

Accepted Manuscript

Oral vaccination of fish: Successes, challenges and future perspectives

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PII: S0145-305X(16)30098-2

DOI: [10.1016/j.dci.2016.03.024](https://doi.org/10.1016/j.dci.2016.03.024)

Reference: DCI 2599

To appear in: *Developmental and Comparative Immunology*

Received Date: 2 January 2016

Accepted Date: 17 March 2016

Please cite this article as: Embregts, C.W.E., Forlenza, M., Oral vaccination of fish: Successes, challenges and future perspectives, *Developmental and Comparative Immunology* (2016), doi: 10.1016/j.dci.2016.03.024.

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10 **Abstract**

11 The limited number of oral vaccines currently approved for use in humans and veterinary
12 species clearly illustrates that development of efficacious and safe oral vaccines has been
13 a challenge not only for fish immunologists. The insufficient efficacy of oral vaccines is
14 partly due to antigen breakdown in the harsh gastric environment, but also to the high
15 tolerogenic gut environment and to inadequate vaccine design. In this review we discuss
16 current approaches used to develop oral vaccines for mass vaccination of farmed fish
17 species. Furthermore, using various examples from the human and veterinary vaccine
18 development, we propose additional approaches to fish vaccine design also considering
19 recent advances in fish mucosal immunology and novel molecular tools. Finally, we
20 discuss the pros and cons of using the zebrafish as a pre-screening animal model to
21 potentially speed up vaccine design and testing for aquaculture fish species.
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24 **Keywords:** Live vaccines; adenoviruses; encapsulation; M-like cells; adjuvants; zebrafish

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26 **Abbreviations:** TLR: Toll-like receptor, NLR: NOD-like receptor, RLR: RIG-like receptor

27 **Highlights**

- 28
- 29 • The current status on fish oral vaccine development is summarized and discussed
 - 30 • Approaches using novel live vaccine vehicles are discussed
 - 31 • Targeting of M-like cells or antigen presenting cells in the gut is discussed
 - 32 • The use and selection of strong mucosal adjuvants is discussed
 - 33 • The zebrafish as pre-screening animal model for aquaculture species is discussed

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