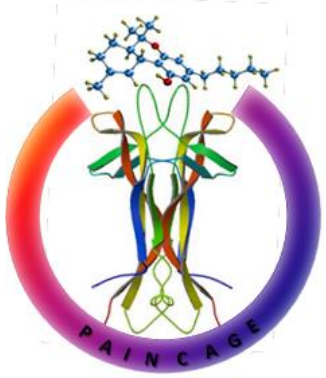
PAINCAGE General Assembly Meeting
Pisa, July 2015



SEVENTH FRAMEWORK PROGRAMME

This project is funded by the European Union under the 7th framework program (GA 603191)

Welcome and Introduction
Scuola Normale Superiore (SNS ï Italy)

Project Title	The NGF System and its interplay with endocannabinoid signalling, from peripheral sensory terminals to the brain: new targets for the development of next generation drugs for neuropathic pain
Project Acronym	PAINCAGE
Contract Number	GA 603191
Project website	www.paincage.eu
Project Duration	1/04/2014 – 31/03/2017

Objectives of the meeting

- Update and reporting of activities
- Successes and problems: opportunities, risks and challenges
- Discuss possible remodulations of activities/tasks
- Preliminary discussions for the mid-term report

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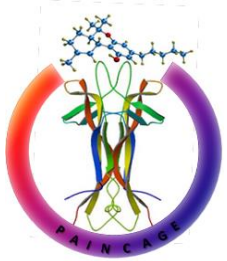
Key events in the field of the Paincage project



- Clinical developments in the field of the
  - NGF system
  - Endocannabinoid system

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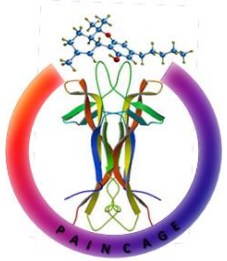
Anti NGF clinical programs



- FDA hold was lifted and anti NGF clinical trials for OA restarted, after the 2010 block, for safety reasons

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Anti NGF clinical programs

Drug developers reboot anti-NGF pain programmes

Pfizer, Eli Lilly, Janssen and Regeneron are advancing a promising class of analgesic drugs, hoping to put concerns around autonomic dysfunction and joint destruction behind them.

Asher Mullard

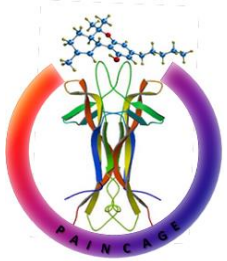
US regulators released Pfizer and Eli Lilly's tanezumab from clinical hold in March this year, raising hopes for the nerve growth factor (NGF) inhibitors that were once considered to have mega-blockbuster potential. The US Food and Drug Administration (FDA)'s hold was implemented in 2010 after an increased incidence of joint destruction was observed in patients on this class of drugs, but an action plan was established to address this red flag in 2012. The subsequent delay has largely been due to preclinical studies that suggested that the drugs could damage the autonomic nervous system. Pfizer, Lilly, Janssen, Regeneron and others hope that Phase III trials will now put both safety concerns fully to rest.

"We are very supportive of the FDA and their careful assessment of safety," says Catherine Stehman-Breen, Vice President of Global Development at Regeneron, which is developing the anti-NGF fasinumab. "No one knew quite what to make of these preclinical findings, and I think [the hold] was a very reasonable and appropriate measure for the FDA to take."

Neither the FDA nor the anti-NGF drug developers have disclosed detailed reasoning for the concerns about effects on the autonomic nervous system, which regulates automatic body processes such as heart rate, blood pressure, breathing and digestion. Last year, however, Regeneron reported that the fears had been triggered by "adverse changes in the sympathetic nervous systems of mature rats and monkeys in neurohistologic studies" of two NGF-specific antibodies that were being developed by other companies. "The FDA raised the question of whether there might be a clinical risk of continual loss of cells and resultant neurological deficits with repeated dosing," they wrote (*Pain* 155, 1245–1252; 2014).

Pfizer told *Nature Reviews Drug Discovery* that the FDA lifted the hold on their tanezumab in March after seeing "a robust body of nonclinical data" demonstrating that "tanezumab administration does not cause neuron cell loss or death in the sympathetic nervous system". "Tanezumab

Anti TrkA clinical program



- **Glenmark Kicks Off Monoclonal Antibody Pain Studies**
- Tue, 04/29/2014
- Glenmark Pharmaceuticals S.A., a wholly owned Swiss subsidiary of Glenmark Pharmaceuticals Ltd., announced that GBR 900, a novel monoclonal antibody is entering human trials. GBR 900 targets TrkA, a receptor for nerve growth factor (NGF) involved in chronic pain signaling.
- In 2010, Glenmark gained an exclusive worldwide license from Lay Line Genomics S.p.A. (Italy) for anti-TrkA antibodies and their entire intellectual property portfolio in the TrkA field. GBR 900 is the optimized anti-TrkA antibody emerging from this exclusive worldwide license.
- Glenmark has now completed the Phase 1 enabling preclinical development program for GBR 900 and has filed a Phase 1 clinical trial application with the MHRA, UK. GBR 900 is the first anti-TrkA monoclonal antibody to enter clinical development.
- TrkA is the pain-signaling receptor for NGF. Monoclonal antibodies directed against NGF represent one of the rare clinical breakthroughs in chronic pain treatment and have shown excellent clinical activity in inflammatory and neuropathic pain. Unfortunately, development of the class has been curtailed due to suspected toxicity.

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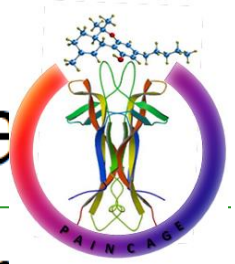
Clinical uses of cannabis

Recent randomized controlled tria



Nabilone

- Neuropathic pain (Frank 2008)
- Fibromyalgia pain (Skrabek 2008) and sleep (Ware 2010)
- Spinal cord injury (Pooyania 2010)

Dronabinol

- MS spasticity (Svensen 2004)
- Chronic pain + opioids (Narang 2008)
- Spinal cord injury (Rinatala 2010)

Cannador (2.5mg THC + 1.2mg CBD)

- Spasticity in MS (Zajicek 2003, 2005, 2012)

Nabiximols (2.5mg THC + 2.5mg CBD)

- Brachial plexus avulsion (Berman 2004)
- Rheumatoid arthritis (Blake 2005)
- MS neuropathic pain (Rog 2007)
- MS Spasticity (Novotna 2011)
- Cancer pain (Portnoy 2012)

Herbal cannabis (1.8-9.4%THC)

- HIV neuropathy (Abrams 2007, Ellis 2009)
- Neuropathic pain (Wilsey 2009, 2013, Eisenberg 2014)
- Post traumatic neuropathy (Ware 2010)
- MS spasticity (Corey-Bloom 2012)
- Crohn's disease (Naftall 2013)

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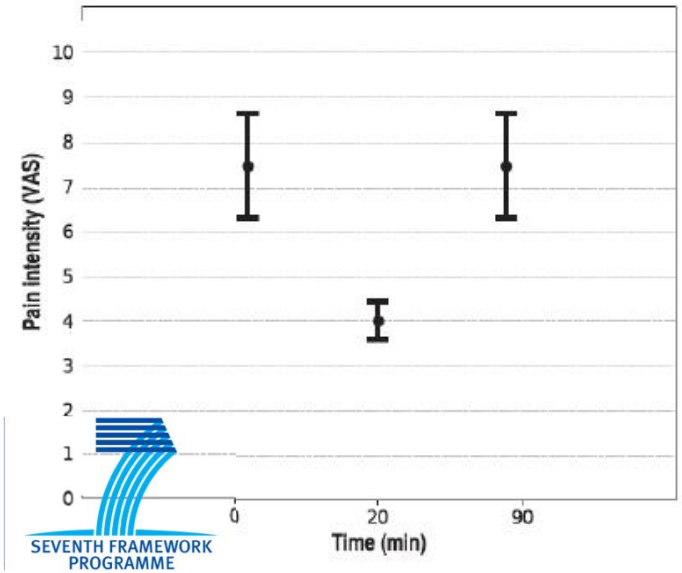
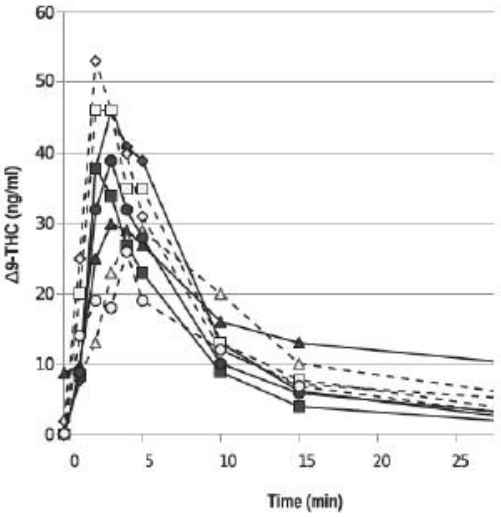
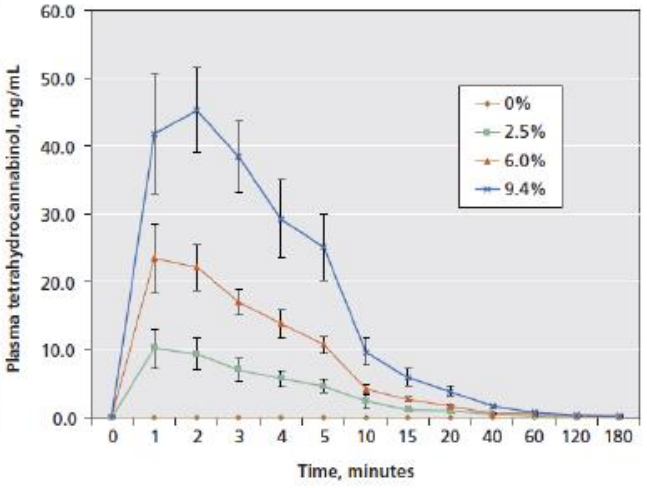
REPORT

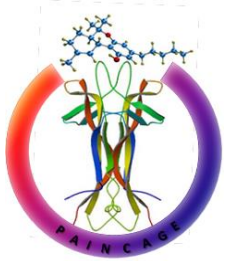
The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study

15 mg herbal cannabis; 19% THC
Single inhalation using Syqe® inhaler
N=10 neuropathic pain patients









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Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy

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- Mechanistic studies within the Paincage project have a direct relevance for ongoing and new clinical trials

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