



SELECTED OPPORTUNITIES IN DERMATOLOGY

A Pak1/2 inhibitor for the treatment of Psoriasis and other NLRP3 Inflammasome mediated IL1b dependent disorders (BIO18509)

A PAK1/2 INHIBITOR FOR THE TREATMENT OF PSORIASIS AND OTHER NLRP3 INFLAMMASOME MEDIATED IL1B DEPENDENT DISORDERS (BIO18509)

Product factsheet

Preclinical

▶ Target:

- ◆ Serine/ threonine-protein kinase PAK 1/2

▶ Potential Product:

- ◆ a PAK1/2 inhibitor (e.g. IPA-3, FRAX567)

▶ Application:

- ◆ Psoriasis and other NLRP3 Inflammasome mediated IL1b dependent disorders

▶ Rational:

- ◆ Rac1 is highly active in human psoriatic lesional skin and keratinocytes
- ◆ Keratinocyte-specific overexpression of an activated mutant of Rac1, in a transgenic mouse model closely mimics the presentation of human psoriasis
- ◆ RAc1 activation leads to PAK1/2 activation and finally to NLRP3 inflammasome activation
- ◆ Polymorphism NLRP3 association with psoriasis have been identified
- ◆ Expression of NLPR3 in Psoriasis Is Associated with Enhancement of Interleukin-1 β and Caspase-1 in human biopsies
- ◆ IL-1 beta is a key cytokine involved in the progression of psoriasis

▶ POC:

- ◆ Overexpression of the active form of PAK1 (T423E) induces activation of NLRP3 inflammasome
- ◆ The inhibition of PAK1 by siRNA specifically blocks the secretion of IL-1 beta dependent on the NLRP3 inflammasome.
- ◆ Inhibition of PAK1 by inhibitors specifically blocks the secretion of IL-1 beta dependent on the NLRP3 inflammasome.
- ◆ The use of a mouse psoriasis model (IMIQUIMOD) allowed us to show the protective role of the Pak1 inhibitor AZ13711265 on the onset of signs of disease

▶ Patent and publication:

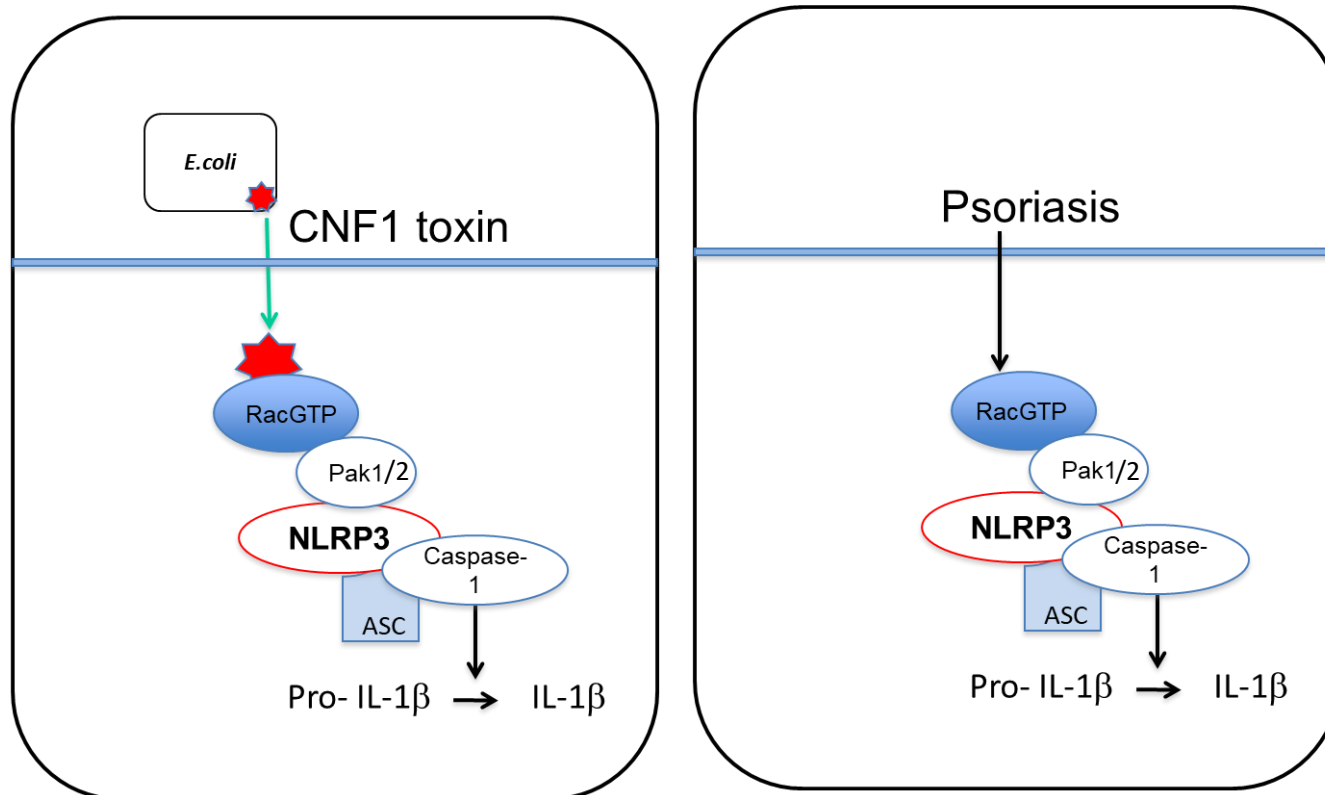
- ◆ EP19 305 502.7 on 2019/04/17 and PCT/EP2020/060701 on 2020/04/16: METHODS AND COMPOSITIONS FOR TREATMENT OF NLRP3 INFLAMMASOME MEDIATED IL-1BETA DEPENDENT DISORDERS

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Proof of concept

Preclinical

Model of NLRP3 inflammasome activation by PAK1



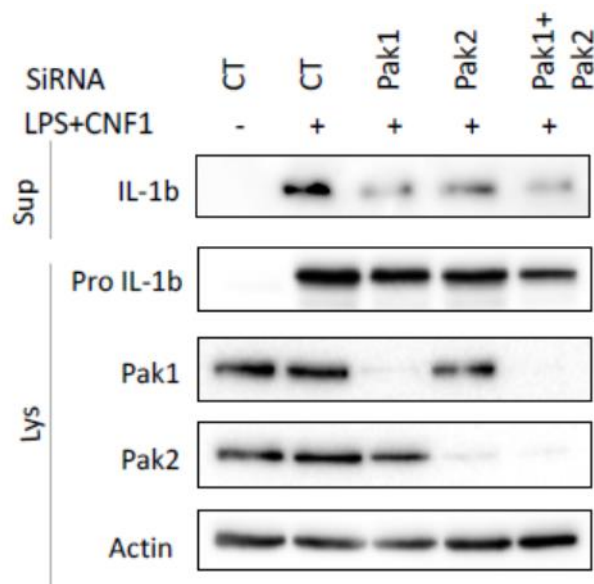
A PAK1/2 INHIBITOR FOR THE TREATMENT OF PSORIASIS AND OTHER NLRP3 INFLAMMASOME MEDIATED IL1B DEPENDENT DISORDERS (BIO18509)

Preclinical

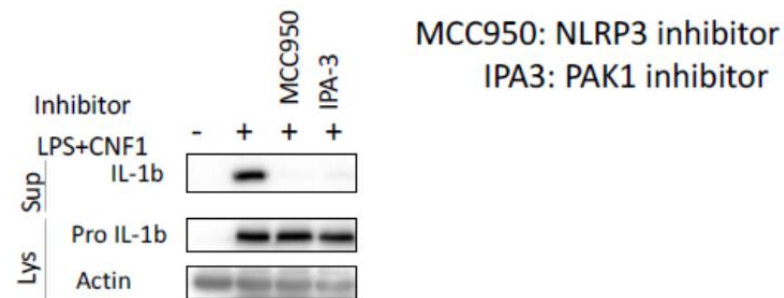
Proof of concept

IL1b secretion is blocked by inhibition of PAK1/2

siRNA experiments



inhibition experiments



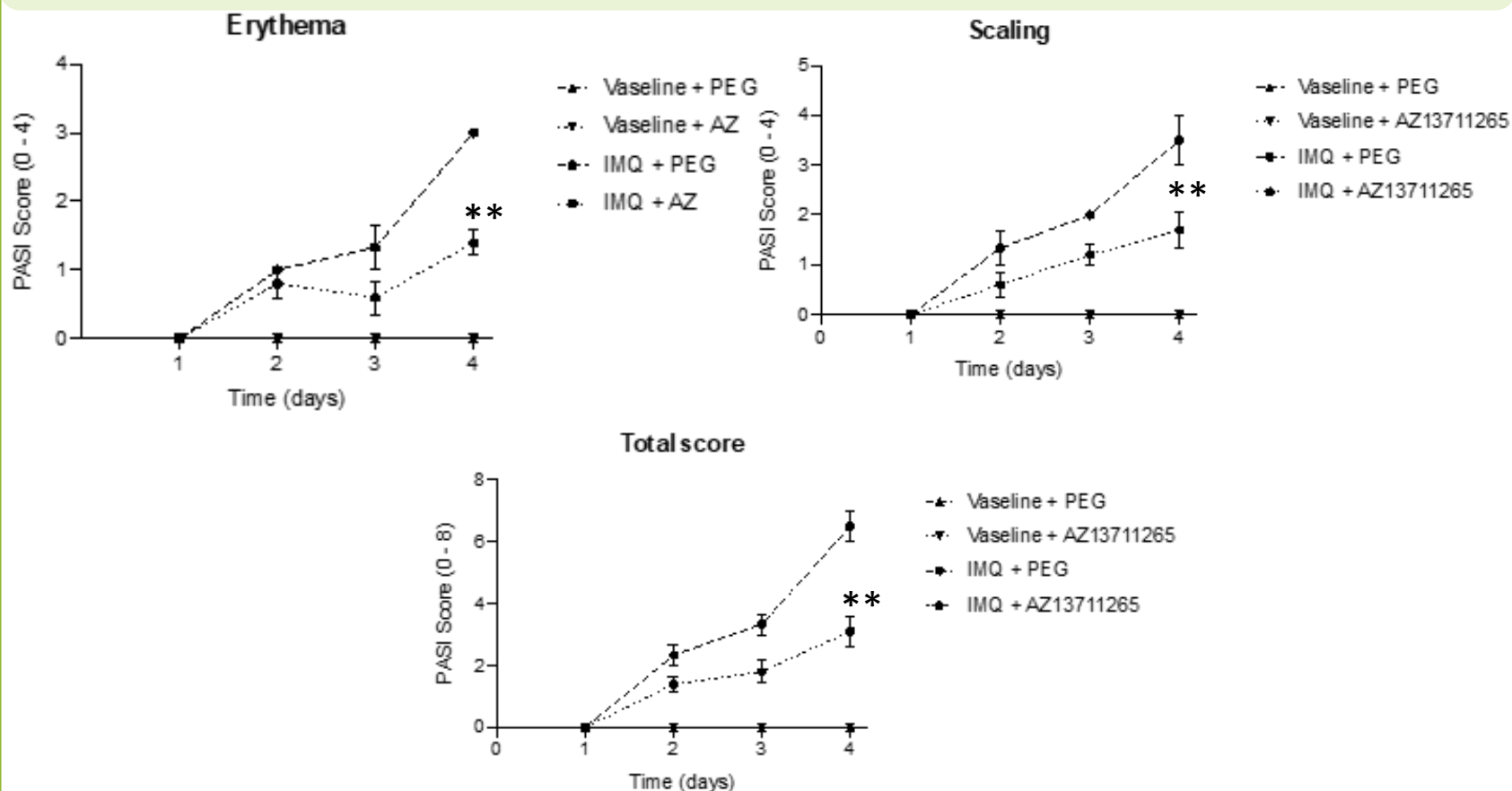
MCC950: NLRP3 inhibitor
IPA3: PAK1 inhibitor

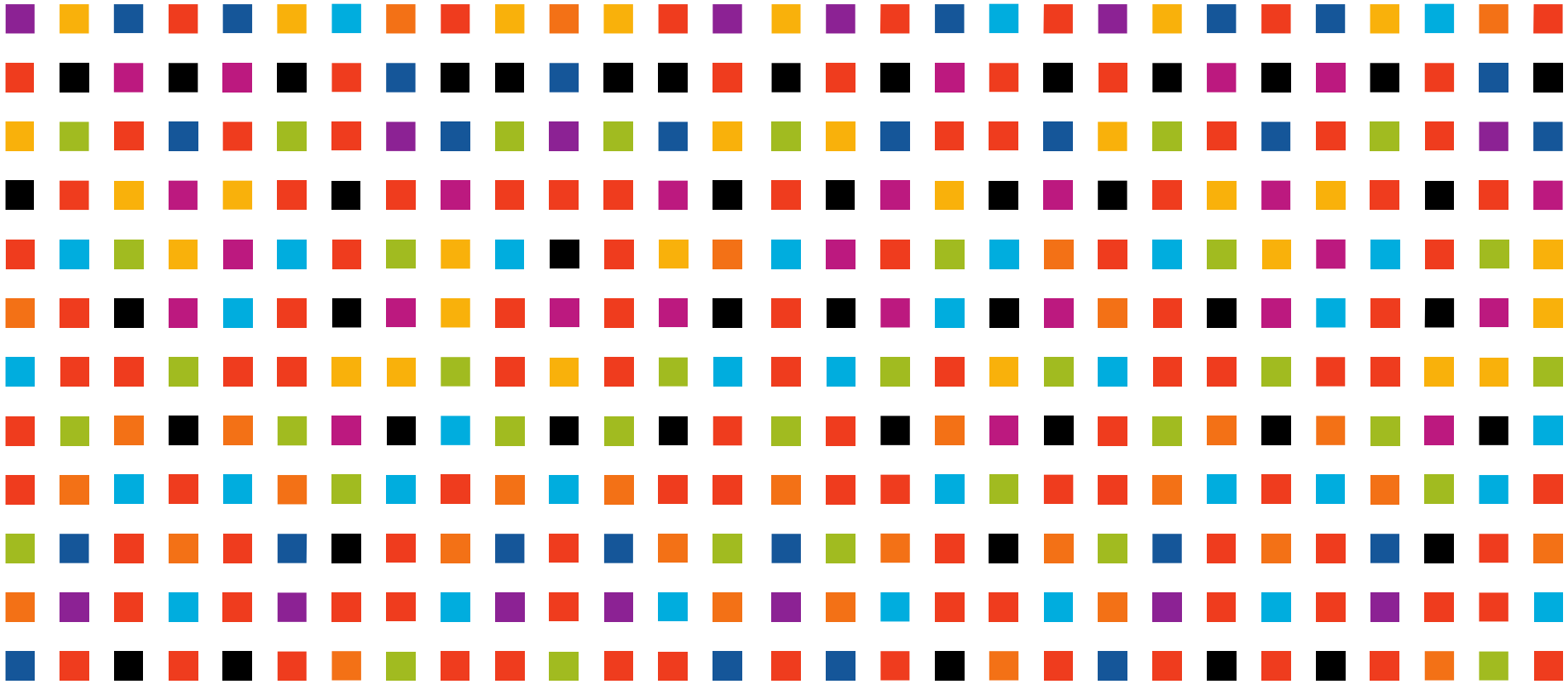
Primary bone marrow derived macrophages isolated from BALB/c mice were treated with vehicle (Control) or treated either with 1µM MCC950 or 5µM IPA-3 for 45 min prior treatment with LPS (100ng/mL) and CNF1 (500ng/mL) for 8h. Supernatants and cell lysates were analyzed by immunoblot.

Primary bone marrow derived macrophages isolated from BALB/c mice were transfected with Pak1 and Pak2 targeting siRNA or with non-targeting siRNA for 72h prior treatment with LPS (100ng/mL) and CNF1 (500ng/mL) for 8h. Supernatants and cell lysates were analyzed by immunoblot.

A PAK1/2 INHIBITOR FOR THE TREATMENT OF PSORIASIS AND OTHER NLRP3 INFLAMMASOME MEDIATED IL1B DEPENDENT DISORDERS (BIO18509)

A Pak1 inhibitor (AZ13711265) has a protective effect on the onset of signs of disease in a mouse psoriasis model (IMIQUIMOD)





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