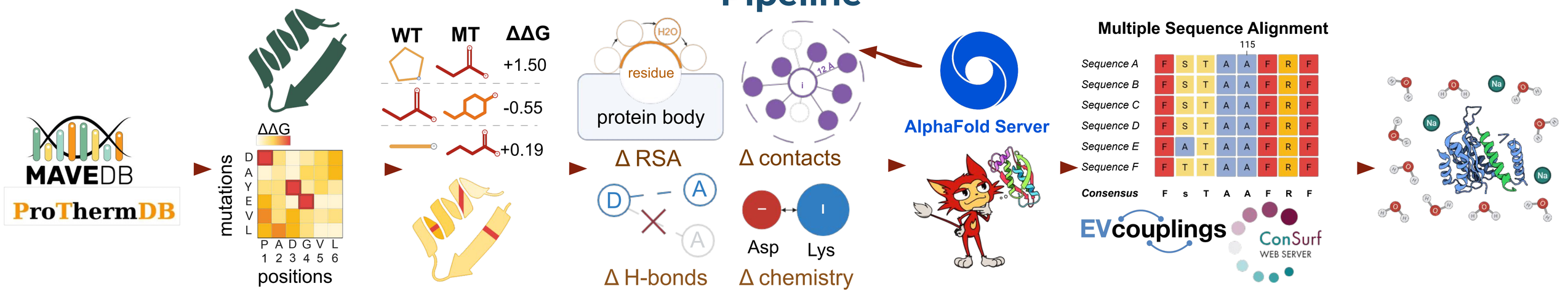
Structural Interpretation of Deep Mutational Scanning Variants

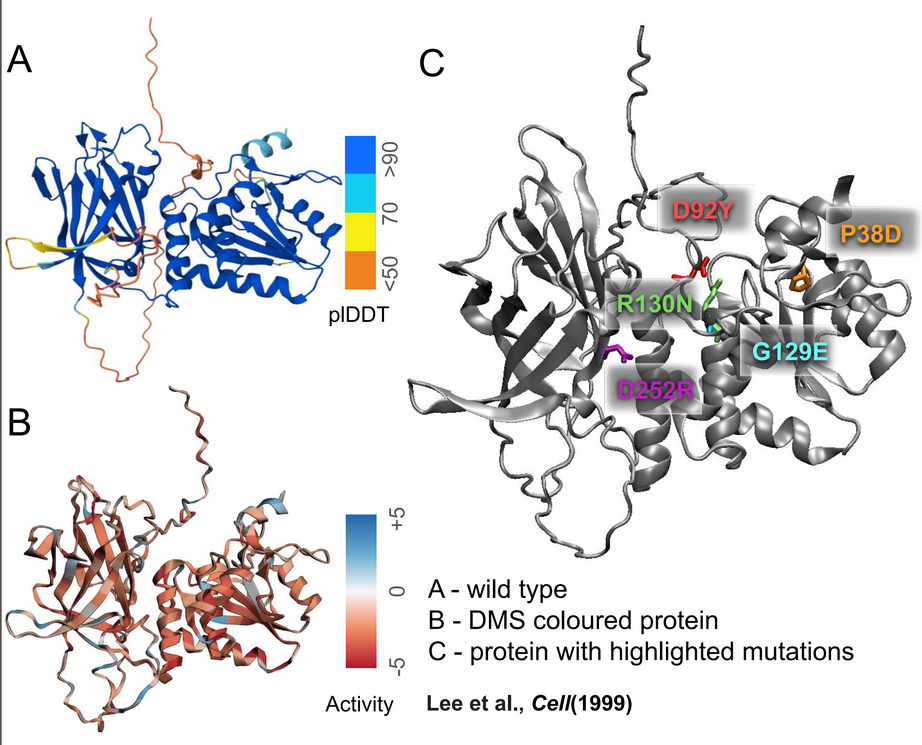
Introduction

- Protein function depends strongly on its 3D structure and physico-chemical properties.
- Deep Mutational Scanning (DMS) identifies variants that affect protein function, structure, and stability (ΔRSA, ΔHbonds, ΔContacts, features of amino acid residues; evaluate DMS data and based on structure choose top 5 and model).
- Structural analysis can help explain how mutations produce these functional effects.

Pipeline



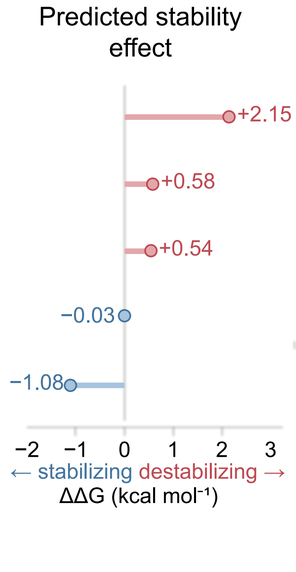
PTEN

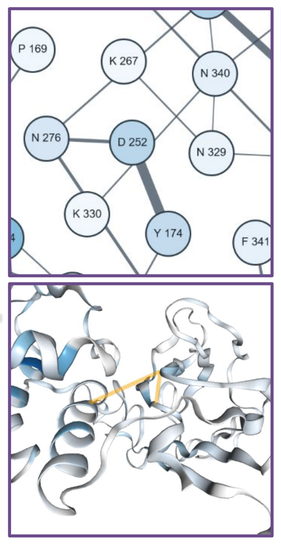


	Structural change in the folded protein				Chemical properties (per residue)		
	ΔRSA	Δ SASA (Å²)	ΔH-bonds	Δcontacts	ΔV (Å³)	ΔRSA	charge
D252R	−0.47	−30.4	+2	+1	+62.3	+0.035	−1 → +1
R130N	+0.41	+25.1	+1	−3	−59.3	+0.056	+1 → 0
G129E	−0.89	−50.6	+4	+6	+82.5	+0.001	0 → −1
D92Y	−0.44	−8.4	−4	+2	+82.5	+0.034	−1 → 0
P38D	−0.16	−9.5	−3	+4	−1.6	+0.000	0 → −1

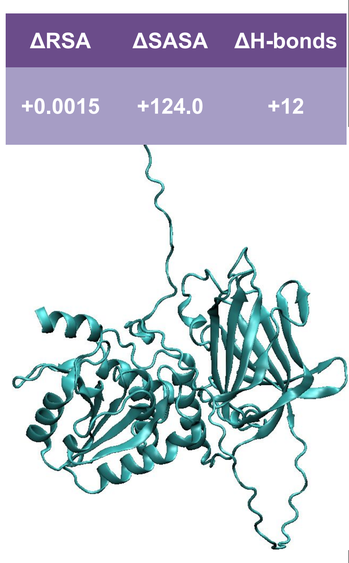
− max 0 + max Δ = mutant − wild type.

Predicted stability effect





ΔRSA	ΔSASA	ΔH-bonds
+0.0015	+124.0	+12

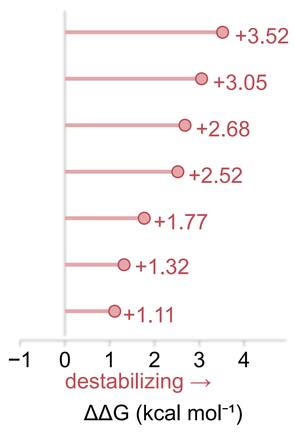


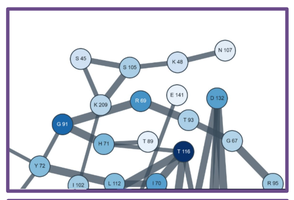
TEM-1 (β-lactamase)

	Structural change in the folded protein				Chemical properties (per residue)		
	ΔRSA	Δ SASA (Å²)	ΔH-bonds	Δcontacts	ΔV (Å³)	Δ RSA	charge
I263K	+0.120	+86.4	−9	−0.023	+1.9	+0.009	0 → 0
D157R	−0.110	+0.5	−10	−0.015	+62.3	−0.021	−1 → +1
S130L	+0.130	+101.0	−6	−0.023	+77.7	+0.036	0 → 0
K234G	+0.040	+26.1	−2	+0.046	−108.1	+0.039	+1 → 0
S70K	−0.020	+25.4	+6	+0.015	+79.6	+0.071	0 → +0.21
E166V	+0.001	+1.2	−4	−0.023	+1.6	+0.004	−1 → 0
K73I	+0.050	+51.7	−6	+0.008	−1.9	+0.000	+1 → 0

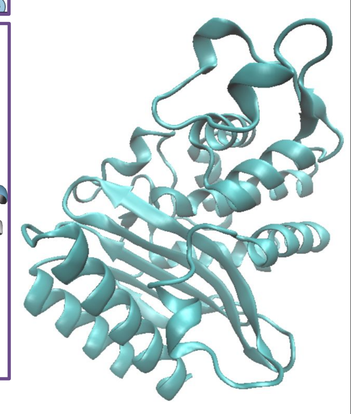
− max 0 + max Δ = mutant − wild type.

Predicted stability effect

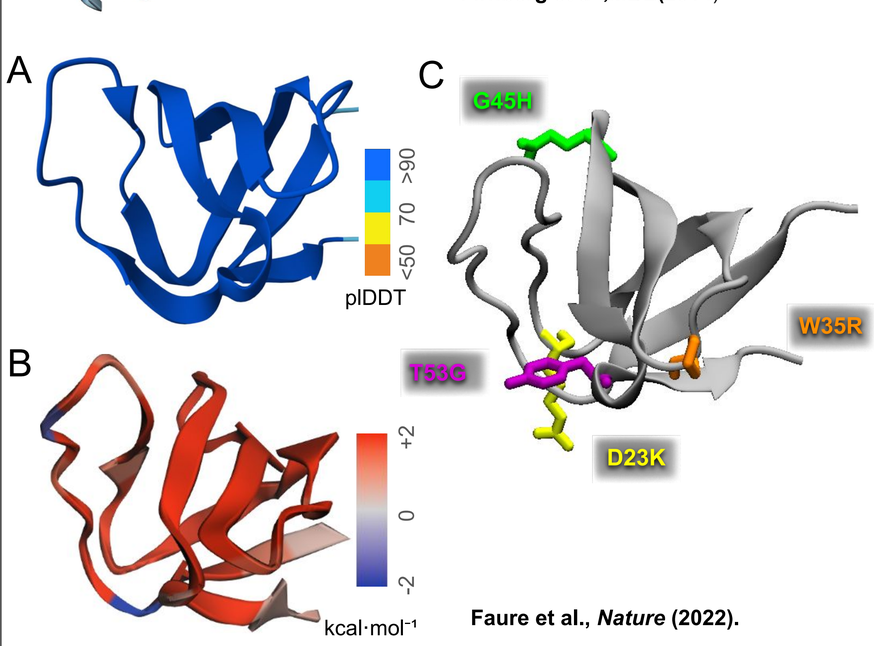




ΔRSA	ΔSASA	ΔH-bonds
+0.02	+0.02	-4



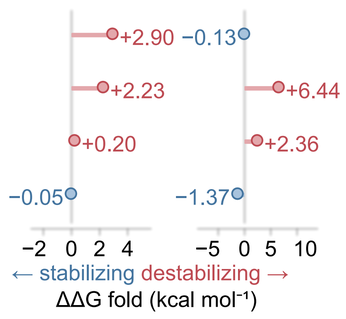
GRB2_SH3 Domain

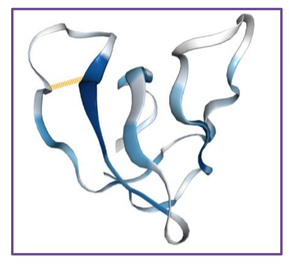


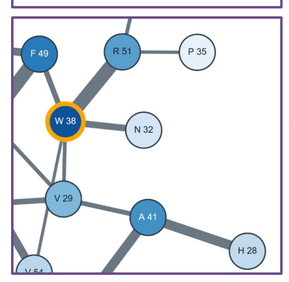
	Structural change in the folded protein				Chemical properties (per residue)		
	ΔRSA	ΔH-bonds	Δcontacts	ΔSASA (Å²)	ΔV (Å³)	ΔRSA	charge
D23K	+0.003	+4	−0.054	+0.45	+57.5	+0.003	−1.0 → +1.0
G45H	−0.01	0	+0.054	−1.7	+93.1	−0.01	0.0 → +0.1
W35R	−0.004	+3	+0.071	−0.59	−54.4	−0.004	0.0 → +1.0
T53G	−0.003	+8	−0.089	−0.67	−56.0	−0.003	0.0 → 0.0

− max 0 + max Δ = mutant − wild type.

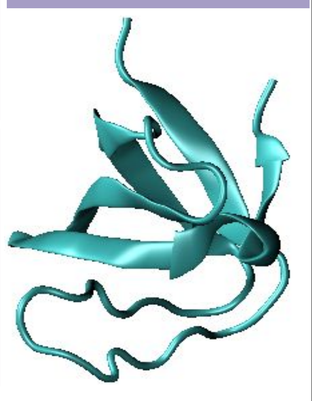
Predicted folding stability/ binding effect







ΔRSA	ΔH-bonds /res	ΔSASA
-0.4	+0.071	-0.81



Conclusion

- DMS and structural analysis help to understand how mutation influence the function.
- Mutations alter stability, contacts, H-bonds, and solvent exposure.
- Combining these features helps prioritize important variants.

Sabancı Üniversitesi

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