Inducible mouse model of skeletal muscle specific deletion of the Vitamin D Receptor (VDR)

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Background

Vitamin D_3 has beneficial effects on skeletal muscle and can prevent falls leading to reduced bone fracture risk.

Excess of glucocorticoids (GC), either endogenous as in aging or due to glucocorticoid administration as immunosuppressants, leads to muscle loss mass and increases the risk of bone fractures.

Earlier findings showed that 1,25$(OH)_2$ vitamin D_3 (1,25D_3) prevents GC-induced skeletal muscle atrophy *in vivo*, in muscle organ cultures *ex vivo*, and in C2C12 myoblasts/ myotubes *in vitro*.

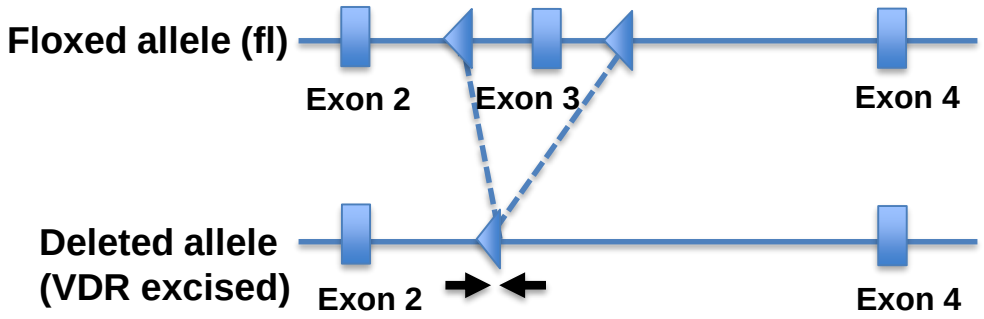
Hypothesis

The beneficial actions of Vitamin D3 in muscle are mediated by direct hormonal effects on skeletal muscle cells.

Purpose

To generate mice lacking the receptor for Vitamin D (VDR) in skeletal muscle and test their response to Vitamin D_3 signaling

Mouse model of inducible skeletal muscle-specific deletion of the Vitamin D3 receptor (VDR)



Genomic structure of the floxed fl/fl and deleted VDR alleles

Genotyping
HSA-MerCREMer: 534 b.p.
CX43 Internal control: 1008 b.p.
VDR excised form: 338 b.p

McCarthy JJ, *et al*. Skeletal Muscle. 2012 May 7;2(1):8.

Nakamichi Y, et al. J Bone Miner Res. 2017 Jun;32(6):1297-1308.

Experimental Design

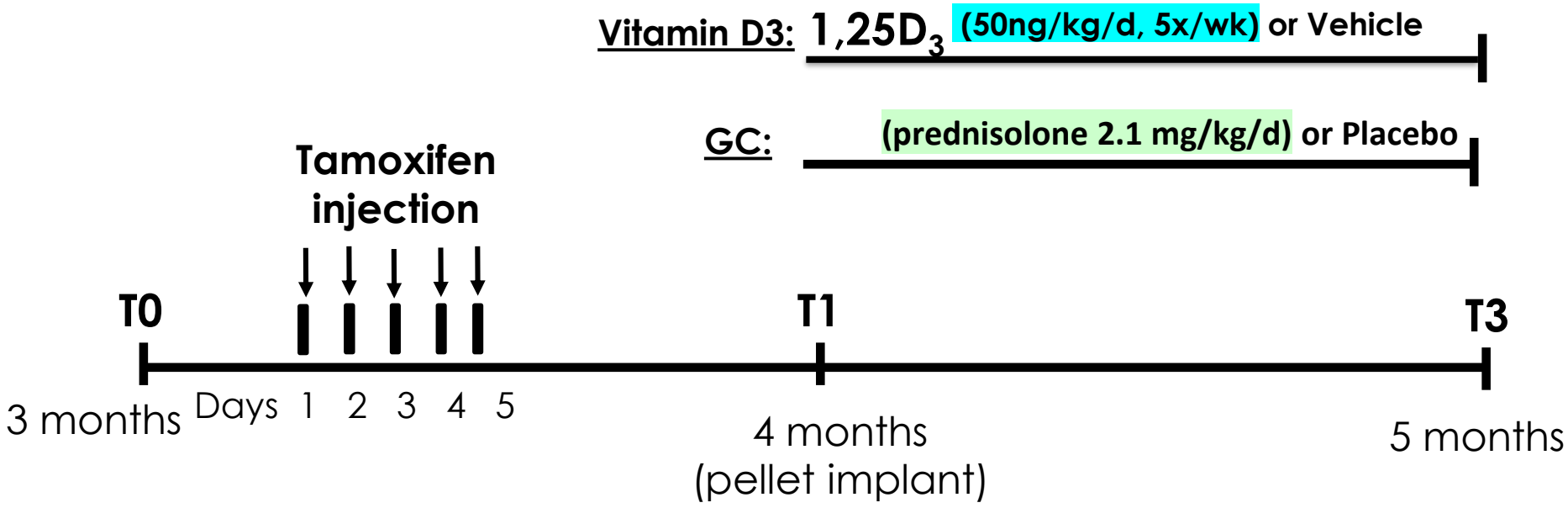
in vivo

C57BL/6 mice
female / male

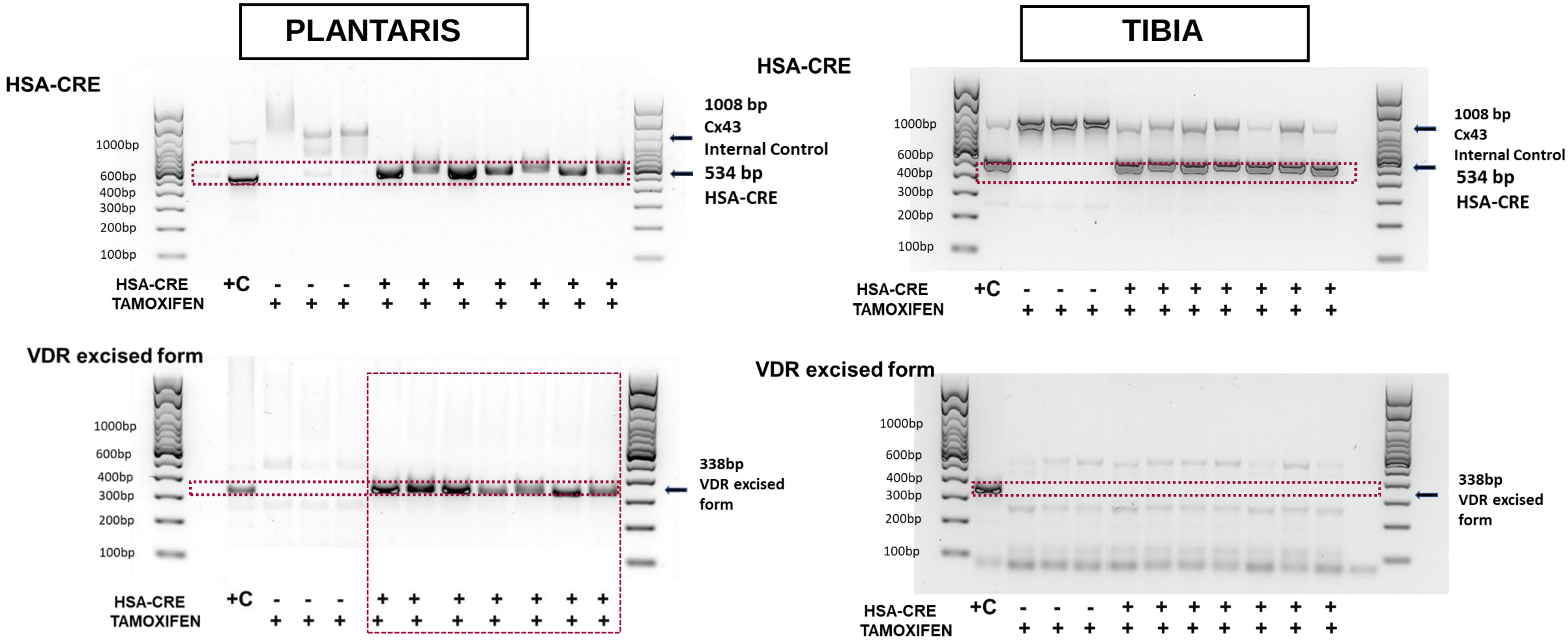
VDR $^{fl/fl}$ x HSA-Mer-Cre-Mer

VDR $^{fl/fl}$;HSA-CRE-/- — CRE -/ Control

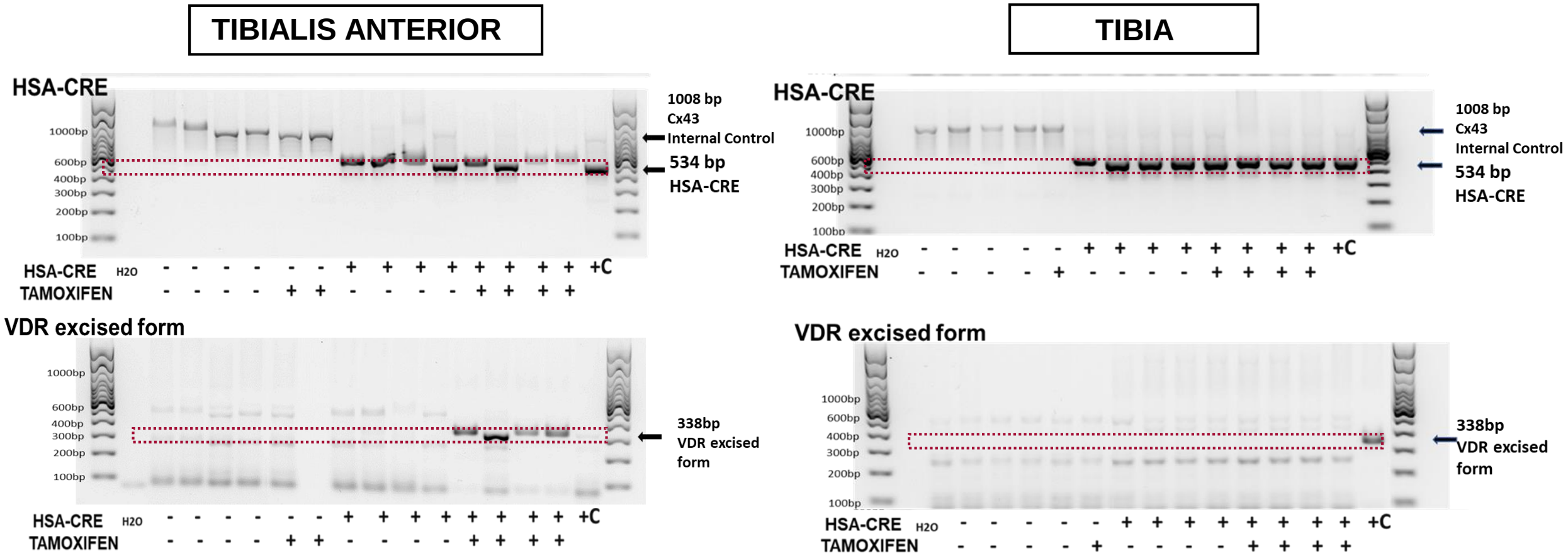
VDR $^{fl/fl}$;HSA-CRE+/- — CRE +



Excised form of VDR is present only in skeletal muscle and not in bone

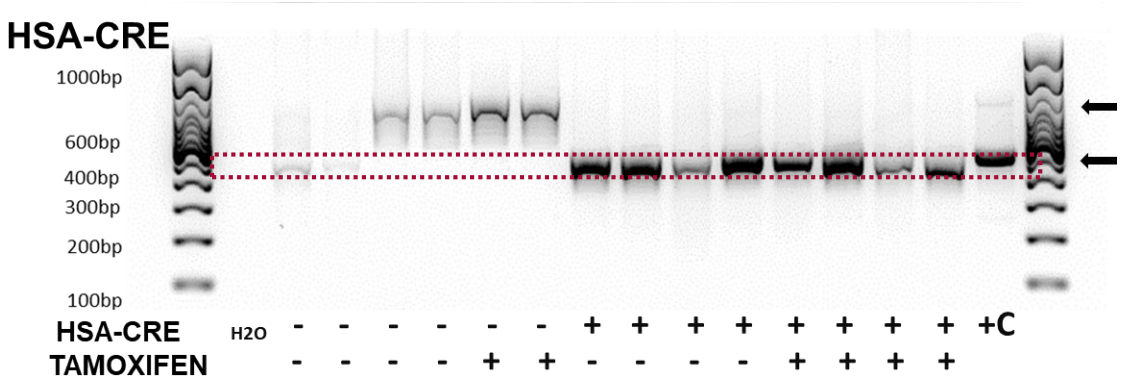


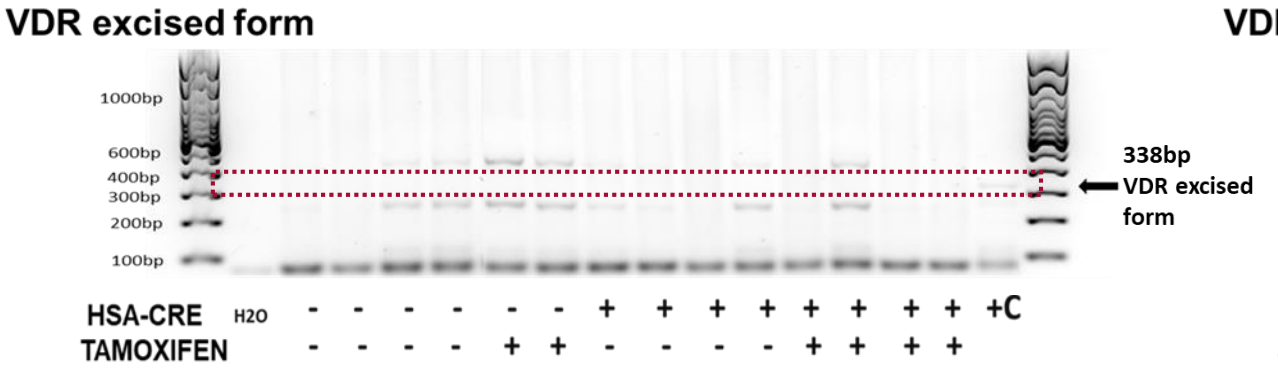
Tamoxifen induces deletion of VDR only in skeletal muscle and not in bone, kidney or small intestine from $VDR^{fl/fl}$;$HSA\text{-}CRE^{+/-}$ mice



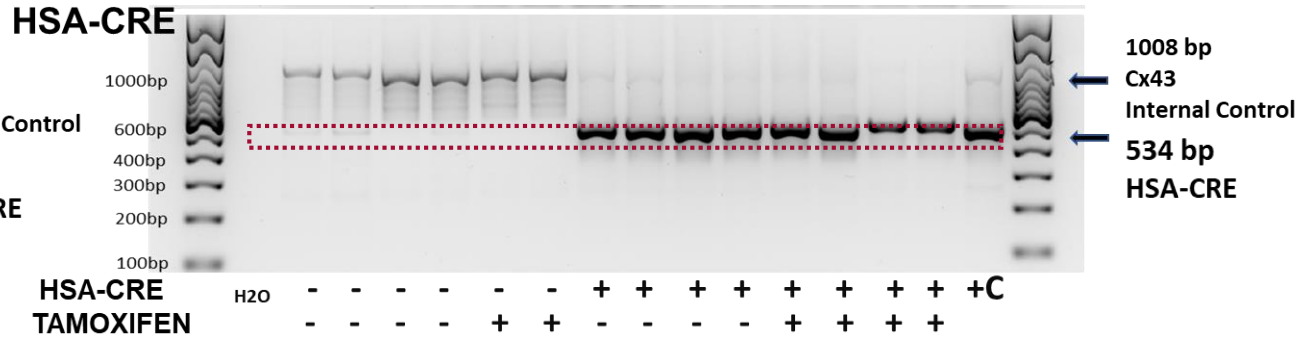
Tamoxifen induces deletion of VDR only in skeletal muscle and not in bone, kidney or small intestine from $VDR^{fl/fl}$;$HSA\text{-}CRE^{+/-}$ mice

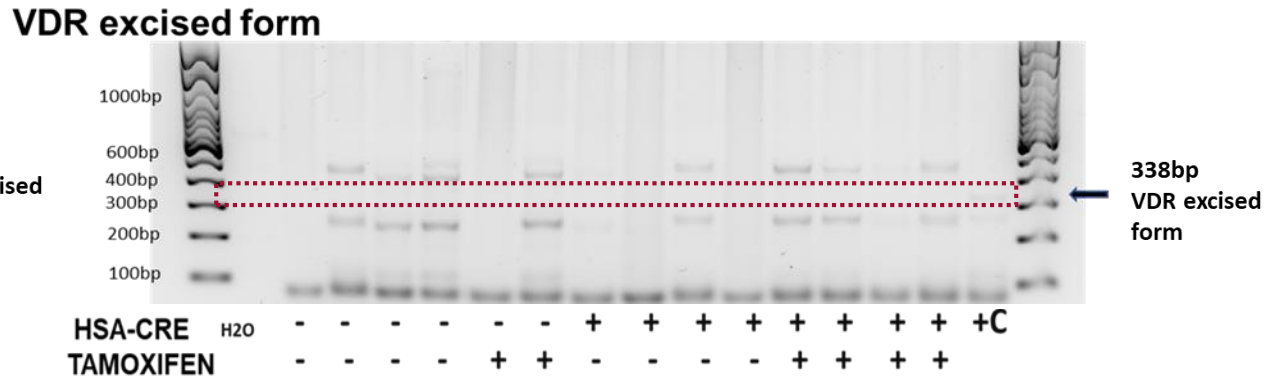
KIDNEY





SMALL INTESTINE





Results

1. The excised form of the VDR is only detected in skeletal muscle (plantaris and tibialis anterior), but not in kidney, intestine, or bone, of Cre positive mice (VDR $^{f/f}$;HSA-Cre +/-) treated with tamoxifen.

2. VDR deletion induced by tamoxifen is only detected in CRE positive mice (VDR $^{f/f}$;HSA-Cre +/-), but not in any tissues from control littermate mice (VDR $^{fl/fl}$;HSA-Cre $^{-/-}$).

Conclusion

This model achieves adult-onset deletion of the VDR in skeletal muscle (Cre and tamoxifen dependent) and thus it will allow its use to determine the direct effects of vitamin D_3 signaling in this tissue.