JANUS KINASE 2 INHIBITION BY PACRITINIB IS A POTENTIAL THERAPEUTIC TARGET FOR LIVER FIBROSIS AND PORTAL HYPERTENSION

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ABSTRACT

- Janus kinase 2 (JAK2) signalling is increased in human and experimental liver fibrosis and portal hypertension. Pacritinib and other JAK2 inhibitors, are already in advanced clinical development for other indications. Activated hepatic stellate cells (HSC) play a key role in the progression of liver fibrosis. Here, we investigated the role of the JAK2 inhibitor Pacritinib on activated HSC *in vitro* and its anti-fibrotic effect in two animal models of liver fibrosis *in vivo*.

METHODS & RESULTS

- Transcriptomic analyses of JAK2 and its activating receptors were performed in liver samples of cirrhotic patients (n=22) and healthy controls (n=8). Migration, proliferation, contraction, collagen expression and the effect of Pacritinib in human (line TWNT-4) and rodent HSC were analyzed *in vitro*. Eight-week old C_{57}BL6/J mice were administered for 7 weeks with ethanol in drinking water (16%) or Western Diet (WD) in combination with CCl_4 intoxication to induce alcoholic or non-alcoholic fatty liver disease. Liver fibrosis, portal hypertension, serum aminotransferases and steatosis were analyzed in fibrotic mice after oral Pacritinib treatment (300µg/kg, twice per week, during 4 weeks) and compared to controls. Protein and mRNA levels of profibrotic markers were analyzed in livers of treated mice and in human and rodent HSC *in vitro*.

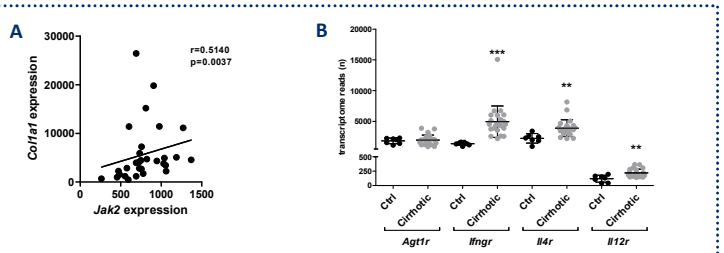

Figure 1. Hepatic transcription levels of JAK2 and its potential activating receptors. *JAK2* expression correlated significantly with type I collagen (*COL1A1*) expression (A). *Agt1r, Ifngr, Il4r, Il12r* were upregulated in liver samples of cirrhotic patients compared to healthy controls (B). Data are shown as Spearman rank coefficient (Rs) and p value. Results are expressed as the mean ± SEM; **p<0.01 and ***p<0.001.

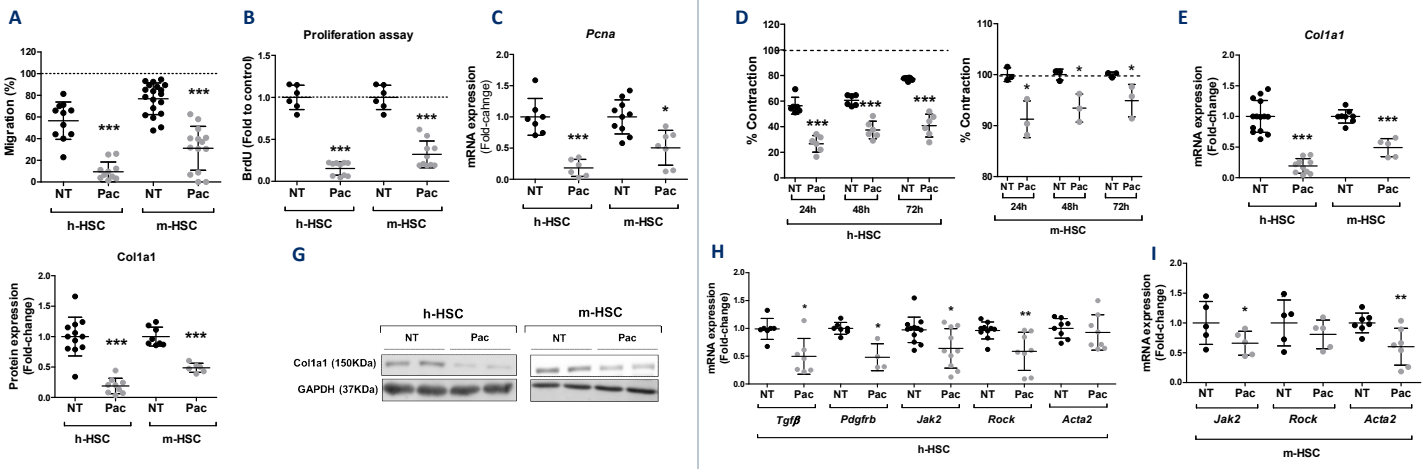

Figure 2. Treatment with Pacritinib decreased migration, proliferation, contraction and fibrosis markers of mouse primary HSC and human-derived HSC. TWNT-4 human HSC and isolated wild-type mice HSC were treated with Pacritinib at 1µM during 24h to assessed migration assay (A), BrdU-proliferation assay (B), Pcna mRNA expression (C), contraction assay (D), Col1a1 gene (E) and protein (F-G) expression and mRNA expression levels of fibrotic markers H-I), . Results are expressed as the mean ± SD; *p<0.05, **p<0.01 and ***p<0.001.

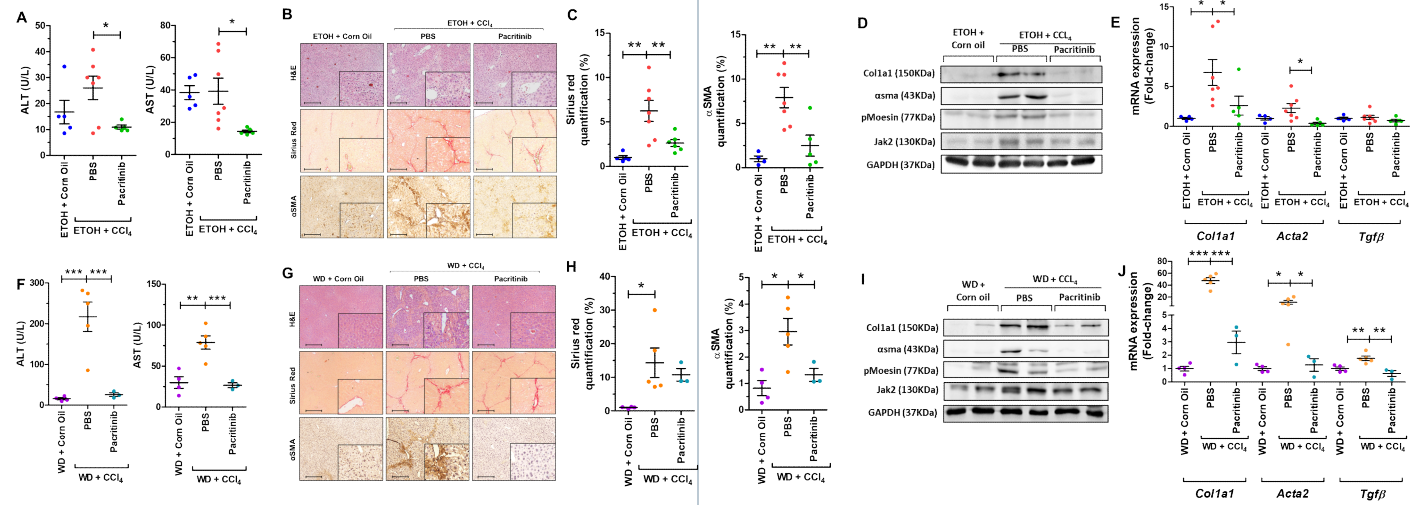

Figure 3. Pacritinib treatment reduces fibrosis development in ASH and NASH mouse model. Serum transaminases levels ALT and AST (A-F), Hematoxilin and eosin (HE), Sirius red (SR) staining and α-SMA immunohistochemistry representative images (B-G), SR and α-SMA quantifications (C-H) , protein (D-I) and mRNA **(E-J)** expression of fibrotic markers. Results are expressed as the mean ± SEM; *p<0.05, **p<0.01 and ***p<0.001. Representative photomicrographs were captured at 100× (scale bars=200µm).

CONCLUSION

- This study demonstrates that the JAK2 inhibitor Pacritinib may be a promising approach to treat alcoholic and non-alcoholic liver fibrosis and portal hypertension in humans.

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