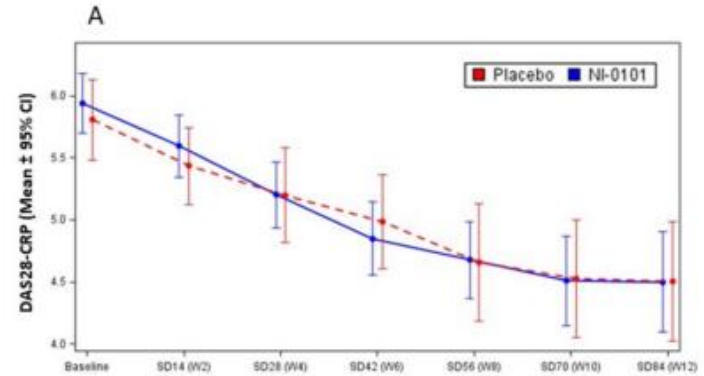
Clin Pharmacol Ther. 2017;101(2). doi: 10.1002/cpt.522

Clinical translation iv LPS - disease

CLINICAL SCIENCE

Efficacy and safety of NI-0101, an anti-toll-like receptor 4 monoclonal antibody, in patients with rheumatoid arthritis after inadequate response to methotrexate: a phase II study


Emmanuel Monnet ¹, Ernest H Choy,² Iain McInnes,³ Tamta Kobakhidze,⁴ Kathy de Graaf,¹ Philippe Jacqmin,⁵ Geneviève Lapeyre,¹ Cristina de Min¹

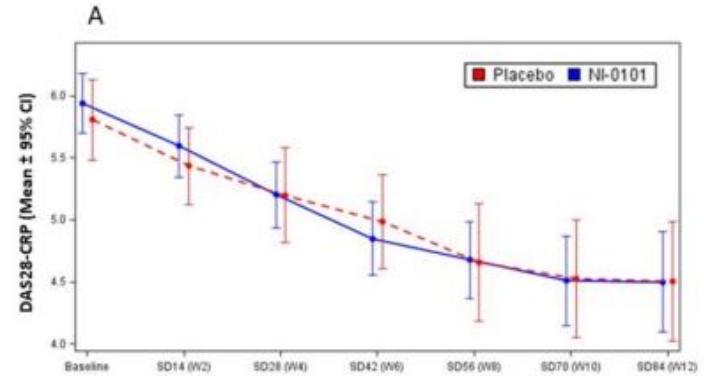


Clinical translation iv LPS - disease

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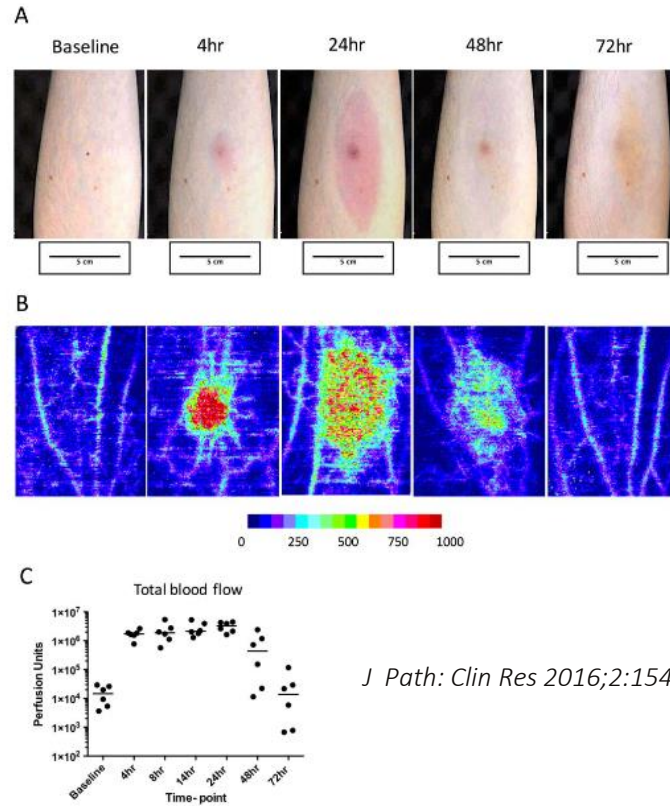
Emmanuel Monnet ,¹ Ernest H Choy,² Iain McInnes,³ Tamta Kobakhidze,⁴ Kathy de Graaf,¹ Philippe Jacqmin,⁵ Geneviève Lapeyre,¹ Cristina de Min¹



- Redundancy of TLR signaling in RA? (TLR2, 4, 5, 7)
- 'TLR4 is likely not a relevant target in RA patients with inadequate response to MTX'
- Systemic LPS-driven inflammation vs pathophysiology of RA

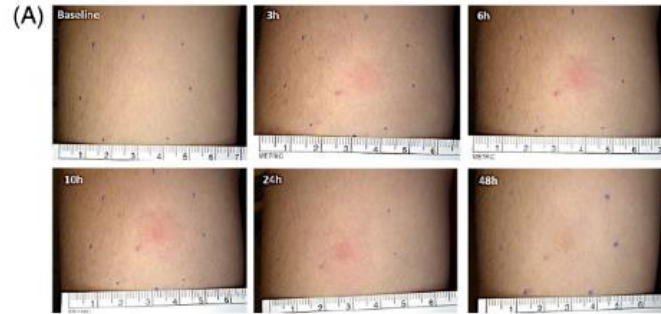
Tissue-based inflammation model

Intradermal injection of
UV-killed *E. coli*

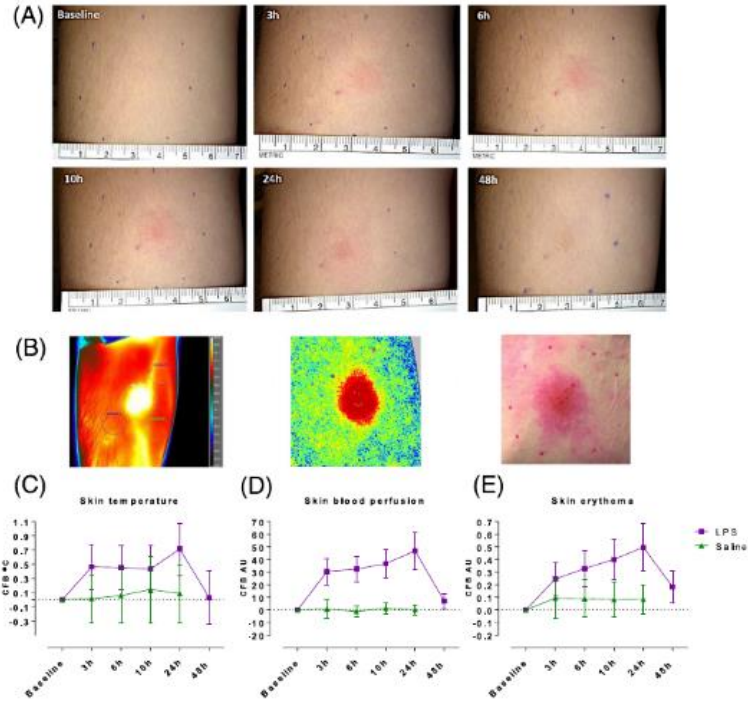


J Pathol Clin Res 2016;2:154–165

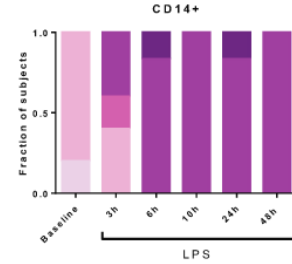
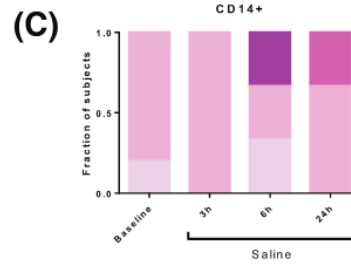
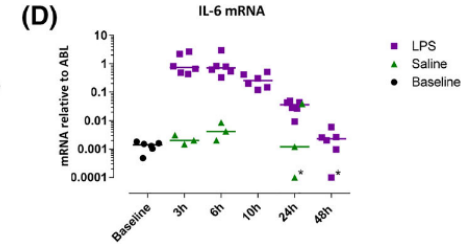
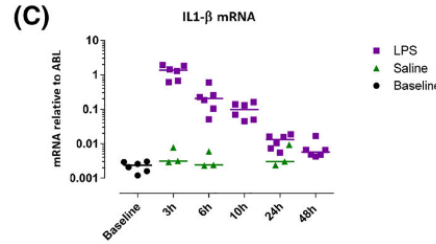
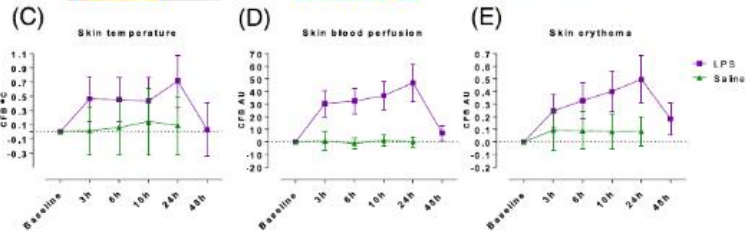
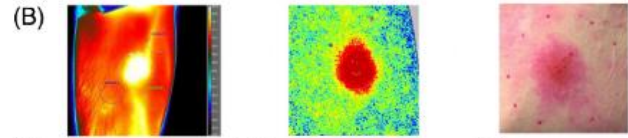
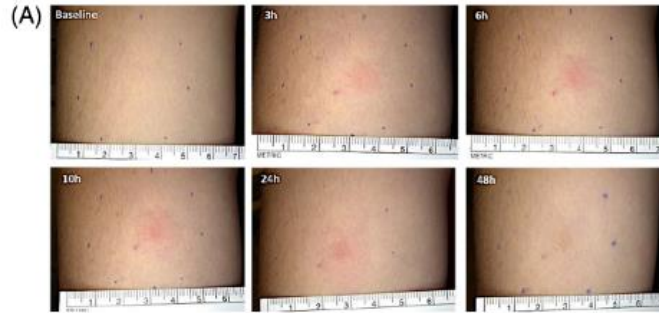
Intradermal LPS challenge



Intradermal LPS challenge



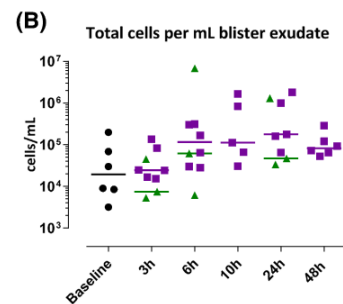
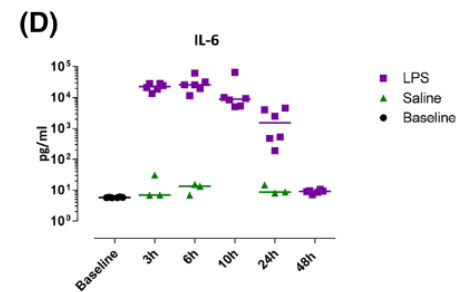
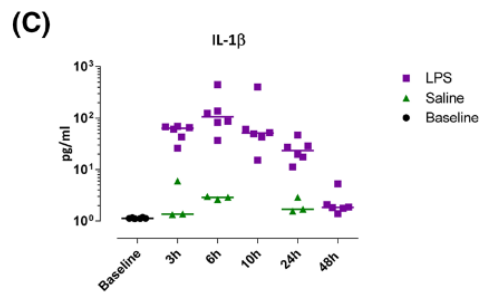
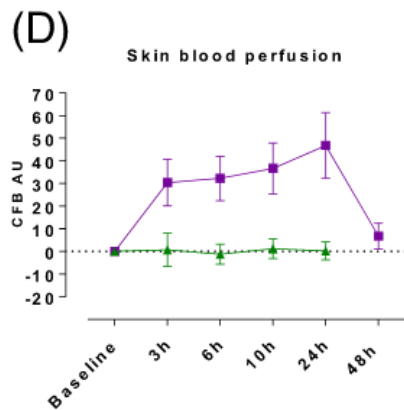
Intradermal LPS challenge



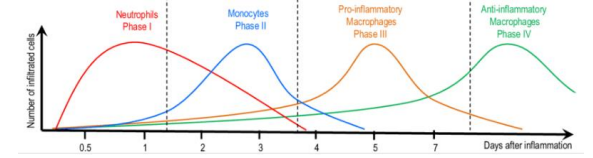
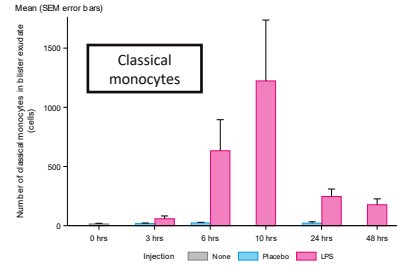
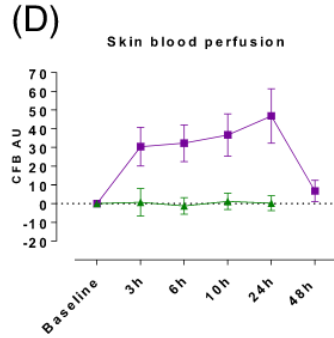
Suction blisters



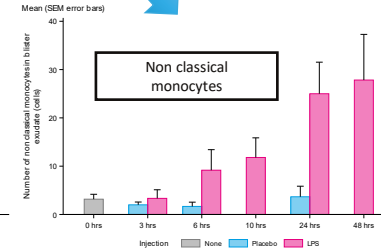
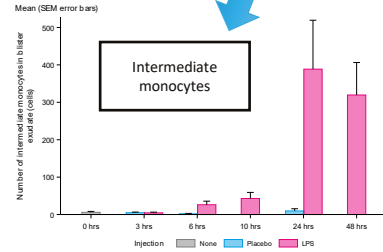
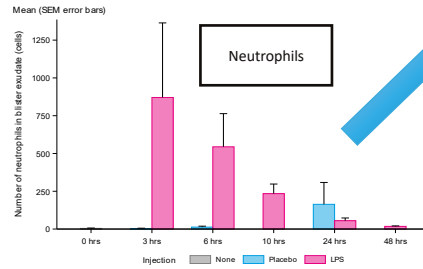
Intradermal LPS challenge – blister fluid



Intradermal LPS challenge

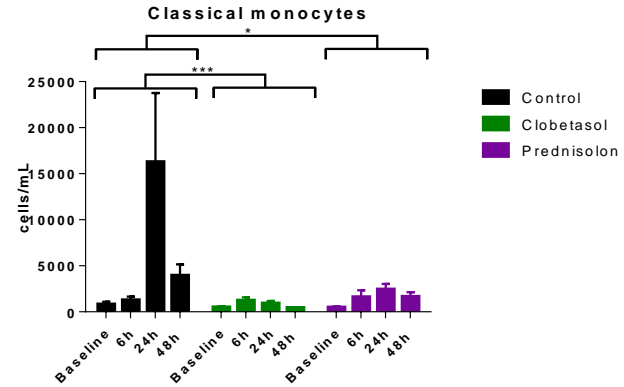
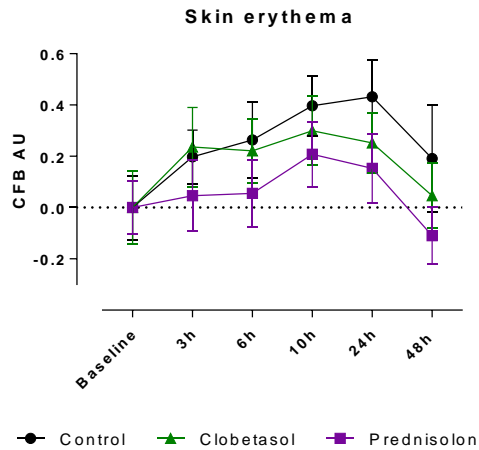


Journal of Cell Biology 2018. 217(4):jcb.201702048



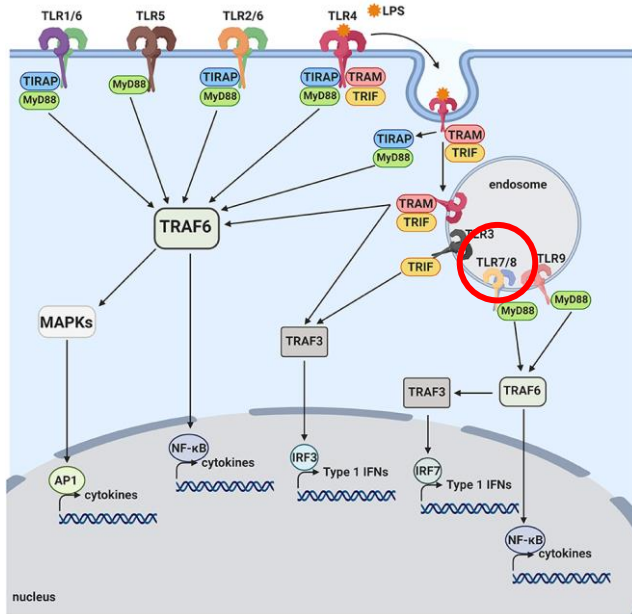
CHDR data on file

LPS response suppression by corticosteroids



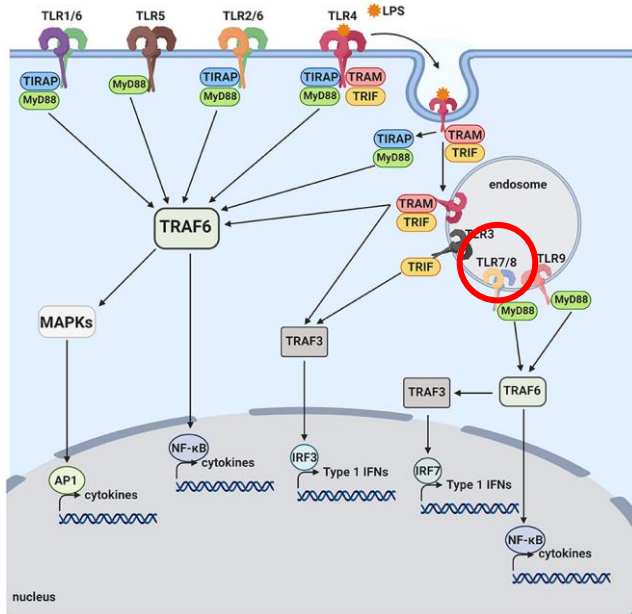
Clin Pharmacol Ther. 2022;111(4):964-971. doi: 10.1002/cpt.2516.

Topical imiquimod challenge

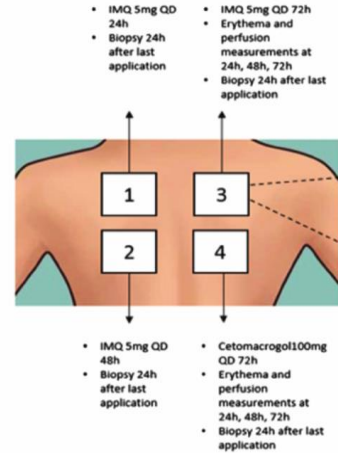


Front. Immunol. 2020. doi.org/10.3389/fimmu.2020.00724

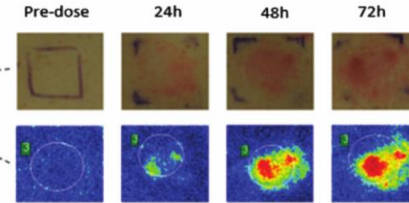
Topical imiquimod challenge



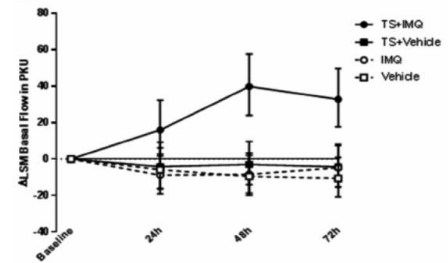
a.



b.



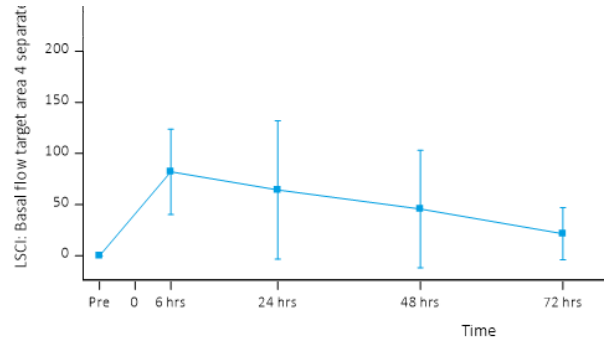
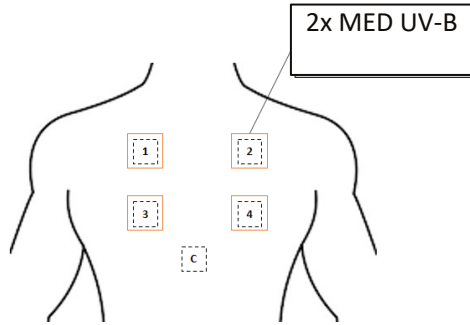
c.



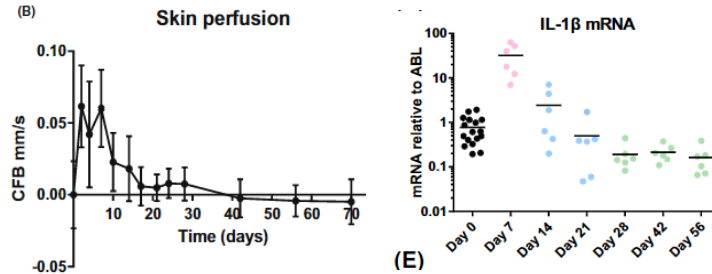
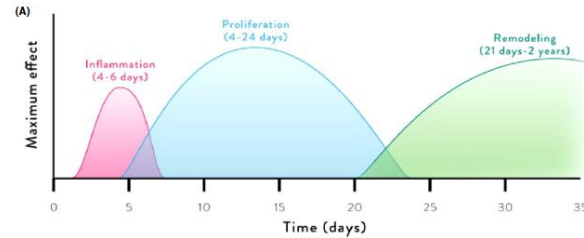
Clin Transl Sci. 2018;11(6):607-615. doi: 10.1111/cts.12563

Tissue injury models

UV-B irradiation



Wound healing following skin punch biopsy



Study design, example

IRAK4 inhibitor A vs B vs prednisolone vs placebo



Methodology

Whole blood challenge

Topical imiquimod

Intravenous LPS

Study design, example

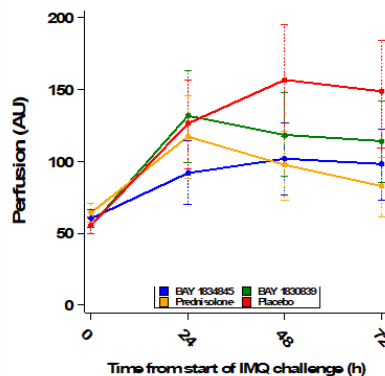
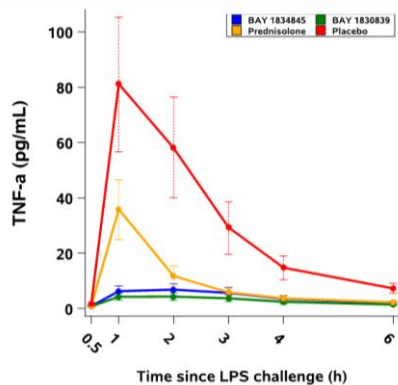
IRAK4 inhibitor A vs B vs prednisolone vs placebo

Methodology

Whole blood challenge

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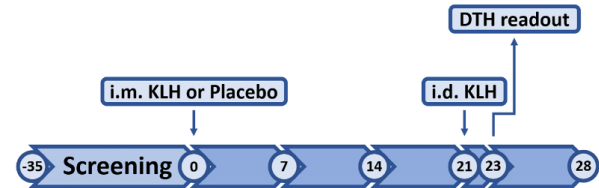
Ten Voorde et al., ISID Tokyo 2023
Manuscript in preparation

Neoantigen challenge (Keyhole Limpet Hemocyanin immunization)



- Metalloprotein from hemolymph of the giant keyhole limpet (mollusk)
- Immucothel®: KLH subunit, for non-invasive bladder cancer

FIGURE 1 Study timeline. Numbers represent visit days; i.m. = intramuscular; i.d. = intradermal; KLH = keyhole limpet haemocyanin; DTH = delayed type hypersensitivity

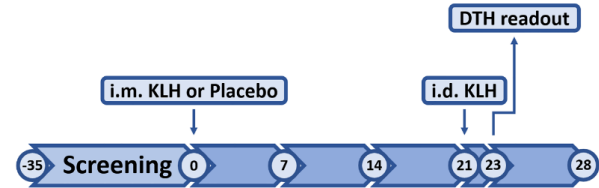


Neoantigen challenge (Keyhole Limpet Hemocyanin immunization)

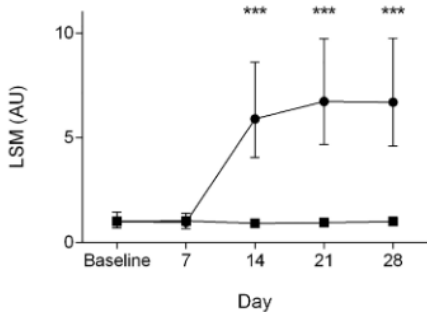


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FIGURE 1 Study timeline. Numbers represent visit days; i.m. = intramuscular; i.d. = intradermal; KLH = keyhole limpet haemocyanin; DTH = delayed type hypersensitivity



(B) Anti-KLH IgG antibody titre



● KLH
■ Placebo

LSCI basal flow

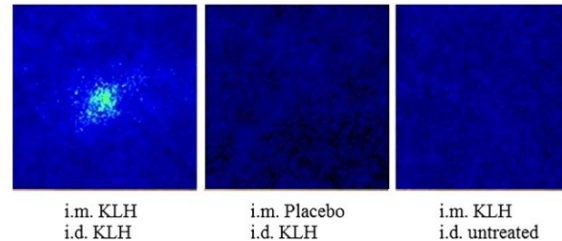
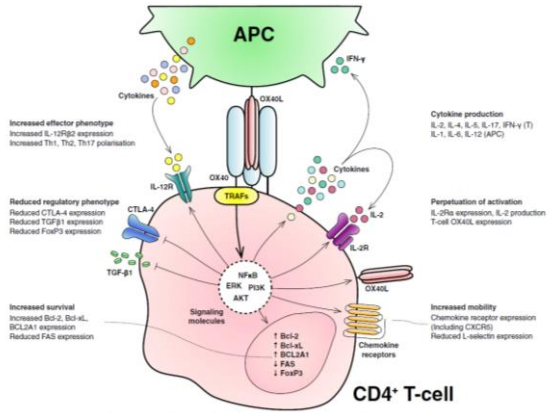
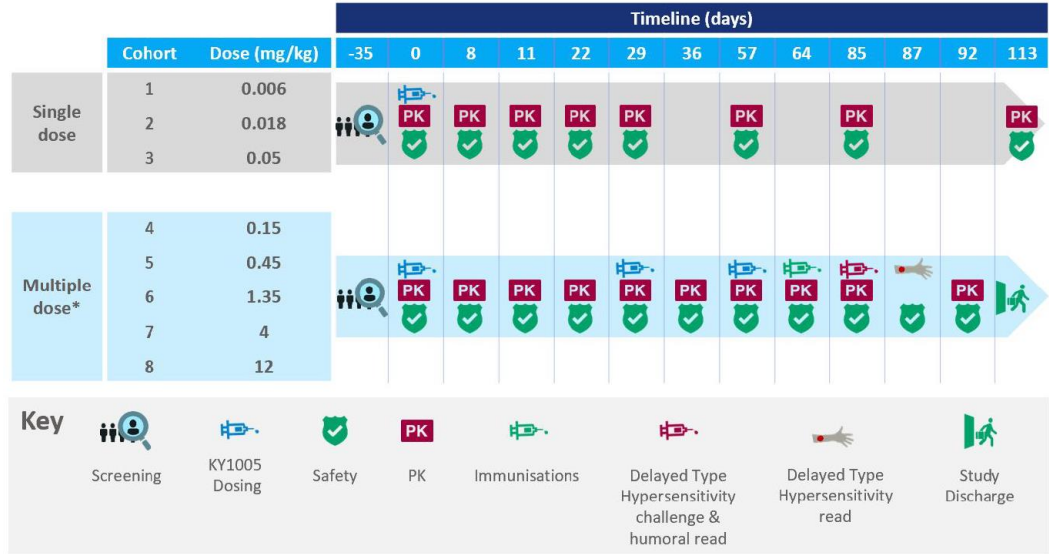


FIGURE 4 Illustrations of laser speckle contrast imaging (LSCI) basal flow and erythema assessed as CIELab a* with multispectral imaging 2 days after intradermal keyhole limpet haemocyanin (KLH) administration of a subject treated with intramuscular KLH immunization and intradermal KLH administration (left images), intramuscular placebo immunization and intradermal KLH administration (middle images) and intramuscular KLH immunization and untreated control arm (right images)

FIH OX40L blocker – POM based on KLH challenge



Clinical Reviews in Allergy & Immunology 50, 312–332 (2016)



*Loading dose followed by two maintenance doses at 50% of the loading dose

World Congress of Dermatology 2019, Saghari et al.

FIH OX40L blocker – POM based on KLH challenge

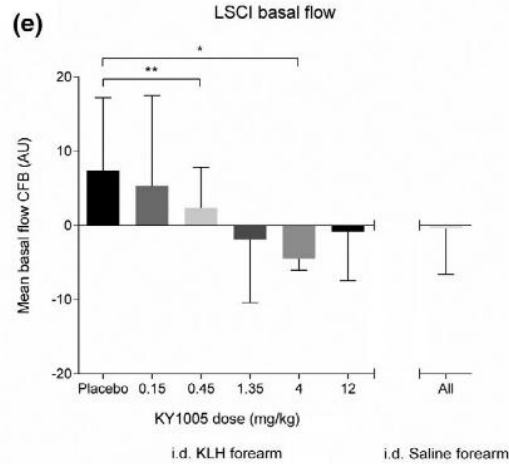
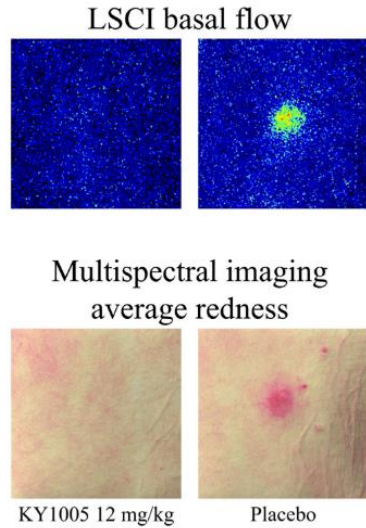


Figure 1 Illustrations of LSCI basal flow and erythema assessed as average redness with multispectral imaging. Images were taken at intradermal KLH injection site 2 days after intradermal KLH administration of a subject treated with an initial KY1005 12 mg/kg dose (left images) and a subject that received placebo (right images). KLH, keyhole limpet hemocyanin; LSCI, laser speckle contrast imaging.

FIH OX40L blocker – POM based on KLH challenge

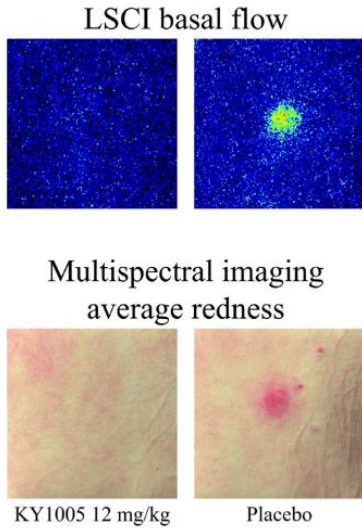
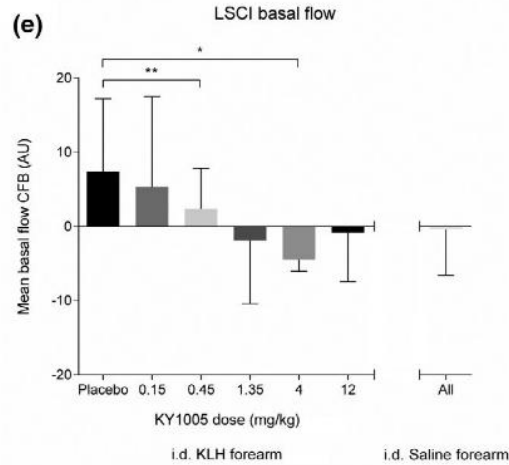


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NEWS

Amlitelimab shows 80 percent improvement in atopic dermatitis

Late-breaking data highlights the emerging clinical profile of amlitelimab in adults with inadequately controlled atopic dermatitis.

By Anna Begley (European Pharmaceutical Review)

4 October 2021

No comments yet

SHARES

Teamwork





CHDR

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