Letter to the Editor

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First, in simplistic terms, this modality uses a two-pronged approach against both virally infected cells and HBV DNA–integrated cells. Data from HIV infection has already shown this biphenotypic capability directed against an immune-dominant HIV epitope as well as escape variants.[3] Monoclonal T-cell receptor molecules boost adaptive immunity by stimulating global T-cell phenotypes, which is crucial in the setting of chronic HBV, in which HBV-specific T cells become exhausted. However, what possibly needs to be understood is the stage of HBV infection at which such molecules will have their impact. Taking an analogy from the HIV studies, even in HBV infection, the potential phase of the applicability of such molecules would possibly be the HBeAg-negative chronic hepatitis phase. If human studies do see the light of the day, we would expect these molecules to be a part of a cocktail of stage-specific anti-HBV therapy and not a standalone game-changer by themselves.

The second consideration that needs to be taken is the safety of these molecules and the risks of hepatic decompensation. Theoretically, the later in the course of HBV infection that such molecules are used, the lesser will be its bystander cytokine effects. The trial using anti-programmed death-1 blockade in patients with HbeAg-negative chronic hepatitis had minimal drug-related adverse events, but it specifically excluded patients with liver stiffness greater than 9 kPa.[4] Hence, although we can expect a similar safety profile in a similar cohort, patients with advanced disease may not be appropriate candidates.

Finally, a potential limitation of the study is the fact that the noncytolytic elimination of HBV was only measured with surrogate entities. In addition, reductions of HBV RNA—regardless of HBeAg levels—need to be explored. We eagerly look forward to future human trials that will determine the mode, phase, and stage of HBV infection that will respond to this therapeutic modality.

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Letter to the Editor: Liver Cell Models for Premature Termination Codon Readthrough Analyses

TO THE EDITOR:

Amzal et al.[1] reported about the prospect of pharmacological premature termination codon (PMT) readthrough of ATP-binding cassette, subfamily B (MDR/TAP), member 11 (ABCB11) mRNA in bile salt export pump deficiency, the latter causing progressive familial intrahepatic cholestasis (PFIC)-type 2. The investigators demonstrate that aminoglycoside antibiotics can stimulate readthrough of nonsense mutation-induced PMT in ABCB11 mRNA, thereby rescuing full-length ABCB11 protein synthesis. The study provides proof of principle for a potential therapy for nonsense mutation-associated PFIC2. The investigators acknowledge that their cell-line–based model does not

take nonsense-mediated mRNA decay (NMD) into account, which, however, determines whether PFIC2 patients may actually benefit from PMT readthrough therapy. Importantly, other cell models exist that do take NMD into account, and we believe these should be discussed as part of the path to bring their exciting findings closer to the clinic.

NMD is a cellular surveillance pathway that safeguards the quality of mRNA transcripts and eliminates most PMT-containing mRNA. NMD efficiency is variable and depends, among others, on the precise nonsense mutation. Because a sufficient amount of target mRNA is a prerequisite for effective PMT readthrough and the synthesis of a sufficient amount of the encoded protein, NMD poses a significant hurdle in the application of PMT readthrough-stimulating drugs in the clinic.[2]

Measurements of patients' baseline ABCB11 mRNA may provide a prognostic indicator of response to PMT readthrough-stimulating drugs, but because ABCB11 is exclusively expressed in hepatocytes, this would require a liver biopsy. Patient-derived somatic cells from blood, skin, or urine are easier to obtain. These can be reprogrammed to induced pluripotent stem cells (iPSCs) and subsequently differentiated to hepatocytes. Human iPSC-derived hepatocytes that form bile canaliculi and express ABCB11 were recently reported,[3] as well as a PFIC2 patient iPSC-derived hepatocyte model for ABCB11 deficiency.[4] The big advantage of patient iPSC-derived hepatocytes is that these express the endogenously expressed—and NMD-responsive—gene variant(s) and reflect individual NMD levels.

With the exciting results from Amzal et al. at hand, confirmatory studies using iPSC-derived hepatocytes promise a better and patient-tailored prediction of PMT readthrough-stimulating drug efficacy, as such or in combination with NMD inhibitors, for the treatment of nonsense mutation-associated PFIC and other hereditary liver diseases.

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