KU LEUVEN

CENTRUM KLINISCHE FARMACOLOGIE

Challenge agents in target engagement models

24 May 2023

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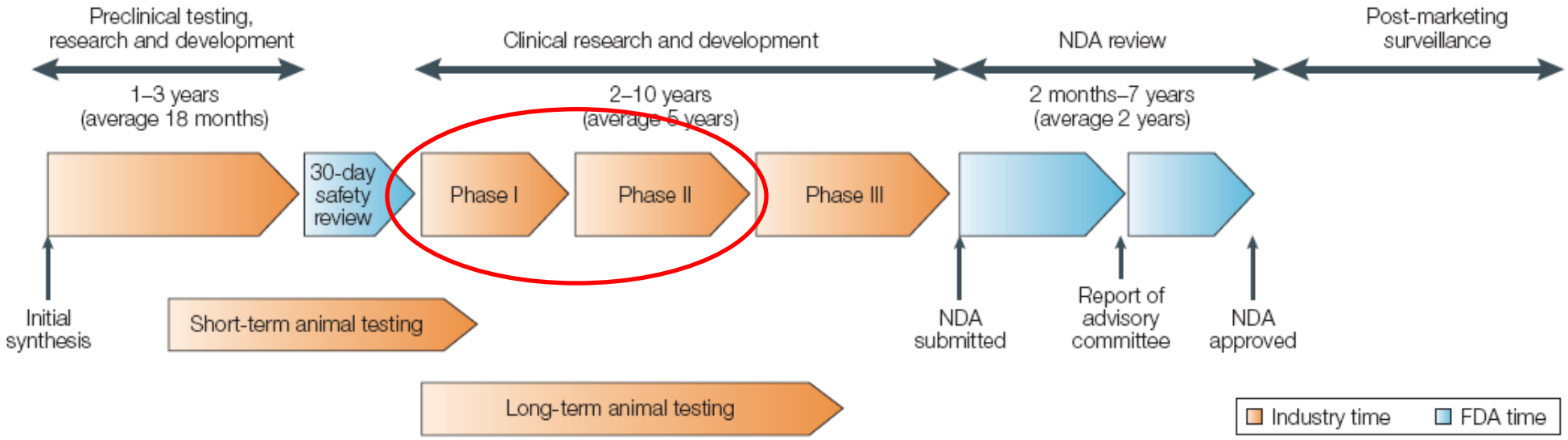
Target Engagement Models

There is a need!



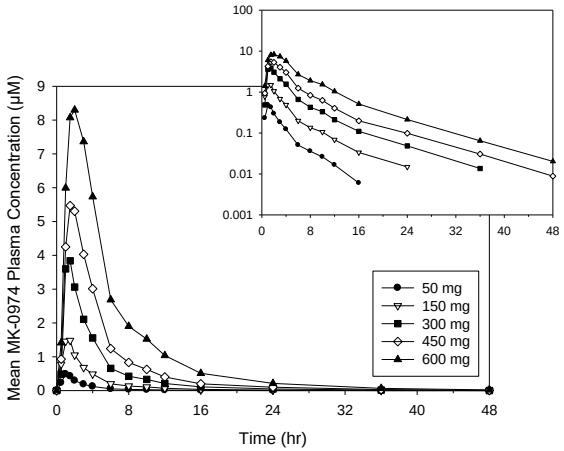
Exploratory phase | **Confirmatory phase**

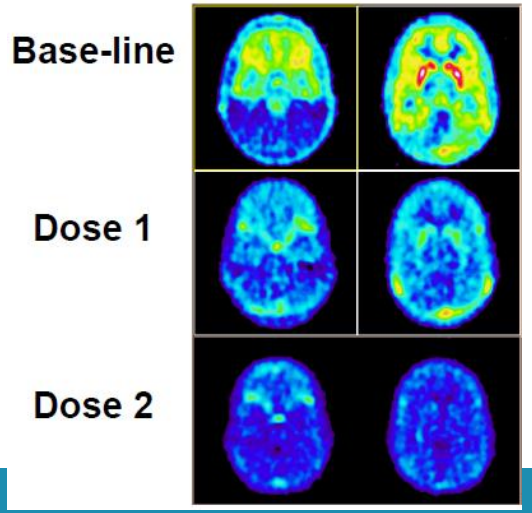
Go / no-go decision
Fail early / fail cheap

Nat Rev Drug Disc 2004; 3: 417-429

Target Engagement Models

There is a need!





DOSE

↓

plasma concentration

↓

target tissue concentration

↓

target receptor concentration

↓

response

⇐ ⇐ ⇐ **pillars of survival**

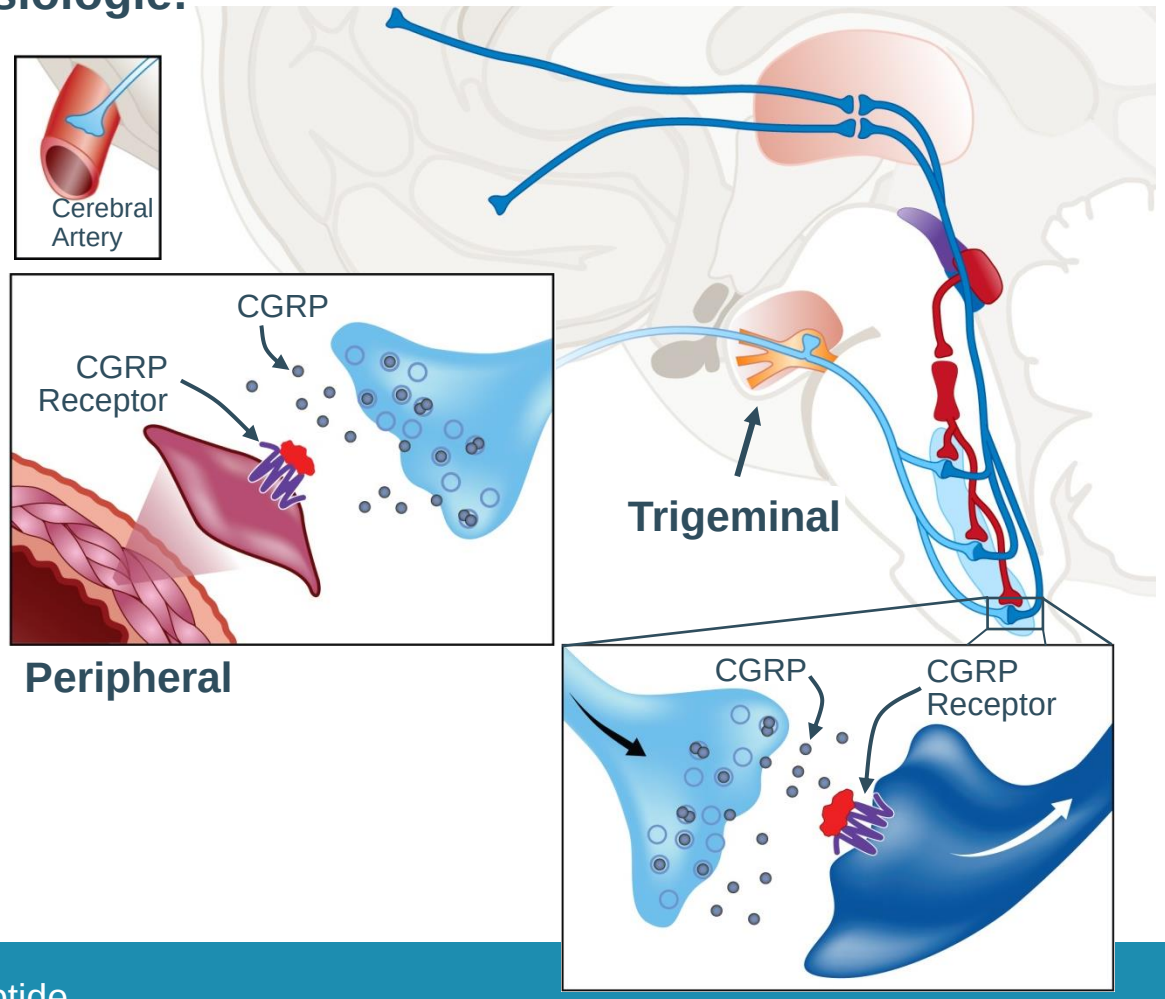
… an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

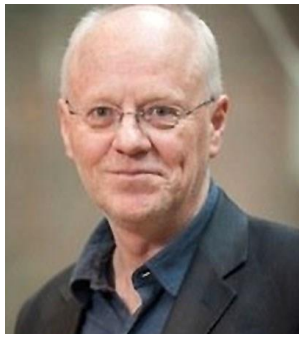
IASP 16 July, 2020

Target Engagement Models

pathophysiology of migraine

Pathofysiologie:





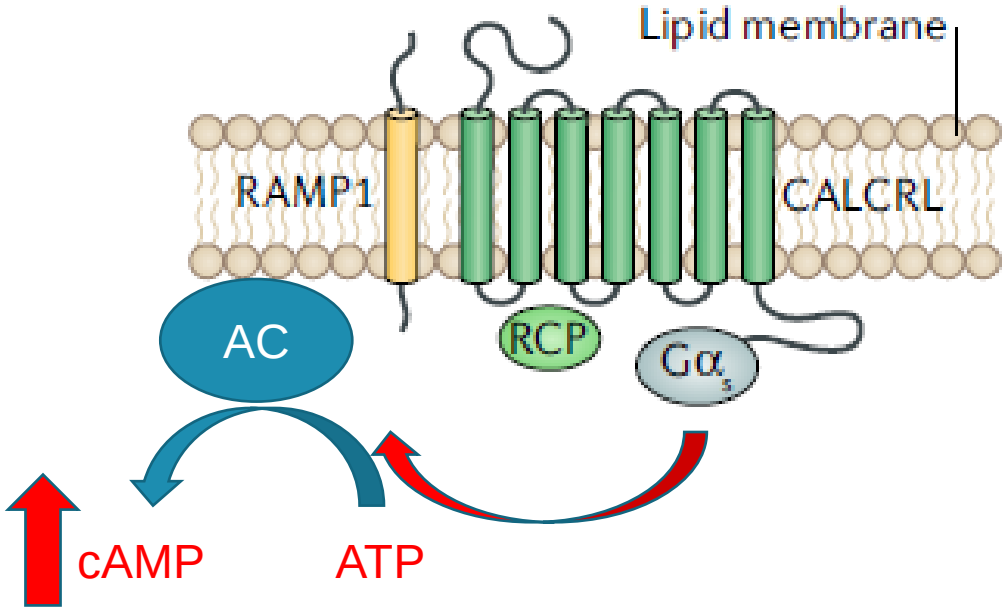
CGRP: Calcitonin Gene-Related Peptide

Target Engagement Models

CGRP: the target to go for…

- Calcitonin Gene-Related Peptide (CGRP):
  - 37 AA neuropeptide
  - Discovered in 1982 (Amara et al.)

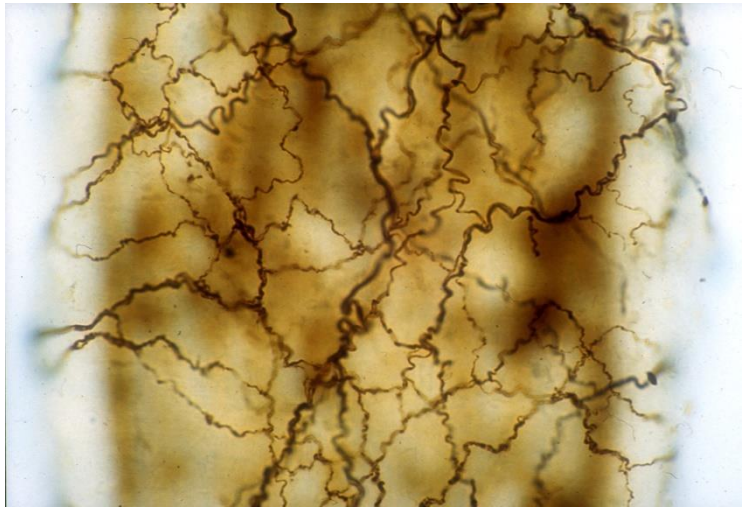
- Interacting with the CGRP-R:
  - G protein-coupled receptor / heterodimer



Target Engagement Models

CGRP: the target to go for…

- Calcitonin Gene-Related Peptide (CGRP):
  - 37 AA neuropeptide
  - Discovered in 1982 (Amara et al.)
- Interacting with the CGRP-R:
  - G protein-coupled receptor / heterodimer
- Very potent vasodilator
- 1990: involvement in migraine



CGRP containing perivascular nerves in rat mesenteric resistance artery

(By courtesy of J. de Mey, Maastricht, The Netherlands)

Target Engagement Models

CGRP: from *concept* to *proof*

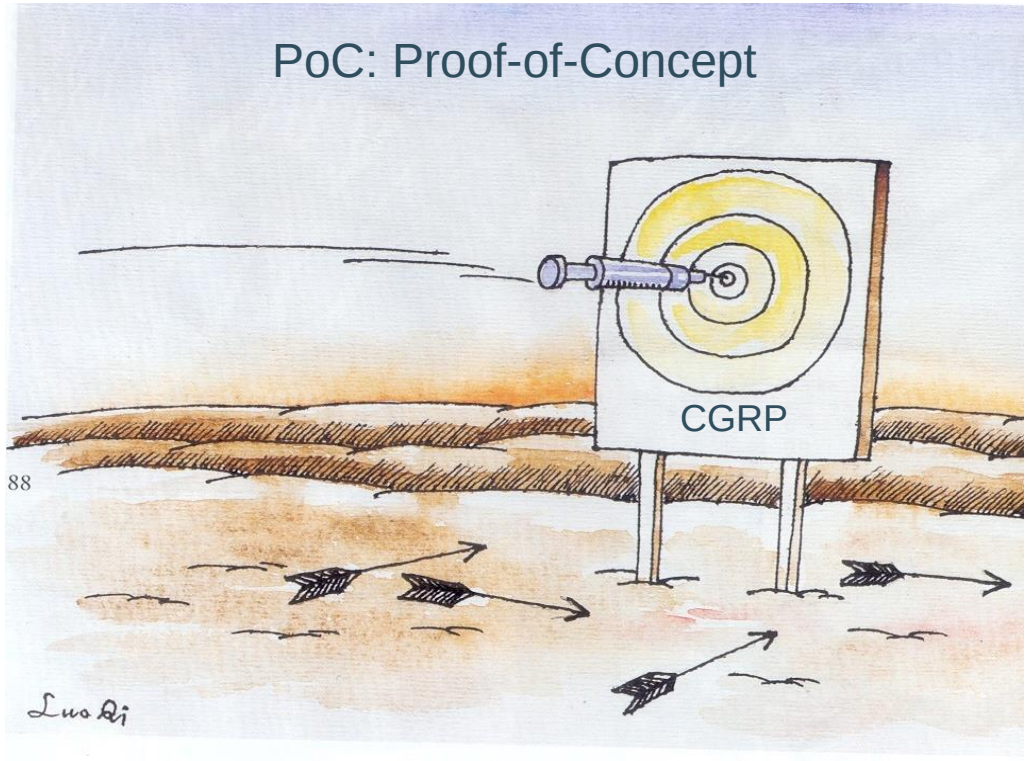
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Calcitonin Gene–Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine

Jes Olesen, M.D., Hans-Christoph Diener, M.D., Ingo W. Husstedt, M.D., Peter J. Goadsby, M.D., David Hall, Ph.D., Ulrich Meier, Ph.D., Stephane Pollentier, M.D., and Lynna M. Lesko, M.D., for the BIBN 4096 BS Clinical Proof of Concept Study Group

N Engl J Med 2004; 350(11): 1104-10



Target Engagement Models

CGRP: from *concept* to *proof*

FARMACOLOGIE

Target Engagement Models

from basic to clinical pharmacology

Calcitonin gene-related peptide is a potent vasodilator

S. D. Brain*, T. J. Williams*, J. R. Tippins†, H. R. Morris† & I. MacIntyre‡

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK
† Department of Biochemistry, Imperial College, London SW7 2AZ, UK
‡ Department of Chemical Pathology, Royal Postgraduate Medical School, DuCane Road, London W12 0HS, UK

Brain S. et al. *Nature* 1985; 313: 54-56

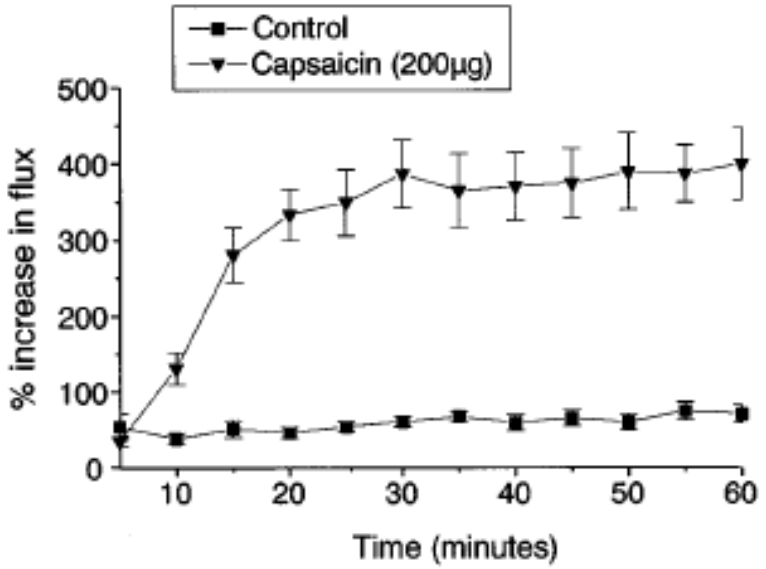
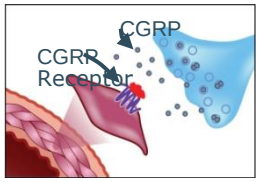


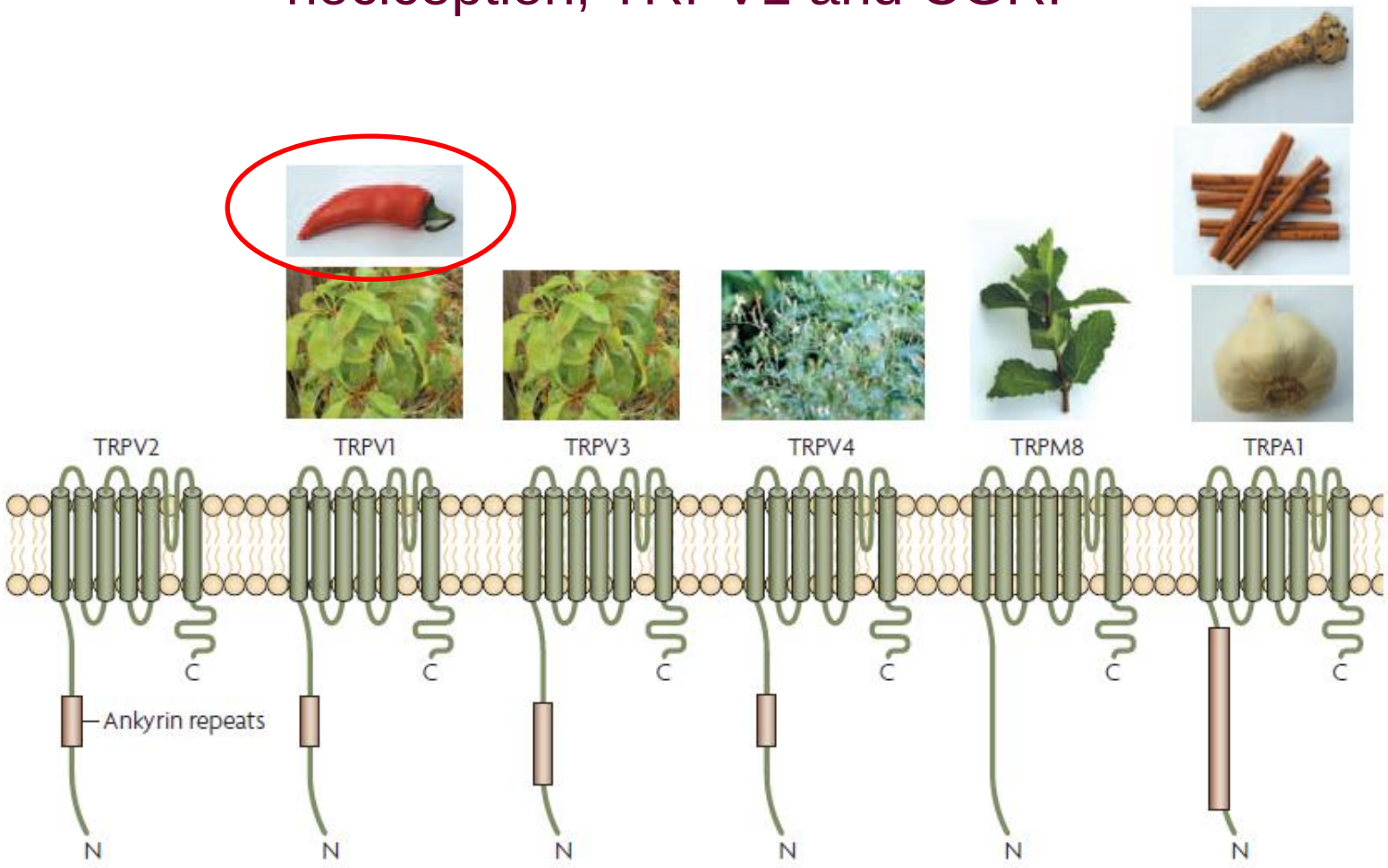
Figure 1 Effect of topically applied capsaicin (200 μg) on blood flow to the CD1 mouse ear, measured over 60 min. Results are expressed as percentage increase over the minimum measured flux, mean ± s.e.mean, $n=10$. $^{**}P<0.01$ compared to ethanol-treated control values.

Br J Pharmacol 2002; 135: 356-362



Target Engagement Models

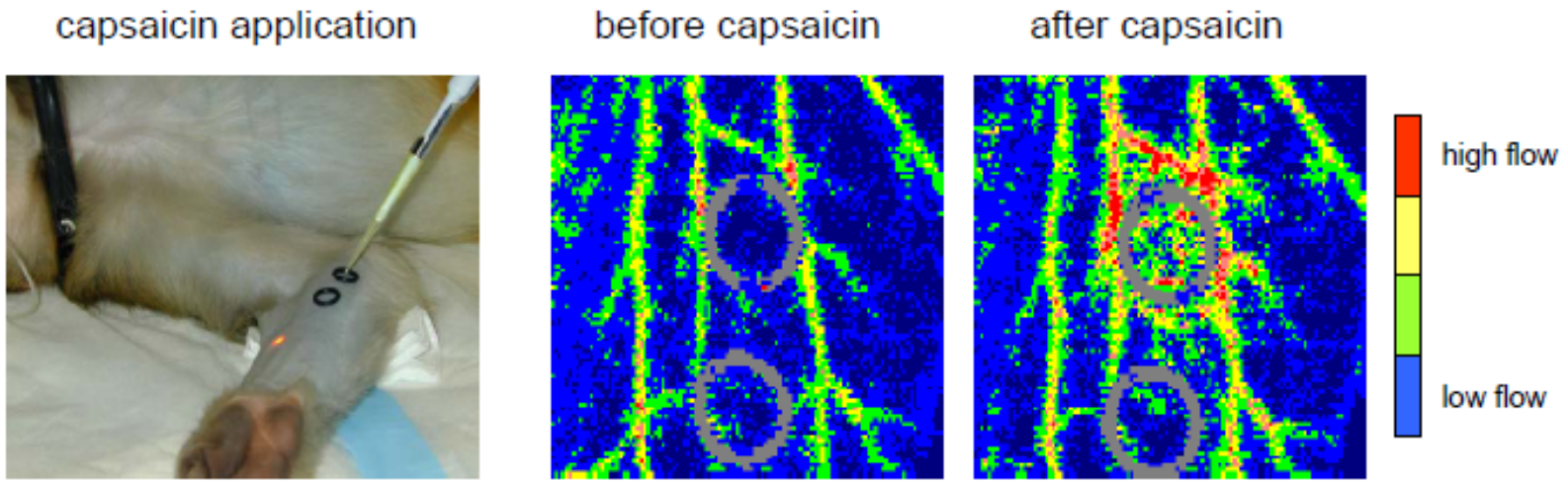
nociception, TRPV1 and CGRP



Nature Drug Rev Disc 2007; 6, 357-372

Target Engagement Models

from basic to clinical pharmacology: non-human primate

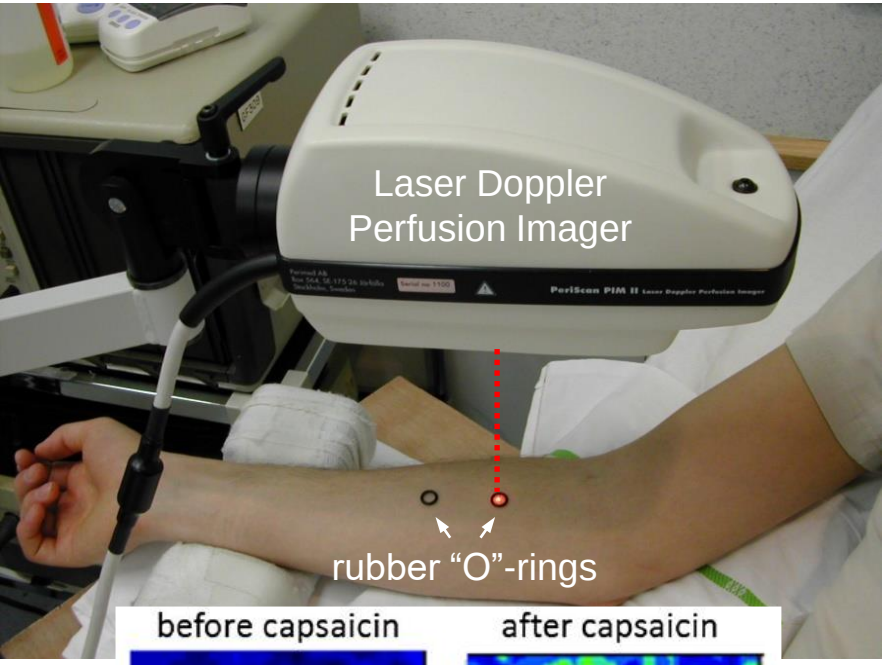


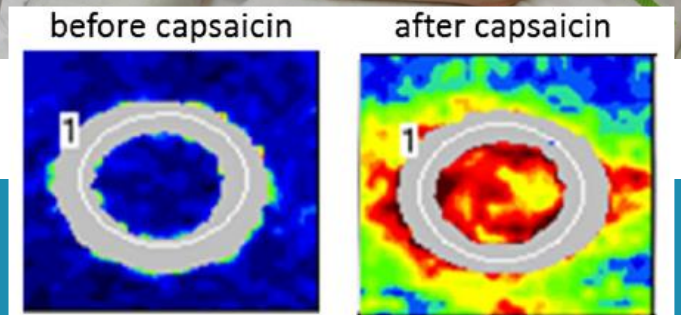
Hershey et al. *Regulatory Peptides* 2005; 127: 71

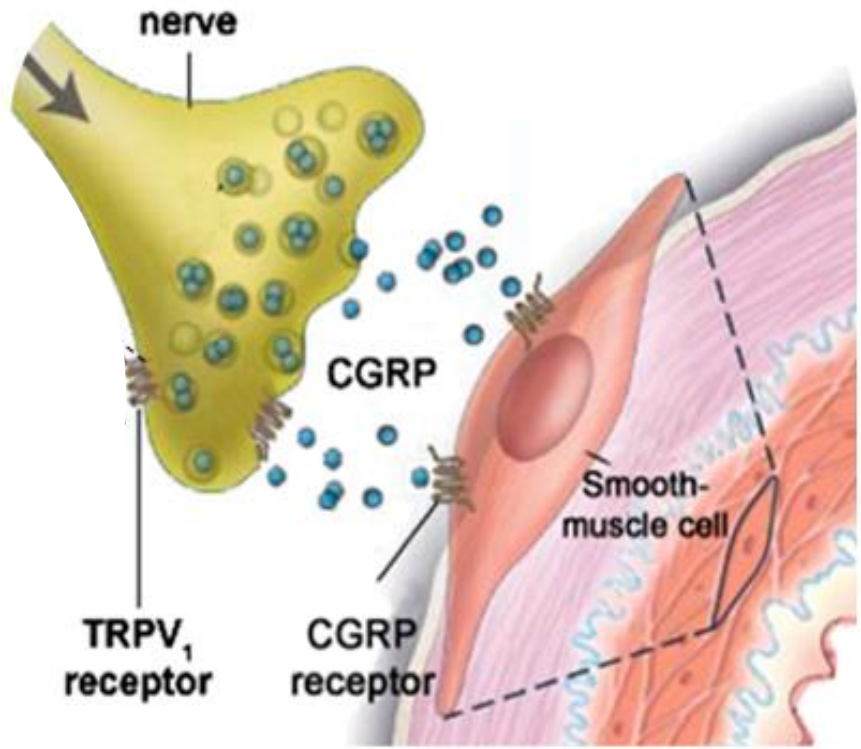
By courtesy of S.A. Kane, Merck Research Laboratories

Target Engagement Models

from basic to clinical pharmacology: human primate…

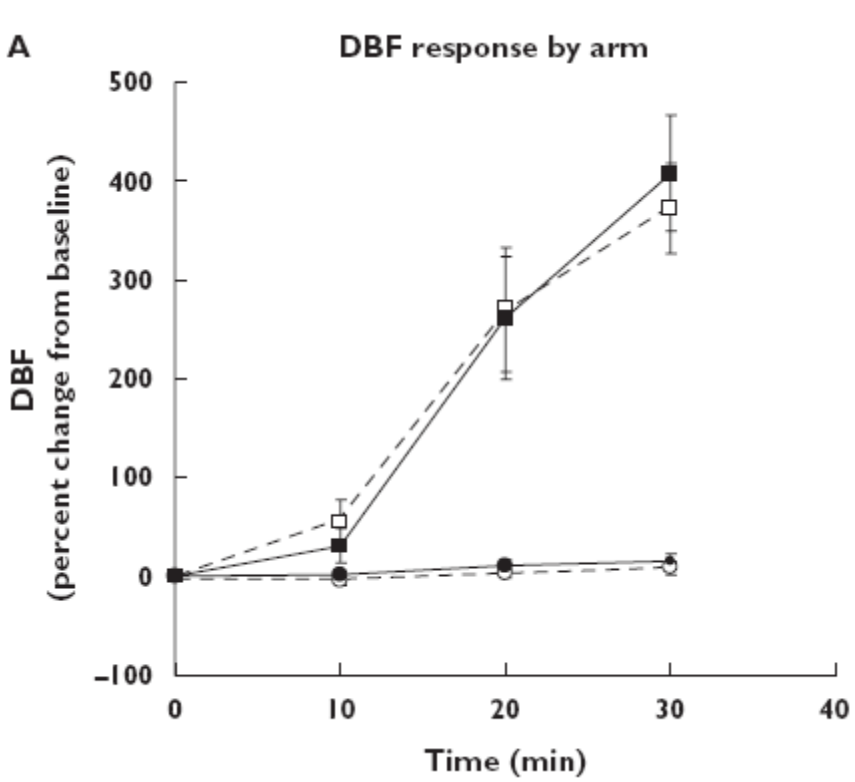


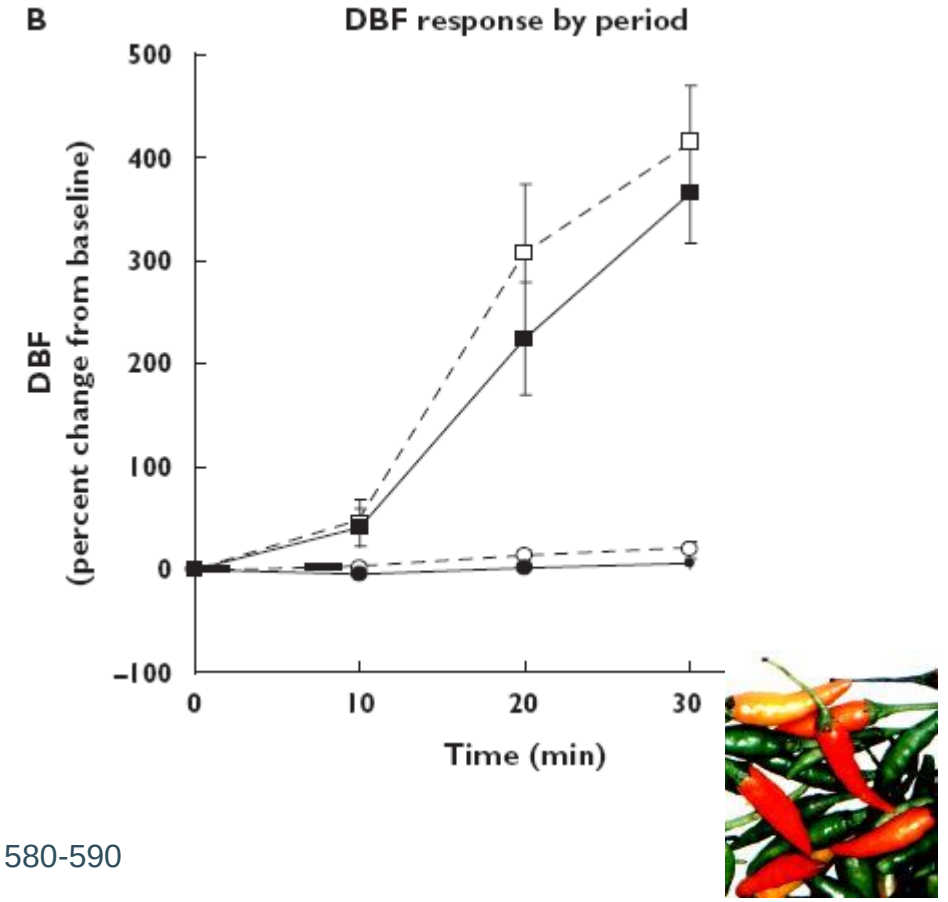




Target Engagement Models

from basic to clinical pharmacology: reproducibility

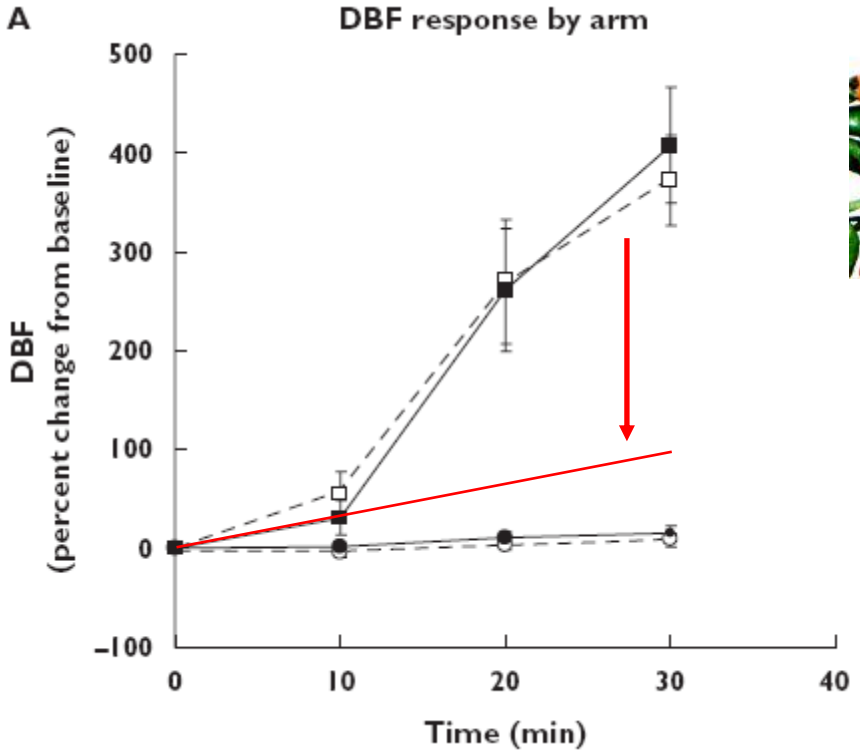


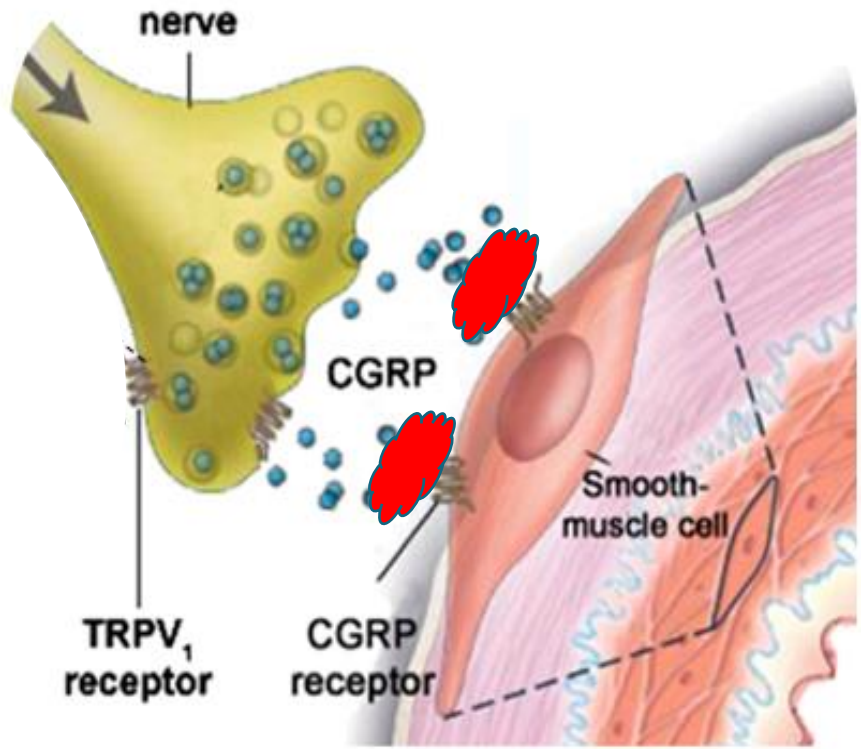


Van der Schueren et al. *Br J Clin Pharmacol* 2007; 64: 580-590

Target Engagement Models

from basic to clinical pharmacology: reproducibility

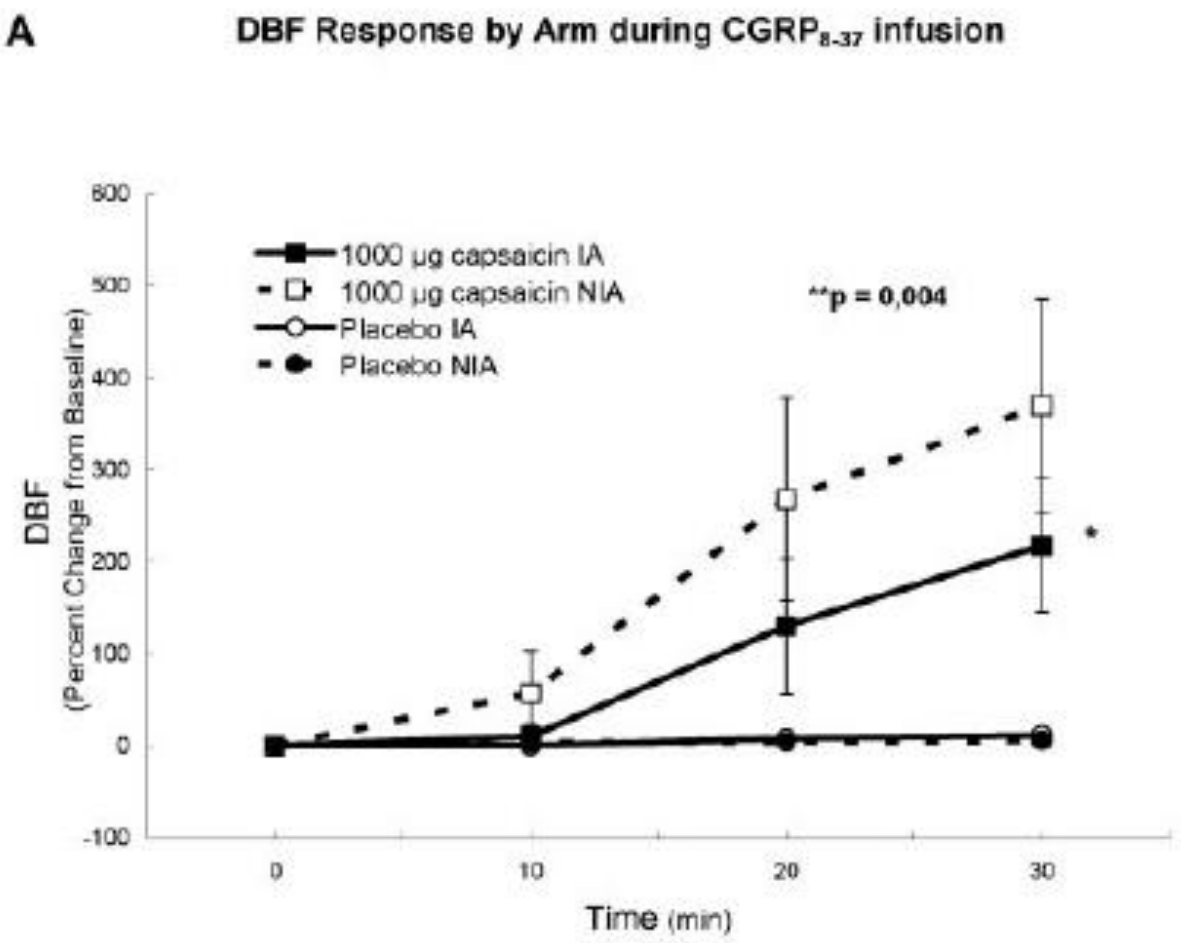




Br J Clin Pharmacol 2007; 64: 580-590

Target Engagement Models

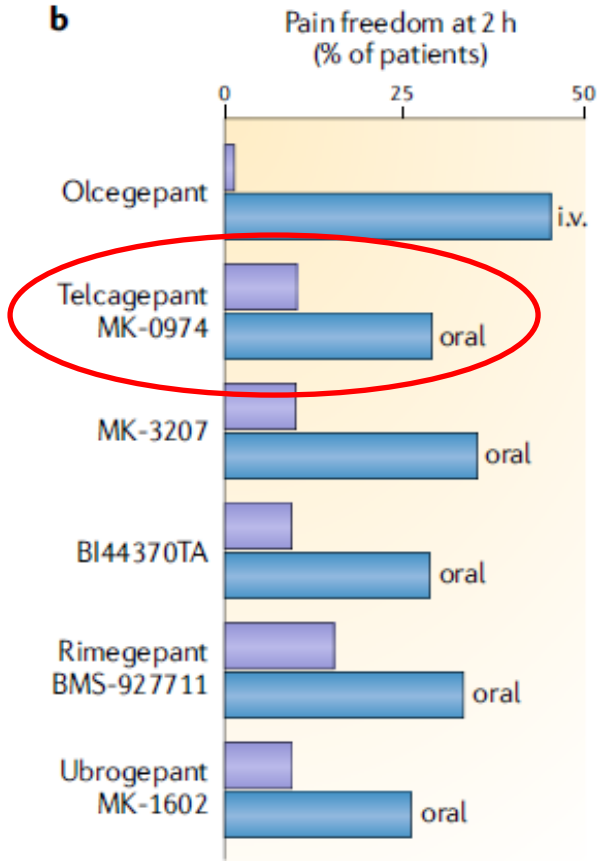
from basic to clinical pharmacology: validation



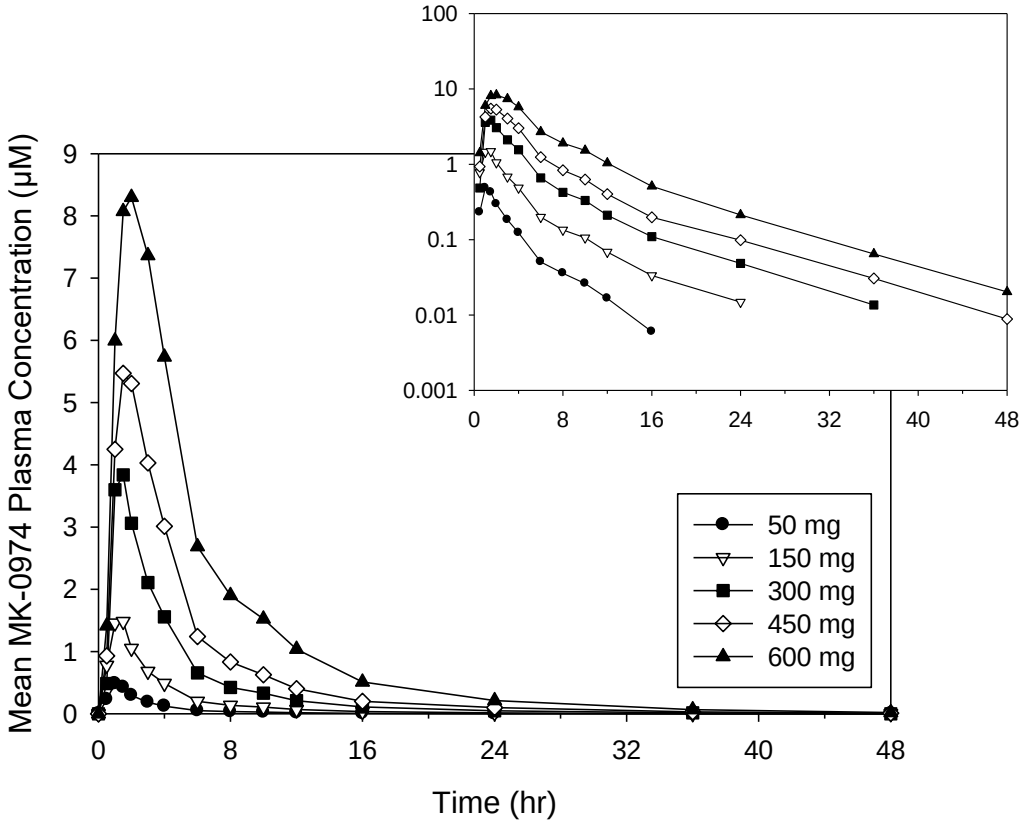
Van der Schueren et al. *J Pharmacol Exp Ther* 2008; 325: 248-255

Target Engagement Models

small molecule CGRP-R antagonists: “gepants”



MK-0974: “born” on 27 September 2004



Nature Rev Neurol 2018

Cephalalgia 2009: Vol. 29 Suppl. 1 PO02 (IHS congress Philadelphia, 2009)

Target Engagement Models

small molecule CGRP-R antagonists: the curse…

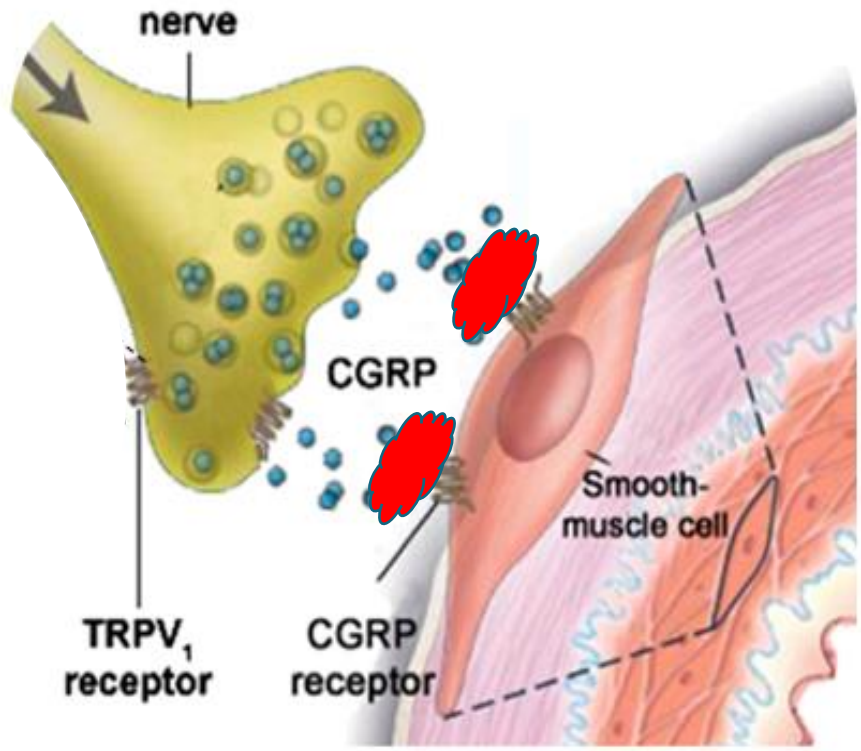
BJCP British Journal of Clinical Pharmacology

Inhibition of capsaicin-induced increase in dermal blood flow by the oral CGRP receptor antagonist, telcagepant (MK-0974)

Br J Clin Pharmacol 2009; 69: 15-22

11 September 2009

U.S. Pharma major Merck & Co provided an update on its migraine drug research pipeline with particular emphasis on the latest results for MK-0974 and MK-3207…



Target Engagement Models

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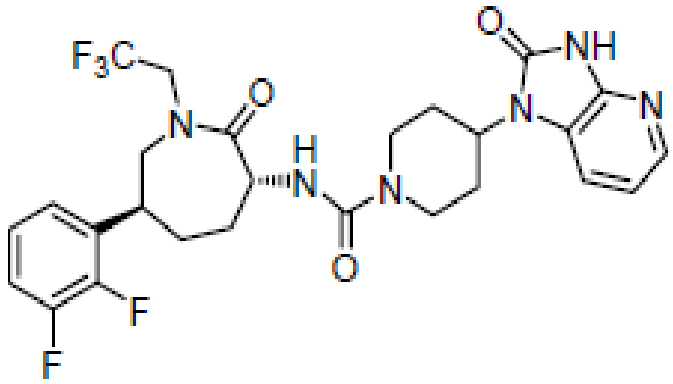
Hepatotoxic!



MK-0974: “killed” by hepatotoxicity

Target Engagement Models

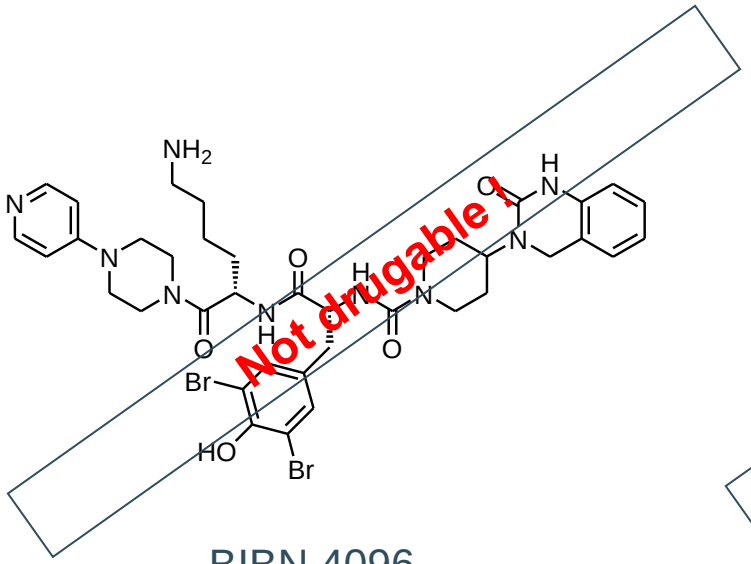
small molecule CGRP-R antagonists: the curse…

Target Engagement Models

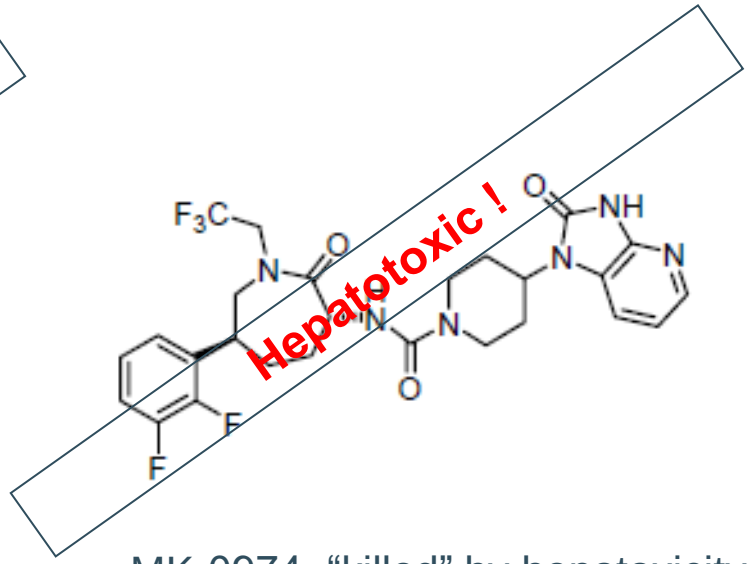
from small molecules to mAbs: from cure to prevention

CGRP-receptor antagonists:

From small molecules (“**gepants**”) to… biologicals



BIBN 4096



MK-0974: “killed” by hepatoxicity

Antibody drugs set to revive flagging migraine target

CGRP makes a comeback as antibodies advance into Phase II trials.

Nature Drug Rev Disc 2013; 12: 249-250

Target Engagement Models

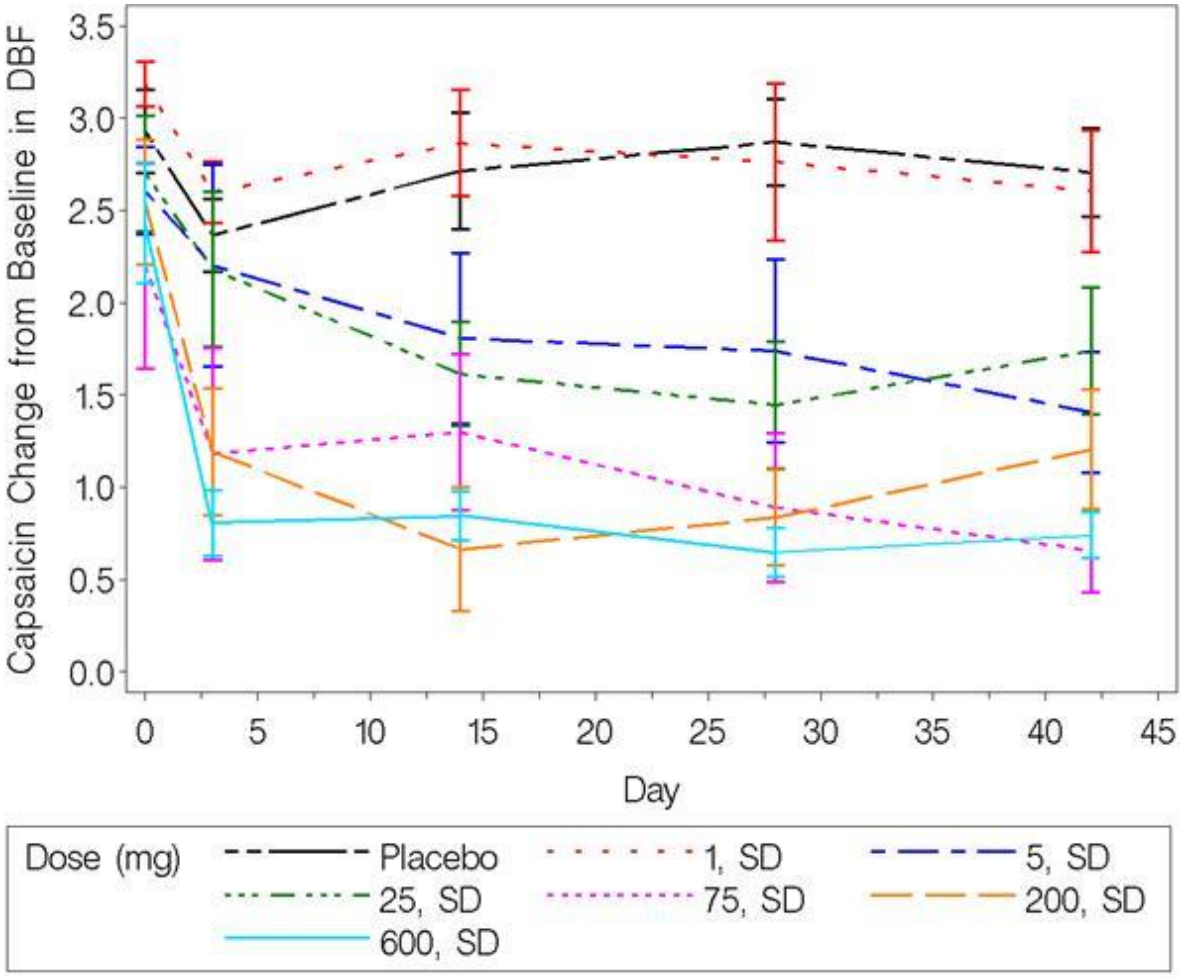
from small molecules to mAbs: from cure to prevention

Code	Name	Target	Class of mAb
LY2951742	Galcanezumab	CGRP ligand	Humanized IgG4
ALD403	Eptinezumab	CGRP ligand	Humanized IgG1
TEV-48125 / LBR-101	Fremanezumab	CGRP ligand	Humanized IgG2a
AMG 334	Erenumab	CGRP receptor	Fully human IgG2

mAb = monoclonal antibody

Target Engagement Models

CGRP binding mAb: LY2951742



J. de Hoon et al., *Cephalalgia* 2013; vol 33(8 Suppl): 247-248, P367; (IHC Boston, 2013)

S. Vermeersch et al., *Cephalalgia* 2013; vol 33(8 Suppl): 249-250, P370; (IHC Boston, 2013)

Target Engagement Models

CGRP binding mAb: LY2951742

mAb	Target	Phase II dose	50% response rate (%)
LY2951742	CGRP	150 mg SC	47
ALD403	CGRP		
TEV-48125 / LBR-101	CGRP		
AMG 334	CGRP-R		

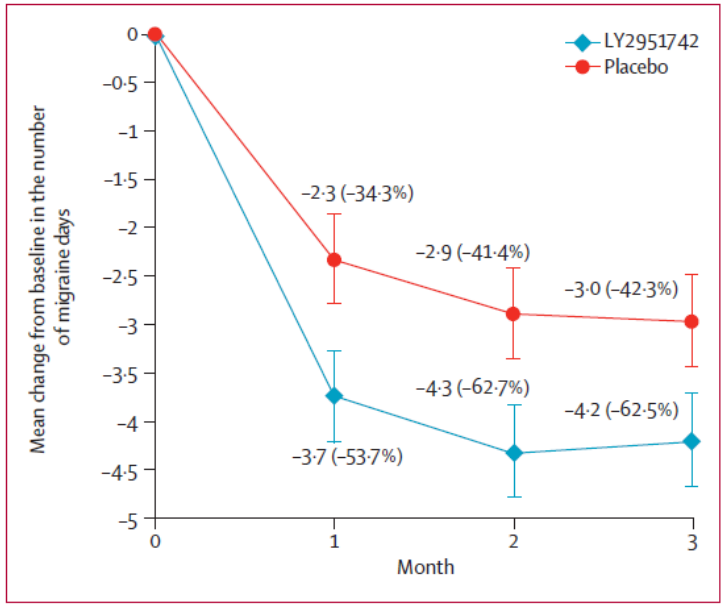


Figure 3: **Mean change from baseline in the number of migraine headache days during the treatment period**
Bars show the 90% CIs. p values were not calculated for months 1 and 2.

Dodick et al., *Lancet Neurol*, 2014; 13: 885-892

Target Engagement Models

CGRP-receptor binding mAb: AMG 334

Phase I, Randomized, Double-blind, Placebo-controlled, Single-dose, and Multiple-dose Studies of Erenumab in Healthy Subjects and Patients With Migraine

Jan de Hoon[1], Anne Van Hecken[1], Corinne Vandermeulen[1], Lucy Yan[2], Brian Smith[2], Jiyun Sunny Chen[2], Edgar Bautista[2], Lisa Hamilton[3], Javier Waksman[4], Thuy Vu[2] and Gabriel Vargas[2]

Phase 1(b) / Phase 2

Phase 1(a)

Table 1 Baseline demographic characteristics

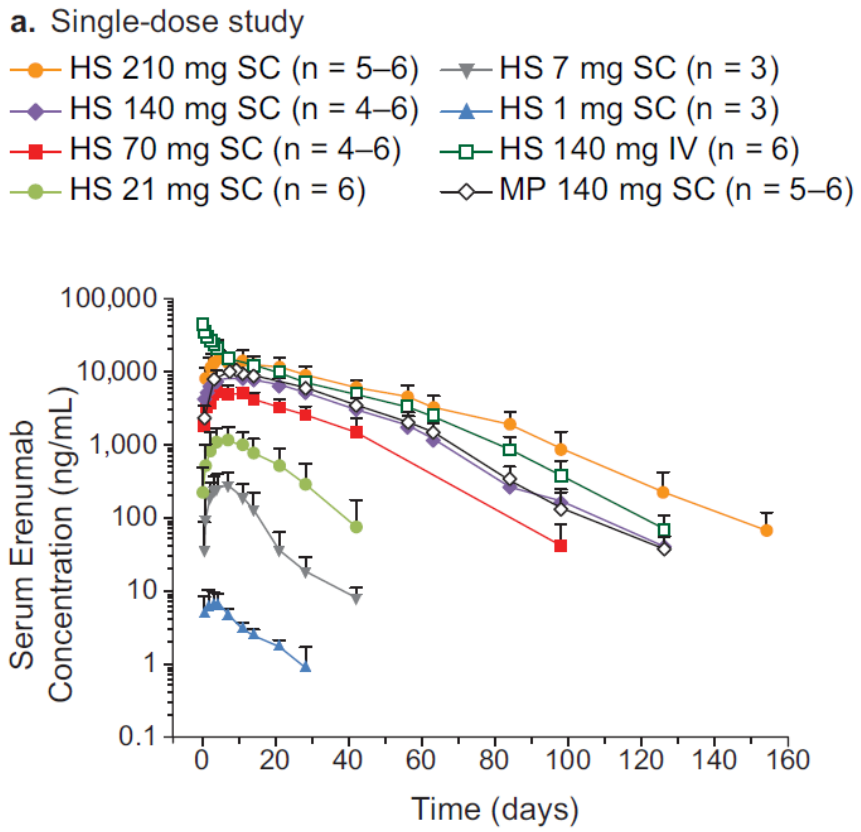
	Single-dose study				Multiple-dose study			
	Healthy subjects		Patients with migraine		Healthy subjects		Patients with migraine	
Variable	Placebo ($n = 12$)	Erenumab ($n = 36$)	Placebo ($n = 6$)	Erenumab ($n = 6$)	Placebo ($n = 8$)	Erenumab ($n = 24$)	Placebo ($n = 4$)	Erenumab ($n = 12$)
Men, n (%)	12 (100)	36 (100)	2 (33.3)	1 (16.7)	8 (100)	21 (87.5)	1 (25.0)	3 (25.0)
Mean age (range), years	28.6 (21–43)	27.1 (19–42)	28.5 (20–50)	23.8 (18–33)	32.1 (20–50)	32.1 (18–55)	37.0 (21–49)	31.5 (19–49)
Mean BMI (SD), kg/m^2	25.5 (1.3)	24.2 (2.6)	22.3 (2.3)	22.4 (3.8)	24.2 (3.8)	23.5 (3.7)	25.8 (2.3)	23.0 (3.1)

BMI, body mass index; SD, standard deviation.

de Hoon et al. Clin Pharm Ther (2017)

Target Engagement Models

CGRP-receptor binding mAb: AMG 334



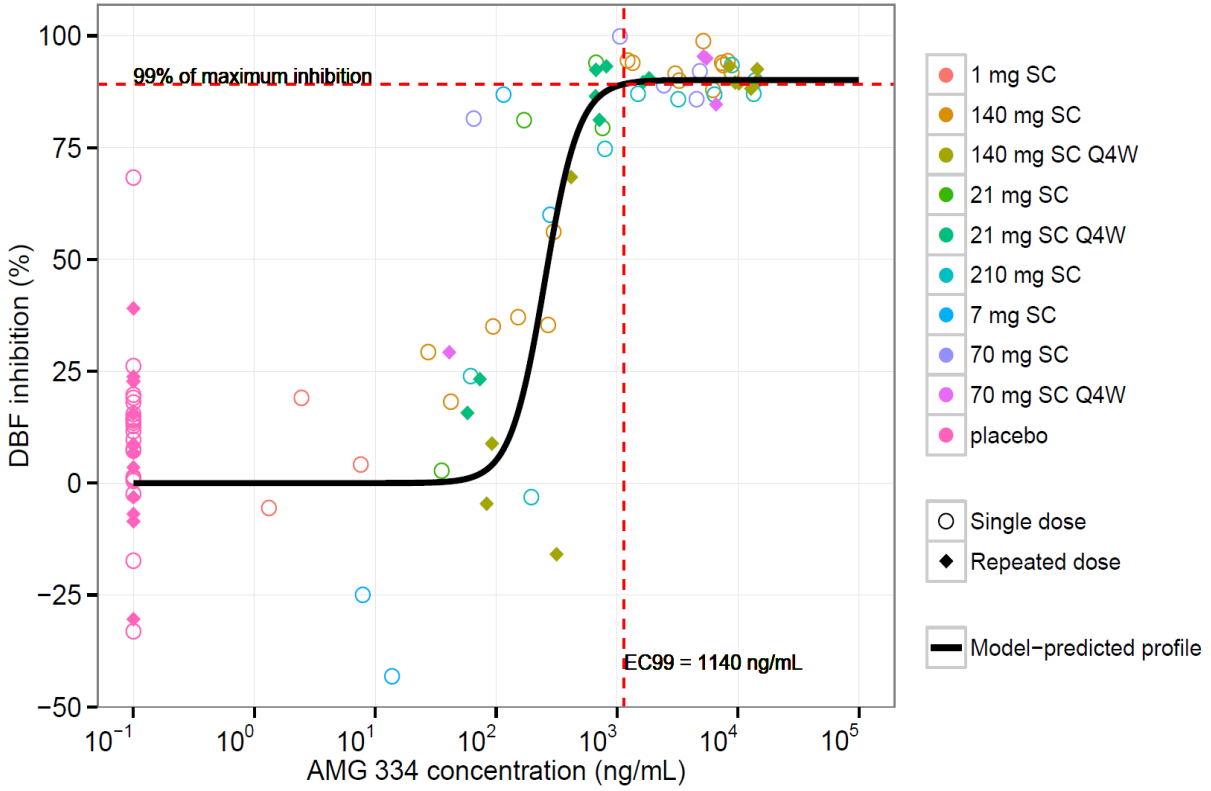
HS, healthy subject; IV, intravenous; MP, patients with migraine; PK, pharmacokinetic; SC, subcutaneous

Figure 1 Mean serum erenumab concentration–time profiles by cohort in the single-dose (a) and multiple-dose (b) studies.

de Hoon et al. Clin Pharm Ther (2017)

Target Engagement Models

CGRP-receptor binding mAb: AMG 334



Target Engagement Models

alternatives?

Annual Review of Pharmacology and Toxicology

TRP Channels as Potential Drug Targets

Magdalene M. Moran

Hydra Biosciences, Cambridge, Massachusetts 02138, USA; email: mmoran@hydrabio.com

Target Engagement Models

TRPA1 and nociception

Neuron

Clinical Study

A Gain-of-Function Mutation in TRPA1 Causes Familial Episodic Pain Syndrome

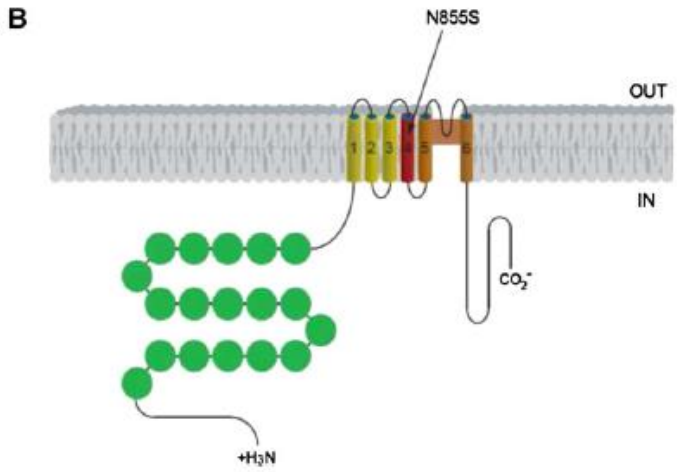
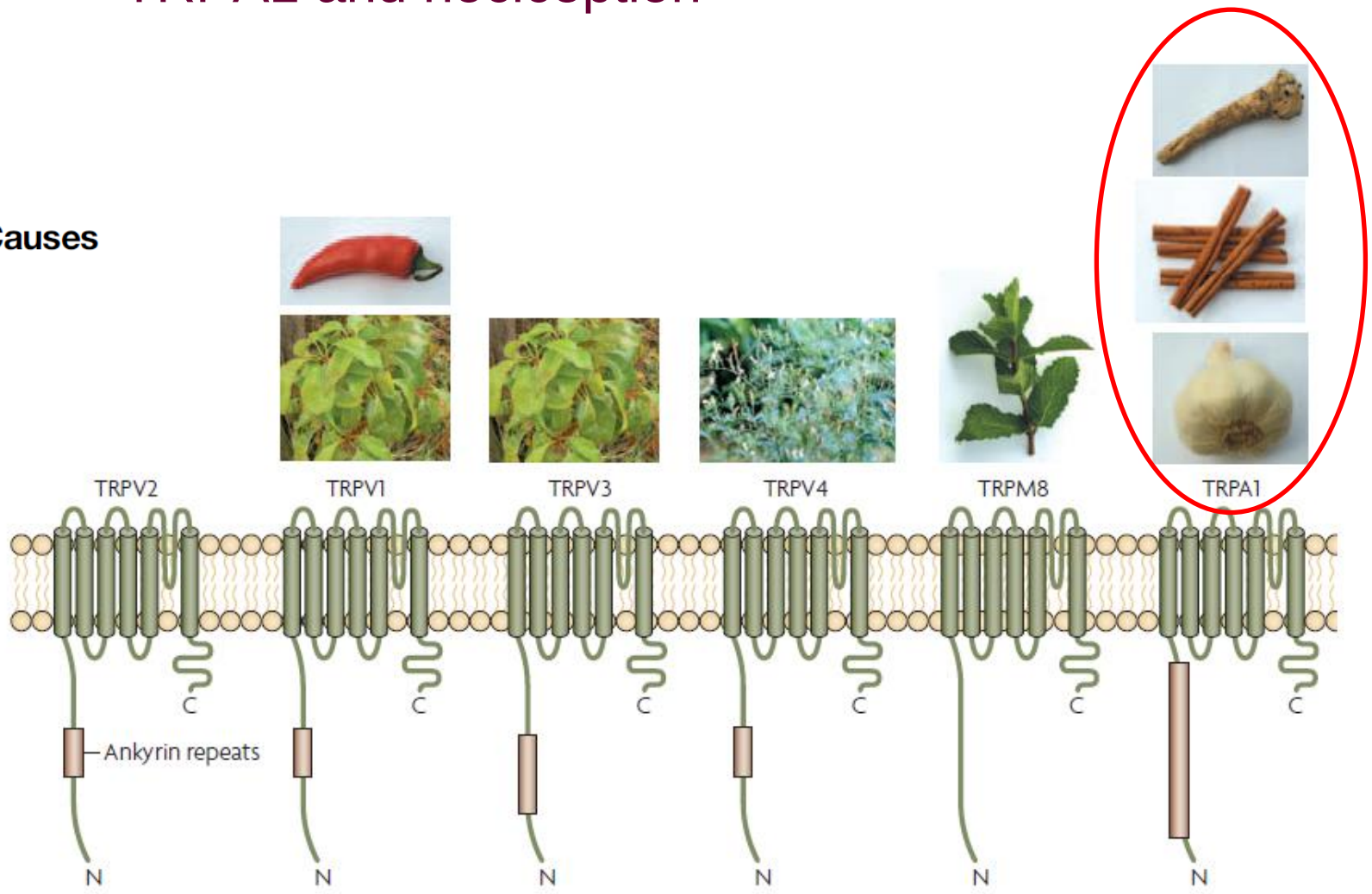


Figure 2. Identification of a Point Mutation Underlying FEPS

Neuron 2010; 66: 671-680



Nature Drug Rev Disc 2007; 6, 357-372

Target Engagement Models

TRPA1: AITC model

Received: 9 December 2019 | Revised: 27 April 2020 | Accepted: 1 May 2020

DOI: 10.1111/bcp.14370

ORIGINAL ARTICLE

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Development of AITC-induced dermal blood flow as a translational in vivo biomarker of TRPA1 activity in human and rodent skin

Victory Joseph[1] | Xiaoying Yang[2] | Simon S. Gao[3] | Justin Elstrott[1] | Robby M. Weimer[1] | Wiebke Theess[4] | Cory Thrasher[5] | Nand Singh[6] | Joseph Lin[4] | Rebecca N. Bauer[7]

Target Engagement Models

TRPA1: AITC model in rodent

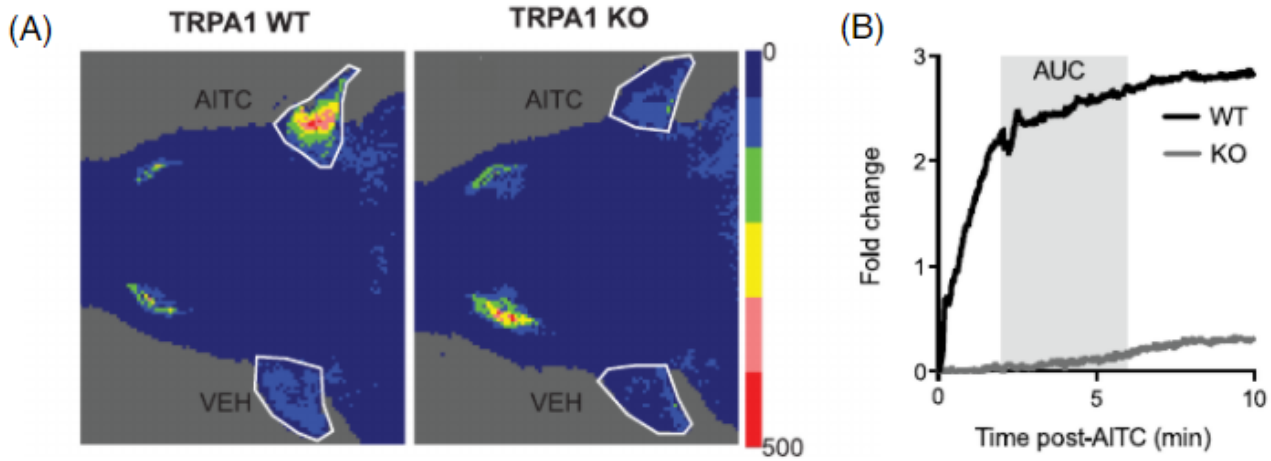


FIGURE 1 Agonist-induced dermal blood flow measured with laser speckle contrast imaging (LSCI) in rats. A, Flux signal 5 minutes after application of mineral oil (VEH) and 5% AITC (allyl isothiocyanate) to the ears of representative TRPA1 WT (left) and TRPA1 KO (right) animals. White outlines indicate regions of interest used for analysis. Colour scale in arbitrary units. B, Time-course of mean fold change in the flux signal for TRPA1 WT (black) and KO (grey) rats on the AITC-treated ear relative to baseline (mean flux signal prior to AITC treatment). Area under the curve (AUC) from 2 to 6 minutes was used to compare change in flux between groups. C, Flux AUC was significantly reduced in TRPA1 KO rats relative to WT rats in response to AITC (left, $P = 0.0001$, t test, n = 8/group) and citric acid (middle, $P = 0.03$, t test, n = 6/group), but not capsaicin (right, $P = 0.7$, t test, n = 4/group). Mean ±SD

Target Engagement Models

TRPA1: AITC model in human

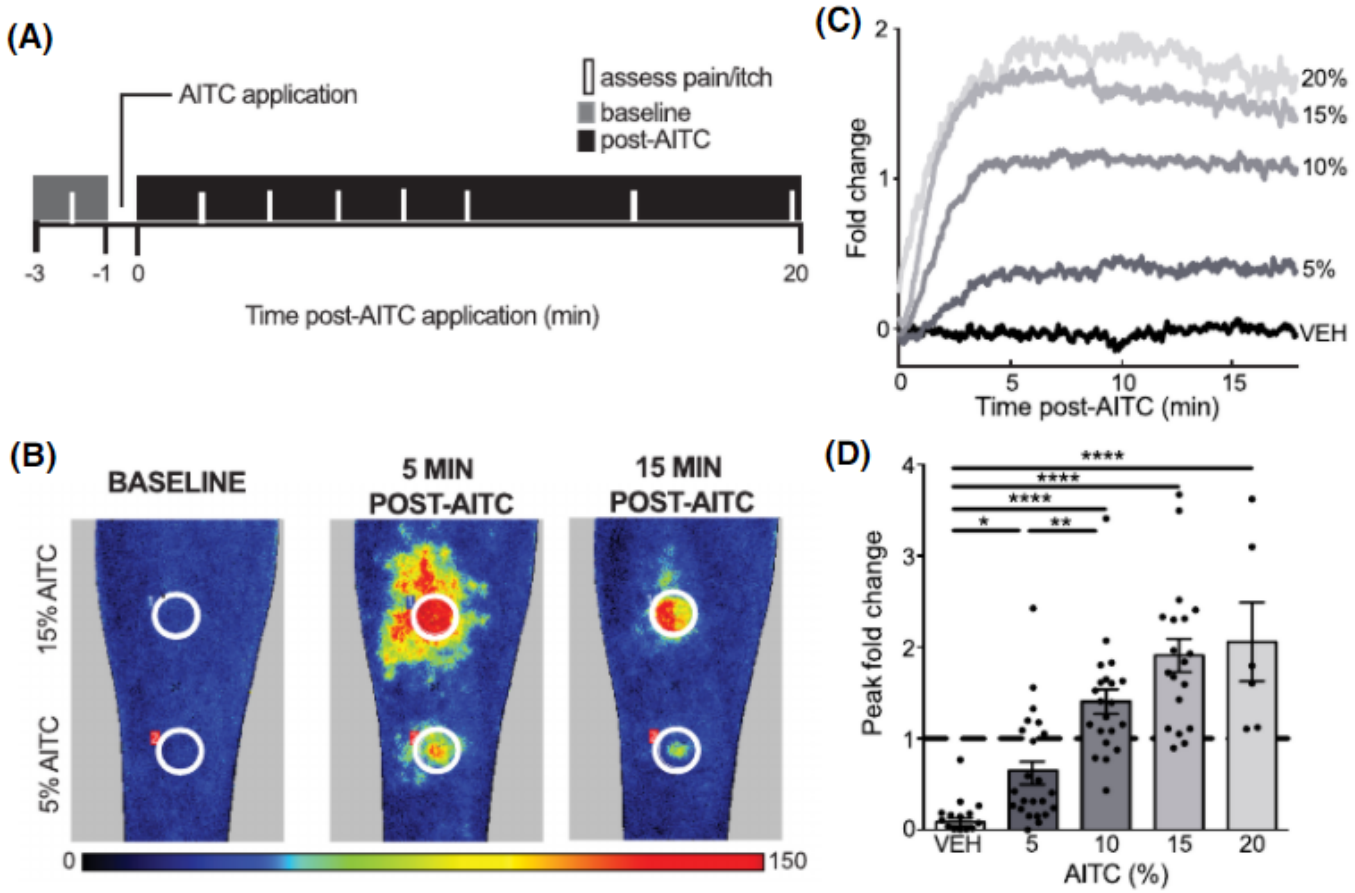


FIGURE 2 AITC-induced dermal blood flow measured with LSCI in humans. A, Schematic of experiment design. Subjects were imaged 2 minutes prior to AITC application (grey box, baseline) and asked to rate their pain and itch (white dashes). Imaging continued during AITC application and for 20 minutes post-AITC application (black box). Pain and itch were assessed at 2, 4, 6, 8, 10, 15 and 20 minutes post AITC

Target Engagement Models

TRPA1: AITC model in human

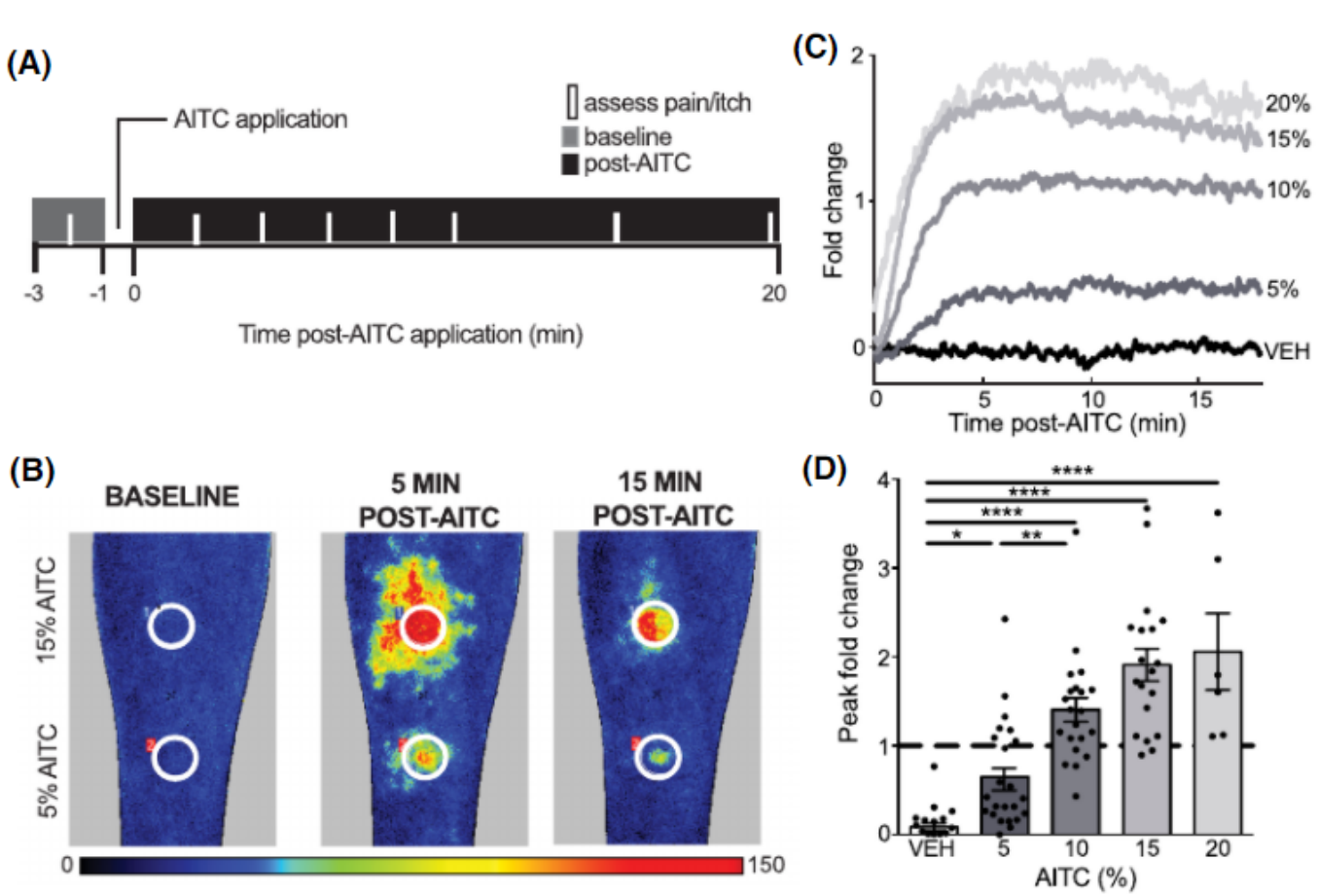


FIGURE 2 AITC-induced dermal blood flow measured with LSCI in humans. A, Schematic of experiment design. Subjects were imaged 2 minutes prior to AITC application (grey box, baseline) and asked to rate their pain and itch (white dashes). Imaging continued during AITC application and for 20 minutes post-AITC application (black box). Pain and itch were assessed at 2, 4, 6, 8, 10, 15 and 20 minutes post AITC

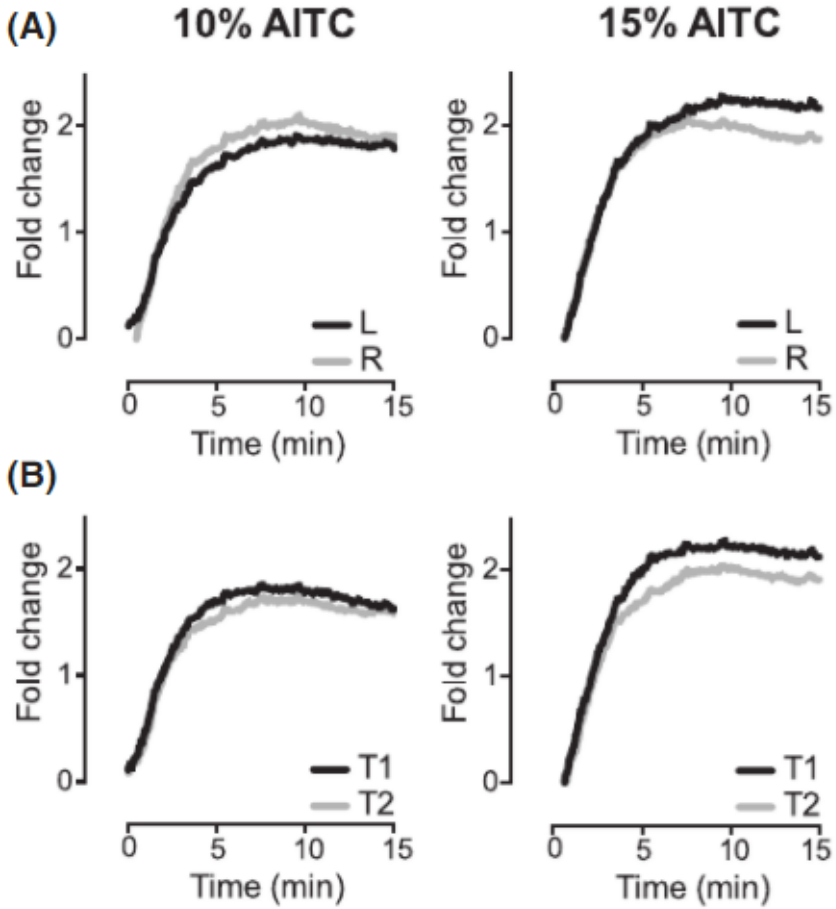


FIGURE 3 Reproducibility of dermal blood flow in humans. A, Time-course of mean fold change in the flux signal on the left (L, black) and right (R, grey) forearm following application of either 10%

Target Engagement Models

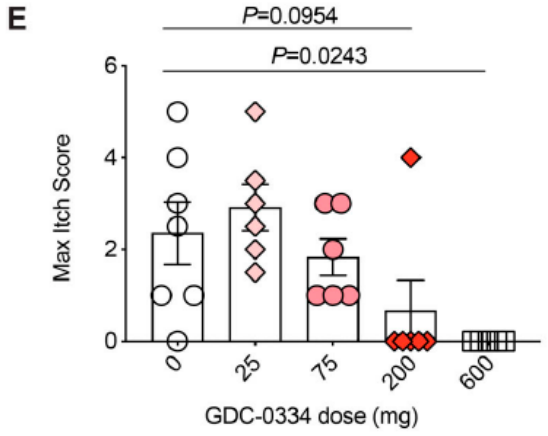
TRPA1 inhibition in AITC model

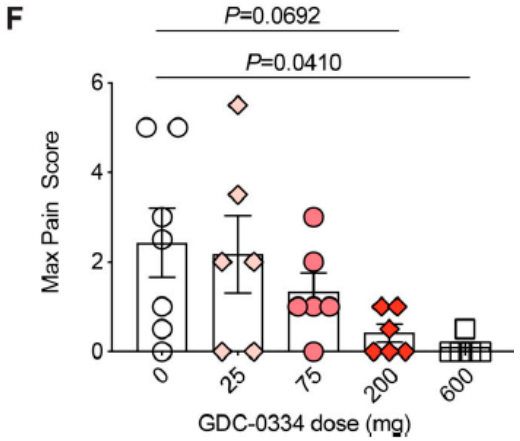
JEM Journal of Experimental Medicine

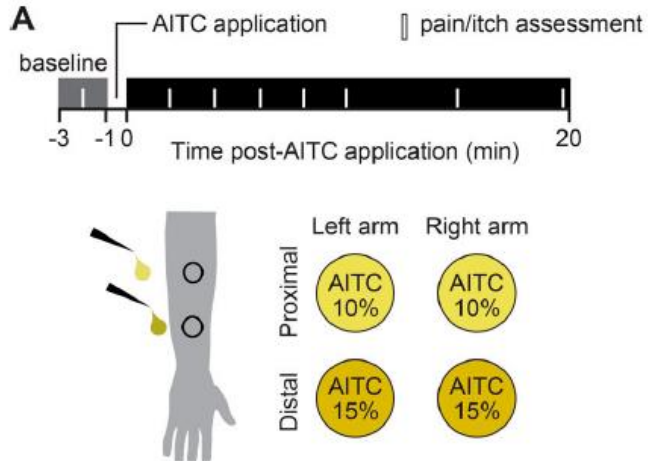
ARTICLE

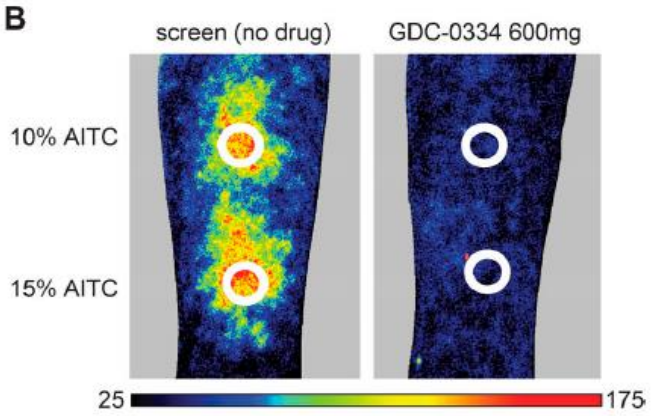
A TRPA1 inhibitor suppresses neurogenic inflammation and airway contraction for asthma treatment

Balestrini et al. *J Exp Med* 2021



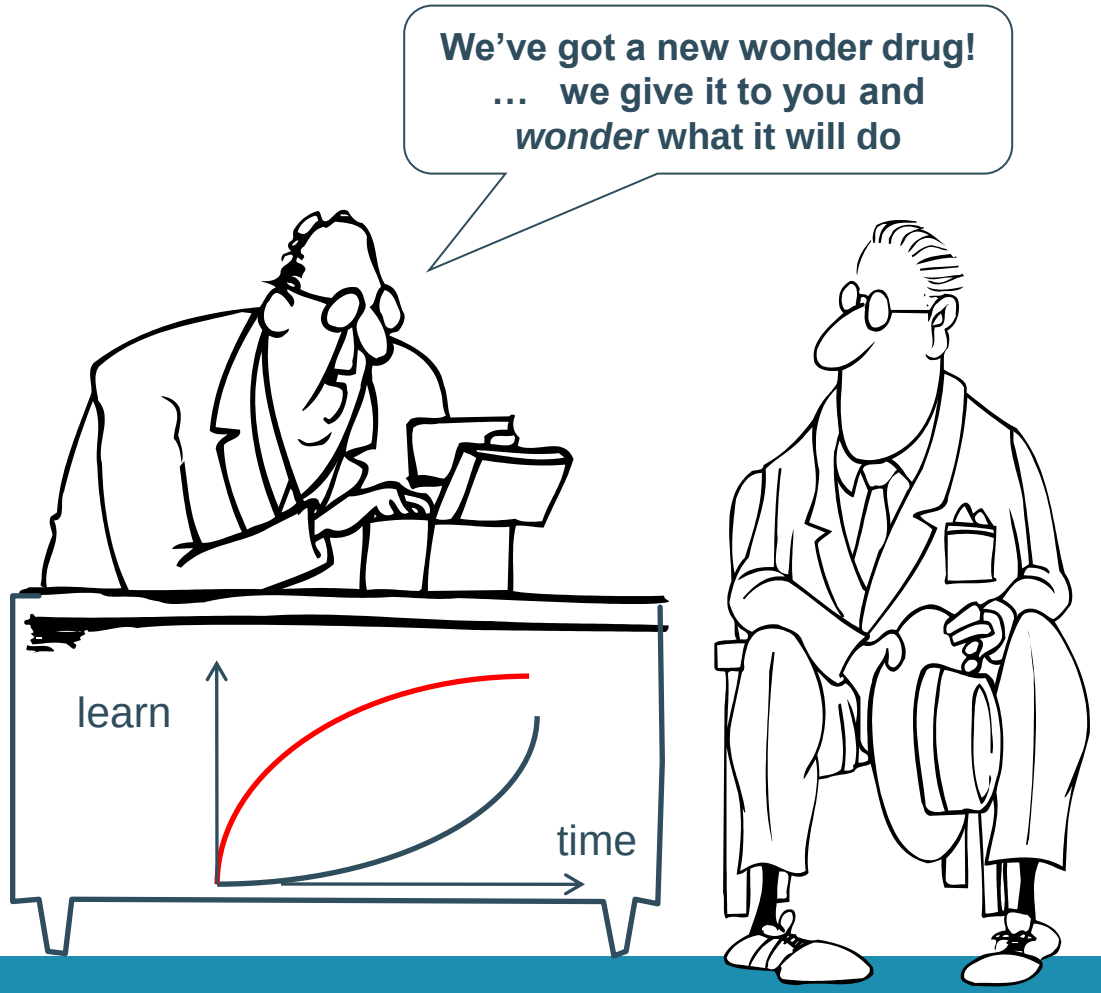






Target Engagement Models

Summary and conclusions



Challenge agents in target engagement models

24 May 2023

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