Title of the Contribution:
Matrix Conditions and
KLF2-Dependent Induction of Heme
Oxygenase-1 Modulate Inhibition of
HCV Replication by Fluvastatin.

Abstract:
HMG-CoA-reductase-inhibitors
(statins) have been shown to interfere
with HCV replication in vitro. We
investigated the mechanism,
requirements and contribution of heme
oxygenase-1 (HO-1) induction by
statins to interference with HCV
replication. HO-1 induction by fluvastatin,
simvastatin, rosvastatin, atorvastatin
was correlated to HCV replication,
using non-infectious replicon systems
as well as the infectious cell culture
system. The mechanism of
HO-1 induction by statins as well as
its relevance for interference with HCV
replication was investigated using
transient or permanent knockdown cell
lines. Polyacrylamide (PAA) gels of
different density degrees or the
Rho-kinase inhibitor Hydroxyfasudil
were used in order to mimic matrix
conditions corresponding to normal
versus fibrotic liver tissue. All statins
used, except pravastatin, decreased
HCV replication and induced HO-1
expression, as well as interferon
response in vitro. HO-1 induction was
mediated by reduction of Bach1
expression and induction of the
Nuclear factor (erythroid-derived 2)-like
2 (NRF2) cofactor Krueppel-like factor
2 (KLF2). Knockdown of KLF2 or
HO-1 abrogated effects of statins on HCV replication. HO-1-induction and anti-viral effects of statins were more pronounced under cell culture conditions mimicking advanced stages of liver disease. Statin-mediated effects on HCV replication seem to require HO-1-induction, which is more pronounced in a microenvironment resembling fibrotic liver tissue. This implicates that certain statins might be especially useful to support HCV therapy of patients at advanced stages of liver disease.