KiNativ™ Application Note

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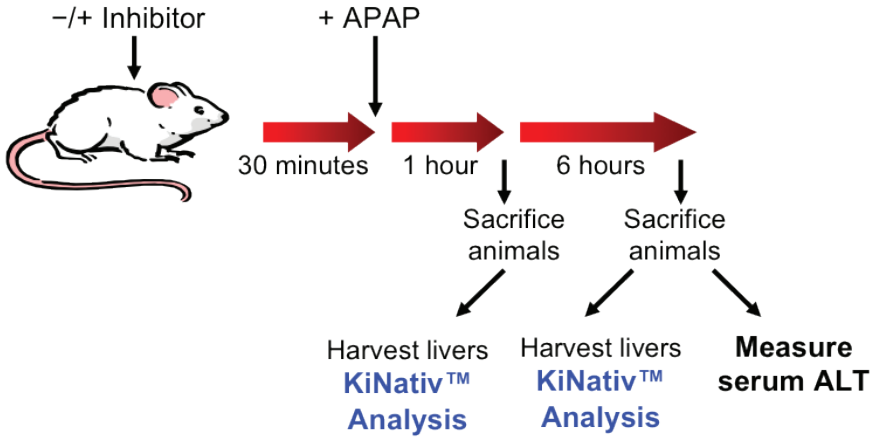
Preclinical/Animal Studies

Assessment of *in vivo* target engagement and inhibitor selectivity

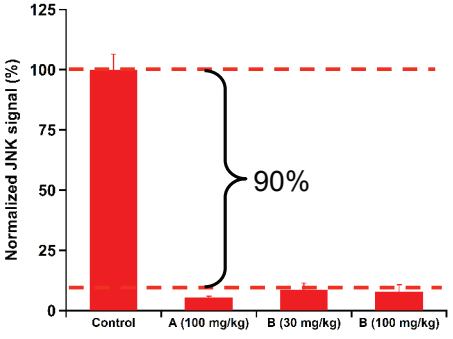
KiNativ™ provides a powerful platform for accurately and efficiently tracking target engagement in treated animals from any tissue in essentially any animal model. Along with critical target potency information, these studies can also indicate relevant off-targets, as well as secondary pathway effects.

- Inhibitors A and B are JNK inhibitors with similar potency against JNK
- These inhibitors were selected for testing in the mouse acetaminophen (APAP)-induced liver injury model

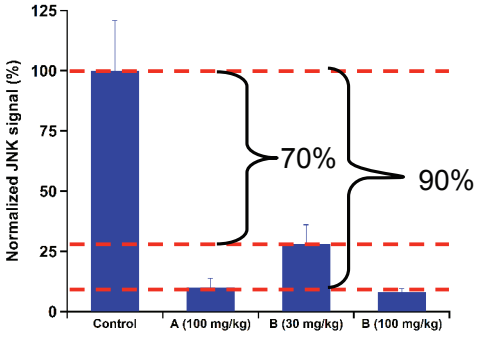


Results from KiNativ™ Profiling

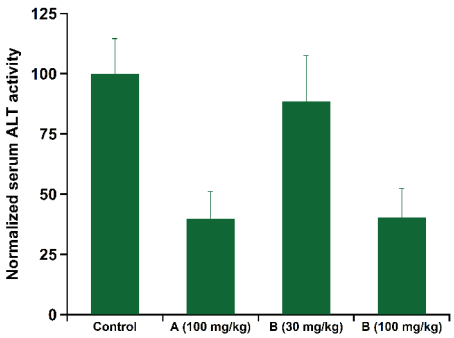
JNK Inhibition, one hour



JNK Inhibition, six hours



Serum ALT activity, six hours



Inhibitors A and B strongly inhibited JNK at one and six hours after APAP treatment at the 100 mg/kg dose (90% inhibition). At 30 mg/kg, inhibitor B demonstrated potent inhibition of JNK at one hour, but markedly reduced activity at six hours (90% versus 70% inhibition). This demonstrates the capacity of KiNativ™ to quantify *in vivo* target engagement at the relevant site of action. Moreover, the reduced JNK inhibition by inhibitor B at 30 mg/kg also correlated with a lack of *in vivo* efficacy as measured by serum ALT levels. Combined, these results indicate that KiNativ™ can quantify *in vivo* target engagement and that is predictive of *in vivo* efficacy.

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