Target safety assessments and their role in de-risking drug discovery: $Na_V1.7$ as an example.

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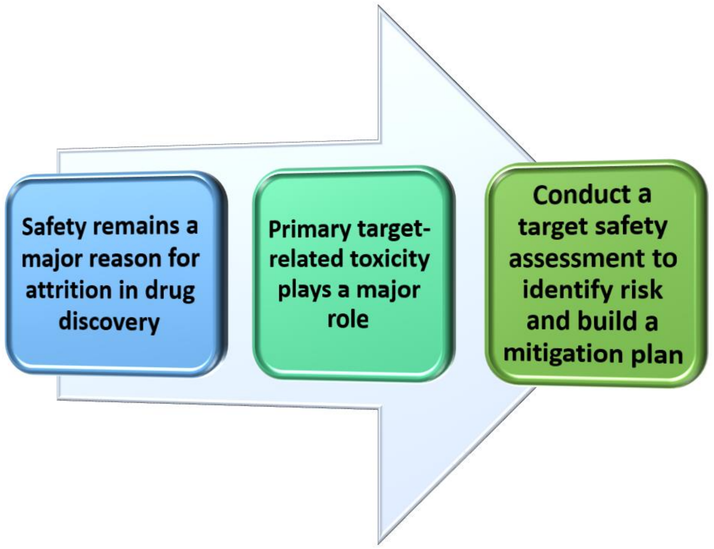
The Issue



- **How well do we understand the role of the intended drug target in normal physiology and the toxicological consequences of its modulation?**

$Na_V1.7$, a potential therapeutic target in pain

- Voltage-gated sodium channels are membrane protein complexes that are fundamental players in animal physiology
- Genetic and functional studies show that $Na_V1.7$ (encoded by the SCN9A gene) is a major contributor to pain signaling in humans

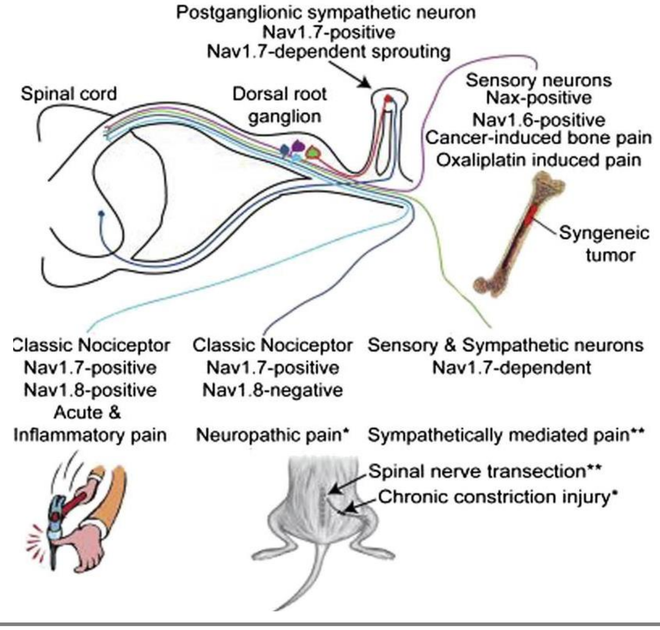


Figure 1. *There are many closely related sodium channels with diverse roles. $Na_V1.7$ is usually expressed at high levels in two types of neurons, the nociceptive (pain) neurons at dorsal root ganglion (DRG) and trigeminal ganglion, and the sympathetic ganglion neurons.*

Table 1. *The homology between human mRNA and rodent mRNA is lower than the homology with dog mRNA.*

Species	mRNA % Homology
Rat	86.72
Mouse	86.37
Dog	91.09

Toxicological Risk Assessment – key findings

- $Na_V1.7$ GOF mutations in human and mice -> pain and increased incidence of seizure
- LOF mutations in human $Na_V1.7$ -> channelopathy-associated insensitivity to pain, itching and complete anosmia
- Mouse homozygote knockouts anatomically normal with phenotype wholly analogous to human congenital indifference to pain
- Completely insensitive to painful tactile, thermal, and chemical stimuli and were anosmic

Gene	Alternative name	Disorders Mutations in gene are associated with
SCN1A	Nav1.1	Epilepsy with febrile seizures, migraine
SCN2A	Nav1.2	Seizure disorders and autism spectrum disorders
SCN3A	Nav1.3	Trigeminal neuralgia & Dravet syndrome
SCN4A	Nav1.4	Myotona & Periodic paralysis disorder
SCN5A	Nav1.5	Long QT syndrome
SCN7A	Nav2.1/2.2	Normokalenic & Hypokalenic periodic paralysis
SCN8A	Nav1.6	Mental retardation, pancerebellar atrophy, ataxia
SCN10A	Nav1.8	Episodic pain syndrome
SCN11A	Nav1.9	Hereditary sensory & autonomic neuropathy

Table 2: *Data derived from gene mutation disorders shows that there are many closely-related sodium channels each associated with different toxicological risks.*

- Potential risk of **inhibition** of $Na_V1.7$ is **anosmia (inability to smell)**
- Due to the role of sodium channels in many physiological processes **ensure selectivity for intended channel -> improve toxicological profile**

Conclusions

- Expert assessment and interpretation of literature and available databases invaluable in **identifying and avoiding target-related risks**

Stage (Purpose)	Early	**Mid**	Late
Purpose	**Selecting between targets**	**Early risk assessment**	**Full assessment of risk & mitigation**
Background (aim, nomenclature, homology, distribution and expression, summary of target biology, human mutation phenotype, transgenic mouse phenotype)	☑	☑	☑
Potential safety risks (including nervous, respiratory, cardiovascular, reproductive, liver, immune and gastrointestinal systems + other relevant for the target)	☑	☑	☑
Clinical data		☑	☑
Suggested risk assessment plan (in silico, in vitro, in vivo and biomarker work including phasing/staging)		☑	☑

Table 3: *Target safety assessments contain level of detail appropriate to project stage*

- Inform target selection and/or prioritization **early in discovery**
- Combine with emerging nonclinical and clinical data to build a picture that mitigates and manages risks **at later stages in the project**