NVBL Molecular Therapeutics

Marti Head
Project Lead
Goal: Leverage the world-leading capabilities of the Department of Energy National Labs...

Chemical, biological, and analytical sciences

Light and neutron sources

High performance computing
... to identify experimentally validated leads for targets across the entire coronavirus life cycle
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Computational and experimental design platforms

Starting points
- Crystal structures and structural models
- Multiple antibody templates
- Databases of purchasable small molecules

Outputs
Designs with probability of:
- Desired activity
- Desired biological effect
- Good physical and safety parameters

Platform capability build funded over time through DOE, LDRD, DARPA, DoD, and other funding sources
Computational Design of Therapeutic Antibodies

Design starting point
- m396, a neutralizing antibody against the spike protein of SARS-CoV-1 that does not bind spike from SARS-CoV-2

Design output
- Experimentally validated designed antibody:
  - Binds to spike protein
  - Neutralizes VSV-SARS-CoV-2 pseudovirus

Modifying 31 m396 locations to identify SARS-CoV-2 binder – $10^{40}$ potential combinations!

Funded by NVBL and DARPA
### Computational Docking for SARS-CoV-2 Proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>Docking Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nsp1</td>
<td>91.1%</td>
</tr>
<tr>
<td>Nsp2</td>
<td>82.9%</td>
</tr>
<tr>
<td>Nsp3</td>
<td>86.5%</td>
</tr>
<tr>
<td>Nsp4</td>
<td>90.8%</td>
</tr>
<tr>
<td>Nsp5</td>
<td>98.7%</td>
</tr>
<tr>
<td>Nsp6</td>
<td>94.8%</td>
</tr>
<tr>
<td>Nsp7</td>
<td>100.0%</td>
</tr>
<tr>
<td>Nsp8</td>
<td>99.0%</td>
</tr>
<tr>
<td>Nsp9</td>
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<td>Nsp10</td>
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<tr>
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<tr>
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<tr>
<td>Nsp13</td>
<td>100.0%</td>
</tr>
<tr>
<td>Nsp14</td>
<td>98.7%</td>
</tr>
<tr>
<td>Nsp15</td>
<td>95.7%</td>
</tr>
<tr>
<td>Nsp16</td>
<td>98.0%</td>
</tr>
<tr>
<td>S</td>
<td>87.0%</td>
</tr>
<tr>
<td>Orf3a</td>
<td>85.1%</td>
</tr>
<tr>
<td>Orf3b</td>
<td>95.0%</td>
</tr>
<tr>
<td>E</td>
<td>96.1%</td>
</tr>
<tr>
<td>M</td>
<td>96.4%</td>
</tr>
<tr>
<td>Orf6</td>
<td>85.7%</td>
</tr>
<tr>
<td>Orf7a</td>
<td>90.2%</td>
</tr>
<tr>
<td>Orf7b</td>
<td>84.1%</td>
</tr>
<tr>
<td>Orf8</td>
<td>45.3%</td>
</tr>
<tr>
<td>N</td>
<td>94.3%</td>
</tr>
</tbody>
</table>

**Protein Functions:**
- **Nsp1** (87.0%): Supports host cell survival
- **Nsp2** (82.9%): Involved in viral replication
- **Nsp3** (86.5%): Involved in viral replication
- **Nsp4** (90.8%): Essential for viral replication
- **Nsp5** (98.7%): Essential for viral replication
- **Nsp6** (94.8%): Essential for viral replication
- **Nsp7** (100.0%): Essential for viral replication
- **Nsp8** (99.0%): Essential for viral replication
- **Nsp9** (98.2%): Essential for viral replication
- **Nsp10** (99.3%): Essential for viral replication
- **Nsp11** (92.3%): Essential for viral replication
- **Nsp12** (98.3%): Essential for viral replication
- **Nsp13** (100.0%): Essential for viral replication
- **Nsp14** (98.7%): Essential for viral replication
- **Nsp15** (95.7%): Essential for viral replication
- **Nsp16** (98.0%): Essential for viral replication

**Protein Complexes:**
- **Nsp3-Nsp4-Nsp6 complex**: Involved in viral replication
- **Nsp7-Nsp8 complex**: Involved in RNA polymerase

**Viral Proteins:**
- **S**: Spike protein
- **Orf3a**: Activates the NLRP3 inflammasome
- **Orf3b**: Essential for viral replication
- **E**: Envelope protein
- **M**: Membrane protein
- **Orf6**: Type I IFN antagonist
- **Orf7a**: Essential for viral replication
- **Orf7b**: Essential for viral replication
- **Orf8**: Essential for viral replication
- **N**: Nucleocapsid protein
- **Orf9a**: Essential for viral replication
- **Orf9b**: Essential for viral replication

**Inhibitor Examples:**
- CBZ-RLGG-AMC
- [5-FAM]-AVLQSGFR-[K(EdABCY1)]-K-amide
- DNP-RLGG-AMC

**Effect of Inhibitor Concentration on Enzymatic Rate:**
- Increasing inhibitor concentration leads to inhibition of enzymatic activity.

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**Graphical Representation:**
- Docking scores for various proteins are color-coded and spatially represented.
- Inhibitor structures are shown with concentration curves indicating inhibition effects.

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**Diagram Notes:**
- Cytotoxic, Inactive, Active states of proteins are indicated.
- Inhibitor effects on enzymatic rates are visualized through time-dependent graphs.

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**U.S. Department of Energy**

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Computational Docking for SARS-CoV-2 Proteins

- Nsp14
  - 98.3%
  - uridine methyltransferase activity
  - Essential for viral replication

- Nsp13
  - 98.9%
  - Nsp16 helicase/3′-5′ exonuclease activity
  - NSP13_Helicase

- Nsp12
  - 100%
  - Nsp16 helicase/3′-5′ exonuclease

- Nsp9
  - 99.0%
  - Nsp16 helicase/3′-5′ exonuclease

- Nsp4
  - 99.3%
  - Essential for viral replication

- Nsp3
  - 98.7%
  - Nsp16 cap methyltransferase

- Orf7a
  - 84.7%
  - Activates the NLRP3 inflammasome

- Orf9b
  - 88.7%
  - Viral helicase involved in viral replication

- Orf10
  - 98.7%
  - Viral methyltransferase involved in viral replication

- Nucleocapsid
  - 92.3%
  - Viral genome

- Type I IFN antagonist
  - 94.8%
  - Viral replication

- Envelope
  - 98.3%
  - Membrane glycoprotein, involved in virus morphogenesis and assembly

- Membrane glycoprotein, virus assembly and release

- Uridine methyltransferase activity

- Essential for viral replication

- Activates the NLRP3 inflammasome

- Nsp16 helicase/3′-5′ exonuclease

- Inhibitor: [5-FAM]-AVLOSGLFR-(K(eDABCYL))-K-amide

- DNP-LRGG-AMC
SARS-CoV-2 Proteases Require a Special Workflow

Prepare Ligands
- Add 3-point fragment
- Select reaction
- Create covalent complex

AutoDockFR
- Flexible side-chain docking
- Ensemble parallel

Extract non-covalent score

QM reoptimization
- Node-parallel

QM frequencies
- Node-parallel

Calculate $\Delta G^0$

Maxwell-Boltzmann Statistics

Predict $K_i$ values

QM Methods: FMO-DFTB3-D3H4 & MOZYME PM6-D3H4

Cytotoxic
Inactive
Active

Effect of Inhibitor Concentration on Enzymatic Rate

% Enzymatic Activity (%) w.r.t.

Preincubation time, min
Nsp1 91.1%: Suppresses host antiviral response
Nsp2 82.9%
Nsp3 86.5%
Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp4 90.8%
Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp5 98.7%
Main protease (3C-like)
Nsp6 94.8%
Nsp3-Nsp4-Nsp6 complex involved in viral replication
Nsp7 100%
Nsp7-Nsp8 complex is part of RNA polymerase
Nsp8 99.0%
Nsp7-Nsp8 complex is part of RNA polymerase
Nsp9 98.2%
ssRNA binding
Nsp10 99.3%
Essential for Nso16 methyltransferase activity
Nsp11 92.3%
Short peptide
Nsp12 98.3%
RNA polymerase
Nsp13 100%
Helicase/triphosphatase
Nsp14 98.7%
3'-5' exonuclease
Nsp15 95.7%
Uridine-specific endoribonuclease
Nsp16 98.0%
RNA-cap methyltransferase
S 87.0%
Spike protein, mediates binding to ACE2
Orf3a 85.1%
Activates the NLRP3 inflammasome
Orf3b 95.0%
E 96.1%
Envelope protein, involved in virus morphogenesis and assembly
M 96.4%
Membrane glycoprotein, predominant component of the envelope
Orf6 85.7%
Type I IFN antagonist
Orf7a 90.2%
Orf7b 84.1%
Orf8 45.3%
N 94.3%
Nucleocapsid phosphoprotein, binds to RNA genome
Orf9b 84.7%
Type I IFN antagonist
Orf9c 78.1%
Orf10 --

Dashboard Records

Search

Team | Score Type | Score | Target | Ordered | Synthesized | RMSE | Product Line | Price | LINK

CBZ-RURGG-AMC
[5-FAM]-AVLQSGFR-[K(εDABCYL)]-K-amide
DNP-RURGG-AMC

Cytotoxic Inactive Active
NVBL Molecular Therapeutics Team

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Srinivas Iyer
Stephan Irle
Stephanie Galanie
Stewart He
Tom Brettin
Tom Desautels
Tony Ferreira
Uma Ganapathy
Vilmos Kertesz
Yihui (Ray) Ren
Yue Yang
Impacts of the Molecular Design Team

• The team formed quickly and applied their broad expertise to:
  – Solve new structures of viral proteins
  – Build multiple computational models
  – Use massive supercomputing resources to identify and design potential hits
  – Develop biochemical assays and use them to
    • Validate computational predictions
    • Experimentally characterize active hits
    • And feed data back into improving computational models
  – Obtain experimentally validated antibody and small-molecule hits
  – All in six months time!

• The team continues to refine experimental hits into therapeutic leads

• The DOE labs worked together to do things no single lab could do alone