Programa Cooperación Farma-Biotech

Jornada IV: Ámbitos terapéuticos relacionados con respiratorio, dermatología, nefrología, inflamación e infección

DD04107, the first peptide of a new class of long-acting analgesics

BCN PEPTIDES

Madrid, 12 July 2011

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Associació catalana d'empreses de biotecnologia

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BCN Peptides is completely focused on the cGMP manufacture of Bioactive Peptides for Pharmaceutical and Veterinary applications

We concentrate our efforts on three main activities

- **Generic Peptides**
- **Custom Synthesis** of proprietary API Peptides
- **Proprietary R+D**, discovery of new peptidic NCEs, new therapeutical applications and new peptide formulations

We are the **Experts**

in the Solid Phase Synthesis of **Bioactive API Peptides**

Key Technologies

- Solid Phase Synthesis
- **HPLC** Purification
- Lyophilisation under **GMP** Conditions
- Sterile grade Peptides

BCN Peptides has the most modern peptide synthesis facility in Europe (approved by the FDA and EDQM)

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DD04107, an **inhibitor of neuronal exocytosis** which displays *in vivo*, **long-lasting analgesic activity** against **chronic inflammatory and neuropathic pain**

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Inhibiting neuronal exocytosis to attenuate pain

- **DD04107** is peptide patterned after the N-terminus of the SNAP-25 protein (a member of the SNARE complex that mediates neuronal, Ca^{2+}-dependent exocytosis) which inhibits *in vitro* the release of neuromodulators involved in pain signaling

- Regulated exocytosis contributes to the inflammatory sensitization of TRPV1 by incrementing its surface expression in nociceptors

- Sensitized nociceptors, especially the peptidergic subpopulation, display an efferent function characterized by the release of the pro-inflammatory peptides SP and CGRP that further enhance pain signals. These neuropeptides also contribute to chronic pain conditions that apparently do not display an inflammatory process

DD04107 fulfills the need to develop small molecules that down regulate the excessive Ca^{2+}-dependent exocytosis occurring in chronic pain states

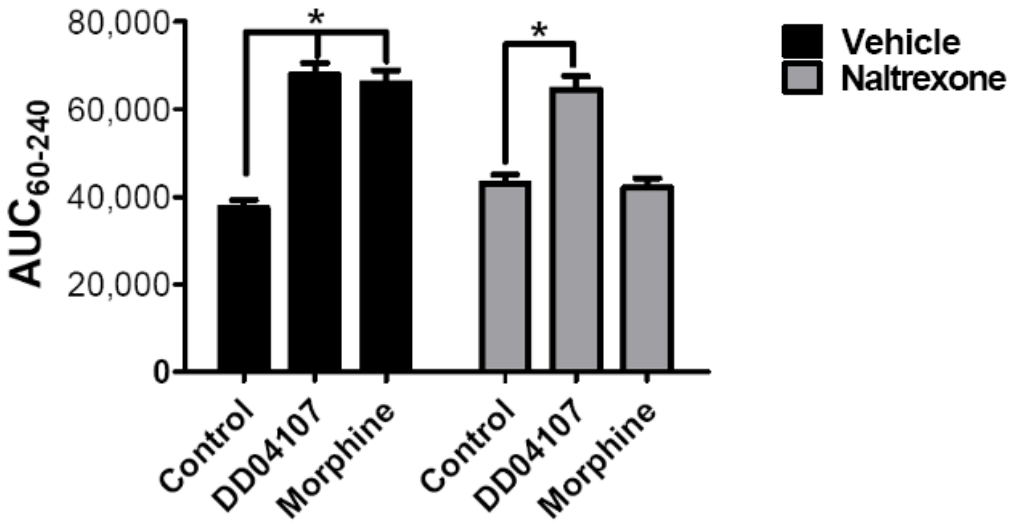
Pharmacology: Summary

	maximum activity	
	Mechanical allodynia	**Thermal hyperalgesia**
Vincristine Neuropathy Model	5 days @ 0.5 mg/kg (sc, rat)	not tested
Taxol Neuropathy Model	8 days @ 0.5 mg/kg (sc, rat)	no efficacy
Osteosarcoma Model	3-5 days @ 3 mg/kg (sc, mice)	2-8 days @ 1 mg/kg (sc, mice)
STZ-induced Diabetes Model	4 hours @ 0.5-5.0 mg/kg (sc, mice) *remarkable effect after 5 days at 5.0 mg/kg*	not tested
CFA Inflammatory Model	5 days @ 1 mg/kg (im, rat)	4 h @ 1 mg/kg (im, rat)
Carrageenin Inflammatory Model	5 hours @ 5 mg/kg (im, rat)	not tested

An *in vivo*, long-lasting analgesic activity was observed in a consistent manner in all the experimental models of chronic inflammatory and neuropathic pain evaluated

DD04107 does not act through a central opioid signaling pathway

The competitive receptor binding *in vitro* study revealed that **DD04107** at 10 μM marginally (≈60%) interacted with the adenosine type 3 receptor (A3), CxCR2 (IL-8B), noreprinephine and dopamine transporters, and the δ2, κ and μ opioid receptors, but **the *in vivo* anti-nociceptive activity is not antagonized by naltrexone**, supporting the notion of a **peripheral mechanism of action** for **DD04107**



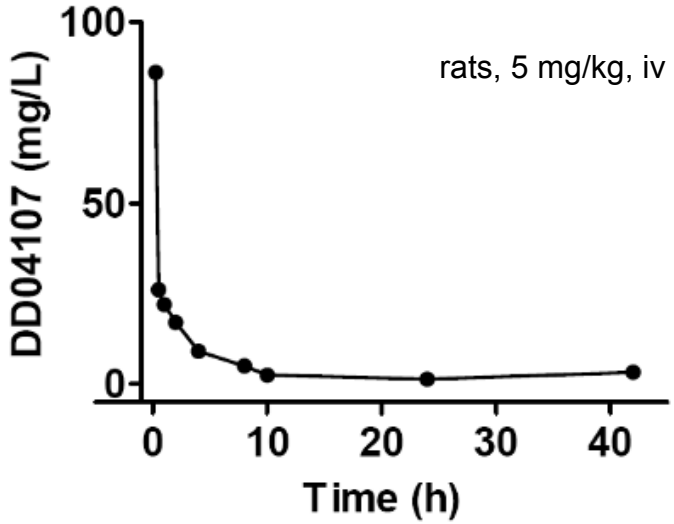
DD04107 was administered sc at 5 mg/kg. Morphine was used sc at 3 mg/kg. Naltrexone was used as opioid antagonist and administered sc at 0.1 mg/kg 30 min before DD04107 or morphine. Mechanical threshold was measured with the Randall-Selitto test just before drug treatment and then 1 h, 2 h and 4 h later

Safety pharmacology

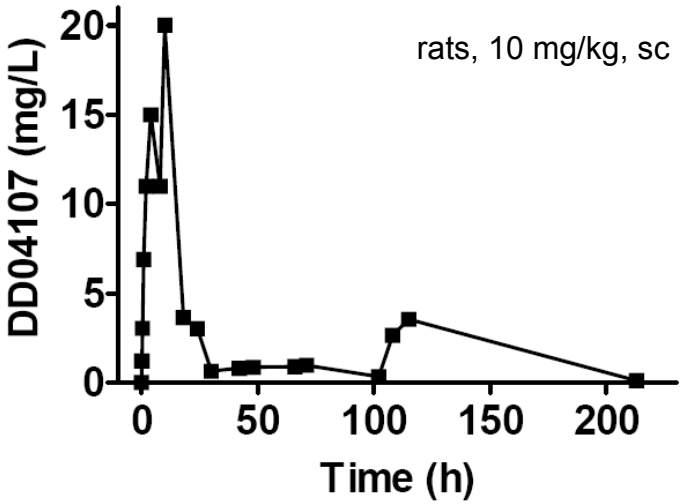
Irwin test	**DD04107** did not affect gross behavior of treated rats, except for transient piloerection at the higher doses (sc, 5 mg/kg & 50 mg/kg)
Body temperature	kept constant even at 50 mg/kg 4 hours after administration
Motor coordination test	not affected (sc, 10 mg/kg)
Locomotor activity test	not affected (sc, 10 mg/kg)
Anxiety	no induction (sc, 10 mg/kg)
Cognitive function: Object recognition test	not impaired (sc, 10 mg/kg)
Cognitive function: Morris Water Maze test	slight delay in learning capacity in the first days after administration, but no impairment of the spatial learning (sc, 10 mg/kg)
Cardiotoxicity: *in vitro* hERG test	not affected at therapeutic doses (0.5-5 μM)
Effect on muscle contraction of isolated organs	no effect of rat atrium, vas deferens and ileum contraction (10 nM- 30 μM)

Pharmacokinetic study

Intravenous injection of **DD04107** resulted in rapid decay of the plasma concentration that was detectable up to 40 h. The data were well fitted to a two-compartment model, with fast initial α decay, followed by a slower β phase



Subcutaneous administration of **DD04107** displayed a bicompartmental profile. Compound **was detectable in plasma samples up to 200 h after single administration**, consistent with a long lasting presence in the plasma



Full preclinical studies under GLP to be finished by end 2011

- ✓ Toxicology
  - dose range, rat
  - MTD, dog
  - 4-w, rat
  - 4-w, dog
- ✓ Safety pharmacology
  - Functional Observational Battery (GLPs)
  - Telemetry
  - Respiratory in rat
  - hERG (GLPs)
- ✓ Bioanalysis/TK/PK
  - Method validation
  - TK dose range, rat
  - TK MTD, dog
  - TK 4-w, rat
  - TK 4-w, dog
  - PK, rat (in life)
  - PK, dog (in life)

- The use of **DD04107** for the treatment of pain and inflammation has been internationally protected by a Spanish patent application in 2008, followed by an international extension (PCT) and national applications (EP, US, JP, CN, AU ...)

- Broad coverage of pain and inflammatory diseases: inflammatory pain, neuropathic pain, diabetes-induced neuropathic pain cancer pain, visceral pain, irritable bowel syndrome, migraine, dry eye syndrome, post-operative pain, fibromyalgia, neurogenic inflammation, atopic dermatitis, rheumatoid arthritis, post-herpetic neuralgia, peripheral neuropathies, trigeminal neuralgia,...

- BCN Peptides is currently developing **DD04107** until complete Preclinical Phase
- We intend to perform Clinical Phase I for which we are seeking experienced partners in the field of pain/inflammation to help us to move forward faster through it
- Formal contact with selected international players started in March 2011
- There are several architecture deals that could be of interest to us
  - global licensing transaction (upfront, milestones and royalties)
  - co-commercialization/co-marketing deals
  - regional commercialization agreements

THANK YOU!

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