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Title

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Understanding the Pathogenesis of *Streptococcus iniae* Infection in Fish and
Development of an Effective Vaccine for Use in Aquaculture

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Project Hypotheses

S. iniae infection has emerged as a serious fish health and economic problem in intensive U.S. aquaculture operations. Current antibiotic options are few and possess severe practical limitations and potential adverse environmental impacts. We believe the major factor contributing to the large burden of *S. iniae* disease in aquaculture is the lack of fundamental knowledge of *S. iniae* virulence factors and the fundamental pathogenesis of infection.

Project Goals and Objectives

Our molecular genetic approach to virulence gene discovery and creation of targeted, well-defined attenuated mutants will facilitate rational design and validation of live-attenuated vaccine candidates. These vaccines offer many theoretical advantages including enhanced mucosal immunogenicity and ease of administration.

Briefly describe project methodology

Virulence gene identification and genetic and phenotypic characterization in the full panel of 23 attenuated transposon mutants.

Precise allelic-exchange mutagenesis to completely delete identified virulence genes thus creating ideal vaccine challenge strains.

Use of isogenic mutants as tools to elucidate basic molecular mechanisms of *S. iniae* virulence in vivo and in tissue culture model systems.

Large-scale vaccination trials with selected deletion mutants in HSB.

Describe progress and accomplishments toward meeting goals and objectives

Goals met in a series of seven published manuscripts

Project modifications

Aims were not changed.

Project outcomes

Seven peer-reviewed basic research publications, provisional patent through UCSD.

Impacts of project

Potential Impacts: Aquaculture large industry worldwide with annual production of more than 25 million metric tons of cultured fish and shellfish. The United Nations Food and Agriculture Organization (FAO) has predicted that in the next generation, consumption of fish will increase by 500% and fully 50% of all fish

eaten worldwide will be farm-raised. However, aquaculture operations are currently providing only 15% of the seafood consumed annually in the U.S. In contrast, 60% of consumed seafood is imported, such that seafood imports (\$6.9 billion) represent the second largest component of the U.S. trade deficit, behind only oil and allied petroleum products. These statistics demonstrate that there is enormous potential for growth of the U.S. aquaculture industry based solely on existing national demand. Furthermore, there is little hope for existing commercial fisheries in the U.S. to satisfy this consumer demand as many traditional fisheries are fully exploited or been subject to intense regulation to allow recovery of depleted stocks (Cook et al., 1997). We believe that expansion of land based U.S. aquaculture industry, consisting of both intensive tank and extensive pond-based culture facilities, represents the most cost-effective and ecologically sensitive means to meet the high national demand for seafood products.

Benefits, commercialization and application of project results

The approach to live attenuated vaccination was protected by the UCSD Technology Transfer office in full partnership with KentSeaTech corporation. We discussed the technology with potential commercial partners including major pharmaceutical companies and larger aquaculture/fish health research organizations but were ultimately unsuccessful.

Economic benefits generated by discovery

USDA National Agriculture Statistics Service data (released 1/00) indicate that U.S. aquaculture production of freshwater fish currently consists primarily of catfish (264 million kg), salmon (50 million kg), trout (29 million kg), tilapia (6 million kg), and striped bass (4 million kg). Each species but catfish is known to be susceptible to *S. iniae* meningoencephalitis, but the U.S. tilapia and striped bass industries have been hit the hardest (note: intensive rainbow trout operations in Israel and Europe have suffered similar high mortalities). Striped bass, HSB and tilapia are excellent candidates for use in intensive aquaculture systems. They are adaptable to controlled environments, exhibit rapid growth rates in captivity, accept artificial feeds, have broad physiological tolerances, and have high commercial value. Following the success of KST, more than 100 commercial start-ups of striped bass farms are underway in several states spanning the entire country.

Issue-based forecast capabilities

Conference papers, proceedings, symposia

Colvin K, Patel S, Timmer A, Van Olst JC, Nizet V, Buchanan J. Strain-associated virulence patterns in *Streptococcus iniae* in hybrid striped bass. Abstract B223. ASM Conference on Streptococcal Genetics, St. Malo, France, June 2006.

Buchanan JT, Patel S, Datta A, Nizet V. Capsule plays a significant role in virulence in the aquaculture pathogen *Streptococcus iniae*. Abstract B221. ASM Conference on Streptococcal Genetics, St. Malo, France, June 2006.

Locke, JB, Colvin KM, Vicknair MR, Nizet V, Buchanan JT. Streptolysin S is required for *Streptococcus iniae* infection in fish. Fifth International Symposium on Aquatic Animal Health (ISAAH). San Francisco, CA, September 2006.

Locke JB, Colvin KM, Vicknair MR, Carlberg JM, Nizet V, Buchanan JT. Characterization of *Streptococcus iniae* virulence factors for vaccine development. International Meeting of the World Aquaculture Society. San Antonio, TX, February 2007.

Milani C, Aziz RK, Locke JB, Nizet V, Buchanan JT. Role of PDI, a novel deacetylase homologue, in virulence of the aquatic pathogen *Streptococcus iniae*. Lancefield International Symposium of Streptococci and Streptococcal Diseases, Porto Heli, Greece, June 2008.

Peer-reviewed journal articles or book chapters

Title: *Streptococcus iniae* phosphoglucosyltransferase is a virulence factor and a target for vaccine development.

Authors: Buchanan UT, Stannard JA, Lauth X, Ostland VE, Powell HC, Westerman ME, Nizet V.

Date: October 2005

Journal Name: Infection and Immunity

Issue/Page Numbers: 73:6935-6944.

Title: *Streptococcus iniae* capsule impairs phagocytic clearance and contributes to virulence in fish

Authors: Locke JB, Colvin KM, Datta AK, Patel SK, Naidu NN, Neely MN, Nizet V, Buchanan JT

Date: Feb 2007

Journal Name: Journal of Bacteriology

Issue/Page Numbers: 189:1279-1287.

Title: *Streptococcus iniae* beta-hemolysin streptolysin S is a virulence factor in fish infection.

Authors: Locke JB, Colvin KM, Varki N, Vicknair MR, Nizet V, Buchanan JT

Date: June 2007

Journal Name: Diseases of Aquatic Organisms

Issue/Page Numbers: 76: 17-26.

Title: Strain associated virulence factors of *Streptococcus iniae* in hybrid striped bass

Authors: Buchanan JT, Colvin KM, Vicknair MR, Patel SK, Timmer AM, Nizet V

Date: Sept 2008

Journal Name: Veterinary Microbiology

Issue/Page Numbers: 131:145-153.

Title: *Streptococcus iniae* M protein contributes to virulence in fish and is a target for live-attenuated vaccine development.

Authors: Locke JB, Aziz RK, Vicknair MR, Nizet V, Buchanan JT

Date: July 2008

Journal Name: PLoS One

Issue/Page Numbers: 3:e2824.

Title: The novel polysaccharide deacetylase homologue Pdi contributes to virulence of the aquatic pathogen *Streptococcus iniae*

Authors: Milani CJ, Aziz RK, Locke JB, Dahesh S, Nizet V, Buchanan JT

Date: Feb 2010

Journal Name: Microbiology

Issue/Page Numbers: 156:543-554.

Title: Evaluation of *Streptococcus iniae* killed bacterin and live-attenuated vaccines in hybrid striped bass through injection and bath immersion
Authors: Locke JB, Ostland VE, Vicknair MR, Nizet V, Buchanan JT
Date: March 2010
Journal Name: Diseases of Aquatic Organisms
Issue/Page Numbers: 89:117-123.

Title: Bionformatic and transcriptional analysis of the precerebellin-like (cbnl) genes in zebrafish
Authors: Carland TM, Locke JB, Nizet V, Gerwick L.
Date: 2010
Submitted

Theses, dissertations

Title: Characterization of Virulence Factors of the Aquaculture Pathogen *Streptococcus iniae* (PhD Thesis)
Authors: Jeffrey B. Locke
Schools: UCSD/SIO
Date: 2008

Media coverage

<http://www-csgc.ucsd.edu/NEWSROOM/NEWSRELEASES/grebel.html>
<http://www.thefishsite.com/articles/387/live-vaccine-is-feasible-for-emstrep-iniae-em-control>
http://www.oar.noaa.gov/spotlite/2008/spot_vaccine.html
<http://www.aquafeed.com/read-article.php?id=2274>

Students

Jeffrey B. Locke
UCSD/Scripps Institution of Oceanography
Marine Biology
Degree program enrolled in: Ph.D.
Theses/dissertation title: Characterization of Virulence Factors of the Aquaculture Pathogen *Streptococcus iniae*
Supported by Sea Grant funds? ☒ yes ☐ no

Tristan Carland
UCSD/Scripps Institution of Oceanography
Marine Biology
Degree program enrolled in: Marine Biology
Theses/dissertation title: Pending
Supported by Sea Grant funds? ☒ yes ☐ no

How many students/volunteers were involved in the project? No response

Cooperating organizations

Industry

Kent SeaTech Corporation - throughout entire duration of project. Provided fish and facilities for all in vivo studies and vaccine trials. They are no longer doing fish farming research, but rather alternative fuel studies with algae.

Keywords

Fish health, bacterial infections, *Streptococcus iniae*, virulence factor, vaccine, aquaculture, striped bass