The Novel Semisynthetic Saponin Adjuvant TQL1055 Enhances the Antibody Response to Pertussis Vaccine with an Improved Tolerability Profile over QS-21

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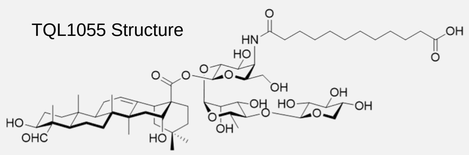
Introduction and Background

Acellular pertussis vaccines are better tolerated than older whole cell vaccines but may require novel adjuvants to enhance their immunogenicity. First-generation natural saponins are potent immuno-enhancers but are reactogenic and have supply constraints [1]. In this work, the novel semisynthetic saponin TQL1055 was evaluated for its potential to augment the immunogenicity of influenza antigens.

TQL1055 is a rationally designed, semisynthetic analogue of the saponin adjuvant QS-21. It is produced by a convergent synthesis from a triterpene prosapogenin core that is covalently linked to a dodecanedioic acid derivative and a linear trisaccharide to form TQL1055.

TQL1055 Structure



TQL1055 has several properties that make it a promising alternative to natural QS-21 adjuvants including:

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+ The hydrolytically labile ester linkage in natural QS-21 has been replaced by an amide linkage in TQL1055, resulting in improved stability compared to QS-21 [2].
+ TQL1055 does not exhibit the hemolytic activity associated with QS-21 [2].
+ increased tolerability (measured by weight loss in mice post-injection) compared to QS-21.
+ Extraction of the triterpene core is not limited to the bark of mature *Quillaja saponaria* trees, increasing the biomass available for extraction and reducing supply constraint issues.
+ TQL1055 retains excellent adjuvant activity.

Materials and Methods

Mouse Experiments

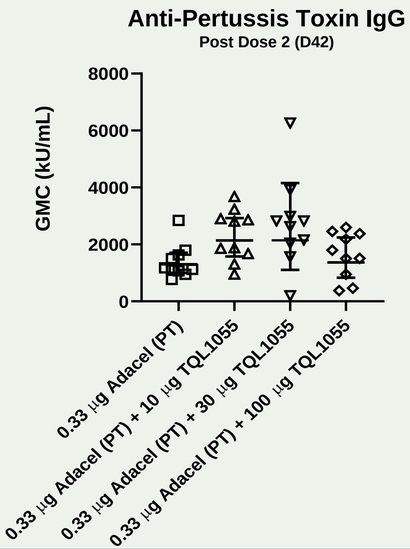
- Vaccine: ADACEL Acellular Pertussis Vaccine, Adsorbed
- Adjuvant: TQL1055 (varying doses) or QS-21 (20 µg/mouse/dose)
- Groups of 10 female C57BL/6J mice, age 6-8 weeks received two subcutaneous immunizations on day 0 and day 28.
- Peripheral blood was collected on day 0, 28 and 42
- Anti-Pertussis Toxin (PT) and anti-Pertactin (PRT) IgG levels were quantified using a commercial ELISA kit.
- Body weights were measured prior to immunization and at day 1, 2, 3 and 7 following the first dose.

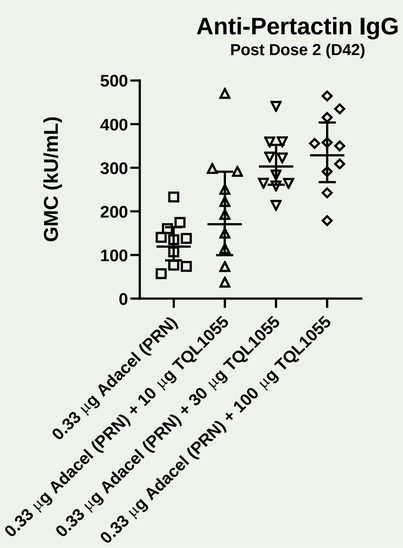
GLP Rabbit Toxicology Study

- TQL1055 was evaluated in a 2-dose series, TQL1055 dose ranging GLP toxicology study.
- New Zealand White rabbits received two IM injections on Day 1 and 15.
- TQL1055 doses ranged from 250 – 2000 µg; TQL1055 at 1000 µg was administered with and without one human dose of ADACEL.
- Rabbits receiving TQL1055 + ADACEL were also evaluated for anti-PT IgG responses.

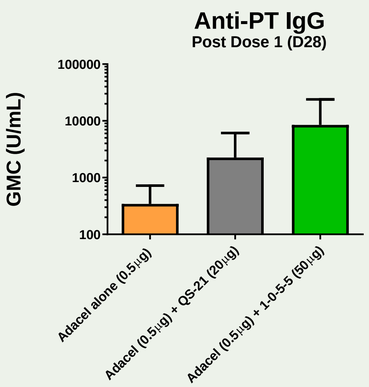
Results

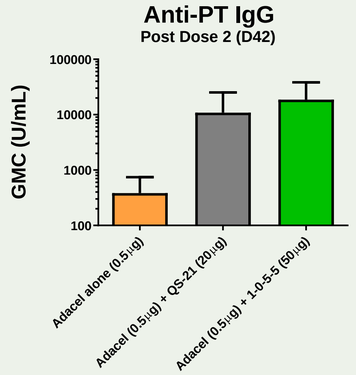
Mice were immunized twice (Day 0 and 28) with increasing doses of TQL1055 + ADACEL. At 14 days post dose 2 (D42), there was a trend for increasing anti-PT GMCs with increasing TQL1055 dose, with the exception of the 100 µg dose. The same trend was observed for anti-Pertactin GMCs, with 30 and 100 µg doses of TQL1055 significantly enhancing GMCs compared to ADACEL alone.

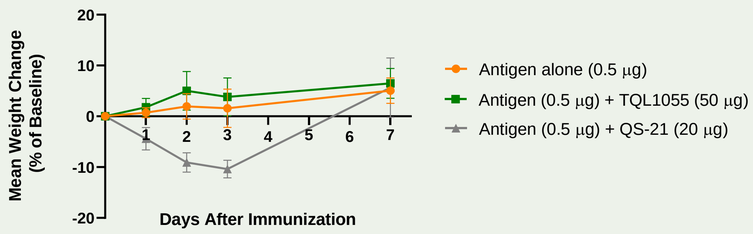




At 28 days following the first dose, mice immunized with ADACEL + TQ1055 had anti-pertussis toxin IgG GMC of 8492 U/mL compared with 2263 U/mL in mice receiving ADACEL+ QS-21 (p = 0.0507). At day 42, 14 days after the second dose, GMCs increased to 18719 U/mL in the TQL1055 group and 10851 U/mL in the QS-21 group (p = 0.2831).



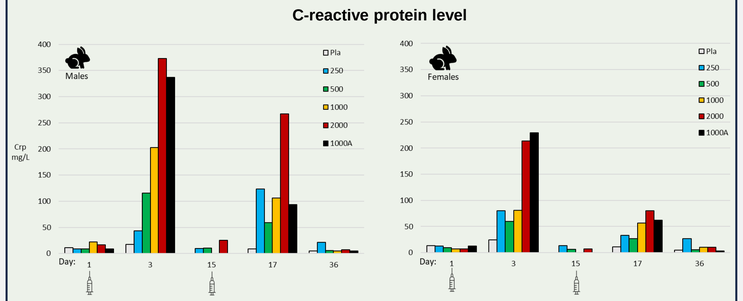




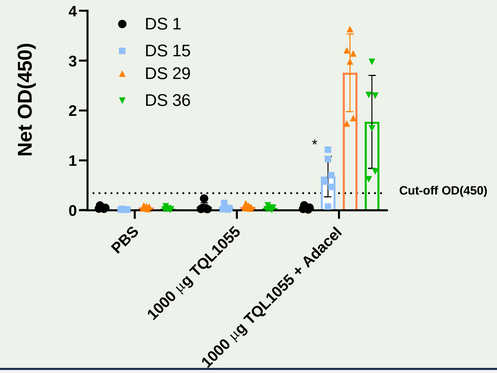
Mice treated with TQL1055 + ADACEL did not exhibit weight loss following immunization, comparable to ADACEL alone treated mice. In contrast, mice receiving QS-21 exhibited significant weight loss after immunization, with mean weight loss of greater than 10% 3 days following immunization.

Results Continued

TQL1055 induced a transient rise in serum C-reactive protein, consistent with an acute phase response. Similar increases in fibrinogen and monocytes were also observed. Mean body weight increased during the study in all groups, suggesting TQL1055 is well tolerated



Rabbits receiving TQL1055 + ADACEL were positive for Anti-PT IgG antibodies following both dose 1 and dose 2.



Conclusions

- TQL1055 is a semisynthetic saponin adjuvant with excellent adjuvant properties and improved tolerability compared to natural QS-21.
- TQL1055 enhances the antibody response to several pertussis antigens compared to the vaccine alone.
- There was a trend for TQL1055 to enhance the antibody response to ADACEL to a greater degree than QS-21.
- TQL1055 has improved tolerability compared to QS-21 in a mouse model and is well tolerated at doses up to 2000 µg in rabbits.
- TQL1055 is a promising adjuvant for improving the performance of acellular pertussis vaccines without increasing reactogenicity.

References

1. Fernandez-Tejada, A., Tan, D.S., Gin, D.Y. “Development of Improved Vaccine Adjuvants Based on the Saponin Natural Product QS-21 through Chemical Synthesis. *Acc Chem Res.* Vol. 49, no. 9, 2016, pp. 41-50.
2. Adams, M. M., et al. “Design and Synthesis of Potent Quillaja Saponin Vaccine Adjuvants” *J Am Chem Soc*. Vol. 132, 2010, pp. 1939-1945.

Acknowledgments

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