HBV Forum 4
Novotel Paris Pont de Sevres Hotel
Summary Report
April 12th, 2018

Welcoming Remarks

Welcome by Veronica Miller and Bill Symonds

Slides: Welcoming Remarks

Presenter: Pedro Goicochea, Forum for Collaborative Research

- The HBV Forum has changed the structure a little bit since HBV Forum 3 due to new themes and topics of interest. There are now two working groups: Surrogate Endpoints and Treatment Combinations. The previously active diagnostics working group is now integrated into the Surrogate Endpoints working group. The treatment combination working group includes the newly formed sub-working group for liver safety monitoring, chaired by Maria Beumont and Robert Fontana.
- We thank the Steering Committee for their continued expert leadership (for members, see slide 6).
- Achievements of the HBV Forum:
    - We are continuing on a collaboration with Janssen on a literature review on HBsAg loss and long-term clinical outcomes.
    - We have a protocol in place for patient level data on HBsAg loss and long-term clinical outcomes in collaboration with Bettina Hansen at the University of Toronto.
    - The treatment combination working group finalized their manuscript: "Combination Drug Trials of Novel Therapies for the Treatment of Chronic Hepatitis B"; it is under review in Gastroenterology (updated since HBV Forum 4).
    - The liver safety monitoring subgroup is working on a manuscript to provide recommendations on liver safety assessment in HBV drug development.

Roadmap on HBV @ EASL 2018

Slides: HBV Roadmap Update from Recent and EASL Presentations

Presenter: Robert Gish, Stanford University, Robert Gish Consultants LLC

- Most current estimates are that ~264 million people with hepatitis B are sAg positive.
- 2 billion people in the world who have residual hepatitis B in their liver in the form of cccDNA.
- Three-dose vaccination programs only running in the 80%.
- Timely birth dose: some countries are as high as 70%, while others are as low as 3%.
- Post-exposure prophylaxis and full-vaccination and hepatitis treatment of mothers who have hepatitis B has been below 10%.
- PCR testing with GeneXpert from Cepheid in developing countries costs $18. It takes 20 minutes to receive quantitative RNA results for HBV/HCV.

- Homie Razavi has a project in 5 countries in Africa where a patient with a positive sAg point-of-care test will be put on a nucs indefinitely.
- Linkage to care including doing all three tests for hepatitis B, staging level of liver disease, then linking patients to HCC surveillance is another priority to be considered for treating all sAg positive patients.
- It is likely that capsid inhibitors will be a sofosbuvir metaphor for hepatitis B.
- There is a GLP compound out of Emory Lab that inhibits HBV DNA replication, eAg secretion, and reduces cccDNA as active in primary human hepatocytes.
- This will not be a single-drug process. What's so interesting is seeing the presentation from Thomas Michler today, looking at combination of the Theravac B and their RNAi therapy.
- sAg loss is the next milestone because of the dollars and energy involved in new drug development. 20% sAg loss at less than a year would be a threshold to be bringing a therapy into phase 3 studies.
- As prices have fallen for hepatitis C therapies, a massive number of patients are now being treated, and pharma and the investment community really needs to be looking how they're going to be pricing and how they're going to get it to the largest number of patients quickly.
- Endpoints: we've heard a huge amount about at this meeting, and the RNA and core-related antigen are tests that I should be followed very closely.
- The world should be focusing on getting a birth dose vaccine to every baby in less than 12 hours. If we could make this a global effort to get a birth dose vaccine, HBIG and nucs may be much less important.

HBV Cure Initiatives in the AIDS Clinical Trials Group (ACTG)

Slides: Advancing the Hepatitis B Virus Cure Research Agenda

Presenter: Mark Sulkowski, Johns Hopkins University

- If you look at the mission statement for the ACTG, which is funded by NIAID, it's to cure HIV infection, reduce the burden and its complications, and it specifically notes TB and viral hepatitis. Obviously, hepatitis B falls into this agenda.
- There are a wide range of clinical trial sites that have already had agreements with the NIH to conduct this work and a lot of infrastructure already built worldwide.
- So how does it work? In general, we start with an idea for a protocol. This is a collaborative effort typically between industry, since one thing the network does not have is drugs, and a concept proposal is put forward. It undergoes a rigorous scientific review, initially with the Hepatitis Transformative Science Group. If it's approved for development, that's essentially akin to being funded. The development goes forward with a lot of oversight and regulatory help. Then it goes to the sites, and every site has the option to participate (including international sites). In addition, it provides the ability to access stored data, both biospecimens and clinical specimens.
- I wanted to highlight this New Works Concept Sheet initiative where stored specimens from studies of nucleotide analogues are being pulled to test for sAg, HBV RNA, and core-related antigen. It's an example of bringing forward some specimens that are now several years old, linked to a clinical database, and we hope to get some insights from the data produced over the next six months.
- The hepatitis B-focused studies (ongoing or in development):
    - A5368: This is a safety, PK, and immunotherapeutic activity of an anti PD-1 antibody in HBV-infected participants who are on suppressive therapy to further examine the idea of checkpoint inhibition in the hepatitis B cure agenda.

    - A5379: The second is going to take the HEPLISAV-B vaccine and test it in HIV-infected patients, a key group that was not assessed in the registration of this particular vaccination strategy.
    - PR754: A randomized controlled trial of the nucleic acid polymer REP 2139. The strategy is to assess this agent in combination with a nucleotide analogue, and with or without interferon.
- The AIDS Clinical Trials Group has really pivoted to focus on hepatitis B cure, an important problem among HIV-infected patients. Roughly 9% are coinfected with hepatitis B, and this group has a history of pushing the envelope forward in mono-infected patients as a tool to get advanced therapeutics.
    - It's a collaborative hepatitis B research model from an NIH grant that is currently funded through 2020 and will be recompeted; hepatitis B will be an important part of the recompetition. The site costs and much of the protocol development is covered by the ACTG Network.

Effects on Combination Therapy on Achieving Cure

Slides: Effect on Combination Therapy on Achieving Cure

Presenter: Barbara Testoni, INSERM

- Complete sterilizing cure nor complete cure where only integration and cccDNA elimination are not likely achievable in the very near future. We are currently struggling to achieve partial functional cure, and to make improvements with HBsAg decline, significant decline, and HBsAg loss.
- cccDNA is the key molecule of the HBV replication-cycle. It is an extremely stable mini chromosome associated with histamines and is epigenetically regulated. It is the only template for the pregenomic RNA, the source of the circular DNA, which is then encapsulated and forms an infective variance which goes in the serum of patients.
- Entry and egress inhibitors and polymerase/RNAseH inhibitors among the current standard of treatment. Additionally core inhibitors, RNA interference, and agents targeting directly cccDNA are available.
    - Myrcludex and the NAPs are very interesting because they could be very useful in the HBV/HDV co-infected patients, and can be combined with other drugs.
    - The Replicor phase 2 study produced some very exciting data: declines of HBV DNA and HBsAg in serum when the NAPs was added to tenofovir, and also, an incredible anti-HBsAg seroconversion.
        - Challenges: mainly, the administration and the safety profile of Myrcludex and increased bile salts in the liver. ALT exacerbation with NAPs, and also the fact that the mode of action is still not know.
    - Capsid assembly inhibitors interfere with the assembly of the HBV core protein in different ways. When they are administered before or concomitant to the viral infection, they affect cccDNA establishment, but not when they are administrated once the infection is already established.
        - There was a Janssen phase 1b study of JNJ-6379presented this morning.
        - An Arbutus study of Entecavir in combination with an RNAi compound showed a nice decline in serum HBV DNA and HBsAg inter-dynamically in injected mice.
    - These compounds are really very interesting because they could decrease the pool of cccDNA in the long term. They are administered orally, and they can be combined with other compounds (i.e. peg-interferon)

    - What about cccDNA targeting and cccDNA activity? RNA interference has raised a lot of interest.
        - The most famous is the Arrowhead study where they demonstrated that according to the siRNA target sequence, you have a different effect in HBsAg positive versus HBsAg negative patients. A very nice HBsAg decline in positive patients, but less promising results in HBsAg negative patients. This was due to the fact that in HBsAg negative patients most of the sAg derives from the integrated forms, and not on cccDNA. The siRNA that was used in the study was designed exactly in the breakpoint of integration of sAg.
        - Another preclinical study in uPA/SCID dehumanized mice using the Roche molecule, which is not RNAi approach, but it is targeting the transcription and activity of cccDNA. It seems that this molecule is able to inhibit sAg transcription specifically versus pregenomic and pre-core transcription in mono therapy. The data on combination with interferon and entecavir are really striking: a strong decrease of viral DNA, sAg and core protein to a lesser extent.
    - What are the pros of these compounds? The decrease of HBsAg in the serum, and the opportunity to be combined with other antiviral agents and immunotherapeutic approaches. The challenges are that the delivery of these compounds is mainly intravenous, the long-term safety profiles, and the fact that they have to cope with the integrated sequences.
- It's clear that monotherapy will not achieve a cure, and that we will need combination of therapies. The question is which combination, which molecules, how many of them, and the timing of administration. Of course, the direct targeting of cccDNA remains a priority in the development of new drugs.

Modelling Kinetics of HBV DNA and Recommendations for Moving Forward

Slides: Modeling Kinetics of HBV Infection and Recommendations for Moving Forward

Presenter: Alan Perelson, Los Alamos National Laboratory

- There's a long history of modeling in HBV. It started in the mid-1990s with this first paper published in PNAS from Howard Thomas and Martin Nowak in 1996. It was based on what we saw with Lamivudine therapy, which in this paper they assumed was 100% effective and estimated the lifespan of affected hepatocytes somewhere between 10 and 100 days. The next real breakthrough came from a Gilead group where they were looking at the kinetics of adefovir therapy. They used a model that I had developed with colleagues for hepatitis C which we call a standard model of viral dynamics. The idea is that you have free viral particles, they interact with target cells in hepatocytes that lead to infected cells which produce more virus.
- Compounds that we have are only partially effective, and we measure that effectiveness with a parameter we called epsilon for effectiveness.
    - What we see (slide 5) is a biphasic decline. There is a first phase where the viral load, at least for hepatitis C, falls very rapidly. A drug that is 90% effective reduces the viral production to 10%.
    - What the model predicts is you would observe a one log decrease, and the rate has to do with how fast the virus can be cleared from a serum once you're blocking its production.
    - So infected cells are not effectively replaced, and what that implies is that we start seeing a much slower decline as these infected cells are dying off. There is a positive feedback effect because there is less viral load and therefore less opportunity for the

reinfection. This slope reflects lifespan of the infected cells, and we have a death rate, something we call delta, here.
    - We can apply the same thing to hepatitis B, and that was done by Manuel Tsiang (Hepatology 1999), and this paper with George Lau (Hepatology 2000) with looking at the effectiveness of Lamivudine along with Lamivudine/Famciclovir.
- Models started including cell proliferation, which gave rise to slightly better fits in some of these examples. Others were involved in acute infection models, trying to understand how the hepatitis B can be cleared during acute infection.
    - Here's a recent paper (Goyal et al., Viruses 2017) where we looked at the role of cell proliferation in terms of the loss of cccDNA. In another (Ciupe et al., PLoS Computational Biology 2014), we examined the effects of antibody responses during our reinfection.
    - Another paper that we published in *PNAS* (Ciupe et al., 2007): we looked at the potential role of cell-mediated immune responses in clearing infection. Basically, what we were interested in is if one looks at infection kinetics, viral load comes up, hits a peak, and starts coming down.
        - Focusing on the places where the viral load measurement is equivalent, the idea was when viral load is going up the infection is uncontrolled. When viral load is coming down, even though you observe the same measurement, the immune system's in a different state. Therefore, it's either preventing infection by antibody responses or it may be generating some sort of refractory state where cells can't become reinfected again very efficiently.
- What about the new agents? What can we do with modeling?
    - Stephan Urban, who you all know is one of the inventors of myrcludex B, presented some data in 2015; a phase 2a clinical trial that has still not been published, where they treated chronically infected HBV patients with myrcludex B. The data for the 10 mg group shows something that looks like biphasic decay.
        - We fit the data extremely well. We can fit the ALT data reasonably well. What's interesting about this model is it postulates that there are two classes of cells that can get infected.
        - Does that have any relevance at all to HBV? There's been recent data trying to show heterogeneity of lymphocytes. Halpern et al. published in *Nature* (2017) with data from both a single molecule FISH and RNA-seq on single cells within the liver. Rather than the standard picture of having a central venule and a transition zone, a periportal zone, they actually found, looking at gene expression patterns, that there were nine distinct zones. Nine distinct sets of gene expression patterns in the liver as you went from a periportal to the central vein.
    - What we discovered is that the simple standard models, say, for HCV don't capture all the kinetics observed with DAAs and combinations of DAAs.
        - We found that in order to explain the very, very fast kinetics that we see with NS5A inhibitors, we needed to develop what we call a multi-scale model. That is, instead of talking about just cells being infected, we really needed to start having cartoon pictures of the actual replication process.
        - Slide 16 shows a model following genomic RNA within a cell. We say the genomic RNA is being produced from a negative strand template, that RNA can get degraded, and the RNA can be packaged and assembled in virions and then secreted.
            - The insight was that we realized the drugs could act at any of these three stages. They could block replication. They can block encapsidation and secretion. They could influence the rates of degradation.

        - What we postulated based on looking at clinical data with very frequent sampling, sending dose study for the NS5A inhibited daclatasvir, was that the compound had a very high effectiveness in blocking replication, but it also had a very high effectiveness in blocking assembly and secretion. We validated that in a cell culture system model.
    - It seemed to me that we can do the same type of modeling for capsid inhibitors. The pregenomic RNA will be produced off of a template to be assembled and secreted, and the rate of production of cccDNA is relatively constant. If you have drugs that could act in both of these ways, we may be able to quantify what the effectiveness of the drugs are in various steps by clinical data.
    - Age-structured models allow us to keep track of how long cells were infected, and put in possible kinetics of cccDNA, both its replication and its increase and its possible decrease, especially if we have proliferation.
- Slide 19 shows data from a patient that was treated with the Arbutus siRNA. What was interesting to me about this patient, who responded the best from a cohort of 10, was that the sAg in this patient declined almost linearly on a log scale. It drops 2.4 logs in seven weeks, and if we estimate the half-life of the surface antigen to be 6.1 days.
    - That resonated with me because what we predicted in interferon-treated HCV was that infected hepatocytes were being lost over the half-life of 6.3 days. Whether this really reflects the loss of infected cells or not is unclear. If it's not the loss of infected cells, it could be the loss of the sAg itself from the serum, assuming the siRNA is blocking new production. That seems awfully long, especially if the sAg is on particles because particles tend to be cleared very, very rapidly. HIV and HCV each have a half-life in a serum of about 45 minutes. For HBV, the estimates vary from minutes to about a day, or 18 hours in eAg positive patients, but nothing along the order of six days. So an intriguing question is where this six-day time scale is coming from.
- Another study that from Arbutus (Lee, AASLD 2017) where they used an AAV mouse model of chronic hepatitis B treating with one of their siRNA analogues. They also gave anti-PDL1 as an immunomodulator and a therapeutic vaccine. Treatment was for 42 days and the mice were followed post-treatment. What happened is instead of the DNA levels going back up to their baseline, they seem to be stabilizing anywhere between one to three logs lower off therapy for long periods of time.
    - That's very exciting because we were involved with an experiment of SIV-infected macaques who were chronically infected, put on antiretroviral therapy. You can see the standard decline (slide 21). Then they were given five infusions of the BMS anti-PDL1s. Then all therapy was stopped, and the viral levels stayed at about 1000 copies instead of going back to 10^6. Here's another monkey. Starts at 10^6. Goes off all therapy and fluctuates around 100 copies. A third one, the same thing.
    - The explanation that we have for this is that you're stimulating the immune system and generating immune control of some sort.
    - We have this very simple model of immune control (slide 22) where you add an "infector cell population" that gets activated by interacting with infected cells, can kill them, undergoes expansion as an innate immune response, and also can get exhausted. By allowing the exhaustion to be reversed, we can get the fits to the model.
    - We think something like that may be possible, at least in a mouse model. Whether or not we can ever get there with humans, we don't know. But it's the start of sort of a functional cure and ways to try to combine a quantitative assessment of both immunotherapy along with antiviral therapy.

- It's important with these new therapies to try to develop multi-scale models where we look inside what might happen to the infected cell based on the mechanism of action of the drugs and predicting all the different interactions.
- I think we also need to do a better job of keeping track of proliferation, to what extent that dilutes out cccDNA or if cccDNA can get back into the nucleus. This has been controversial in animal models, and I think we need to develop better models of the immune system's interaction with HBV, so we can really understand what goes on when we're trying to modulate it.

Discussion: Kinetics and Modeling

Presenter: Barbara Testoni, INSERM; Alan Perelson, Los Alamos National Laboratory

- Alan, just to start with you. You actually did a ton of work on the HIV side and the HCV side. I think we all found that very helpful as we were making development decisions along the way. In a way, HCV, of course, was a lot easier because it was an RNA virus. So how do you think about applying how these concepts from much earlier in the development process now as drugs are just getting to phase 1 and phase 2? How do you think about collaborating to use this information to drive more effective decision making?
    - That was the reason I tried giving you all of these little examples where modeling may be helpful. I agree, we're very early in the development. Clinical data is very sparse right now. I think it's important that if we want to take a quantitative approach, as we have in both HIV and HCV, that we start collecting really frequent samples. I was involved in many sub-studies. You may have a big trial with 100-200 patients, but you pick 5-10 that you're going to sample frequently for a viral kinetic sub-study and try and measure as many markers as possible. The other reason that it's very interesting to know what the viral kinetic patterns are—if it's single phase, multi-phase, how many phases there are—that in the cases of HCV, and to some extent in HIV, allowed us to make early predications of the durations of therapy. We weren't always right in HIV before we really appreciated latently infected cells. We knew that therapy had to go on for three or four years just based on initial biphasic decay. As the drugs and assays got better, we discovered there were slower phases that are recurrent in lower levels.
    - The same thing has occurred in HCV. As we've started to move from interferon therapy into DAAs, we started to see that the rates of declines were getting faster and faster. We were able to predict, based on early data, very fast second phase declines that might be possible to eliminate all the infected cells in eight to 12 weeks of therapy. That helped to stimulate at least some of the companies to start moving from one year to 12-week studies with DAAs. As you all know, that has proven to be correct. Whether we can do the same thing in HBV, I don't know. But I think it's an approach that we should try taking, and that will require a lot of work defining what goes on in the patients with these different agents and whether or not we can interpret all of these phases.
- Based on your experience from HIV and HCV, which you successfully modeled and leads to very good control, how far are we lagging behind in the HBV field? How are we going to advise and how are we going to push from concerted efforts that we need more solid data to build up the scientific model?
    - The models and data work hand-in-hand. The insights I've gotten in both HIV and hep C was by looking at the patterns of decline and getting time scales and then trying to interpret them. Then using that data to stimulate experiments. For HBV, we no longer have chimps available and the various woodchuck and other models are not quite as good, but at least it might give us some indication. As I said, there is the ability to do

fine needle aspirates. Andy Talal has done that in HCV. I presume it can be done in HBV to get some other information about cellular markers. Also, trying to combine the serum markers we have in a cogent way to get as much information as we can while simultaneously looking at the HBV DNA, the pregenomic RNA, the core-related antigens, eAg, sAg.

  - If we can define what the various kinetics are for all of these markers and try and build a biological model, in terms of understanding… One last thing. In terms of understanding things that go on, I think we have to take a scientific view to understand the mechanisms of action for individual agents and what their potencies are rather than just going into trying to understand random combination therapies. In HCV, by understanding the mechanisms of NS5A inhibitors, protease inhibitors, nucs, and polymerase inhibitors, we were able in a s/l content study to pick combinations that made sense. We had different modes of action of them, and each one was contributing something. George and Ray Schinazi were involved in a study which showed proof-of-principle that you could cure HCV in an Asian population with three weeks of therapy.

- We have pretty bad assays right now. How do you model this half-life? I heard 10 to 100 days. How did you get to those numbers?
  - That was work done, as I said, in this first paper by Martin Nowak, and that was just based on the decline of the HBV DNA. They weren't looking at cccDNA at all. The HBV DNA reflects the ability of infected cells to produce it. If it goes down, then the infected cells must be going down somehow.
- What do you need to model cccDNA kinetics?
  - I either need direct measurements of cccDNA. or have a biomarker that's at least reliable so that if we see full changes, we believe those full changes even if we don't have it absolutely. We clearly can do that in various animal models. It would be nice to resolve this whole issue of whether or not cccDNA survives proliferation or if it's just getting diluted. It would be nice to be sure what the levels of cccDNA are, whether it's things like three or four copies per unit hepatocyte. We're working with Ashwin Balagopal with the single-cell laser captures microdissection, looking at biopsy materials and trying to measure the amount of cccDNA per cell. Those technologies are getting better but it's limited by the assays right now. In principle, that can be done.
  - I'd like to remind people that we started in hepatitis C with this paper in 1998, and it's only now that we have these multi-scale models where you can account for the action of DAAs. That took 15 years in terms of modeling and experimentation, and understanding it wasn't instantaneous by any means. It takes a lot of data, a lot of experiments, and a lot of compounds to build our understanding of how to interpret what's going on in these diseases.
- What are the special challenges of then bringing in immune therapies when you're looking at these kinetics?
  - We don't understand the immune system at all to a large extent. We don't understand how the viruses evade the immune system. These interactions are very complicated. Because of the successes in cancer and immunotherapy, people are collecting a lot of data on this issue of exhaustion, having multiple cell types, and how you can modulate and stimulate immune system cells in various ways. How these cells get into the tumor environment or how they get into the liver will be an issue just as it has been in cancer and chemotherapy. You may end up needing agents that just allow the immune system cells to enter into the liver. Some of you may know old experiments by Frank Chisari where they were looking in biopsies of infected chimps and that they did in CD8 cells going into the liver for about two months after infection for hepatitis B. Why were they not going in? I don't think anybody understands that now, but there's

something different that's going on in how hepatitis B interacts with the immune system.

- If you had a request, let's say somebody's doing a combination study like what we saw earlier today with the therapeutic vaccine and antivirals, what would you ask of them to sample? What kind of sampling would be ideal?
    - I think we need to get enough early data to get some idea of how these markers are going to decay. You can't just do it every month because you miss things. We might start weekly, and if things look like they're changing, go back and take samples more frequently. In our first studies of HIV using protease inhibitors, we followed patients roughly daily for over two weeks before realizing that things might be more complicated. A collaborator, David Ho, then put some patients into a clinical research center, put an indwelling line on, and got 15 data points for seven days. The initial kinetics were taken every two hours because we realized that we were probably missing the clearance of virus, and we wanted to know what that was. According to some of these models there should've been another time scale. We will just have to do the same thing. We have to get some idea of what we're working on and why things are so much slower in hepatitis B. Is it that drugs aren't acting well and there's a lot of reinfection going on? Are there other biological processes underlying things?
    - Back in the day when hepatitis B oral agents were first being developed, the FDA didn't accept HBV DNA as a surrogate marker. With the way that a drug was approved, whether it was lamivudine development or maybe with adefovir for hep B, you had to do a baseline and a one-year biopsy to show change in necroinflammation with no worsening of fibrosis. That made trials very difficult to do, but the wonderful thing about having had to do biopsies is that then gave us liver samples that we were able to use to look at cccDNA in work that we did with Alan and with Fabien Zoulim and Stephen Locarnini. We were able to then compare the, I want to say log change, the minimal or almost no change in cccDNA to the kind of both first and second phase kinetics we saw in sAg and HBV DNA. We're in a different situation now because we don't do liver biopsies. We use HBV DNA, and back at the time, there were efforts by colleagues to try to come up with serum or plasma tests for cccDNA, but they didn't correlate well with what you saw in tissues. The good news is we're farther ahead and there's so many new classes of compounds. The bad news is we don't have liver tissue to be able to do the kind of kinetic work that we did that told us that therapy was probably going to be lifelong for most people.

Expanding Immune Monitoring in HBV Trials - Part I

Slides: Expanding Immune Monitoring in HBV Trials - Part 1

Presenter: Adam Gehring, University of Toronto

- We have two basic strategies for immunotherapeutic options in chronic hepatitis B patients. One is to improve T cell activation, looking at either therapeutic vaccines or checkpoint inhibitors. The other is to stimulate innate immunity, inducing cytokine production that might have an antiviral effect, T cell co-stimulatory effect, or alter the liver microenvironment.
- There has been a lot of work done towards the adaptive immune response to really understand the mechanisms of T cell dysfunction. We know they are prone to apoptosis. We know they express inhibitory molecules, and we know they have metabolic dysfunction. These therapeutic options are being designed to overcome these inhibitory mechanisms, and boost both the frequency and their function. The goal of therapeutic vaccines really is to increase the magnitude of HBV-specific T cells, hopefully providing the co-stimulation to overcome these inhibitory mechanisms.

    - Checkpoint blockade is really looking to restore the function of these T cells and improve their target cell recognition. Whether or not that will increase their magnitude is yet to be determined. There's also this ongoing hypothesis that antigen reduction is going to restore HBV-specific immunity.
- Overall the goal is to increase the adaptive anti-HBV immunity. What are the major questions that need to be addressed: How much increase is going to be possible by boosting the adaptive immune system? How much increase is actually needed to get an antiviral effect? Is that just going to be magnitude of the HBV-specific T cells? Is it going to be addressing their function? Is it going to be a combination?
    - With therapeutic vaccines: will the antigens incorporated into the vaccines provide sufficient coverage for the different genotypes? Will they induce epitope spreading to broaden the immune response? Will there be an anti-HBsAg B cell recovery or stimulation with these different therapies? Will antigen reduction restore T cell responses or is this a stepping stone to combination therapy?
    - In terms of innate stimulation, right now the drugs that are the furthest along in clinical trials are orally delivered drugs. They stimulate cytokine production in the liver. We know from the transgenic mouse models that when you activate the toll-like receptors, you see a reduction in HBV DNA from the liver. This is highly dependent on interferon-alpha in the mouse. However, there has been some evidence that the innate effector cells' activation, like NK T cells, also leads to clearance of HBV DNA in the liver. We know these drugs targeting the toll-like receptors are bioavailable in humans.
- A bigger question for innate immunity and stimulation is the mechanism of actions in patients, which is not particularly clear yet. Also, is the response that we expect in the liver the same as the data we get from the blood?
    - We know from a lot of work that the composition of immune cells in the liver is different. There are a lot more innate effector cells in the liver compared to the blood, mainly comprised of NK cells. There are also differences in the myeloid population which are likely to respond to these pattern recognition receptor agonists with an expansion in particular of this double-positive CD14/16 monocyte population that tends to produce more cytokines than the classical CD14 monocytes. If this does have an antiviral effect, is it going to be a direct antiviral effect? Is it going to be induction of interferon-alpha like it is in the mouse? Or is it going to be an indirect effect? Is it going to stimulate one of the innate effector cells like NK cells, MAIT cells, or gamma delta T cells to induce that antiviral activity? And if it does, what are the populations that will be responding? What effective function of that population is going to be responsible for that antiviral effect? Is it going to be necessary to separate efficacy from toxicity?
- The basic fact of the matter is if we are going to stimulate immunity, we need to be able to measure immunity. As I mentioned, most of these drugs have an immunological component. Vaccine and checkpoint inhibitors are targeting T cells. Innate immunomodulators are targeting cytokines, and potentially lymphocyte activation. But there is also a lot of talk about the immune response. Companies are working on siRNA, sAg inhibitors, nucleic acid polymers, reduction of antigens. Will these restore immunity? It's not clear. Even with capsid inhibitors: if you're breaking down more core antigen into hepatocytes, is that going through the class I processing pathway? Is it actually making them a better T cell target?
- When you look at the immunology that's been done, the immunology has really been relegated to sub-studies in later trials. I'm here to argue that we really need to include immunology in these early stage trials, these phase 1b and 2a studies. To do that, the immune monitoring has to become more efficient. You have to realize they have a 12 or 24-week treatment window, and there's a real limitation on the amount of blood that the guidelines say you can draw in eight weeks. When you look at the baseline visits, you have early PK studies,

this eats up a lot of blood. We have a limit on the critical baseline samples for immunology, and the remaining blood goes PK, safety, and new virological biomarkers that are easy to measure in the serum.

- Today, what I wanted to do is go through and show what we've been working on: what you can do with two 10 mL tubes of blood. You get about 8 to 12 million PBMCs, so on average about 10 million. What we can start to do is get a broad impression of what's happening in the immune response in the blood. We can look at seven different populations in myeloid cells and phenotypic markers for co-stimulatory molecules or inhibitory molecules by flow cytometry. We can look at eight different populations of lymphocytes in the peripheral blood to observe how these populations are changing, and we can look at specific cell types.
    - This is a B cell panel that we've done looking at activation and differentiation in memory B cells. We can do this for NK cells. We know we can do it for T cells as well.
    - We know the HLA type. We can add tetrameters in here. You can get the entire profile of inhibitory inactivation status of these T cells in the peripheral blood.
    - If you do this by flow cytometry and you start to see a signal in one of these populations, you can do this analysis and sort the cells at the exact same time. This not only allows you to see what they look like. You can start to get transcriptomic profile by NanoString, RNA-seq, or even if you want to go that deep into single-cell RNA-seq.
    - We use a panel of TLR agonists, RIG-I, STING, CD3, CD28 to look at T cell responses. These can be customized or comprehensive panels, in addition to measuring these in the serum, to understand what the response is in these different populations. You can do a very broad analysis of all these different cell population and functions, start to dive down deeper into these individual populations, or you can combine all these panels and use CyTOF for comprehensive analysis in a single sample.
- The broad analysis is good, but of course we're working on immunotherapy for hepatitis B, so it is going to be important to measure hepatitis B-specific immunity. This is where the second tube of blood comes into play. With the second 10 mL tube of blood, we can identify what is happening ex vivo with the HBV-specific T cell response.
    - The fact is this is not routinely performed any more. Because, one, the reagents are pretty expensive to buy. Some technical expertise limits their use, and you also need the instrumentation to read out the plates. However, I think the more practical reason why ex vivo ELISpot is not really done anymore is that if you look historically at most of the studies, ex vivo HBV-specific T cells are often detected in less than 10% of patients.
- We really wanted to address this aspect of measuring immunity for hepatitis B, and we worked really hard to optimize this ELISPot assay. We worked on the culture conditions, the stimulation, and the numbers. So now, instead of getting ex vivo T cell responses in less than 10% of patients, we're able to see ex vivo T cell responses in greater than 70% of our chronic HBV patients. Many of these patients have spots up into the 100 or 200 count; we're getting robust measurement of HBV-specific T cells ex vivo. This takes about six million cells.
- Of course, T cells are only half of the immune response. What's been completely neglected in clinical trials are the B cells. We've also been working hard to develop an ELISpot that allows us to look at HBsAg-specific memory B cells. This takes about two million cells of input. This assay is getting more and more sensitive as we optimize the different conditions.
- It is important to measure in the blood, but what we're all really interested in is what is happening in the liver. We know the difficulties now with core biopsies, but I've been fortunate to team up with Harry Janssen in Toronto who pioneered the use of these fine-needle aspirate biopsies (FNAB).
    - These are performed during the regular patient clinic visit. Within an hour, the FNAB is done and the patient goes home. There are no callbacks, no radiology. This is done with a 25-gauge needle and allows us to do regular longitudinal sampling. We've done

as little as one week between fine needle aspirates. The nice thing about these studies is that they can go from the liver to the experiment in less than an hour.

- There are caveats: You don't have architecture. We get 50 to 150,000 cells: 90% of these are leukocytes with 5-10% hepatocytes. Even though these are relatively few cells, with the available technology you can generate an incredible amount of data.
- The pipeline that we are establishing right now is 1) to look at how these populations in the liver are changing with therapeutic interventions, and 2) we're running single-cell RNA-seq on these total leukocytes from the liver. We can see the transcriptomic profiles of all these cells, and oftentimes we'll have cells left that we can cryopreserve.
    - We can look at 13 different populations of immune cells with these 20,000 individual cells. When you start to put this together, you get this fantastic kind of distribution of the frequency. Once we start doing this longitudinally, you can really look to see how these different immune cells are changing over time with therapy intervention.
    - Then we're using the 10x Genomics 3' single-cell RNA-seq to do single-cell sequencing on around 2000-2500 individual cells per sample.
    - What we've done is taken an FNAB at time zero when the patients are still on drug and then at time four which is four weeks after stopping drug when HBV DNA is rebounding. What you can see here is the lymphocyte cloud (slide 19): all the lymphocytes between T0 and T4 co-localize in the same cloud. What you can clearly see is that the brown and the blue are completely non-overlapping. Although the lymphocytes are all together, the transcriptomic profiles are clearly different, suggesting a response to that reactivation before ALT increase.
- Think about a sub study for FNAB samples: 5-10 patients followed longitudinally. You can see how these populations are changing by flow, and measure that change by RNA-seq. This gives you a comprehensive picture of the immunological response to therapeutic intervention, and we can use this to start to identify biomarkers.

Expanding Immune Monitoring in HBV Trials - Part II

Slides: Expanding Immune Monitoring in HBV Trials - Part II

Presenter: Mala Maini, University College London

- I want to reiterate that we don't need to only do immune monitoring for immunological drugs, we need to include it for combination trials where there is an antiviral arm and an immunomodulatory arm. Additionally, it is critical to think about looking at restoration of immunity in antiviral therapies, especially in early phase trials. It is particularly important in the trials where the drug doesn't work especially well. When it has either failed, is suboptimal or is toxic, we have the opportunity to understand what went wrong immunologically. This will inform future drug development, allowing tailoring of the therapy, selection of better combinations that work with the deficits of that particular drug, and uncover the mechanism of any toxicity. These studies are important in suboptimal or ineffective trials because they provide clarity for which immune markers to use in future big-scale clinical studies; so you can then select your responders and you can also think about the timing of therapy withdrawal.
    - It is important to consider which immune mediators are most likely to be relevant for your particular drug target.
        - It is important to decide whether to do the comprehensive, unbiased type of approaches that Adam mentioned: with single-cell RNA-seq or cytokine beta arrays where you are looking at the whole array of possible

responses, or whether you are interested in pursuing a particular hypothesis-driven focused approach.
        - With T cells, are you going to look at global T cells or HBV-specific responses? Are you going to look *ex vivo* after *in vitro* expansion? Are you just going to do some phenotyping of those responses or actually try to look at functional recovery? Are you just going to stick to the blood or are you going to try to get into the liver? Don't forget to think about what the drug is actually targeting.
- The desired focus of immune monitoring will be determined by what the primary goals are.
    - If the primary interest is looking at antiviral potential, then the focus would be on whether there is induction of effective immune responses. Those will be either robust immune responses that are actually reducing the affected hepatocytes and/or inducing long-term immune responses that are going to provide immune surveillance so that even when your other drugs (i.e. direct-acting antivirals) have eliminated most of the cccDNA, there is a long-term immune response in place in the liver that will detect any recrudescence.
        - Focus on the detailed immunological mechanism of action, immunomodulatory effects of the drugs or trying to understand any toxicity and how immunopathology is being induced.
    - HBV-specific T cells and the B cells will provide an indication of whether the drug-induced immune response is capable of HBV control. It may also be prudent to consider indirect effects through cytokines that could be produced by the innate cells in the liver, for example.
    - For T cells, the mainstays of assessment are ELISpot, intracellular cytokine staining and HLA-peptide multimers. They do allow some assessment of function of both cytolytic and non-cytolytic activity, but it is essential that we work as a field to standardize a peptide panel.
        - It is feasible to use peptides spanning the whole proteome due to their relatively small size. Ideally, the field will shift to using pan-genotypic peptides, optimized to cover most genotypes, and move towards a simplified version of this peptide-specific response, like the QuantiFERON that is used in TB monitoring.
    - *Ex vivo* analysis using HLA-peptide multimers is also very helpful. However, these are limited because they are only available for pre-defined epitopes, which in HBV are mostly A2-restricted. However, they do allow you to do *ex vivo* phenotyping useful for mechanistic studies.
    - There are very nice studies emerging from HIV showing the actually efficacy of antibodies and other B cell functions in maintaining viral control.
- Working with Antonio Bertoletti's group, we've tried to understand a bit more about B cell defects by direct *ex vivo* staining with labeled bait reagents for the sAg.
    - B cells specific for sAg do persist in a large number of patients with chronic HBV, but they are highly defective. There is an expansion of an atypical B cell subset that is upregulated by coinhibitory receptors. It seems there are many parallels with the T cell response, and that allows us to start to look at ways of manipulating and boosting B cell immunity as well. However, boosting immunity has the potential of inadvertently making the situation worse.
        - By boosting regulatory populations, immunosuppressant populations could be downregulating specific immunity as a bystander effect. For example, if NK cells are highly activated, and express this death ligand trail, they can actually delete viral-specific T cells.
        - On the other hand, there are some ways of boosting immunity indirectly through, for example, induction of IL-12, which enhances functionality of HBV-specific T cells or interferon gamma that can come from NK cells.

        - To understand the mechanism of a drug in more detail, particularly with regards T cells, there is a great deal more complexity to consider. It would be important to consider the immunosuppressant populations involved in regulating the T cells extrinsically, or the intrinsic mechanisms that could be limiting the T cell response.
            - For example, blocking PD1. One of the concerns is that there are many different coinhibitory receptors on T cells. Even if you block this particular interaction, other coinhibitory receptors might be preferentially upregulated to compensate.
        - Similarly, there is a lot of underlying metabolic and epigenetic defects in T cells that can't necessarily be reversed just by blocking one of the surface receptors.
- What about the issue of immunopathology and side effects?
    - Of course, hepatitis B is non-cytopathic, so the liver disease is thought to be entirely immune-mediated. Unfortunately, the same immune responses that are able to induce antiviral effects are also able to induce immunopathology.
        - For example, hepatitis B specific T cell cytotoxicity is very useful for eliminating infectious hepatocytes, but will inevitably cause some liver damage. Even if they're predominantly cytokine-producing, this can initiate an inflammatory infiltrate and drive some liver inflammation.
        - It may be possible to try to focus the toxicity by specifically boosting virus-specific populations and limiting bystander inflammation. For example, there are populations which can dampen down the non-antigen-specific T cells in the liver. I think most people agree that hepatic flare is important to induce an effective immune response against HBV.
    - How do we get around this? Minimizing antigen load is not only a good idea in terms of allowing the immune response to work better, but it would also increase safety in terms of flares. There needs to be more studies investigating the extent of infected hepatocytes and the different phases of disease to know a bit more about the liver reserve that we would have if we did wipe out most of the infected hepatocytes.
- As you all know, there has been a move away from regular liver biopsies and liver sampling because of the strength of non-invasive fibrosis tests, but I think that it is critical that some liver sampling is done, particularly in early phase studies, to look at viral reservoirs, cccDNA, and integrated DNA.

HBV Cure Roadmap: Follow-up from Hepatitis B Foundation Meetings with NIAID, NIDDK and NCI Regarding an NIH HBV Cure Agenda

Slides: HBV Cure Roadmap: Follow-up from Hepatitis B Foundation Meetings with NIAID, NIDDK and NCI Regarding an NIH HBV Cure Agenda

Presenter: Carol Brosgart, University of California, San Francisco

- This is a report of the virtual conference set to identify all the unmet areas of research needed to get us to a cure in hepatitis B. Additionally, there were also two publications: the research agenda for cure in chronic hep B virus infection published in *Hepatology* (Alter et al., 2018), and a second in *Antiviral Research* (Block et al., 2018). At the end of my presentation, there will be the links for these articles and for a copy of the Hepatitis B Foundation "Roadmap for a Cure."
- In the report, we focus on the broad areas of research: virology and viral therapeutics, immunology, liver cancer and cirrhosis, and research agents, reagents and experimental

models. We also speak a little bit to the outcomes of the 2 million or more Americans who have chronic hepatitis B.
    - If we were to try to eliminate chronic hepatitis B by 2030, what is the differential cost if you actually treat someone and prevent progression of disease versus dealing with disease as it progresses? It is cheaper on an annual basis to treat people before progression, and it would even be cheaper in the long run to be able to cure CHB.
- The figure on slide 8 is a roadmap for both cellular function and the various targets. Currently, our targets are primarily limited to the inhibition of the polymerase with nucs, but we're beginning to see data at other targets.
- We met separately with three institutes. One was a meeting with Tony Fauci who is the director of the National Institute of Allergy and Infectious Diseases (NIAID), and his broad leadership. We then had a meeting with the Division of Digestive Diseases and Nutrition, the Liver Research Branch, at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Jay Hoofnagle was the lead for that meeting, but all of the relevant leadership within liver disease was there. The third meeting was at NCI with Doug Lowy who is the acting director.
    - Those from the Foundation that attended were Tim Block; the president and the co-founder of the Hep B Foundation and the Baruch S. Blumberg Institute, Bill Mason from Fox Cancer Center, Alan Brownstein who many of you knew in his previous life at the American Liver Foundation; now Vice President for Public Policy at the Hepatitis B Foundation, I was there as a member of the board of the Foundation, and our consultants, Mike Hall and Alyson Lewis who are our public policy and legislative analysts.
    - The summary of the meeting from NIAID:
        - The attendance was significant. In addition to Tony Fauci, Hugh Auchinloss; principal deputy director, Carl Dieffenbach; director of DAIDS, Rajen Koshy; program officer, Sarah Read; director of the Therapeutics Research Program, Cristina Cassetti; Virology Branch Chief, Beverly Alston; chief of Complications and the Co-Infection Research Branch, and Henry Masur.
        - We discussed the two program announcements that had been released in May of 2017 done in collaboration with NCI and NIAAA. They also have an upcoming RFA coming out of the Division of AIDS, and while it will deal with HIV/HBV co-infection, it also has a mono-infection component. NIAID was very supportive of the cross-collaboration NIH effort with NIDDK and NCI.
    - At NIDDK, in addition to Jay Hoofnagle, Greg Germino; deputy director, Stephen James; the deputy director, and Jake Liang; head of the Liver Diseases and the branch chief.
        - They were also supportive of the cross-NIH initiative. They want to work on finding a cure for hep B, and they think that this is the time. The scientific opportunities are there and ready. They were supportive because they understood that a cure would reduce the associated morbidity and mortality from cirrhosis, end-stage liver disease, liver cancer, and liver transplantation. We encouraged NIDDK to prioritize and increase funding for hep B research in their upcoming funding announcements. They acknowledge this was just right before the budget, but that their research priority would be constrained without additional funding.
    - At NCI we discussed the need to accelerate the pace of discovery to prevent and improve outcomes of liver cancer and presented the current data regarding the rising incidence of liver cancer and deaths due to hepatitis B, both domestically and globally.
        - He felt that the three most important and the promising areas for liver cancer research were to have a better understanding of the molecular pathogenesis of hepatocellular carcinoma, the trade-offs of earlier versus later treatments,

and HBV drug development. He also agreed that the scientific opportunities were now and that with investment we could make great progress.

- The next step following these meetings is to meet with Francis Collins, the NIH director, to walk him through the HBV research cure agenda and initiative.
    - There has been a recent budget increase for NIH with specific language about hepatitis B that will help direct funds for our research purposes.
- We were encouraged by the meetings. We are going to continue communication with those three institutes. We are going to meeting with Francis Collins. Importantly, the NIH did get a 3.1 billion increase in funding, of which 1 billion was not committed. It is that 1 billion that we need to be going after.
    - The language for that in the budget is "institutes see fit to continue investments and research that will save lives, lead to new drug and device development, reduce health care costs, and improve the lives of all Americans."
    - One of the things that the NIH leadership told us is the more proposals that are submitted to them on hepatitis B, on hepatitis B cure, on liver cancer, the bigger the chance that there will be funding for those efforts.

Community Perspectives on the Road to HBV Cure

Slides: Community Perspectives on the Road to HBV Cure

Presenter: Joan Block, Hepatitis B Foundation; Maureen Kamischke, Hepatitis B Foundation; Michael Ninburg, Hepatitis Education Project; Su Wang, Saint Barnabas Medical Center, World Hepatitis Alliance

- We have been serving as the community representatives for the HBV Forum. We often don't say much because we're just listening, but it's really been an honor to be here. The work that you're doing is something that we take back to our communities. It provides hope for so many of our patients. Today, we want to introduce ourselves, briefly tell you our stories, and talk to you about the community perspectives on the road to hep B cure.

Su Wang

I'm an internal medicine physician by training, I direct the Center for Asian Health at a community hospital in Livingston, NJ, and I'm the board member of the World Hepatitis Alliance representing the Americas. Before this position, I was at the Charles B. Wong Community Health Center in New York City. As many of you know, New York City is the epicenter for hep B in the USA.

In our health center, we had about 8000 hep B patients in our registry. Based on necessity, I became very adept at caring for hep B. I'm also a hep B patient myself and only started talking about this as a physician in the past few of years. I'm happy to say that I have four kids who are hep B free, thanks to the vaccine. A report came out from Polaris this year saying that 1.8 million five-year-olds currently have hep B. Just because we have the vaccine doesn't mean we are going to have a generation free of hep B, and those kids are going to need a cure.

Patient engagement is going to be vital on the road to cure. My favorite quote from the World Hepatitis Summit in Sao Paolo last year was from the patient perspective: "Nothing about us or for us without us." We think that the patients can really do a lot to help propel all the work that you're doing to fruition. We can help elevate hep B as a priority area for policy makers, funders, and providers.

What are some of the current challenges just that will get us to real hep B elimination? As we know, there is still very low awareness in the general public and physician community. It is obvious to those of us on the ground, seeing patients, how disjointed medical care is. All the great guidelines we have are not being followed to the extent that we want them to be. Patients aren't

getting ALT and viral load measurements or meds as recommended. A recent CDC study showed that 50% of cirrhotics in good settings, like Kaiser, were not even on medication. There's a lot of work we still need to do to get to where we want to be.

One of my pet peeves, a reason I believe HBV is not really a priority, is that hep B care is not a quality measure on any federal reporting programs. We all know that meaningful use and QF measures are how hospitals and a lot of healthcare providers receive their incentives through Medicare. We as a community really need to push for hep B to become a quality measure, like diabetes, for people to really care. For example, I have had issues with insurance carriers to cover meds, radiology, even blood tests. I've had patients who I couldn't get a liver function test (AFP) covered. Insurance denied my AFP, and I thought, *Really?* Even with a diagnosis of hepatitis B.

Michael Ninburg

I am a former hepatitis C patient. I run the Hepatitis Education Project which is a nonprofit group based in Seattle. I've been doing that for almost 20 years. I also serve as president to the World Hepatitis Alliance, which is a patient-run and patient-driven organization with over 80 countries representing about 300 patient groups around the world.

I met my wife in graduate school about 15 years ago. She's from China. I had hepatitis C at the time. It was something that came up early in our relationship, and I had talked to her about what it was, what that meant, and asked her if she had ever been tested for hepatitis B, understanding where she was born and grew up. She hadn't. She wasn't really that familiar with it. She did get tested and turned out to have chronic hepatitis B, fortunately inactive. We were married a few years later, have two beautiful boys, both of whom were protected from chronic hepatitis B through vaccination and HBIG.

Speaking from the patient perspective, my wife is very practical; doesn't really see the need in going to the doctor very often. She has a recommendation to get a regular ultrasound for her inactive hepatitis B, which she doesn't really do. I don't think she has been to get an ultrasound in about two or three years. I still get an annual ultrasound having been a hepatitis C patient, cured, who had progressed to cirrhosis. In talking to Joan, I said, "I don't know how to get my wife to go and get her ultrasound." She said, "Why don't you make a date out of it?", and last month we had our first ultrasound date. I think it was the first that she had had in at least two or three years.

I will say I think all of you keep the patient in mind. You all do great work. What it means to a patient to be cured—we're not there with hepatitis B. We may be close. We may be closer or further than some of us would like to be. But I want to talk about what it was like to be cured of hepatitis C.

I had this virus that I knew was something that kills people. I was diagnosed in 1990, so really before treatment was even an option. I lived through the mono interferon/ribavirin/peg days, opting not to do treatment, and I waited and waited. I finally decided to do treatment when I had the opportunity to get into a trial for Telaprevir, which cured me. For those of you who worked with Telaprevir, I do accept your sympathy. I would do it again. My cirrhosis has regressed. I've got mild liver disease. And you're all familiar with what happens when you cure a patient of hepatitis C. You know the clinical impact. You know the improved histology. You know the improvement in quality of life, and I think the psychosocial impact is one that doesn't get appreciated as much as it should.

For me, I started treatment when my older boy was seven months old. I had progressed to cirrhosis. I knew what that might mean. When I was finally cured after 48 weeks, the biggest impact for me was knowing that I had a much better chance to be around to watch him grow up, to be with my wife, and be there for her and for us to be there for him. Now, we have

another little imp, and I'll be there for him. That's the promise of a hepatitis B cure, and that's the reason that we're all in this room.

Maureen Kamischke

I'm the social media and outreach manager for the Hepatitis B Foundation. My story really started 20 years ago when we adopted our daughter, Maren, from China. We didn't know it at the time, but she had hepatitis B when she came to us. She wasn't just your typical baby with asymptomatic immune-tolerant hep B. She was very sick. She had liver damage. At 14 months, she started interferon treatment. We saw Kathy Schwarz at Johns Hopkins. We received great care, and today Maren is 20 and hep B-free. She's really one of the lucky ones, but it was a tough road getting there. We dealt with stigma and discrimination. There was talk of a transplant, but then all of a sudden, she was fortunate enough to spontaneously seroconvert. That led me to the Hepatitis B Foundation. Working as a social media and outreach manager with the Foundation, I've really been able to interact with a lot of different people, and not people like Maren that had access to Johns Hopkins and the expertise that they have there.

I wanted to introduce you to a few of our patients. At the Hepatitis B Foundation, we have consulted with over 24,000 people over the last six years. We do that via email. They call. They write. They talk to us on Facebook. We have a very active community. There are over 10,000 people on our Facebook page. So, it's busy, and a lot of the reason that they're there is because of you guys. They're waiting for the cure. They want to know what's next.

One of them is Imran (slide 9). He is from Pakistan, and he has been contacting me over the last year. He was diagnosed with hepatitis B. His fiancée left him at the altar. He can't work. He's severely depressed, suicidal, as he describes, "I am the living dead." His father started contacting me on Facebook, and we communicate very regularly. These are the kinds of things that we hear from people that contact us. "I am the living dead." "I am suffering." That's how the whole conversation begins.

I also wanted to introduce you to Joyce (slide 10). She is from Uganda. When she became pregnant, she was tested for hepatitis B, found out she was positive, and contacted me. Her doctor had told her that the baby didn't need the vaccine for the first six months. We talked about that. I told her how important the birth dose is, but of course only 11 countries in Africa actually have the birth dose. Gavi supplies the pentavalent vaccine that starts at six weeks. As a workaround in Africa, they have a tendency to give the pentavalent vaccine as the birth dose. That is not what is recommended, but in Africa there are so many barriers. There are workarounds for everything. They often don't have access to even the very basic diagnostic tests that we take for granted. They may be in the government hospitals, but they don't have access to them in all the clinicals. That leaves them very vulnerable to some of the traditional herbal healers in Africa. These people are really desperate. They're discriminated against. They're ostracized. So, they turn to people that offer them a promise of a cure, but unfortunately that's not there.

This is Sheena (slide 11). She is from the Philippines. She had a baby with a very high viral load. Most likely, the baby failed prophylaxis. In the Philippines, they have the vaccine available but no HBIG, and nobody gets antiviral treatment unless they have a significant amount of money. They just don't have the resources. There are no programs in most of Africa or in a place like the Philippines. The other issue with the Philippines is that there's a high unemployment rate, which is 30% higher with those living with hepatitis B. In the Philippines, it is very popular to travel and work in the UAE because they can get high-paying jobs and send the money home, but they're not eligible to get work if they test sAg positive. It is very important to understand where their situation.

I'm concerned about where we go next. Although we have a vaccine, it's been almost 30 years, and we still can't get that right. We have treatments that actually can control this virus, but most of these people—and you figure this is a small number of people can't afford this treatment, so they're deferring. We update the drug watch page at the Hepatitis B Foundation once every couple of months, but they're contacting me every week, "What's up? What's with the cure? Is it coming out soon?" Just to let you know they're out there. They're waiting for the cure, and in order for them to live their lives to the fullest, they really need to be sAg negative.

Joan Block

I wanted to say for many of you who don't know that the Hepatitis B Foundation was started with a love story 30 years ago. Many of you know my husband Tim Block. When I married Tim, he promised to love me through better or worse. Little did we know that within a year, it'd be for worse because I was diagnosed with hepatitis B. If all of you older folks remember, 30 years ago hepatitis B was horrible. The vaccine wasn't available. People in the hospitals were treated like HIV patients. I lost my job as a nurse. My child was kicked out of daycare until he was tested and cleared. It was a really terrible, terrible time. During that period, Tim decided he needed to start a foundation to find a cure to make sure that I could live a long, healthy life with him and our son and now our daughter.

Over the past 30 years, through the Foundation, I've heard tens of thousands of stories like mine: the horror, the shock, the tremendous stigma and discrimination. I think people have to realize that there is still so much stigma and discrimination. A lot less now than 30 years ago, but we still hear examples every day at the Foundation: the man who was left at the altar, the woman who can't get into school, the child who can't get a playdate because they have hepatitis B.

The other thing is the cost. We need a cure because the cost of being on these oral nucs is expensive. To be very personal, hepatitis B drugs are now specialty pharmacy drugs. I have to panic every single month whether I'm going to get my drug in time because there is a small window. You can't renew before a certain date, and if you don't renew it within a certain date, you run out of medication. There are many times when I am literally taking a pill every three days while I'm waiting to get my next dose, and then the doctors wonder why you're not adherent. It's because of that.

We fielded calls from Medicare patients who couldn't afford their drugs. A 66-year-old said recently "I used to pay $80 a month. It's now $500 a month. I can't afford it. I can't afford to pay for the medication." Well, some of you might say, well, at 66 what's the risk? We all live with the risk.

The other thing is healthcare. This disease needs to be personalized. I'm sitting here in front of you. Many of you have known me for many years. I went through a whole liver cancer scare last year, as I was trying to step down from the Foundation, they saw something on my ultrasound. For six to eight months I was having an MRI every three months to figure it out. Those were six months where I really thought, *I don't know if I'm going to live. Did I retire just in time to die? Or am I going to live?* Well, the good news is that they were cysts. It wasn't HCC, but this is what we go through. This is what patients go through.

I'm now 59. I don't care about stigma and discrimination. I'm retired. You can't fire me anymore. I have my husband and lovely kids. I can't be denied that. I'm very fortunate. Tim has a great healthcare plan, so I'm covered. I'm now retired, so I can remember to call the drug company and get my drugs in time. I'm fortunate that I have my health. I did go through that scare. For those people, at the World Hepatitis Summit last year, some clinician said, "Well, there's really not a need for a cure. We can control hepatitis B. It's an entirely controllable disease." That is not good enough for people living with it. Even me at my age of 59, I want a cure for the younger people, and I'd love to see a cure for myself. We started the Foundation 30 years ago. I would really love to see a cure before I die, but I really want a cure for the 20-year-olds, the 8-year-olds. There needs

to be a cure. We have the best and the brightest in the room. I really think there is tremendous hope.

The final challenge is for the group here is to come up with a new term. A “functional cure” is not a cure. I know there’s lots and lots of discussion about this, but from the patient perspective if you tell me I have a functional cure, that is not the same as a complete cure. You are misleading me. You are giving me false hope, and you are going to twist yourself into knots trying to explain this to patients. I really challenge this group to try to come up with another term. I will credit Carol Brosgart at the last Forum for coming up with the term “remission”. I like that a lot. Some of you were there last year. Tim and I argued about it in public. I like it because it is a cancer term, and hepatitis B is a cancer-causing agent. If the functional cure means that patients still need to be monitored, it’s a remission. It reminds patients that you still need to be monitored. If you tell them you have a functional cure, they will walk out of that office thinking they are cured and you won’t see them again.