PROVID

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Pharma Capital Partners
*Confidential*

# *Provid Concept for Autoimmune Disease Therapeutics*

***Presentation Overview***

- Autoimmune diseases are genetic diseases
- Association with MHC class II genes

***Provid MS Drug Candidate***

- Blockade of disease-associated MHC HLA DRB1*15:01
- Antagonist drug design and results
- Focus on second-generation drug candidates
- Clinical concept & development strategy
- Other DRB1*15:01 targets

# *Genetic Association with Specific MHC Class II*

- Autoimmune diseases are genetically associated with specific MHC class II molecules
  - Multiple Sclerosis — HLA-DR2b (DRB1*15:01)
  - Goodpasture's disease — HLA-DR2b (DRB1*15:01)
  - Lupus nephritis, PR3-ANCA — HLA-DR2b (DRB1*15:01)

  - Rheumatoid arthritis — DR4 (DRB1*04:01); DR1 (DRB1*01:01)
  - Celiac disease — DQ2.5 (DQB1*02:01) and DQ8 (DQB1*13:01)
  - Type 1 diabetes — DQ2.5 and DQ8
  - Pemphigus vulgaris — DR4 (DRB1*0402)

***Therapeutic Target, Biomarkers, Personalized Therapy***

  - Direct therapy to patients who carry disease-associated MHC II
  - Treat with specific inhibitors of disease-associated MHC II

# *MS Drugs–Current status*

**Current drugs: No genetic association. Widely used, seriously flawed**

- **First-line drugs** modest effect in RRMS, acceptable safety
  - Interferons: Betaseron, Avonex, Rebif (flu-like side effects), Copaxone
- **Second-line "Disease modifying" drugs** (serious safety issues)
  - Tysabri (Biogen) PML infections; 192 deaths in US thru 12/1/2016)
  - Gilenya (Novartis) PML, heart; multiple other S1P drugs in development
  - Aubagio/teriflunomide (Genzyme) Incr. ALT
  - Tecfidera/dimethyl fumarate (Biogen) GI and flushing, lymphopenia, PML (5)
  - Lemtrada/alemtumzumab; campath (Genzyme); 3rd line; stroke risk
- **Recent Approvals**
  - Ocrevus/ocrelizumab (Genentech) (PPMS; RRMS B-cell immunosuppressive)
  - Mavenclad/Cladribine (EMD Serono) (B cell immunosuppression)
  - Mayzent/siponimod (Novartis) (S1P analog) heart, infections; efficacy in SPMS)
- **Total Sales in 2018 $20 Billion; Est. 1 million patients in US**
- **NONE OF THESE DRUGS BLOCK DRB1*15:01**

# *Concept: Targeting MS Disease Mechanism*

In MS, the myelin nerve insulation is attacked by the patient's own immune system by autoreactive T cells activated via myelin antigen binding to HLA-DRB1*15:01

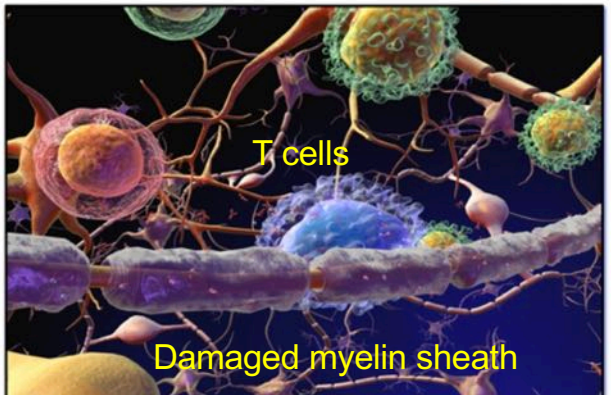
MHC – peptide antigen complex is recognized by autoreactive T cells, triggering downstream pathology

Association of MS with EBV (molecular mimicry)

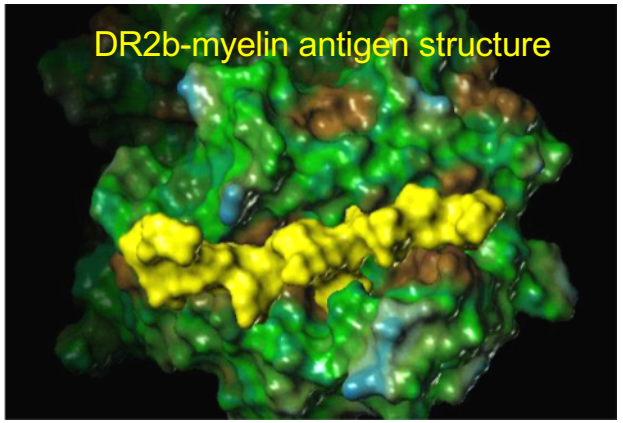
⇒ **BLOCK DRB1*15:01 = INHIBIT MS**

⇒ Selective DRB1*15:01 blockade promises high efficacy without compromising normal

*Provid has succeeded in blocking DRB1*15:01 with small molecule peptide mimetic antagonists*

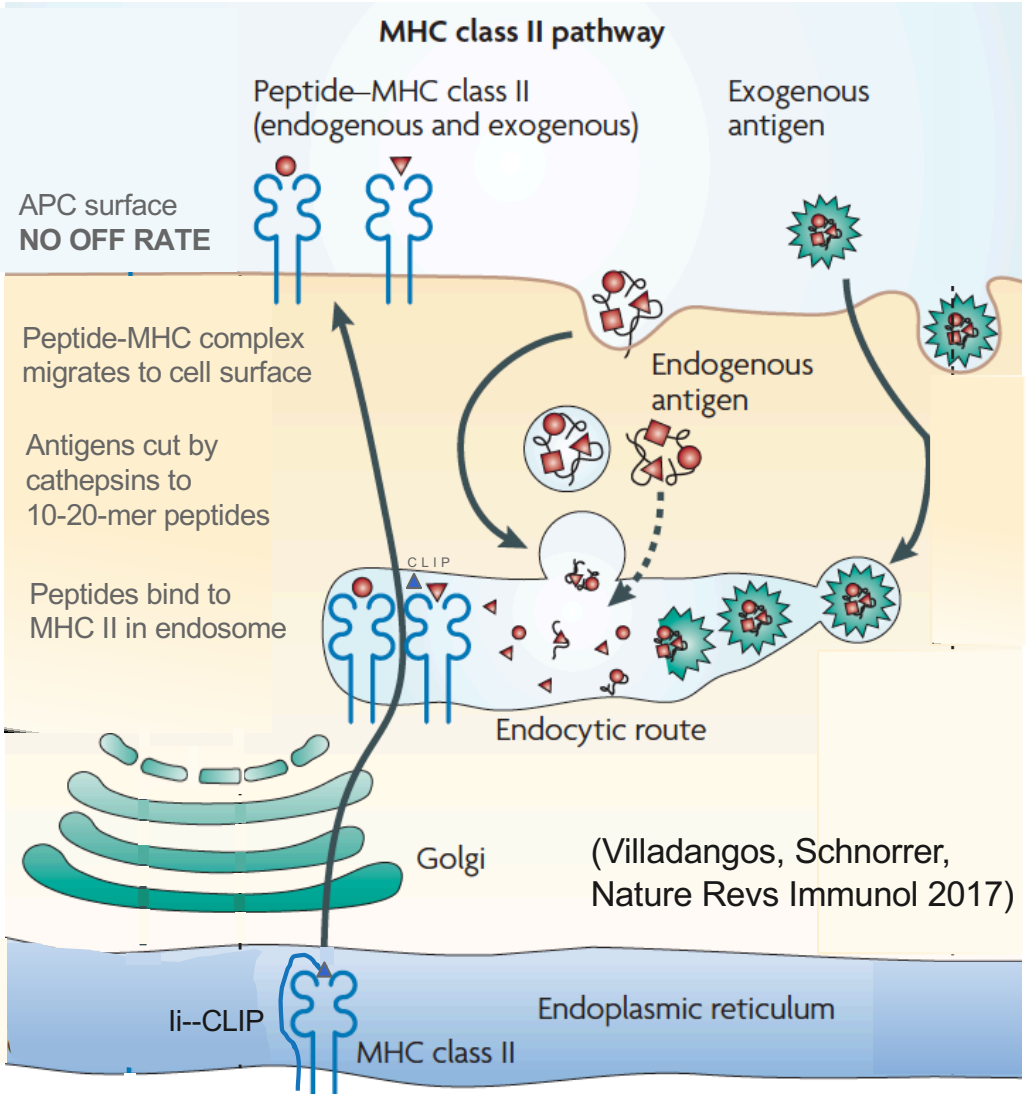


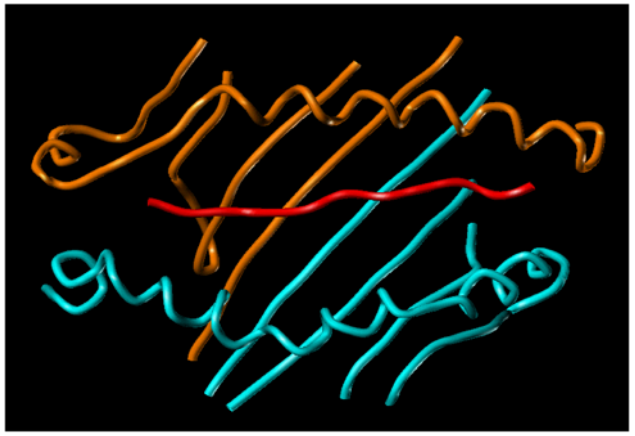

BruceBlaus [CC BY-SA 4.0 (https://creativecommons.org/licenses/by-sa/4.0), from Wikimedia Commons




Wiley et al. JEM 1998

# *Antigen Binding and Presentation*



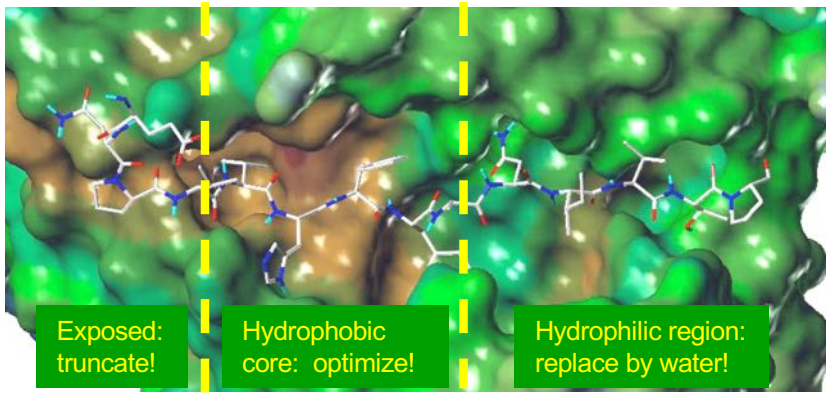
Stern, Wiley1994 Nature DRB1*0101 - HA

**Critical features for successful antagonist**

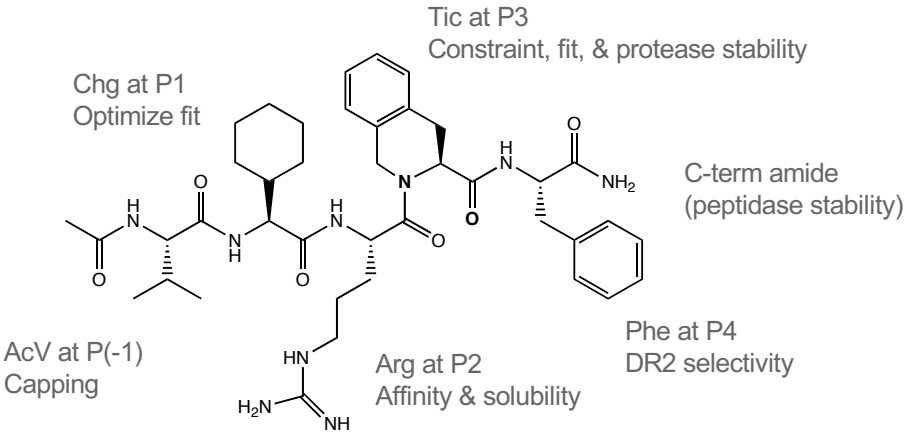
- High DRB1*1501 affinity
- Competition in APC endosome
- Stability toward cathepsins
- High selectivity vs other MHCs
- Not antigenic

# **PV-267** *Design and Optimization*

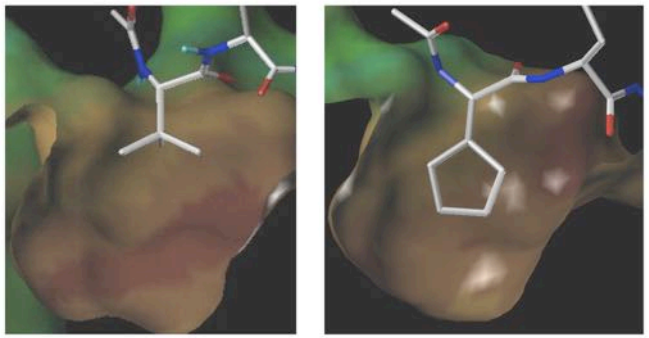
## Truncation to P1 – P4 core




H2N-Asp-Glu-Asn-Pro-Val-Val-His-Phe-Phe-Lys-Asn-Ile-Val-Thr-Pro-Arg-Thr-OH



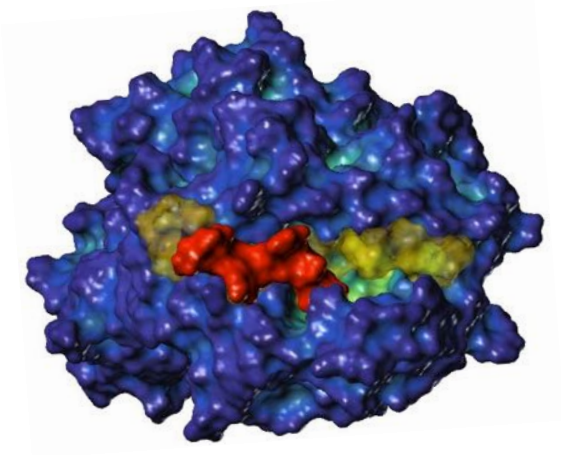

## Optimization of fit (P1)



707 nM
Valine

16 nM
Cyclopentyl-glycine

## PV-267



**IC 50 = 2 nM DRB1*15:01**

**Highly selective for DRB1*15:01**

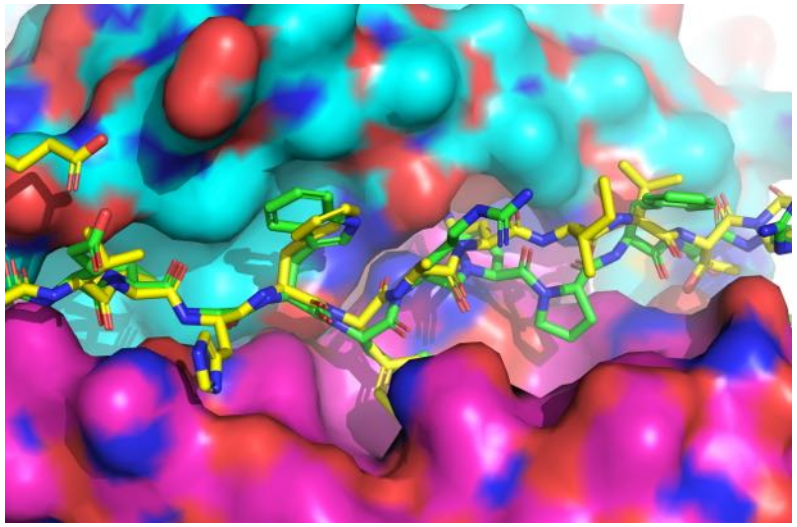
**Stable to cathepsins**

**Stable in plasma**

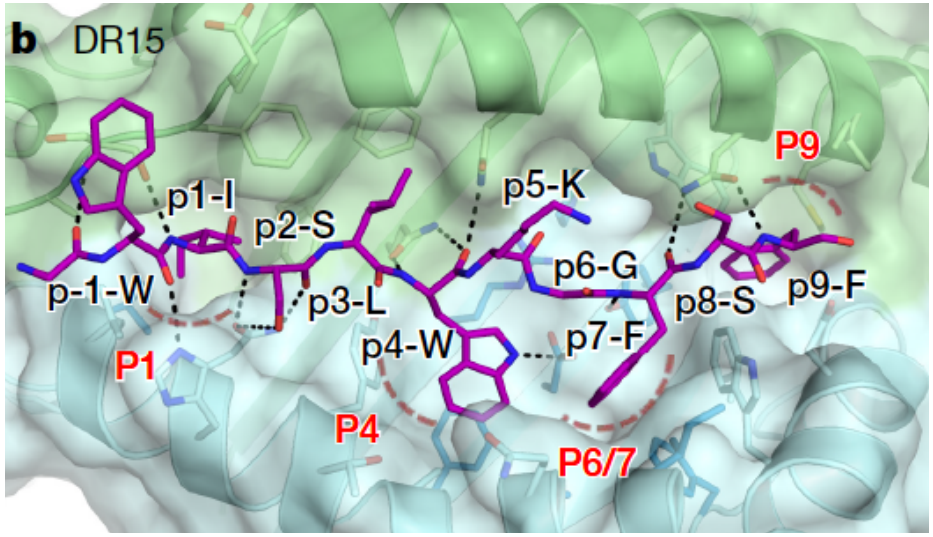
**MW 760**

# *Antigen binding: DRB1*15:01 with MOG, MBP, α3(IV)*

## *Common Binding Core*



MOG 35-55 MEVGWYRSPFSRVVHLYRNGK
MBP 85-99 ENPVVHFFKNIVTPR
P1234




$\alpha 3_{135\text{-}145}$ DWISLWKGFSF

Goodpasture's antigen: α3 chain of type IV collagen ($\alpha 3_{135–145}$)
Ooi, Kitching, et al., Nature (2017), 545, 243-247.

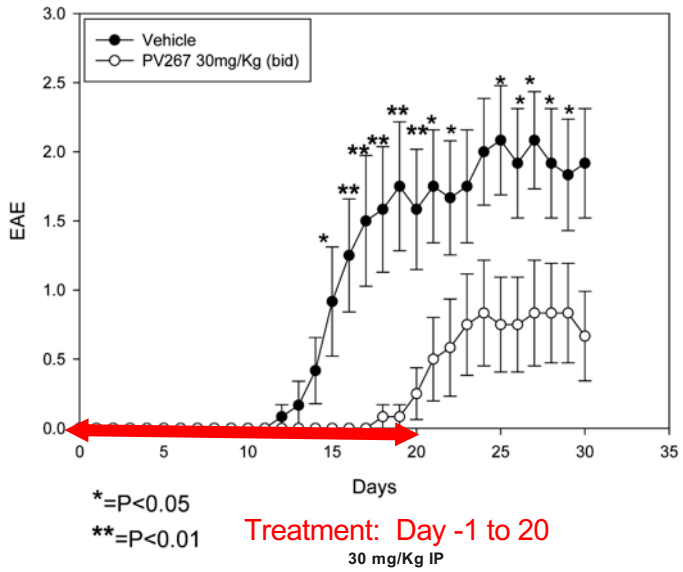
Take-home: PV inhibitors block MHC DRB1*15:01 regardless of antigen

# *High Efficacy of PV-267 in EAE and Human Cells*

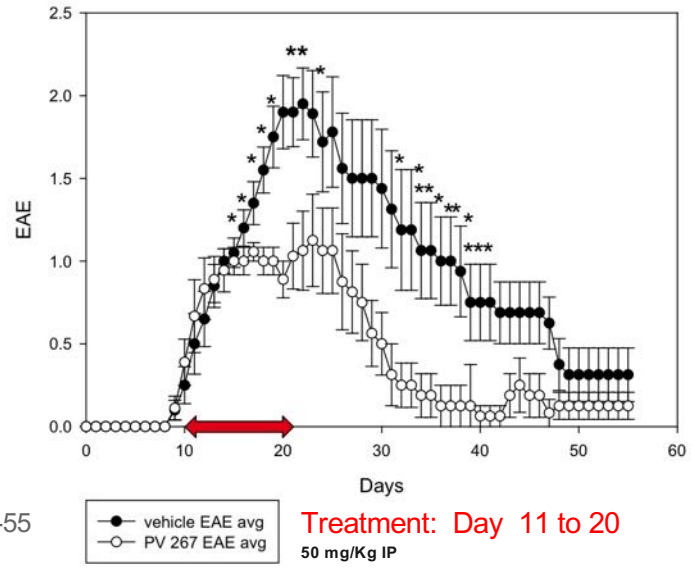
*DRB1*15:01 Transgenic Mice & Human Cells from DRB1*15:01+ MS Patients*

DR2b mice

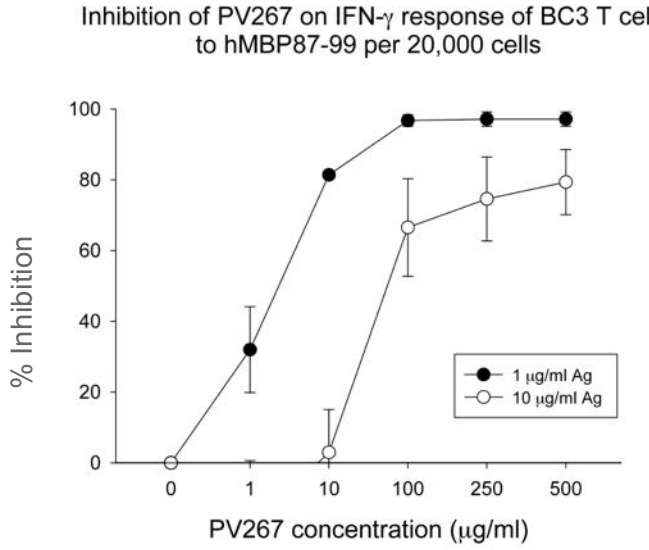
"Prevention Mode"




"Treatment Mode"




Human Cells
(Elispot)




N. Hayward, T. Forsthuber, et al.

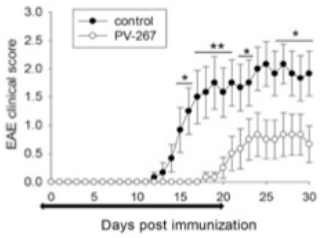
PV-267 blocks DRB1*15:01 responses but is otherwise immunologically inert

# *Results Highlighted in Journal of Immunology*

In This Issue

The Journal of Immunology

## A Small Molecule Step toward Treating MS




Multiple sclerosis (MS) is characterized by the presentation of autoantigens by MHC II molecules that trigger activation of and cytokine production by autoreactive T cells and subsequent destructive inflammatory processes. Sixty percent of MS patients express the disease-associated MHC II allele HLA-DR2b (DRB1*15:01) that presents various myelin Ags, leading to an immune response against the myelin nerve sheath and disease symptoms. Different therapeutic attempts, such as modifying downstream inflammation, specific immunotherapy, and T cell–targeted approaches, have been only modestly successful due to undesirable immune responses and safety concerns. In this study, Ji et al. (p. 5074) describe the development of PV-267, a small molecule inhibitor of peptide binding and presentation by HLA-DR2b. Using the crystal structure to visualize key interactions of HLA-DR2 with bound MBP85–99 peptide, the authors identified a five-residue sequence, PV-267, exhibiting high HLA-DR2 binding affinity and selectivity. PV-267 inhibited both Ag-induced cytokine production and proliferation of HLA-DR2b–restricted T cells from an MS patient. This inhibitory effect did not affect anti-CD3–stimulated T cells, showing that inhibition was specific for MHC:peptide-mediated signaling. PV-267 specifically inhibited responses from HLA-DR2b–restricted T cells but not from nonspecific T cells or PBMCs from healthy donors expressing other MHC molecules. The authors evaluated the efficacy of PV-267 on experimental autoimmune encephalomyelitis (EAE) prevention and treatment using HLA-DR2b transgenic mice inoculated with MOG35–55 peptide. Treatment with PV-267 prior to induction of EAE significantly delayed disease onset and severity, whereas treatment with PV-267 after EAE onset ameliorated disease and led to a faster recovery. These results support the use of a small molecule inhibitor of HLA-DR2b as a promising therapeutic strategy for the treatment of MS with minimal risk of off-target effects.

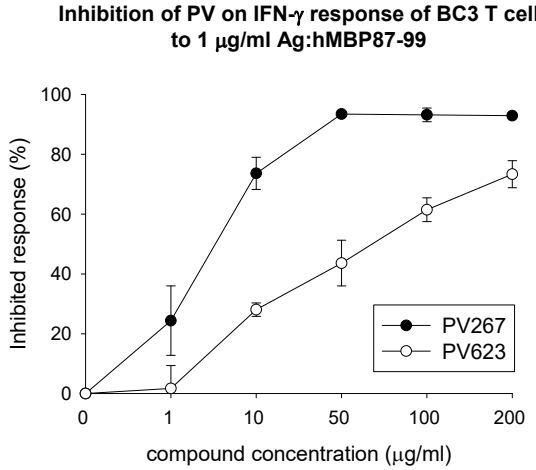
Journal of Immunology, November 15, 2013

# 2nd Generation Compounds

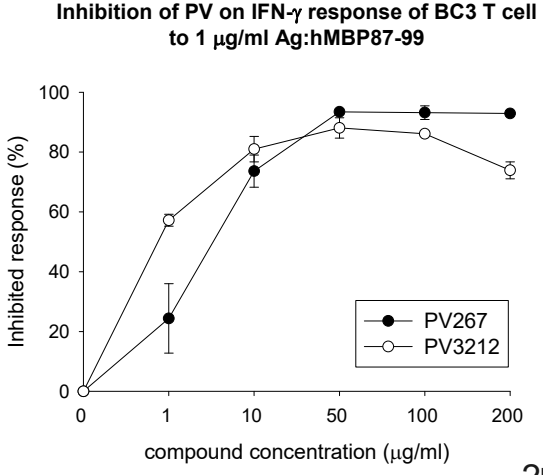
## *High Potency, Superior Stability, 20+ yrs Patent Life*

PV-267 Ac-V(Chg)R(Tic)F-$NH_2$

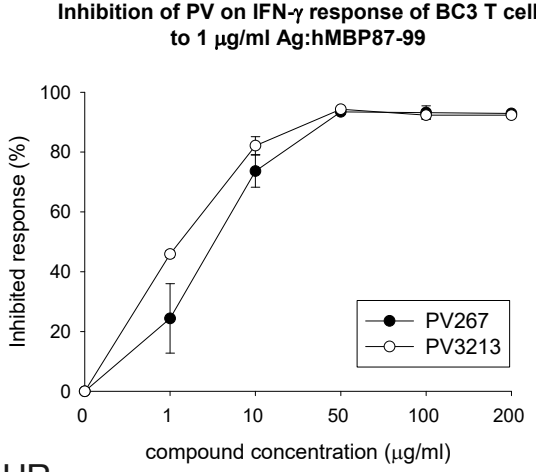
PV-623 Ac-V(Chg)R(Tic)F-OH




Acid metabolite PV-623 is active, but less potent (ca. 4-fold) than the amide




2nd generation analogs are at least as potent as PV-267

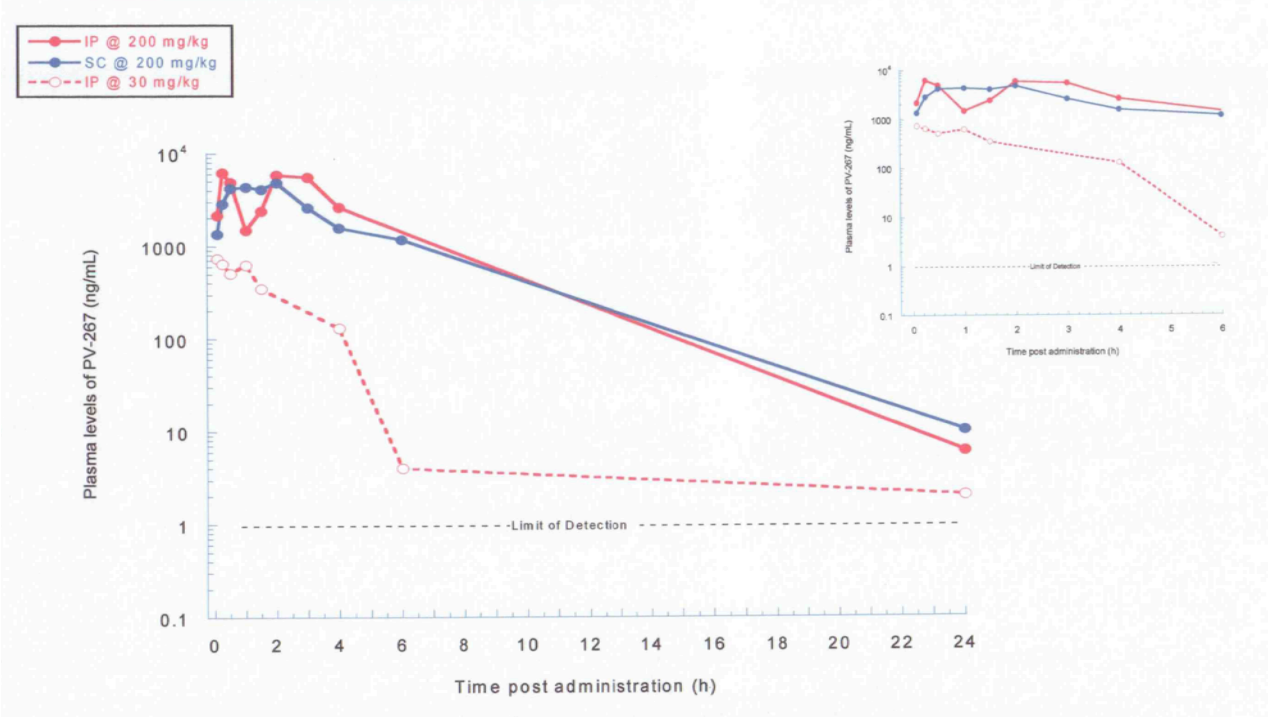



2nd Gen: Ac-V(Chg)R(Tic)F-NHR

20,000 BC3 T cells + $0.5x10^6$ autologous hPBMCs (Mean ± SEM)

# *PK*

- Initial mouse PK studies (CRL) for PV-267 showed good plasma levels after IP and SC administration
- Subsequent study (Absorption Systems) showed that PV-267 (C-terminal amide form) was partially converted to PV-623 (C-terminal acid form)
- 2nd generation compounds stabilized against deamidation



# *2nd Generation PK (PV-03212): High In Vivo Stability*

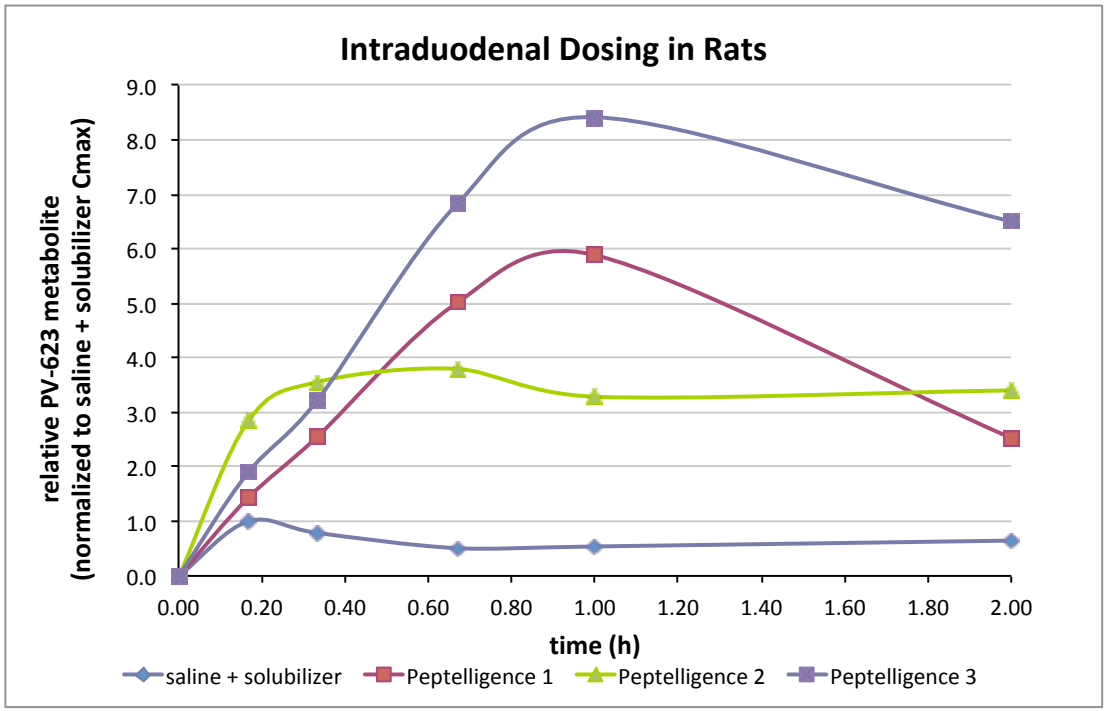
*Mouse PK, 10 mg/Kg IP*

| *Compound* | Mean Conc. (µg/mL) *0.25 hr* | *0.5 hr* |
|---|---|---|
| **PV-267** (Amide) Ac-V(Chg)R(Tic)F-$NH_2$ | 275 | 91.5 |
| **PV-623** (Acid metabolite) Ac-V(Chg)R(Tic)F-OH | 169 | 65.3 |
| ---------- | | |
| **PV-3212** ($2^{nd}$ Gen) Ac-V(Chg)R(Tic)F-NHR $t_{1/2}$ 3.23 hr | 741 | 195 |
| **PV-623** (Acid metabolite) Ac-V(Chg)R(Tic)F-OH | 8.54 | 3.57 |

# *Oral Bioavailability (Enteris Peptelligence™ Formulation)*

PV-267/PV-623 ID, rat model (not optimized)

| Formulation | $C_{max,}$ ng/mL | AUC (ng*hr)/dose (mg/Kg) |
|---|---|---|
| IV, (saline, solubilizer) | 8900 | 2270 |
| ID A (saline, solubilizer) | 2188 | 836 |
| ID B (Peptelligence™ 1) | 13883 | 4591 |
| ID C (Peptelligence™ 2) | 10678 | 4182 |
| ID D (Peptelligence™ 3) | 21833 | 10420 |



# *ClinicalTrial Plan*

*Unique Biomarker Strategy in Proof-of-Concept Trial*

***Establish mechanistic POC and dose range in initial trial***

- Screen for DRB1*15:01 gene (blood test)
- Treat DRB1*15:01+ individuals with PV-267 compounds and evaluate blockade of specific immune response *ex vivo*
- Establish dosage and frequency of administration needed to achieve blockade of DRB1*15:01 response
- First line therapy for DRB1*15:01 patients

***Efficacy trials***

- Accelerated using phase I results
- Gd-enhanced MRI lesions as surrogate
- Establish efficacy (relapses, progression) in phase II/III and superior safety profile

# *Intellectual Property*

*Inhibitors of antigen presentation by MHC class II molecules and methods of use thereof*

- I**ssued US patent 7,439,231** (composition of matter)
- **Issued US patent 8,222,215** (use)
- **Issued US patent 8,598,312** (composition of matter)

Current US DR2 Patents valid through 2025 and extendable up to 5 yrs for FDA review

Orphan/rare drug status for Goodpasture's, PR3 ANCA, etc.

**Oral formulation (not yet filed)**

**2nd Generation Compounds** (not yet filed; 20+5 years patent life)

# *Goodpasture's Disease*

## *Collaboration with Monash University*

- Goodpasture's disease/anti-glomerular basement membrane disease (anti-GBM) is a rare, orphan autoimmune disease affecting the kidney and lung. Incidence is 1-2/million population.
- Disease is strongly associated with DRB1*15:01

*Results:*

- PV-267 inhibits autoreactivity to the immunodominant T cell epitope antigen, $\alpha 3_{135\text{-}145}$, and attenuates disease in experimental autoimmune anti-GBM disease in DRB1*15:01 transgenic mice

- **HLA-DR15-specific inhibition by PV-267 attenuates autoreactivity to the Goodpasture antigen**
  Megan Huynh, Peter J. Eggenhuizen, Gary L. Olson, N. Bhaskara Rao, Christopher R. Self, Yanjun Sun, Stephen R. Holdsworth, A. Richard Kitching, Joshua D. Ooi, *J. Autoimmunity 2019 May 16. pii: S0896-8411(18)30665-6. doi: 10.1016/j.jaut.2019.05.004. [Epub ahead of print] PubMed PMID: 31104947.*

# *Preclinical Development*

*Completed for PV-267; Model for 2nd Generation*

- Chemical Synthesis
  - Solid Phase (Provid; Bachem)
  - Solution Phase (ChemVeda)
- Formulation
  - Salts, excipients for PV-267 (Wolfe Labs)
  - Oral:  Enteris Biopharma
- HLA binding, cathepsin stability
- ADME
- PK (PV-267; mouse)
- Exploratory toxicology (mouse, ip, acute and 2-week; CRL)
- *Next steps:  IND-enabling safety*

# *Summary*
## *Lead Drug Candidates for MS*

**PV-267 (1st generation)**

- PV-267 blocks **MHC class II HLA DR2b (DRB1*15:01)**
- Active in human MS patient cells and Tg mouse models
- Doesn't otherwise affect the immune system. The unique DRB1*15:01 inhibitory mechanism promises **high efficacy and superior safety**

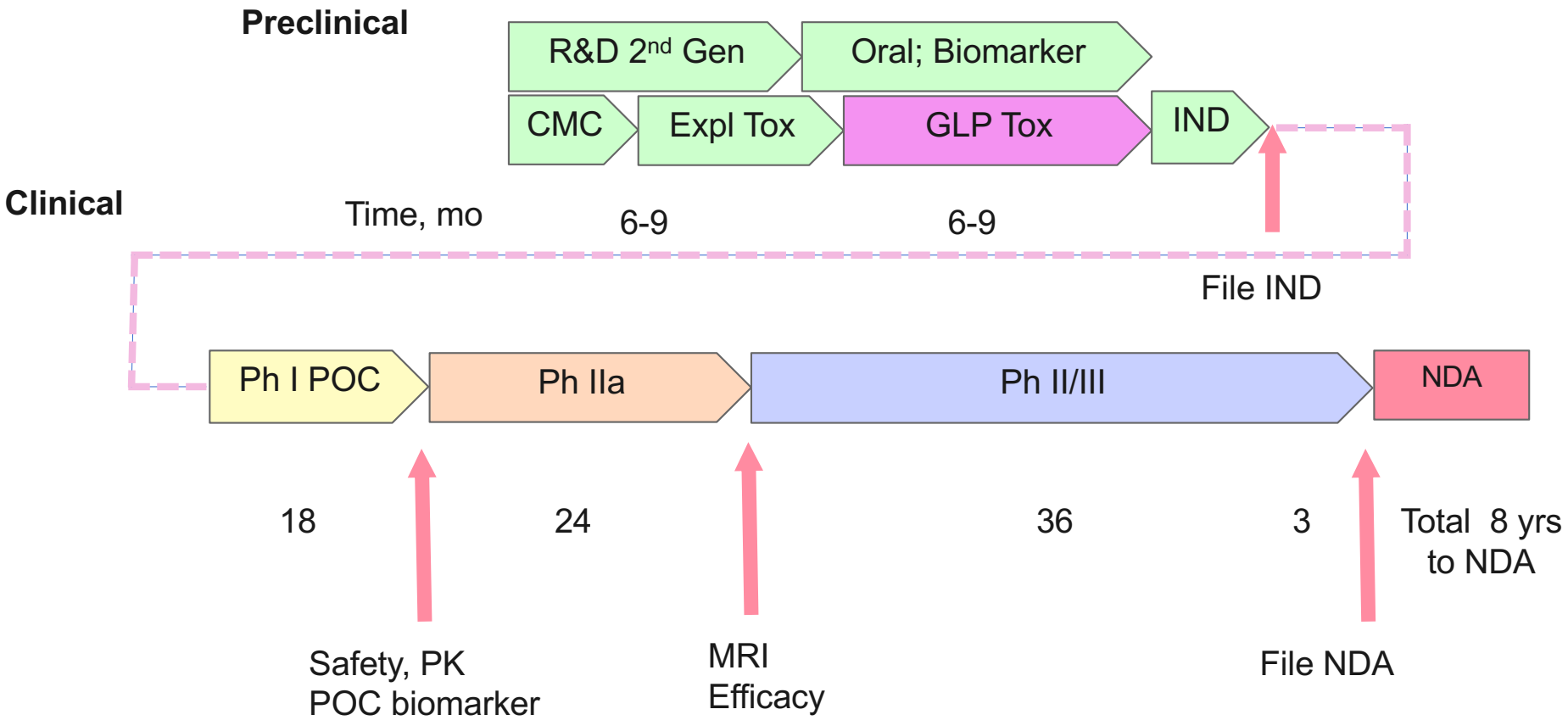
**2nd Generation, novel analogs**

- 2nd generation analogs with 20+ yrs patent life
- At least equivalent potency to PV-267 in human MS patient cells
- Commercial value: ***First line therapy*** for DRB1*15:01+ patients
- Oral formulation (Enteris)

Ready for IND-enabling studies leading to clinical POC trial

# *Development Timeline (DRB1*15:01 Inhibitor for MS)*

*(2nd Generation)*



# *Provid Prior Funding*

- **To date**: PV compounds developed primarily with non-dilutive financing (NIH, NJEDA, Fast Forward/NMSS, Daiamed**)**
- Founders $521,596
- Series A $1,810,000
  - Sequenom Inc. ($1MM)
  - Fast Forward/NMSS ($310K)
  - Investors: Wood, Tamarelli, Miller ($500K)
- Daiamed collaboration $ 4,704,374
- NJEDA Edison Venture loan $1,275,000
- Non-dilutive grants/fees (all programs) $750,000
- Revenues 2001-2018 from services $12,602,318

# *Provid Team*

## *Management & Board of Directors*

- Founded 2001 by leading scientist-executives (ex-Roche, Praecis)
- Pioneers in field of peptide mimetics technology
- Venture, finance, and operating expertise on Board of Directors

***Gary Olson***
*CEO*
*Columbia, Stanford PhD*
*Roche, Praecis*
*Provid Co-founder*

**Christopher Self**
Director
*London, Imperial PhD*
*Roche UK/US, Praecis*
*Provid Co-founder*

**Brian Wood**
Director
*VPI, Harvard MBA*
*Gould Inc.*
*Alta Berkeley founder*

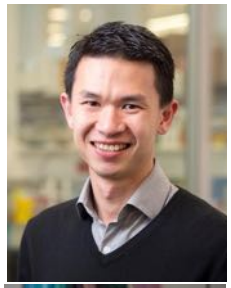
**A. Wayne Tamarelli**
Director
*Carnegie-Mellon PhD*
*NYU MBA*
*AWT Private Inv.*

**Edwin Thomas**
Director
*U Penn,*
*Wharton MBA*
*Eleison, Avid, CMI*

# *Scientific Advisors and Collaborators*

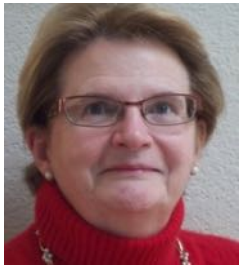
Thomas Forsthuber PhD MD
(UT San Antonio, Immunology)

Lawrence Steinman MD PhD
(Stanford, Immunology; Clinical Advisory Chair)



Joshua Ooi PhD
(Monash U. Research Fellow)

Ann Welton PhD
(Consultant, preclinical development)



A. Richard Kitching
(Director, Monash U. Center for Digestive Disease)

Suhayl Dhib-Jalbut MD
(Rutgers RWJ Center for MS, Neurology)

Amos B. Smith, III PhD
(U. Penn, Chemistry; co-founder with Prof. Ralph Hirschmann)

Warren Strittmatter MD
(Duke, Neurology)

# *Provid Collaborators & Advisors*

*Autoimmune Disease Therapeutics and Peptide Mimetics Platform*

***Collaborators***

- *Dr. Thomas Forsthuber* (U. Texas San Antonio; immunology)
- Dr. Bernard Maillere (CEA, France; binding assays)
- Drs. Don Wiley, Kai Wucherpfennig, (Harvard; structural biology)
- Dr. Neil Hayward & colleagues (Daiamed)
- Dr. Ed Rosloniec (Memphis VA; DR4 assays)
- Drs. Joshua Ooi, Richard Kitching (Monash U; Goodpasture's)

***Provid SAB and Advisors***

- Dr. Lawrence Steinman (Stanford)
- Dr. Warren Strittmatter (Duke)
- Dr. Jeffery Kelly (Scripps)
- Dr. Ann Welton (J&J, ret.)
- Dr. Suhayl Dhib-Jalbut (UMDNJ)

***Co-founders***

- Dr. Christopher Self
- Dr. Charles Cook
- Dr. Amos B. Smith (U. Penn)
- Dr. Ralph Hirschmann (U. Penn)

***In Partnership with Fast Forward-National Multiple Sclerosis Society***
***External funding from NIH, Daiamed, NJEDA, Fast Forward***