HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight October 2016

☐ Co-ordinated with the Director of the Institute / Research Unit

Instiute of Virologie

PSP-Element:
G-502700-003

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Title of the highlight:
Blocking sense strand activity improves potency, safety and specificity of anti-hepatitis B virus short hairpin RNA

Keywords:
HBV; RNAi, AAV; Gene Therapy; Hepatitis

Central statement of the highlight in one sentence:
Blocking shRNA sense strand activity improves safety and increases efficacy of anti-HBV gene therapy

Text of the highlight:
Hepatitis B virus (HBV) is a promising target for therapies based on RNA interference (RNAi) since it replicates via RNA transcripts that are vulnerable to RNAi silencing. Clinical translation of RNAi tech- nology, however, requires improvements in potency, specificity and safety. To this end, we systematically compared different strategies to express anti-HBV short hairpin RNA (shRNA) in a pre- clinical immunocompetent hepatitis B mouse model. Using recom- binant Adeno-associated virus (AAV) 8 vectors for delivery, we either (i) embedded the shRNA in an artificial mi(cro)RNA under a liver-specific promoter; (ii) co-expressed Argonaute-2, a rate- limiting cellular factor whose saturation with excess RNAi triggers can be toxic; or (iii) co-delivered a decoy ("TuD") directed against the shRNA sense strand to curb off-target gene regulation. Remarkably, all three strategies minimised adverse side effects as compared to a conventional shRNA vector that caused weight loss, liver damage and dysregulation of > 100 hepatic genes. Impor- tantly, the novel AAV8 vector co-expressing anti-HBV shRNA and TuD outperformed all other strategies regarding efficiency and

persistence of HBV knock-down, thus showing substantial promise for clinical translation.
- impact on science and economics, next innovative steps
Therapies based on RNAi interference have many potential applications in human medicine, as these can suppress expression of virtually any protein (host or foreign). Thus, our approach should also be applicable to other diseases. We currently evaluate if the suppression of HBV proteins by our newly developed vector restores HBV-specific immunity and if it enhances the efficacy of therapeutic vaccination.

Publication:
EMBO Mol Med. 2016 Sep 1;8(9):1082-98. doi: 10.15252/emmm.201506172.
Blocking sense-strand activity improves potency, safety and specificity of anti-hepatitis B virus short hairpin RNA. Michler T(1,3), Große S(2), Mockenhaupt S(2), Röder N(2), Stückler F(2), Knapp B(2), Ko C(1), Heikenwalder M(1,3), **Protzer U**(1,3), Grimm D(2).
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Taking account of the HMGU mission:
RNA interference constitutes a promising method to develop future medicines for a variety of diseases. However, first concerns about safety have to be addressed which is the focus of our study using . With the developed approach we propose an imprtant step to meke RNAi-based therapies safer.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
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