Modulators of IDO Signaling Activity

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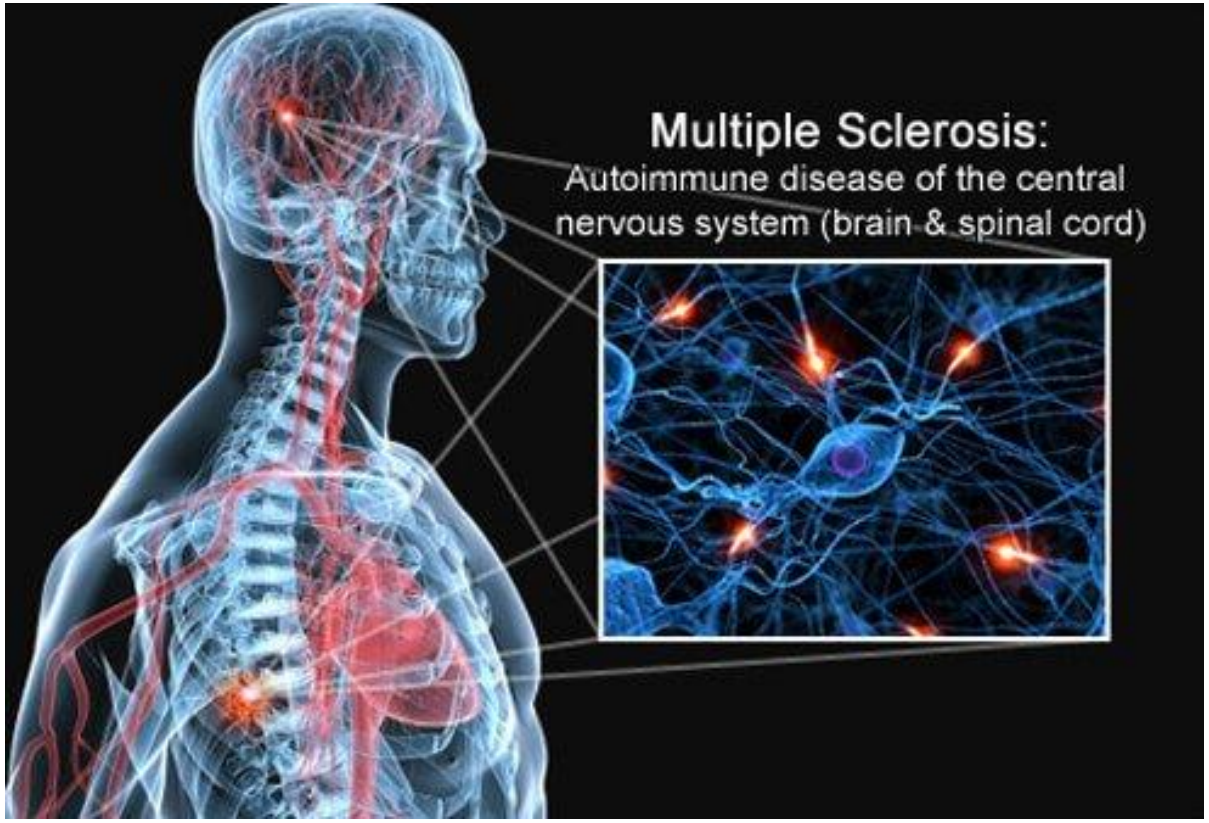
The Problem: Multiple Sclerosis

https://www.medicinenet.com/multiple_sclerosis_ms/article.htm



- **Multiple Sclerosis** (MS) represents a **worldwide economic burden** and **urgent unmet clinical need** lacking effective curative therapeutics.

- Current clinical management of MS distinguishes between relapse-remitting MS (**RRMS**) and primary progressive MS (**PPMS**) and involves **expensive** and **ineffective** treatments with **mild to extremely severe side-effects** with an **inverse correlation between efficacy and safety.**

- **Multiple agents** are in **(pre)-clinical development** as novel therapies for MS, including monoclonal antibodies, (tyrosine) kinase inhibitors, remyelinating agents, oxidative-stress modulators, cholesterol-lowering agents and anti-histamines.

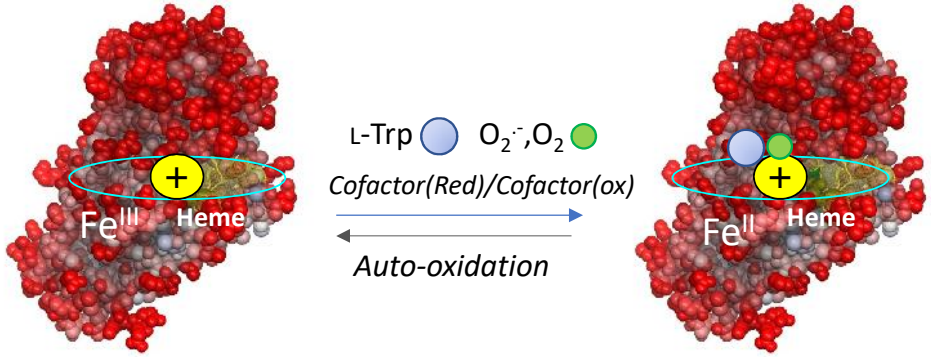
Current Therapies in (Pre)-Clinical Development

STRENGTHS	WEAKNESSES	CLINICAL DEVELOPMENT PIPELINE
• All agents bar one in Phases II-III are **orally** administered **small molecules** (**cheap** manufacturing and formulation). • Phase II agents include **over-the-counter** anti-histamines. • **Remyelination agents** which could **reverse** debilitating neuronal damage (particularly in **PPMS**) present in **Phase II** and **pre-clinical stages** • Phase II agents include a novel **immune tolerance-inducing** potential therapy. • Pre-clinical threat exhibits **dual functionality** since it promotes **both** remyelination **and** immune suppression.	• Phase III and Phase II biologics require more **expensive manufacturing** and **formulation**. • Phase III **S1P modulators** associated with **severe side-effects**. • Phase II biologics associated with **poor blood-brain barrier permeability** (BIIB003) and are administered intravenously and intradermally**.** • **Phase III-II biologics** associated with high frequency of adverse **injection site reactions** and risk of **adherence issues**. • Dual remyelinating and immunosuppressant agent yet to demonstrate **clinical efficacy**.	• **Extensive repurposing** of various agents from distinct classes and therapeutic indications: anti-leukaemic (CLL) monoclonal antibodies, statins, anti-neoplastics, antioxidants and vitamin H. • **S1PR** modulators feature **prominently** in Phase III pipeline • **Novel targets** include bruton's tyrosine kinase (**BTK**) which controls B-cell-mediated inflammation and migration. • **Neuroprotective** and **remyelinating** agents present in clinical development in addition to immune modulators. • **Phases I-III**: 122 studies currently planned or recruiting. • **Phase I-III:** 53 active, non-recruiting, ongoing trials.

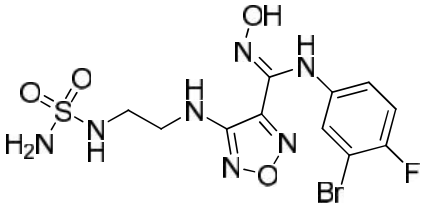
Our Solution: IDO1 is a Druggable Target

- IDO1 catalyzes **degradation of >95% of tryptophan** from diet to produce **bioactive kynurenine metabolites**.
- IDO1 expression is **highest in cancer cells**.
- **Small molecule inhibitors** of **IDO1 catalytic activity** are in clinical development as single **anticancer therapy** or in combination therapies with immuno-checkpoint inhibitors.

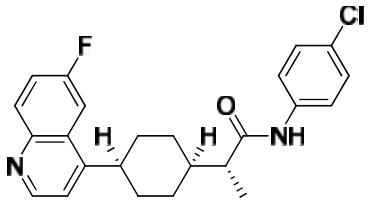
A. Catalytic Activity



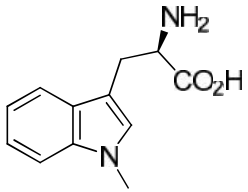
(Heme Oxidized) *(Heme Reduced)*



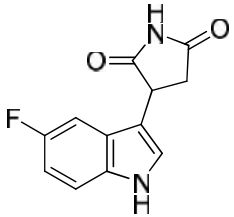
Epacadostat (INCB024360)
Incyte
PHASE III



F001287, BMS986205
Bristol-Myers Squibb
PHASE I/IIa



Indoximod
1-Methyl-D-Tryptophan
NewLink Genetics
PHASE II



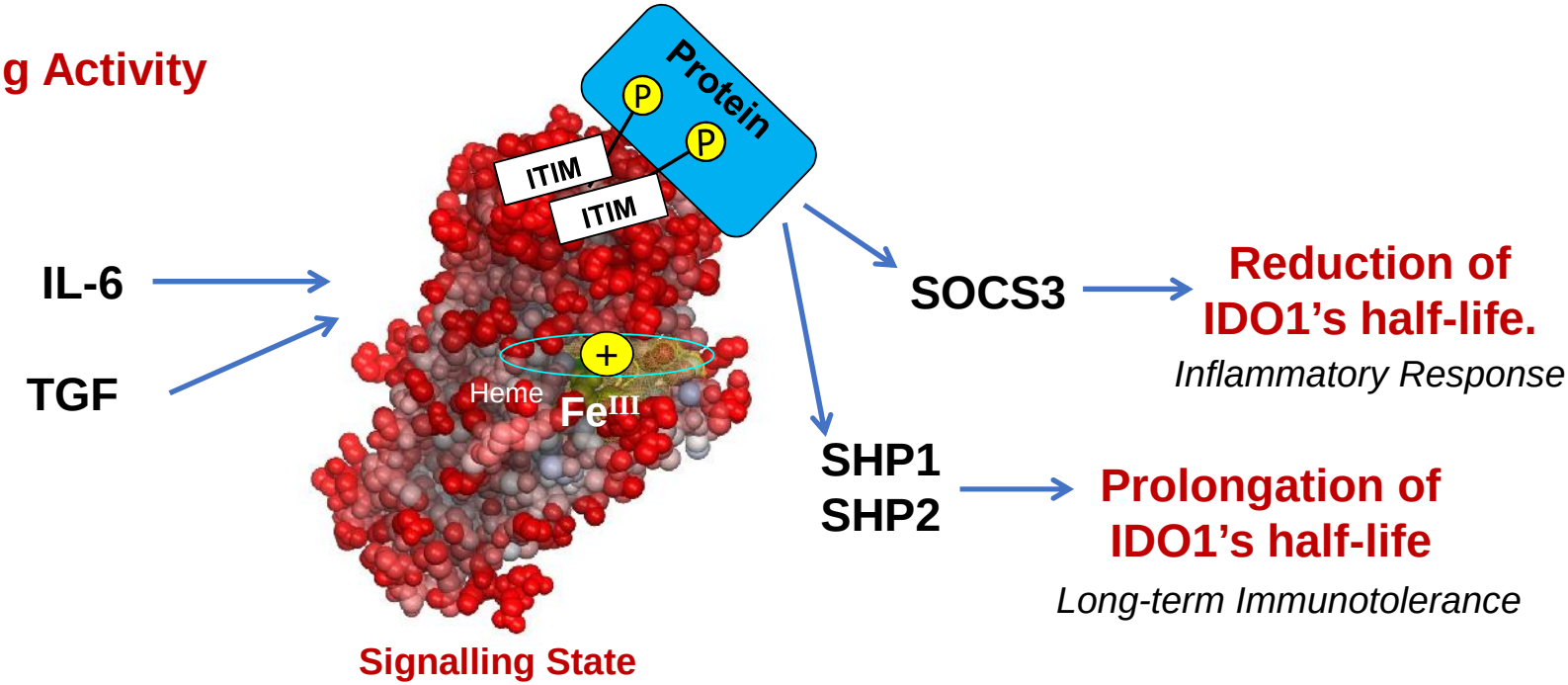
PF-06840003
Pfizer
PHASE I

Sono, M., et al. *Chem Rev* 1996
Munn D.H. et al. *Science* 1998.
Uyttenhove C. et al. *Nat. Med.* 2003.
Fallarino F. *et al. Nat Immunol*. 2003.

Our Solution: IDO1 is a Signalling Protein

- IDO1 is a **moonlighting** protein and shows **signalling activity**.

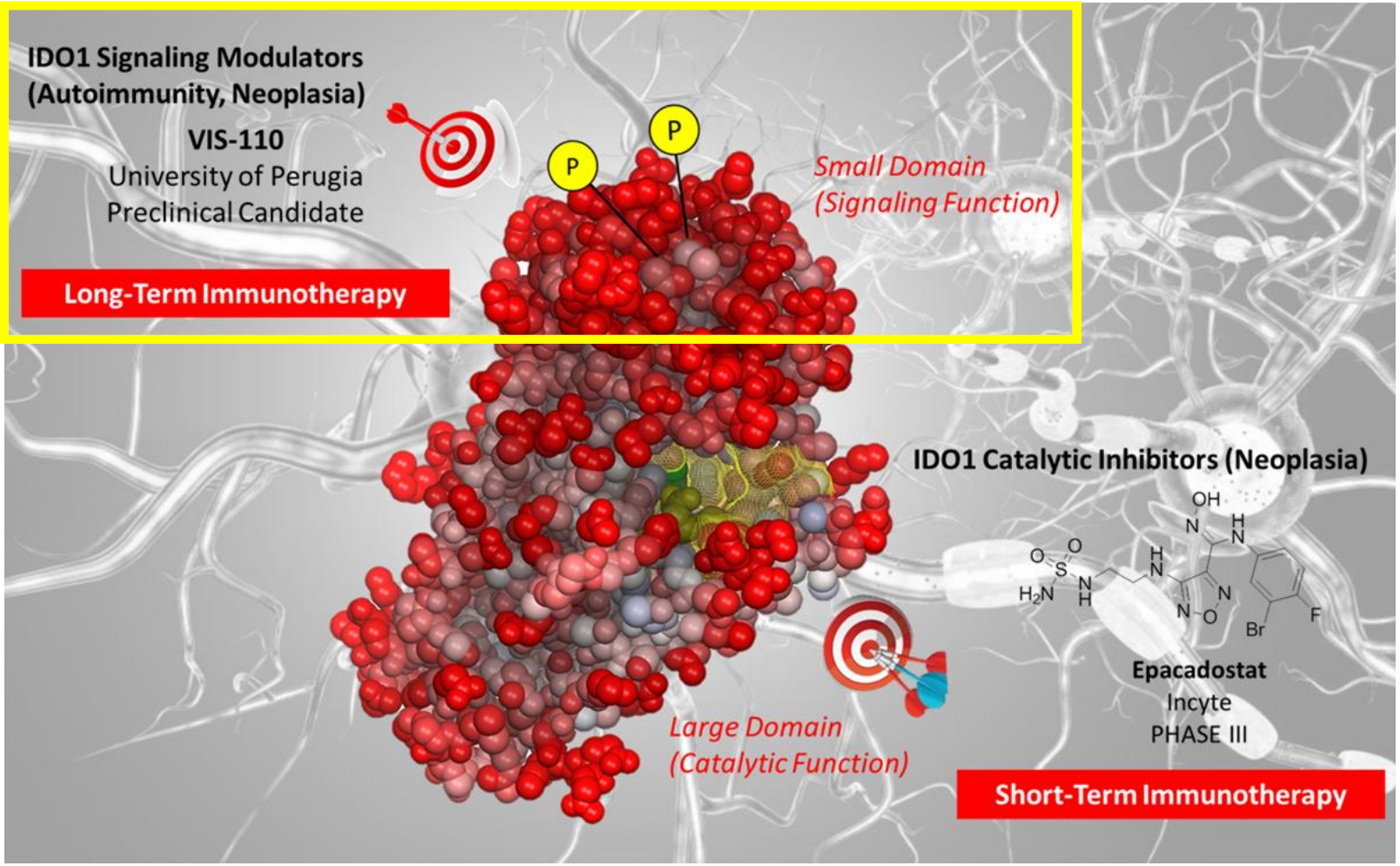
B. Signalling Activity



- IDO1 expression is **highest in dendritic cells** (DC).
- **RRMS is** shown to be **characterised by high serum levels of IDO1**.
- **High IDO1 levels correlate with clinical onset of relapse**.

Pallotta M. T. et al. *Nat. Immunol*. 2011
Mancuso R, et al. *PLoS One*. 2015
Cha L, et al. *Clin Transl Immunology*. 2018

Our Solution: Novel Mechanism of Action



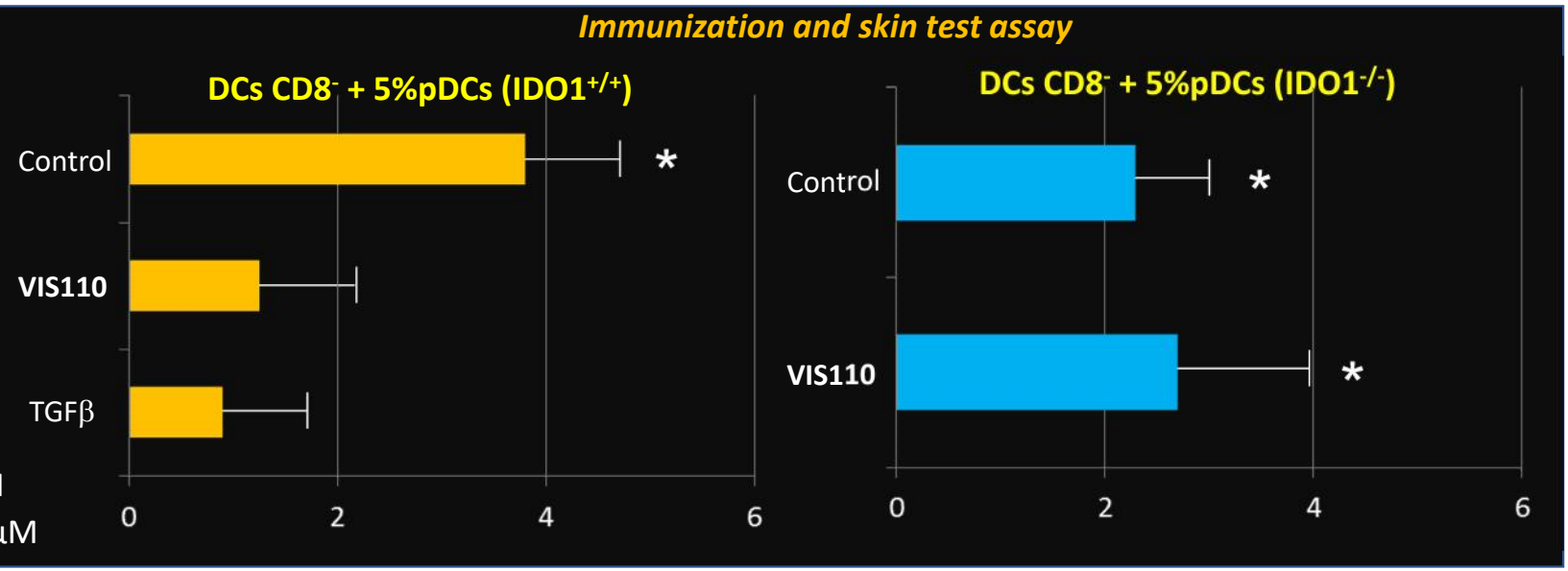
www.knowledge-share.eu/en/patent/modulators-of-ido1-signaling-activity-and-methods-of-use-thereof/

The invention relates to the discovery of **small molecules** (e.g. **VIS-110**) that bind to IDO1 enzyme and modulate its **signalling activity**, reprogramming immune responses towards **long-term immune-tolerogenic effects**.

Our Solution: Targeting IDO1 Signalling

Properties

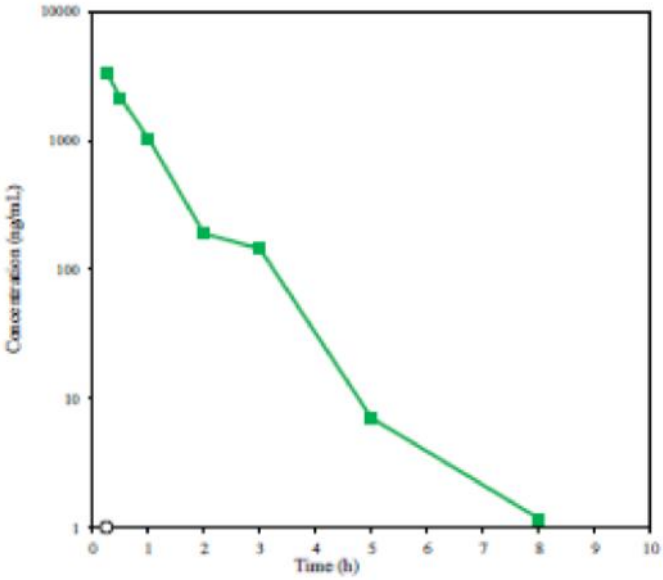
Kd = 21.5±3.1 µM
IC_{50} > 100 µM
MW = 191
pKa1 = 2.77
pKa2 = 8.15
logS (potenziometric) = -2.43
logP (Potenziometric) = 1.21
CYP-P450 Inh. <30% @ 10µM
ASBT, NTCP Inh. < 20% @ 10µM



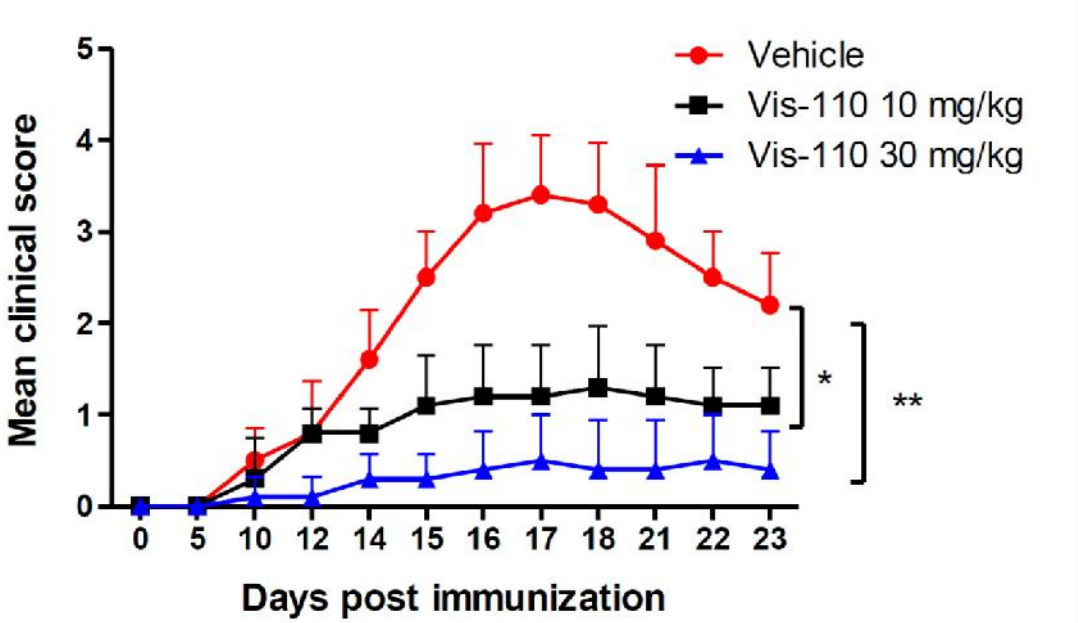
- VIS-110 has **good water solubility** (LogS = -2.43)
- VIS-110 binds to IDO1 **stabilizing a signaling active state** of the enzyme (Kd = 21.5±3.1 µM)
- VIS-110 is **NOT an inhibitor** of IDO1 catalytic activity (IC_{50} > 100 µM)
- VIS-110 induces a **IDO1 dependent tolerogenic phenotype** in immunization and skin test assay.

Our Solution: Targeting IDO1 Signalling

Plasma concentrations (ng/mL) of VIS110 (@ 30mg/kg) in oral gavage dosed C57BL/6 mice



Clinical course of experimental autoimmune encephalomyelitis (EAE) murine model



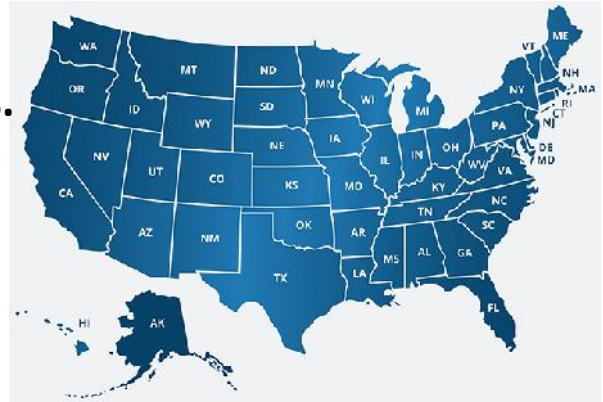
- VIS-110 is **orally bioavailable** ($t_{1/2}$ = 0.74 hour; T_{max} = 0.25 hour; C_{max} = 3394 ng/mL)
- VIS-110 **reduces the disease clinical course** of experimental Multiple Sclerosis in a dose-dependent manner.

Commercial Potential

- Prevalence (EU): 108 in 100,000[1].
- EU Population: 512.6 million[2].
- Total Addressable Market (TAM): 108/100,000 x 512.6M = **553,608 patients**.
- 85% of patients have RRMS -> TAM: **470,566 patients**[3].
- 10-15% of patients have PPMS -> TAM: **83,042 patients**[3].

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856596/
2. https://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00001&plugin=1
3. https://www.nature.com/articles/s41572-018-0041-4

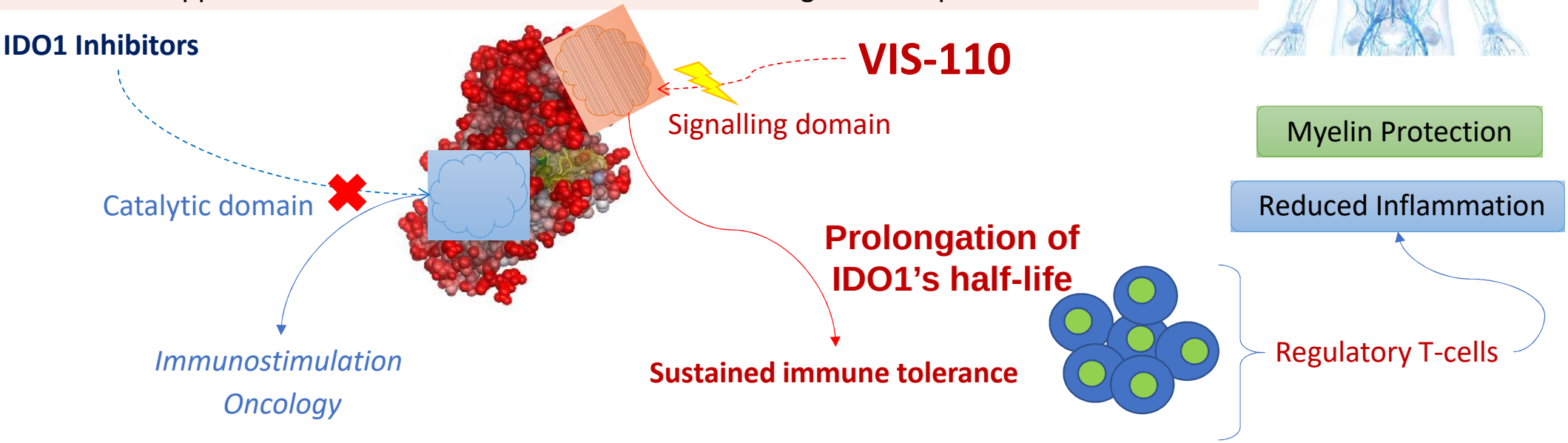
- Prevalence (USA): 110-140 in 100,000[1].
- USA Population: 325.7 million[2].
- Total Addressable Market (TAM): 140/100,000 x 325.7M = **455,980 patients**.
- 85% of patients have RRMS -> TAM: **387,583 patients**[3].
- 10-15% of patients have PPMS -> TAM: **68,397 patients**[3].



1. https://www.healthline.com/health/multiple-sclerosis/facts-statistics-infographic#3
2. https://www.census.gov/popclock/ (2017)
3. https://www.nature.com/articles/s41572-018-0041-4

Unique Selling Points (USPs)

Factors Differentiating VIS-110 from Competition.
Mechanistically distinct from current disease modifying therapies as it targets novel pathway.
Relatively **cheap manufacturing** and formulation since small molecule (c/w biologics).
Potentially **administered orally** (no injection-related side-effects).
Promotes immune-tolerance as opposed to immunosuppression (**reduced side-effects**).
Induces amelioration of disease symptoms in a murine model of MS (**Proof of Concept**).
Potential for application to **other autoimmune diseases** with high IDO1 expression.



Development Status

Feb.2014 — ERC-2013-AdG 338954-DIDO — Jan.2019

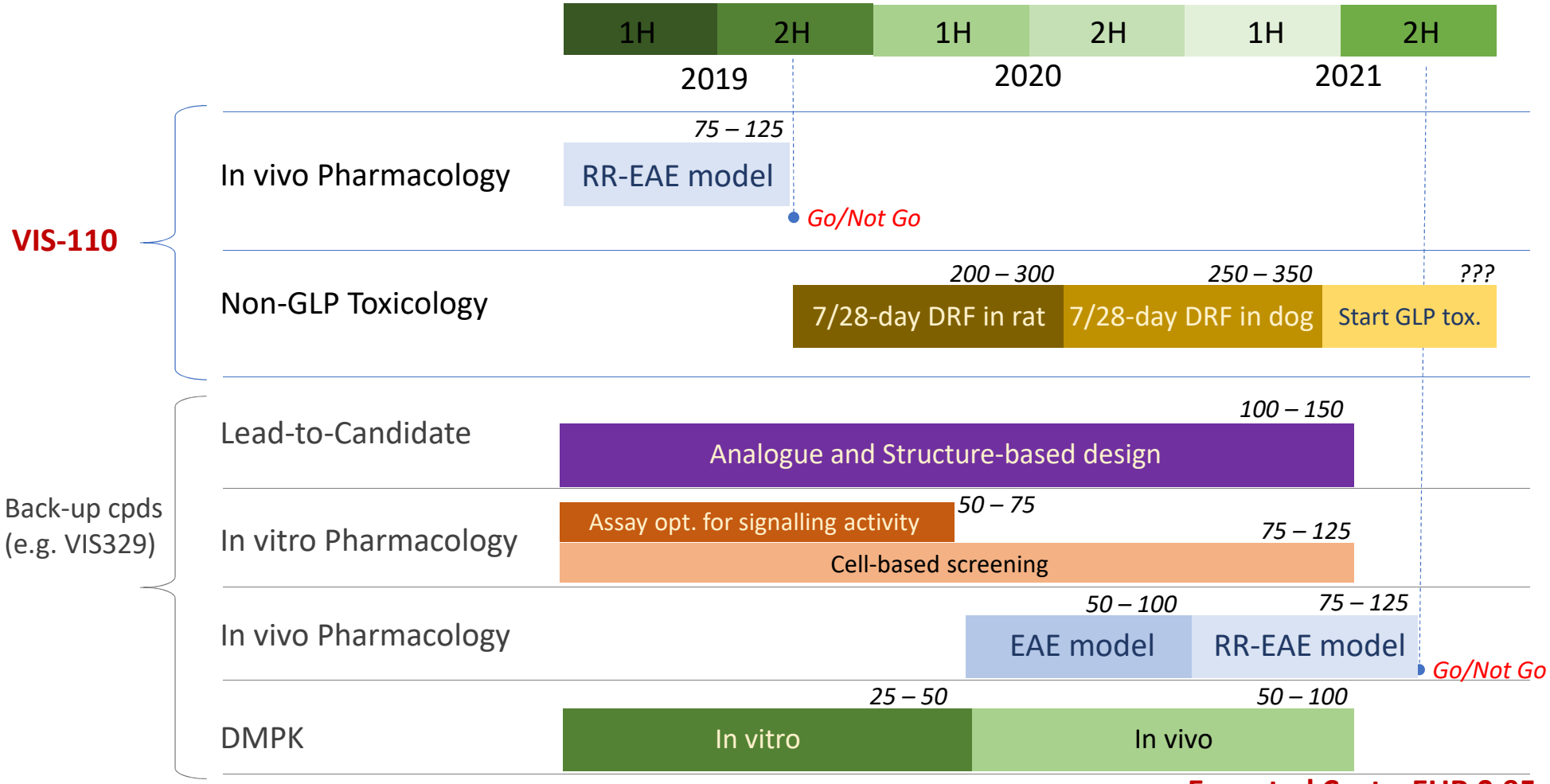
- ☑ Identification of VIS110 as first-in-class IDO1 ligand able to stimulate enzyme **signalling activity** towards **long-term immune-tolerogenic effects.**
  Patent status*: PCT application submitted.*
- ☑ Proof-of-concept of in acute model of MS (EAE model).
- ☑ DMPK studies.
- ☑ Identification of VIS110 back-up compounds (e.g. VIS329) with unique properties of IDO1 modulation.
- ☑ Unprecedent x-ray structure of IDO1 in complex with non-inhibitor compound.

Feb.2018 — Jul.2019

ERC-2017-PoC-780807-DIDO-MS

- ☐ Proof-of-concept of VIS110 in chronic model of MS (RR-EAE model).
- ☐ Non GLP-toxicology studies of VIS110.
- ☐ Development of back-up compounds (e.g. VIS329) for additional PCT patent applications.
- ☐ In vitro pharmacology.

Resources Needed and Key Activities



Expected Costs: EUR 0.95 - 1.5 millions

SWOT Analysis

STRENGTHS	WEAKNESSES
• IDO1 signalling is a **novel** target pathway for multiple sclerosis • VIS-110 promotes **immune tolerance**, not immunosuppression. • Potentially **orally** administered, thus avoiding injection side-effects • Small molecule: **cheap** manufacturing & formulation. • VIS-110 is **efficacious *in vivo*** in acute murine models of MS (EAE, prof-of-concept) and orally bioavailable ($t_{1/2}$ = 74 min). • Potential for use in **other autoimmune diseases** in which IDO1 function is disturbed (e.g. rheumatoid arthritis) could expand target market.	• **Off-target effects** on monoamine oxidases (risk of hypertensive crisis with tyramine-rich diet if MAOs inhibited). • **No** comprehensive *in vivo* toxicology assessment available yet. • **No** demonstration of efficacy in chronic murine models of MS (RR-EAE) available yet. • **No** demonstration of **superiority** in comparison to (or **synergy with**) **standard-of-care** (e.g. IFN-β1, glatiramer acetate, teriflunomide) *in vivo* available yet. • **Limited** applicability to primary progressive multiple sclerosis (PPMS) since PPMS is not characterised by inflammation but neurodegeneration.
OPPORTUNITIES	**THREATS**
• **Favourable** market (**EU & USA:** Markets with highest incidence/prevalence. • Lack of clinically available immune tolerance-inducing agents in current MS DMT market fosters **creation of own market niche**. • Incorporation as **1st line DMT** for RRMS and possible amplification of PPMS-focused therapeutic repertoire (for PPMS with active inflammation only) • Induction of immune tolerance may reduce need for harmful 2nd line DMTs and **therefore reduce healthcare costs** and associated socioeconomic burden.	• New breakthrough agents (e.g. ocrelizumab, ozanimod) expected to occupy **substantial** share of global market by 2022 (USD $4 billion). • Prospect of **successful** clinical trials and approval of novel small molecules and biologics (e.g. opicinumab, ATX-MS-167). • Market growth may **fuel** development of more novel immunomodulatory or immune tolerance-inducing agents. • Possible translational **failure** of VIS-110 from *in vivo* models to Phase 1 clinical trials in multiple sclerosis patients. • **Poor** tolerability and safety in patients.

Contacts

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