

Coiled-coil Peptides to Promote the Death of Cancer Cells

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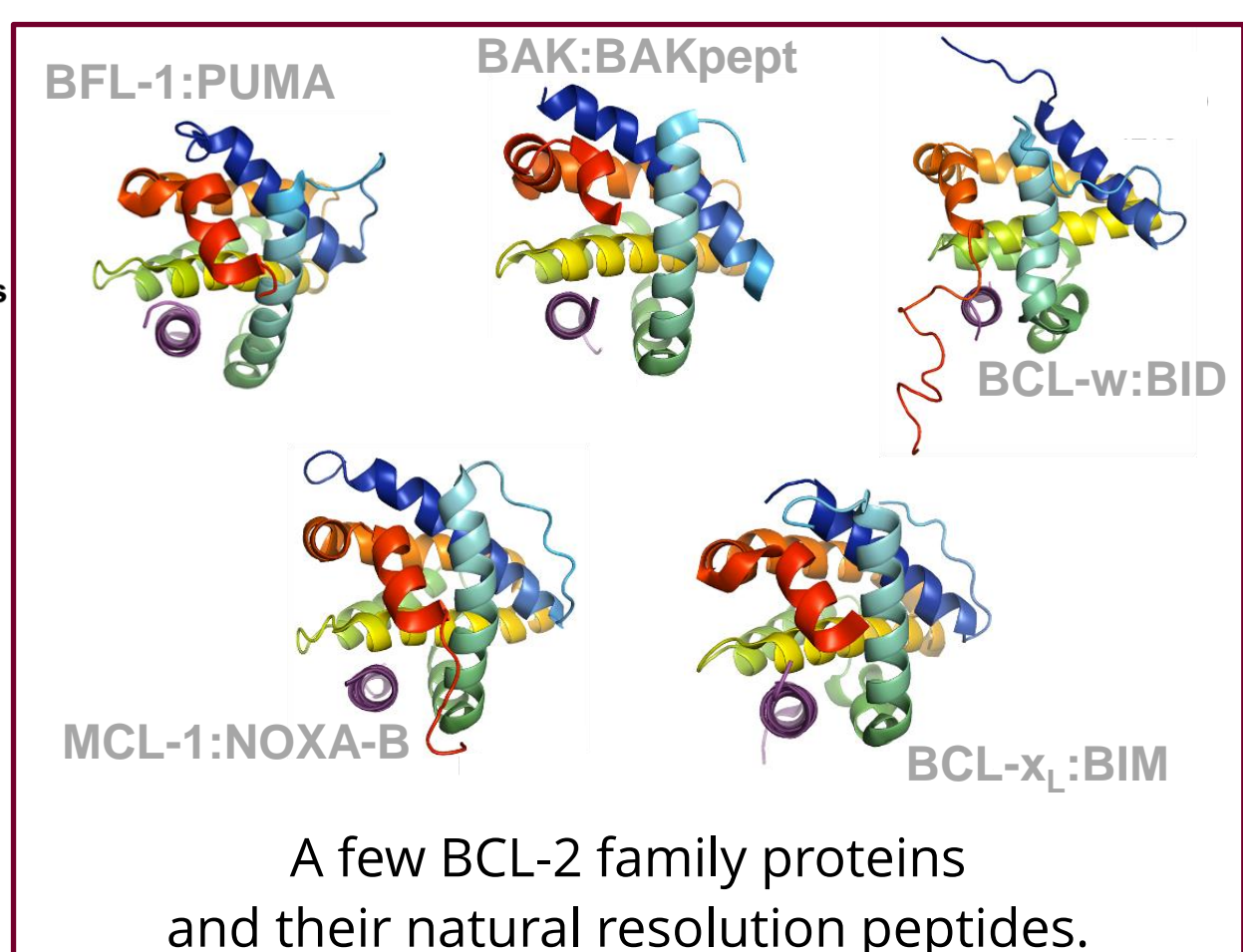
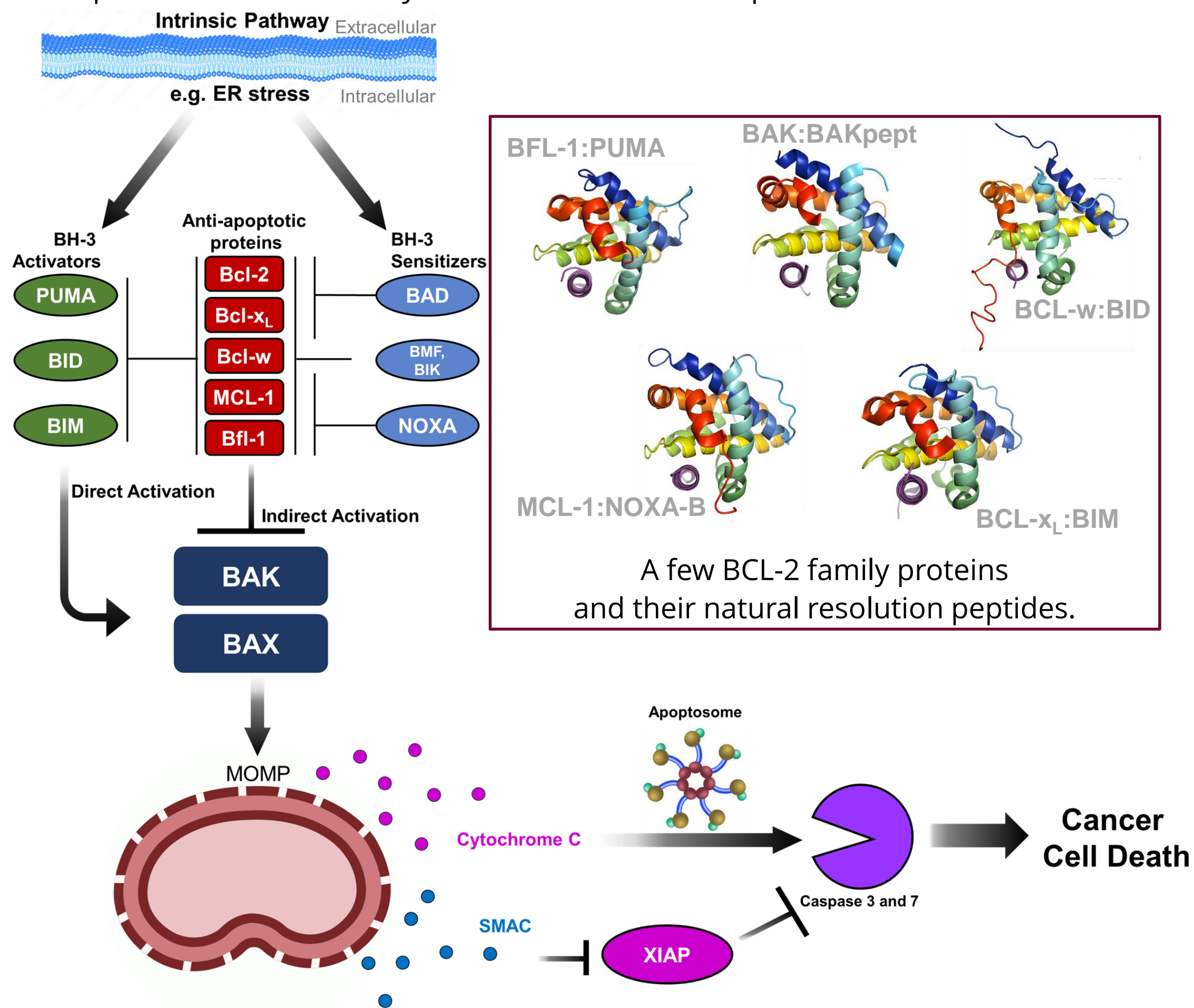
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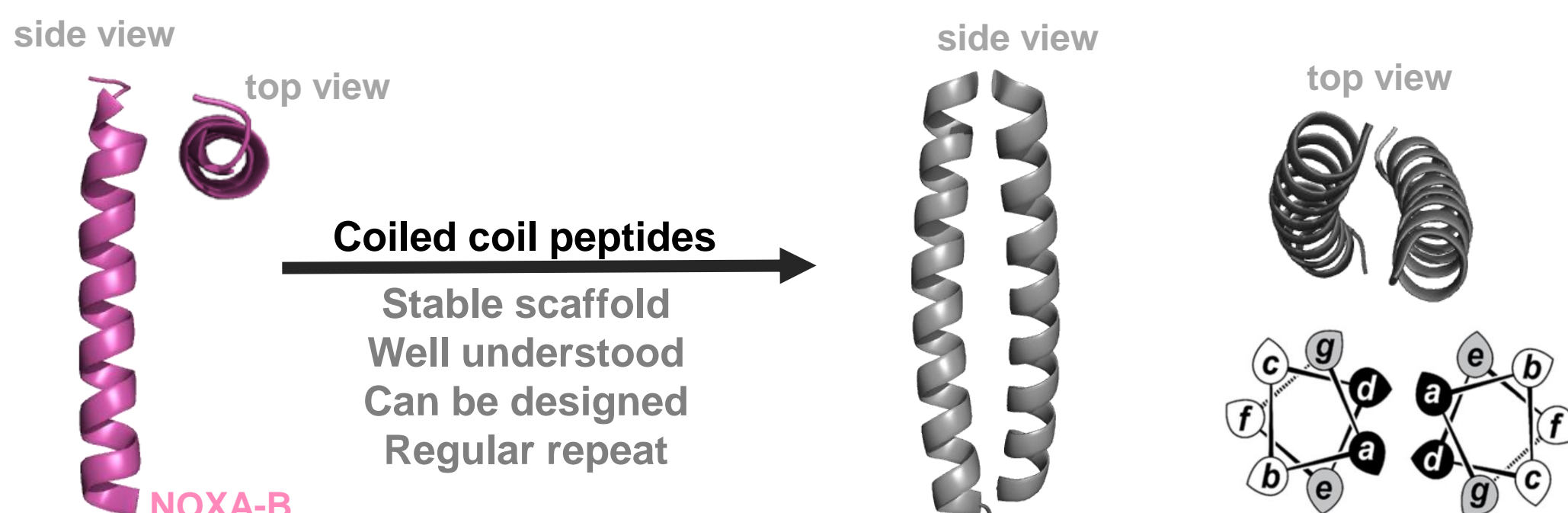
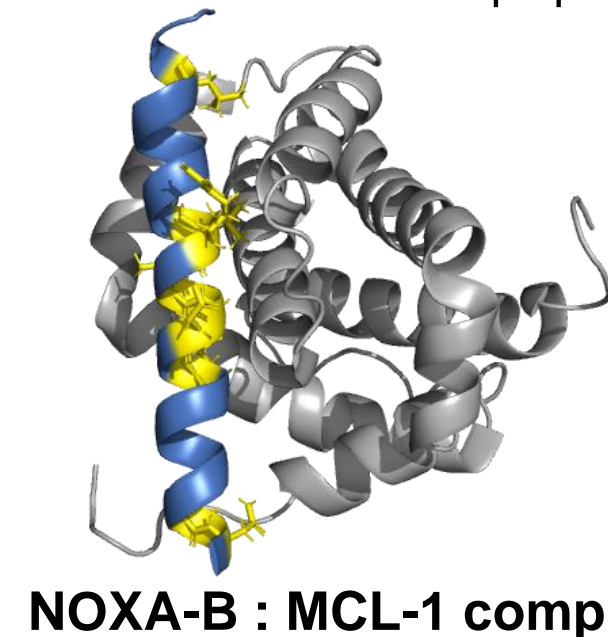
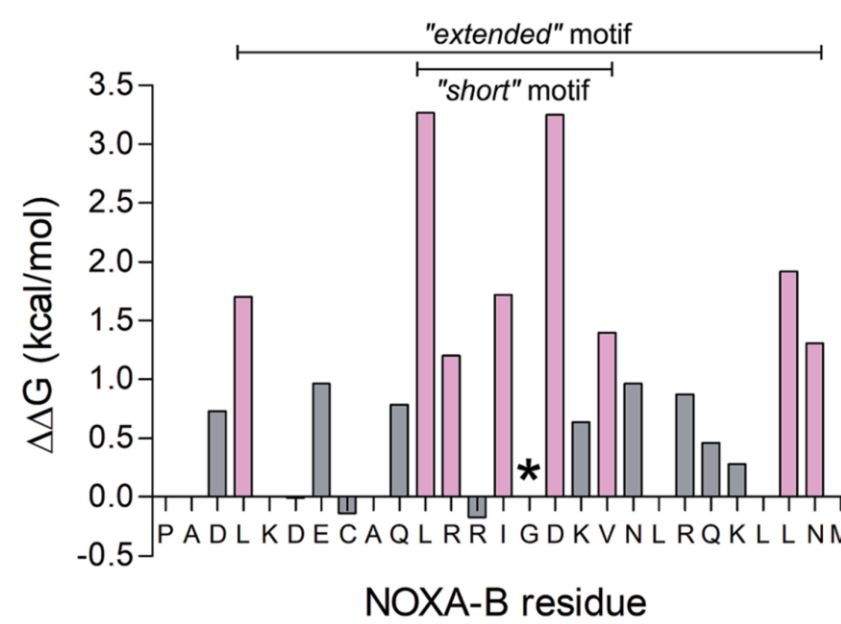
BCL-2 Family Proteins, Cell Death and Cancer

BCL-2 proteins are unnaturally abundant in cancer and prevent the death of tumor cells.

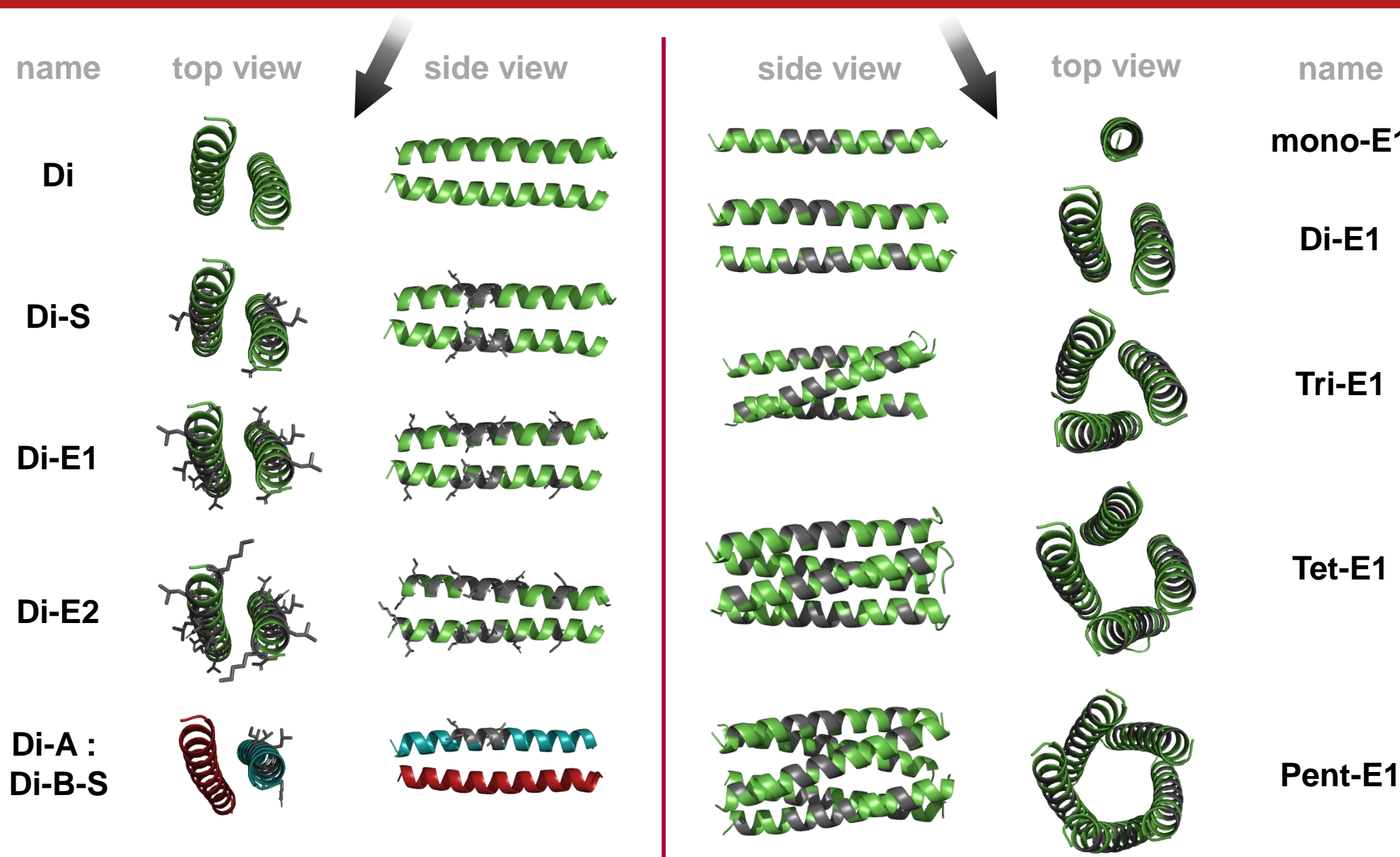


Mimicking Nature's Resolution Peptides

Finding stabilizing interactions and altering the structure of the peptide scaffold.



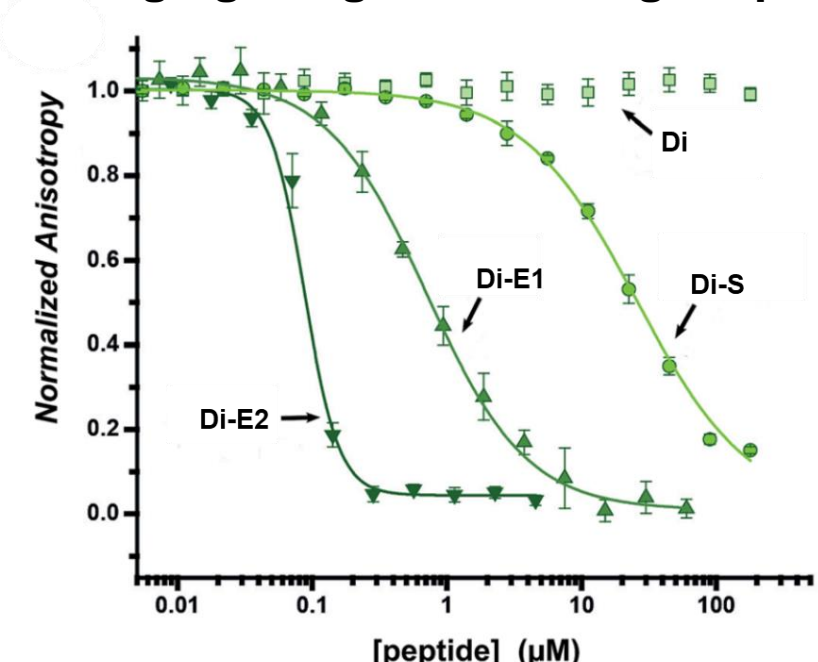
How does changing the mimicked sequence and the scaffold type affect binding?



Measuring Binding of Scaffolds

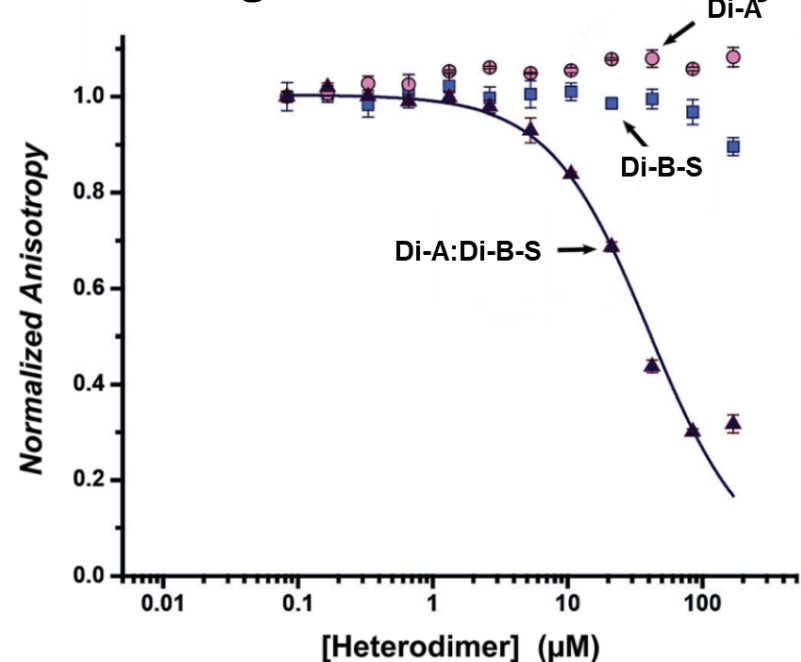
Fluorescence anisotropy can be used to determine binding if one component contains a dye.

Changing Length of Binding Sequence



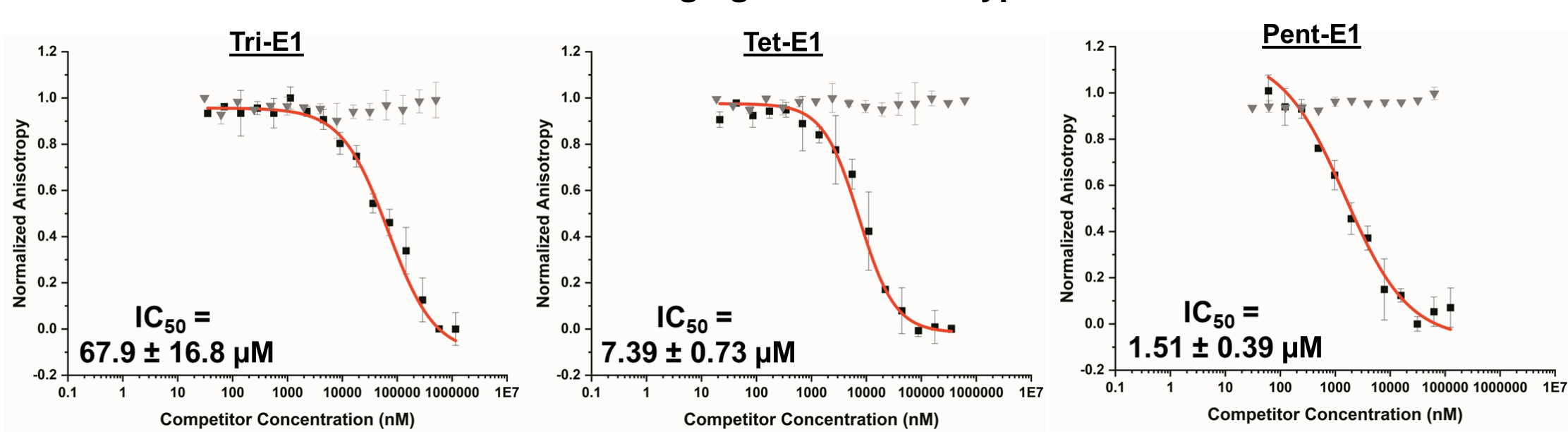
Di-S : 26 ± 1 μM
Di-E1 : 706 ± 5 nM
Di-E2 : 87 ± 1 nM

Binding Site on One Side Only



Di-A : Di-B-S : 40 ± 2 μM

Changing the Scaffold Type



IC₅₀ = 67.9 ± 16.8 μM

IC₅₀ = 7.39 ± 0.73 μM

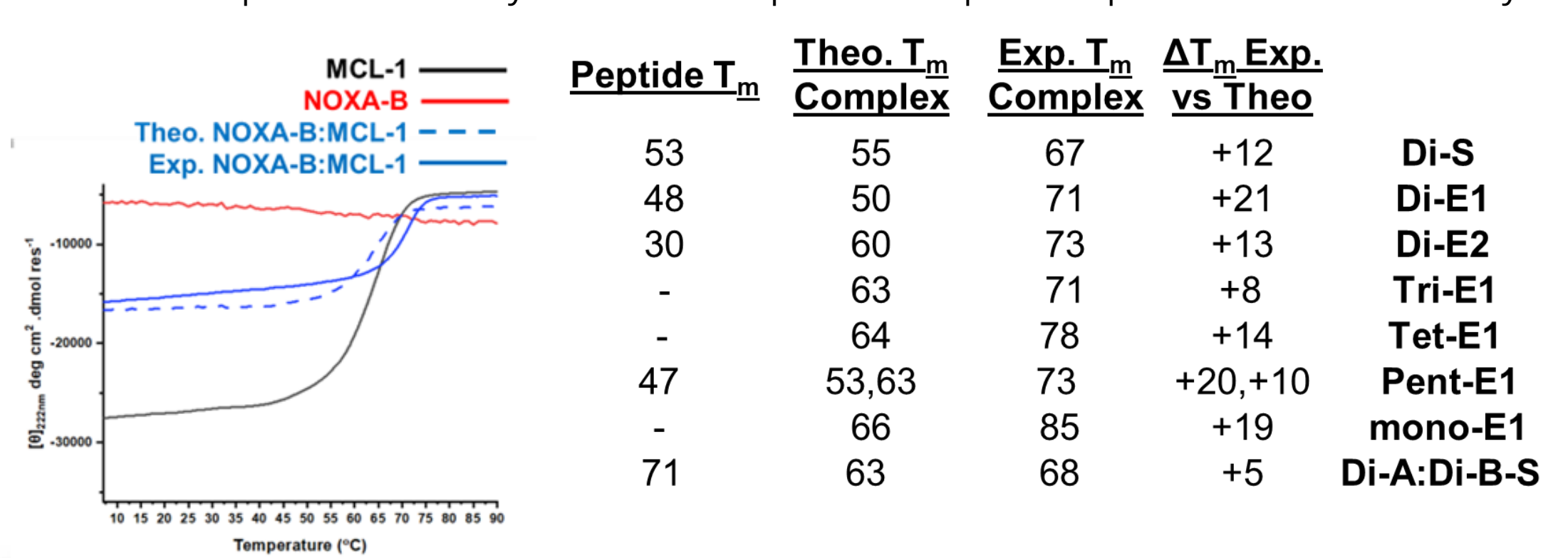
IC₅₀ = 1.51 ± 0.39 μM

Peptide Library

heptad	gabcdef	gabcdef	gabcdef	gabcdef
NOXA-B	P ADLKDEC	AQLRFRIG	DKVNLKQ	KLLNM
Di	Ac-G EIAALKQ	EIAALKK	ENAALKQ	EIAALKQ GYG-NH ₂
Di-S	Ac-G EIAALKQ	EILRLIG	DNVALKQ	EIAALKQ GYG-NH ₂
Di-E1	Ac-G EIALKQ	EILRLIG	DNVALKQ	EILNLKQ GYG-NH ₂
Di-E2	Ac-G KILALEQ	EILRLIG	DNVNLKQ	EILNLKQ GYG-NH ₂
Tri-E1	Ac-G EILAIKQ	EILRLIG	DNVAIKQ	EILNLKQ GYG-NH ₂
Tet-E1	Ac-G ELLAIKQ	ELLRLIG	DLVAIKQ	ELLNLKQ GYG-NH ₂
Pent-E1	Ac-G EFLAFKQ	EFLRFIG	DFVNFQ	EFLNLKQ GYG-NH ₂
mono-E1	Ac-G EALAAKQ	EALRAIG	DAVAKQ	EALNAKQ GYG-NH ₂
Di-A	Ac-G EIAALEQ	EIAALEK	ENAALQ	EIAALEQ GYG-NH ₂
Di-B-S	Ac-G KIAALKQ	KILRKIG	DNVALKQ	KIAALKQ GYG-NH ₂

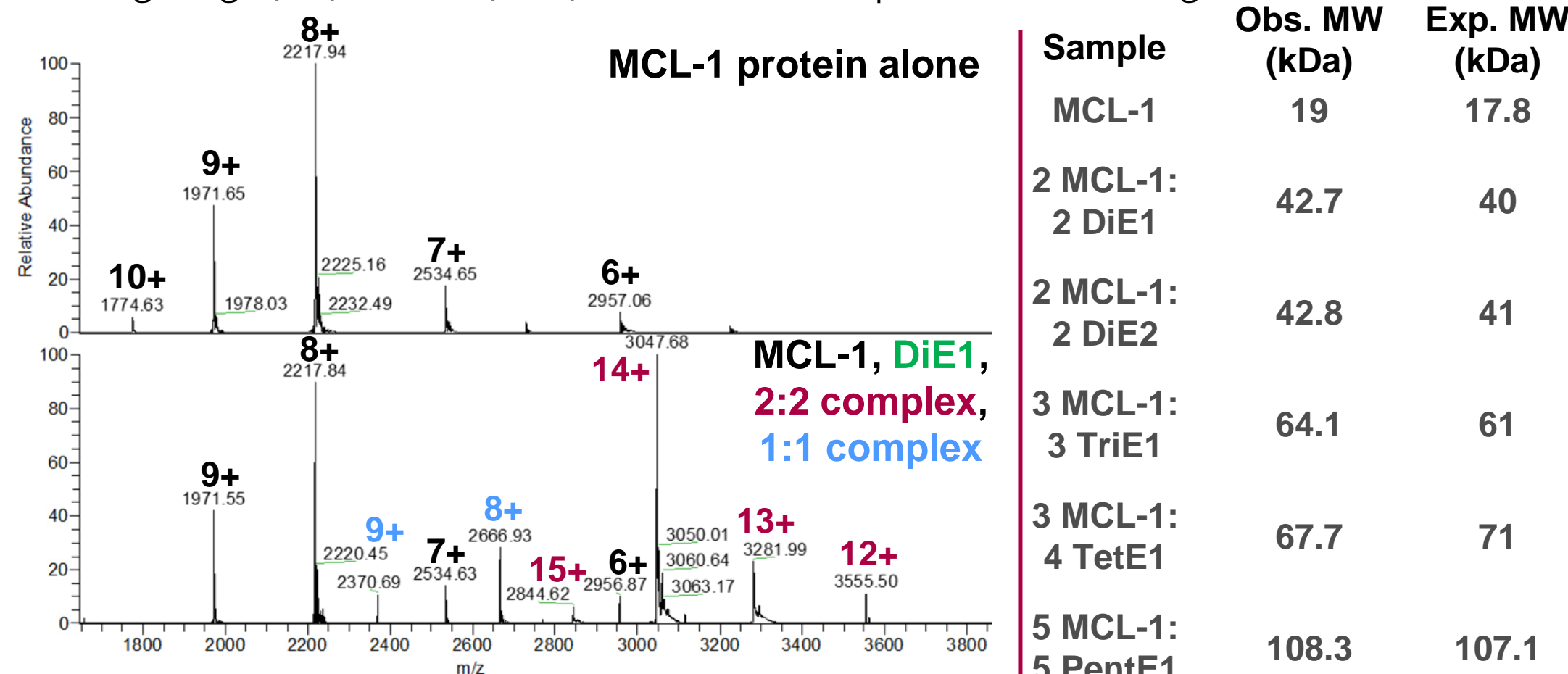
Binding Cooperativity

How does the predicted stability of the scaffold:protein complex compare to the actual stability?



Confirming the Expected Interaction

Using a high (MS) and low (FIDA) resolution technique to observe designed interaction.



Conclusions

- Stabilizing interactions bind target cancer protein regardless of scaffold
- Inclusion of stabilizing interactions does not prevent scaffold folding
- Scaffolds can recruit multiple copies of target cancer protein (multivalent)
- Scaffolds and target cancer protein interact in the designed manner

References:

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