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## Target Genes of WT1 in Leukemic Cells

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## Conclusion

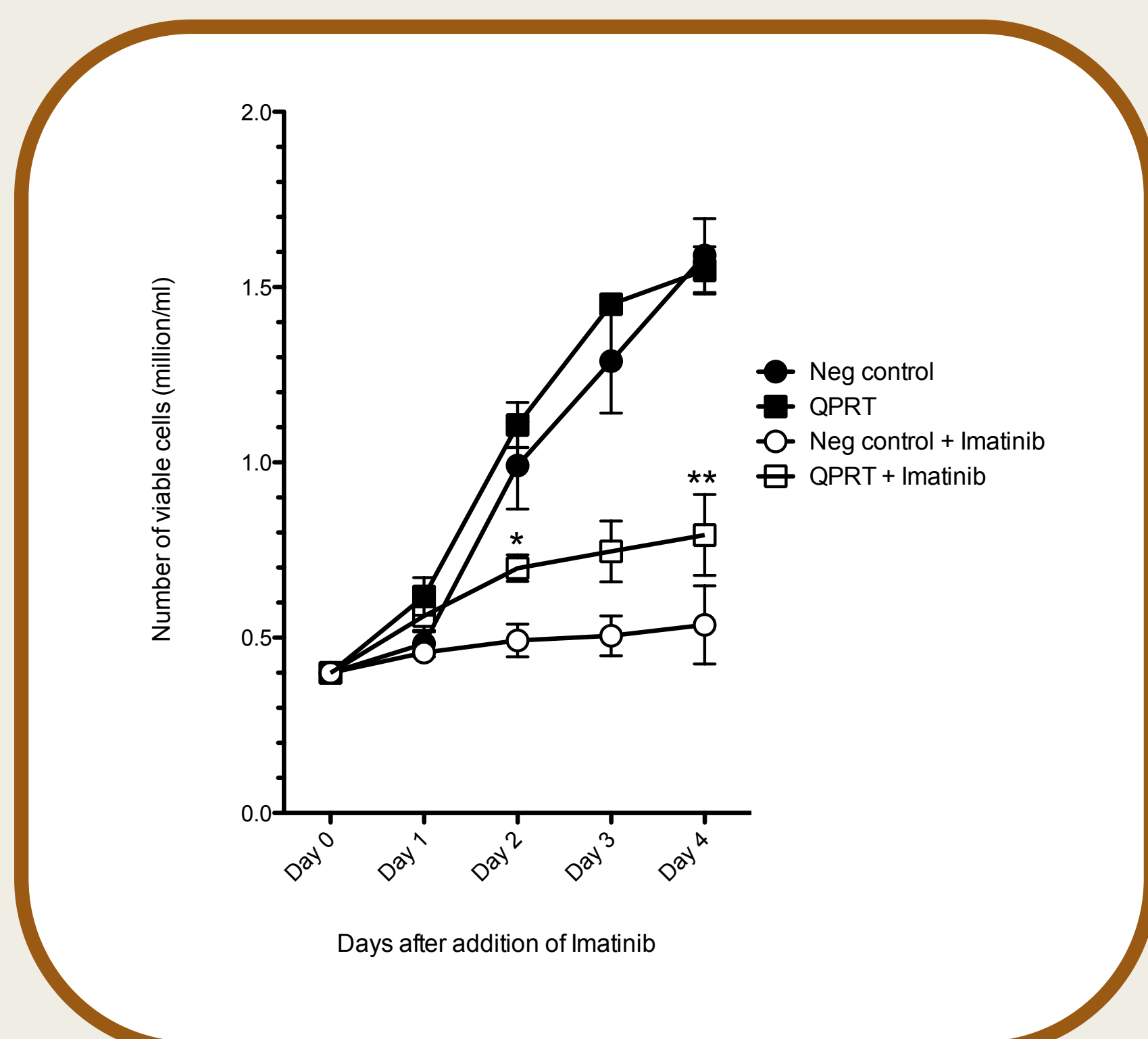
Overexpression of the oncogene *WT1* is common in acute myeloid leukemia (AML). *QPRT*, *NAB2*, and possibly *FSCN1* have been found to be direct target genes of the transcription factor WT1. *QPRT*, *NAB2* and *FSCN1* may be important for the leukemic phenotype.

## Introduction

Wilms' tumor is a childhood kidney cancer, in which the gene *Wilms' tumor gene 1 (WT1)* is involved in about 20% of the cases. The transcription factor WT1 is also recurrently mutated in acute myeloid leukemias (AMLs). Mutations and high expression of *WT1* associate with a poor prognosis in AML (1). In mice, overexpression of *WT1* contributes to the induction of acute leukemia (2), further emphasizing a role for WT1 in leukemia development. Molecular mechanisms and target genes for WT1 in leukemia are, however, incompletely understood.

## Background to the study

High expression of the transcription factor *WT1* is found in leukemic blasts from most AML patients (1). To identify putative novel target genes for WT1 in leukemia, we identified partial correlations in gene expression between *WT1* and other genes in a large cohort of 3,844 AML patients. We found that *QPRT* (quinolinate phosphoribosyltransferase), *NAB2* (NGFI-A binding protein 2), and *FSCN1* (fascin) were genes with high transcriptional correlation to *WT1*. This finding led us to investigate functional relationships between *WT1* and putative target genes.

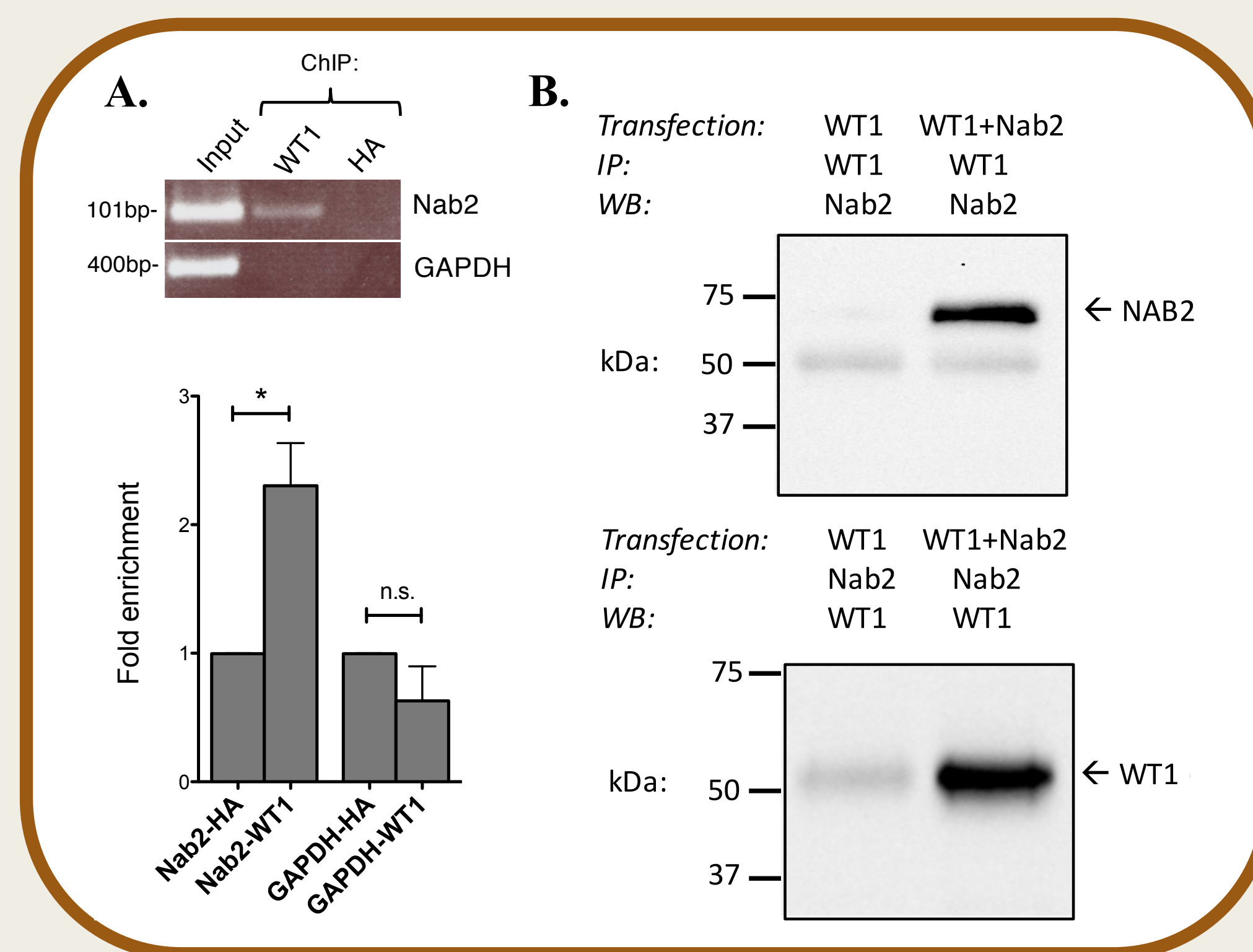


**Figure 1. QPRT overexpression in K562 cells reduces sensitivity to imatinib.**

*QPRT*, encoding a key enzyme in the *de novo* NAD<sup>+</sup> synthesis pathway, was transfected into K562 cells. Cells stably overexpressing the QPRT protein and control cells, were then exposed to imatinib for 96 h. There was a significant difference in survival between QPRT overexpressing cells and controls.

By chromatin immunoprecipitation (ChIP), we have shown that WT1 binds to a conserved site of the *QPRT* promoter (see also fig 2).

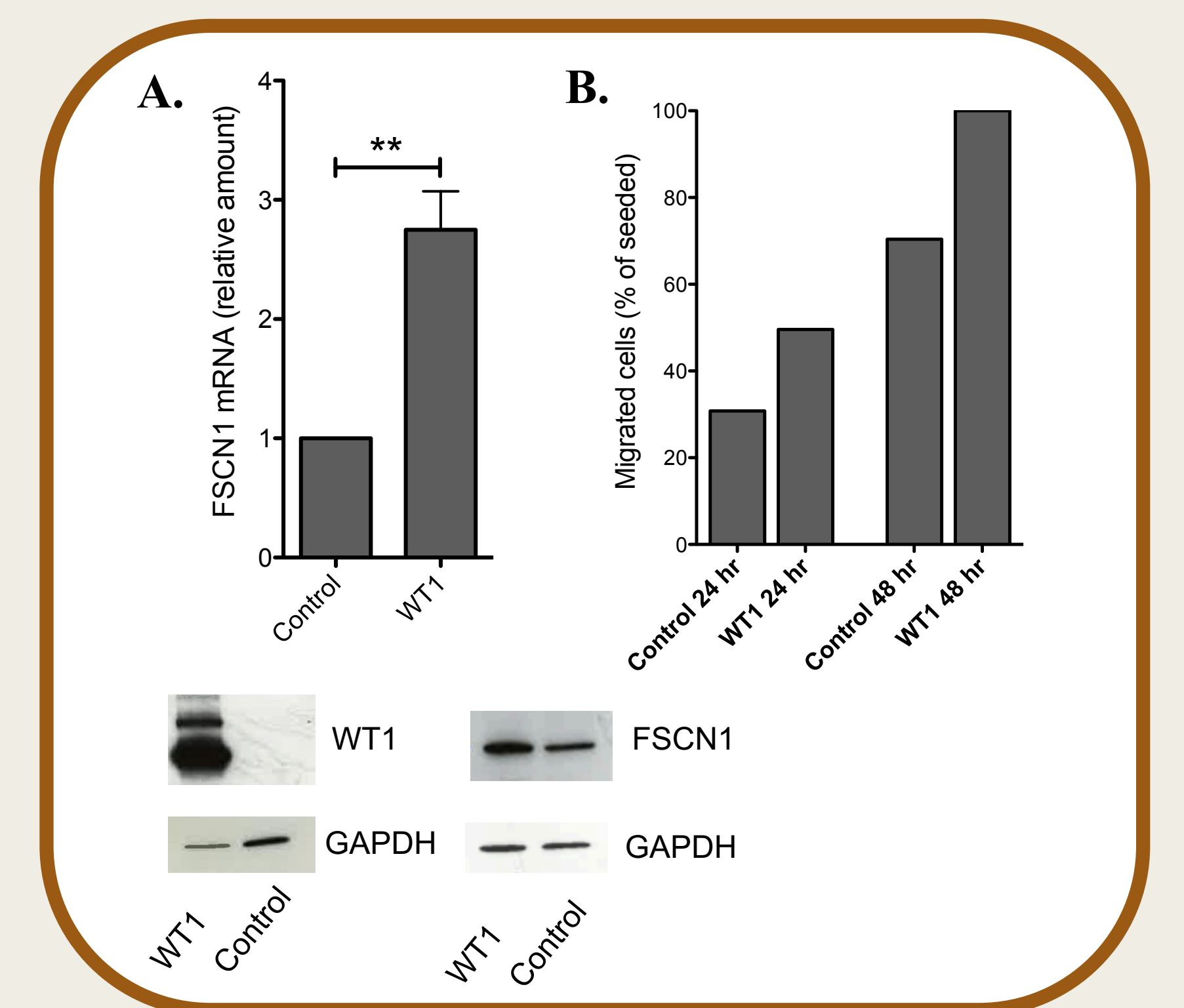
Thus, *QPRT* is a direct target gene of WT1, encoding a protein with anti-apoptotic properties (3).



**Figure 2. WT1 binds to the *NAB2*-promoter *in vivo*.**

*NAB2*, encoding a zinc-finger protein influencing cellular differentiation, proliferation, and cell death, was analyzed by ChIP to evaluate if its promoter has binding sites for WT1. Nuclear extracts from K562 cells, expressing endogenous WT1 and *NAB2*, were precipitated and the DNA was amplified by PCR (A). Fold enrichment was determined by densitometry (A, lower). GAPDH and anti-HA were used as negative controls.

As shown by others (3), *NAB2* and the transcription factor EGRI, with similarity to WT1, bind directly to each other (4). To investigate the situation of *NAB2* and WT1, 293T/17 cells were cotransfected with *WT1*<sup>+/−</sup> and *NAB2*, co-immunoprecipitated, and analyzed by Western blot (B), demonstrating binding of *NAB2* to WT1 (5).



**Figure 3. FSCN1 levels rise in U937 cells overexpressing WT1 and cells show higher migration.**

*FSCN1* is a globular actin-bundling protein, involved in cancer cell migration, invasion, and metastasis. We decided to look into its possible influence on WT1 and its potential role in migration of leukemic cells.

When we overexpressed WT1 in U937 cells, the *FSCN1* levels rose (A). Moreover, U937 cells overexpressing WT1 migrated to a higher extent compared to control (B), possibly due to *FSCN1* modulation of WT1.

Further investigations into the functional role of *FSCN1* in leukemia are ongoing.

## References

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