Snyder-Robinson Syndrome and spermine synthase

Using small molecules to rescue the effect

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The goal of this work is to identify small molecule candidates, which upon binding to defective SMS proteins, can help restore the native function and mitigate the effects associated with Snyder-Robinson Syndrome.
Spermine Synthase

The Spermine Synthase gene codes for the Spermine Synthase protein

- Spermine Synthase is an enzyme that is an essential element in the polyamine biosynthesis pathway
- mediates conversion of spermidine to spermine

Spermine
- cell growth and division,
- the production of new proteins,
- the repair of damaged tissues
Spermine Synthases Structure

Spermine Synthase protein (SMS)

- Homo-dimer - Two nearly identical monomer chains

- Structural and biochemical studies revealed that Spermine Synthase protein is an obligate dimer.

- If the dimer is not formed – the activity is practically zero
Spermine Synthase Structural Domains

Each monomer has 3 domains

1. **C-terminal domain**, which contains the active site
2. **Linker domain** made up of 4 beta-strands
3. **N-terminal domain** dimerization occurs mainly through interactions between the N-terminal domains
Spermine Synthases: Importance of the N-terminal Domain

1. Dimerization occurs mainly through the N-terminal

   After dimerization:
   16% of the total surface area for each subunit is buried, of which 71% was from the N-terminal domain.

2. N-terminal mutations affect function

   Experimentally shown:
   Deletion of the N-terminal domain led to a complete loss of activity, suggesting that dimerization is likely required for activity (Wu et al. 2008)

N-terminal mutations -> LOSS OF DIMERIZATION -> Loss of SMS activity

Mutations within N-terminal predicted to affect Dimerization
SNYDER-ROBINSON SYNDROME

SRS is a rare genetic disease affecting a small population of a few families, but its impacts on the patients and their family’s quality of life is significant.

Physical and mental deformities prevent patients from functioning normally in society.
Mutation investigated:
Disease causing mutation: M35R, G56S, F58L ,P112L
Polymorphic mutations:T21S, M35K and S38L
All in N-domain

Amis: Mutations’ effect on structure, binding and folding.

Methods:
Webserver: NeEMO, PoPMuSiC, DUET, CUPSAT
Software: SAAMBE, Foldx
Change of folding free energy

ddG > 0 Stabilize  ddG < 0 Destabilize

M35R  G56S  F58L  P112L  T21S  M35K  S38L
Change of binding free energy

ddG > 0 Stabilize  ddG < 0 Destabilize
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SEQUENCE ALIGNMENT

- **HUMAN**: LSQDSTGRVKRLPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
- **DANRE**: LLDGNIQRIKRPALIRGSDVDRYWPTADGRLMEYDIDEVVYEKDSAYQNIKILH
- **ICTPU**: LLHGTIQTVKRLPALQRGGEVDRYWPTADGRLIEYDIDEVVFDKDSAYQNIKILH
- **OPHHA**: LFHKSIKRIKRPVIMRGAIDRYWPTADGRLVEYDIDEVVYDEESVYQNIKILH
- **MOUSE**: LSQDSTGRVKRPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
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- **HORSE**: - - - - STGRVKRPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
- **CALJA**: LSQDSTGRVKRPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
- **PANTR**: LSQDSTGRVKRPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
- **MACMU**: LSQDSTGRVKRPPIVRGGAIDRYWPTADGRLVEYDIDEVVYDEDSPYQNIKILH
M35R: Buried Residue, not in the binding interface

(a) M35

(b) R35
STRUCTURE

- G56S: In the binding interface

(a) G56

(b) S56
STRUCTURE

- F58L: In the binding interface

(a) F58

(b) L58
**STRUCTURE**

- P112L: In the binding interface

(a) P112  
(b) L112
STRUCTURE

- T21S: Total exposed in the water

(a) T21  
(b) S21
STRUCTURE

- S38L: exposed in the water

(a) S38

(b) L38
CONCLUSION

- M35R and M35K affect protein’s stability.
- G56S, F58L and P112L affect dimerization.
- T21S and S38L are not disease-causing mutations.
Rescuing Binding
Affinity effects with
Small Molecule Binding
Autodock Vina predict the bound conformations of receptors and small molecules starting with their unbound structures.

- Side chain bond angles can be treated as rigid or flexible
  - Rigid-structure SMS receptor & flexible-structure small molecules

Autodock Tools Software used to prepare proteins for docking and determine the search space.
Small Molecule Binding Protocol

1. Prepare structure files for docking
   - Removing water molecules

2. Define Search Space to target regions that may restore native biophysical property
   - Biophysical effects of mutations

3. Autodock Vina completes docking prediction
   - Small molecule database

4. Filter results based on affinity score to Narrow possibilities to few best candidates
   - High binding affinity scores are not absolute, for ranking

5. Visually inspect candidates for desirable binding modes

6. Extend search space to whole protein and eliminate modes outside target region
   - Protocol can be used to restore decreased stability of P112L and G67E
Small Molecule Binding for Dimerization Protocol

(1) Prepare structure

(2) Define Search Space
Small Molecule Binding for Dimerization Protocol

(3) Autodock Vina

FDA-approved drugs

1. “Safe”
2. Cost Effective
3. Availability

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<td>1</td>
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<tr>
<td>2</td>
<td>-8.0</td>
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<tr>
<td>3</td>
<td>-8.0</td>
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<td>-7.8</td>
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Filtering results by binding affinity score:

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Small Molecule Binding for Dimerization Protocol

Visual Inspection of Binding Modes

Desirable Modes

Undesirable Modes
### Visual Inspection Results

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<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
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59 → 19 Candidates with Desirable Modes
Small Molecule Binding for Dimerization Protocol

Extend search space & Inspect again

19 → 9 Final Candidates for experimental testing
SMALL MOLECULE BINDING RESULTS

1. ligand_2105
2. ligand_291
3. ligand_1994
4. ligand_1236
5. ligand_1863
6. ligand_500
7. ligand_1977
8. ligand_2317
9. ligand_1979
Small Molecule Binding Results

2105 – Top Candidate
Small Molecule Binding Results
Conclusion

1
2
3
1
3182
59
19
9
Major Findings

- Established protocol for binding small molecules to defective proteins

- P112L
  - Mutation slightly reduces stability of SMS
    - Small molecules could be used to address effect
    - Mutation slightly increases the binding affinity

- G67E
  - Mutation reduces stability of SMS
    - Small molecules could be used to address effect
    - Mutation increased the binding affinity

- G56S
  - Both stability and dimerization are reduced (Confirm experimental)
  - Identify 9 possible prescription medications that may restore dimerization
    - Will be moving forward with experimental testing
**Bromosulfophthalein sodium**

- An organic sodium salt that is the disodium salt of bromosulfophthalein
- Used as a dye in liver function tests
Carminomycin; O-Demethyldaunomycin; Carubicin

- **Carubicin**: A very toxic anthracycline-type antineoplastic, introduced 1991

- Anthracyclines are a class of drugs used in cancer chemotherapy

- leukemias, lymphomas, breast, uterine, ovarian, bladder cancer, and lung cancers
P112L SPERMINE SYNTHASE MUTANT
UREA UNFOLDING OF P112L

![Graph showing the fraction unfolded vs. [Urea] (M) for hSMS WT Unfolding, hSMS WT Refolding, hSMS P112L Unfolding, and hSMS P112L Refolding.](image-url)
# P112L SUMMARY OF EXP DATA

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<th>hSMS P112L</th>
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<td>17% α-helix</td>
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<tr>
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<td>31% β-strand</td>
<td>32% β-strand</td>
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<td>Secondary Structure in 2QFM</td>
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<td>26% β-strand</td>
<td></td>
</tr>
<tr>
<td>$Cm$ (M)</td>
<td>3.6 ± 0.2</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>$m$ (kcal mol$^{-1}$ M$^{-1}$)</td>
<td>0.67 ± 0.03</td>
<td>0.71 ± 0.02</td>
</tr>
<tr>
<td>$\Delta G_{app}^{H_2O}$ (kcal mol$^{-1}$)</td>
<td>2.39 ± 0.12</td>
<td>1.82 ± 0.09</td>
</tr>
<tr>
<td>$\Delta \Delta G_{app,1}^{H_2O}$ (kcal mol$^{-1}$)</td>
<td>N/A</td>
<td>0.57</td>
</tr>
<tr>
<td>$\Delta \Delta G_{app,2}^{H_2O}$ (kcal mol$^{-1}$)</td>
<td>N/A</td>
<td>0.76</td>
</tr>
</tbody>
</table>