

a personal perspective on preclinical drug development



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How can industry discover and develop strong, non-addictive pain relievers?

- Precedented targets likely to give diminishing returns
- No shortage of novel target candidates
 - And not really any secrets
- New mechanisms much harder
 - Lack of good compounds
 - Not clear what models to use

Big pharma

- Has the resources to generate tool compounds
- Tends to play “by the book”
 - Stereotyped, standardized assays
 - Artificial goals

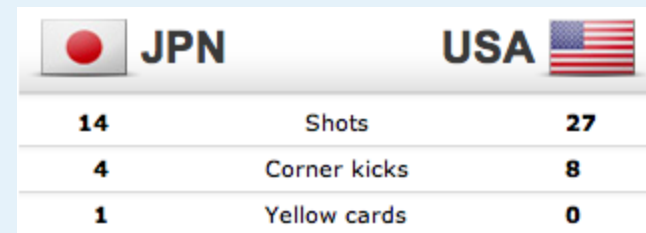
Problems with big pharma

- We play the numbers game
 - all about “shots on goal”



UEFA.com LIVE

FC BARCELONA		CHELSEA FC
2	GOALS	2
22 (5)	ATTEMPTS (ON TARGET)	7 (3)
1	SAVES	3
10	CORNERS	1
1	OFFSIDES	1
90.76 km	DISTANCE COVERED	88.29 km
660 (85%)	PASSES COMPLETED	117 (46%)
73%	BALL POSSESSION	27%
8	FOULS COMMITTED	10
2	YELLOW CARDS	6
0	RED CARDS	1



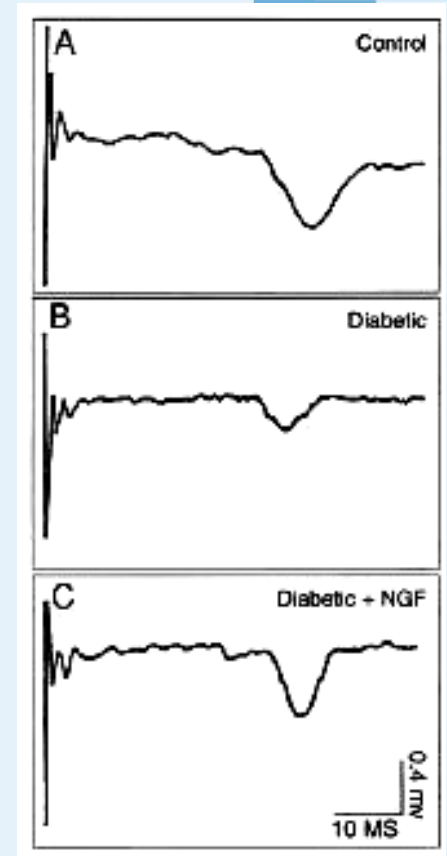
JPN		USA
14	Shots	27
4	Corner kicks	8
1	Yellow cards	0

Biotech

- Limited resource, so often limited to a single shot

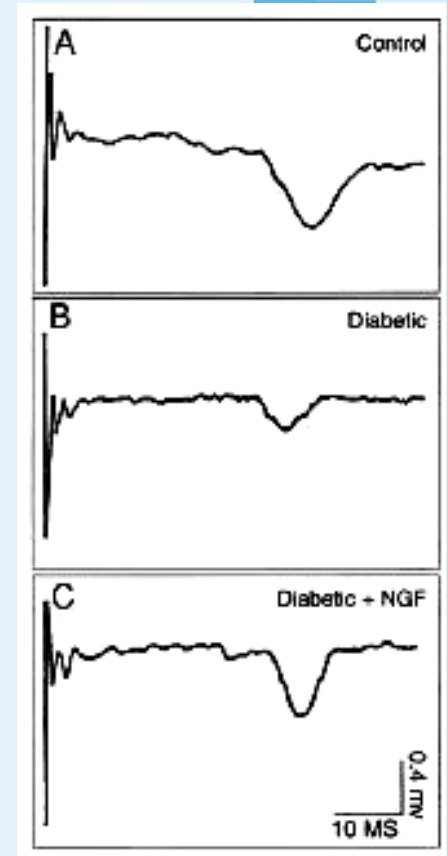
NGF as a Therapy for Neuropathy

- NGF a trophic factor and controls survival of various neurons during development (Hamberger, Montalcini)
- NGF acts to protect adult neurons from a variety of insults
- Preclinical evidence that NGF can prevent or reverse diabetic neuropathy
- Led to clinical trials of NGF



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 - **Pain is dose limiting side effect**



NGF Causes Pain in Humans

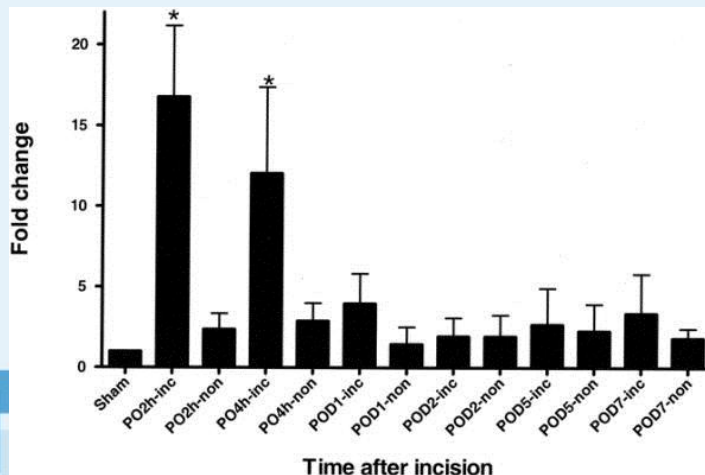
Neurology, Vol 48, Issue 2 501-505, Copyright © 1997 by American Academy of Neurology

Intradermal recombinant human nerve growth factor induces pressure allodynia and lowered heat-pain threshold in humans

PJ Dyck, S Peroutka, C Rask, E Burton, MK Baker, KA Lehman, DA Gillen, JL Hokanson and PC O'Brien

Peripheral Neuropathy Center, Rochester, MN, USA.

NGF increased by inflammation



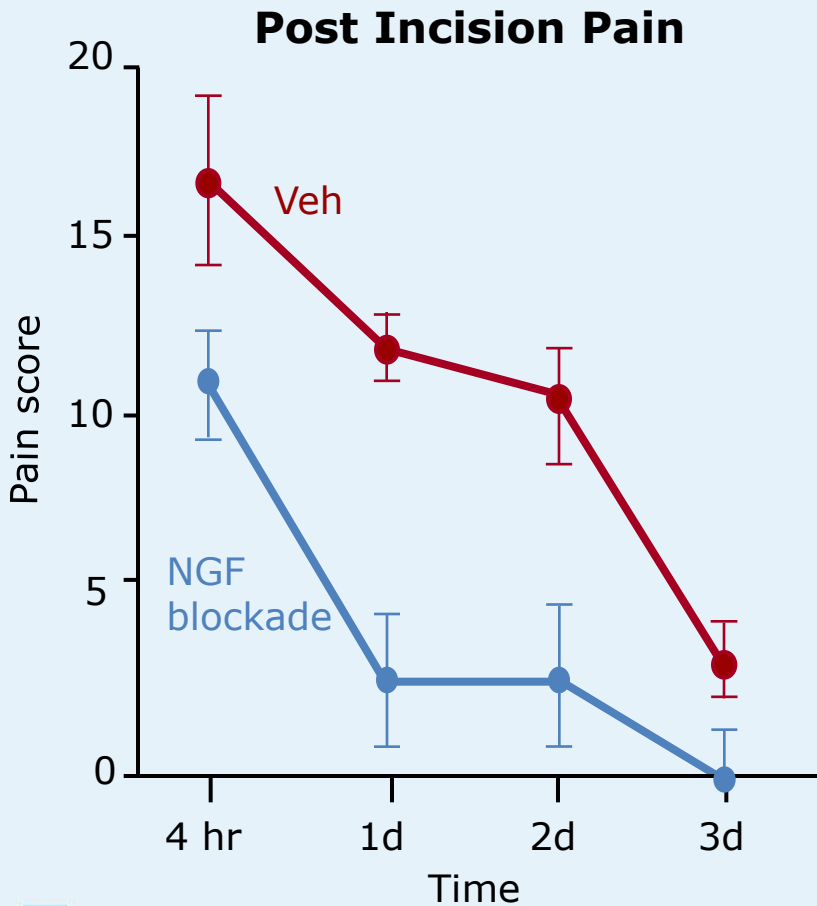
- First by Weskamp and Otten, 1987

Wu, Boustany, Liang, and Brennan, 2007

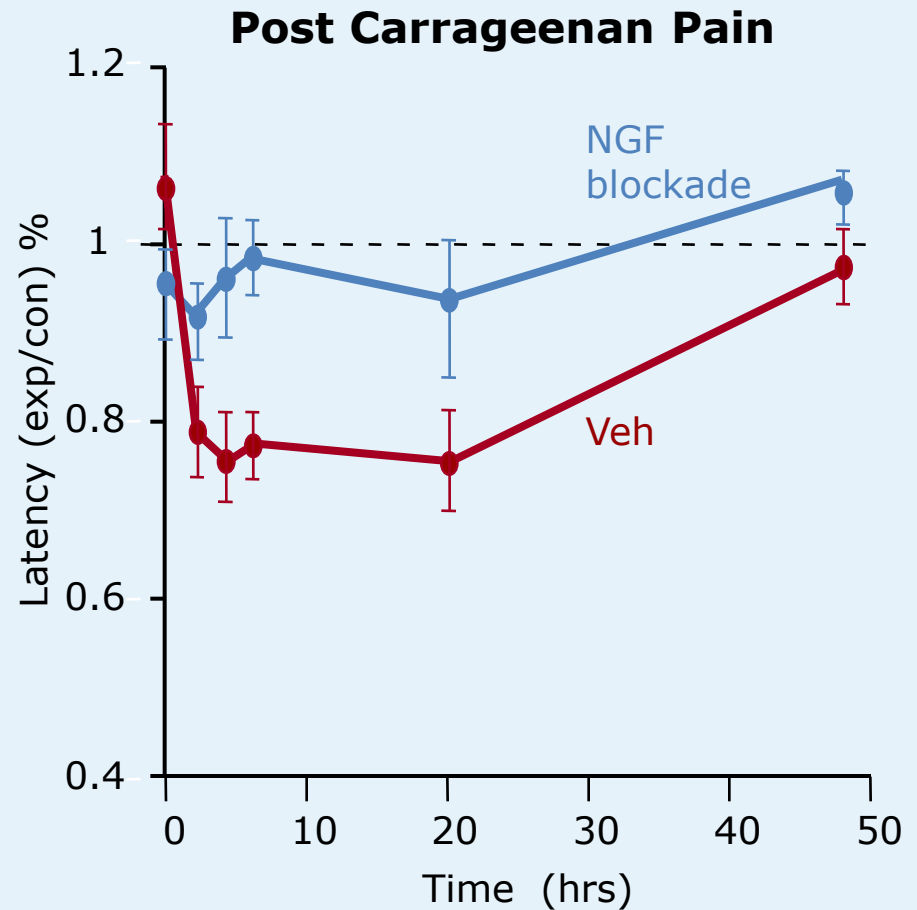
Scientific Rationale for NGF as target?

- NGF causes pain in humans and animals
- NGF is up-regulated in painful conditions

Blocking NGF Blocks Cutaneous Hypersensitivity

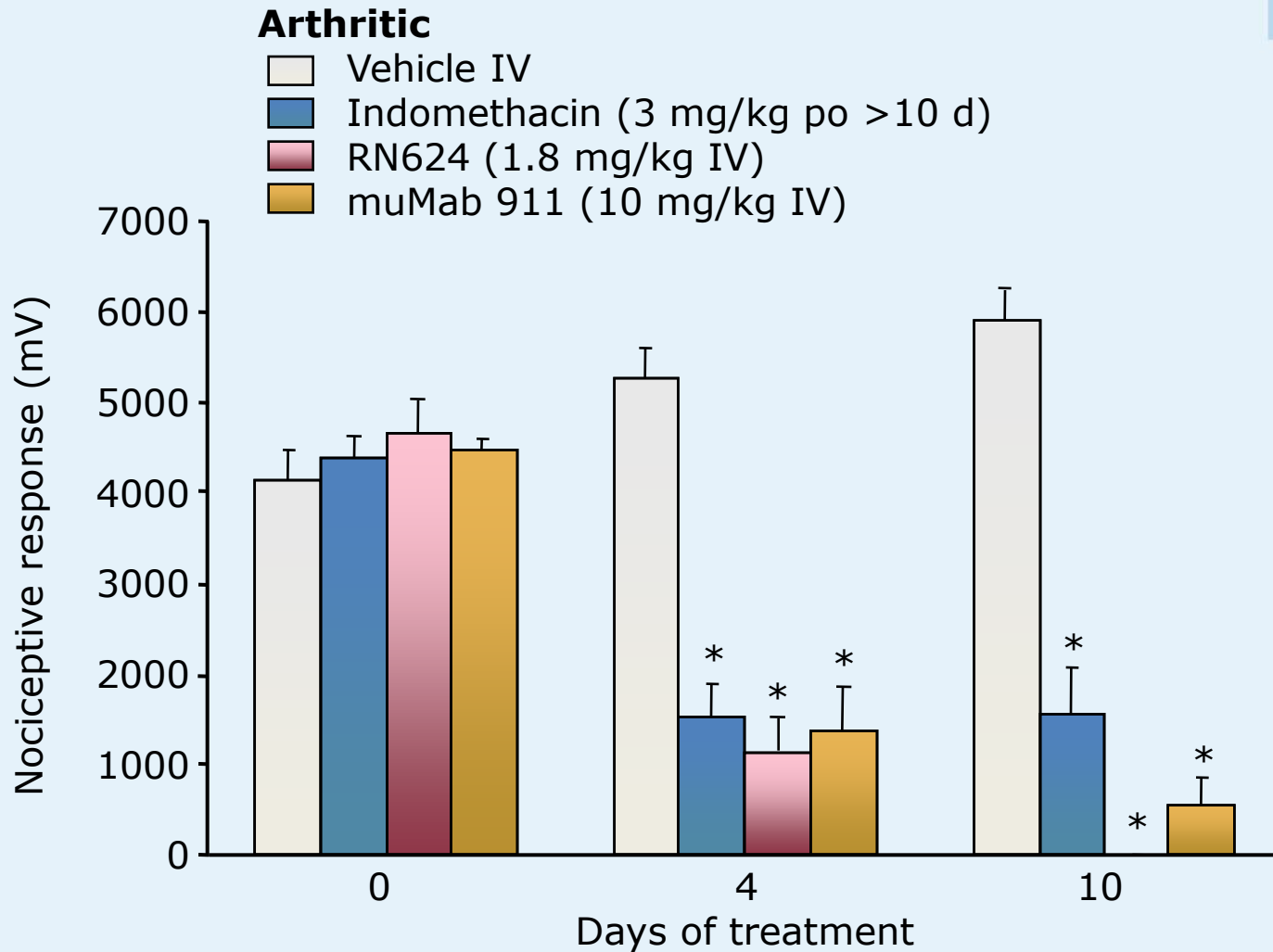


Brennan et al. 2004.



Bennett et al. 1995.

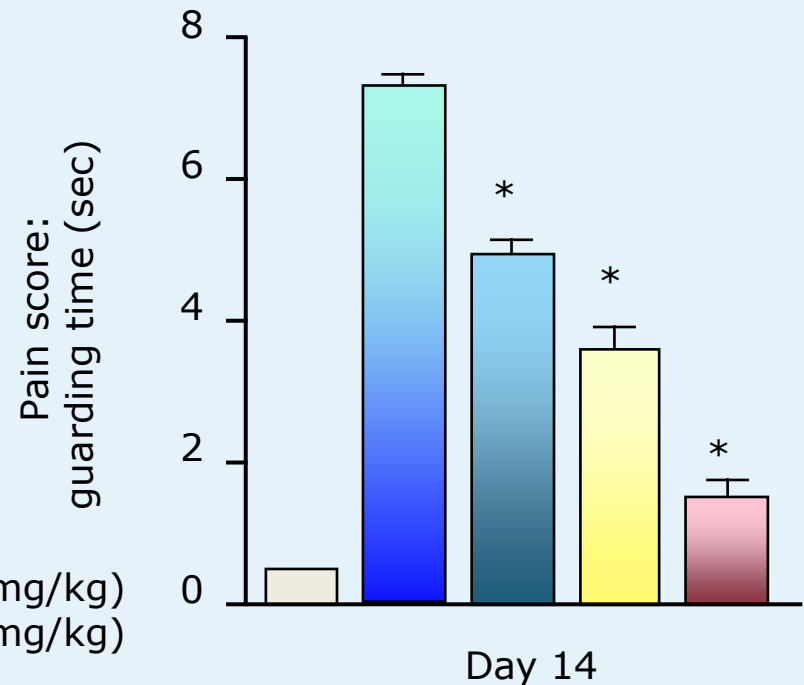
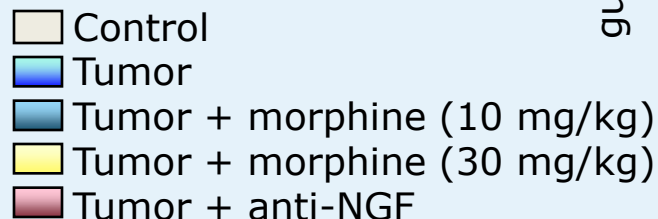
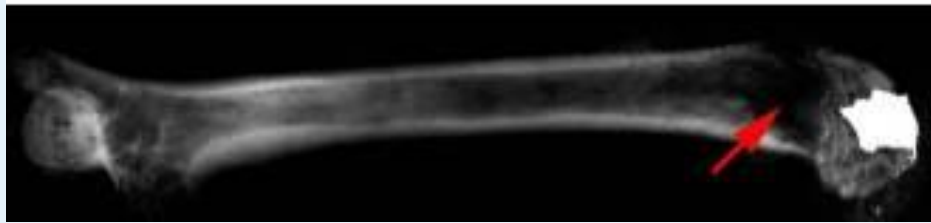
Efficacy in Arthritis Pain Model



- RN624 and MuRN624 at D14 and D18.
- Mean \pm SEM; * $P < 0.05$; $n = 10$ animals per group

Efficacy in Sarcoma Pain Model

- Osteolytic murine sarcoma cells transferred to mouse femur
- Injection of anti-NGF (10 mg/kg every 5 days) beginning on Day 6 after tumor transfer
- End points: multiple types of ongoing and evoked pain on Day 14 following tumor transfer



Published Animal Model Studies

Pain Model	Agent	Effect	Reference
Models of cutaneous inflammatory pain			
CFA inflammatory hyperalgesia	Anti-NGF	Reduction of hyperalgesia	Woolf et al. 1994
Carrageenan inflammatory pain	TrkA-IgG	Reduction of hyperalgesia	McMahon et al. 1995
IL-1 β injections in hind paw	Anti-NGF	Reduction of hyperalgesia	Safieh-Garabedian et al. 1995
CFA inflammatory hyperalgesia	Anti-NGF	Reduction of hyperalgesia and activity of spinal cord neurons	Ma and Woolf. 1997
Models of visceral pain			
Turpentine-induced bladder inflammation	TrkA-IgG	Blockade of bladder hyperreactivity	Dimitrieva et al. 1997
Turpentine-induced bladder inflammation	TrkA-IgG	Reduction of referred (limb) hyperalgesia	Jaggat et al. 1999

lessons?

- New targets may give meaningful boost to outcome
 - But no precedent
 - May have to look for new models
- Collaborate widely on varying animal models
 - The “good ones” will show
- Or ignore animal models and go straight to clinic
 - But in which pain state in clinic??

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