limitations including protease degradation, high dosing requirements, subcutaneous administration, and emergence of resistant HIV strains. Based on these data, we present herein the synthesis and the anti-HIV evaluation of new D-peptide analogs, expected to be resistant to proteolytic degradation and endowed with improved bioavailability, as specific inhibitors of the hydrophobe pocket of the gp41N trimer. Using a similar cyclic D-peptide approach, a consensual 8-mer sequence with 4 recurrent amino acids (D-Glu9, D-Trp10, D-Trp12, and D-Leu13) has been previously defined by other research groups. First, our efforts were devoted to understand the key elements responsible for their pharmacological activity using molecular modelisation/dynamic approaches. This initial study showed that D-Glu9, D-Trp10, D-Trp12, and D-Leu13 interact with residues in or on the edge (D-Glu9) of the hydrophobe pocket and, that C- and N-terminal terminations govern structural changes in cyclic peptides and probably their antiretroviral effects. Then, considering these data, more than 40 cyclic analogs were synthesized and evaluated against HIV-1-LAI by measuring virus-induced cytopathogen effects (CPE) and the production of the major HIV nucleocapsid p24 protein in acutely infected MT-4 cells. Retro and/or inverso peptides as well as 7-mer D-peptides showed no antiviral effects. Only the substitution of D-Trp12 and D-Leu13 residues by l-napthyl and/or cyclobutyl group(s) have improved antiretroviral efficacy.

doi:10.1016/j.antiviral.2011.03.023

38

Activity of Novel Cyclophilin Inhibitors based on the Polyketide, Sanglifehrin A, against HIV

Michael Bobardt[1,*], Steven Moss[2], Udayan Chatterji[1], Mohammad Nur-E-Alam[2], Tony Warneck[2], Barrie Wilkinson[2], Philippe Gallay[1], Matthew Gregory[2]

[1] *The Scripps Research Institute, La Jolla, USA*
[2] *Biotica Technology Ltd, Cambridge, United Kingdom*

Cyclophilin inhibitors, such as Cyclosporine A (CsA) and analogues, such as DEBIO-025 (Alisporivir) have previously shown activity in *in vitro* antiviral assays against HIV isolates (Ptak et al., 2008), however, when tested clinically, DEBIO-025 only reduced HIV-1 RNA levels by $\geq$0.5 and >1 $\log^{10}$ copies/mL in nine and two patients respectively, whilst 27 of the treated patients showed no reduction in HIV-1 RNA levels (Steyn et al., 2006). DEBIO-025 was trialled in HCV/HIV coinfected patients, showed better efficacy against HCV (Flisiak et al., 2008), and was followed by a substantial focus in HCV treatment. Sanglifehrin A (SfA), a polyketide natural product, has been shown to bind Cyclophilins (CyPs), such as CyPA, and to have antiviral activity in HCV replicon assays. Novel analogues with improved drug like properties were generated through proprietary biosynthetic engineering technology and semi-synthetic methods. These analogues were tested *in vitro* against HIV, and were seen to have significantly improved potency, both in terms of EC_{50} and maximal antiviral effect. Novel SfA analogues offer additional advantages over other virus-targeting agents under development for HIV and detailed profiling of selected candidates is underway.

References

Flisiak, et al., 2008. Hepatology 47 (3), 817–826.
Ptak, et al., 2008. Antimicrob. Agents Chemother. 52 (4), 1302–1317.
Steyn, et al., 2006. Int. Conf. Retroviruses Opportunistic Infec, vol. 13 , Abs 516.

doi:10.1016/j.antiviral.2011.03.024

39

OBR-5-340—A Novel Pyrazolo-Pyrimidine Derivative with Strong Antiviral Activity Against Coxsackievirus B3 *In Vitro* and *In Vivo*

Heike Braun[1,*], Vadim A. Makarov[2], Olga B. Riabova[2], Elena S. Komarova[2], Martina Richter[1], Peter Wutzler[1], Michaela Schmidtke[1]

[1] *Institute of Virology and Antiviral Therapy, Jena University Hospital, Jena, Germany*
[2] *Institute of Biochemistry, Russian Academy of Science, Moscow, Russia*

There is no specific medication to address diseases induced by CVB3, e.g. harmless respiratory infections, diarrhea, myocarditis, meningoenceophalitis, pneumonia, and pancreatitis until now.

In the present study, the toxicity and anti-CVB3 activity of OBR-5-340, a novel pyrazolo-pyrimidine derivative was determined *in vitro* and *in vivo*. OBR-5-340 is well tolerated (CC_{50} > 500 μM) and exhibits strong dose-dependent antiviral activity against the pleconaril-resistant CVB3 31-1-93 in HeLa cells. The IC_{50} determined for CVB3 31-1-93 was 0.03 μM. In contrast, pleconaril included as control was inactive. For the *in vivo* studies, adult male NMRI mice were infected intraperitoneally with 5^{-4} pfu of CVB3 31-1-93. OBR-340 and the control compound pleconaril were administered orally twice daily (100 mg/kg). In pleconaril- and placebo-treated CVB3 31-1-93-infected mice disease onset was observed at day 3 or 4 p.i. Between day 5 and 10 p.i. severity of disease, lost of body weight were maximal (−15% related to day 0 p.i.). OBR-5-340 treatment almost completely prevented CVB3 31-1-93-induced disease. No loss of body weight was observed and the histopathological scores in heart and pancreas tissue as well as the viral load in heart tissue were significantly reduced compared to pleconaril- or placebo-treated mice. *In conclusion*, OBR-5-340 exhibits a strong antiviral effect against a pleconaril-resistant CVB3 variant *in vitro* and *in vivo*. It represents a promising new drug candidate for the treatment of CVB3 infections.

doi:10.1016/j.antiviral.2011.03.025

40

Occurrence of Opportunistic Infections in People Living with HIV/AIDS Following Antiretroviral Therapy in West Bengal, India

Sayan Chakraborty*, Mehebubar Rahman, Bibhuti Saha

Calcutta School of Tropical Medicine, Kolkata, India

As per the data of 2008, approximately 33.4 million people are living with HIV/AIDS worldwide and there were around 2.0 million AIDS related deaths in that year. Occurrence of opportunistic infections (OIs) is the main cause of morbidity and mortality in HIV infected patients. OIs encompass a wide variety of microorganisms that produce fulminant infections in immunocompromised HIV infected patients. HIV makes the infected person immunocompromised by destroying his CD4 T-lymphocytes. CD4 T-lymphocyte count (or CD4 count) is a standard laboratory marker to monitor disease progression in HIV infected patients. When the CD4 count of a HIV infected person decreases he or she becomes susceptible to OIs due to the compromised immune system. Antiretroviral Therapy (ART) decreases multiplication HIV and thereby decreases CD4 cell destruction. So there is increase in CD4 count and improvement in immunity which leads to less occurrence of OIs in HIV patients. We followed 88 patients for 3 years, who were getting first line ART at ART center, Calcutta School of Tropical Medicine. For analysis we divided 88 patients into 5 groups based on their initial CD4 count i.e.