BIT225, a Novel Inhibitor of HIV-1 Release from HIV-1 Reservoirs of the Myeloid Lineage

- John Wilkinson -

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IAS 2013 Towards an HIV Cure Symposium

BIT225
(N-[5-(1-Methyl-1H-pyrazol-4-yl)-napthalene-2- carbonyl]-guanidine)

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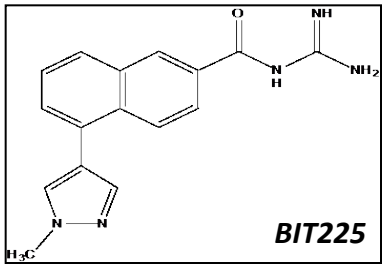
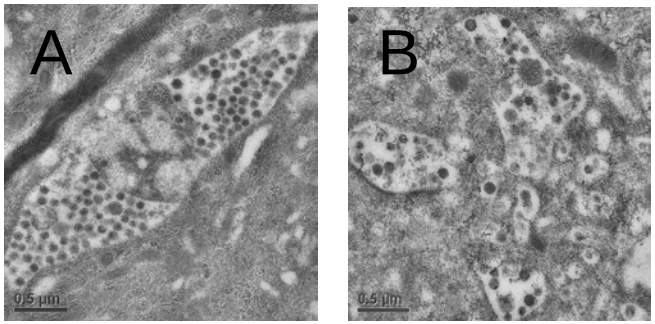
- First-in-class drug targeting HIV-1 within cells of the myeloid lineage (selected as lead from ~250 compound library designed to target Vpu)

- Anti-HIV-1 activity in primary human $CD14^+$ MDM assay:
  - *>90% inhibition of HIV-1 release (RT & p24)*
  - *IC_{50} of ~1.1 ± 0.4 uM TC_{50} of 212 uM*



- Also active in DCs
- Targets Vpu ion channels, with no effect on HIV-2
- No effect on reverse transcription or on the RTase or protease enzymes
- Acts post-integration
- EM suggests defects in virion packaging/budding

- Good safety and PK profiles in preclinical toxicology studies and Phase 1 human trials



Visualisation by EM of (A) DMSO (B) BIT225 treated cells

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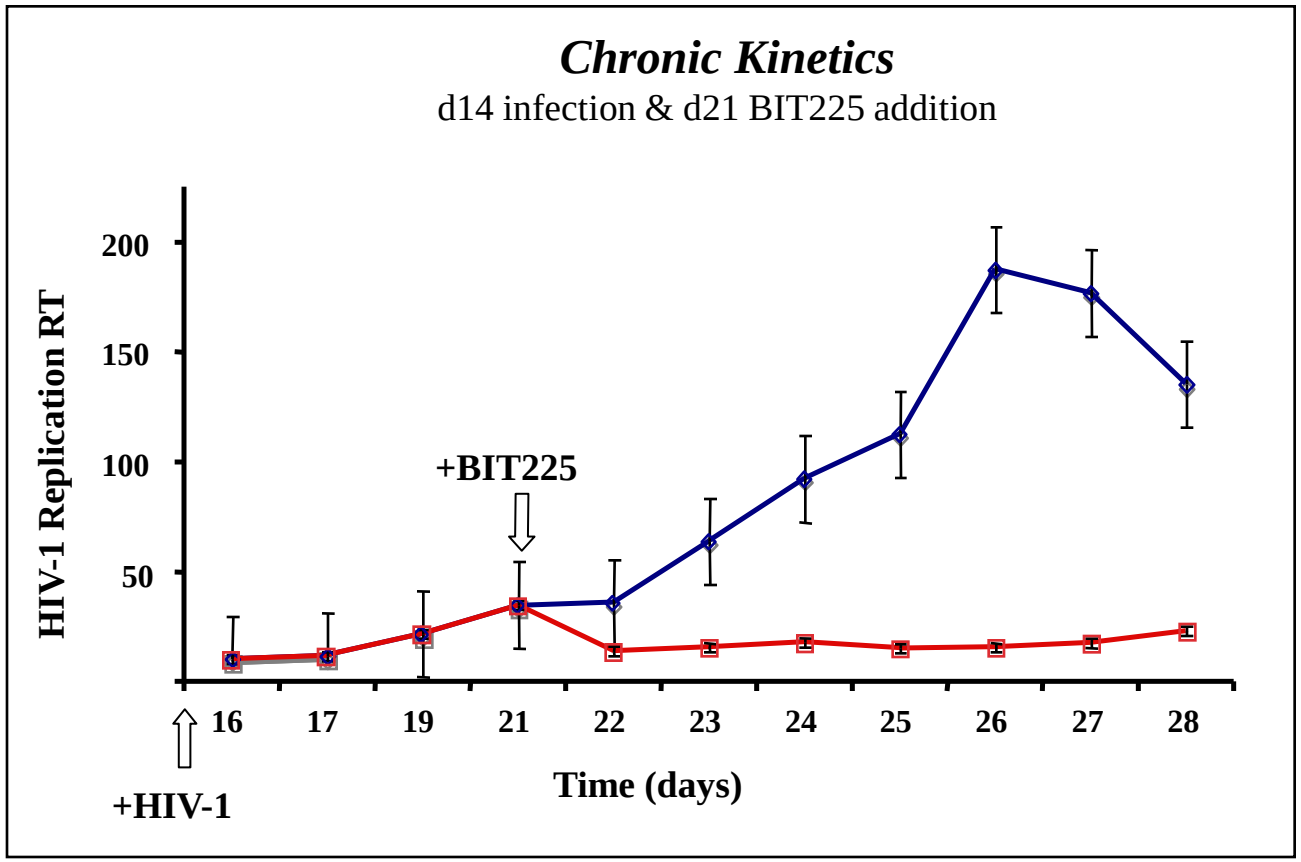
Significant HIV-1 Reduction in Human Macrophages *in vitro* with BIT225



Khoury et al., Antimicrobial Agents and Chemotherapy. 2009

Monocytes and HIV-1 Infection

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- $CD14^+$ monocytes (~30%) are long lived cells with reports that once infected they can disseminate virus for 6 weeks *in vitro* (Sharova *et al* EMBO J 2005)
- The minor $CD16^+$ subset (5-10% of monocytes) are preferentially infected; higher CCR5 levels (Ellery *et al* JI 2007)
- Circulate in the blood for ~1 day before entering the tissue -> MØ
  - Important wrt transmission and seeding the tissues (brain)
- HIV-1 can be isolated from monocytes (Wang *et al* Plos One 2013), their HPC precursors (Carter *et al* Nat Med 2010) and thought to contribute to viral persistence (Le Douce *et al* Retrovirology 2010)
- Treatment regimens fail to inhibit HIV-1 DNA persistence in monocytes (Sonza *et al* AIDS 2001; Zhu *et al* JV 2002; Llewellyn *et al* JLB 2006) but they are not a major reservoir in elite suppressors (Spivak *et al* JV 2011)

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A Phase 1b/2a Trial with BIT225

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BIT225-004, a Phase 1b/2a, Placebo-Controlled, Randomised Study of the Safety, Pharmacokinetics and Antiviral Activity of BIT225 in Patients with Human Immunodeficiency Virus-1 Infection

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BIT225-004: Synopsis

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Primary objective

The safety and tolerability of 400 mg of BIT225 BID compared with placebo in patients with HIV-1 infection that are antiretroviral therapy naïve

Secondary objectives

- The pharmacokinetics of 400 mg of BIT225 administered daily on day 1 & 10 and twice daily on days 2 - 9
- The antiviral activity of BIT225
- Evaluate BIT225 levels in cerebrospinal fluid at day 10 (optional day 9)

Study design

- A randomized, parallel, double-blind study of BIT225 in patients with HIV-1 infection that are antiretroviral therapy naïve
- Males and females, aged 18 to 65 years, with HIV-1 infection (viral load >5,000 copies/mL; CD4+ count >350 cells/mm^3) and that are antiretroviral therapy naïve
- 14 patients receiving 400 mg BIT225 and 7 receiving placebo

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BIT225 Antiviral Activity in a Clinical Setting

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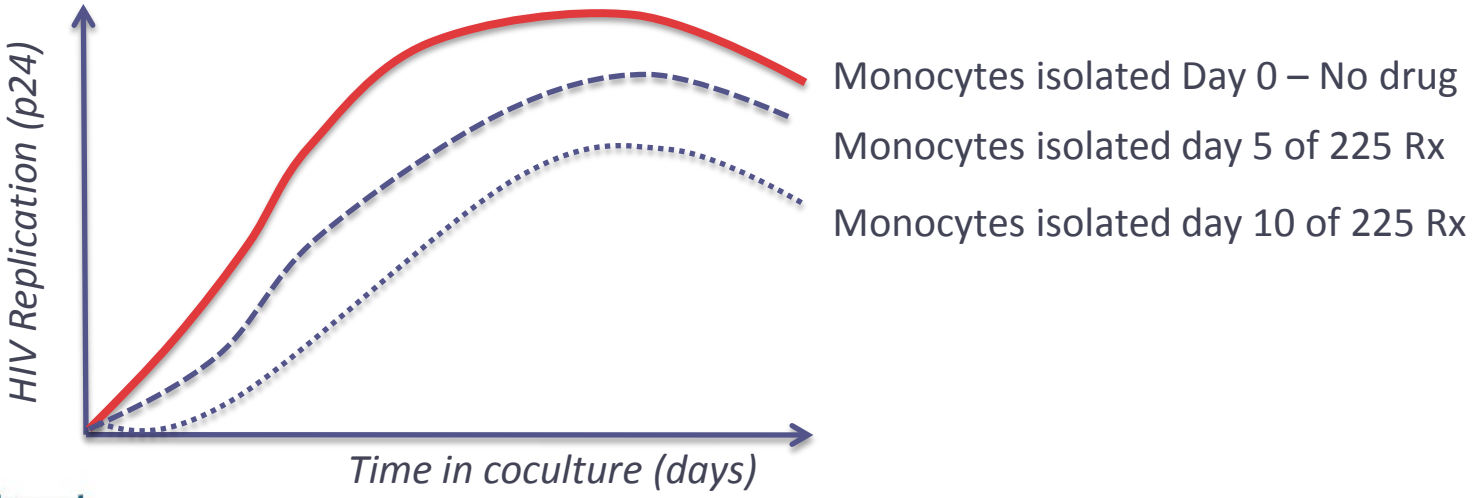
In a study of only 10 days with a drug targeting cells of the myeloid lineage, dramatic decreases in HIV-1 viral load and concomitant increases in $CD4^+$ T cell number are unlikely to be observed. Issues with access to macrophages

Aim: To determine the effect of BIT225 on the viral burden in circulating $CD14^+$ monocytes in HIV-1^+ individuals

Method: $CD14^+$ monocytes were isolated with magnetic beads on days 0, 5, 10 and 20 and co-cultured with MT4 HIV-1^- T cells for 25 days



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Monocyte Co-Culture Assay

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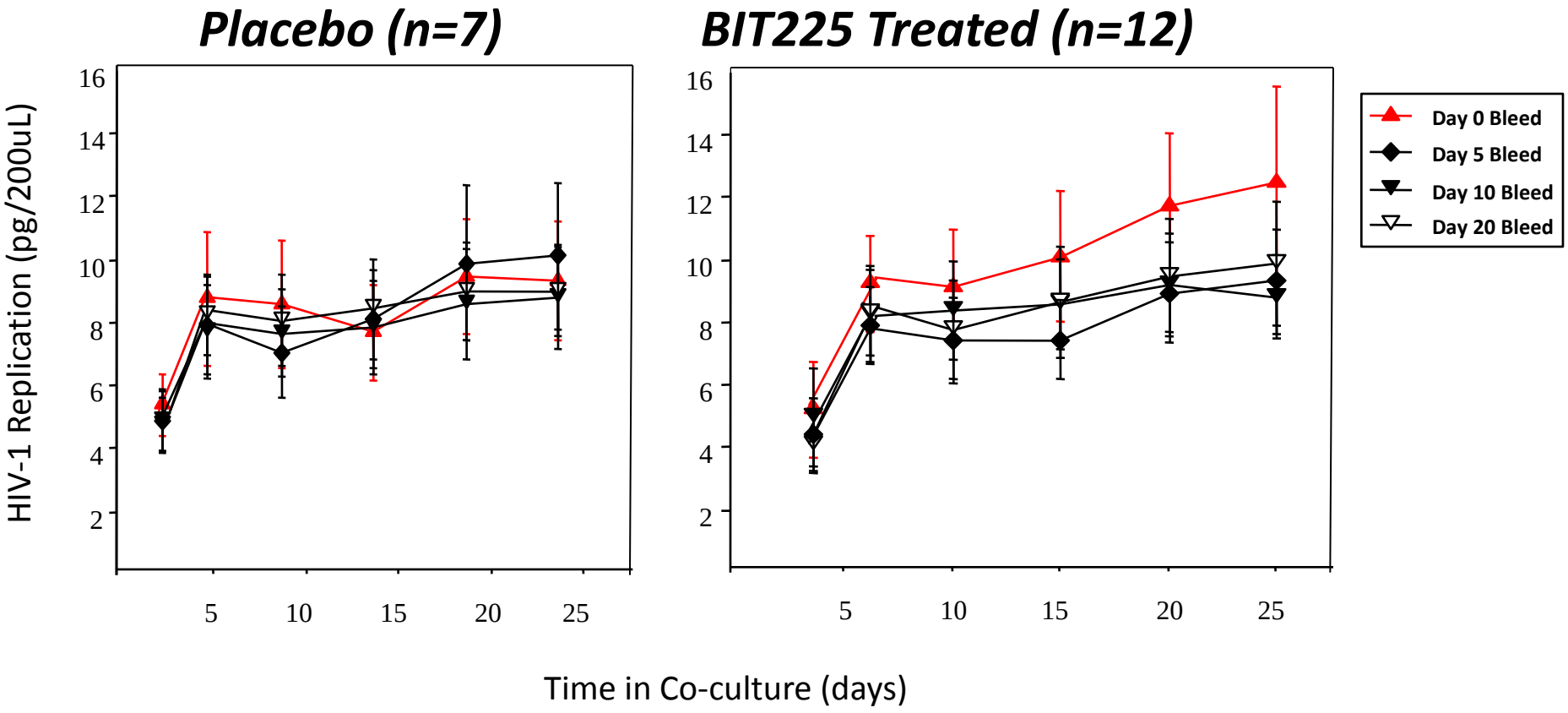

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Monocyte Co-Culture Assay
BIT225 Treated: High Viral Load n=6

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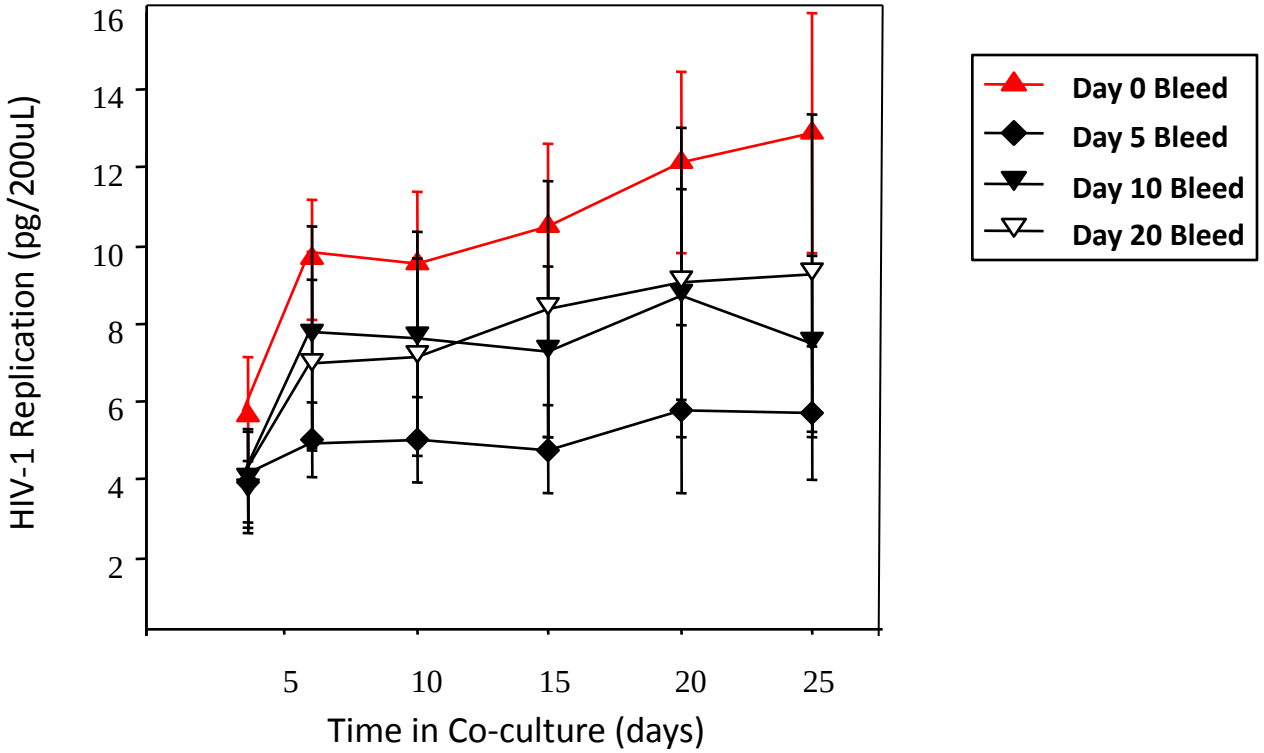

Mann-Whitney p=

0 v 5	0.25	0.09	0.1	**0.05**	**0.04**	0.2
0 v 10	0.25	0.31	0.31	0.42	0.44	0.28
0 v 20	0.25	0.28	0.31	0.37	0.35	0.54

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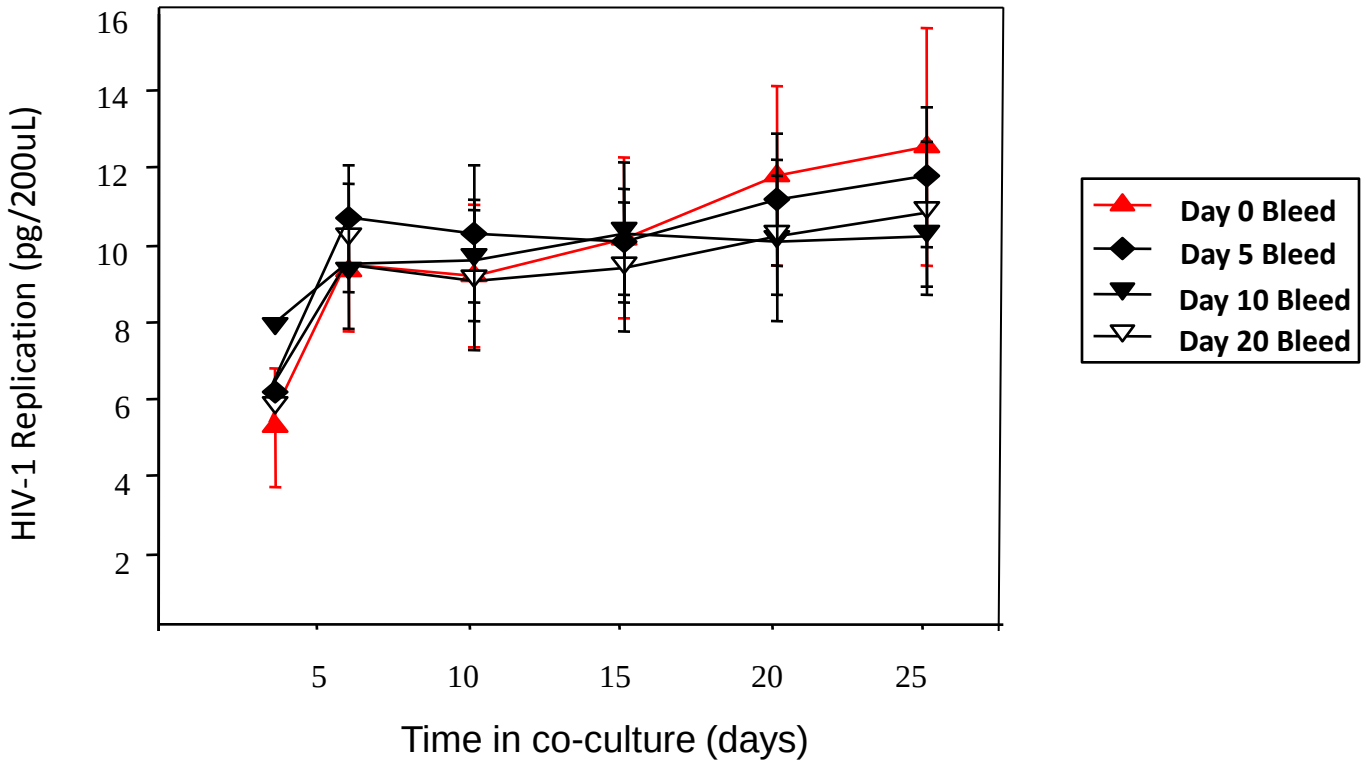
Monocyte Co-Culture Assay
BIT225 Treated: Low Viral Load n=6



In Summary

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- This study strengthens our previous findings *in vitro* and *ex vivo*, supporting the role for BIT225 as a novel drug targeting HIV-1 within the myeloid compartment
- In those patients with high HIV-1$^+$ viral loads, treatment with BIT225 for 10 days significantly reduced the amount of infectious HIV-1 within the circulating CD14$^+$ monocyte population
  - Single Copy HIV-1 RT-PCR Analysis: For 21 patients at the 4 bleeds, RNA and DNA (in triplicate) has been isolated and stored for HIV RNA and HIV DNA analysis
- By targeting these cells and preventing the (re)seeding of the reservoirs, is there a potential role for BIT225 in the eradication strategy?

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