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YB1 -a Cancer Biomarker and a Drug Resistance Factor

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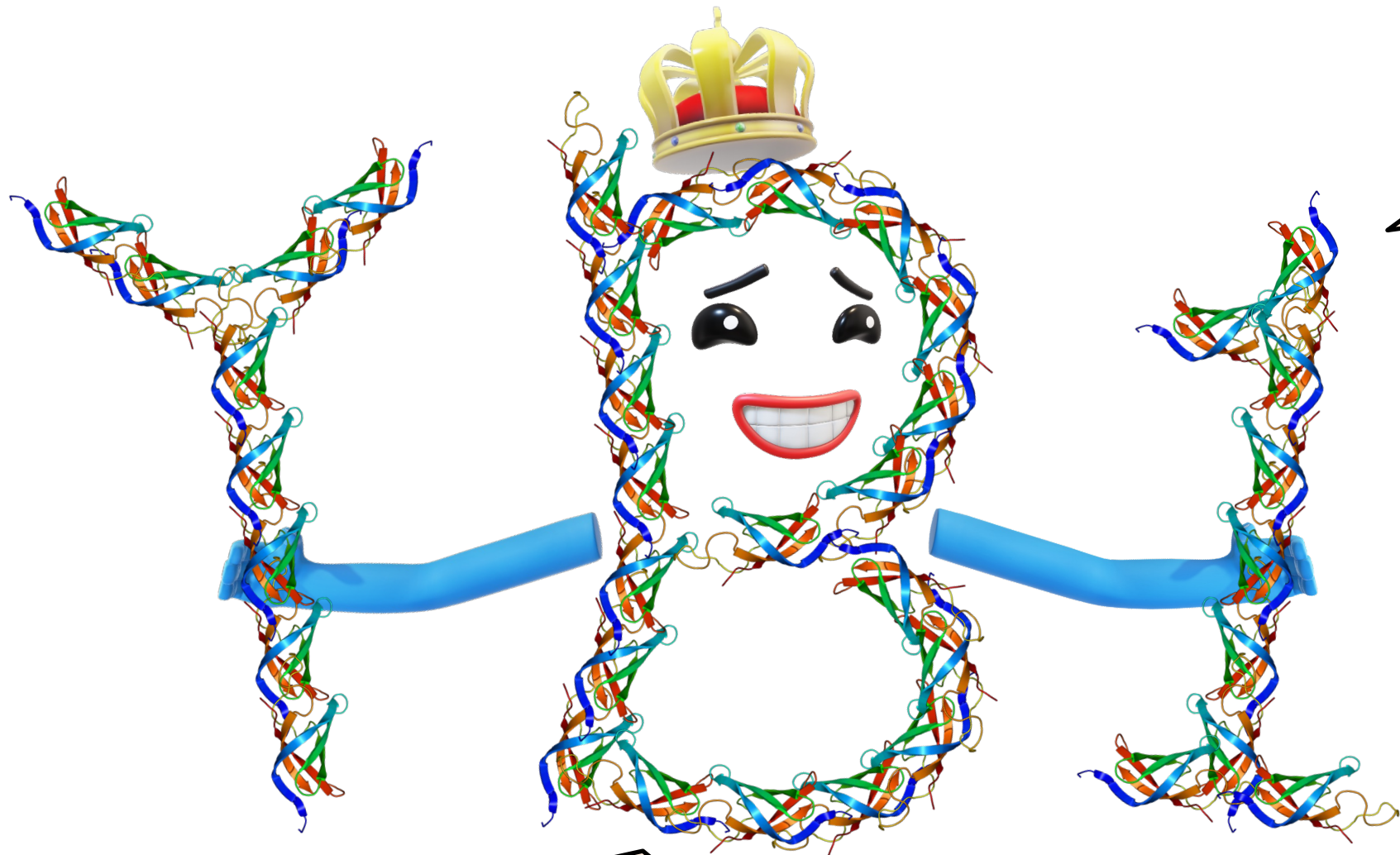
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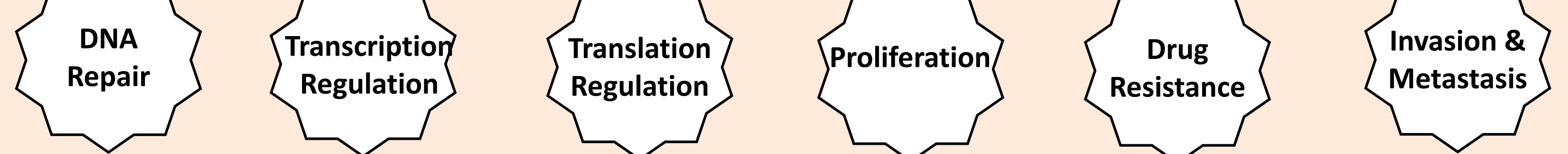
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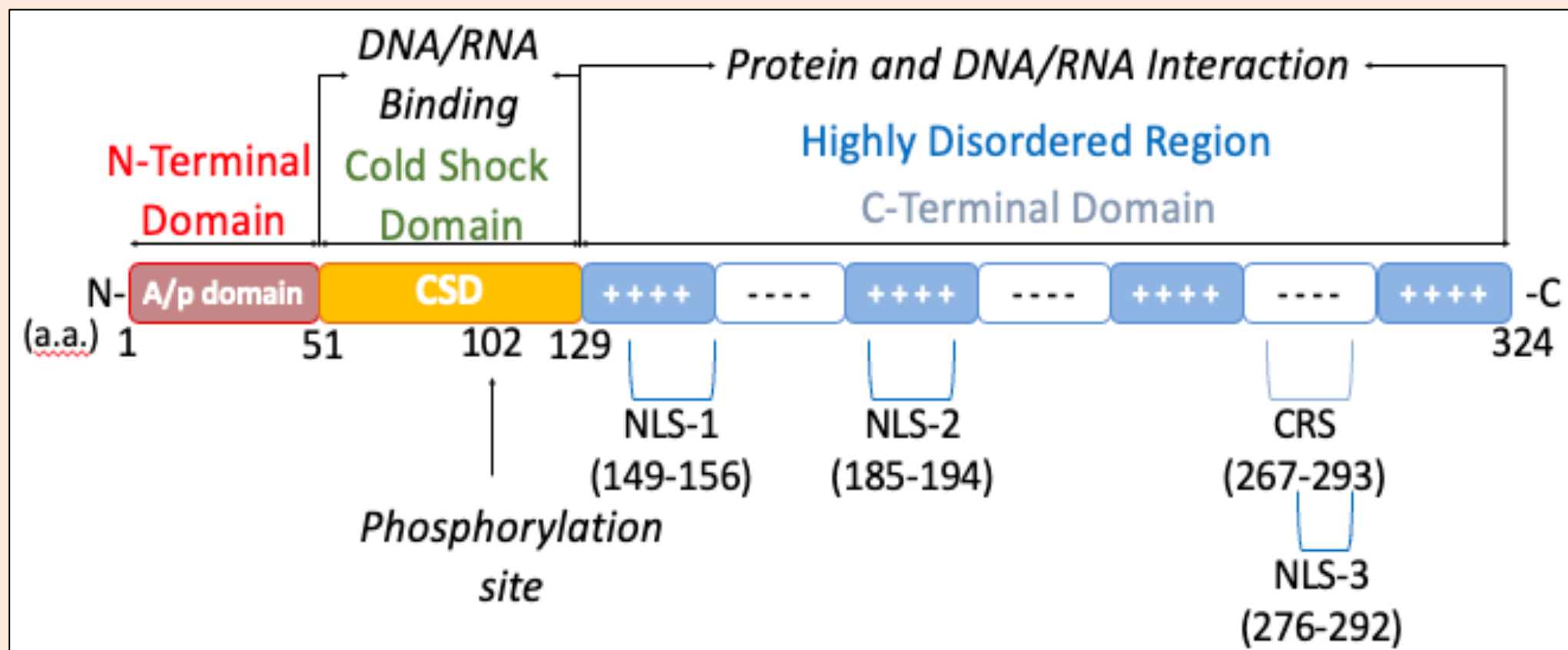
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Introduction: Y-box binding protein 1 (YB1) is a member of the **cold shock protein** family, which is known for its DNA- and RNA-binding. YB1 has **multiple functions** in normal and cancerous cells, some of which are listed below:



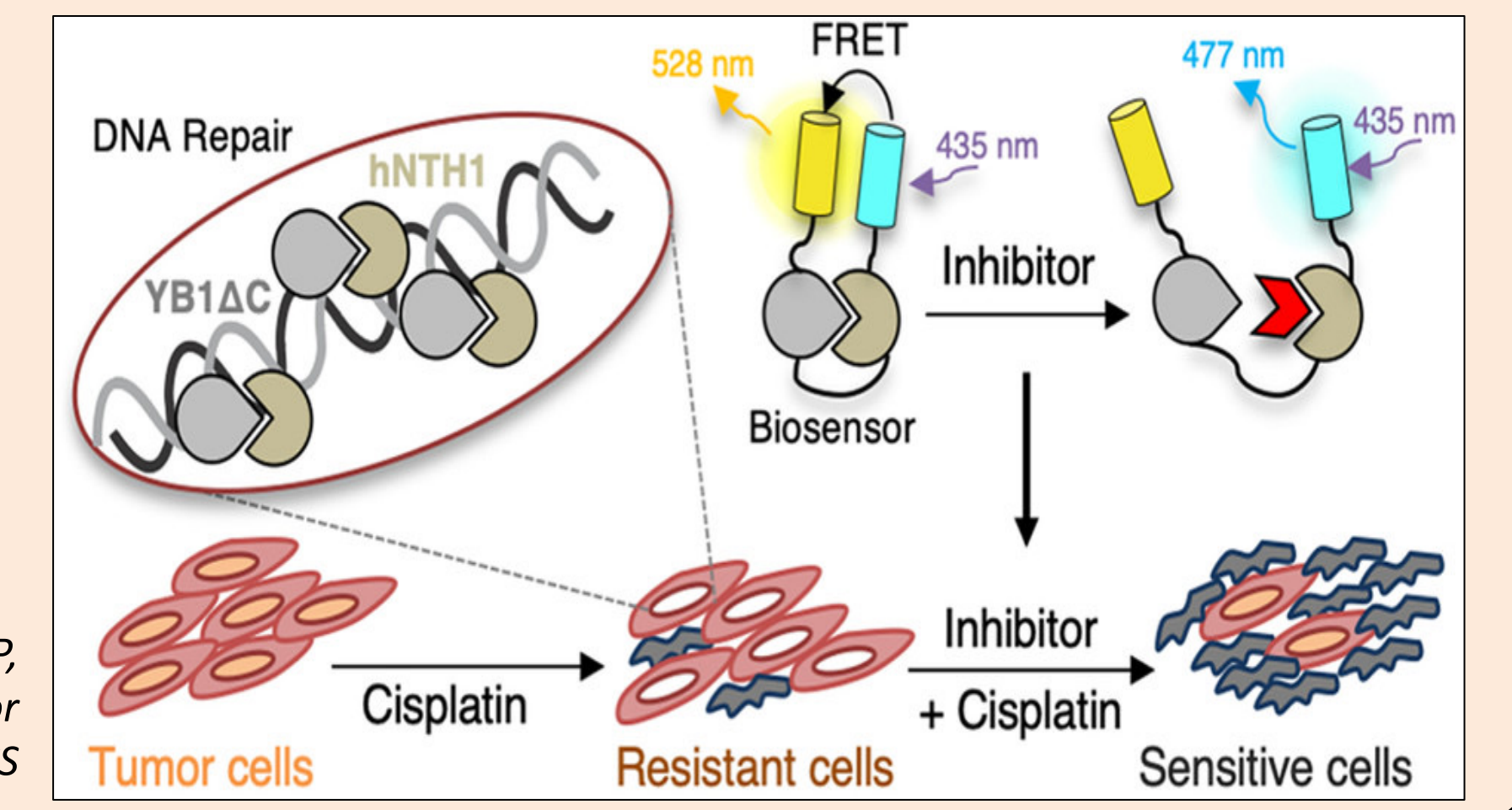
YB1 Domain Organisation



Origin of the Project:

Our team has shown that YB1 interacts with NTH1 and stimulates its DNA repair activity [1]; NTH1 is a DNA repair enzyme of the base excision repair (BER). As shown in the figure, this interaction is enhanced in MCF7 breast cancer-derived cells treated with first-line chemotherapeutic agents, such as cisplatin, leading to **resistance to anti-cancer treatment**.

[1] Senariso M, Barette C, Lacroix F, De Bonis S, Stelter M, Hans F, Kleman JP, Fauvarque MO, Timmins J. Förster Resonance Energy Transfer Based Biosensor for Targeting the hNTH1-YB1 Interface as a Potential Anticancer Drug Target. ACS Chem Biol. 2020 15(4):990-1003.



Objective:

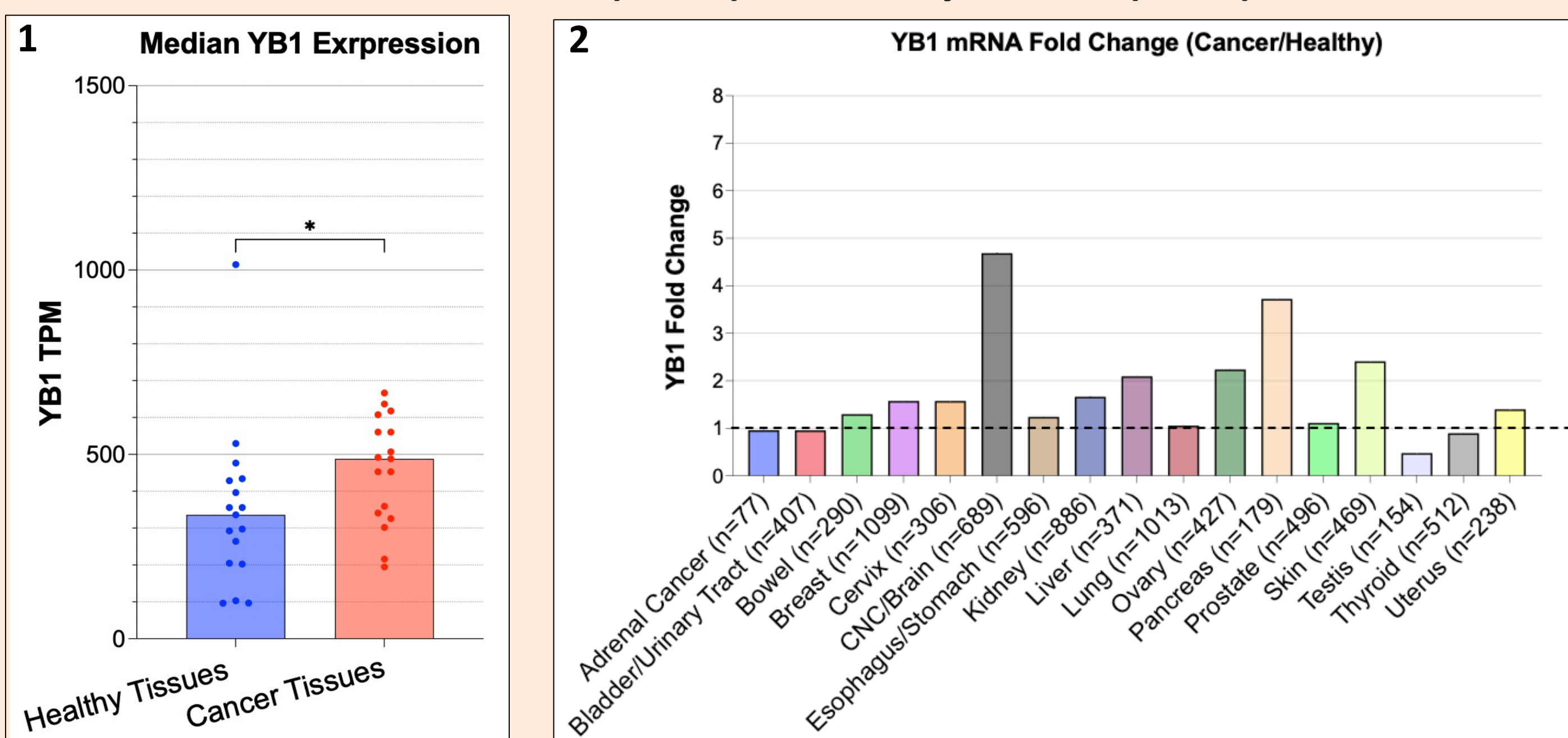
This urged the team to evaluate the potential of YB1 as a key biomarker in cancer biology and to characterize its precise role in cancer progression, DNA repair and chemoresistance. Our **first goal** was to perform a bioinformatic analysis of public databases to **identify cancer types** overexpressing YB1 compared to the equivalent healthy tissue, showing a correlation between YB1 and BER factor expression, and having Yb1 as a potential factor for early diagnosis and prognosis.



Results: Bioinformatics Analysis

A- YB1 mRNA Expression (TPM): Cancer vs Healthy

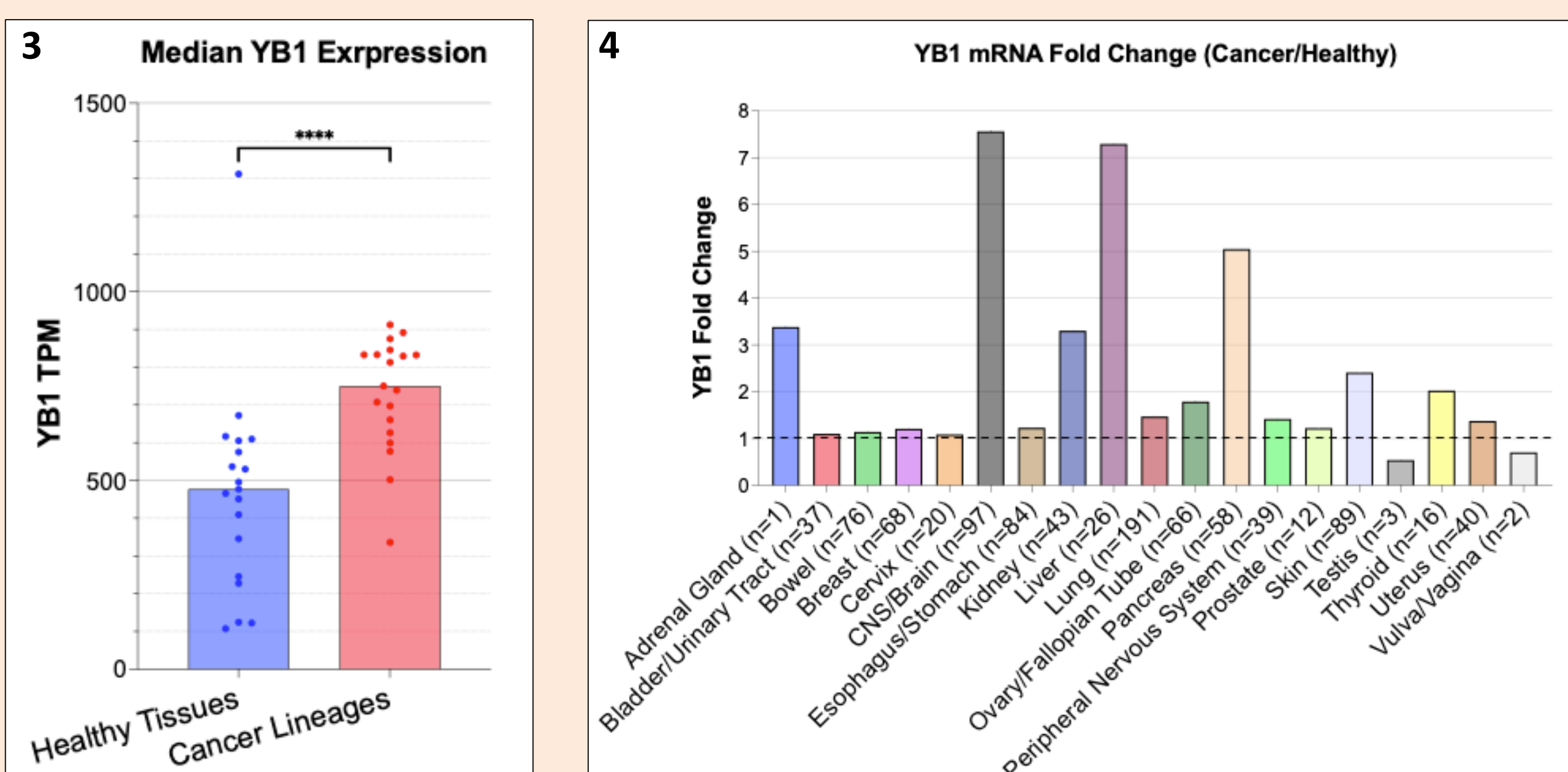
Cancerous Tissues (TCGA) vs Healthy Tissues (GTEx)



Cancer tissues show an overall significant overexpression of YB1 compared to healthy tissues.

YB1 is significantly overexpressed in most cancer tissues. This profile supports the overexpression results observed in the cancer cell lines (in Panel 4).

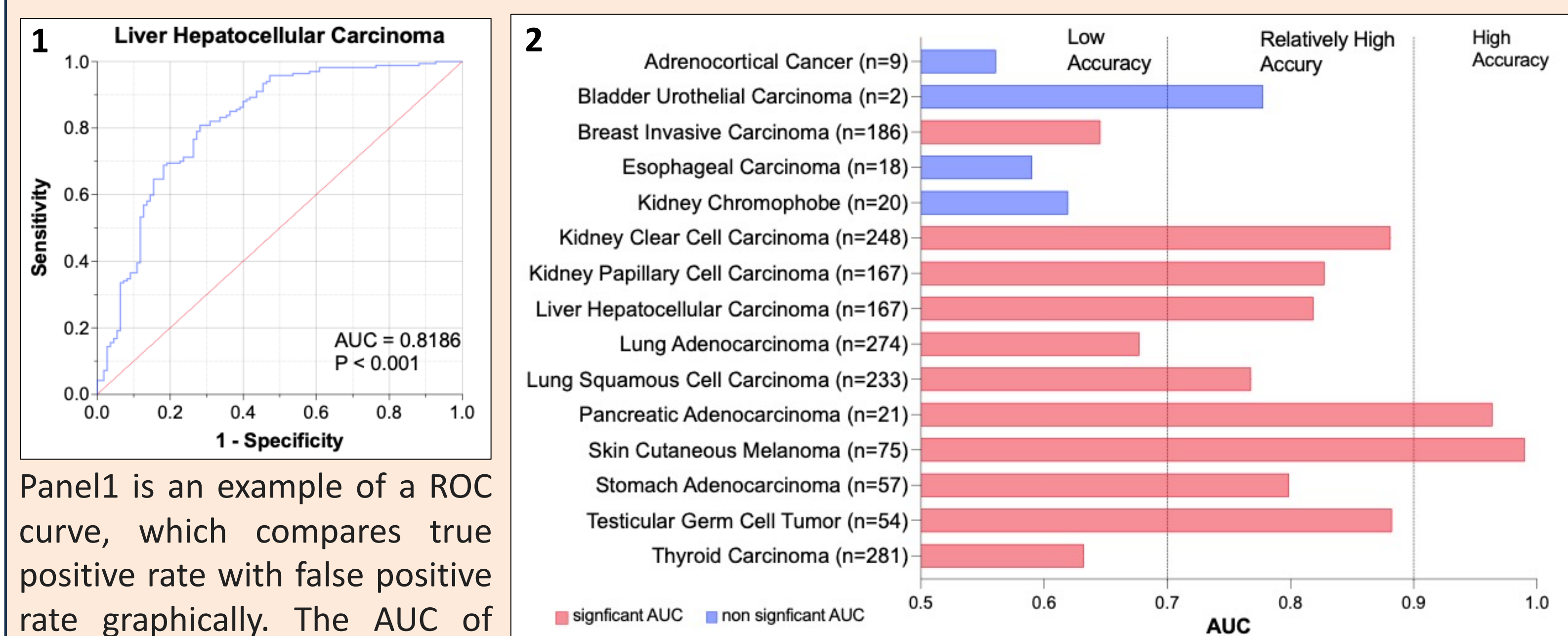
Cancer Cell Lines (CCLE) vs Healthy Tissues (GTEx)



Cancer cell lines show an overall significant overexpression of YB1 compared to healthy tissues.

YB1 is significantly overexpressed in most cancer cell lines.

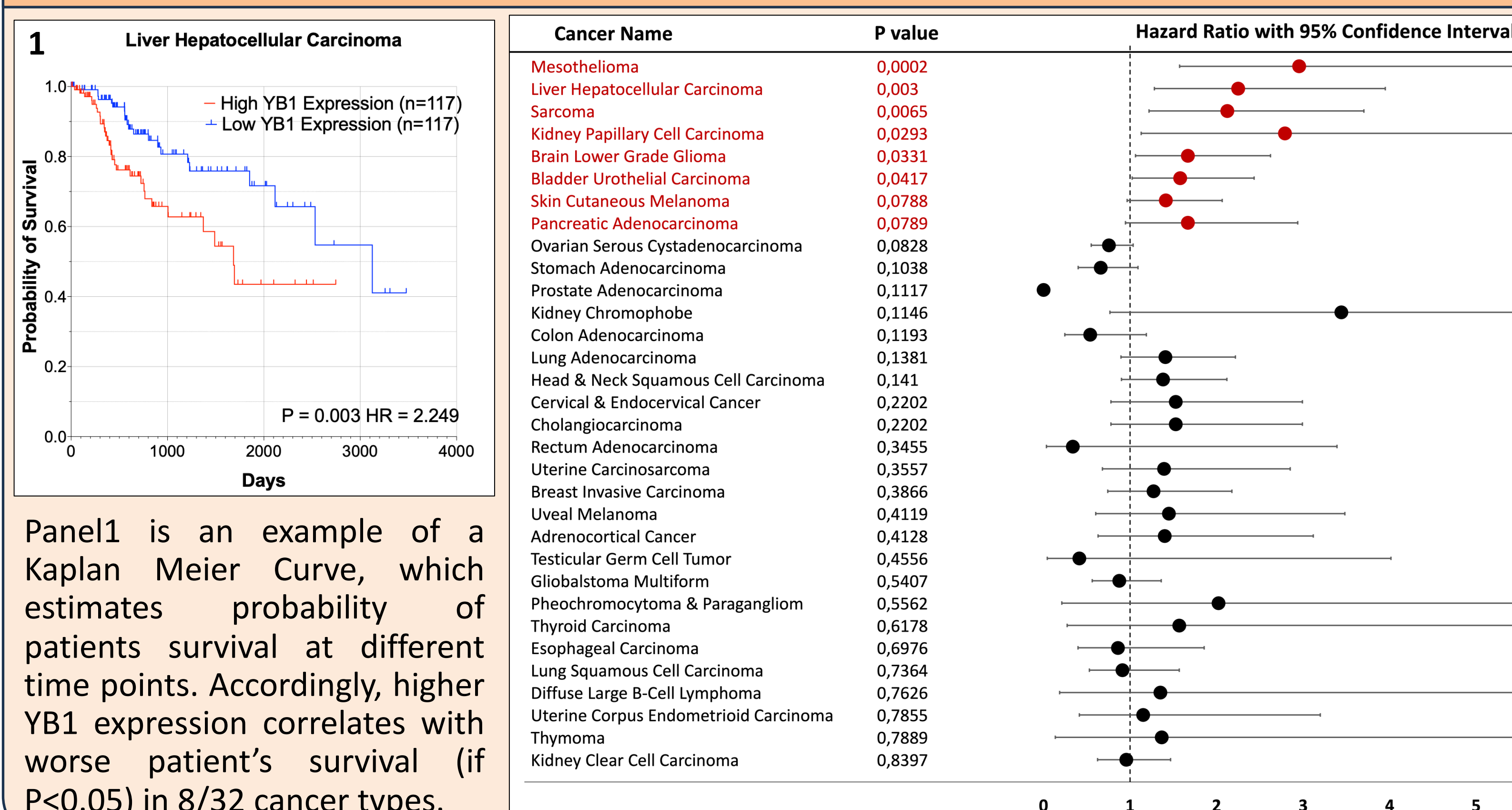
B- YB1 mRNA Expression and Early Diagnosis



Panel1 is an example of a ROC curve, which compares true positive rate with false positive rate graphically. The AUC of this curve is used to determine the diagnostic potential of YB1.

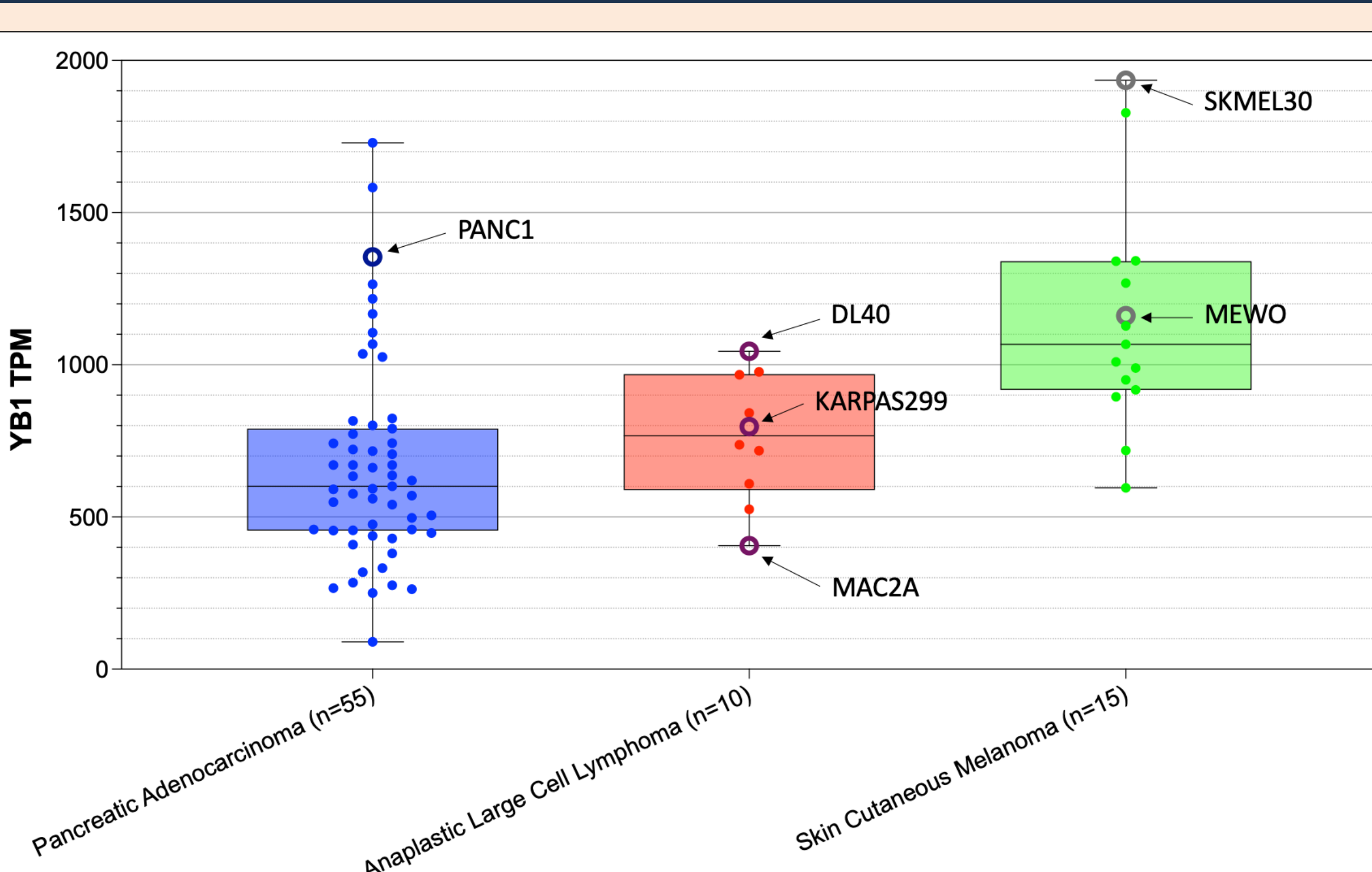
Based on Panel2, YB1 could potentially be used as an early diagnostic factor ($1 > AUC > 0.7$) in 8/15 cancer types.

C- YB1 mRNA Expression and Prognosis



Panel1 is an example of a Kaplan Meier Curve, which estimates probability of patients survival at different time points. Accordingly, higher YB1 expression correlates with worse patient's survival (if $P < 0.05$) in 8/32 cancer types.

D- Cancer Cell Lines Selection



PANC1:

- High YB1 expression.
- Goal: Perform drug resistance analysis (DRA) before and after YB1 knockdown.

DL40, KARPAS299, MAC2A:

- Different YB1 expression profiles.
- Goal: Compare DRA between the three different profiles.

SKMEL30 & MEWO:

- Two contrasting YB1-NTH1 profiles (higher YB1-lower NTH1 vs lower YB1-higher NTH1)
- Goal: Compare DRA between the two different profiles.

Portals and Databases

- **CCLE:** Cancer Cell Line Encyclopedia (Cell lines data; Broad Institute)
- **TCGA:** The Cancer Genome Atlas (Patients data; National Cancer Institute and National Human Genome Research Institute)
- **GTEx:** Genotype-Tissue Expression (Healthy tissues data; Broad Institute)

Conclusions

- The over expression of YB1 (shown) and several BER factors (not shown) in patients (TCGA), supports our selection of the cell lines.
- YB1 is a potential diagnostic and prognostic factor in several cancer types.
- We will experimentally study the correlation between YB1 expression, DNA repair, and drug resistance in the selected cancer cell lines through different techniques like Western Blot, RTqPCR, siRNA Knockdown, drug sensitivity tests...etc.

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