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Development of novel vaccine strains of *Vibrio cholerae* and studies on the role of serotype in epidemic spread of cholera

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs Universitet, kommer att offentligt försvaras
i hörsal Ivan Östholm, Medicinaregatan 13 Göteborg

fredagen den 17 oktober 2014 kl. 09:00

Stefan Karlsson

Fakultetsopponent
Dr **Sun Nyunt Wai**
Institutionen för molekylärbiologi
Umeå universitet, Umeå.

Avhandlingen baseras på följande delarbeten:

Paper I **Construction of Novel Vaccine Strains of *Vibrio cholerae* Co–expressing the Inaba and Ogawa Serotype Antigens.**
Michael Lebens, Stefan L Karlsson, Susanne Källgård, Margareta Blomquist, Annelie Ekman, Erik Nygren, Jan Holmgren.
Vaccine, 2011. 29(43): p. 7505–13.

Paper II **Development of Stable *Vibrio cholerae* O1 Hikojima Type Vaccine Strains Co–expressing the Inaba and Ogawa Lipopolysaccharide Antigens.**
Stefan L Karlsson, Elisabeth Ax, Erik Nygren, Susanne Källgård, Margareta Blomquist, Annelie Ekman, John Benktander, Jan Holmgren, Michael Lebens.
Published in PLoS ONE 2014–09–28.

Paper III **The evolution of O1 *Vibrio cholerae* during annual cholera outbreaks in an endemic setting.**
Stefan L Karlsson, Nicholas Thomson, Ankur Mutreja, Thomas Connor, Dipika Sur, Mohammad Ali, John Clemens, Gordon Dougan, Jan Holmgren, and Michael Lebens.Submitted.

Paper IV **Non-radom distribution of mutations leading to the Inaba serotype in O1 *Vibrio cholerae* from the El Tor lineage of 7th pandemic.**
Stefan L Karlsson and Michael Lebens
Manuscript.

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Abstract

Cholera, caused by bacterium *Vibrio cholerae* O1, is a severe diarrheal disease with an estimated 3-5 million cases and more than 140 000 deaths every year particularly affecting children under 5 years of age.

It can be found all over the world and often causes cholera in places where access to clean water or proper sanitary facilities are limited or compromised. Typically cholera follows in the wake of natural disasters or man-made catastrophes but it is also endemic in many countries including India and Bangladesh.

Today there are two licensed vaccines available on the market in more than 60 countries. Despite the fact that these vaccines are effective they are both expensive and complicated to manufacture and there is scope and motivation for creating a new cheaper and more effective vaccine against cholera.

First, we have shown that it is possible by genetic manipulation to generate a single strain vaccine expressing two phenotypically different phenotypes and shown that the candidate vaccine strains elicit similar immune responses as the current licensed vaccine Dukoral. This is a huge benefit since it will significantly simplify manufacture and reduce production costs.

Further, we have investigated the naturally occurring Inaba serotype mutants and generated a hypothesis as to why O1 serogroup *Vibrio cholerae* maintains a serotype polymorphism. We have conducted a unique study where we could show that selective pressure on the circulating strains in the environment is almost certainly what is driving serotype transition.

Taken together, results from this thesis show how the use of bioinformatics can be used to target genes and even specific amino acids for mutagenesis in order to modify the phenotype of a vaccine strain and understand the unique and fundamental role of serotype with respect to epidemic and endemic cholera.

Keywords: Cholera, *Vibrio cholerae*, Serotype, Ogawa, Inaba, Hikojima, Vaccine, Immunogenicity, serotype switching, *wbeT*.
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