Compounds related to 3-alkylamine-1*H*-indolyl acrylate and their use for the treatment of neurodegenerative diseases

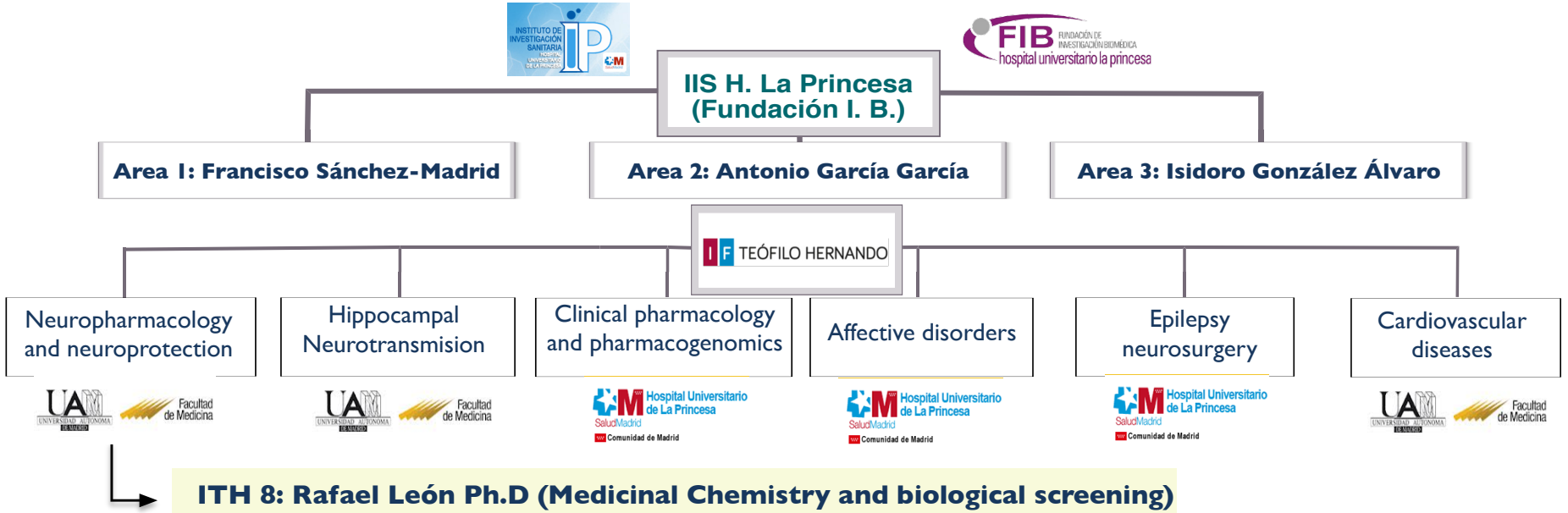
Rafael León Ph.D.

Barcelona, october 20th 2015

Content

1. The Institution
2. The Product
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. Partnering Opportunities

INSTITUTION: IIS HOSPITAL UNIVERSITARIO LA PRINCESA



Dr. Leon MedChem group: Current members

- **Giammarco Tenti**: Postdoctoral Student
- **Zulay Pardo**: Postdoctoral Student (Juan de la Cierva fellowship)
- **Patrycja Michalska**: Ph.D. Student (FPU fellowship)
- **Isabel Gameiro**: Ph.D. Student (FPI fellowship)
- **Sheila Abril:** Ph.D. Student (FPU fellowship)
- **Michelle Satriani**: Erasmus Student
- **Guillermo Furones**: Pharmacology Master Student
- **Alberto Ruiz Priego**: Pharmacology Master Student

Dr. Leon MedChem group: Financial support

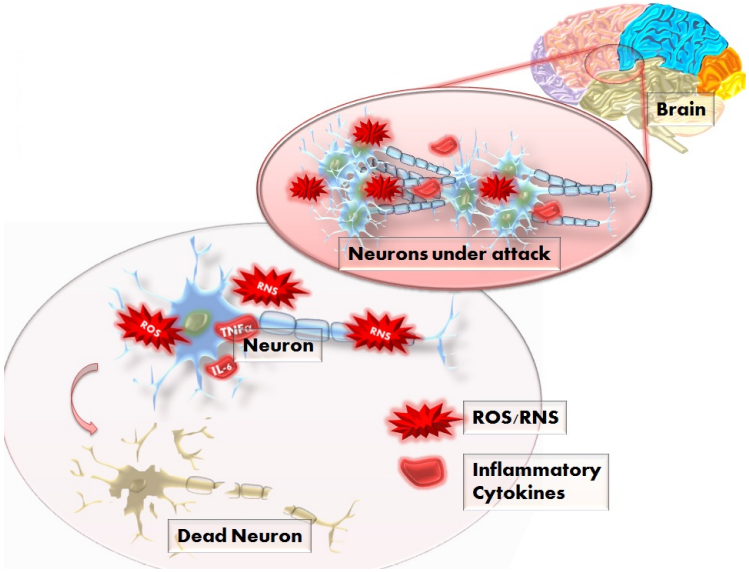
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
Instituto de Salud Carlos III
European Commission
SEVENTH FRAMEWORK PROGRAMME
Bayer HealthCare
MARIE CURIE ACTIONS
GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española
farmaindustria

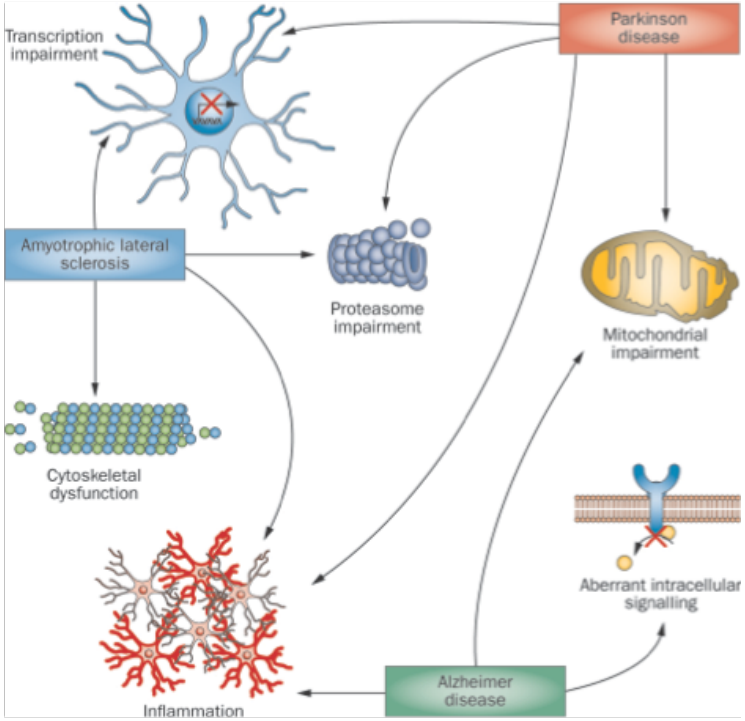
Content

Neurodegenerative and inflammatory diseases

Neurodegenerative diseases: Cognitive degeneration and chronic neuroinflammation

- Common physiopathological hallmarks: Directed drug design





- Aberrant protein aggregates
- Mitochondrial dysfunction
- Extensive oxidative stress
- Neuroinflammation
- Autophagy failure
- Detoxification pathways failure
- Synaptic deregulation

nature REVIEWS NEUROLOGY

Cooper-Knock, J. *et al.* (2012), ***Nat. Rev. Neurol.***156

Neurodegenerative and inflammatory diseases

Target indications

- **Neurodegenerative diseases (600 pathologies described as NDDs)**
  - Alzheimer disease (claim 11)
  - Parkinson's disease (claim 12)
  - Huntington's disease (claim 13)
  - **Multiple sclerosis (claim 14)**
  - Cerebral ictus (claim 15)
  - Peripheral neuropathic diseases (claim 16)
  - Amyotrophic lateral sclerosis (claim 17)

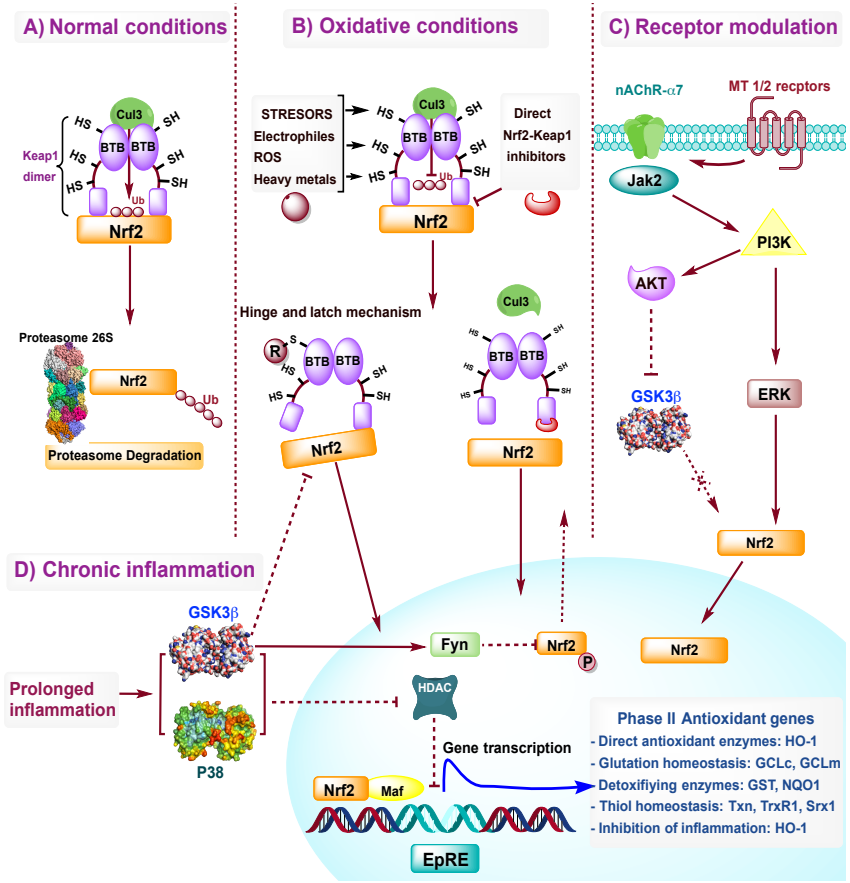
Potential target indications

- **Wide range of application not included in the first patent due to its mechanism of action**
  - Cancer
  - Chronic obstructive pulmonary disease (seeking financial support, ITH-Evgen pharma, UK)
  - Retinal neurodegenerative diseases (*In vitro* and *in vivo* studies in progress, UA-ITH-Bayer Healthcare)
  - Chronic kidney disease (*In vitro* and *in vivo* studies in progress, FJD-ITH)
  - Crohn disease

Content

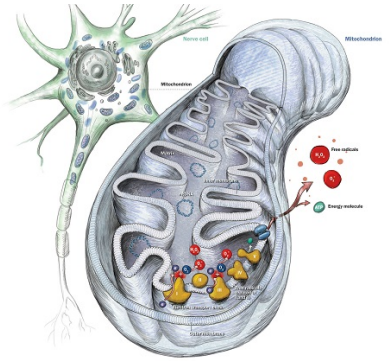
Nrf2-ARE pathway as innovative mechanism of action

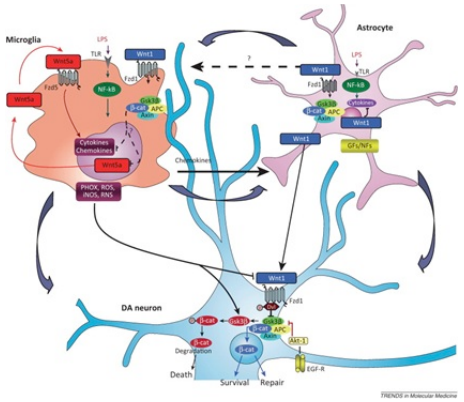
Nrf2-ARE pathway… combined with:



León et al, *Pharm. & Therap.* **2015,** in press.

Oxidative stress regulation and neuroinflammation





- Oxidative stress
- Neuronal loss
- Neuroinflammation

- High CNS vulnerability
- Crosslinks between oxidative stress and protein aggregates
- Mitochondrial dysfunction

Sultana, R.; Butterfield, D. A. *J Alzheimers Dis* **2010,** 19, 341-53.

- Glial overactivation (ROS and protein agregates)
- Pro-inflammatory cytokines and infiltration

Glass et al, *Cell* **2010,** 140, 918-34.

Nrf2-ARE pathway as innovative mechanism of action

Nrf2-ARE pathway target of BG12 (Tecfidera®)

2012-17 growth driven by new therapies, satisfying the unmet needs of convenient administration and more efficacious therapy

TECFIDERA (dimethyl fumarate): Providing a strong oral option for MS treatment

Anticipate broad appeal to a large segment of prescribing neurologists and MS patients

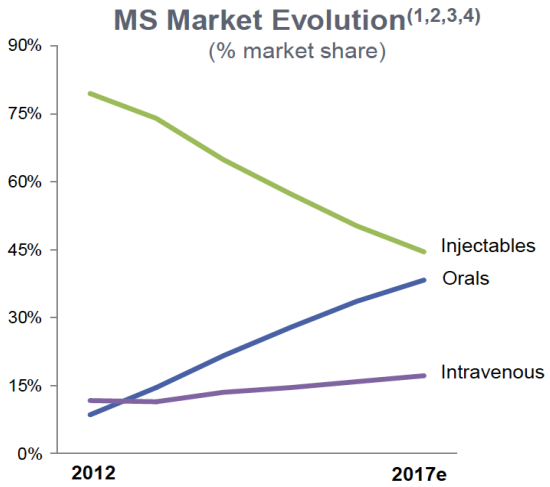
FDA Approved March 27, 2013

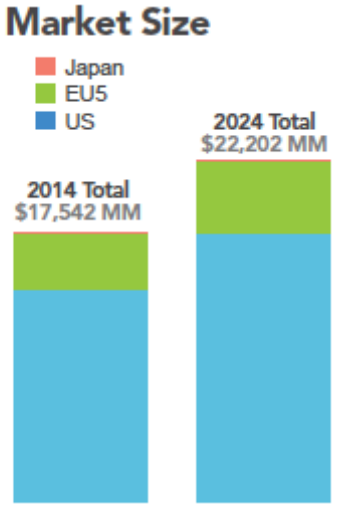
- Strong efficacy
- Favorable safety profile
- Convenience of oral administration
- High physician awareness

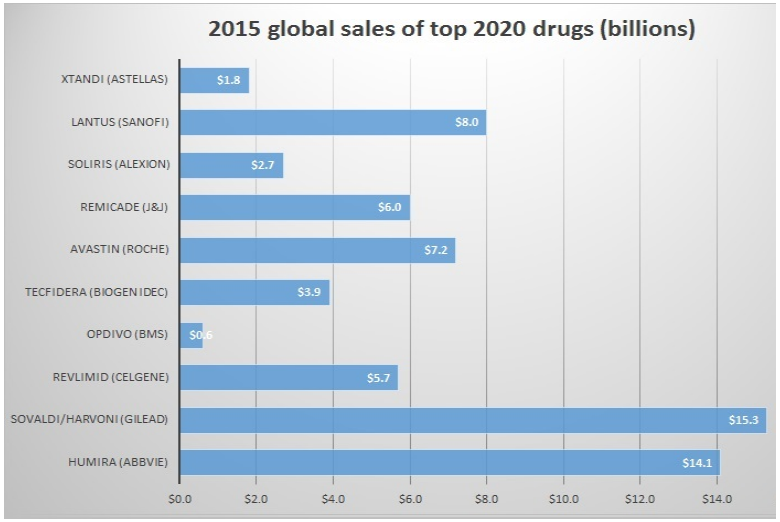
Improved IP offers protection until 2028

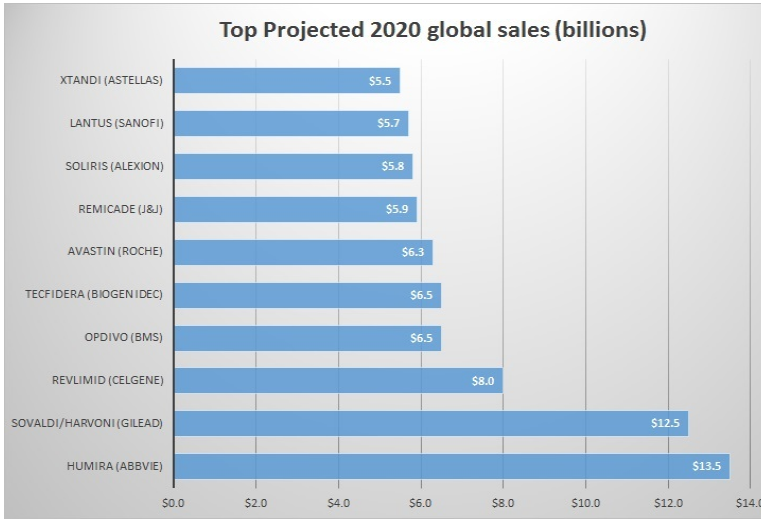
biogen idec

10 *Under Active Review with EMA









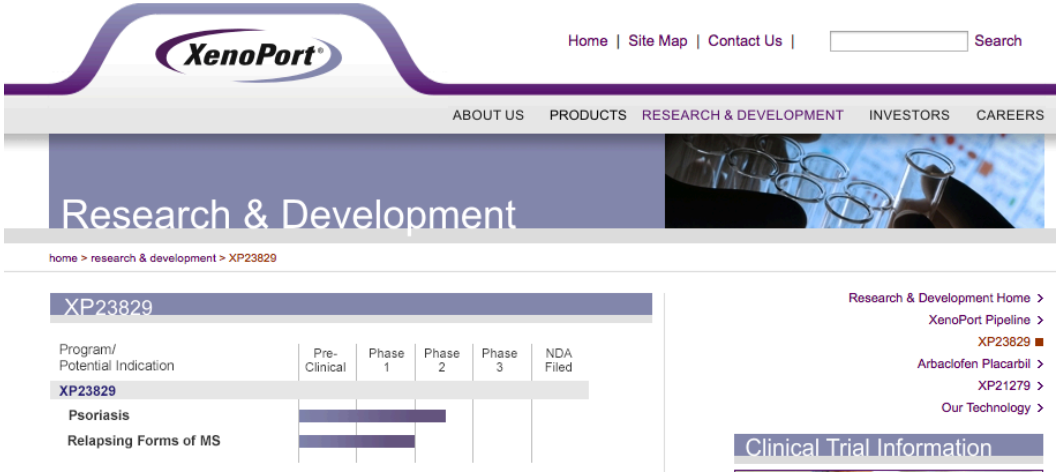
Source: DR/Decision Resources, LLC

(3) 2016e: Adapted from Evaluate Pharma report - December 2011

Nrf2-ARE pathway as innovative mechanism of action

2nd generation of Nrf2 inducers are generating great interest

- XenoPort: Biopharmaceutical company is developing a "ME TOO" derivative of Tecfidera



Background: Fumaric Acid Ester Products

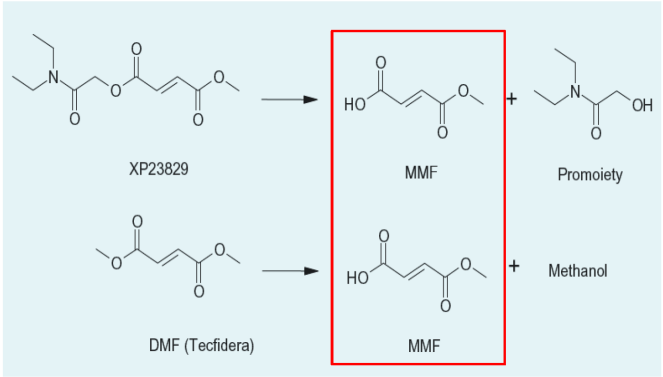
XenoPort

- FUMADERM (mixture of dimethylfumarate and monoethyl fumarate salts)
  - Approved in 1990s and widely used for the treatment of psoriasis in Germany
- TECFIDERA (dimethylfumarate)
  - Approved in March 2013 in the United States and February 2014 in EU for the treatment of relapsing forms of MS
  - Q1 2014 TECFIDERA revenues were $506 million ($460 million in U.S.; $46 million in sales outside the U.S.)
- XP23829 has novel chemical structure that produces the same active metabolite as TECFIDERA (dimethylfumarate)

June 2014 Jefferies Healthcare Conference 22

DMF and XP23829 are Prodrugs of the Same Active Moiety MMF

XenoPort



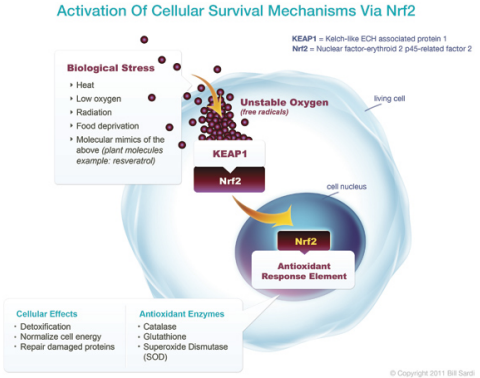
June 2014 Jefferies Healthcare Conference 23

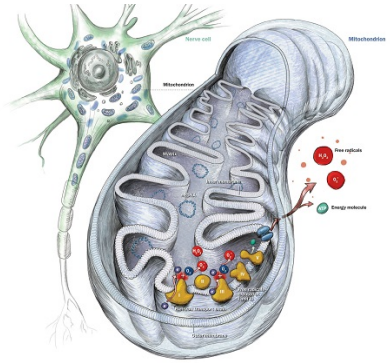
Content

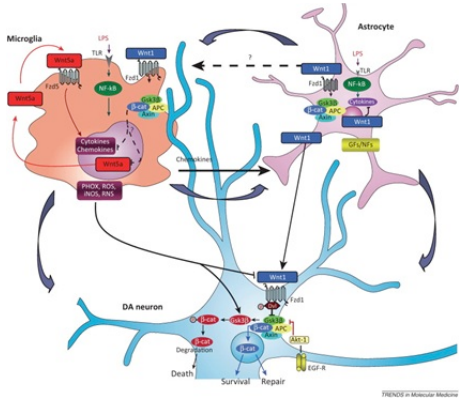
Advantages and differences of NCE facing the market

3-alkyl-1H-indolyl acrylate derivatives Vs BG12 (Tecfidera®)

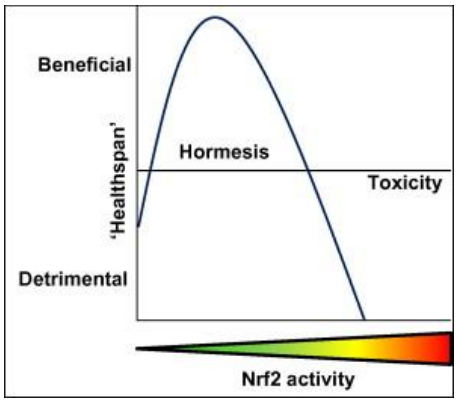
- Nrf2 induction is not enough: **1st Combination of mechanisms (Nrf2 induction – free radical scavenger – anti-inflammatory)**

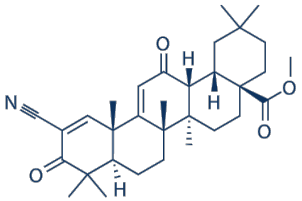






- Nrf2 induction potency control: **2nd Strong Nrf2 induction is TOXIC¡¡¡**





REATA PHARMACEUTICALS

- **Bardoxolone RTA-402**
- **Clinical Trial phase III BEACON NCT00664027**
- **Result: TERMINATED (Safety concerns October 2012)**

Advantages and differences of NCE facing the market

- 3rd Improved activity without increasing toxicity might led to:
  - Lower incidence/ less sever side effects
  - Improved compliance, fewer treatment failures
  - Onset and/or magnitude of immunomodulation
  - Earlier onset of immunomodulation

- 4th Improvement in efficacy due to combination of action mechanism:
  - Dosing frequency
  - Once-a-day rather than BID (TECFIDERA)

- 5th Novel chemical entity with many substitution possibilities:
  - Pharmacokinetic and pharmacodynamics properties modulation

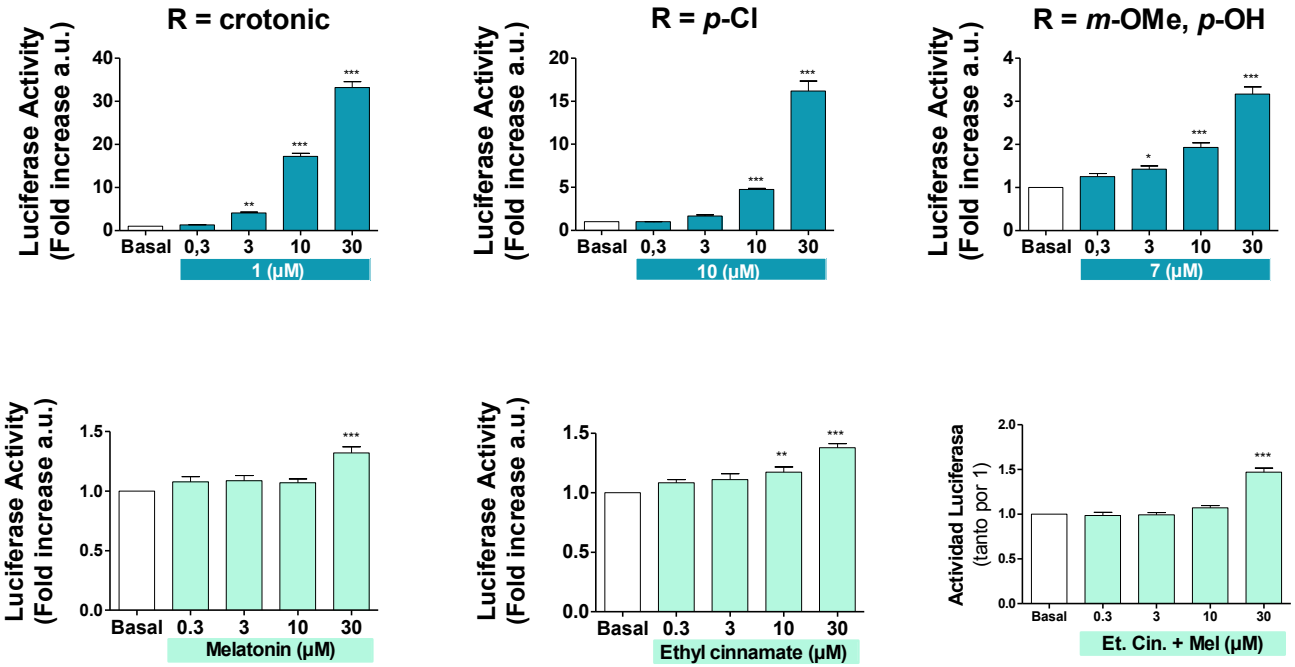
Unmet Needs in RMS

- ✓ Therapies that offer improved disease control for relapsing forms of MS
- ✓ Additional safe and well-tolerated oral therapies
- ✓ Therapies appropriate for long-term use
- ✓ Agents that halt and / or reverse disability

Content

Development status 3-alkylamine-1H-indolyl acrylate derivatives

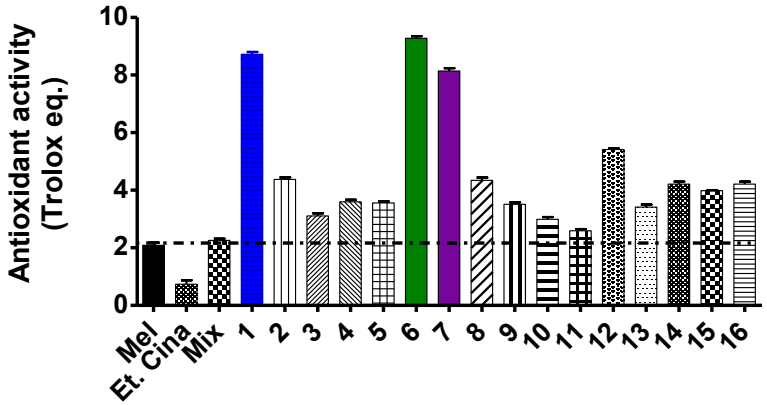
In vitro characterization: Nrf2 induction



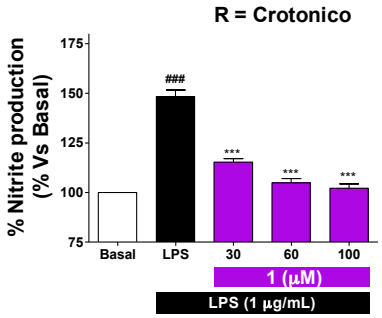
Nrf2-induction properties are easily tuneable

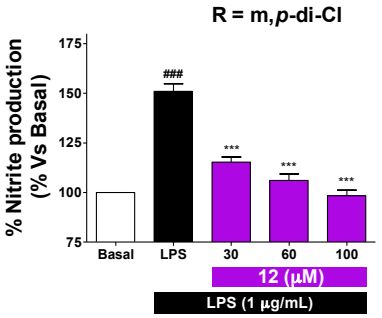
Development status 3-alkylamine-1H-indolyl acrylate derivatives

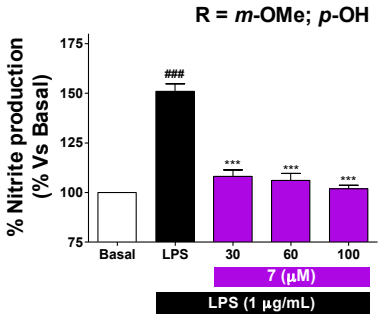
In vitro characterization: Antioxidant effect



In vitro characterization: Anti-inflammatory effect (LPS response blockade)

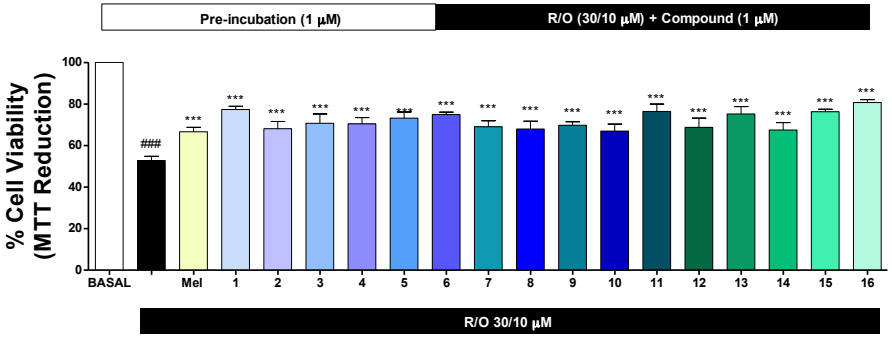


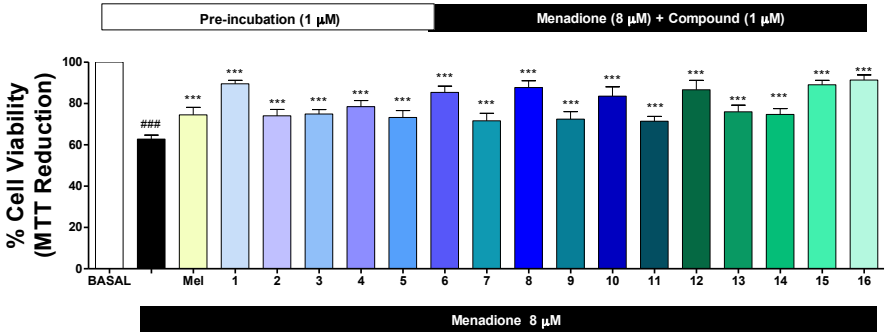




Development status 3-alkylamine-1H-indolyl acrylate derivatives

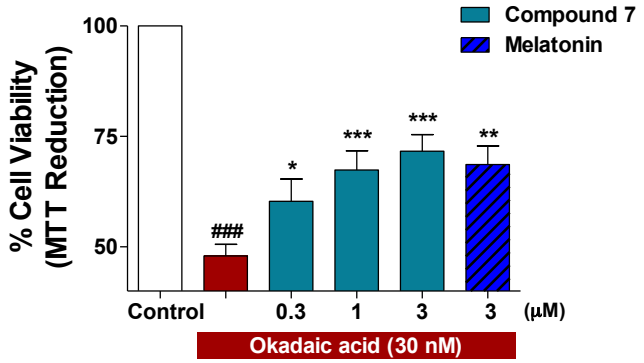
In vitro characterization: Neuroprotective effect against oxidative stress



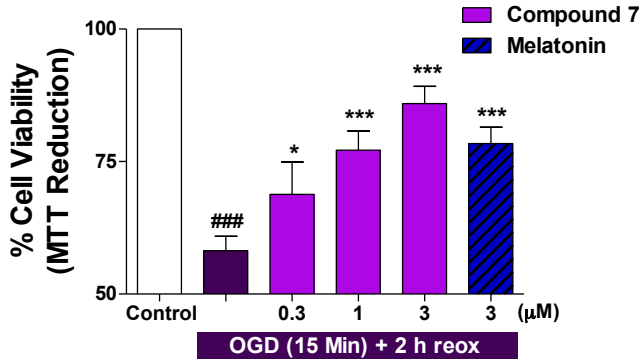


Neurodegenerative diseases specific models

- Tau hyperphosphorylation



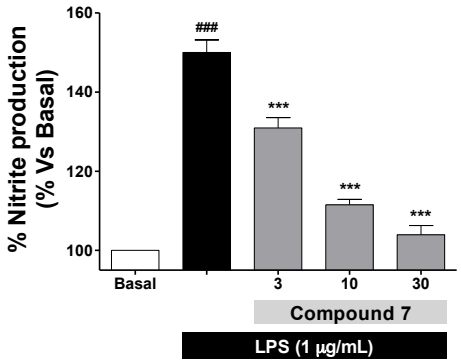
- Cerebral ictus (hippocampal slices)



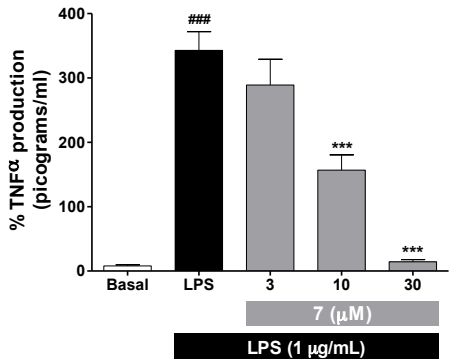
Development status 3-alkylamine-1H-indolyl acrylate derivatives

Neuroinflammation inhibition (Primary rat glial cultures)

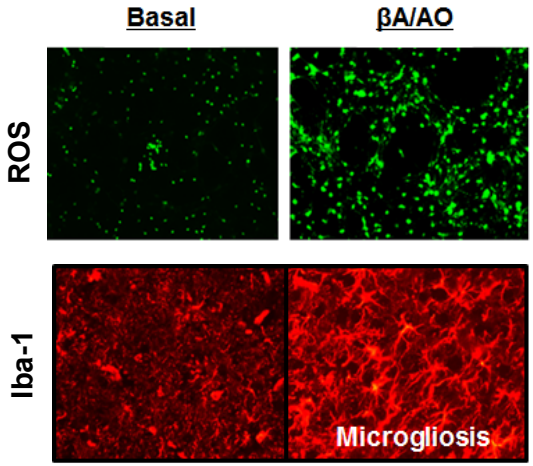
- Lipopolysaccharide model of inflammation
  - Nitrite release reduction

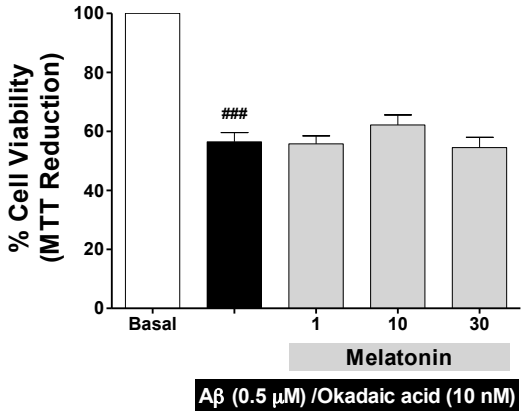


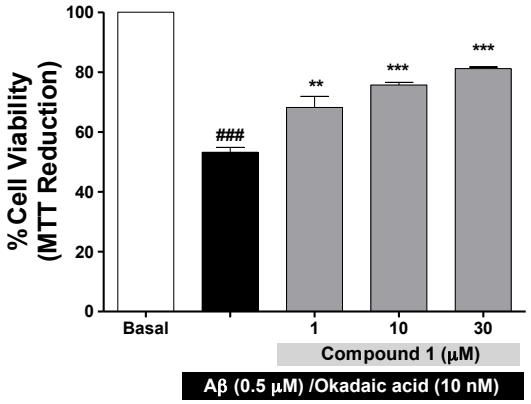
  - TNFα release inhibition



- Amyloid ß and Okadaic acid combination





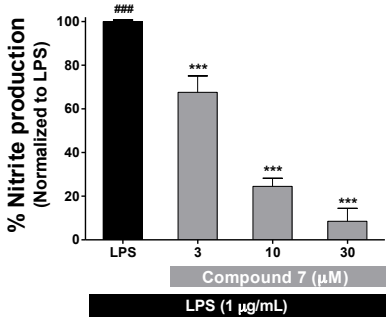


Development status 3-alkylamine-1H-indolyl acrylate derivatives

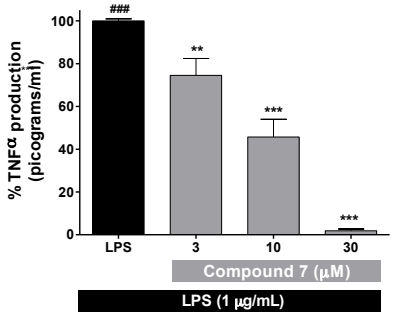
Compound 7 Vs BG-12

Compound 7

- Nitrite release reduction

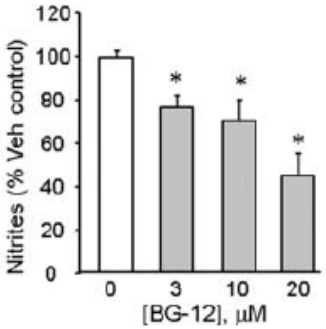


- TNFα release inhibition

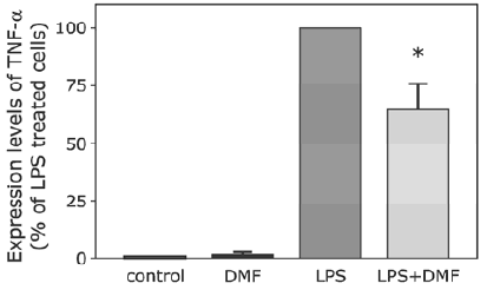


BG-12

- Nitrite release reduction

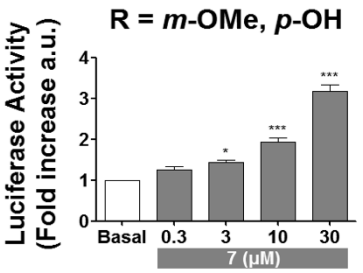


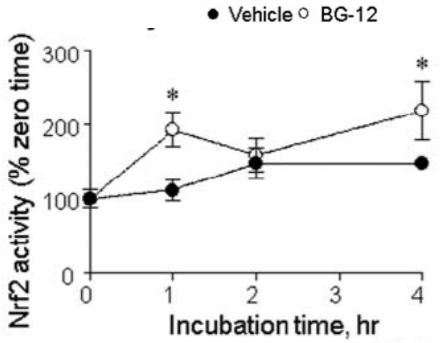
- TNFα release inhibition



Treatment with 10 ngr/mL LPS and 10 μM BG-12

- Nrf2 induction





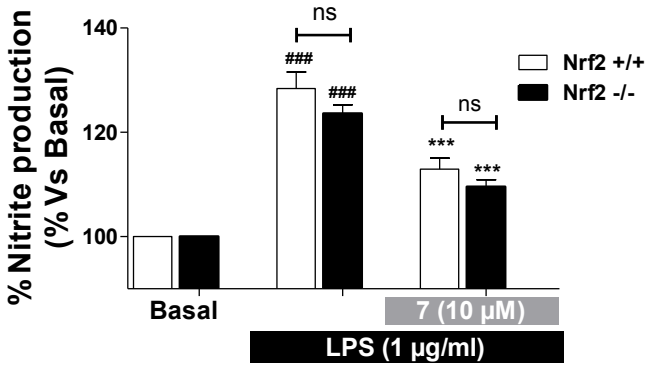
Wilms, H.; J. Neuroinflammation **2010,** 7, 30.

Development status 3-alkylamine-1H-indolyl acrylate derivatives

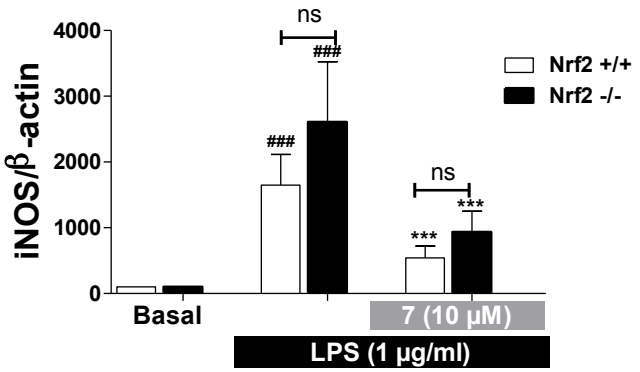
Differentiating aspects facing commercialization:

Anti-inflammatory effect in Nrf2 KO mouse (Primary mouse glial cultures)

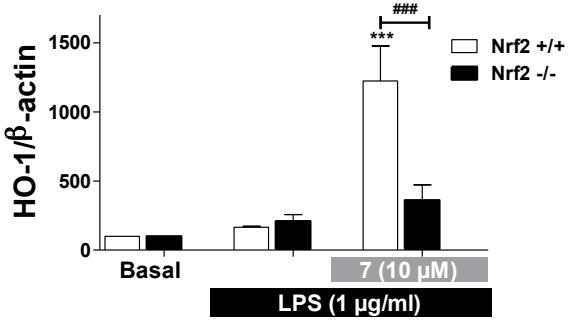
- Nitrite release reduction



- iNOS expression inhibition



- HO-1 expression



THE ANTI-INFLAMATORY EFFECT IS NOT Nrf2-DEPENDENT

Content

3-alkylamine-1H-indolyl acrylate derivatives

IPR status

- **Patent status:**

Derivatives of 3-alkylamine-1H-indolyl acrylate and their use for the treatment of neurodegenerative diseases

- Priority date: **15/10/2014**
- Application number: **P201400810**
- Priority country: **Spain**
- **PCT application: 15/10/2015**
- **Priority country: Europe**

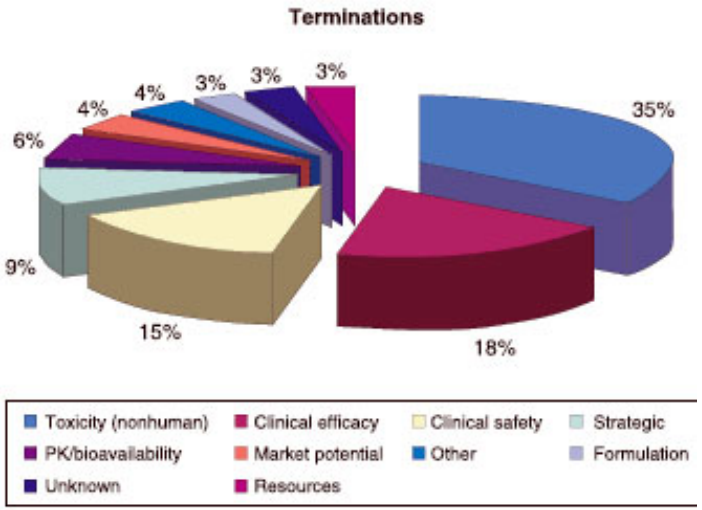
- **Holder: IS Hospital La Princesa /**
- **Universidad Autonoma de Madrid**
- **DNS Neuroscience**

- **Authors: Rafael León, I. Buendia, E. Navarro, P. Michalska, I. Gameiro, A. López, J. Egea, A. García, M. García.**

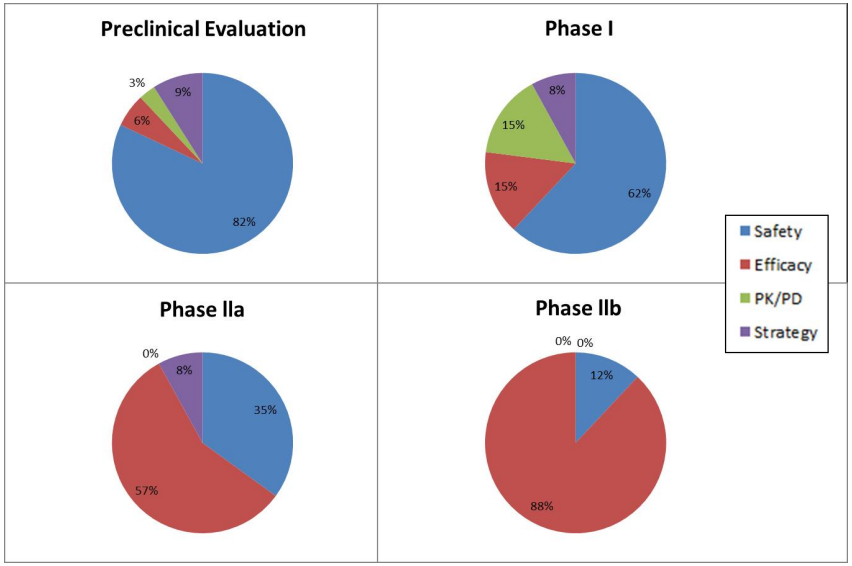
- 19 claims
- Chemical core structure protected
- Chemical substructure protected
- Biological activity protected
- Chemical substituents included
- Anti-inflammatory effect protected
- Use as drugs for Neurodegenerative diseases included as claim
- Common formulations, salts and excipients included for core structure
- Use in COPD, kidney disease or macular degeneration suitable for new patent applications

Content

Pitfalls & risk to be considered



- Rational design of proposed drug
- Target validation already demonstrated
- In vitro activity demonstrated
- Preliminary toxicity performed: Non-hepatotoxic



Content

Partnering Opportunities

Pre-clinical evaluation

- MS mouse model (MOG injection): Scheduled to be started in January 2016
  (Miguel P. Soares Ph.D, European expert in inflammation)
- Pre-clinical toxicity: Big Pharma or CRO companies (Financial support applications: European commission projects)
- ADMET properties
  - Safety pharmacology –CVS, CNS, RS
  - Pharmacodynamics
  - Pharmacokinetics
  - Acute toxicity: 2 species by 2 routes of administration
  - Repeat dose toxicity: rodent and non-rodent; two 14 day studies before human trial
  - Carcinogenicity
  - Reproductive toxicity: Embryo/foetal development studies – 2 species
  - Genotoxicity
  - Mutagenesis: Chromosomal abnormality

Pre-clinical evaluation financial support: Public-private partnership

- Innovative Medicines Initiative (IMI): Next call 12 January 2016 (Budget 93M €)
- 3er Health Program: 3 different calls to be open, including preclinical studies projects
- ERA-NET actions under H2020 program: Public-Private partnerships and cofounded actions
- Joint Technology Initiatives: Specific program in H2020

Compounds related to 3-alkylamine-1H-indolyl acrylate and their use for the treatment of neurodegenerative diseases

Thank you

Barcelona, 20 de octubre de 2015