FKBP51 as a promising therapeutic target for the prevention of chronic posttraumatic pain

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>90% of individuals are exposed to at least one traumatic stress event in their lifetime.

Kilpatrick et al. 2013 *Journal of traumatic stress*
Chronic pain develops in a substantial subset of individuals following traumatic stress events

Unfortunately, little-to-no effective interventions for the prevention/treatment of chronic posttraumatic pain are available to date.

Important to identify novel therapeutic strategies.
Data from both humans and animals indicate that FKBP51, a key regulator of the HPA axis stress response, plays a central role in chronic pain development

Genetic variants in *FKBP5* that increase FKBP51 levels strongly predict chronic pain development following traumatic stress exposures


Knocking down/out FKBP51 reduces long-term pain behaviors after noxious inflammatory and spared nerve injury

Hypothesis 1:
FKBP51 inhibition prevents enduring stress induced hyperalgesia development in a rat model of traumatic stress exposure
Single Prolonged Stress (SPS) Animal Model

- Well characterized model of rodent stress
- 2 hour restraint, 20 min swim stress, diethyl ether
- Causes enduring hyperalgesia that lasts 16 days

Liberzon et al. 1997 *Psychoneuroendocrinology*
In the absence of tissue injury, following single prolonged stress exposure, animals develop enduring hyperalgesia.

Data consistent with: Sun et al 2016 Molecular Pain; He et al 2013 Molecular Pain; Zhang et al 2012 Molecular Pain
To inhibit FKBP51, we used a potent and highly specific small molecule inhibitor called SAFit2.

**SAFit2**

Gaali et al 2015 *Nature Chemical Biology*

**Intraperitoneal injections**

Courtesy of Dr. Felix Hausch, University of Darmstadt
Continued FKBP51 inhibition, beginning in the early aftermath of stress, abolishes mechanical hypersensitivity

Wanstrath et al Journal of Pain 2022
Inhibition of FKBP51 early after stress exposure reduces long-term hyperalgesia in male and female animals

Wanstrath et al. *Journal of Pain* 2022
Hypothesis 2:

The effect of FKBP51 inhibition on enduring stress induced hyperalgesia would be time-dependent relative to traumatic stress exposure, with the greatest duration of reduction in pain-like behavior observed with FKBP51 inhibition in the early aftermath of traumatic stress exposure.
Inhibition of FKBP51 three days following stress exposure temporarily reduces stress induced hyperalgesia

Wanstrath et al *Journal of Pain* 2022
Timing of inhibition of FKBP51 following traumatic stress exposure influences the duration of reduction in enduring stress induced hyperalgesia

Wanstrath et al, *Journal of Pain* 2022
In the presence of tissue injury (plantar incision), FKBP51 inhibition does not reduce acute hyperalgesia but does reduce enduring stress induced hyperalgesia.
Conclusions

FKBP51 inhibition reduces stress induced hypersensitivity in male and female animals.

Inhibition of FKBP51 early following stress exposure leads to long-lasting reduction in hyperalgesia.

FKBP51 inhibition has little effect on acute hypersensitivity that develops after tissue injury but reduces long-term hyperalgesia.
Future Directions

- Assess the mechanisms through which FKBP51 inhibition reduces pain-like behavior following traumatic stress exposure.

- Assess whether FKBP51 inhibition causes adverse effects on health or behavior or increases risk for addiction/abuse.
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