XIII Encuentro de Cooperación Farma-Biotech

BN201 and 2nd generation program in orphan neuro-ophthalmology

bionure

Promoting Neuroprotection

Barcelona, 20 de octubre de 2015

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

Content

1. The Institution
2. BN201
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
3. Second-generation program
4. Pitfalls & Risks to be considered
5. Partnering Opportunities

1. HQ in Menlo Park, CA – Subsidiary in BCN

San Francisco

- HQ & Clinical Operations
- IP, exclusive worldwide rights
- Raising $15M series A

Barcelona

- Raised $8M in funding (dilutive & non-dilutive), access to EU grants
- Preclinical & 2nd generation program

1. Founders & SAB

Albert G. Zamora, MBA
Co-founder, CEO

Pablo Villoslada, MD, PhD
Co-founder, CSO

Joaquim Trias
Board Member and
Member of the SAB

David Buffenbarger, CPA
Chief Financial Officer

Louis Lehot
Corporate Counsel

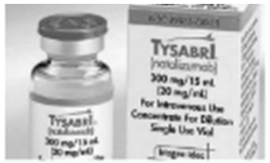
1. Founders & SAB

Strategy & Biz | Neuro-immunology, MS | Neuro-ophthalmology, ON, NMO

Joaquim Trias

Vicuron Pharmaceuticals
TETRAPHASE PHARMACEUTICALS
Anthera PHARMACEUTICALS, INC.
Peninsula PHARMACEUTICALS, INC.

Larry Steinman



ATRECA
Neurocrine BIOSCIENCES
BAYHILL THERAPEUTICS
nuon THERAPEUTICS

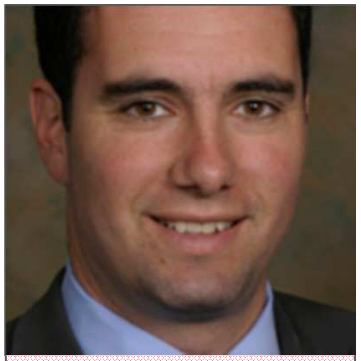
Steve Hauser

UCSF ANNALS of Neurology

Presidential Commission for the Study of Bioethical Issues

Craig Smith

NOVARTIS
Genentech
OPTIC NEURITIS TREATMENT TRIAL ONTT
BILL & MELINDA GATES foundation



Ari Green

UCSF
MS National Multiple Sclerosis Society
EPIC Study

2. Bionure candidate and recent progress

BN201 is a small molecule, NCE, first-in-class drug intended for an intravenous, acute and recurrent intervention in AON and NMO.

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Development Milestones

Preclinical	**MOA described** First-in-Class, SGK agonist	**Neuroprotection + Remyelination**
Regulatory	**Orphan status** by FDA (US) and EMA (Europe)	**Clinical plan** agreed with the FDA
CMC		
IP, Patents	**Patent granted** (composition of matter)	

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**Completing IND studies for IND clearance according to FDA conversations*

2. Funded by the National MS Society

National Multiple Sclerosis Society

Fast Forward
Speeding Treatments To People With MS

Bionure and National MS Society enter into a collaboration to support the development of a new chemical entity for Optic Neuritis and MS

- The National Multiple Sclerosis Society is aimed at accelerating the development of new and improved therapies for MS
- The National MS Society will provide funding to Bionure for the late-preclinical development of BN201 to enable IND filling to support the Phase 1 clinical study in Acute Optic Neuritis (AON). Optic neuritis is often a first sign of multiple sclerosis.

Funded by the National MS Society (2015)

2a. Target indications & Huge Line Extension

NEURODEGENERATION

NEURODEGENERATIVE DISEASES

ALZHEIMER PARKINSON

MULTIPLE SCLEROSIS

AMYOTROPHIC SCHIZOPHRENIA

LATERAL SCLEROSIS DEMENTIA

GLAUCOMA SPINAL MUSCULAR ATROPHY

FRIEDREICH'S ATAXIA

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STRAGEGIC FOCUS: NICHE, ORPHAN DISEASES

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Acute and rare disease of the eye

2a. Clinical & regulatory risks optimized in AON

Acute and rare disease of the eye

Reduces timing
Reduces costs
Improves trial sensitivity

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rare

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Less patients required

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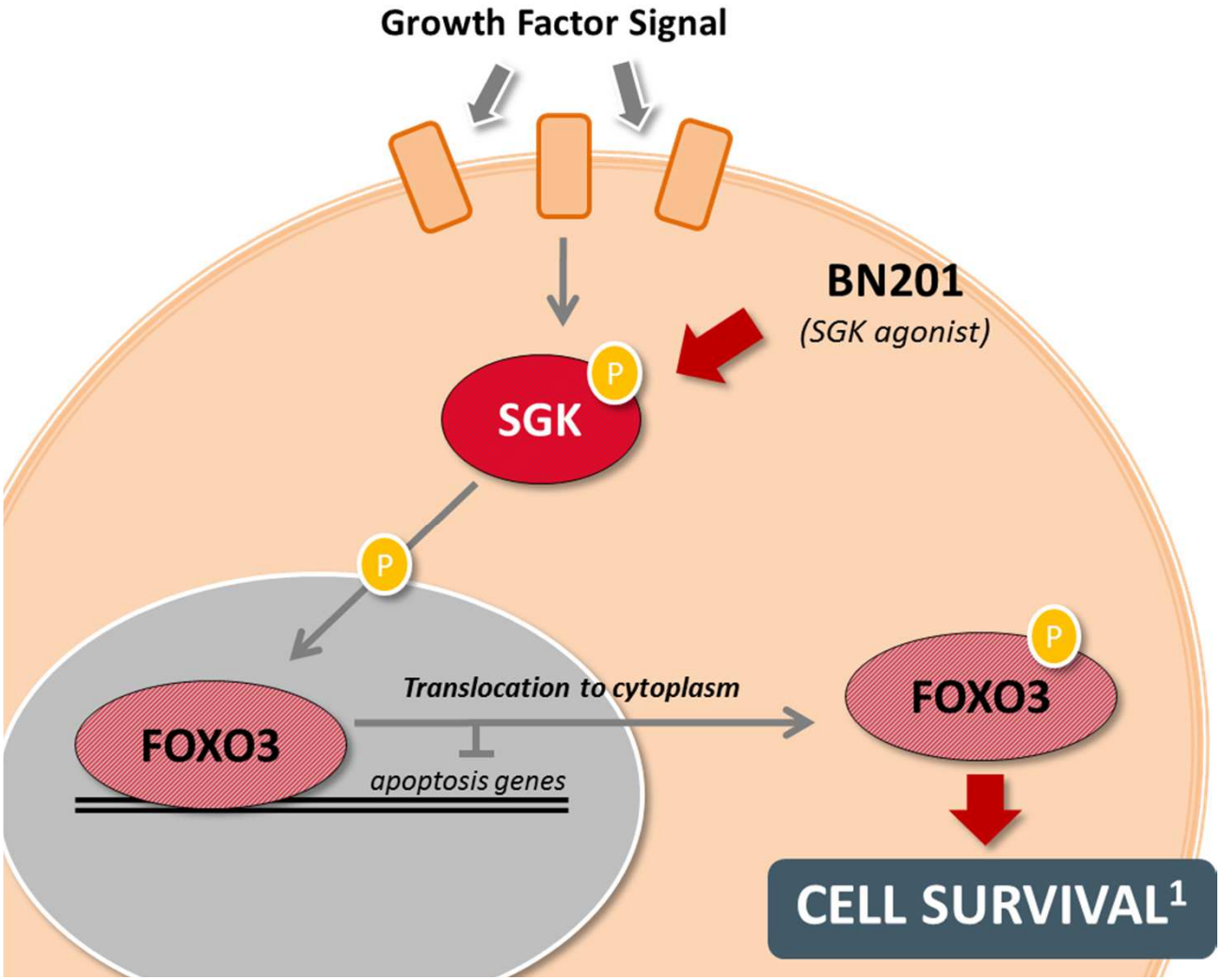
- Cost-effective (less $ than avg)
- Fast regulatory path established
- Clinical endpoints accepted
- Best path to demonstrate neuroprotection

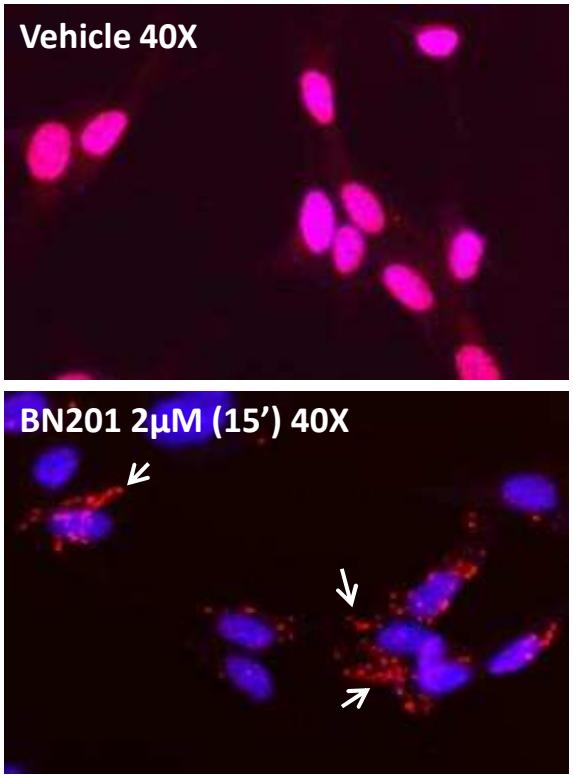
Thanks to this strategy we avoid the main risk in trials* and leverage a huge potential in CNS line extension (e.g. MS)

**Costly trials (many patients required in long trials) that may fail late at Phase III (because of difficulties for measuring efficacy)*

2b. MOA of BN201: SGK agonist



FOXO-3 staining by immunofluorescence in SH-SY5Y after BN201 exposure (in vitro)



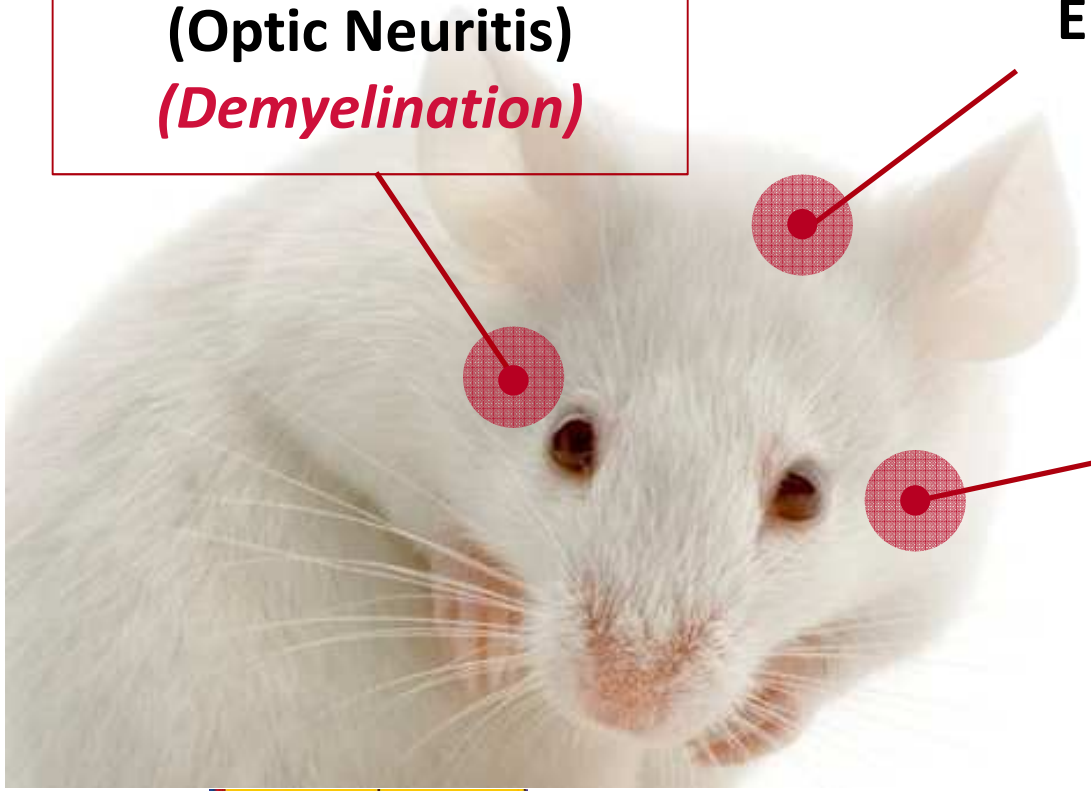
[1]*Brunet A, Park J, Tran H. et al. Protein kinase SGK mediates survival signals by phosphorylating the forkhead transcription factor FKHRL1 (FOXO3a); Mol Cell Biol 21(3):952-965 (2001)*

2b. Neuroprotection + Remyelination activity

BN201 is highly efficacious in animal models

Lysolecithin-induced demyelination model (Optic Neuritis)
(Demyelination)

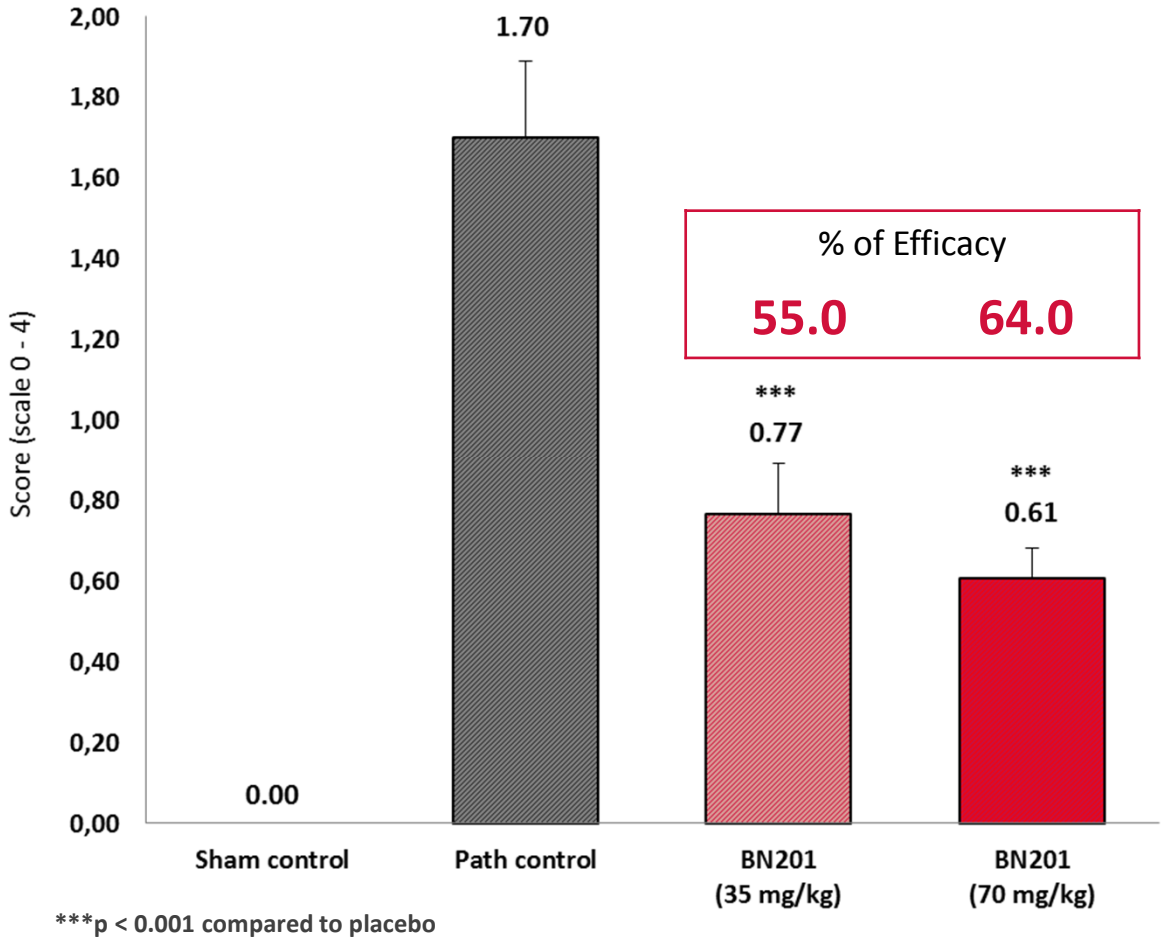
Experimental Autoimmune Encephalomyelitis model (Multiple Sclerosis)
(Inflammation)



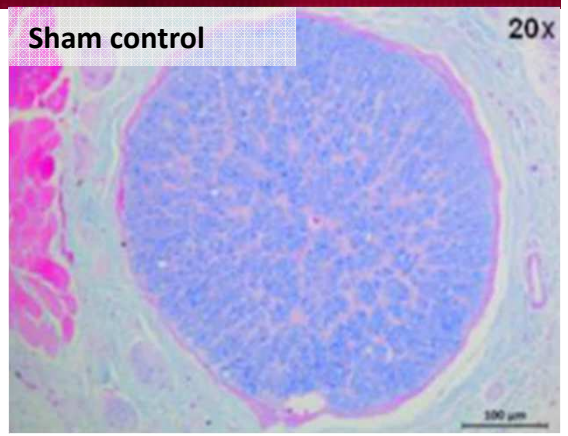
Hypertensive Glaucoma
(Neurodegeneration)

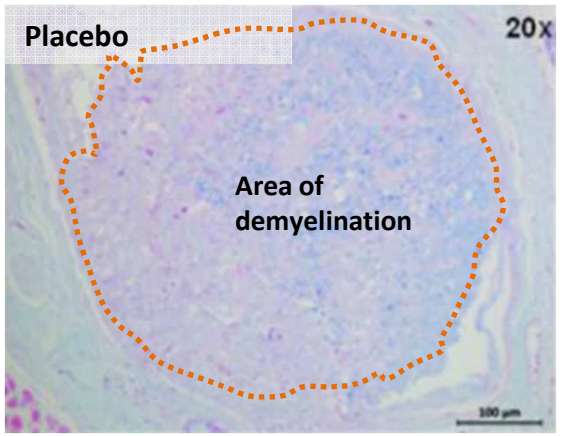
2b. BN201 prevents demyelination in LPC model

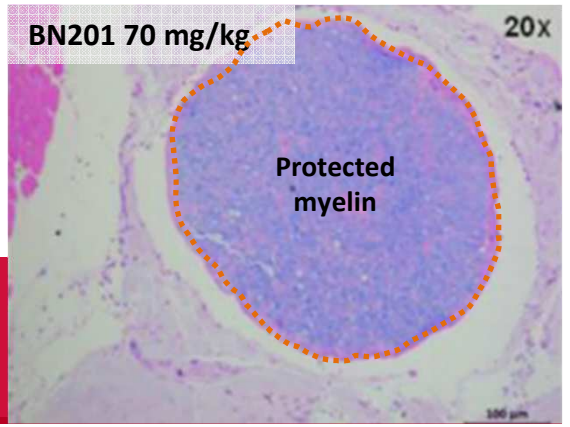
LFB staining for optic nerve demyelination



***p < 0.001 compared to placebo



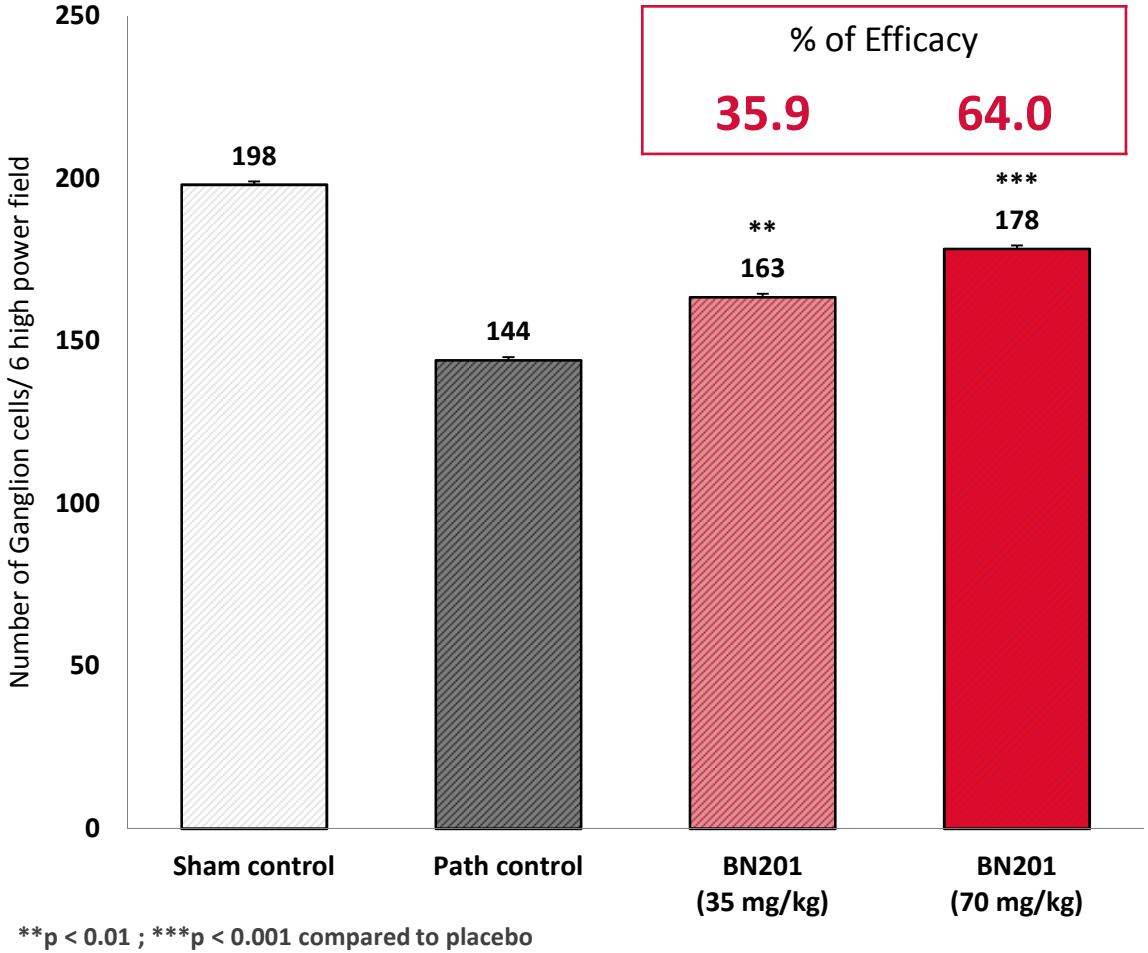




i.p. BN201 protects myelin in the lysolecithin induced demyelinating model in rat

2b. BN201 promotes neuroprotection in LPC model

H&E for Retinal Ganglion Cell (RGC) count



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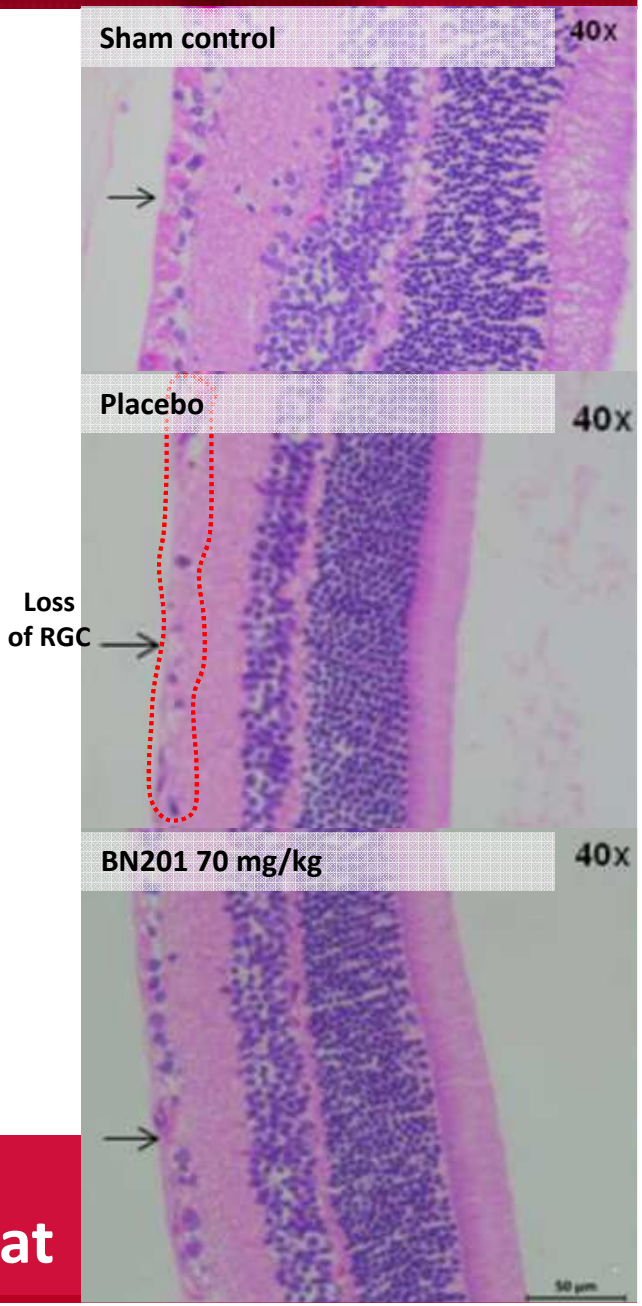

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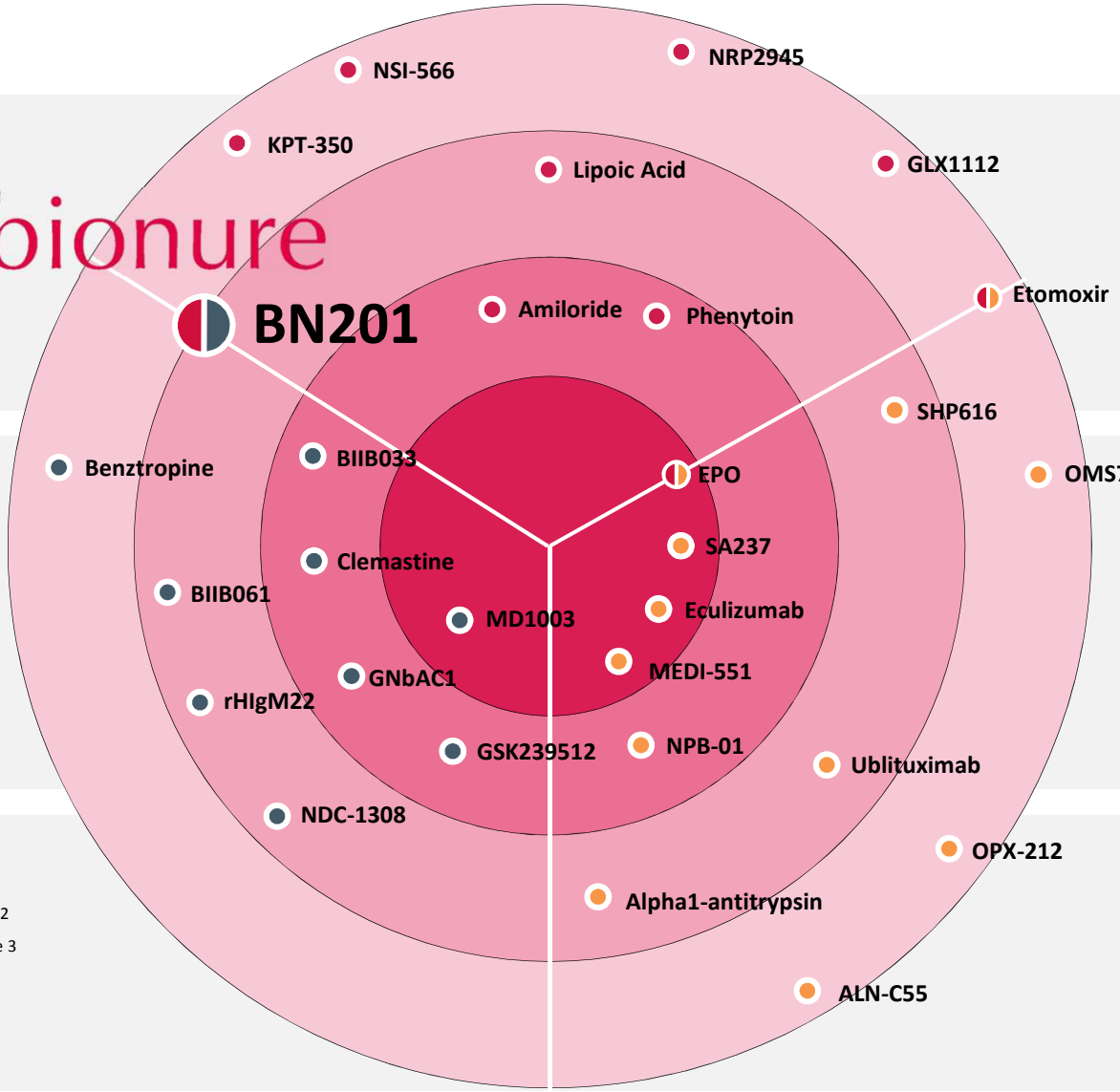
2c. Market differentiation: AON/MS and NMO

- Biogen's BIIB033 is the most promising remyelinating drug
- Neuroprotectants: academy-led
- All immunosuppresants target Neuromyelitis Optica



- **Neuroprotection**
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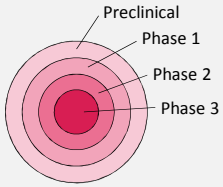

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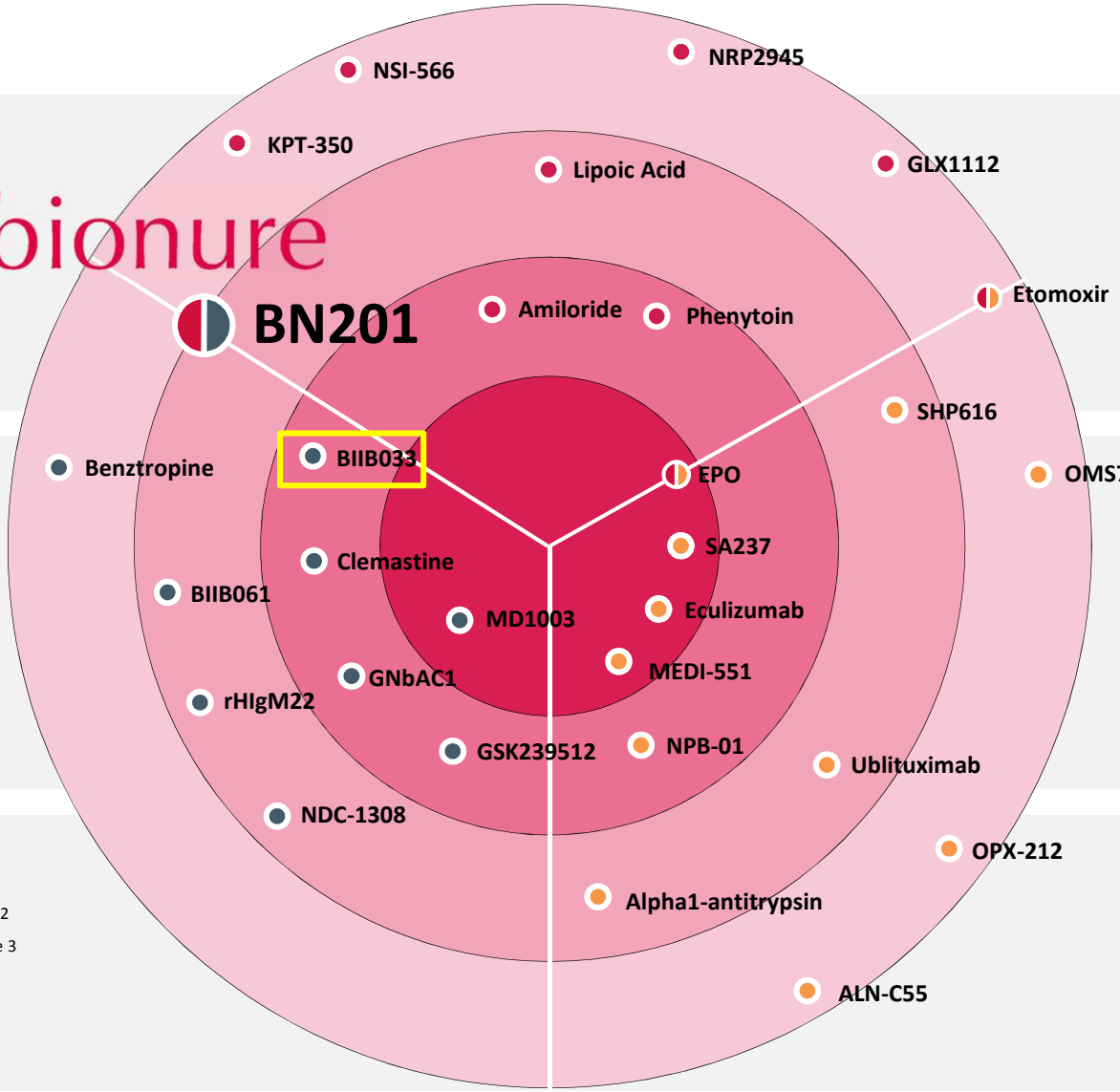

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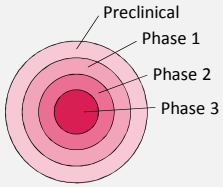

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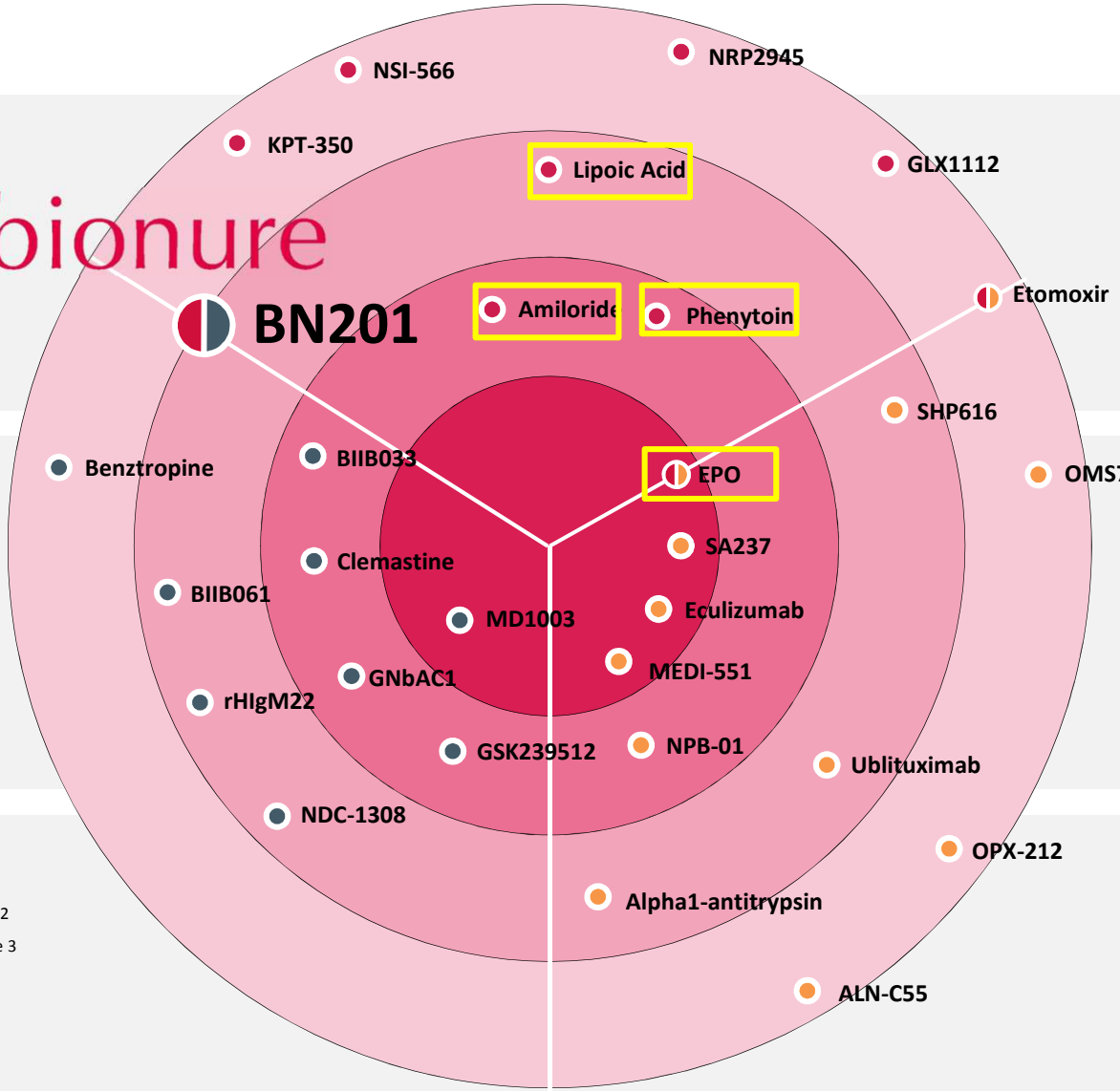

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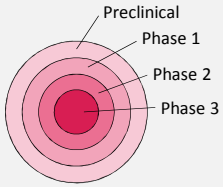

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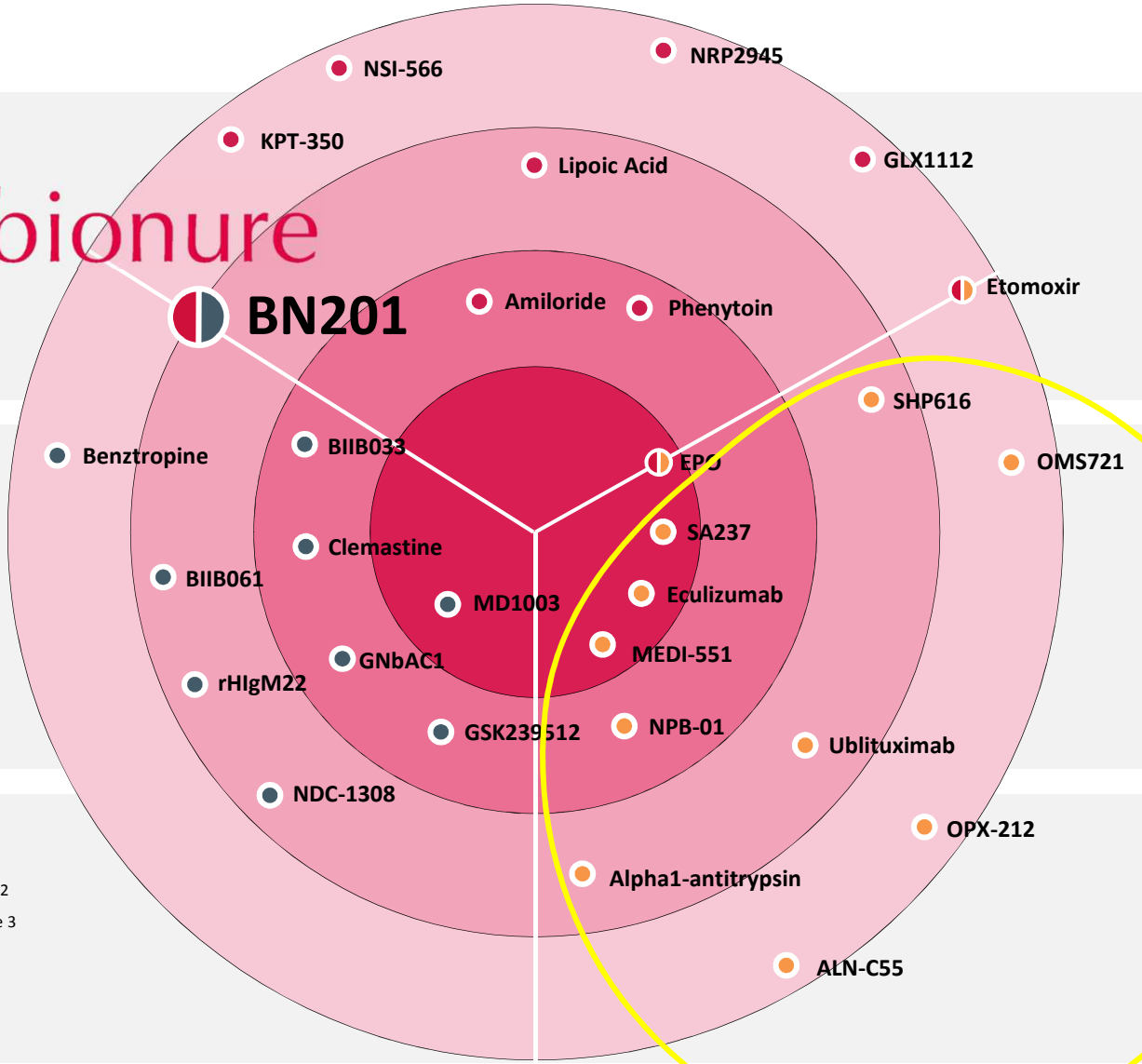

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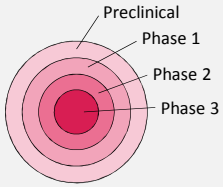

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Unique profile
neuroprotection
+ remyelination

bionure

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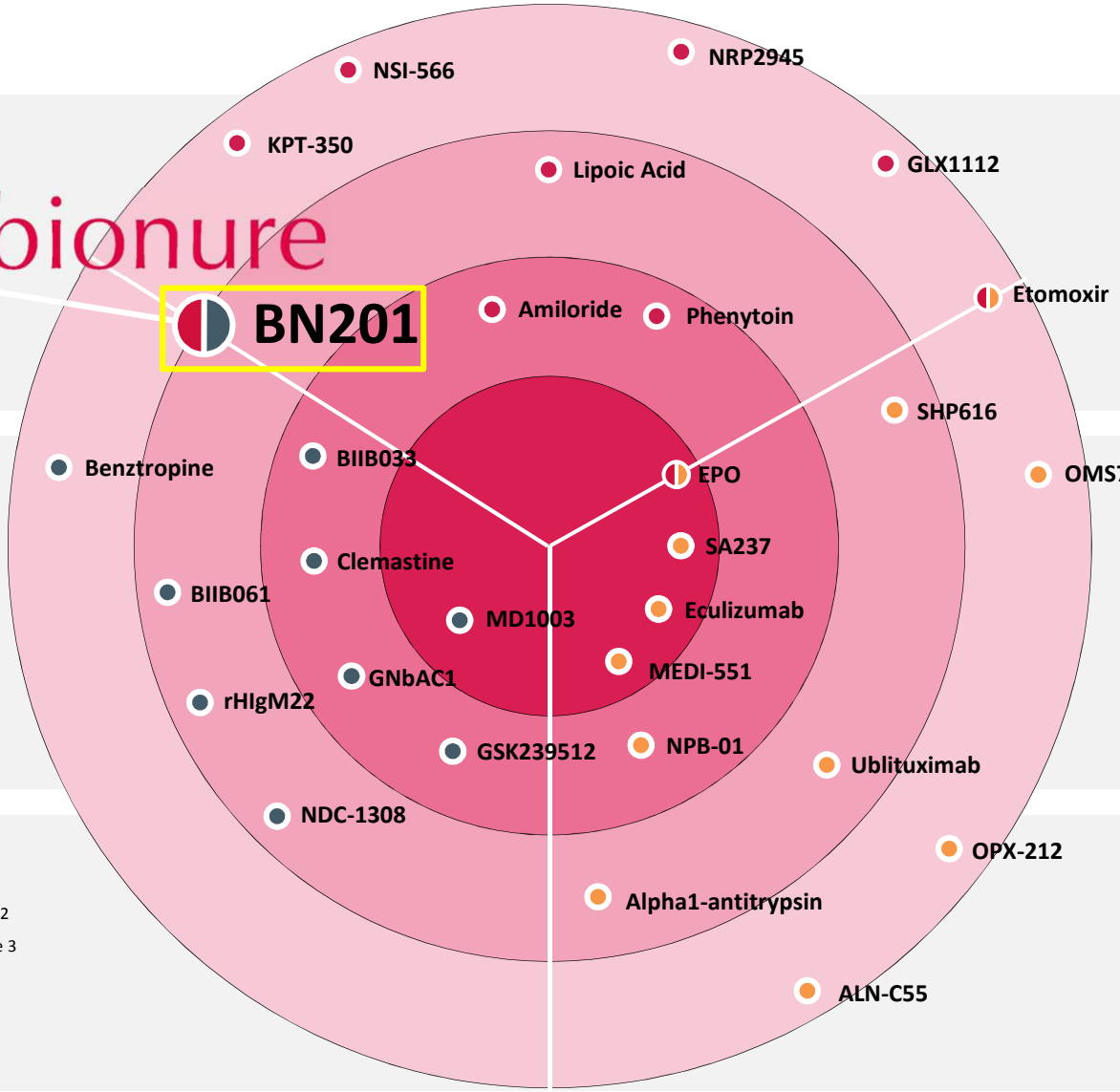

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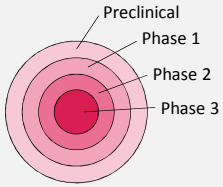

BN201: the most promising candidate in the pipeline

"The interest in remyelinating compounds has recently dramatically increased as one of the hottest areas in drug discovery, together with immuno-oncology and gene therapy. But you can't remyelinate when there are no axons left.

Promoting neuroprotection plus remyelination may be the way"

Prof. Larry Steinman, Stanford

2d. Status of development: milestones

Development Milestones

Preclinical	**MOA described** First-in-Class, SGK agonist	**Neuroprotection + Remyelination**	**GLP Toxicology** completed
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PHASE 1 (SAD + MAD)

- 32 healthy volunteers | Treatment duration: SAD, one single 1-h infusion; MAD, 5 days
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PHASE 2a (AON, 1st episode)

- 75 patients | Type of treatment: BN201 (IV route / QD / 5 days) + add-on steroids
- Endpoint: Change in thickness of the Ganglion Cell Layer/Inner Plexiform Layer at Week 12

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PHASE 2/3 (NMO)

- 105 patients | Type of treatment: BN201 (IV route / QD / 5 days) + add-on steroids and SoC allowed
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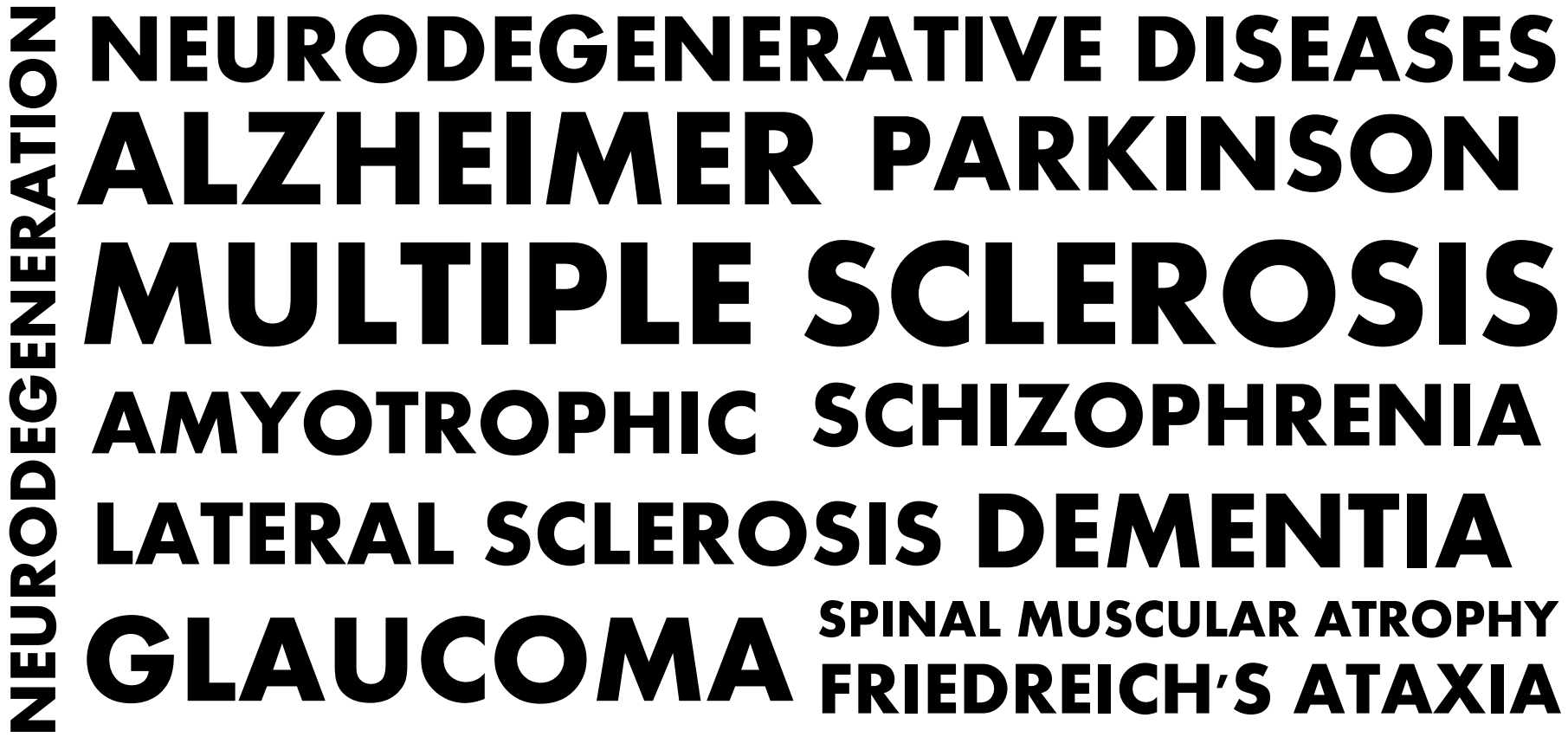
IV, acute, recurrent intervention for **AON** and **NMO**

Leveraging Huge Line Extension Potential



3. Second Generation Program Outline

Goal: Develop new compounds (BN201-related) and new formulations for new indications

- 2-3 years program; 2.5M$ (including FTEs for chemistry)
- New compounds designed based on Structure-Activity Relationships (SAR). Milestones to achieve:
  1. Determination of active pharmacophores of BN201 (SAR)
  2. Identify candidates with enhanced potency and bioavailability
  3. Validate new candidates identified in a disease model

Flexible models for collaboration with pharma industry

4. Pitfalls & Risks to be considered

Technical/Clinical Risk

- Translation from animal models to human
- Clinical design/endpoints
- Clinical execution

Regulatory risk

- Feedback from agencies

Financial risk

- Fundraising
- Partnership with biotech/pharma cos.

4a. Technical/Clinical risk

Translation from animal models to clinic

Translation from animal models to clinic

Erythropoietin
(Ph2, RNFL by OCT)

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NEJM Journal Watch

Erythropoietin Reduces Axonal Loss After Optic Neuritis

Robert T. Naismith, MD reviewing Süihs K-W et al. Ann Neurol 2012 Feb 28.

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MEDPAGE TODAY

MEETING COVERAGE 04.24.2015

Early Study Provides First Evidence of Remyelination

— A monoclonal antibody improved nerve signaling in acute optic neuritis.

34-41% efficacy

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AMERICAN ACADEMY OF NEUROLOGY

Phenytoin is Neuroprotective in a Phase 2 trial in Optic Neuritis

30-34% efficacy

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(Ph2, VEP)

MEDPAGE TODAY

MEETING COVERAGE 04.24.2015

Early Study Provides First Evidence of Remyelination

— A monoclonal antibody improved nerve signaling in acute optic neuritis.

34-41% efficacy

Phenytoin
(Ph2, RNFL by OCT)

AMERICAN ACADEMY OF NEUROLOGY

Phenytoin is Neuroprotective in a Phase 2 trial in Optic Neuritis

30-34% efficacy

- ***OCT for neuroprotection ; VEP for remyelination***

4a. Technical/Clinical risk

Clinical design/endpoints

Larry Steinman, MD

SAB - Neuroimmunology

STANFORD UNIVERSITY

TYSABRI® (natalizumab)

Stephen Hauser, MD

SAB - Neuroimmunology

UCSF

Ari Green, MD

SAB - Neuro-ophth.

UCSF

nature medicine

Figure 5: Clemastine enhances the kinetics of remyelination and promotes remyelination in mice after gliotoxic injury with lysolecithin.

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Biogen

Biogen Presents New Anti-LINGO-1 Phase 2 Acute Optic Neuritis Data Demonstrating Neurological Repair

4a. Technical/Clinical risk

Clinical execution

Former Clinical Team at Genentech

Craig Smith, MD
Chief Medical Officer

NOVARTIS
Genentech
BILL & MELINDA GATES foundation
OPTIC NEURITIS TREATMENT TRIAL ONTT

- Former SVP, Novartis and Global Medical Director, Genentech
- PI in neuro-ophthalmology trials, including ONTT and Genentech's rituximab late-stage trials for MS

Jennifer Reichuber
Clinical Operations

Genentech
Roche
ORACLE
Altani Associates

Natalie Rossignol
Clinical Operations

Genentech
BILL & MELINDA GATES foundation
Altani Associates

4b. Regulatory risk

- CTA clearance by the Netherlands Agency to start Ph1
- Studies recommended by FDA for IND clearance ongoing
- Clinical program designed according to FDA (pre-IND)

5. Partnering Opportunities

Second-generation program

- Open for collaboration
- Flexible regarding structure

BN201

- M&A, option, licensing agreement
- Direct investment

XIII Encuentro de Cooperación Farma-Biotech

Back-up slides

bionure

Promoting Neuroprotection

Barcelona, 20 de octubre de 2015

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

2. Target Indications: orphan ophthalmology

Acute Optic Neuritis	Neuromyelitis Optica
Acute inflammation of the optic nerve (incidence >5/100,000) >120,000 new patients/year in US and Europe	Chronic inflammation and demyelination of the optic nerve and spinal cord (prevalence 1-5/100,000) >20,000 patients in US and Europe
Significant visual impairment Eye pain and vision loss	Blindness, paralysis and death
Short recurrent IV treatment Market potential >$900M	Short recurrent IV treatment Market potential >$300M
IV corticosteroids for acute events	IV corticosteroids for acute events Immunosuppression to prevent relapse

Lack of therapies and strong unmet need

2b. Role of SGK in neuroprotection

bionure

SGK is an **intracellular serine/threonine** kinase

Activated in response to **stress** (glucose, pH, ions, oxidative stress) and **trophic factors**

Promotes **cell protection**, mediated by Foxo3 and Nedd4.2

- SGK mediates the signaling of trophic factors (e.g. IGF or BDNF) and modulates ion channels. Both mechanisms are related with neuronal protection and survival, as well as protecting against neuroexcitability, neuronal apoptosis, neurodegeneration and promoting axonal regrowth[2,3]

[2]Lang F et al. (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoforms. Physiol Rev 2006;86:1151-1178

[3]Park J, et al. Serum and glucocorticoid-inducible kinase (SGK) is a target of the PI 3-kinase-stimulated signaling pathway. EMBO J. 1999 Jun 1;18(11):3024-33.

- SGK modulates potassium channels (Kv7.2/3), modulating M-current and protecting against excitotoxicity[5]

[5]Miranda P et al. The neuronal serum- and glucocorticoid-regulated kinase 1.1 reduces neuronal excitability and protects against seizures through upregulation of the M-current. J Neurosci 2013;33:2684-2696.

- SGK promotes neuronal survival and axonal regrowth of dopaminergic neurons in animal model of Parkinson and Huntington disease[4,8]

[4]Chen X, et al. Neurotrophic effects of serum- and glucocorticoid-inducible kinase on adult murine mesencephalic dopamine neurons. J Neurosci 2012;32:11299-11308.

[8]Rangone H, et al. The serum- and glucocorticoid-induced kinase SGK inhibits mutant huntingtin-induced toxicity by phosphorylating serine 421 of huntingtin. Eur J Neurosci. 2004 Jan;19(2):273-9

- SGK is expressed in oligodendrocytes and neurons after injury and is involved in axonal regeneration and creation of new dendrites[6,7]

[6]Imaizumi K et al. Differential expression of sgk mRNA, a member of the Ser/Thr protein kinase gene family, in rat brain after CNS injury. Mol Brain Res 1994;26:189-196.

[7]David S et al. Expression of serum- and glucocorticoid-inducible kinase is regulated in an experience-dependent manner and can cause dendrite growth. J Neurosci 2005;25:7048-7053.

2b. Lysolecitin induced demyelination (LPC) model

- Demyelination induced by injection of Lysolecithin in the optic nerve of rats. Curative treatment with i.p. BN201 started 1 hour after injection.

- Model of demyelination for Optic Neuritis with no inflammatory component. Target: myelin (mainly), axons and neurons (RGCs)

Readouts

- Hematoxylin-eosin (H&E) for RGC count
- Luxol Fast-Blue (LFB) for demyelination
- Bielchowsky silver impregnation (BSI) for axonal loss

2.4 Phase 1 trial in healthy volunteers

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of the Safety, Tolerability, PK and PD of BN201 in Adult Healthy Volunteers

- SAD and MAD with 2 single- and 2 multiple dose cohorts (32 volunteers, 24 on drug). Alternating escalating (Leap Frog) design for SAD including 4 doses
- Duration of treatment: 5 days for MAD; one single 1h infusion for SAD
- Primary Endpoint(s):
  - Safety and tolerability of BN201 I.V. injection following a single and multiple dose in healthy subjects.*
  - PKPD of different doses of BN201 I.V. injection compared to placebo.**
- Location: PRA Health Sciences, the Netherlands

PRAHEALTHSCIENCES

CTA approved on August 2015 by Netherlands Agency

**The safety of BN201 I.V. Injection will be assessed by adverse event reports, neurological examination, cognitive examination using the Mini-Mental test (MMT), neuropathic pain assessment, cardiovascular assessment: 1) telemetry, 2) electrocardiogram (ECG); 3) Holter (24h), electroencephalographic (EEG) assessment, laboratory measurements (chemistry, hematology, urinalysis), and vital signs.*

***Ratio of Foxo3 translocation from nucleus to cytoplasm in peripheral blood mononuclear cells by immunofluorescence*

2.4 Phase 2a in Acute Optic Neuritis (MS)

A Randomized, Double-Blind, Parallel-Group, Placebo Controlled PoC Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of BN201 in Subjects with First Episode of Acute Optic Neuritis (AON).

- Population selected: 75 patients (2 doses of BN201 and placebo, 50 will be on drug) with confirmed diagnosis of first episode of unilateral AON with an onset within 2 weeks prior to study dosing 1/baseline.
- Type of treatment: Two different doses of BN201 (IV route / QD / 5 days), add-on therapy to corticosteroids (placebo refers to second infusion)
- **Primary endpoint: Change in thickness of the Ganglion Cell Layer/Inner Plexiform Layer at Week 12** for the affected eye as determined by OCT. *Note: 12 weeks because most of the disability is established during this period of time.*

FDA: GCL thickness (measure by OCT) is an adequate endpoint for a Ph2a and the primary endpoint can be evaluated at 12 weeks for registry, with additional visits at months 6 and 12 for labeling purposes

Gabilondo et al. Dynamics of retinal injury after acute optic neuritis. *Ann Neurol*. 2015: Atrophy of the GCL in the first month is a strong predictor of long-term visual disability. A decrease of 4 µm in GCL/ is highly predictive of LCVA.

CLÍNIC BARCELONA Hospital Universitari · CHARITÉ · JOHNS HOPKINS UNIVERSITY · VU medisch centrum · UCSF University of California San Francisco · University of Zurich[UZH] · NYU

Access to patients: extensive network of experts and collaborators, key in orphan diseases

2.3 Second-generation Program

- 2-3 years program; 2.5M$ (including FTEs for chemistry)
- New compounds designed based on SAR study
- 4 rounds of 20 new potential hits synthesized
- Evaluation of potency and bioavailability in parallel and final validation in disease model
- First compounds validated expected after 18 months (1st round)