PEP2BRAIN Project

About Pain

Recent statistics from the World Health Organization, "one in five people worldwide suffer from moderate to severe chronic pain, and that, one in three are unable to maintain an independent lifestyle due to their pain"1.

Pain is the most common clinical symptom for which people seek medical care2.

According to the International Association for the Study of Pain3:
"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. (...) However, many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons." (...)

International Campaign

2009–2010 Global Year Against Musculoskeletal Pain
2010-2011 Global Year Against Acute Pain
2011-2012 Global Year Against Headache
2012-2013 Global Year Against Visceral Pain

[1] - World Health Organization. (2004) World Health Organization supports global effort to relieve chronic pain.
[2]- Ueda, H., Rashid,MH., Molecular mechanism of neurophatic pain. Drug News Perspect., 2003. 16(9): p. 605-13.
[3]- http://www.iasp-pain.org

Motivation for the Project

Little has changed during the XX century in pain relief and anti-neurodegeneration compared to the achievements of drug discovery in other areas. In light of the huge global burden of chronic pain and neurodegeneration, that have a trend to increase due to increase aging of the populations, a question worth asking is where the best hope lies for developing better treatments.

Kyotorphin (KTP) is an endorphin-like analgesic dipeptide (L-Tyr-L-Arg) that was firstly isolated from bovine brain in 19791. This dipeptide was subsequently found in the brain of several mammals and in human cerebrospinal fluid2,3. Although its activity is 4-fold higher relative to endogenous opioids4, it is effective only if injected directly in the brain. This limitation prevents its pharmacological application.

Development of improved derivatives, with enhanced metabolic stability and blood-brain barrier (BBB)-crossing ability was devised as an approach to improve peptide-delivery to the central nervous system (CNS). Academic researchers from the University of Lisbon (Portugal) and Girona (Spain) conceived and synthesized a KTP derivative, named KTP-amide (BLV200703/4), that revealed great pharmacological interest: preliminary in vitro and in vivo tests have shown that BLV200703/4 is able to cross the BBB, has an anti-nociceptive action at the CNS and has a great potential in the treatment of neurodegenerative disorders5.

[1]- Takagi, H., et al., Morphine-like analgesia by a new dipeptide, L-tyrosyl-L-arginine (Kyotorphin) and its analogue. Eur J Pharmacol, 1979. 55(1): p. 109-11.
[2]- Kolaeva, S.G., et al., Effects of L-thyrosyl - L-arginine (kyotorphin) on the behavior of rats and goldfish. Peptides, 2000. 21(9): p. 1331-6.
[3]- Nishimura, K., et al., [Kyotorphin like substance in human cerebrospinal fluid of patients with persistent pain]. Masui, 1991. 40(11): p. 1686-90.
[4]- Shiomi, H., H. Ueda, and H. Takagi, Isolation and identification of an analgesic opioid dipeptide kyotorphin (Tyr-Arg) from bovine brain. Neuropharmacology, 1981. 20(7): p. 633-8.
[5]- Ribeiro, M.M., et al., Inhibition of nociceptive responses after systemic administration of amidated Kyotorphin. Br J Pharmacol, 2011. 163 (5): p. 964-973.

Project

BLV200703/4 is a small molecule discovered jointly by groups from the University of Lisbon (Portugal) and Girona (Spain) that proved its efficacy in analgesia from behavioural tests in rats. The same molecule was tested in a platform that screens potential pharmacological molecules/compounds for neurodegenerative diseases with positive results. The platform is owned by Bioalvo, SA (Portugal). The preliminary results obtained regarding efficacy and toxicology of the molecule were encouraging and the academic inventors and the industrial developers have joined efforts.

A starting phase of lead optimisation was followed, by combining in vitro and in vivo assays, in order to achieve the best pharmacological and ADME/toxicity characteristics. This required technology, knowledge and innovation transfer since the inventors and Bioalvo were unable to perform this endeavour on their own. Synovo, a German company expert in ADME/tox tests and the University of Tuebingen, with a group expert in Medicinal Chemistry, joined Bioalvo and the Universities of Lisbon and Girona to transfer all knowledge, technology and innovation necessary to make possible that BLV200703/04 or one of its future derivatives reaches pre-clinical stage

Project Details

Project Acronym: PEP2BRAIN
Contract Type: Industry-Academia Partnerships and Pathways (IAPP), Grant Agreement Nº 230654
Duration: 2009-03-01 to 2013-02-28 (total: 48 months)
Status: Ended
Hosting organisation: Instituto de Medicina Molecular
Participants: See Team

Goals

The control of suffering remains a touchstone for everything that biomedical science is trying to achieve. Moreover, by 2040 the World Health Organization predicts that, as a result of a growing ageing population, neurodegenerative diseases will have overtaken cancer to become the world's second leading cause of death, after cardiovascular disease.

BLV200703/4 has the unique potential power, supported from our preliminary data, to be a significant step forward in both fronts simultaneously: pain control and neurodegeneration treatment.

The main objective of this research programme was to bring an identified lead compound, BLV200703/4 (or an improved derivative), into pre-clinical development for the treatment of pain and/or neurodegenerative disorders.

This compound was discovered by researchers from the University of Lisbon (Portugal) and Girona (Spain), and recently patented (WO/2009/123487 and WO/2009/123486) by other project partner - Bioalvo, SA.

Deliverables

The project has started with a peptide drug lead that had to be modified and optimised in order to have the stability, low toxicity and efficacy needed to be used in humans.

Efficacy of the starting drug lead was reasonable, albeit not optimal, and the toxicity profile was very encouraging. Yet, stability had to be improved, which challenged the researchers to conceiving improved variants of the peptide drug lead. New derivatives were synthesised and then tested in vitro and in vivo for stability, safety and efficacy. Several approaches were considered in the design of such derivatives, namely, the innovative combination of Ibuprofen (IBP), one of the safest NSAIDs (non-steroid anti-inflammatory drug), to the starting amidated-molecule.

Overall, our data show enhanced brain targeting and analgesia in the absence toxicity and major side-effects (usually associated with opioids), which makes these new molecules extremely promising compounds for future pharmaceutical development.

Publications in peer review Journals:

Ribeiro MM, Pinto A, Pinto M, Heras M, Martins I, Correia A, Bardaji E, Tavares I and Castanho M. (2011) Inhibition of nociceptive responses after systemic administration of amidated Kyotorphin. British Journal of Pharmacology. 163 (5): 964-973.

Ribeiro MM, Pinto A, Domingues M, Serrano I, Heras M, Bardaji E, Tavares I and Castanho M. (2011) Chemical conjugation of the neuropeptide kyotorphin and ibuprofen enhances brain targeting and analgesia. Molecular Pharmaceutics. 8 (5): 1929-40.

Ribeiro MM, Franquelim HG, Torcato IM, Ramu VG, Heras M, Bardaji ER, Castanho MA. (2012) Antimicrobial properties of Analgesic Kyotorphin peptides unraveled through Atomic Force Microscopy. Biochemical and Biophysical Research Communications. 420 (3): 676-9.

Ribeiro MM, Sá Santos S, Sousa DS, Oliveira M, Santos SM, Heras M, Bardaji E, Tavares I and Castanho M. (2013) Side-effects of analgesic Kyotorphin derivatives: advantages over clinical opioid drugs. Amino Acids. [DOI 10.1007/s00726-013-1484-2]

Book Chapter:
Ribeiro MMB, Serrano ID and Sá Santos S. (2011) Turning endogenous peptides into New Analgesics: the example of Kyotorphin derivatives, In: Castanho M. and Santos N. (Eds), Peptide Drug Discovery and Development: Translational Research in Academia and Industry, first ed. WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany pp 171-188. ISBN: 978-3-527-32891-8.

Team

This project involves intersectorial (industry-academia) training of young researchers, international technology transfer and drug R&D.

Participants	Legal Entity	Person-in-charge	Country
UL	Instituto de Medicina Molecular – iMM Lisboa (Universidade de Lisboa)	Miguel Castanho	Portugal
BLV	Bioalvo S.A	Patrícia Calado	Portugal
UdG	Universitat de Girona	Eduard Bardají	Spain
Synovo	Synovo GMBH	Michael Burnet	Germany
UT	Eberhard Karls Universitaet Tuebingen	Stefan Laufer	Germany

Mobility

There were five inter-sectorial secondments during the project, four of them being international. One academic researcher spent six months working abroad for a company and four biotech researchers of a company spent six months-periods in academia, three of them abroad.

Marta M B Ribeiro was a PhD student at Physical Biochemistry Unit, IMM (University of Lisbon), Portugal. She was a secondment at Synovo GMBH (Tubingen - Germany) for 6 months, starting in October 2009.
On November 2012, Marta successfully defended her PhD thesis entitled "Improved analgesic Kyotorphin derivatives - correlating membrane interaction, brain targeting and pharmacological activities" (University of Lisbon, Doctorate in Biomedical Sciences). Supervisor of her doctoral thesis was Professor Miguel Castanho. Marta is now working as Technology Tranfer Officer in Spain.

Marta Cerejo and Gonçalo Andrade are both researchers at Bioalvo, SA, Lisbon, Portugal. They were seconded to the Pharmaceutical/Medicinal Chemistry group at the Eberhard-Karls-University of Tubingen (Germany).

Cátia Rodrigues is also a researcher at Bioalvo, SA. She was a secondment at the Physical Biochemistry Unit, IMM (University of Lisbon), from April to September 2009.

Ricardo Pinto is also a researcher at Bioalvo, SA. He was seconded to Laboratori d'Innovació en Processos i Productes de Síntesi Orgànica (LIPPSO), Chemistry Departament, University de Girona (Spain) during the 2nd year of the project.

Recruitment

- Marie Curie Fellowships - three researchers have been recruited as predicted:
Kátia Conceição (PhD, Brazil) was recruited by IMM (University of Lisbon).
Alexander Kuvshinov (PhD, Russia) was recruited by Bioalvo, SA.
Vasanth Ganga Ramu (PhD, India) was recruited by UdG (Universitat de Girona).

- Fundação para a Ciência e a Tecnologia (FCT) support to Marie Curie Actions in FP7 – one national recruitment by IMM of a postdoctoral fellow:
Sónia Sá Santos (PhD, Portugal) joined Prof. Miguel Castanho´s group in December 2009.

Links

World Health Organization
International Association for the Study of Pain
PAIN® The Journal of the International Association for the Study of Pain

Project in the Media

- Youtube Videos for non-technical audiences:
"Peptides against pain" (explaining the project itself)
"Blood Brain Barrier" (workshop, project event)
- A Web site in Portuguese is available for non-technical audiences, explaining the molecular and physiological basis of pain, with a sub-section devoted to the project itself URL: http://www.dor.biochemistry-imm.org
- Special attention was devoted to journalists and the press; news on the project have been diffused not only in the Portuguese radio but also internationally (for instance, Radio Paris International; broadcasted 15 September 2009).

Some examples in the national radio and press:

- Visão magazine, about project approval by the EC (6 November 2008);
- Rádio Renascença, broadcasted 13 October 2009- concerning the Grunenthal Foundation Award in Pain Research (edition 2008), assigned to the iMM team and Oporto collaborators;
- Correio da Manhã, article about Grunenthal Foundation Award (13 October 2009);
- TSF- Rádio Jornal, a full-program interview (~45 min) about the Project and science in general; broadcasted 6 November 2009.

Contact Us

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Project Partners