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Hepatitis Experts Create Roadmap for Accelerating the Development of Targeted Therapies for Hepatitis C Virus

WASHINGTON, DC (December 14, 2010) – To improve the care for individuals infected with the hepatitis C virus, a major health problem and a leading cause of chronic liver disease around the world, nearly 200 international hepatitis experts have taken an important step in escalating the introduction of a new class of targeted therapies for HCV -- direct-acting antivirals (DAAs).

Meeting December 6 at a major scientific meeting -- *Advancing HCV Drug Development: A Collaborative Approach* -- convened by the Forum for Collaborative HIV Research, researchers, hepatitis advocates, members of industry and representatives from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) created the roadmap for accelerating the development of DAAs, agreeing that this new class of drugs targeting specific hepatitis C virus proteins has the same potential to improve treatment outcomes for people with HCV as antiretroviral drugs changed the standard of care in HIV. Currently, two DAA compounds have advanced into phase 3 development in the United State and EU, and many more are in phase 2 trials and likely to advance to the phase 3 research phase in the near future.

"If there was ever a time when we can change the course of HCV, it is now," said Veronica Miller, Ph.D., Director of the Forum. "We are now where we were with HIV more than a decade ago and can apply many of the lessons learned from HIV drug development to significantly accelerate the progress in bringing new and better HCV therapies to market."

DAAs directly attack the ability of the hepatitis C virus to replicate and can increase the cure rate in certain HCV patients to between 60 and 70 percent– a major advance over the 40 percent success rate associated with the currently recommended treatment for chronic HCV infection, the combination of pegylated interferon and ribavirin. Although the first DAAs still require concomitant use with current HCV medications, these new compounds will shorten the length of time on pegylated interferon and ribavirin therapy, which hepatitis specialists noted is often difficult to tolerate and has significant adverse event profiles that limit treatment in many patients. According to the latest data, between 15 and 30 percent of HCV patients started on current HCV therapy are unable to complete the year of treatment now required because they cannot tolerate the side effects.

Charting the future of HCV drug development, the meeting participants applied FDA's new guidance on conducting clinical trials on DAAs, which was issued in September 2010 in draft form and expected to be finalized in 2011. According to Jeffrey S. Murray, M.D., M.P.H., Deputy Director of the Division of Antiviral Drug Products in FDA's Center for Drug Evaluation and Research, the draft guidance follows the same approach FDA uses in developing HIV and oncology drugs. For early clinical testing, FDA recognizes that most if not all DAAs for HCV will be used in combination with other approved drug and therefore, recommends

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studies examining the relationship between the new DAA agent and both pegylated interferon and ribavirin as well as testing the combination antiviral activity. FDA's draft guidance also calls for using the results from proof-in-concept trials (meaning a study in HCV infected patients that demonstrates initial activity as measured by reductions in the HCV viral load) to guide dose selection for subsequent Phase 2 trials in which DAAs are studied for longer durations as part of a combination regimen. FDA is further encouraging drug sponsors to design development plans for combinations of two or more DAAs.

"The good news for the HCV community is that more drugs are coming," said Jur Strobos, MD, JD, FACEP, Deputy Director of the Forum. "The bad news is we don't know how to combine them and that is what we need to study."

With FDA's guidance as the framework, the hepatitis experts also identified the major factors researchers must take into account when designing clinical trials for DAAs and other new HCV therapies. Among the major issues cited are the emergence of resistant virus and its potential management, and including in future DAA clinical trials those special populations with significant unmet needs in HCV therapy. These patients include individuals co-infected with HIV, liver transplant recipients, patients with decompensated cirrhosis, opioid users and those on opiate substitution therapy, and children. According to the Centers for Disease Control and Prevention (CDC), between 5 and 6 percent of infants born to HCV infected women contract the infection from their mothers and the majority of those infants will develop a chronic infection.

Focusing on the special needs of pediatric patients, leaders from both FDA and EMA agreed that the time to start investigating DAAs in children is when sufficient safety data exist in adults. As explained by specialists in pediatric liver disease, children with HCV often tolerate drug therapy better than adults, which is why the ideal age to start children in pediatric trials for DAAs is when they are 3 years old. According to hepatitis experts, the beneficial impact of a 'cure' for children, preferably before they start school, cannot be overestimated.

Reducing Disparities in HCV Clinical Trials

Because identifying potential differences among groups treated with a therapeutic regimen is an important goal of human studies, the HCV community singled out the under-representation of women, older people and different ethnic subgroups in clinical trials as the problem requiring immediate attention and change at a systemic level. Although there is a higher prevalence of HCV in men than women, women metabolize HCV drugs differently and are more affected by autoimmune diseases, which share similar symptoms with HCV. Women also are twice as likely as men to suffer from depression, which is a common side effect of treatment with HCV medications.

Even more challenging for the HCV community is increasing the representation of older HCV-infected adults in HCV clinical trials, even though Baby Boomers constitute the majority of hepatitis C infections in the United States and are often less responsive than younger generations to antiviral treatment. Compounding the problem, older HCV patients are more difficult to treat, due to the increased prevalence of co-morbid conditions, such as diabetes, dyslipidemia, and other metabolic conditions that are correlated to chronic liver disease. Aging is also strongly associated with liver fibrosis progression, which means older HCV patients are likely to have advanced liver disease and a high risk for impending liver complications. But despite this reality, few studies have examined the

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age-specific factors of chronic HCV infection and the clinical management of the infection in this patient population.

More than an issue of fairness, HCV experts associate better designed clinical research studies with the increased ability of scientists to catalog and understand the influence of genetic and non-genetic factors on individual and group responses to new treatments. Findings from the large amount of genetic data generated to date show that more than 90 percent of the observed genetic variations occur within, rather than between groups. This underscores the fact that gender and ethnicity have biomedical consequences when evaluating patients with more resistant virus and with more severe disease.

Designing the Research Roadmap to Address a Growing Public Health Threat

Accelerating the development of DAAs to improve HCV treatment outcomes is especially warranted now that the hepatitis C virus has become the most common chronic blood borne infection in the U.S. According to new government estimates, approximately 4.1 million Americans are infected with HCV, of whom 60 to 70 percent will develop chronic liver disease. Currently, almost half of all liver transplants in the U.S. are performed for end-stage hepatitis C. Moreover, because liver disease is one of the leading causes of death in the U.S., the CDC predicts that deaths from chronic liver disease attributed to hepatitis C will double or triple over the next 15 to 20 years.

To change these statistics, hepatitis specialists focused on ways to advance HCV drug development so DAAs and other new classes of drugs for HCV can reach the market quickly. Here, the experts reached agreement on a number of issues:

- Exposure to new single agents – because HCV remains sensitive to ribavirin and pegylated interferon, longer initial studies may be recommended to evaluate single drugs and novel combinations of drugs
- Composition of patients in early studies (phase 1 and 2a) – early studies should be large enough so results with one type of virus or one group of patients can be easily discerned. Focusing on specific genetic sub-populations will also ensure that early studies do not produce confusing results
- Drug resistance in HCV patients – unlike HIV, drug resistance in HCV may not be as large a concern because HCV does not integrate into host DNA as HIV does. Thus, resistant strains are not archived and there is the potential that resistant patients can be retreated with different combinations regimens, as and when they become available
- Baseline parameters – there is the need to develop predictive algorithms based on baseline characteristics such as gender, body weight, HCV genotypes and subtypes
- Exclusion of former and current drug users in clinical trials – exclusion is unnecessary and does not serve the field well. Over 60 percent of patients with HCV are infected through drug use, indicating the need to have quality data to guide treatment decisions in this patient population

As a next step, the Forum for Collaborative HIV Research will publish the consensus of this scientific meeting to advance the research agenda. Once published, the report will be distributed widely to the Forum's many constituencies -- government, industry, patient advocates, healthcare providers, foundations, health insurers and academia -- with the goal of advancing research on HCV and driving public policy.

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About the Forum for Collaborative HIV Research

Now part of the University of California (UC), Berkeley School of Public Health and based in Washington, DC, the Forum was founded in 1997 as the outgrowth of a White House initiative which called for an ongoing collaboration among stakeholders to address emerging issues in HIV/AIDS and set the research strategy. Representing government, industry, patient advocates, healthcare providers, foundations and academia, the Forum is a public/private partnership that is guided by an Executive Committee that sets the research agenda. The Forum organizes roundtables and issues reports on a range of global HIV/AIDS issues, including treatment-related toxicities, immune-based therapies, health services research, co-infections, prevention, and the transference of research results into care. Forum recommendations have changed how clinical trials are conducted, accelerated the delivery of new classes of drugs, heightened awareness of TB/HIV co-infection, and helped to spur national momentum toward universal testing for HIV. http:// www.hivforum.org

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