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VHsquared

A Protease-resistant Oral Domain Antibody to TNFα Delivers High Concentrations of Active Compound in Ileal Fluid of Subjects with an Ileostomy

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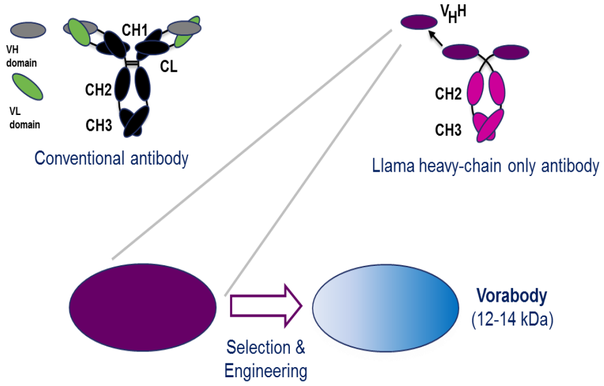
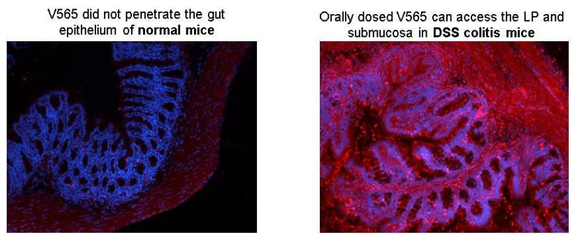
INTRODUCTION

Monoclonal antibodies to TNFα, administered parenterally, have transformed the treatment of patients with IBD. However, the current administration routes, and the potential for systemic suppression of TNFα, are not ideal. Oral delivery of therapeutic concentrations of anti-TNFα, direct to the site of TNFα production in the lamina propria (LP) of the gut mucosa, could benefit patients with IBD. However, historically the oral delivery route has proven to be technically challenging.

V565 is a domain antibody (Vorabody™) derived from the variable region of a llama heavy chain only antibody. V565 was engineered to resist intestinal proteases, while retaining potency against human TNFα, and has been formulated in enteric coated minitablets to ensure timed release after exiting the stomach, once the pH reaches 6.5.



In preclinical experiments, V565 had similar potency to adalimumab in neutralising TNFα *in vitro.* In mice with DSS colitis, V565 transited to the LP to a high degree after oral dosing (V565 is detected in red, below), but not in normal mice with intact epithelia.



Fluorescent staining: Cell nuclei are in blue (DAPI). V565 is detected in red.

Following oral dosing to cynomolgus monkeys, there was minimal systemic absorption, and following an intravenous dose to monkeys V565 was rapidly renally cleared with an elimination half-life of approximately 50 minutes.

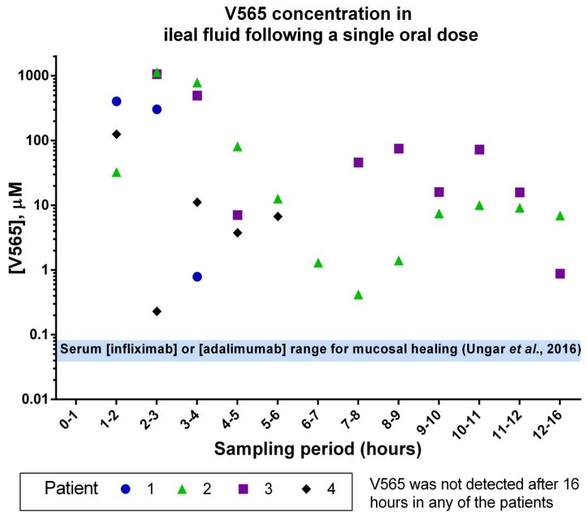
AIMS and METHODS

This open label assessment was performed to confirm and measure the delivery of active V565 to the terminal ileum of four patient volunteers after oral dosing. Patients with a Crohn's disease diagnosis were excluded.

Four patients with terminal ileostomy (three with a diagnosis of UC, one with a prior sigmoid stricture) took a single oral dose of 1665mg V565, formulated in minitabs. Ileostomy bags were collected hourly for the first 12 hours post dose, and then at 16, 20 and 24 hours post dose. Contents were analysed for [V565] by competitive ELISA with protease inhibitors.

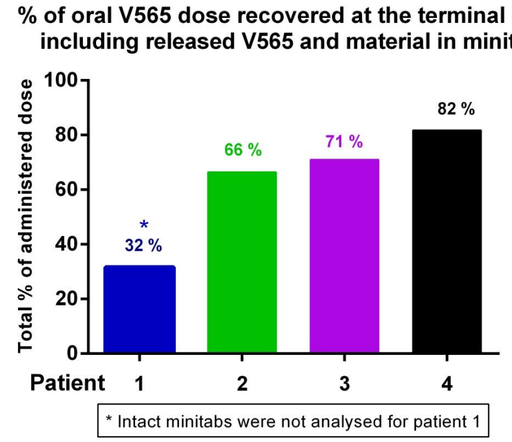
RESULTS

After a single oral dose of 1665mg, high concentrations of released, active V565 were detected in the ileal fluid of all subjects:



V565 was not detected after 16 hours in any of the patients

In addition to fully released V565, partially dissolved minitablets were present in the ileostomy bags of all four subjects 2-3 hours after dosing. For subjects 2, 3 and 4 these minitablets were stored and analysed for the presence of V565. This was a post hoc analysis, and the minitablets from subject 1 were not stored in a way that allowed reliable analysis. Combining both the V565 in ileal fluid, and the V565 retained in the partially released minitablets, a high percentage of the single oral dose was recovered at the terminal ileum.



* Intact minitabs were not analysed for patient 1

CONCLUSIONS

V565 was released in micromolar concentrations in ileal fluid, over several hours, following a single oral dose. These concentrations are orders of magnitude greater than those required in the serum for clinical anti-TNFα antibodies to induce mucosal healing in IBD patients (Ungar *et al.,* 2016).

In a patient without ileostomy, V565 retained in partially dissolved minitablets will become available in distal parts of the GI tract as the minitablets continue to dissolve during transit. Coupled with high protease stability of V565, the minitab formulation should provide coverage for ileal to distal colonic IBD.

V565 can access the LP of mice with colitis after oral dosing and inhibits human TNFα at low-nanomolar (≤5 nM) IC_{50}.This suggests that the luminal concentrations delivered following oral dosing with V565 will result in therapeutic levels in the lesions of patients with IBD.

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Ungar *et al.* (2016). *Clin Gastroenterol Hepatol.* 14(4). 550-557