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”
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

Elias et al. 1998.
NGF as a Therapy for Neuropathy

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• 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
  – Pain is dose limiting side effect

Elias et al. 1998.
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

**Post Incision Pain**
- Veh
- NGF blockage


**Post Carrageenan Pain**
- Veh
- NGF blockage

Bennett et al. 1995.
Efficacy in Arthritis Pain Model

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

Shelton et al. 2005
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

*P<0.05

# Published Animal Model Studies

<table>
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<tr>
<th>Pain Model</th>
<th>Agent</th>
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<td><strong>Models of cutaneous inflammatory pain</strong></td>
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<td>CFA inflammatory hyperalgesia</td>
<td>Anti-NGF</td>
<td>Reduction of hyperalgesia</td>
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<td>IL-1β injections in hind paw</td>
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<td>CFA inflammatory hyperalgesia</td>
<td>Anti-NGF</td>
<td>Reduction of hyperalgesia and activity of spinal cord neurons</td>
<td>Ma and Woolf. 1997</td>
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<td><strong>Models of visceral pain</strong></td>
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<td>Turpentine-induced bladder inflammation</td>
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<td>Blockade of bladder hyperreactivity</td>
<td>Dimitrieva et al. 1997</td>
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<td>Turpentine-induced bladder inflammation</td>
<td>TrkA-IgG</td>
<td>Reduction of referred (limb) hyperalgesia</td>
<td>Jaggar et al. 1999</td>
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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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