

**KHV Vaccine Development World Wide**  
**A status report by the Project KHV team**  
November 2006

Seven groups (world wide) are reported to be working on KHV vaccines: Hebrew-University-Hadassah Medical School in Israel; Henderson Morley of Brittan, North Carolina State University-College of Veterinary Medicine, University of Georgia, the Mie University and the Tokyo University of Marine Science and Technology in Japan, and Novartis in Canada.

The techniques being pursued include killed virus, attenuated live virus and DNA, and delivery methods range from oral preparations to immersion and injection. Hopefully some of these projects will be successful and we will have several usable vaccines in the not too distant future. Even one would be nice.

The problems that face the vaccine developers are many. The two biggies are technical and regulatory. The challenge of developing and producing an effective vaccine is only the beginning. Once developed, there are government approvals to be reckoned with and these can be every bit as challenging as the development. Typically, government regulations have two important aspects: safety and effectiveness.

A killed virus vaccine is typically the least expensive and quickest to develop. And with regard to safety, a killed vaccine must prove that the virus is, in fact, killed/inactivated and therefore not capable of infecting fish as well as demonstrate the vaccine and/or its adjuvant (stuff that enhances the desired reaction to the vaccine) does not precipitate an unfavorable immune response. Killed vaccines are relatively inexpensive to produce, but they may not trigger the most effective antiviral immune response.

A modified live virus is generally the next least expensive to develop and typically takes the next longest time to develop. It is, however frequently the most effective in producing a strong, long lasting effect. The rub with modified live virus vaccines comes in proving they are safe, i.e., proving that the modified virus will not revert to the form that can produce the disease. Proving safety is reported to be a real bear on this type! Additionally, keeping the vaccine "alive" until it's administered adds another layer of complexity and expense to a final product.

DNA vaccines are generally considered to be the vaccines of the future. A portion of the viral DNA (gene) is incorporated into plasmids and introduced into the host, in this case our koi or food carp. Once in the host, the viral DNA is incorporated into the host DNA. The theory is the host (carp) then manufactures the antigenic proteins of the viral coat resulting in a protective antibody response to the virus. Since only the viral gene(s) are injected rather than the whole virus, there is safety regarding potential spread of disease. Unfortunately, not all DNA vaccines work to protect the host from viral disease.

There is an ongoing debate regarding the safety of DNA vaccines. Major concerns with regards to safety are that 1) the viral DNA may interrupt the fish cell DNA and produce some disease, or 2) that the DNA may trigger an aberrant immune response in the fish that might be harmful. In regards to food animals, there are concerns that the vaccine DNA might end up in other bacteria

where it could be transferred to non-target plants and animals. Debate and controversy regarding regulation and licensing of DNA based immunization continues.

Once developed, DNA vaccines are typically the least expensive to produce, but the regulatory process is essentially uncharted waters at this point as there are currently precious few DNA vaccines and that makes this part of the equation a large unknown.

Information reported about the specific groups working on KHV vaccine development is as follows:

#### Israel:

Kovax, has been testing a modified live vaccine (developed by Perelberg, Kotler and others at the Hebrew-University-Hadassah Medical School) for two years and now has it approved for use within Israel. They report having vaccinated about 7 million carp within Israel in the year 2005 with very acceptable protection rates for both immersion and injection vaccinations. There are also reports that they are trying to obtain approval to sell the vaccine outside Israel. We suspect the Israeli effort is ahead of the others contenders.

#### United Kingdom:

In October of this year, Henderson Morley plc, a UK pharmaceutical company, announced it has been working on a vaccine against Koi Carp Herpes virus for the past 10 months and is now ready to start field trials of a candidate vaccine in a collaboration with Hagerman Aquaculture Research Institute in Idaho under the supervision of the Institute Director, Professor Ron Hardy. The report did not mention the type of vaccine nor the method of delivery.

#### United States:

A University of North Carolina State University, College of Veterinary Medicine team lead by Drs. Levine and Shivappa report they have two candidate DNA vaccines ready for initial efficacy testing. In 2005 Project KHV agreed to fund this vaccine research. After sending a first payment, they received money from a federal grant that also covered their work on KHV vaccine. They returned the money. So the work goes on and the money is back in the fund, a good/good result.

In 2004, a funding effort by NAWGS and Dr. Erik Johnson reportedly raised over \$50,000 for Dr. Branson Ritchie's KHV vaccine efforts at the Univ. of GA. We have no information on what the status of that work is. We do know that a year or so ago, the group inadvertently developed a strain of KHV that would not reliably infect and kill fish, i.e., an attenuated virus.

#### Japan:

In May of 2005 a press release reported that Tetsuro Yoshimura and Teruo Miyazaki at Mie University in Japan had developed an oral vaccine for KHV. The team gave koi feed incorporating a KHV liposome vaccine. The oral administration of vaccine resulted in antibodies five to 25 times greater than the usual levels. Compared with conventional methods of injecting vaccines, the newly developed method requires less time and work. The research team plans to mass-produce the oral vaccine and conduct a large-scale experiment to obtain authorization from the Ministry of Agriculture, Forestry and Fisheries and other related ministries.

We have no specific information on the vaccine development reportedly underway at the Tokyo University of Marine Science and Technology and associated with Dr. T. Aoki. It was this group that was the first to completely sequenced the KHV genome.

Canada:

In a March 2006 press release, the government of Canada announced that, Novartis is developing an immunization strategy for the prevention of koi herpesvirus... While preventing KHV in koi carp is a priority for hobbyists and sellers to protect the breeding, export, wholesale and retail markets, the control of the disease will reduce the risk of infection in the food carp industry which is of great importance in developing nations. This project, with total estimated costs of \$2.5 million, will receive up to \$1.8 million from the Atlantic Innovation Fund over a five-year period.

Additionally, Novartis has acquired rights to a patent covering the use of DNA vaccines in fish and also to another patent covering a unique delivery methodology.

Project KHV sees all the work in KHV vaccines as extremely encouraging and believes the “push” in the vaccine area is logical for two major reasons: a) it is almost undoubtedly the best hope for effective control and possible eradication of the disease and b) it is the area most likely to produce good profits for any group that develops a successful vaccine.

Therefore we at Project KHV have concluded that while we will certainly continue tracking the progress of the various vaccine developments and will try to be helpful when and where we can, we will now concentrate our efforts elsewhere. We will pursue projects in areas that are also very important to the prevention and control of the disease but which are not nearly so likely to produce the return on investment that vaccines promise. These other areas include:

- Education - prevention and control
- Epidemiology (studying how the disease spreads)
- Etiology (or aetiology in the U.K. <grin>) – studying how the virus causes the disease
- Testing – better, safer, easier, cheaper and less invasive

We see progress in these areas as critical to our stated goals of near-term prevention and control and the longer-term eradication of the disease.

Toward this end we have funded a Phase 1 project that focuses on the education of koi dealers and hobbyists. It intends to prepare and deliver educational materials on prevention and control of the disease. This will be done in several ways (see:

<http://www.akcaprojectkhv.org/updatejune06.htm>) :

1. Regional presentations
2. Presentations at technical and trade meetings
3. Web-based information
4. Free printed and electronic information

The Phase 1 grant group is scheduled to start its public education efforts in March of 2007. Watch the Project KHV web site for a schedule. See: <http://www.akcaprojectkhv.org/> .

Recently we released an updated fact sheet on KHV that was primarily the result of a literature survey and provides what is currently known, what is unknown and a brief but current best practices for preventing the disease. See: <http://www.akcaprojectkhv.org/KHVfactsheet-final.pdf>

Additionally we are soliciting and otherwise seeking projects that enhance our educational efforts, e.g., a Best Health Practices Certification program for koi retailers (see: <http://www.akcaprojectkhv.org/RFP-BHPC-KoiRetailers.pdf>). We are also seeking proposals in the other areas, e.g., the study of where the virus persists when it's not causing disease (latency and/or environmental persistence).

It's not easy to find good, targeted programs to support. To date we have funded two requests but have turned down several others. We have our eyes on the goals and are working hard to make sure we get a reasonable bang for the buck. We are making progress but it's certainly not time to let up. We need to build our fund so when we find projects that meet our criteria, we'll have the money to pursue them.

You know the drill. If you leave it up to someone else, it won't get done. So please send us a check today. We will thank you in advance and we'll keep working hard to make it happen and to keep you updated.

Make checks payable to AKCA Project KHV.

Send contributions to:

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