Computational Design of the Structure and Sequence of a Protein-Binding Peptide

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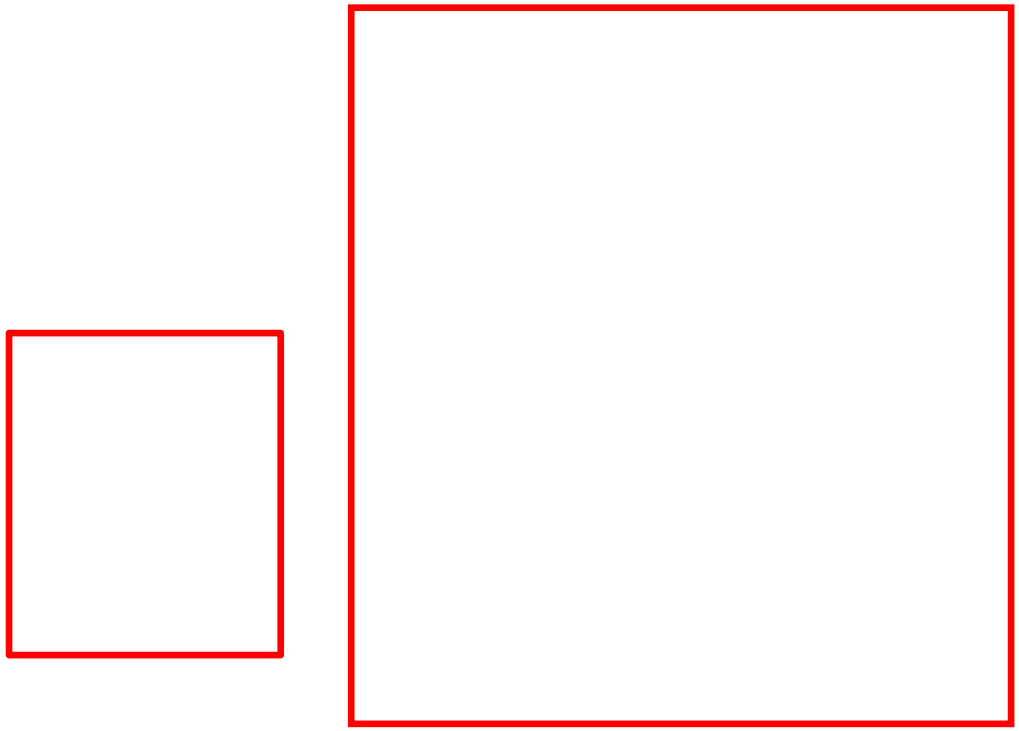
Protein-Peptide Interface Design – Target Complex

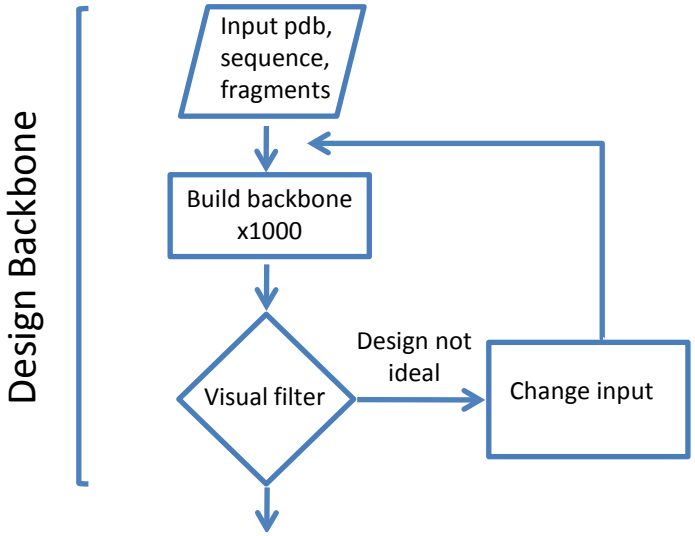


GoLoco (BLUE), $G\alpha_{i1}$ (GREEN)
(PDB ID=2OM2)

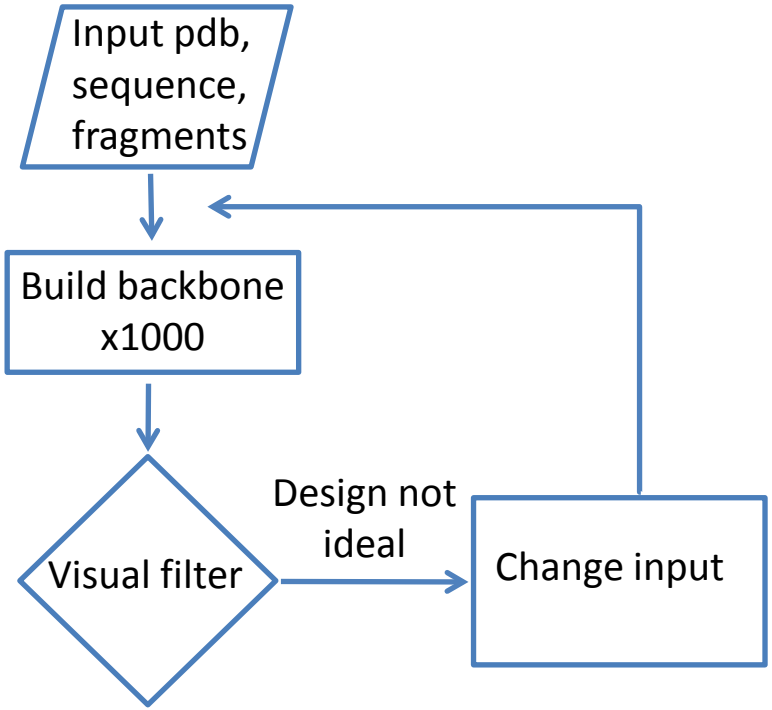
Interface Design – Growing a Helix

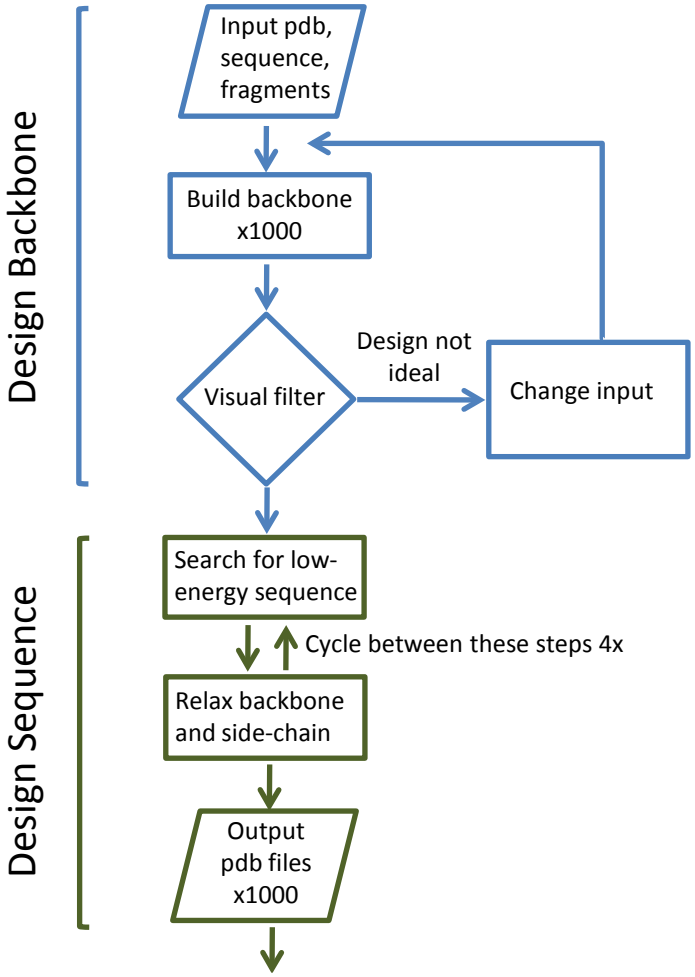
GoLoco (BLUE)
$G\alpha_{i1}$ (GREEN)

GoLoco with Modeled Helix

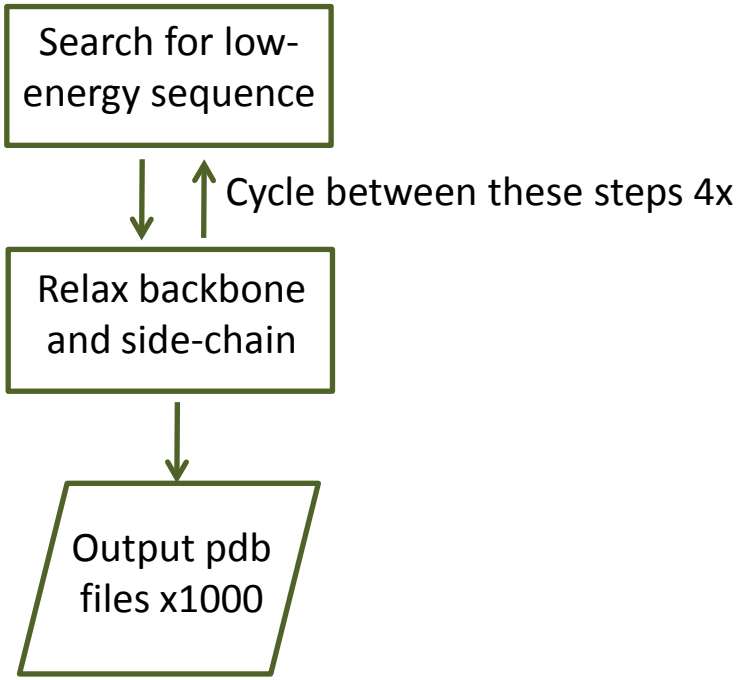


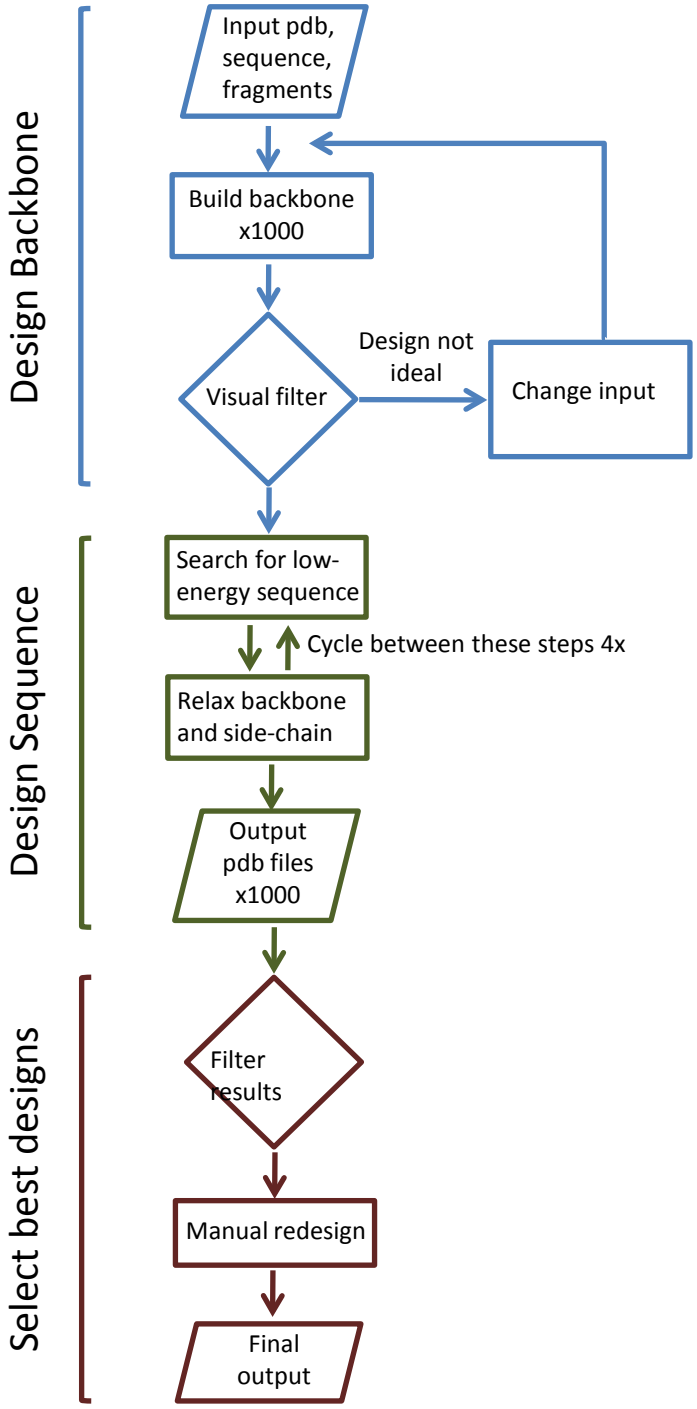
Backbone Design



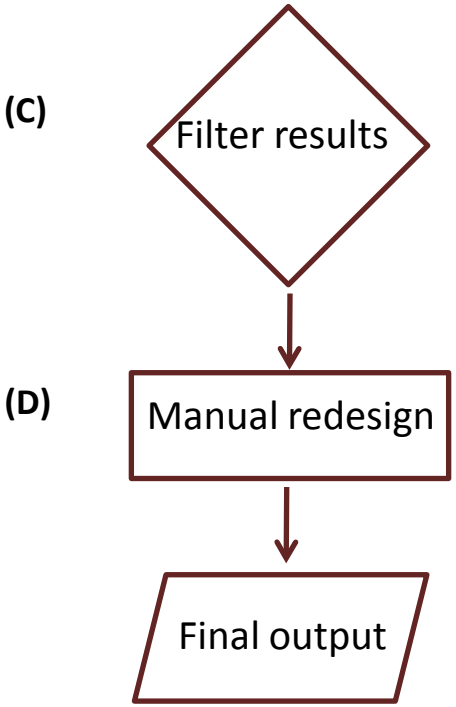


Sequence Design





Selecting designs for characterization



(C) Filters: See next slides

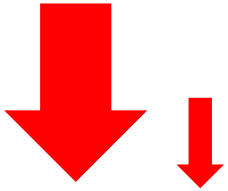
(D) Manual redesign: solvent-exposed side-chains were changed to enhance solubility

Selecting Designs for Experimental Characterization

- Filter – remove deigns with unsatisfied hydrogen bond partners

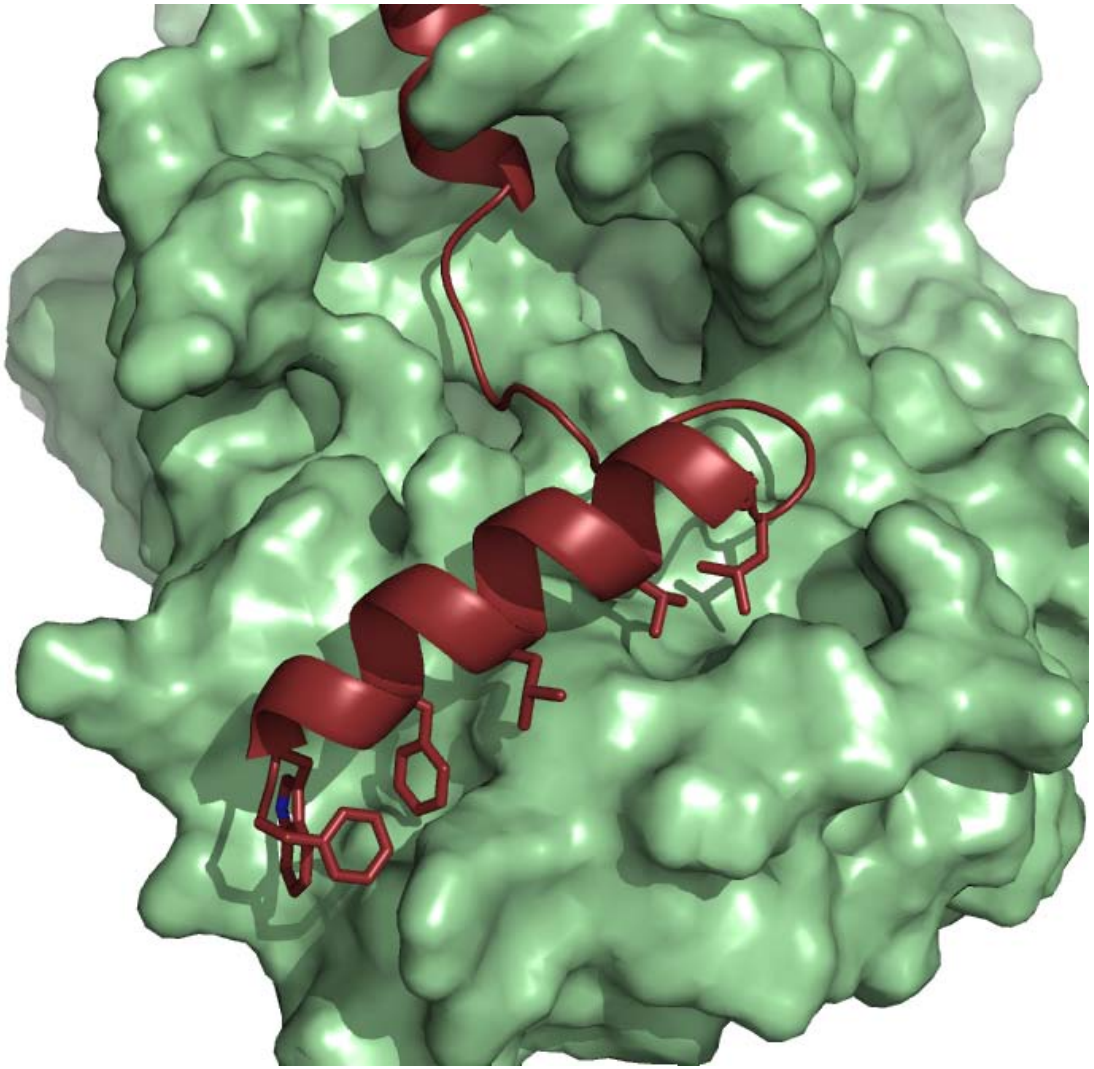
- Sort
  - First sort by “Score” (ΔG)
  - Second sort by $SASA_{pack}$

Sorted Results - Selecting Designs for Experimental Characterization

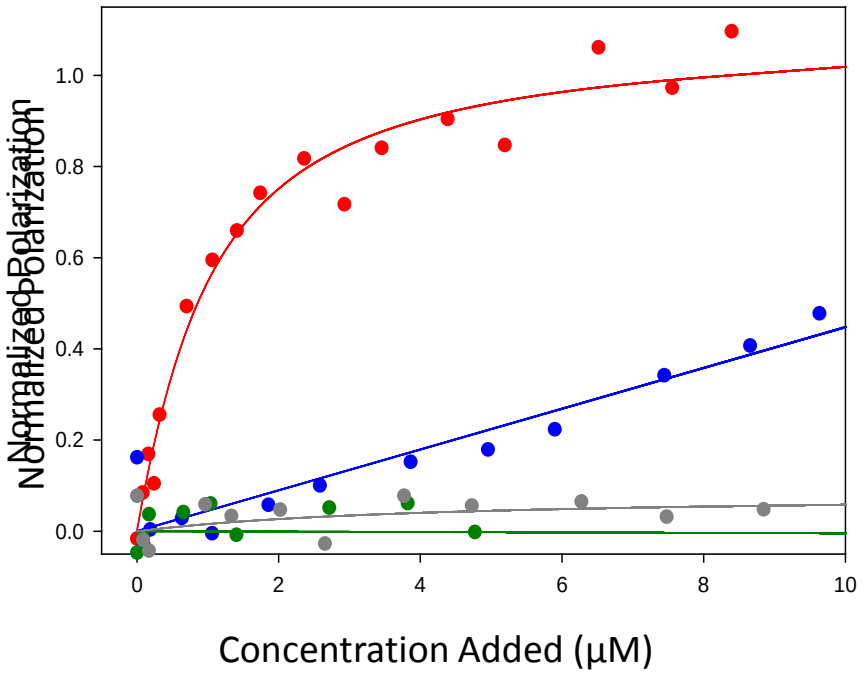


	LJ_{atr}	LJ_{rep}	Sol	Hb	Elec	Tot.	$SASA_{pack}$	$BBHb_{UNS}$	$SCHB_{UNS}$	Design #
1	-88.9	7.1	43.8	-9.9	-4.1	-52.8	-0.7702	1	4	0273
2	-91.3	9.7	44.6	-11	-3.9	-52.7	-0.0853	1	4	0441
3	-89.2	7.6	44.6	-10.4	-4.4	-52.6	-0.7939	1	2	0845
4	-87.4	6.8	43.1	-10	-4.4	-52.6	-0.0397	1	3	0988
5	-88	8.8	42.4	-9.6	-5	-52.3	-0.1033	1	2	0216
6	-88.3	8.9	43.3	-11	-4.1	-52	-0.7602	1	4	0951
7	-88	9.3	43.5	-10.6	-5.4	-52	-0.2395	1	3	0480
8	-87.8	7	43.9	-9.9	-4.3	-52	-0.1541	1	3	0450
9	-88.8	7.6	43.7	-9.9	-3.8	-52	-0.0796	1	2	0620
10	-87.3	7.7	44.7	-11.3	-4.9	-51.9	-0.8178	1	3	0763

Model Structure of $G\alpha_{i1}$ – GoLoco helix



Characterization of 4 Best Designs



GL_{helix}-4 : K_D 800 nM

GoLoco $_{496}$DIEGLVELLNRVQSSGAHDQRGLLRKEDLVLPEFLQ$_{531}$

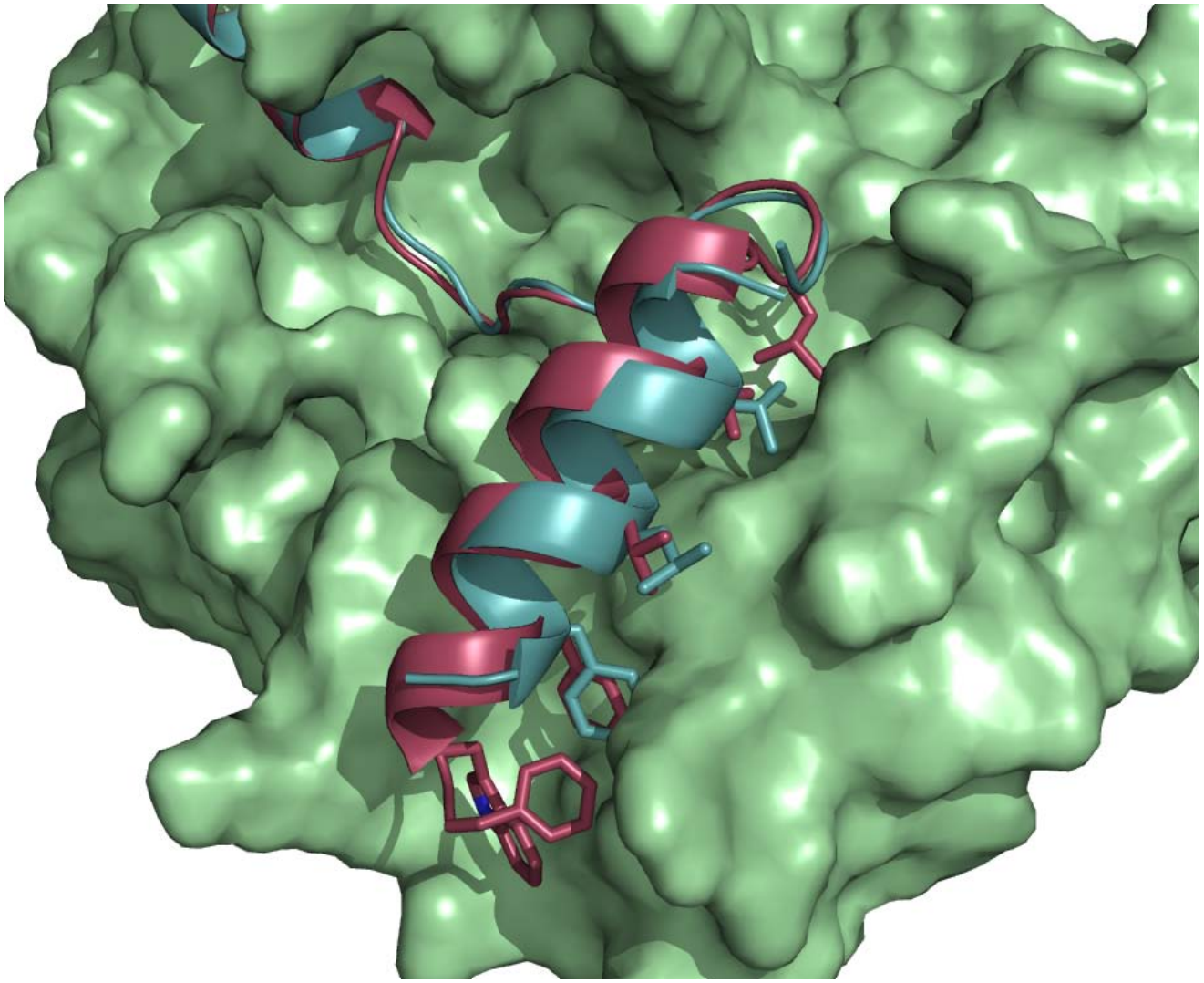
GL_{helix}-1 $_{496}$DIEGLVELLNRVQSSGAHDQRGLLILQRLEEDFRKWLRMLR$_{536}$

GL_{helix}-2 $_{496}$DIEGLVELLNRVQSSGAHDQRGLSEWQRFWRRWLEWLIYLF$_{536}$

GL_{helix}-3 $_{496}$DIEGLVELLNRVQSSGAHDQRSLLRQEEMQRAIRDFAKWF$_{535}$

GL_{helix}-4 $_{496}$DIEGLVELLNRVQSSGAHDQRGLLSNEEVFRALRDFDRWF$_{535}$

$G\alpha_{i1}$-GL_{helix}-4 : Crystal Structure with Design Structure



Acknowledgements

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