A Biomarker Beauty Contest

HBF Princeton Workshop Focuses on Early Detection of Liver Cancer

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Princeton, NJ

The "war against cancer" has made huge strides forward in the past several decades, with an overall decrease in cancer rates. Long-term survival has dramatically improved as the result of earlier diagnosis and better treatment options. But for primary liver cancer – known as hepatocellular carcinoma (HCC) – progress has been limited and the prognosis remains grim.

According to the National Cancer Institute, primary liver cancer has become the fastest growing cancer in the U.S., and the numbers are expected to rise even more in the next 20 years, due to surging cases of chronic hepatitis B and C infections. Liver cancer is currently the fifth most common cancer in the world, and ranks eighth among leading causes of cancer death for Americans.

If only, many experts say, there was a good way to find the cancer early enough to effectively treat it. With this in mind, the Hepatitis B Foundation (HBF) strayed from tradition and partnered with the National Cancer Institute's Early Detection Research Network (EDRN) for this year's 12th Annual Princeton Workshop, held October 24-25, 2006 in Princeton, NJ, to focus on an urgent unmet need – identification and development of biomarkers for the early detection of liver cancer, the most fatal complication of chronic hepatitis B infections.

Need for Biomarkers

This year 30 thought leaders from academe, industry and government participated in the HBF workshop to review and debate eight liver cancer biomarkers in the research pipeline, and make recommendations about which seemed the most promising to reach the clinic. Participants unanimously agreed that alternative, non-invasive markers need to be developed for the early detection of liver cancer. Currently, a painful liver biopsy is the standard method for diagnosis.

"The ideal biomarker would be used in a blood test that could predict who has liver cancer or is at high risk," said **Robert Gish**, **M.D.**, medical director of the Liver Transplant Program at California Pacific Medical Center in San Francisco. "It could also be used to determine both an individual's risk of recurrence or treatment response."

According to **Paul Wagner**, **Ph.D.**, program director of the National Cancer Institute's Cancer Biomarkers Research Group, the difficulty in finding sound biomarkers is not peculiar to liver cancer. "It's easy to find a marker in the blood that is increased in half of the individuals with a certain cancer, but very difficult to find such a marker in all people with that cancer," he said. "A challenge is to find a marker that picks up most people with cancer but doesn't give a lot of false positives."

For decades, the most widely used biochemical blood test for liver cancer has been alpha-fetoprotein (AFP), which is a protein normally made by the immature liver cells in the fetus. Yet, this test is controversial because it is not highly sensitive or specific enough for liver cancer. "AFP is often elevated because of liver injury or regeneration, and doesn't necessarily indicate the presence or absence of liver cancer," Gish said, though it might be useful in detecting an increased risk.

Most Promising Biomarkers

Of the eight biomarkers discussed at the workshop, several stood out as most promising. Elevated levels of the biomarker, **AFP (L3)**, or fucosylated AFP, a slightly different version of AFP, is a sign of heightened risk of developing liver cancer, for example, said Gish. For those with liver cancer and elevated AFP (L3), the chance of recurrence is higher. He termed AFP (L3) "a small, promising step forward in predicting risk and recurrence that needs further testing in trials."

DCP (des-gamma-carboxy prothrombin), an abnormal protein apparently made by cancer cells, is another promising biomarker. Workshop attendee **Jorge Marrero**, **M.D.**, at the University of Michigan, is working with a company, Wako Diagnostics, in Richmond, VA, to develop a panel of biomarkers that includes DCP.

GP73 (a golgi protein marker) and its fucosylated form – discovered by **Timothy Block** , **Ph.D.** and **Anand Mehta**, **D.Phil.** (HBF and Drexel U.) – was found to correlate with a diagnosis of liver cancer, even if the standard AFP test is negative. Continuing with a "glycosylation" theme, **glypican** and **glyco-cirrhosis** are biomarkers that show great promise. In addition, viral mutant and HBV-induced host gene markers that are in the research pipeline were also discussed.

Large-scale validation studies for a number of liver cancer biomarkers, including DCP and AFP (L3), are being organized by the National Cancer Institute's EDRN. Studies will compare the use of these biomarkers in 450 patients with liver cancer, and 450 patients with cirrhosis as controls, to see which works best in identifying cancer. Biomarkers that are deemed more useful than the standard AFP would be tested in prospective screening trials.

"We want to able to say to patients who come in for screening, 'This biomarker is increased, and although we can't confirm anything by ultrasound, we think it's very likely that you have liver cancer,'" said Wagner. "That would be the next step if our markers look good in our validation study."

Looking Forward

Primary liver cancer, of which 80% is caused by chronic hepatitis B, is a growing public health problem and workshop participants agree that early detection is important for its effective management. Current methods, however, are very limited in usefulness or practicality. The high mortality associated with liver cancer - because by the time it is diagnosed, it is often unresponsive to treatment – makes the development of biomarkers an urgent unmet need. With the current five year survival rate of liver cancer less than 5%, early detection biomarkers would certainly save lives.

About the Princeton Workshop

Sponsored by the Hepatitis B Foundation

In 1995, the Hepatitis B Foundation initiated a novel concept – to host a meeting that would bring together in one room a small group of the world's thought leaders from academe, industry and government for highly focused roundtable discussions of new and innovative therapeutic strategies for chronic hepatitis B.

Today, the prestigious *Princeton Workshop* serves an important role in promoting

international scientific exchange and collaborations dedicated to the problem of hepatitis B. Despite the crowded scientific conference schedule, the *Princeton Workshop* continues to draw leaders in the field because of its small size and unique format.

"Some of the most influential leaders in the field are invited to our workshop, which has minimal structure, allowing for a vigorous exchange of ideas," said Dr. Timothy Block, HBF co-founder and president. "It's unique from all other scientific meetings because it encourages interactive discussion at a level that is unprecedented, and fosters new relationships and research collaborations that would not occur otherwise."

And new research directions, Block added. For example, the list of HBV Research Priorities identified at the 2000 Princeton Workshop were part of the National Institutes of Health first 10-Year Liver Disease Action Plan, published in 2004.

"What makes the meeting special is that it always combines basic scientists and academics with those in the pharmaceutical industry who actually make the drugs," said W. Thomas London, M.D., senior scientist at the Fox Chase Cancer Center in Philadelphia, PA. Because there are no formal workshop proceedings published, pharmaceutical executives can freely discuss – up to a point – what they are working on.

The Princeton Workshop is held annually, and now alternates between Princeton, NJ and Hawaii, in conjunction with the larger HepDART meeting. The meeting is by invitation only and expenses are covered by the HBF.