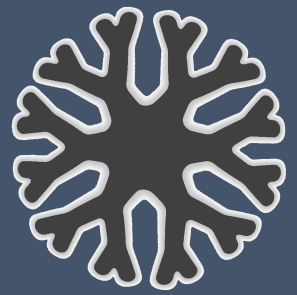
What if we could treat chronic inflammatory diseases without triggering deleterious side effects ?



IMD-pharma

Chronic Inflammatory Conditions

A major health problem lacking innovation

Concerns 5-7% of the population
Related to deregulated and unbalanced immune system.

Current treatments target only 1 inflammatory actor
Most compounds in development are me-too or repositioned drugs

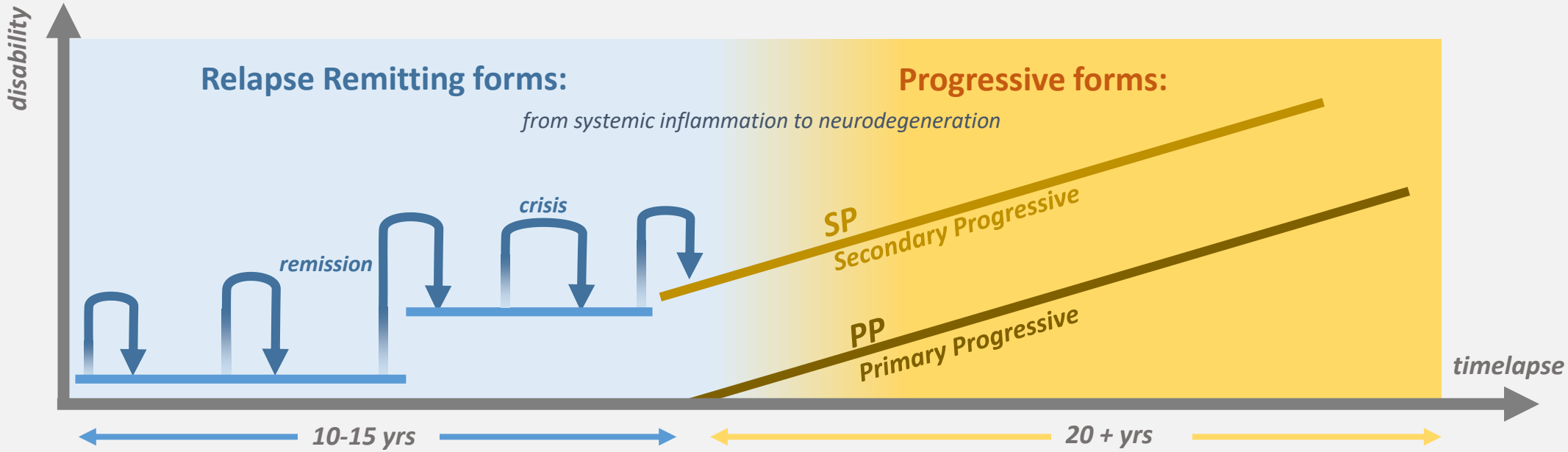
and provoke an ON-OFF effect on the immune system
(strong specific interaction with one single target)

which is responsible for serious side effects and
therapeutic failure…

= Unmet medical needs

Multiple Sclerosis

Strongly disabling condition related to immune-mediated myelin degradation



Myelin is reconstructed during remission period	Myelin is never reconstructed. **Neurodegradation** is continuous
Efficient treatments with anti-inflammatory drugs to contain inflammation during crisis	No treatment can provide anti-inflammatory effects & neuroprotection

UNMET MEDICAL NEED for PROGRESSIVE MS

Estimated market = 4 billions US$ in 2020 (GlobalData)

Market and patient expectations

In the complicated MS market landscape, true innovation is scarce and biologics have commercially succeeded despite severe side effects

True innovation is scarce

- most drugs are repositioned from oncology or other markets
- absence of new synthetic compound in phase I

Biologics are controversial compounds with severe (to dramatic) side-effects

- reported deaths during clinical phases and withdrawals after approval
- anti-CD20 Rituximab fails in phase 2 BUT anti-CD20 Ocrelizumab is approved

Small molecules are also repositioned from other markets and show severe side effects

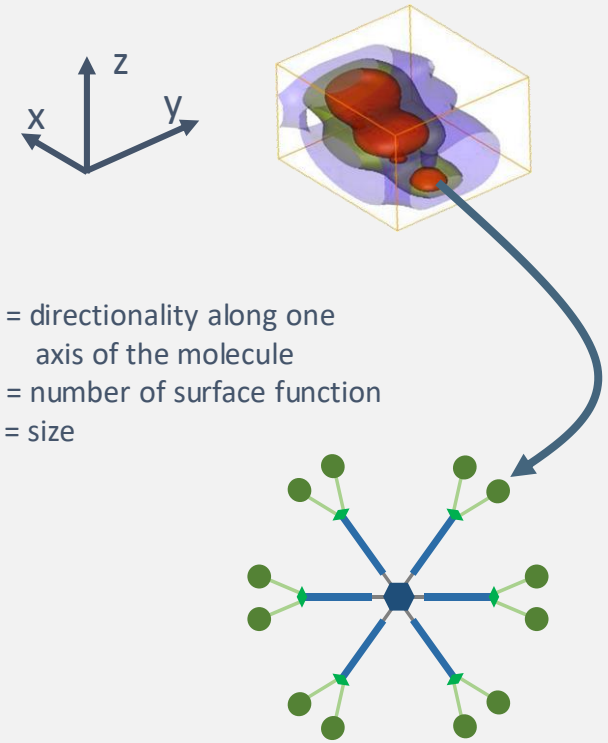
- Fingolimod (SPR inhibitor, retains Th17 lymphocytes in the nodes). Initially developed by Novartis as an immunosuppressive drug for renal transplantation.
  -> Side effects strongly affecting patients life
- Mitoxantrone (cytotoxic intercalating drug). Initially developed in the 80s for anti-cancer purposes.
  -> Increased risk of acute myeloid leukemia and colorectal cancer

Market and patients are waiting for safe & efficient drugs for progressive MS

New concept for the rehabilitation of immune cells

15 years of academic and translational research to afford a modular chemical platform for the design of immune cell rehabilitating molecules.

Proprietary chemical space of active molecules (dendrimers)

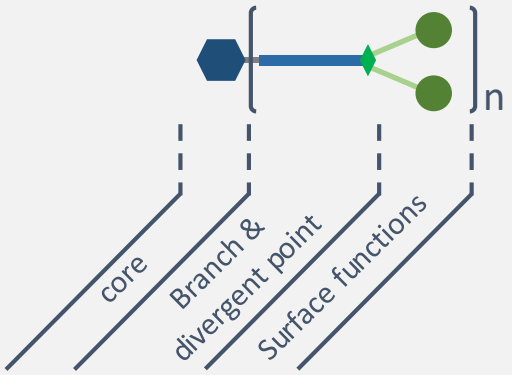


x = directionality along one axis of the molecule
y = number of surface function
z = size

chemical platform (2D view)

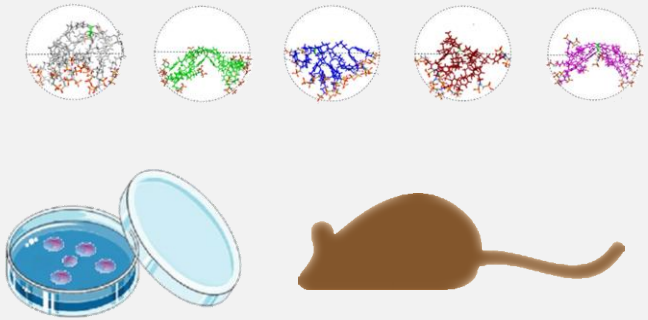
Modular approach based on a versatile chemical platform.

chemical platform (linear view):



These structural parameters can be finely tuned. They strongly affect other key functionnal parameters (like x, y and z).

In vitro and in vivo validation of activities

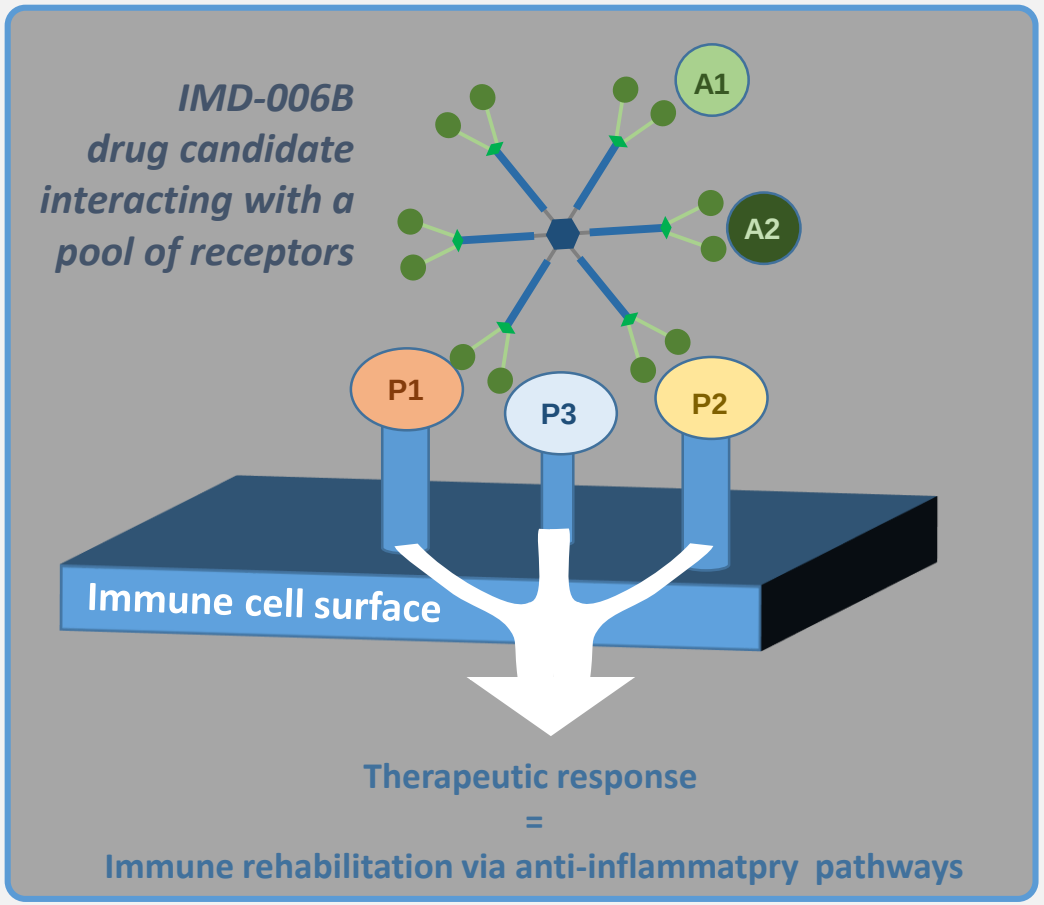


Systematic studies of :
- Anti-inflammatory
- Immunoregulating
- Neuroprotecting
- Adverse effects

Poupot, Turrin et al. *Nature Commun.* **2015**, *6*, 7722

New concept for the rehabilitation of immune cells

15 years of academic and translational research to afford a unique mechanism of action based on the recognition of a pool of receptors



Coll. INOVIEM, TTT

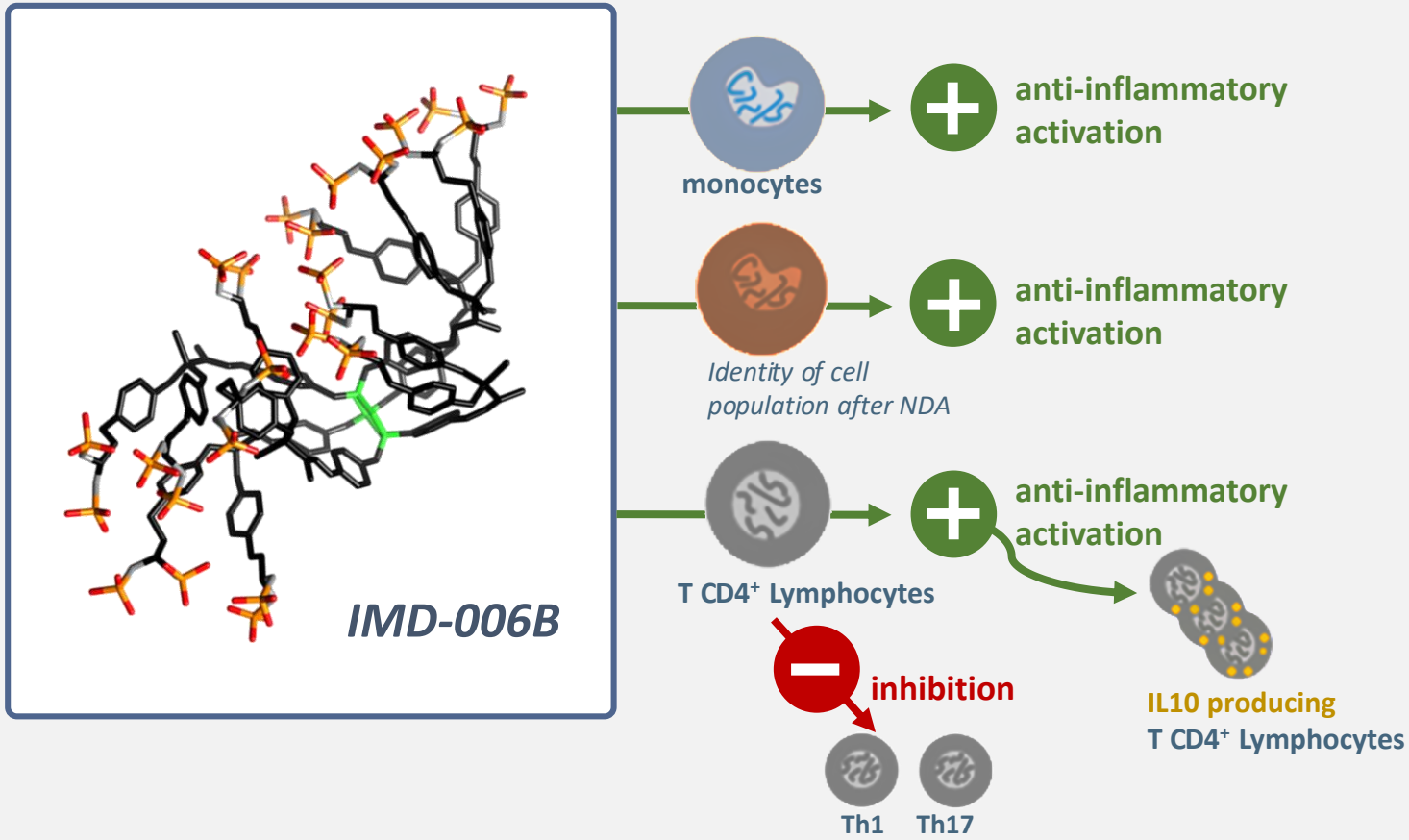
Most drugs interact with a single molecular target (receptor) with very high specificity (Kd in the 10^{-9} range). This interaction is a kind of ON-OFF effect on the target cell triggering a strong metabolic response which is the therapeutic effect.
When this receptor is located on an off-target cell, the same ON-OFF effect may trigger deleterious side effects.

IMD drug candidates do not interact with a single receptor but with a pool of receptors.
This new concept for drug design based on multi-receptor pooling is now supported by theoretical and experimental studies (see back-up slide).

Our advanced compound IMD-006B recognizes 2 soluble alarmins and 3 membrane proteins on the surface of monocytes with K_d in the 10^{-7}-10^{-8} range.

IMD-006B, lead of a new first-in-class series

15 years of academic and translational research to afford a drug candidate able to rehabilitate key immune cells

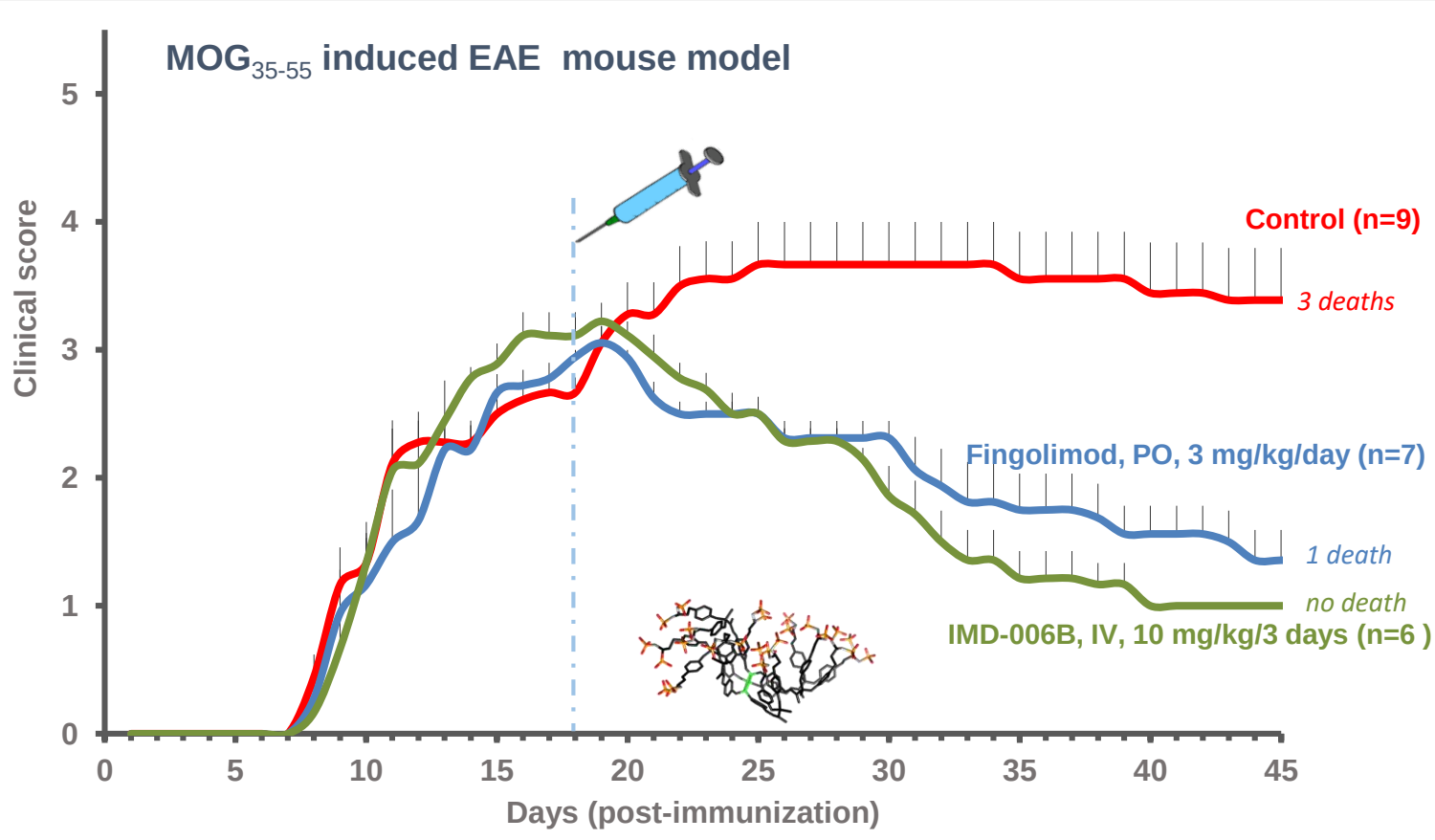


Our publications on IMD-006B:

FASEB J. **2006**, *20*, 2339-2351
Angew. Chem. Int. Ed. **2007**, *46*, 2523-2526
Chem. Eur. J. **2008**, *14*, 4836-4850
J. Leukoc. Biol. **2009**, *85*, 553-562
Tetrahedron Lett. **2009**, *50*, 2078-2082
Bioorg. Med. Chem. Lett. **2009**, *19*, 3963-3966
J. Transl. Med. **2009**, *7*, 82
Sci. Transl. Med. **2011**, *3*, 81ra35
Molecules, **2013**, *18*, 9305-9316
Arthritis Res. Ther. **2014**, *16*, R98
Nanotoxicology **2015**, *9*, 433-441
Nat. Commun. **2015**, *6*, 7722
Nanoscale **2015**, *7*, 17672-17684
Biomacromolecules **2015**, *16*, 3425-3433
Phys. Chem. Chem. Phys. **2016**, *18*, 21871-21880
Nanomedicine **2016**, *12*, 2321-2330
Biomacromolecules **2018**, *19*, 712-720

IMD-006B drug candidate for MS treatment

More efficient than gold standard Fingolimod



Biomacromolecules **2015**, *16*, 3425-3433

- IMD-006B reverses all symptoms and is more efficient than Fingolimod.
- Further studies (in vitro & in vivo) on IMD-006B (available upon NDA) confirm its complementary bioactivities. IMD-006B is
  - Immuno-regulating
  - Anti-inflammatory
  - Neuro-protecting
  - Anti-oxidant (redox regulating)
- IMD-006B is orally efficient
- POC in other inflammatory disease (Psoriasis, Rheumatoid Arthritis) available
- IMD-006B is prepared in Kg batch at reasonable cost

Safety - tolerability

IMD-006B does not present adverse effect and is well tolerated

Genotoxicity (Pasteur Lille, 2004): BN Ames' test

Salmonella typhimurium, 3 mutants, w/o metabolic activation: → no significant increase of revertants

Early toxicity in mice (Pasteur Lille, 2004): Maximal Tolerated Dose (MTD)

Single IV injection: → MTD = 100 mg/kg (next dose: 150 mg/kg)

Early toxicity in rats (Ricerca-MDBiosciences, 2011): Maximal Tolerated Dose (MTD)

Single IV inj → MTD = 100 mg/kg (next dose: 200 mg/kg)

Repeated IV inj → MTD = 60 mg/kg/day (daily, 7 days - next dose: 120 mg/kg/day)

Early safety on action potential parameters in isolated rabbit Purkinje fibers (Phyiostim, 2015)

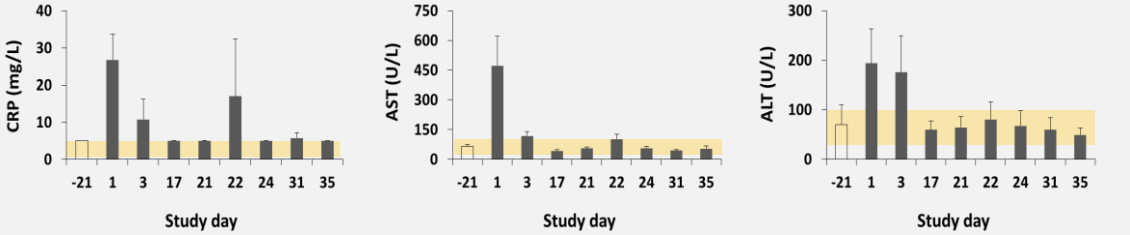
Early safety and immuno-safety in Non-Human Primates (Cynbiose, 2013):

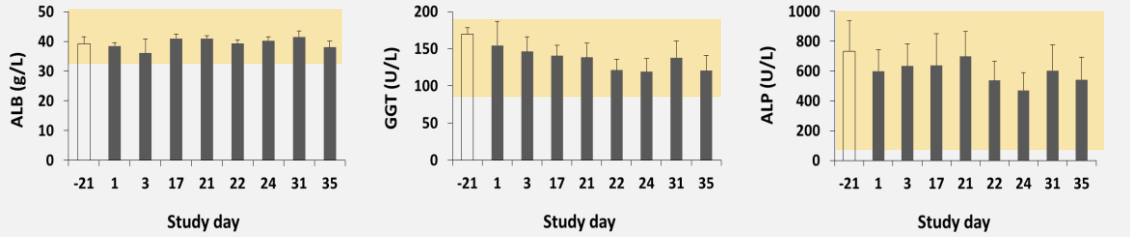
4 monkeys, 4 IV injections each, at 10 mg/kg with 1 week intervals

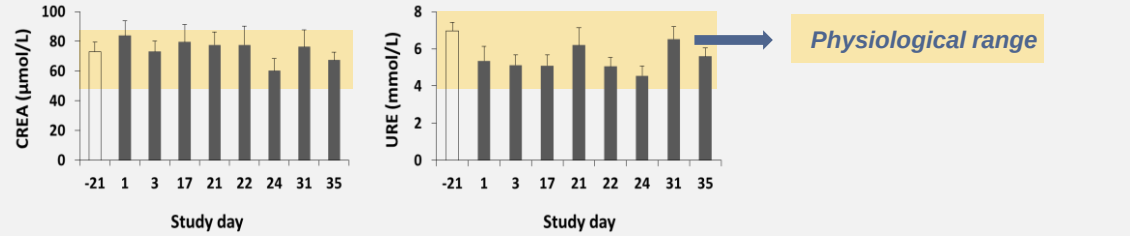
A 56 day follow-up of clinical observations and clinical pathology (10 biochemical and 16 hematological parameters, immunology, histo-pathology):

- Some subacute variations / Back to normal level within 2/3 days
- No cumulative effect during the time-course of the study
- No immune suppression & no adverse effect: mild inflammatory response, no renal and hepatic toxicities, normal anatomo-pathological observations

Early safety and immuno-safety in Non-Human Primates







Nanotoxicology **2015**, *9*, 433-441

All-in-one

In addition to its highly favorable safety profile, IMD-006B covers all the effects of its competitors.

Targeting cells vs targeting molecules:

Because it does not targets a single molecular actor of inflammation but key cellular actors of immunity and inflammation, IMD-006B shows significant advantages over its competitors.

IMD-006B vs biologic competitors:

- IMD-006B does not depletes immune cells (like anti-CD20) but rehabilitates them to produce anti-inflammatory interleukine IL10
- IMD-006 does not block IL2 (like anti-CD25) but controls its concentration
- IMD-006B doe not block negative regulators of myelinisation (like anti-LINGO1) but activates microglia towards anti-inflammatory /neuroprotective responses, a pre-requisite for neuroregeneration.

IMD-006B vs small molecule competitors:

- IMD-006B is more efficient than S1PR modulator Fingolimod
- Unlike several modulators of sphingosine-phosphate receptors (Fingolimod), IMD-006B does to lead to the sequesters lymphocytes in lymph nodes.
- IMD-006B increases serum concentration of anti-inflammatory interleukine IL10 (Th1->Th2 switch like Laniquimod)

More than just anti-inflammation. More than just neuroreparation.

Intellectual Property strategy

Products and applications are protected by 2 WO patents.
We raise barriers to entry with a clear IP renewal strategy.

products: **WO2005052031**
Until 2024/11/23 in Europe

application: **WO201013086**
Until 2028/01/08 in Europe and US
+5 years CCP in Europe after market authorization

2 PRINCEPS PATENTS

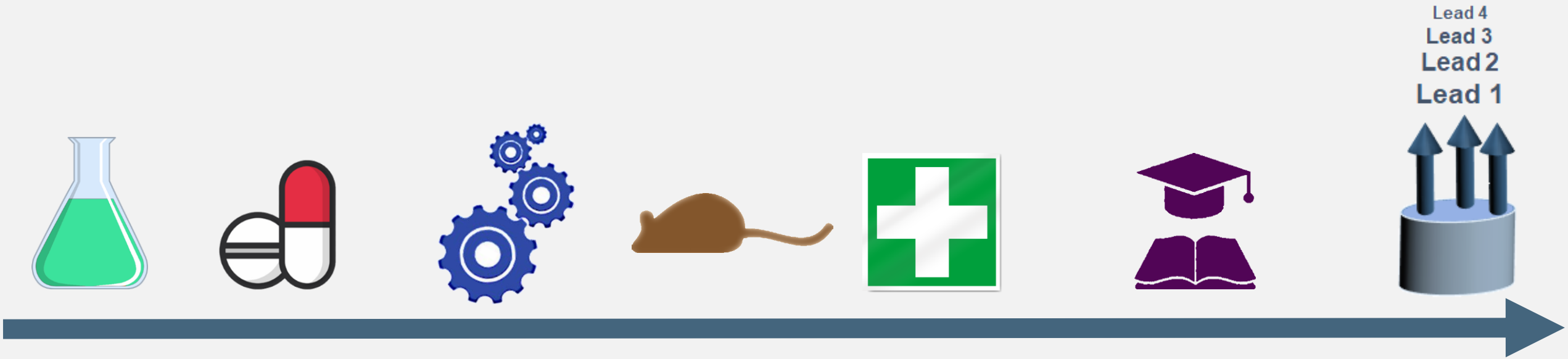
exclusive license

Ongoing R&D

- Applicative patent: NCE1 /indication 1
- Applicative patent: Galenic Formulation 1
- Applicative patent: NCE2 /indication 2
- Applicative patent: Galenic Formulation 2

Strengths and barriers to entry

The synthetic pathways associated to disruptive MOA give many advantages to IMD products.



AFFORDABLE CHEMISTRY

ORALLY BIOAVAILABLE

no formulation = upside.

DISRUPTIVE MOA

STRONG POC

FAVORABLE SAFETY PROFILE

ROBUST SCIENTIFIC BACKGROUND and IP

COMMON R&D PIPELINE

Founders and partners

C.O. Turrin & R. Poupot have been collaborating for 15 years on this project and partnered with S. Calet in 2015

July 2016: launching

Cédric-Olivier Turrin (PhD)
Cofounder
In charge of chemistry development
CNRS research director.
Ready for full time commitment

Rémy Poupot (PhD)
Cofounder
In charge of biomedical development
Full professor

Serge Calet (PhD)
Cofounder
Part-time manager
Freelance with other commitments
(50% devoted to IMD)

2018: new associate partners

Anne-M. Caminade (CNRS)
KOL in dendrimer science

TOULOUSE TECH TRANSFER

LOI + maturation contract
TTO for CNRS and Toulouse University

2019: challenging opportunities

Funding opportunities

2-step strategy based on a 1:1 mix of dilutive and non-dilutive

Step 1: achieve 1M€ funding to complete regulatory tox studies

Step 2: achieve +5M€ to reach and complete phase I

Restructuration of the company

The next step funding will imply a restructuration of IMD-Pharma (which has been anticipated).

Investment opportunities

1 M€ million euros to complete regulatory toxicity studies

2019	1 M€	**250k€ -> 1 Kg batch + stability studies** **750k€ -> Regulatory tox studies**

5 M € to achieve phase I and develop our R&D pipeline

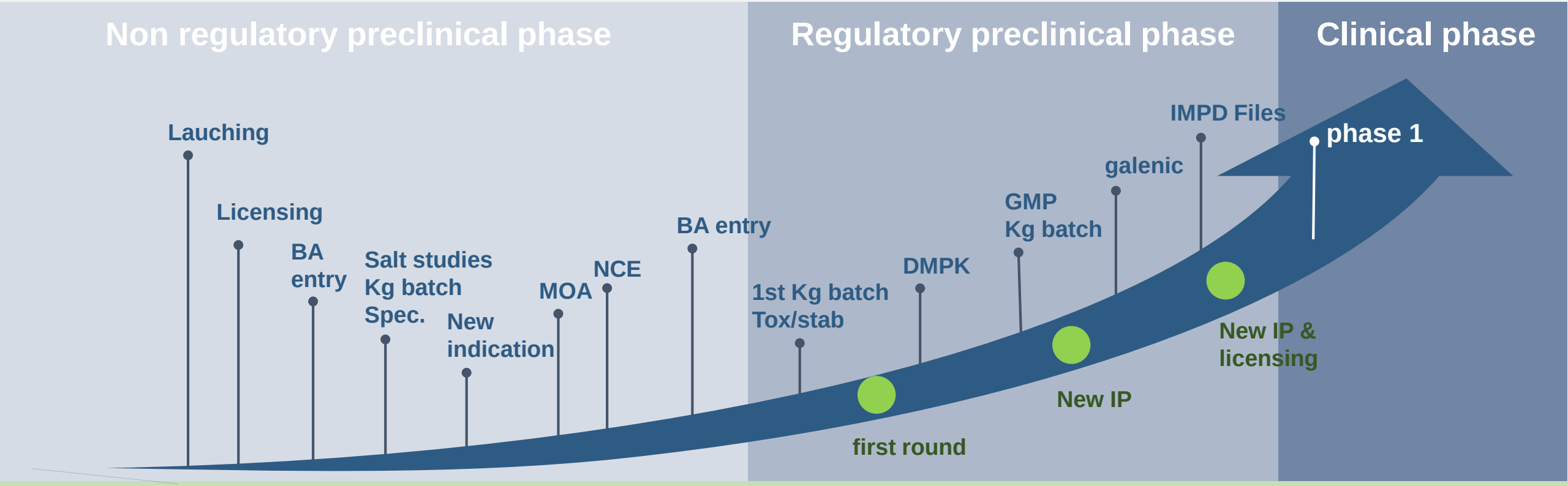
2019	1 M€	**R&D + DMPK studies**
2020	2 M€	**R&D + 1Kg C-GMP Batch + full spec + IP costs + DMPK studies**
2020	2 M€	**R&D + IMPD files + Phase 1 + galenic studies + DMPK studies**

Buy-out deal range s (rights to develop, licenses, partnerships)

Buy-out deals for similar projects during phase I or phase II: from 200 M€ to 600 M€

Moving forward

Focusing on clinical test and ensuring barriers to entry with disruptive R&D



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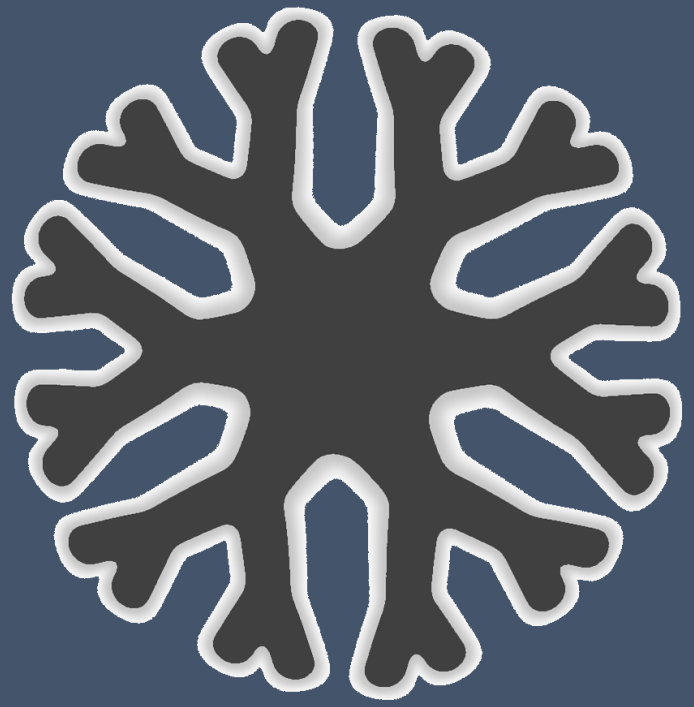


More information

Point of views

"Despite recent improvements in pharmacotherapy for relapsing remitting multiple sclerosis, treatment options in progressive multiple sclerosis are extremely limited in the absence of relapses. There is great need for safe, effective, and conveniently administered therapies for progressive MS."

Robert J. Fox, Cleveland Clinic, **Managing Director of the NARCOMS MS Patient Registry**

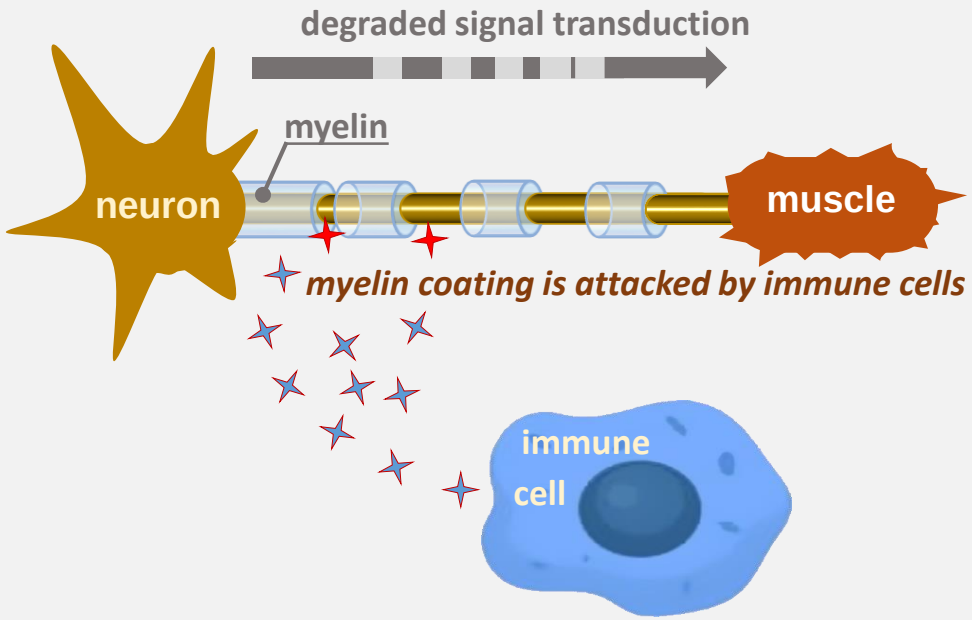
GlobalData.

"Despite the increasingly competitive nature of the MS market, lucrative opportunities remain for products that target unmet needs. […] Targeting progressive MS will be an ongoing opportunity, as competition for market share in this segment will be considerably less fierce than in relapsing remitting MS."

G. Li (Global Data) dec 2017

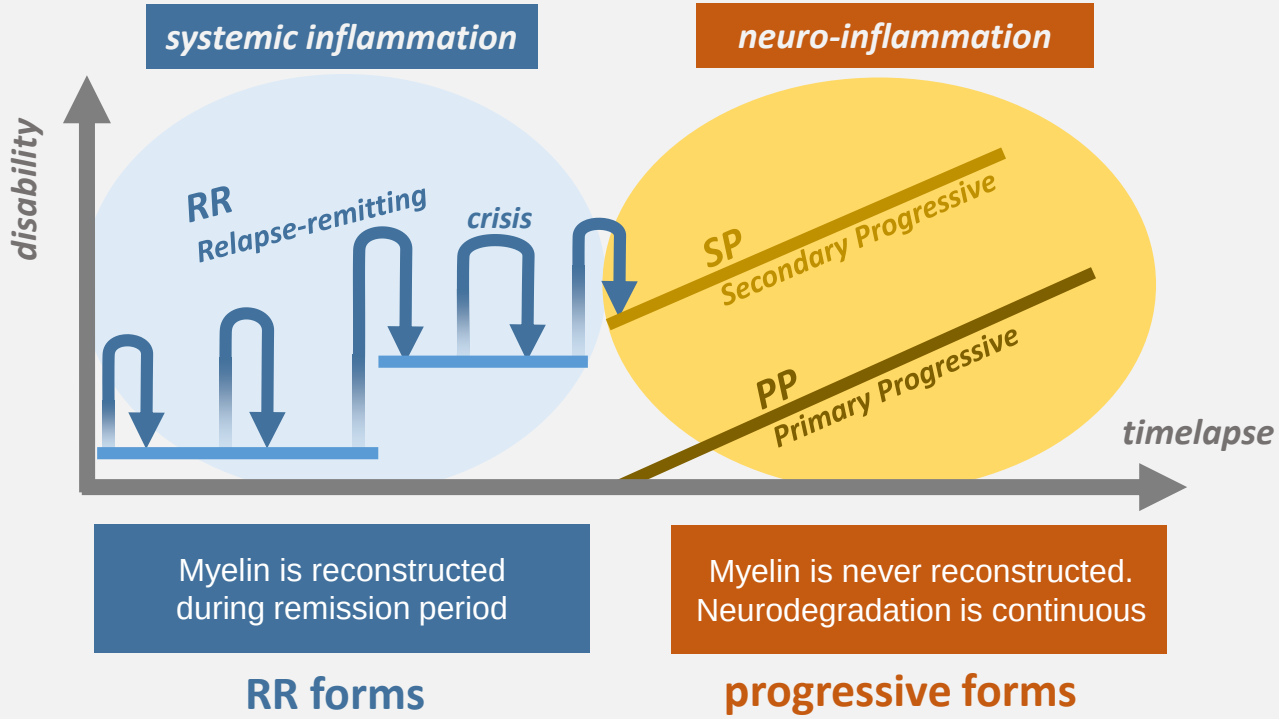
Multiple Sclerosis

Strongly disabling condition related to immune-mediated myelin degradation



- MS is due to an abnormal response of the body's immune system against the central nervous system.
- The immune system causes inflammation that damages the myelin, which is the insulating cover of nerve cells in the brain and spinal cord.
- This damage disrupts the ability of parts of the nervous system to communicate, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems.
- The cause of MS is still unknown. It is considered an autoimmune disease.

2.5 M patients with different pathophysiologies



- Most people with MS have a relapsing-remitting disease (RRMS). They suffer periods of new symptoms or relapses during days or weeks followed by periods of disease remission that can last months or even years. During these quiet period the myelin stealth is reconstructed.
- RRMS is generally followed by a continuous progression of symptoms, with or without periods of remission, known as secondary-progressive MS (SPMS). The disease progression varies a lot among people with SPMS.
- Some people with MS experience a gradual onset and continuous progression of symptoms (no relapse). This form is known as primary-progressive MS (PPMS).

New concept for the rehabilitation of immune cells

… in the footsteps of pioneering discoveries on multivalency.

We have demonstrated in a preliminary study that our most advanced compound, **IMD-006B** interacts with human monocytes with a pool of receptors through smooth interaction.[1] This discovery is a pivotal argument to rationalize the absence of deleterious side-effect and the immuno-modulatory effects of our compounds towards key immune cells.
This finding is highly related to multivalency effects that were described by Whitesides et al. in a seminal review article,[2] and more recently by Varner et al.[3]

In 2002, the group of L. Kiessling reported that "*Multivalent ligands can function as inhibitors or effectors of biological processes. […] Effector functions […] are influenced not only by apparent affinities but also as alternate factors, including the ability of a ligand to cluster receptors […] Multivalent ligands can be potent effectors that promote a specific biological response via signal transduction. One unique determinant of effector function is the ability to dimerize or oligomerize receptors* ». In this article, dendrimers are clearly identified as potent multivalent effectors.[4]

Multivalent effectors can overhaul issues related to low affinity receptors[5] or increase the metabolic response of monovalent effectors.[6]
Multivalent effectors are also prone to agregate pools of receptors to modify the physiology of cells in vitro and in vivo.[7]

Theoretical studies on these new concepts related to multi-receptor pooling have been initiated during this decade.[8,9]

The following verbatim by Curk et al summarizes the challenging opportunities in the field:
« *A key challenge in biomedical research is the ability to specifically target cells and tissues. Targeting typically relies on identifying a suitable marker, e.g., a highly expressed receptor, and choosing a ligand that strongly and specifically binds to the marker. However, this procedure fails when a suitable marker unique to the targeted cells cannot be identified[…]. We show that properly designed multivalent targeting of multiple cognate receptor types results in a specificity toward a chosen receptor density profile, thus demonstrating a general route toward targeting cells without particularly dominant markers* ». [10]

[1] *Nanoscale* **2015**, *7*, 17672; [2] *Angew. Chem. Int. Ed*. **1998**, *37*, 2754 ; [3] *Biomacromolecules* **2015**, *16*, 43 ; [4] *J. Am. Chem. Soc.* **2002**, *124*, 14922 ; [5] *Chem. Soc. Rev.* **2009**, *38*, 3463 ; [6] *TRENDS in Biochemical Sciences* **2001**, *26*, 305 ; [7] *Nature Nanotechnology* **2013**, *8*, 831 ; [8] *Nature Chemistry* **2010**, *2*, 1077 ; [9] *Nature Chemistry* **2011**, *3*, 317 ; [10] *Proc. Natl. Acad. Sci.* **2017**, *114*, 7210.

All-in-one

In addition to its highly favorable safety profile, IMD-006B covers all the effects of its competitors.

Biologic competitors	IMD-006B effects	biological context	Our publications/patent
anti-CD20 (Ocrelizumab just approved, includ. Progressive MS)	mitigates APC (B cells) abilities	*in vivo*, EAE mouse model	M. Hayder et al. Biomacromolecules (2015)
anti-CD25	controls serum [IL-2]	*in vivo*, IL-1 ra KO mice	M. Hayder et al. Science Transl Med (2011)
anti-LINGO1 (neurorepair)	activates microglia towards anti-inflammatory/neuroprotective responses	*in vivo*, IL-1 ra KO mice	**New IP**
Activator of myelin metabolism in the CNS (neurorepair)	activates microglia towards anti-inflammatory/neuroprotective responses	*in vivo*, IL-1 ra KO mice	**New IP**

Chemical competitors	IMD-006B effects	biological context	Our publications/patent
S1P receptor modulator	as efficient as Fingolimod	*in vivo*, EAE mouse model	M. Hayder et al. Biomacromolecules (2015)
Laniquimod Th1 -> Th2 switch	increases serum [IL-10]	*in vivo*, EAE mouse model *in vivo*, IL-1 ra KO mice	M. Hayder et al. Biomacromolecules (2015)
	increases the production of IL-10	*ex vivo*, stimulated splenocytes of IMD-006B treated IL-1 ra KO mice	M. Hayder et al. Science Transl Med (2011)
	promotes proliferation of IL-10 producing T-cells	*ex vivo*, human primary immune cells *in vivo*, EAE mouse model	D. Portevin et al. J Transl Med (2009) S. Fruchon et al. J Leukoc Biol (2009) M. Hayder et al. Biomacromolecules (2015)

Funding

1+5 millions euros to complete phase I and develop our R&D pipeline

	R&D (people + costs) (1.7 M€)		PRECLINICAL & CLINICAL (CROs & CMOs) (3.1 M€)	G&A (1.2 M€)
Year 1 *2 M €*	NCE design 200 k€ 1 PhD + 1 research engineer	In vitro validation 200 k€ 1 PhD + 1 research engineer	***Step 1 1 M€*** 1Kg batch + stability 250 k€ Reg tox studies 750 k€	300 k€ *3 persons*
Year 2 *2 M €*	NCE caracteriz. 230 k€ 1 technician + 1 PhD + 1 research engineer	In vivo validation 230 k€ 1 technician + 1 PhD + 1 research engineer	DMPK studies 450 k€ 1Kg GMP + specifications 350 k€ IP 300 k€	400 k€ *4 persons*
Year 3 *2 M €*	NCE scale-up 230 k€ 1 technician + 1 PhD + 1 research engineer	In vivo validation 230 k€ 1 technician + 1 PhD + 1 research engineer	IMPD files for Phase I 100 k€ Phase I 500 k€ Galenic studies 300 k€ + DMPK (cont) 500 k€	500 k€ *5 persons*

Publications

1. Design of phosphorylated dendritic architectures to promote human monocyte activation
   M. Poupot, L. Griffe, P. Marchand, A. Maraval, O. Rolland, L. Martinet, F.E. L'Faqihi-Olive, C.-O. Turrin, A.-M. Caminade, J.-J. Fournié, J.-P. Majoral, R. Poupot
   FASEB J. **2006**, *20*, 2339-2351
2. Multiplication of Human Natural Killer cells by Nanosized Phosphonate-capped Dendrimers
   L. Griffe, M. Poupot, P. Marchand, A. Maraval, C.-O. Turrin, O. Rolland, P. Métivier, G. Bacquet, J.-J. Fournié, A.-M. Caminade, R. Poupot, J.-P. Majoral
   Angew. Chem. Int. Ed. **2007**, *46*, 2523-2526 (couverture intérieure)
3. Tailored Control and Optimisation of the Number of Phosphonic Acid Termini on Phosphorus-Containing Dendrimers for the Ex-Vivo Activation of Human Monocytes
   O. Rolland, L. Griffe, M. Poupot, A. Maraval, A. Ouali, Y. Coppel, J.-J. Fournié, G. Bacquet, C.-O. Turrin, A.-M. Caminade, J.-P. Majoral, R. Poupot
   Chem. Eur. J. **2008**, *14*, 4836-4850
4. Anti-inflammatory and immuno-suppressive activation of human monocytes by a bio-active dendrimer
   S. Fruchon, M. Poupot, L. Martinet, C.O. Turrin, J.P. Majoral, J.J. Fournié, A.M. Caminade, R. Poupot
   J. Leukoc. Biol. **2009**, *85*, 553-562
5. Efficient synthesis of phosphorus-containing dendrimers capped with isosteric functions of amino-bisméthylène phosphonic acids
   O. Rolland, C.-O. Turrin, G. Bacquet, R. Poupot, M. Poupot, A.-M. Caminade, J.-P. Majoral
   Tetrahedron Lett. **2009**, *50*, 2078-2082.
6. Dendrimers ended by non-symmetrical azadiphosphonate groups: Synthesis and immunological properties
   P. Marchand, L. Griffe, M. Poupot, C.-O. Turrin, G. Bacquet, J.-J. Fournié, J.-P. Majoral, R. Poupot, A.-M. Caminade
   Bioorg. Med. Chem. Lett. **2009**, *19*, 3963-3966
7. Regulatory activity of azabisphosphonate-capped dendrimers on human CD4+ T cell proliferation for ex-vivo expansion of NK cells from PBMCs and immunotherapy
   D. Portevin, M. Poupot, O. Rolland, C.-O. Turrin, J.-J. Fournié, J.-P. Majoral, A.-M. Caminade, R. Poupot
   J. Transl. Med. **2009**, *7*, 82.
8. A phosphorus-based dendrimer targets inflammation and osteoclastogenesis in experimental arthritis
   M. Hayder, M. Poupot, M. Baron, D. Nigon, C.-O. Turrin, A.-M. Caminade, J.-P. Majoral, R.A. Eisenberg, J.-J. Fournié, A. Cantagrel, R. Poupot, J.-L. Davignon
   Sci. Transl. Med. **2011**, *3*, 81ra35 (couverture)

Publications

9. An azabisphosphonate-capped Poly(PhosphorHydrazone) dendrimer for the treatment of Endotoxin-Induced Uveitis
S. Fruchon, A.M. Caminade, C. Abadie, J.L. Davignon, J.M. Combette, C.O. Turrin, R. Poupot
Molecules, **2013**, *18*, 9305-9316

10. Modulation of pro-inflammatory activation of monocytes and dendritic cells by aza-bis phosphonate dendrimer as an experimental therapeutic agent
Y. Degboé, S. Fruchon, M. Baron, D. Nigon, C.O. Turrin, A.M. Caminade, R. Poupot, A. Cantagrel, J.L. Davignon
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