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# Rational design of a miniprotein to inhibit the oncogenic transcription factor MYC

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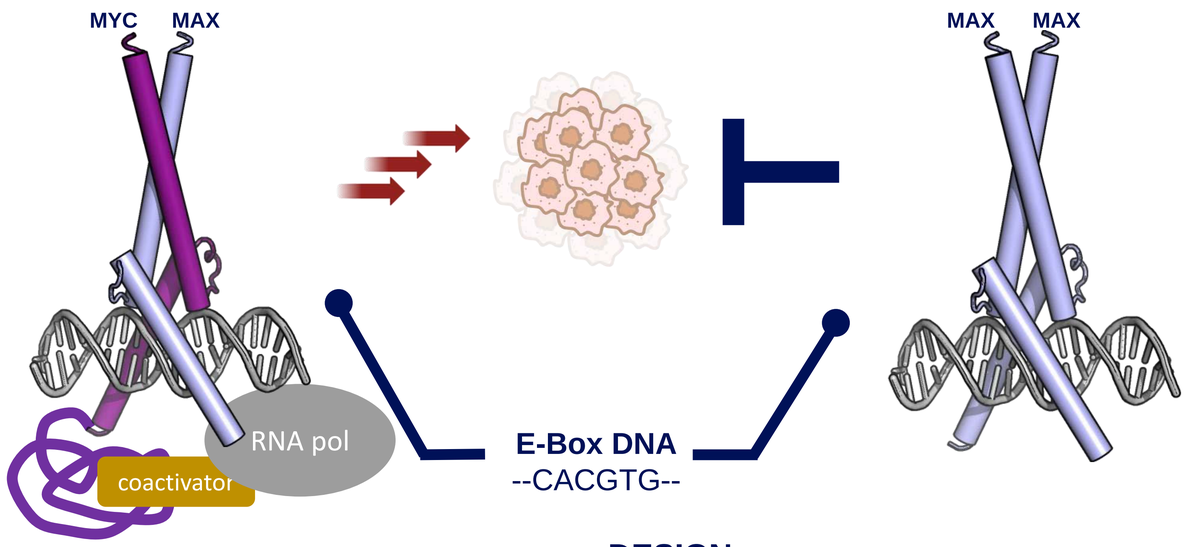
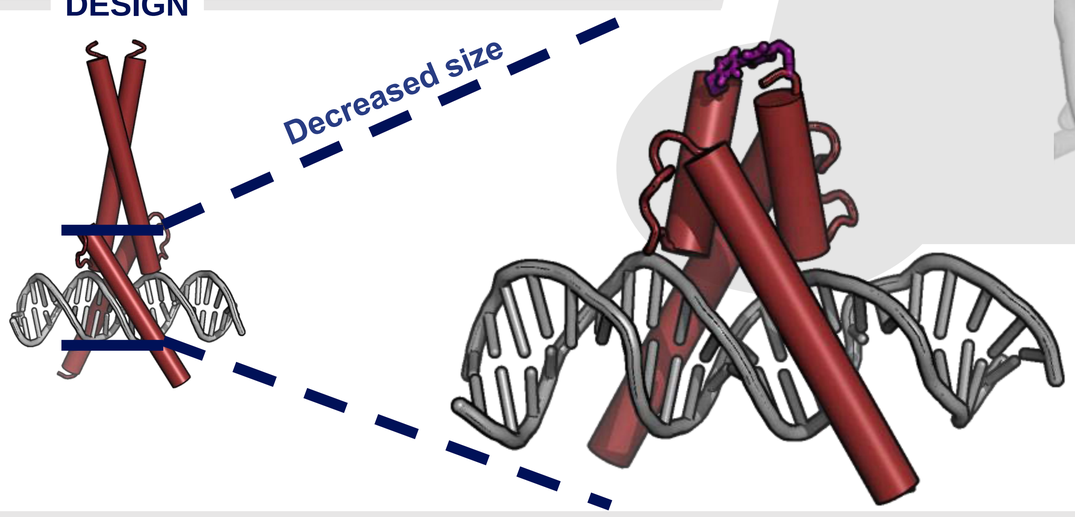
## The master regulator MYC is involved in >50% of human cancer

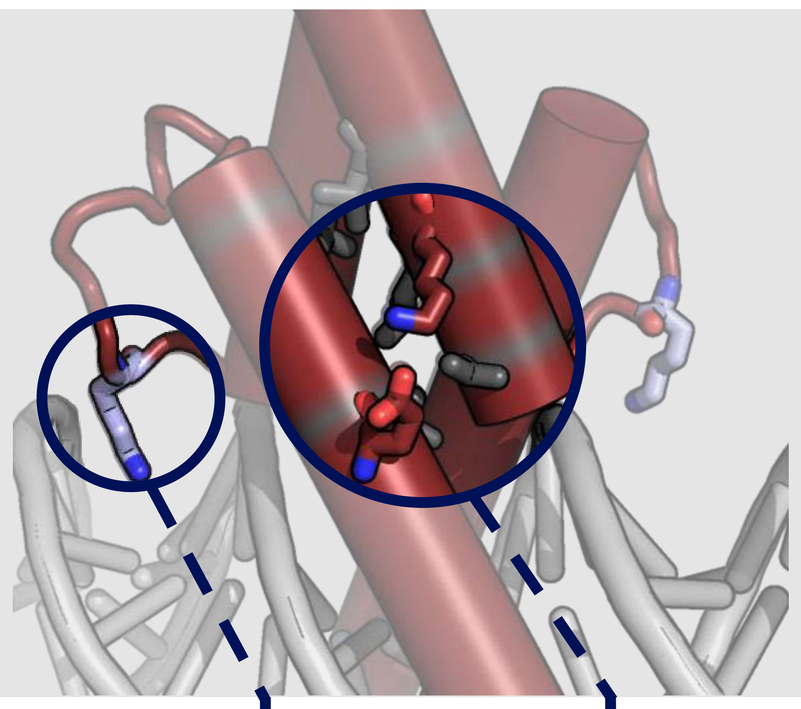



- **Omomyc** targets E-box DNA.[1]
- **Decreasing** protein size can **increase** cell permeability.[2]
- **DuoMYC** has been engineered to **inhibit** MYC activity.

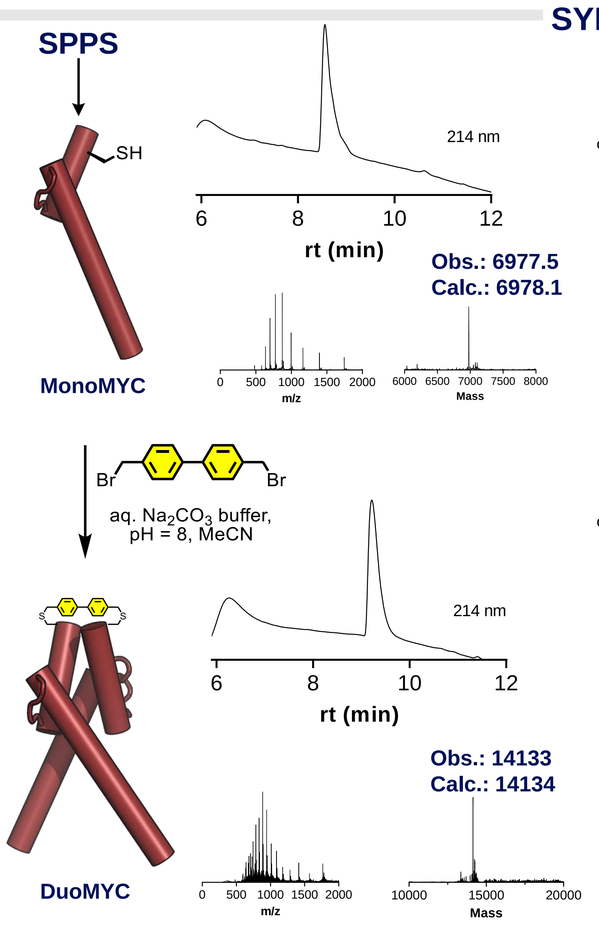
## DESIGN

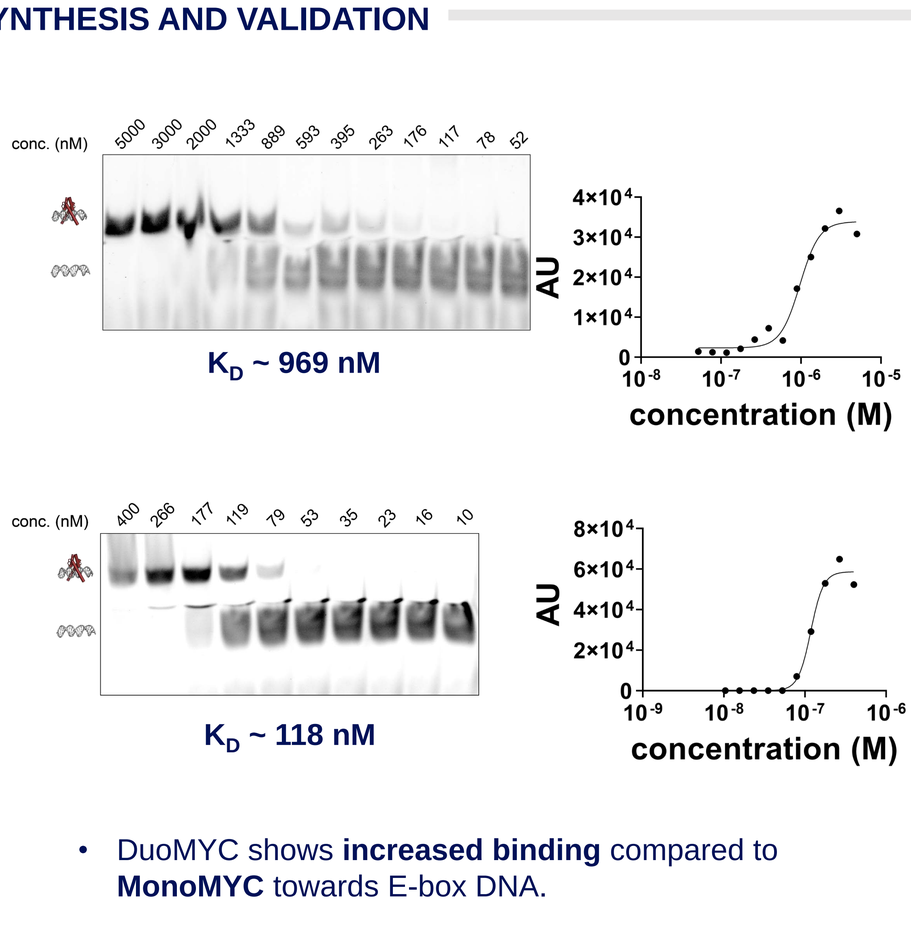



## INTERACTION




## SYNTHESIS AND VALIDATION

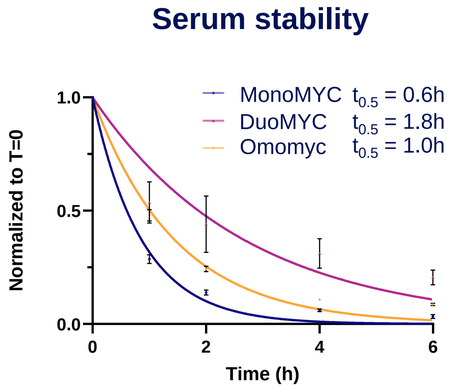


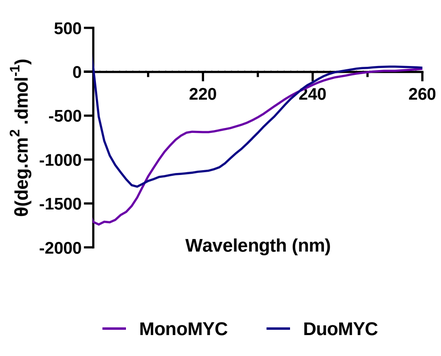

- DuoMYC shows **increased binding** compared to **MonoMYC** towards E-box DNA.

## CHARACTERIZATION

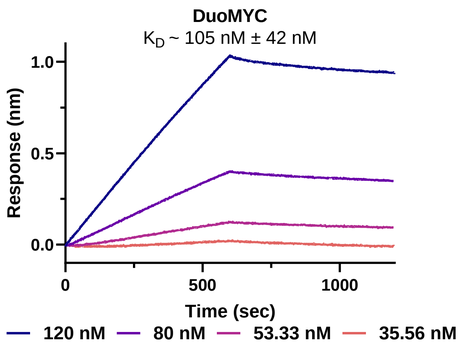
### Serum stability




### Circular Dichroism

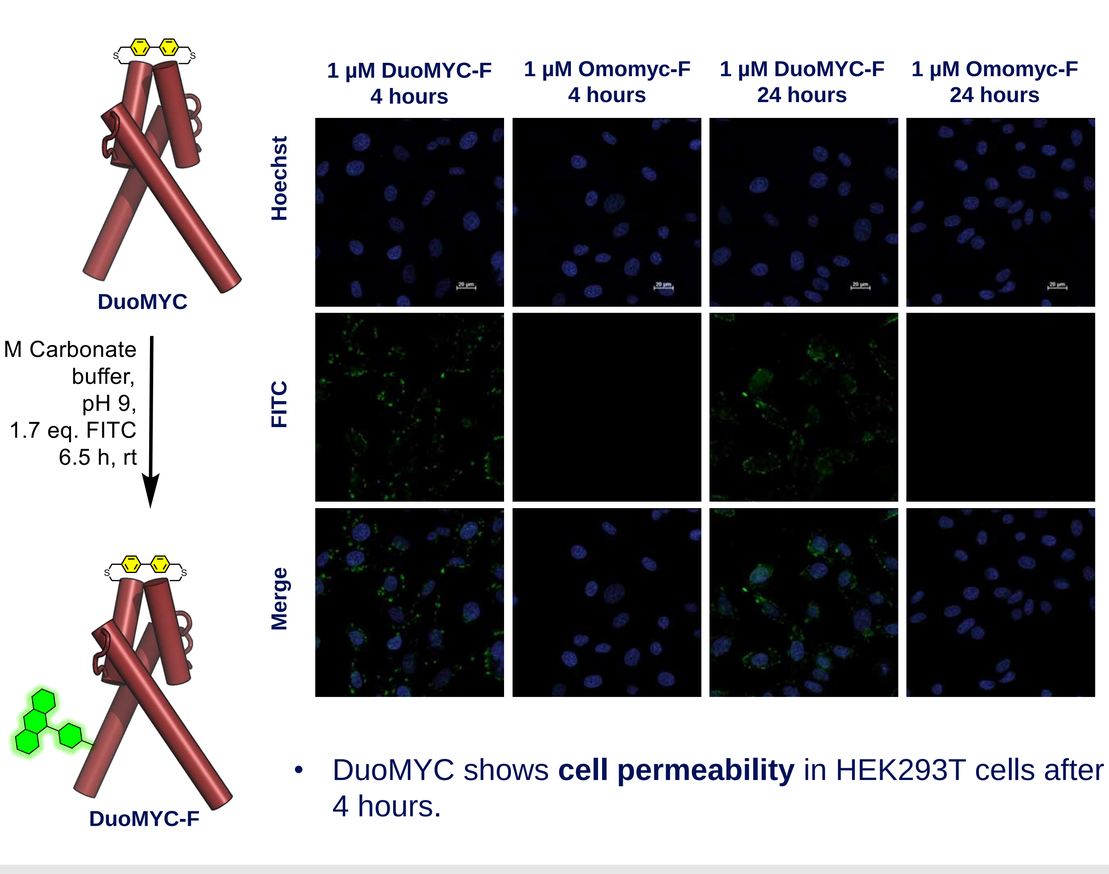



### Biolayer interferometry (BLI)




- **DuoMYC** shows serum stability.
- **DuoMYC** adopts a partial α-helix in solution.
- BLI **confirms** strong binding to E-box DNA.

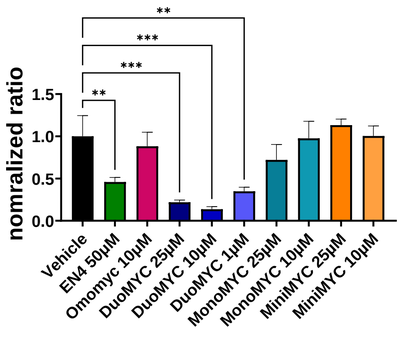
## CELL PENETRATION



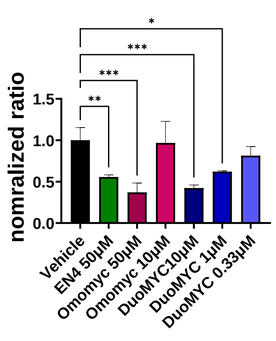

- DuoMYC shows **cell permeability** in HEK293T cells after 4 hours.

## CELLULAR ACTIVITY

### MYC reporter gene assay in HEK293T cells

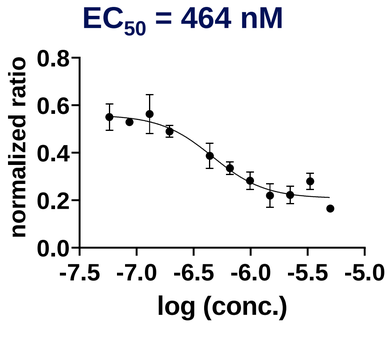



### MYC reporter gene assay in Hela cells




### MYC reporter gene assay in HEK293T cells

$EC_{50}$ = 464 nM




- DuoMYC shows **cellular activity** in multiple cell lines.

## CONCLUSION

- We designed a small miniprotein called **DuoMYC** were we successfully replaced the leucine zipper domain with a chemical linker.
- DuoMYC shows **stability** in **human serum** and partial α-helix formation.
- DuoMYC shows **cell permeability.**
- DuoMYC successfully **inhibits** MYC from **binding** as shown in the reporter gene assays.

## REFERENCES

[1] L. Soucek, M. Helmer-Citterich, A. Sacco, R. Jucker, G. Cesareni, S. Nasi, *Oncogene 1998 1719* **1998**, *17*, 2463–2472.
[2] N. J. Yang, M. J. Hinner, in Methods Mol. Biol., NIH Public Access, 2015, pp. 29–53.
PDB structures used: 5I50, 1NKP

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