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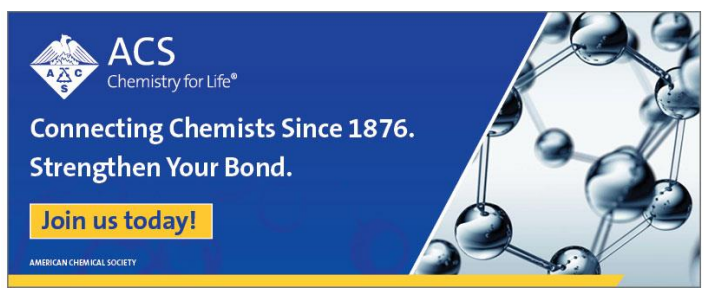

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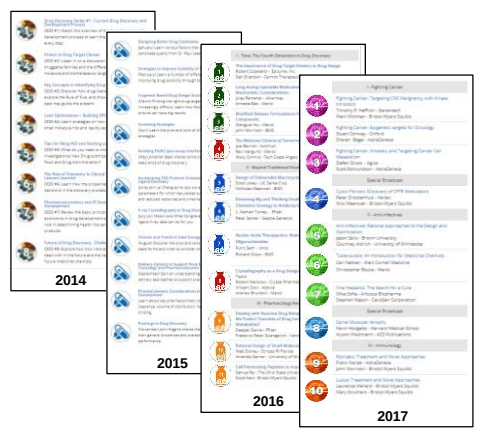

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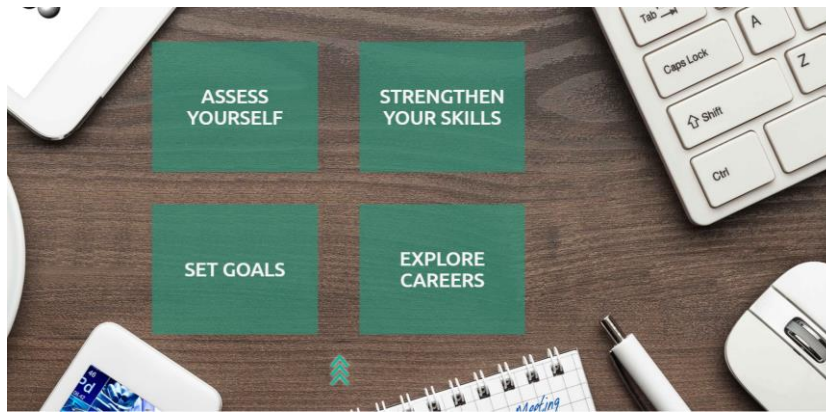

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Antagonising PAR2 with a Monoclonal Antibody"

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Founder, President and Chief Scientific Officer
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Senior Scientist, Neuroscience Biology Team,
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Introduction

A Novel Strategy for the Treatment of Chronic Pain:
Antagonising PAR2 with a Monoclonal Antibody

NURULAIN T. ZAVERI, PhD
Astraea Therapeutics
Mountain View, CA

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WHAT IS CHRONIC PAIN ?

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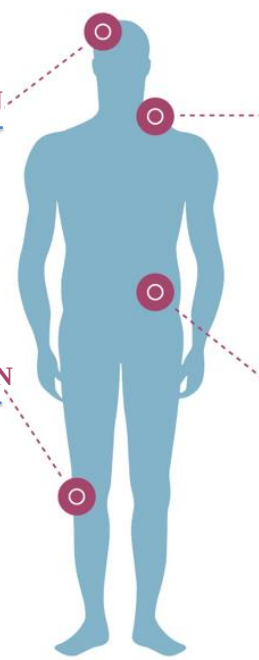
MANY CONDITIONS...DIFFERENT ETIOLOGIES...DIFFERENT SENSATIONS



NEUROLOGICAL PAIN

- Postherpetic Neuralgia
- Neuropathic Pain
- Severe Migraines

NECK & BACK PAIN

- Disc Degeneration
- Herniated Discs
- Back Pain
- Neuropathic Pain

JOINT or MUSCLE PAIN

- Arthritis
- Fibromyalgia
- Rheumatoid Arthrits
- Knee Pain

OTHER CONDITIONS

- Cancer Pain
- Headaches
- Pelvic Pain
- Phantom Limb Pain
- Post surgical Pain
- PTSD

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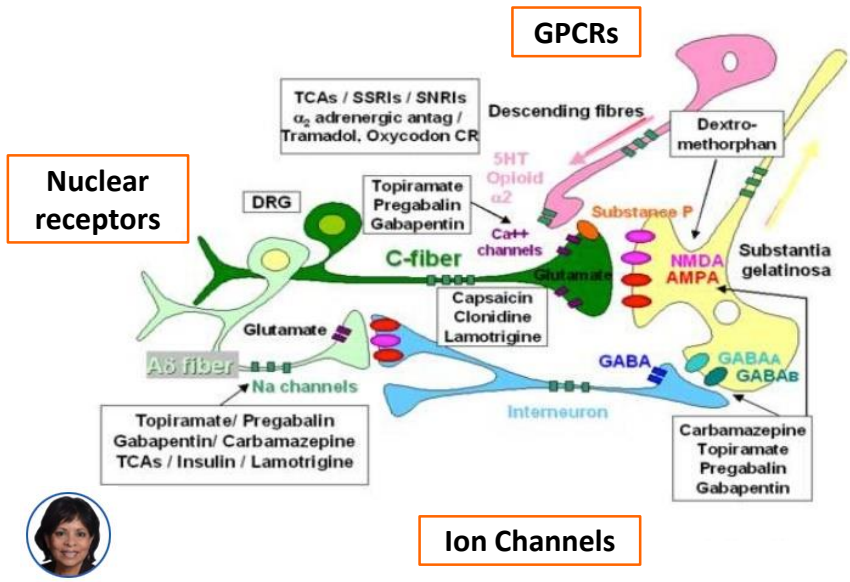
TARGETS FOR PAIN MEDICATION DISCOVERY



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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Can you rank the following diseases in order of MOST patient sufferers: Heart disease, diabetes, pain and cancer?

- Heart disease > pain > cancer > diabetes
- Pain > diabetes > heart disease > cancer
- Cancer > pain > heart disease > diabetes
- Heart disease > cancer > pain > diabetes

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AstraZeneca

A Novel Strategy for the Treatment of Chronic Pain: Antagonising PAR2 with a Monoclonal Antibody

Pete Thornton

Neuroscience, IMED Biotech Unit, AstraZeneca

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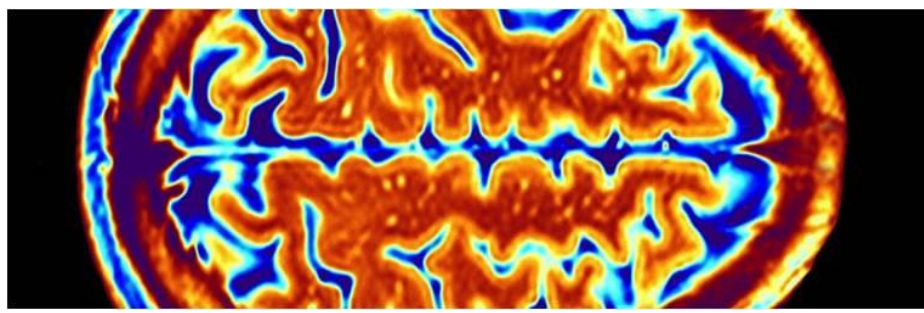
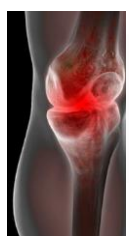
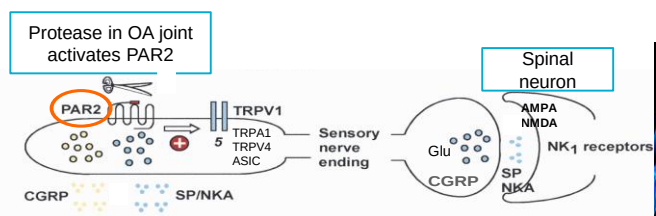


Protease activated receptor (PAR)-2 and pain

- PAR2 is activated by serine proteases which generate a novel N-terminal tethered ligand
- Receptor and activating proteases are elevated in osteoarthritis (OA)
- Expressed in nociceptors, synoviocytes, mast cells, fibroblasts, keratinocytes





- PAR2 activation and signaling
  - potentiates cation channels
  - leads to peripheral sensitisation and activation of pain fibres
  - drives neurogenic inflammation

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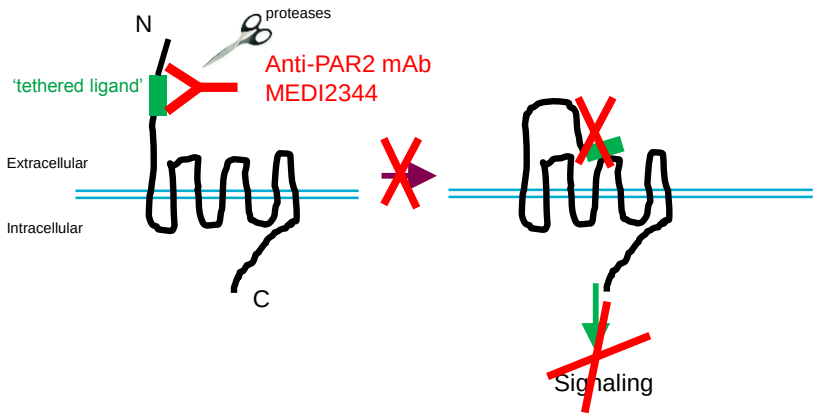
Goal: Develop a novel antagonist of PAR2 for the treatment of chronic pain



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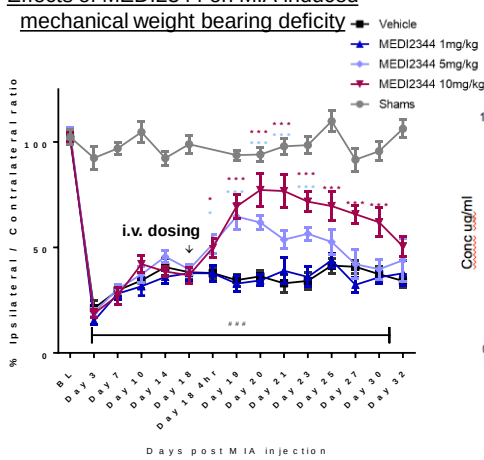
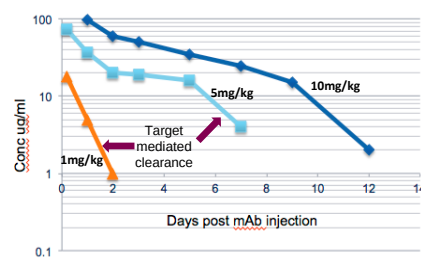
MEDI2344: A novel, high affinity anti-PAR2 mAb

Effects of MEDI2344 on MIA-induced mechanical weight bearing deficity



- Dose-dependent inhibition of weight-bearing deficit in pathologically-relevant model

PK profile of MEDI2344



- High, non-linear clearance in rat
- Predicted human dose: 6mg/kg IV Qweek
- Impossible production challenge

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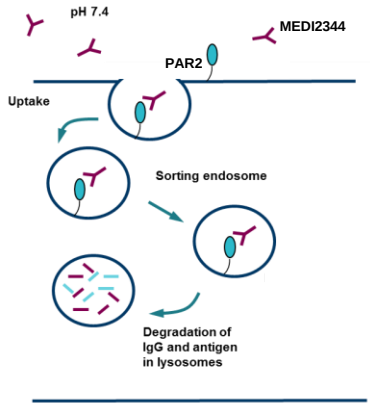
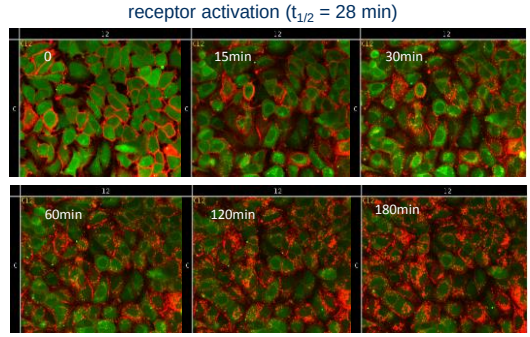
PAR2 receptor internalisation rapidly eliminates MEDI2344



MEDI2344 internalizes in A549 cells without receptor activation ($t_{1/2}$ = 28 min)



- Target-Mediated Drug Disposition (TMDD) prevented further development of MEDI2344
- An innovative strategy was employed to overcome TMDD of MEDI2344

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James Dodgson & Lorraine Irving

Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What is the pH of an endosome, and what percentage of Histidines within an endosomal protein will carry a positive charge?

- pH 5.0, Histidine 10 % charged
- pH 4.0, Histidine 30 % charged
- pH 6.0, Histidine 50 % charged
- pH 6.0, Histidine 100 % charged

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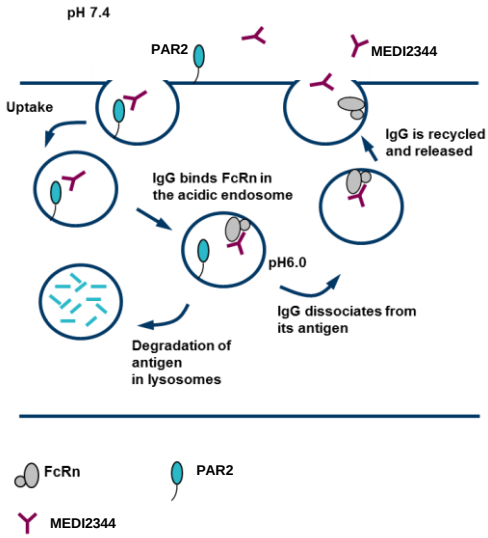
Overcoming TMDD by reducing PAR2 affinity at pH 6.0



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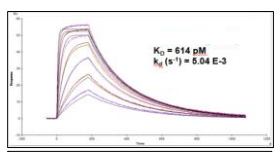
Overcoming TMDD by reducing PAR2 affinity at pH 6.0

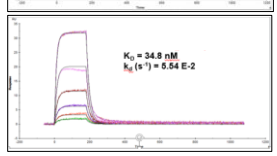
IgG	Recombined CDRs	VHCDR2	VHCDR3	Total nº of histidines
MEDI0618	H2, H3	XXXXHXXHXXXHXXXHH	XHHXXXXX	7

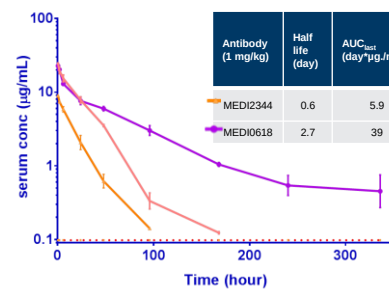
MEDI0618 (SPR)

Hu PAR-2 pH 7.4



Hu PAR-2 pH 6.0





Antibody (1 mg/kg)	Half life (day)	AUC_{last} (day*µg./mL)	Clearance	
			(ml/kg/day)	Fold difference to MEDI2344
MEDI2344	0.6	5.9	165	-
MEDI0618	2.7	39	25	6.5

- MEDI0618: our candidate displays > 50-Fold lower KD at pH 6.0 vs. pH 7.4
- Clearance is in expected range for a human IgG in rat

Claire Dobson, Sadhana Podichetty, Phil Newton and Gareth Rees

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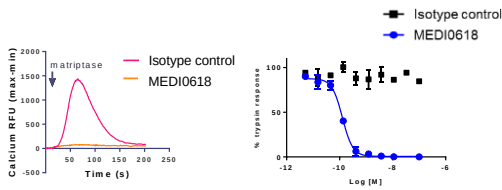
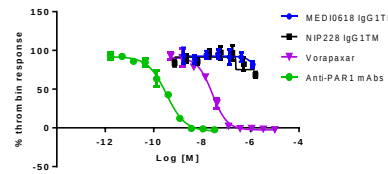
MEDI0618 is a potent and specific antagonist of PAR2

MEDI0618 blocks protease-trigged calcium release in PAR2-expressing human A549 cells



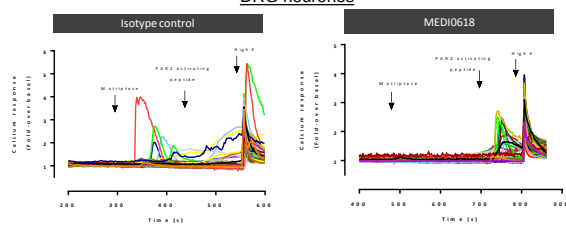
MEDI0618: no effect on thrombin-PAR-1 Ca response Anti-PAR1 mAbs and vorapaxar fully effective



Inhibition of PAR2 in FLIPR assays

Cell line	PAR2 IC_{50} [nM] (± SEM)
Human A549	**0.11 (± 0.01)**
Cyno CYNOM-K1	0.05 (± 0.004)
Rat KNRK	0.52 (± 0.07)
Mouse LL/2	0.05 (± 0.02)

MEDI0618: blocks protease-induced calcium in DRG neurones



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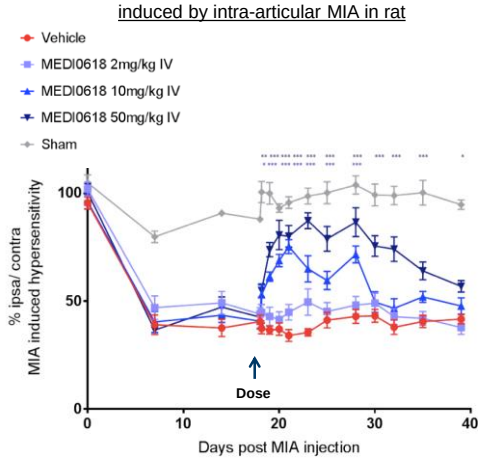
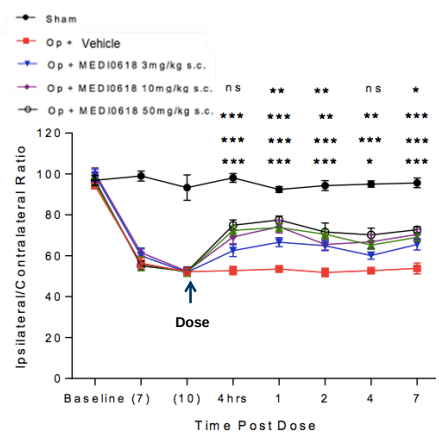
MEDI0618 is analgesic in rodent OA and nerve injury models

MEDI0618 reverses weight-bearing deficit induced by intra-articular MIA in rat



MEDI0618 reverses mechanical allodynia induced by peripheral nerve damage in mouse



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Summary

- We have shown that monoclonal antibodies to PAR2 potently inhibit receptor activation
- However, due to target sink and receptor-antibody internalisation, the high affinity anti-PAR2 mAb MEDI2344 displays high clearance
- Engineering in pH-dependent binding of MEDI2344 to PAR2 improved PK profile in candidate MEDI0618
- PAR2 is a challenging target but we have succeeded where others have failed: none failed due to lack of efficacy
- MEDI0618 represents best in class, first in class opportunity to antagonise PAR2 in chronic pain states – FTIH dosing to commence Jan 2019

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Acknowledgements

- Tharani Chessell
- Jon Hatcher
- Ian Gurrell
- Claire Dobson
- Dic Williams
- Keith Tan
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- Phil Newton
- Gareth Rees
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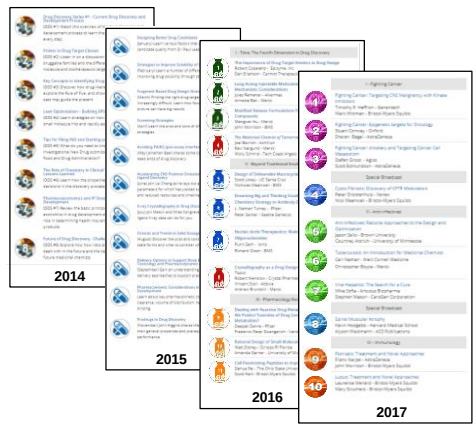

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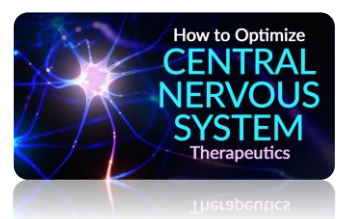

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