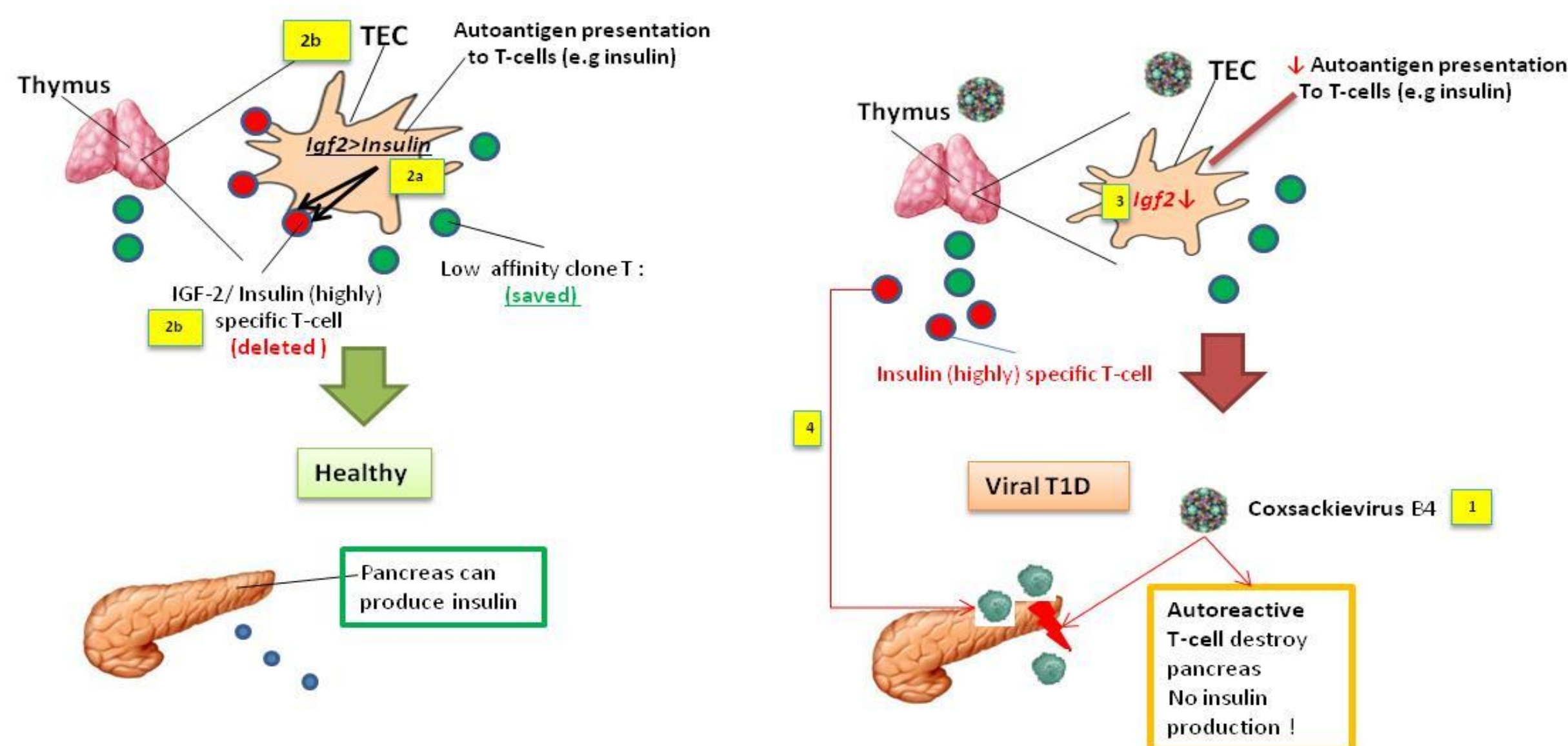# Mechanisms of *Igf2* inhibition in thymic epithelial cells infected with CVB4 E2

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BACKGROUND

In type 1 diabetes (T1D), β cells are destroyed by self-reactive T-cells resulting in progressive insulin deficiency. More and more studies show that T1D could be initiated/favored by viral infections and especially Coxsackievirus B4 (enterovirus family, CVB4) but the mechanism is still not clear (1). T-cells are produced in the **thymus** and selected by **thymic epithelial cells (TEC)** in order to tolerize self-antigens like insulin (2a). TEC express numerous self-antigens, including insulin, and and Insulin-like growth factor 2 (IGF-2) is the dominant thymic peptide of the insulin family (2a). As IGF-2 is **structurally highly similar to insulin**, IGF-2 expression in the thymus could increase the negative selection of insulin specific T-cell and thus play **a protective role** against T1D (2b). We have shown that CVB4 is able to infect the thymus (*in vivo* and 3D culture) including TEC (primary cells and cell line), and is able to **decrease *Igf2*** (TEC cell line) (3) . We hypothesize that **CVB4 could also affect thymic selection** and induce a tolerance break against insulin family, thus feeding the autoimmune mechanism in T1D (4).The goal of this project is to decipher the mechanisms which are implicated.
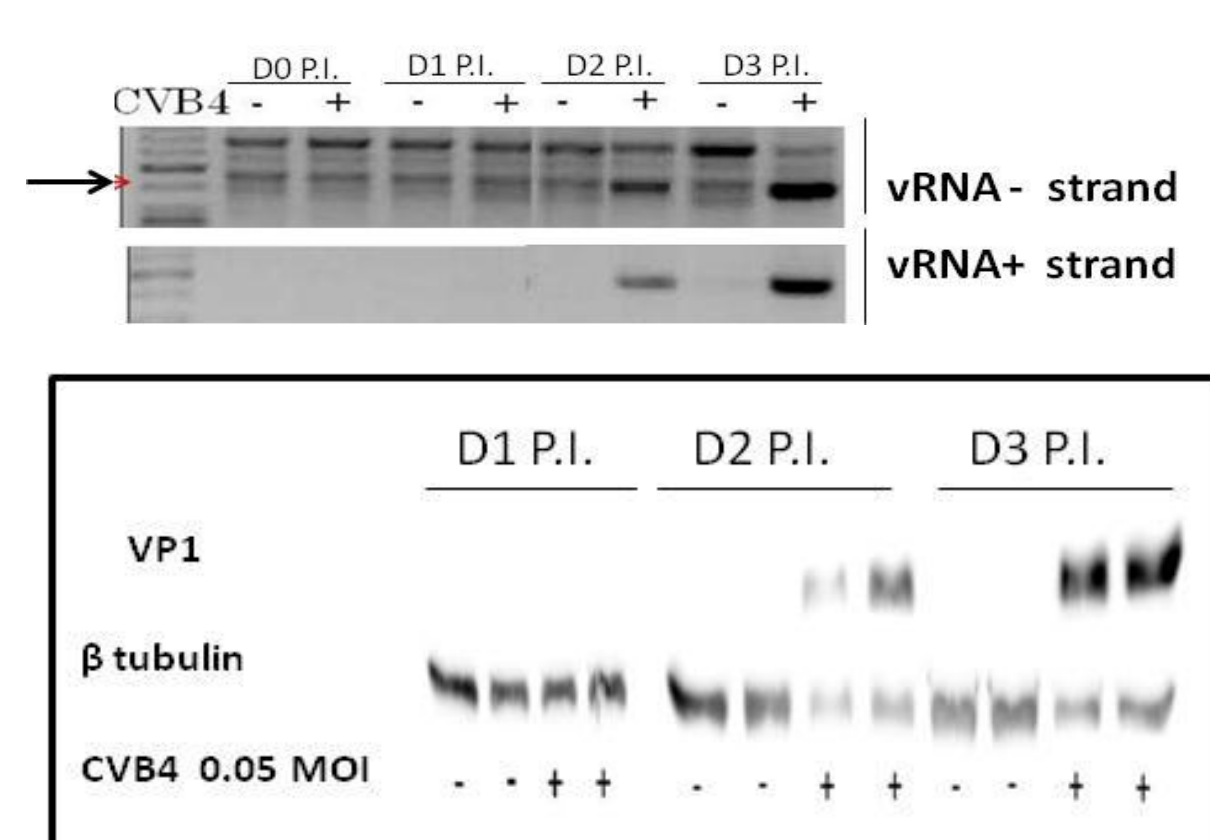
METHODS
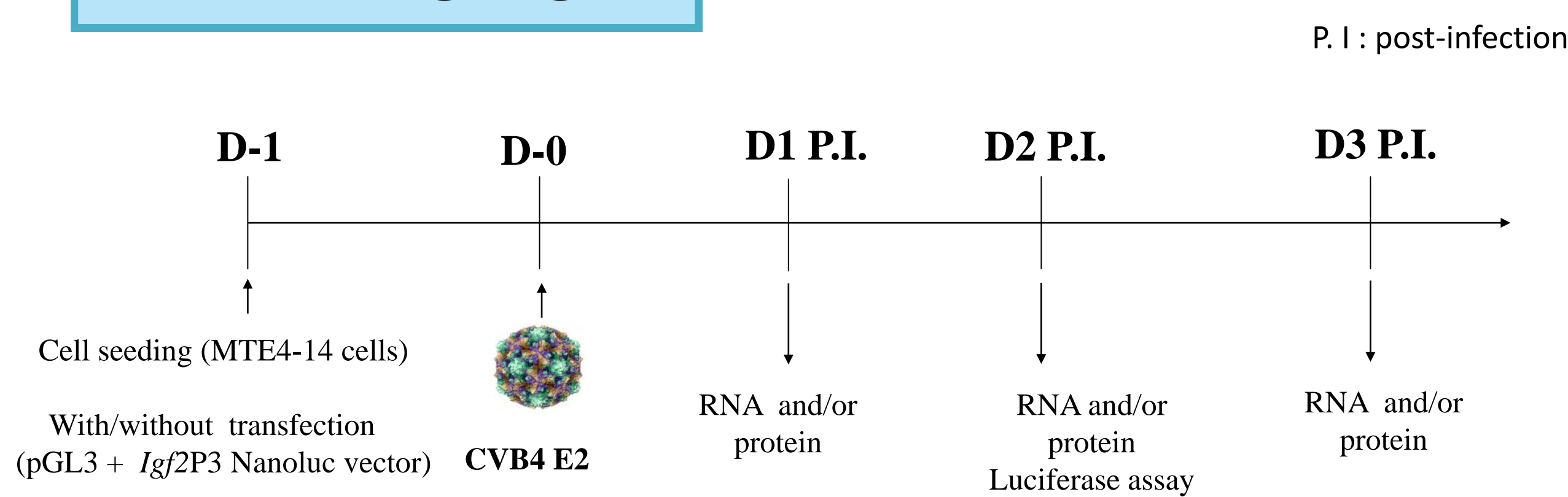
RESULTS

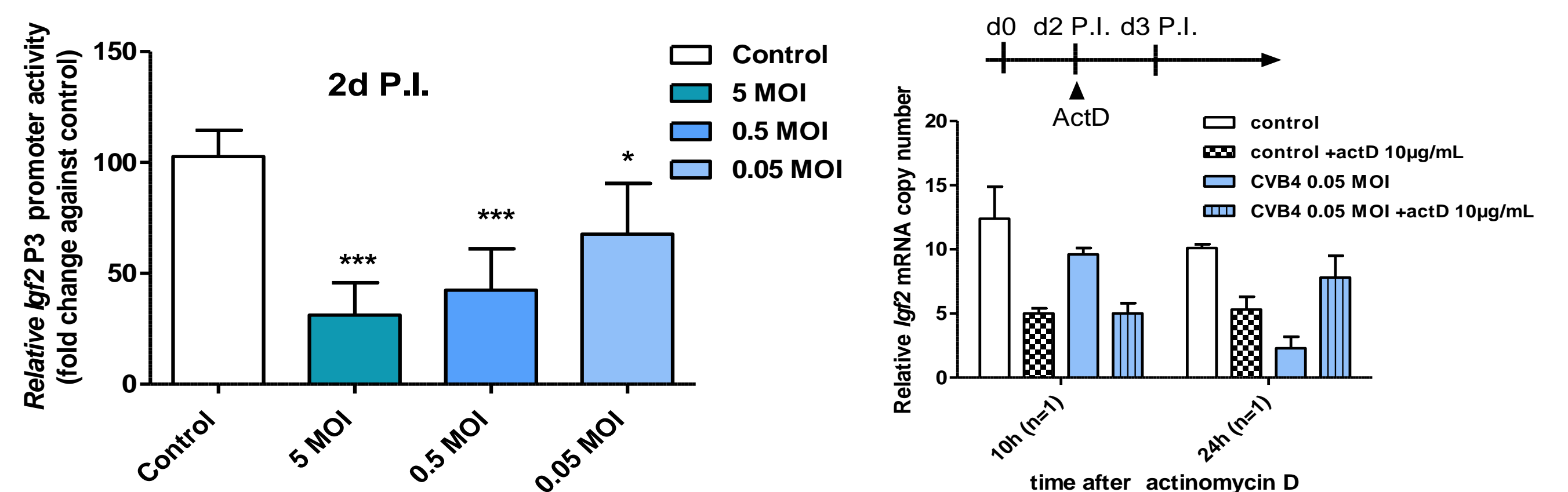### 1. CVB4 decreases *Igf2* including variant 3 mRNA
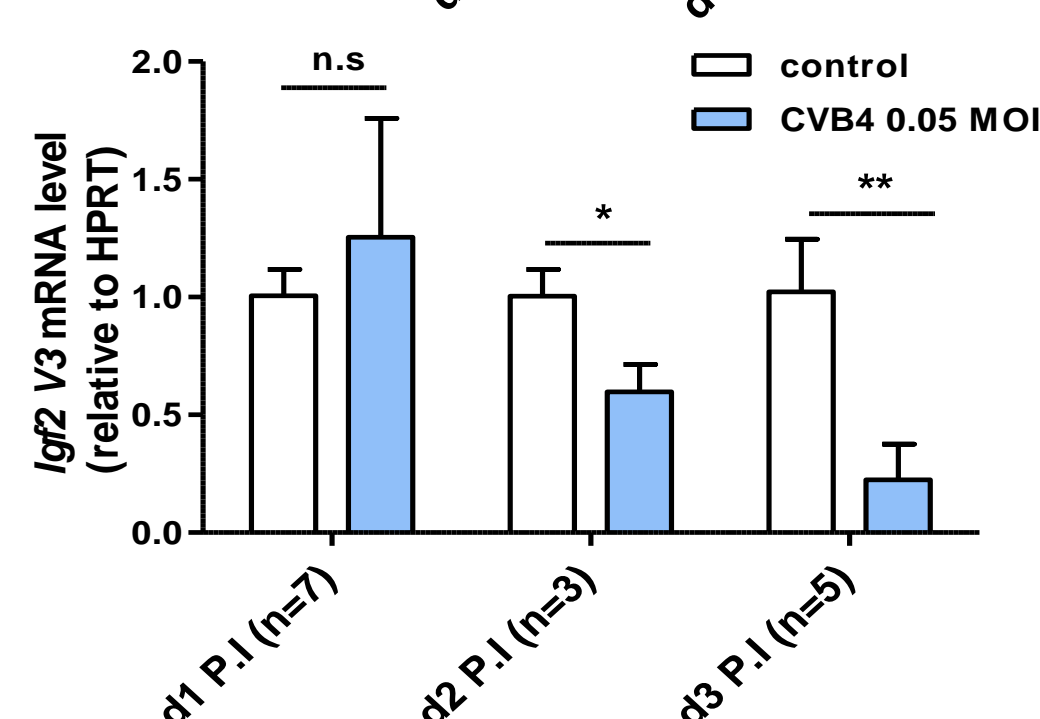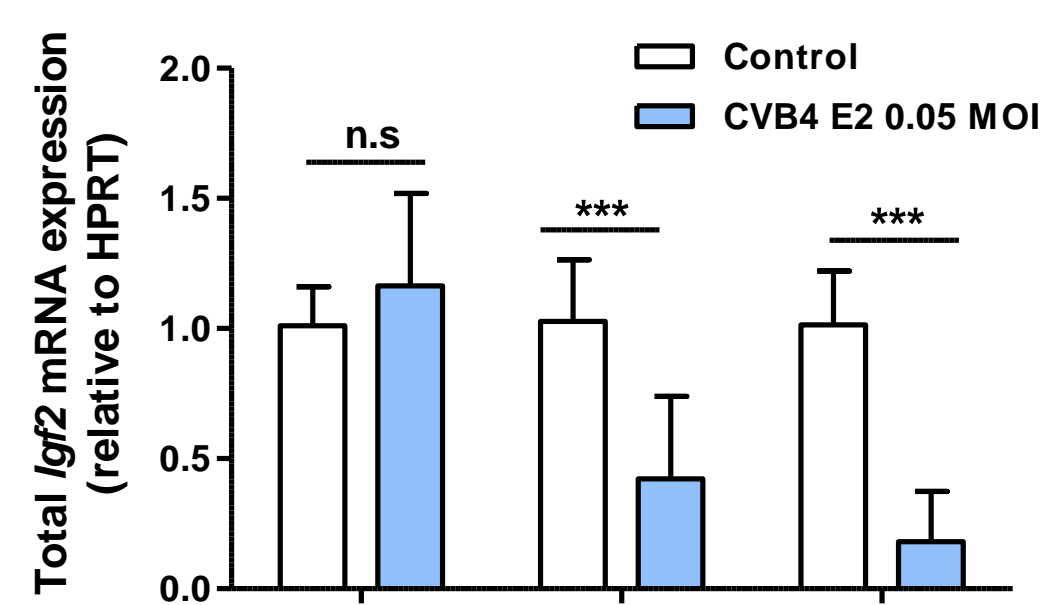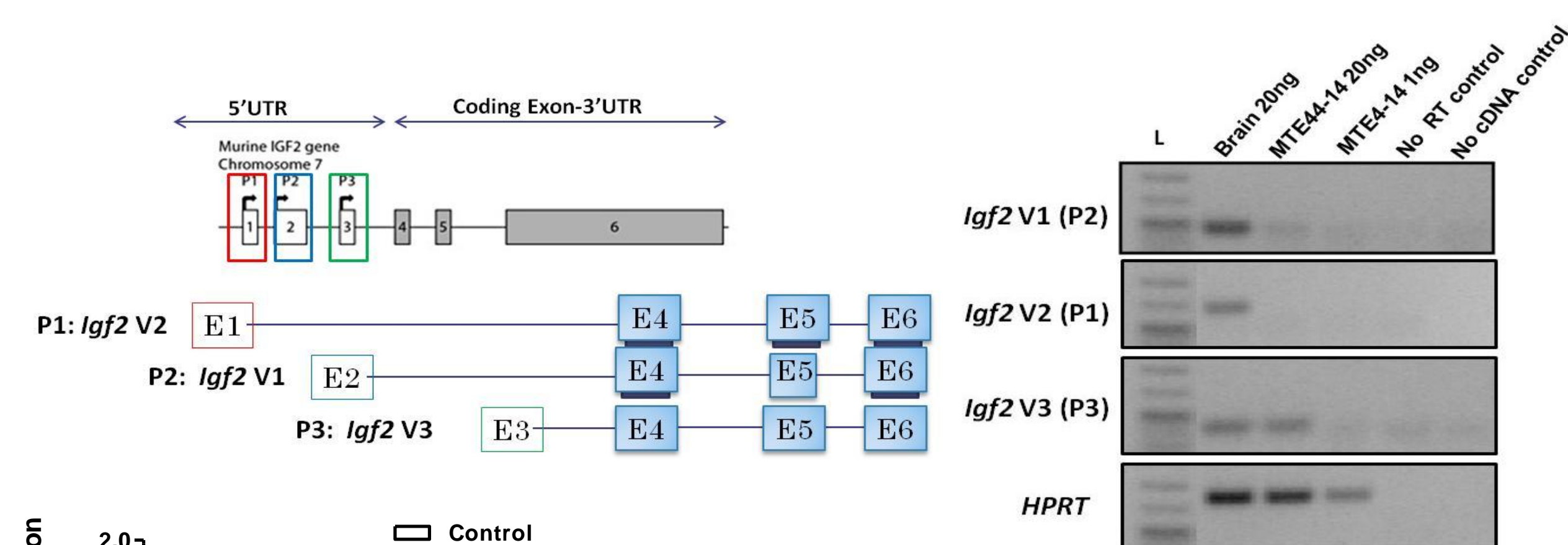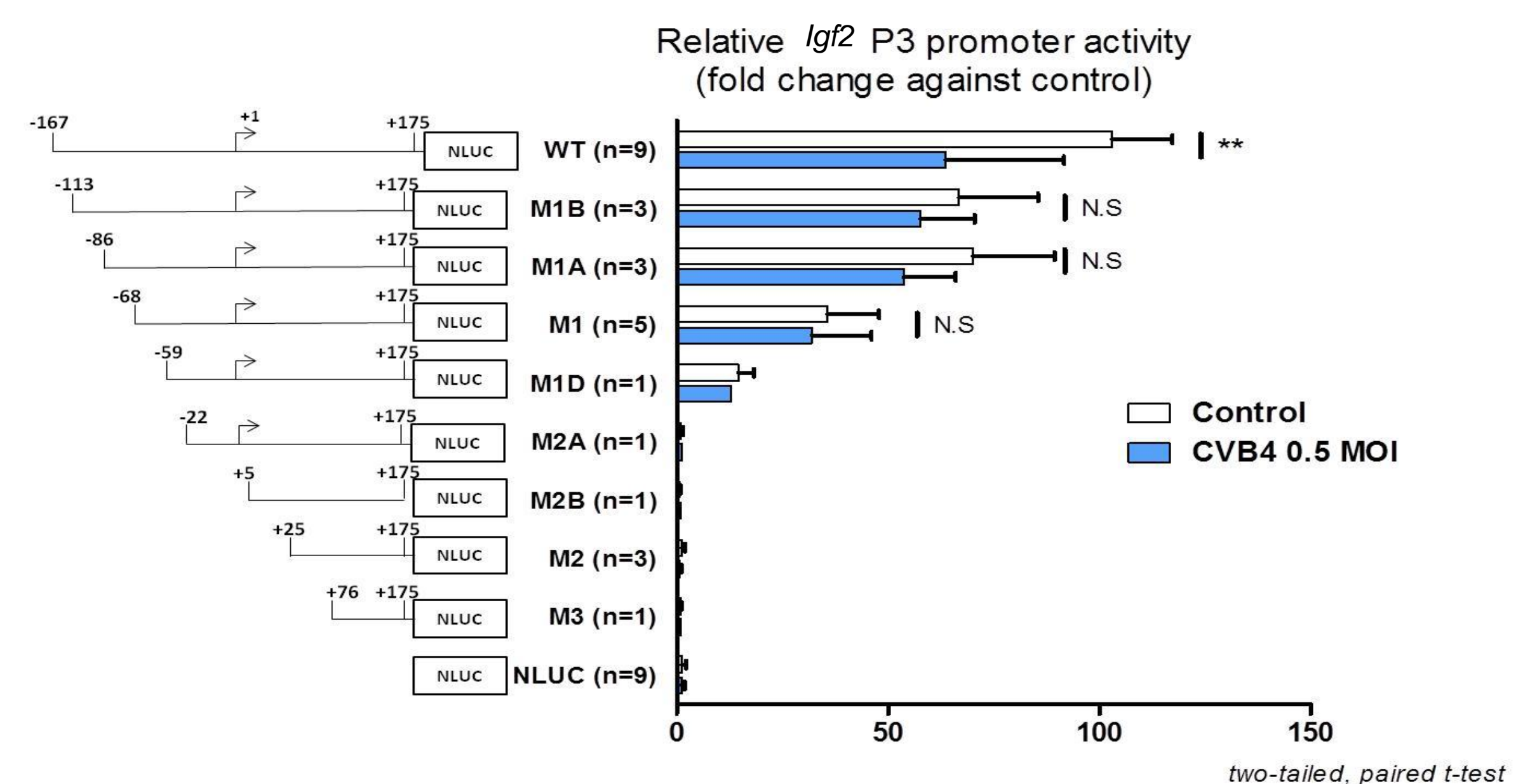

MOI : multiplicity of infection

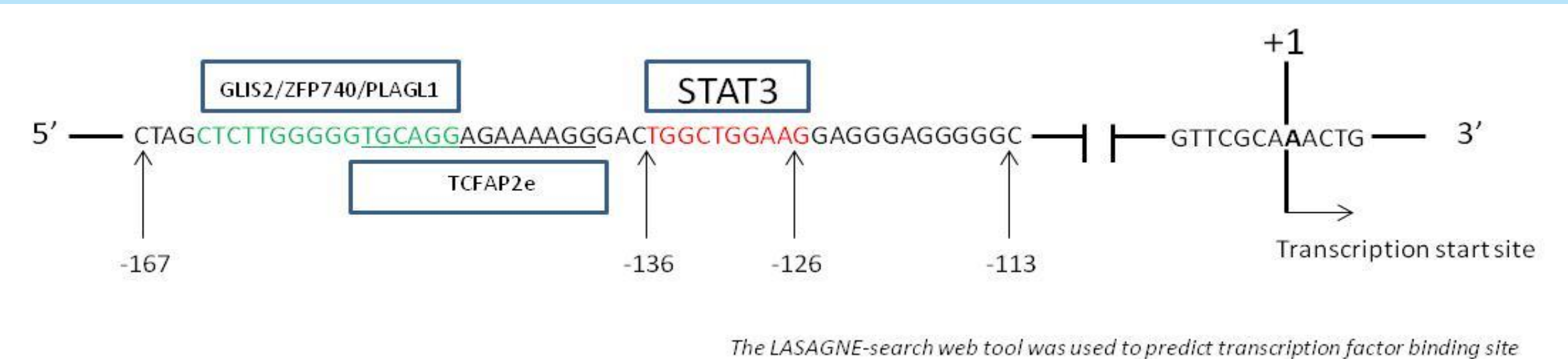### 2. CVB4 replication in MTE4-14 cells

### 3. CVB4 decreases *Igf2* P3 promoter activity and does not affect *Igf2* mRNA degradation

4. CVB4 affects promoter activity only in the −167 to -113 region

two-tailed, paired t-test

5. *In silico* analysis of the -167/-113 region reveals STAT3 binding site

The LASAGNE-search web tool was used to predict transcription factor binding site

6. CVB4 decreases STAT3 phosphorylation
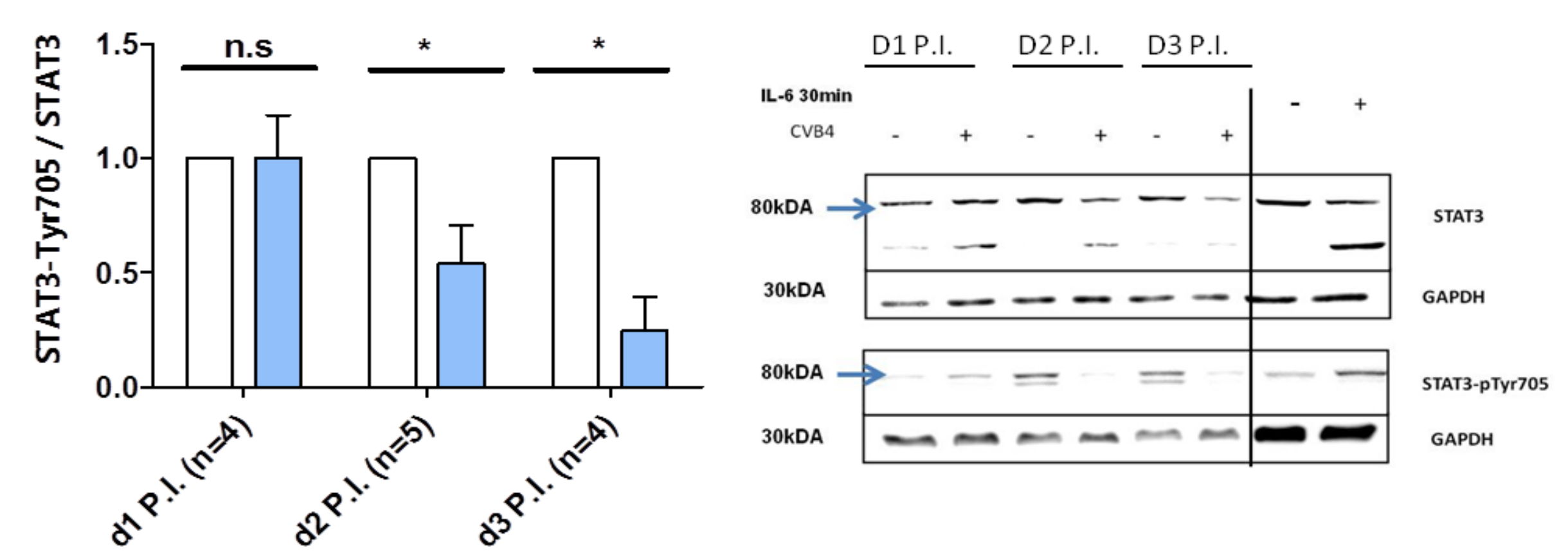
CONCLUSIONS

These results show that the CVB4-induced decrease in *Igf2* expression, and more precisely *Igf2* V3 mRNA, could result from a decrease in *Igf2* P3 transcriptional activity (without *Igf2* mRNA degradation). This loss of transcriptional activity could probably result from a modulation of the transcription factor STAT3 activity, since STAT3 phosphorylation decreases during CVB4 infection.

CONTACT

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