Virtual screening and 3D protein structure model optimization of the DSP family

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Proposed Research

- **Using virtual screening methods to find a specific inhibitor for SSH-2**
- Because proteins in the DSP family have a highly conserved active site, compounds must be screened for affinity across the entire family
- Proteins in the family without x-ray crystallography structures had 3D structures generated by homology comparison program MODELLER
- 3D structures must be refined in order to get more accurate results from docking
  - Energy refinement with UCSF Chimera
  - Loop refinement with MODELLER
  - Compound screening with DOCK6

Week 8 Progress

- Script for finding and removing AMBER errors adjusted to find multiple types of errors
- Results of SSH1, SSH3, DSP21, and DSP19 sorted and compared to results of SSH2 in order to determine most specific inhibitor
- Script written to check which app folder matches to which slice of ligands

Results: Organization

- Energy scores and AMBER scores of ligands were sorted from lowest to highest using rerank.pl
  - Usually the only the highest 2 ligands showed significantly different scores compared to the remaining ligands
  - Energy scores and AMBER scores tended to only agree on the highest scoring ligand
- The overall ranking was taken by weighing the scores equally and resorting the results using consensus2.pl
- Finally, the results were compared to the ranked results of SSH-2 using rankssh.pl

Results

zinc id	ssh2 rank	ssh1 rank	difference	ssh3 rank	difference	dsp21 rank (dock only)	difference	dsp19 rank (dock only)	difference
ZINC05260817	1	7289	-7288	5959	-5958	17661	-17660	433	-432
ZINC03869281	2	4039	-4037	1340	-1338	7378	-7376	39	-37
ZINC04543673	3	745	-742	510	-507	4534	-4531	121	-118
ZINC02384698	4	524	-520	609	-605	5217	-5213	956	-952
ZINC03869935	5	5349	-5344	3653	-3648	16822	-16817	25	-20
ZINC04521532	6	8330	-8324	6928	-6922	3676	-3670	737	-731
ZINC04543675	7	665	-658	1233	-1226	5716	-5709	134	-127
ZINC02522549	8	1228	-1220	628	-620	409	-401	135	-127
ZINC04652516	9	44	-35	538	-529	1179	-1170	14381	-14372
ZINC02637978	10	303	-293	364	-354	105	-95	3556	-3546
ZINC01516594	11	9365	-9354	8929	-8918	4365	-4354	13213	-13202
ZINC01325418	12	111	-99	173	-161	168	-156	15801	-15789
ZINC02149821	13	9054	-9041	9473	-9460	1029	-1016	732	-719
ZINC06815633	14	70	-56	390	-376	1766	-1752	11839	-11825
ZINC03276848	15	8674	-8659	3966	-3951	3692	-3677	3266	-3251
ZINC04107594	16	1583	-1567	1451	-1435	1076	-1060	11864	-11848
ZINC06046393	17	14538	-14521	6597	-6580	11881	-11864	6430	-6413
ZINC05444608	18	5368	-5350	923	-905	17534	-17516	18420	-18402
ZINC00411161	19	1250	-1231	2977	-2958	5772	-5753		19
ZINC05373221	20	207	-187	132	-112	474	-454	14480	-14460

Results

- The best candidates for specific inhibitors of SSH-2 would be ones with a large difference in ranking between SSH-2
  - ZINC05260817 (SSH-2 rank 1)
  - ZINC02384698 (SSH-2 rank 4)
  - ZINC03869935 (SSH-2 rank 6)

Future Goals

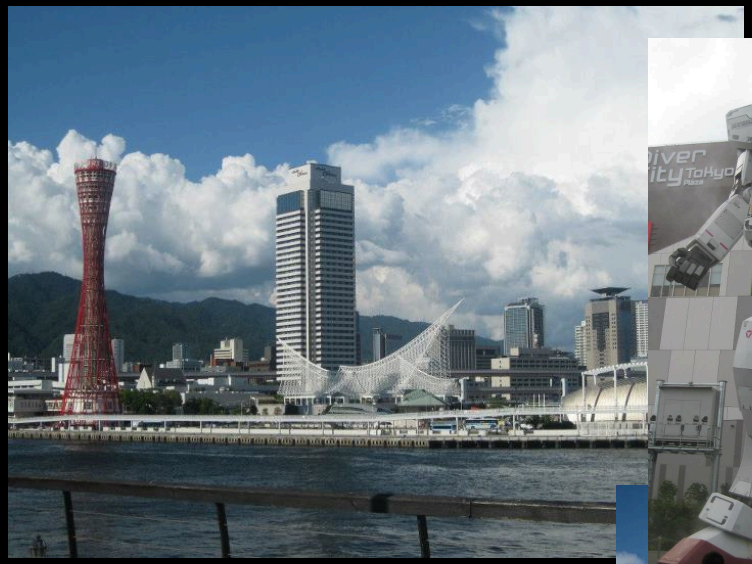
- Test ligands found from this summer in vitro in order to determine accuracy of virtual screening
- Better understand grid system
- Learn more efficient programming skills

Conclusion

- Virtual screening is used as a method to theoretically predict ligands with high affinity for target proteins, and therefore can only be used to narrow down possible effective drug candidates
- Further development would require in vitro testing of the highest ranked ligands in order to determine their actual effectiveness and specificity
- Remaining members of the dual-specificity phosphatase family may also be screened to narrow down more specific SSH-2 inhibitors

Clockwise, from top left:
-Kobe port area
-Gundam statue at Odaiba
-Tori gate at Shirahama beach
-Shinkansen
-Tori gate at Miyajima
-Food stalls at Hakata

Culture!



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