

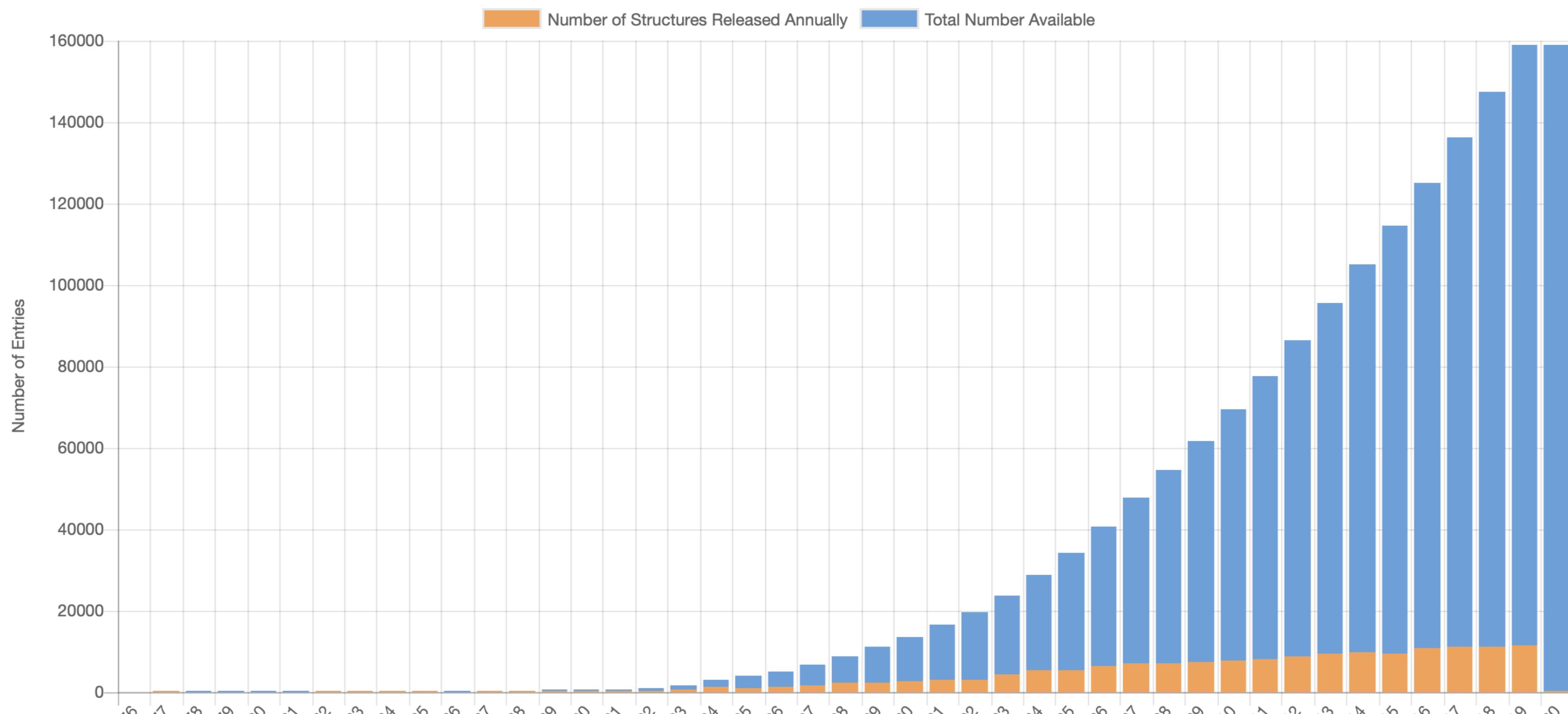
9/11/2024 Target Selection

- This lecture is intended to help you achieve the following learning objective: Analyze the prospects of a biological macromolecule (usually a protein) as a target for ligand design, from a community, scientific, and business perspective.
- This module will consist of a lecture interspersed with discussions, an interactive database search exercise, and a review
- At the end of this module, you should be able to address the question of what is necessary and what is desirable for a biological macromolecule to be a suitable target for structure-based drug design.
 - What is necessary/desirable about the physiological role?
 - What is necessary/desirable about the structural properties?
 - What are some business considerations that pharmaceutical companies use to decide whether to develop a drug for a particular target?
- You should also know about some databases that you can use to help find a suitable target for SBDD

The exponential growth of biomacromolecule structures is an opportunity for SBDD

PDB Statistics: Overall Growth of Released Structures Per Year

Other Statistics ▾



<https://www.rcsb.org/stats/growth/overall>

Predictive structural modeling further expands the range of accessible targets

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RESEARCH ARTICLE | PROTEIN FOLDING



nature > articles > article

Article | Open Access | Published: 15 July 2021

Highly accurate protein structure prediction with AlphaFold

John Jumper , Richard Evans, ... Demis Hassabis  + Show authors

Nature 596, 583–589 (2021) | Cite this article

566k Accesses | 983 Citations | 2993 Altmetric | Metrics

Abstract

Proteins are essential to life, and understanding their structure can facilitate a mechanistic understanding of their function. Through an enormous experimental effort^{1,2,3,4}, the structures of around 100,000 unique proteins have been determined⁵, but this represents a small fraction of the billions of known protein sequences^{6,7}. Structural coverage is bottlenecked by the months to years of painstaking effort required to determine a single

Deep learning takes on protein folding
Abstract
Supplementary Material
References and Notes

Deep learning takes on protein folding

In 1972, Anfinsen won a Nobel prize for demonstrating a connection between a protein's amino acid sequence and its three-dimensional structure. Since 1994, scientists have competed in the biannual Critical Assessment of Structure Prediction (CASP) protein-folding challenge. Deep learning methods took center stage at CASP14, with DeepMind's AlphaFold2 achieving remarkable accuracy. Baek *et al.* explored network architectures based on the DeepMind framework. They used a three-track network to process sequence, distance, and coordinate information simultaneously and achieved accuracies approaching those of DeepMind. The method, RoseTTA fold, can solve challenging x-ray crystallography and cryo-electron microscopy modeling problems and generate accurate models of protein-protein complexes. —VV



What is necessary/desirable about the physiological role of a SBDD target?

What is necessary/desirable about the physiological role of a SBDD target?

Disease Relevance. Altering activity (usually by inhibition) should affect disease progression.

**Brainstorm: How can disease
relevance be predicted?**

How can disease relevance be predicted?

- Mechanistic rationale, e.g.
 - the enzyme HIV protease has key role in viral life cycle. blocking it will slow viral reproduction.
 - the H⁺/K⁺-ATPase system is involved in stomach acid production. blocking it will reduce stomach acid and can be used to treat acid reflux.
- Mutations in a protein known to affect disease progression
 - in the clinic
 - in the laboratory
- Chemical probes affect disease progression
- Essential targets are better, e.g. NADH:ubiquinone oxidoreductase (NQR) is essential for *Vibrio cholerae* (common gut infection in developing tropical countries) and *Chlamydia trachomatis* (common STD) [1] but not *Pseudomonas aeruginosa* (common hospital infection)

Liang, P.; Rosas-Lemus, M.; Patel, D.; Fang, X.; Tuz, K.; Juárez, O. Dynamic Energy Dependency of Chlamydia Trachomatis on Host Cell Metabolism during Intracellular Growth: Role of Sodium-Based Energetics in Chlamydial ATP Generation. *J. Biol. Chem.* 2018, 293 (2), 510–522. <https://doi.org/10.1074/jbc.M117.797209>.

**Brainstorm: What is necessary/
desirable about the structural
properties of a SBDD target?**

What is necessary about the structural properties of a SBDD target?

- High-resolution structure available
 - Resolution of < 2.5 Å [1]
 - Homology models less trustworthy
 - can still be useful, perhaps to guide structure determination
 - Experimental structures/homology models can be refined by molecular dynamics simulation
- “Druggable”
 - precedence - previously targeted
 - structure-based
 - cavities or pockets
 - comparing physicochemical and geometric properties of pocket with known druggable targets
 - as a caveat, concept is about history and does not account for innovation

[1] Anderson, A. C. The Process of Structure-Based Drug Design. *Chemistry & Biology* 2003, 10 (9), 787–797. <https://doi.org/10.1016/j.chembiol.2003.09.002>.

What is desirable about the structural properties of a SBDD target?

- Small
 - less ambiguity regarding binding site
 - more amenable to molecular simulation
- Rigid
 - molecular docking is more accurate
 - molecular simulation requires less sampling
- Binding site is
 - unique, favoring specificity
 - evolutionarily conserved, less susceptible to resistance

There are multiple online databases to help you identify suitable targets

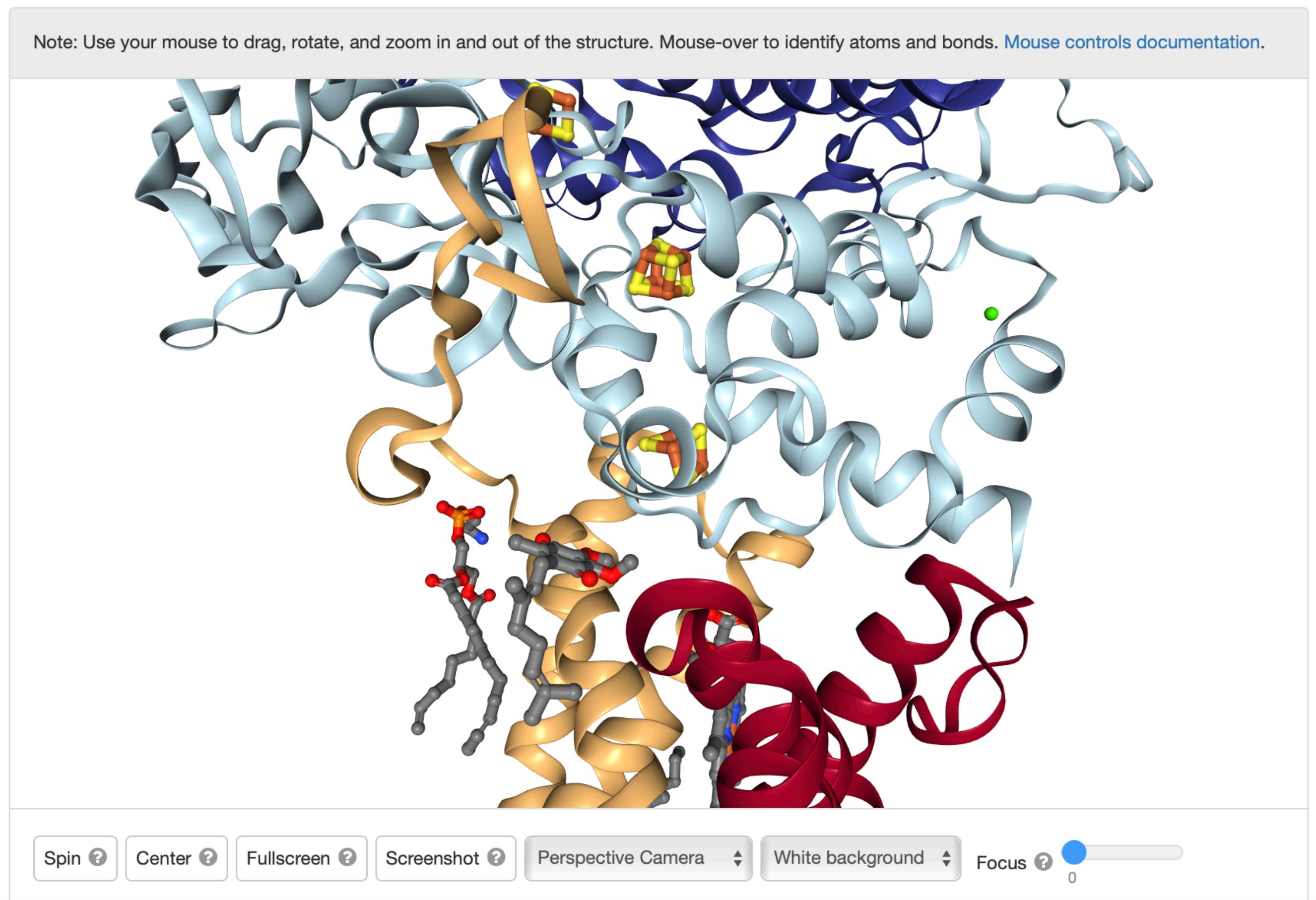
- The Special Programme for Research and Training in Tropical Diseases (TDR) Targets (<https://tdrtargets.org/>) - A database that allows you to apply various filters to identify drug targets. Focuses on neglected tropical diseases.
- Therapeutic target database (<http://idrblab.net/ttd/>) - “A database to provide information about the known and explored therapeutic protein and nucleic acid targets, the targeted disease, pathway information and the corresponding drugs directed at each of these targets.” This can help you determine precedence for a target.
- BindingDB (<http://www.bindingdb.org/bind/index.jsp>) - “BindingDB is a public, web-accessible database of measured binding affinities, focusing chiefly on the interactions of proteins considered to be drug-targets with small, drug-like molecules.” BindingDB can help you determine whether any small molecule (not necessarily a drug) has been found that binds to a target.

Interactive Database Exercise

- Oscar Juarez has worked on discovering inhibitors for Complex II, a.k.a. Succinate Dehydrogenase (SDH), from *Pseudomonas aeruginosa*
- The structure of E. Coli SDH has been solved at a resolution of 2.6 Å
- Subunit B (cyan) has Iron-Sulfur centers
- He has targeted the ubiquinone site at the interface of subunits B, C (yellow), and D (red)

1NEK

Complex II (Succinate Dehydrogenase) From E. Coli with ubiquinone bound

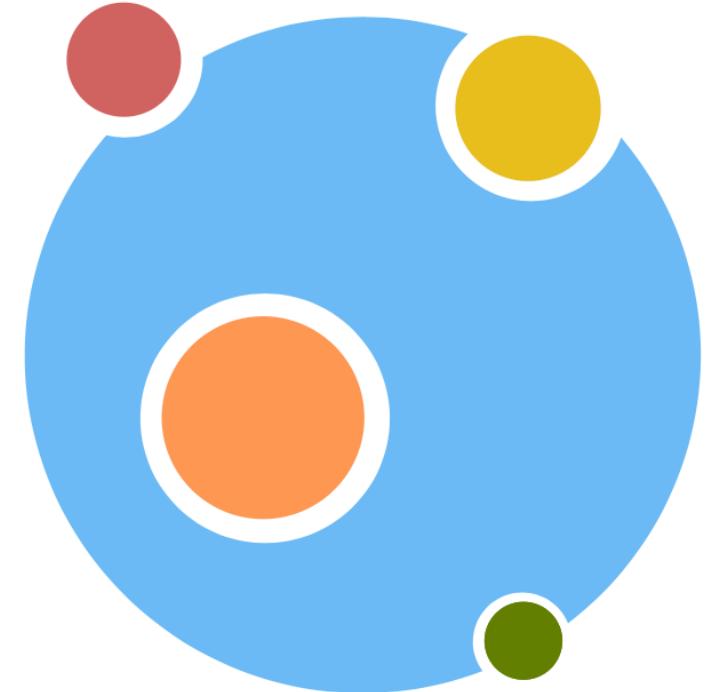


- We think it's a good drug target but I want to see what the online databases suggest
- First, let's try TDR targets (<https://tdrtargets.org>). It is possible that an SDH drug for *P. Aeruginosa* may also work on some neglected tropical diseases.

Leverage diverse datasets to facilitate drug discovery for neglected disease pathogens

TDR Targets functions both as a **website** where you can look for information on targets, drugs and/or bioactive compounds of interest, and as a **tool** for prioritization of targets in whole genomes.

The name of the database includes the initialism 'TDR' for Tropical Disease Research, a special programme within the World Health Organization.

Target search

Look for information on targets of interest. Prioritize targets in whole genomes.

[Targets »](#)

Drug search

Search for drugs and potential drug-target relationships. Explore bioactivities.

[Drugs! »](#)

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 © 2005 – 2012 The TDR Drug Targets Network (WHO/TDR)

TDR Targets Development Release v6.1, Revision: 1513 (29.Nov.2019)
 Contact Us: <info at tdrtargets.org>



- Try a “Quick Search...” for “succinate dehydrogenase”. This yields many results that are various subunits of the enzyme from different species
- Compared to the ubiquinone binding site, the “flavoprotein subunit” is on the opposite side of the complex

Target list

Search results for query: #2 (succinate dehydrogenase)

Show query parameters

Convert this list of targets into a list of drugs: [More information?](#)

Retrieve: [All Associations \(Curated and Predicted\)](#) [Curated Associations](#) [Target Putative Associations \(predicted\) ▾](#)

Organism	Name ▾	Ortholog group	Product
<i>B. malayi</i>	Bm1_17325	OG5_126927	succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
<i>B. malayi</i>	Bm1_17330	OG5_126927	succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
<i>B. malayi</i>	Bm1_17690	OG5_126893	succinate dehydrogenase [ubiquinone] iron-sulfur protein, mitochondrial
<i>B. malayi</i>	Bm1_30090	OG5_129614	Succinate dehydrogenase cytochrome b560 subunit, mitochondrialprecursor
<i>B. malayi</i>	Bm1_35660	OG5_129488	Succinate dehydrogenase
<i>C. trachomatis</i>	CT_591	OG5_126893	succinate dehydrogenase iron sulfur subunit
<i>C. trachomatis</i>	CT_592	OG5_126927	succinate dehydrogenase flavoprotein subunit
<i>E. granulosus</i>	EgrG_000416000	No group	succinate dehydrogenase ubiquinone iron sulfur

- A few of the hits had “iron-sulfur subunit” in the name. The iron-sulfur subunit is B, one of those next to the ubiquinone binding site.
- Try a “Quick Search...” for “succinate dehydrogenase iron-sulfur”.

Search results for query: #7 (succinate dehydrogenase iron-sulfur)

Show query parameters

Convert this list of targets into a list of drugs: [More information?](#)

Retrieve: [All Associations \(Curated and Predicted\)](#) [Curated Associations](#) [Target Putative Associations \(predicted\) ▾](#)

9 records found Showing page 1 of 1 (records 1-9) Number of records to display 25 <input type="button" value="Find orthologs in select species"/>			
Organism	Name ▾	Ortholog group	Product
<i>L. Loa</i> (eye worm)	LOAG_10155	OG5_126893	succinate dehydrogenase iron-sulfur protein
<i>M. ulcerans</i>	MUL_1370	OG5_126893	succinate dehydrogenase iron-sulfur subunit
<i>S. mansoni</i>	Smp_089640.2	OG5_126893	succinate dehydrogenase iron-sulfur protein
<i>S. mansoni</i>	Smp_089640.3	OG5_126893	succinate dehydrogenase iron-sulfur protein
<i>T. brucei</i>	Tb927.8.3380	OG5_126893	succinate dehydrogenase iron-sulfur subunit
<i>T. brucei</i>	Tb927.9.5960	OG5_126893	succinate dehydrogenase iron-sulfur subunit, putative
<i>T. cruzi</i>	TcCLB.504949.30	OG5_126893	succinate dehydrogenase iron-sulfur subunit
<i>T. cruzi</i>	TcCLB.509769.60	OG5_126893	succinate dehydrogenase iron-sulfur subunit
<i>W. endosymbiont of Brugia malayi</i>	Wbm0600	OG5_126893	succinate dehydrogenase iron-sulfur subunit

- Click on Tb927.8.3380 and scroll down to Essentiality Data
- Suppose that we discover a SDH inhibitor in our SBDD campaign against the ubiquinone binding site of *P. Aeruginosa*. Based on these data, which other species would be most worth testing its efficacy against? Which would be least worth testing?

Essentiality			
Tb927.8.3380 has direct evidence of essentiality			
Gene/Ortholog	Organism	Phenotype	Source Study
mtu1581	Mycobacterium tuberculosis	non-essential	nmpdr
mtu3379	Mycobacterium tuberculosis	non-essential	nmpdr
Tb09.160.4380	Trypanosoma brucei	no significant loss or gain of fitness in bloodstream forms (3 days)	alsford
Tb09.160.4380	Trypanosoma brucei	significant gain of fitness in bloodstream forms (6 days)	alsford
Tb09.160.4380	Trypanosoma brucei	no significant loss or gain of fitness in procyclic forms	alsford
Tb09.160.4380	Trypanosoma brucei	significant gain of fitness in differentiation of procyclic to bloodstream forms	alsford
Tb927.8.3380 this record	Trypanosoma brucei	significant loss of fitness in bloodstream forms (3 days)	alsford
Tb927.8.3380 this record	Trypanosoma brucei	significant loss of fitness in bloodstream forms (6 days)	alsford
Tb927.8.3380 this record	Trypanosoma brucei	significant loss of fitness in procyclic forms	alsford
Tb927.8.3380 this record	Trypanosoma brucei	significant loss of fitness in differentiation of procyclic to bloodstream forms	alsford
b0724	Escherichia coli	non-essential	goodall
b4153	Escherichia coli	non-essential	goodall

- Click on Tb927.8.3380 and scroll down to Essentiality Data
- Suppose that we discover a SDH inhibitor in our SBDD campaign against the ubiquinone binding site of *P. Aeruginosa*. Based on these data, which other species would be most worth testing its efficacy against? Which would be least worth testing?
- The inhibitor should be tested against *T. brucei* and *T. gondii*. It probably won't be effective against *M. tuberculosis* and *P. berghei*.

Essentiality			
Tb927.8.3380 has direct evidence of essentiality			
Gene/Ortholog	Organism	Phenotype	Source Study
mtu1581	Mycobacterium tuberculosis	non-essential	nmpdr
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Tb09.160.4380	Trypanosoma brucei	no significant loss or gain of fitness in procyclic forms	alsford
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b0724	Escherichia coli	non-essential	goodall
b4153	Escherichia coli	non-essential	goodall

- Also take a look at “Structural information”
- There is no crystal structures and the homology models from Modbase are not high quality. The homology model could be a guide, but I would not base an SBDD campaign against a *T. brucei* homology model.
- We can also look at AlphaFold

Structural information

Modbase 3D models:

There are 3 models calculated for this protein. More info on these models, including the models themselves is available at: [Modbase](#)

Target Beg	Target End	Template	Template Beg	Template End	Identity	Evalue	Model Score	MPQS	zDope
32	156	1zoy (B)	16	151	46.00	0	1	0.950829	0.33
32	156	4ysx (B)	40	175	46.00	0	0.99	0.956829	0.26
168	229	5i9f (A)	348	409	23.00	0.53	0.98	0.708498	-1.37

[+ Help me make sense of these data.](#)

Target Beg: first modeled residue
Target End: last modeled residue
Template: template structure used for modelling (PDB accession and chain)
Template Beg: first template residue in target-template alignment
Template End: last template residue in target-template alignment
Identity: sequence identity
Evalue: E value for target-template hit
Model Score: GA341 score (>0.7 for reliable model)
MPQS: ModPipe Quality Score (>1.1 for reliable model)

- Let's try “succinate dehydrogenase” in the Therapeutic Target Database (<http://idrblab.net/ttd/>)
- Did you find SDH?

The screenshot shows the homepage of the Therapeutic Target Database (TTD). At the top, there is a banner featuring the TTD logo (orange dots), the text "Therapeutic Target Database", and logos for BIDD (Bioinformatics and Drug Design group) and IDRBL (IDRBL). Below the banner is a navigation bar with links: Home, Advanced Search, Target Group, Drug Group, Patient Data, Model & Study, and Download. A large orange search bar contains the placeholder text "Search Whole Database". Below the search bar is a smaller input field labeled "Search for Targets:" with the value "succinate dehydrogenase". To the right of this input field are two buttons: "Search" and "Reset". At the bottom of the search area, there is a link to examples: EGFR; Vascular endothelial growth factor; Peramivir; Renal cell carcinoma ...

- Now try “succinate dehydrogenase” in the Therapeutic Target Database (<http://idrblab.net/ttd/>)
- Did you find SDH?
- Looks like it is there, as T39811.

The screenshot shows the homepage of the Therapeutic Target Database (TTD). At the top, there is a banner featuring the TTD logo (a stylized orange and yellow dot cluster), the text "Therapeutic Target Database", and logos for BIDD (Bioinformatics and Drug Design group) and IDRB. Below the banner is a navigation bar with links for Home, Advanced Search, Target Group, Drug Group, Patient Data, Model & Study, and Download. The main search area has a large orange button labeled "Search Whole Database". Below this is a search input field containing the text "succinate dehydrogenase". To the right of the search input are two buttons: "Search" and "Reset". A note below the search field says "Examples: EGFR; Vascular endothelial growth factor; Peramivir; Renal cell carcinoma ...".

- Are there currently any drugs that target SDH?

Therapeutic Target Database

Home Advanced Search ▾ Target Group ▾ Drug Group ▾ Patient Data ▾ Model & Study ▾ Download

Target Information

Target General Information	
Target ID	T39811 (Former ID: TTDI01376)
Target Name	Succinate dehydrogenase (SDHD)
Synonyms	Succinate-ubiquinone reductase membrane anchor subunit; Succinate-ubiquinone oxidoreductase cytochrome b small subunit; Succinate dehydrogenase complex subunit D; Succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial; SDH4; QPs3; CybS; CII-4
Gene Name	SDHD
Target Type	Literature-reported target
Function	Membrane-anchoring subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q).
UniProt ID	DHSD_HUMAN 🔗
Sequence	MAVLWRLSAVCAGALGGRALLRTPVVRPAHISAFLQDRPIPEWCVGQHIHLSPSHSGSK AASLHWTSERVSVSLLLGLPAAYLNPCSAMDYSLAAALTGHGWLGQVVTDYVHDAL QKAAKAGLLALSALTFAGLCYFNYHDVGICKAVMLWKL

References

REF 1	Succinate dehydrogenase is a direct target of sirtuin 3 deacetylase activity. PLoS One. 2011;6(8):e23295. 🔗
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If you find any error in data or bug in web service, please kindly report it to [Dr. Wang](#) and [Dr. Li](#).

- Are there currently any drugs that target SDH?
- No

Therapeutic Target Database

Home Advanced Search ▾ Target Group ▾ Drug Group ▾ Patient Data ▾ Model & Study ▾ Download

Target Information

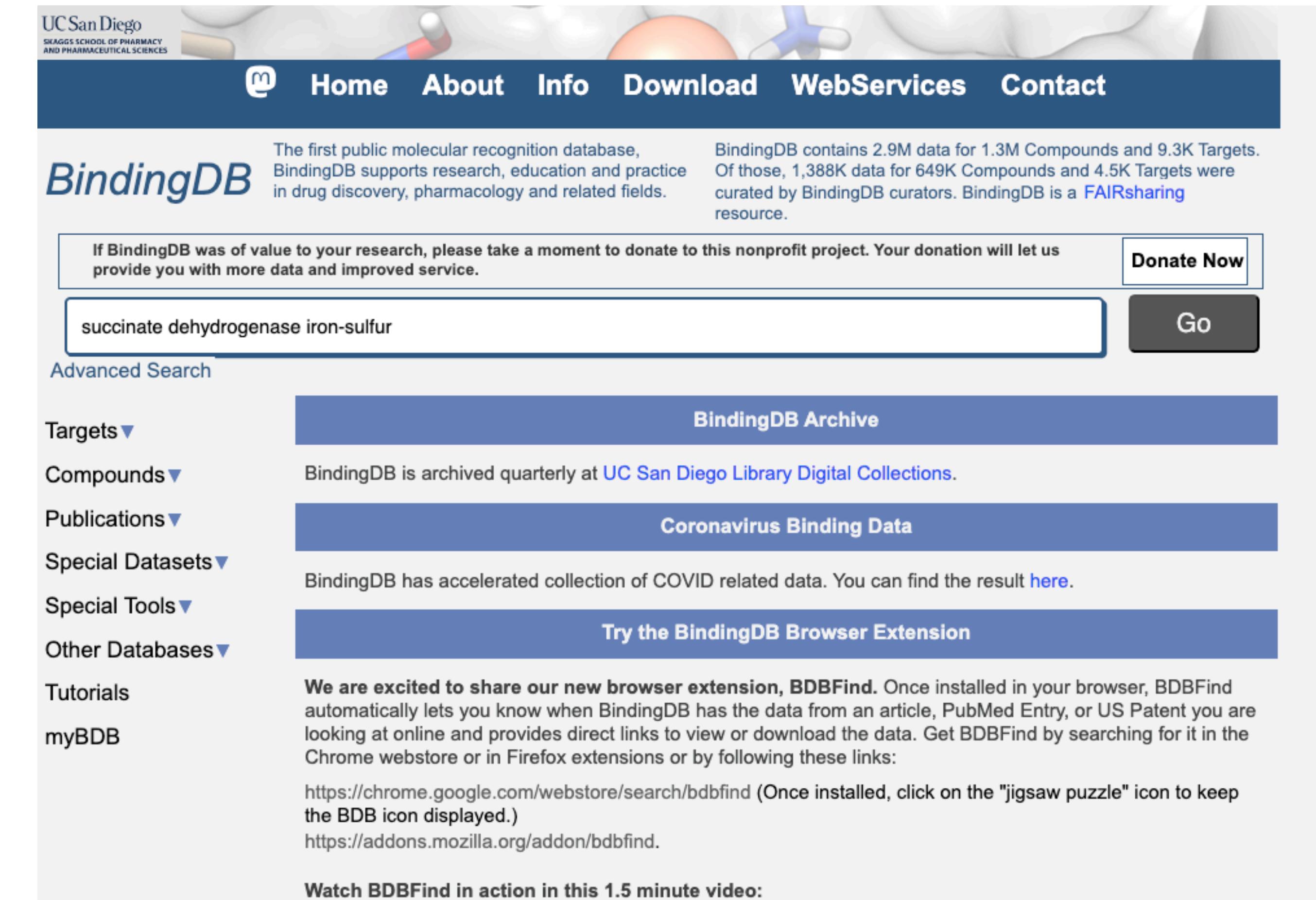
Target General Information	
Target ID	T39811 (Former ID: TTDI01376)
Target Name	Succinate dehydrogenase (SDHD)
Synonyms	Succinate-ubiquinone reductase membrane anchor subunit; Succinate-ubiquinone oxidoreductase cytochrome b small subunit; Succinate dehydrogenase complex subunit D; Succinate dehydrogenase [ubiquinone] cytochrome b small subunit, mitochondrial; SDH4; QPs3; CybS; CII-4
Gene Name	SDHD
Target Type	Literature-reported target
Function	Membrane-anchoring subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q).
UniProt ID	DHSD_HUMAN 🔗
Sequence	MAVLWRLSAVCGALGGRALLRTPVVRPAHISAFLQDRPIPEWCVGQHIHLSPSHSGSK AASLHWTSERVVSVLLGLPAAYLNPCSAMDYSLAAALTGHGWLGQVVTDYVHDAL QKAAKAGLLALSALTFAGLCYFNYHDVGICKAVMLWKL

References

REF 1	Succinate dehydrogenase is a direct target of sirtuin 3 deacetylase activity. PLoS One. 2011;6(8):e23295. 🔗
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If you find any error in data or bug in web service, please kindly report it to [Dr. Wang](#) and [Dr. Li](#).

- Finally let's try BindingDB (<http://www.bindingdb.org/bind/index.jsp>)
- Search for “succinate dehydrogenase iron-sulfur”. Then click on “iron-sulfur subunit of complex ii”.
- How many hits do you get?



The screenshot shows the UC San Diego Seaggs School of Pharmacy and Pharmaceutical Sciences logo at the top left. The main navigation bar includes Home, About, Info, Download, WebServices, and Contact. Below the navigation, the **BindingDB** logo is displayed with a brief description: "The first public molecular recognition database, BindingDB supports research, education and practice in drug discovery, pharmacology and related fields." To the right, it states that BindingDB contains 2.9M data for 1.3M Compounds and 9.3K Targets, with 1,388K data for 649K Compounds and 4.5K Targets curated by curators. It is identified as a FAIRsharing resource. A "Donate Now" button is visible. The search bar contains the query "succinate dehydrogenase iron-sulfur". Below the search bar are links for Advanced Search, Targets, Compounds, Publications, Special Datasets, Special Tools, Other Databases, Tutorials, and myBDB. To the right, there are sections for the BindingDB Archive (archived quarterly at UC San Diego Library Digital Collections), Coronavirus Binding Data (accelerated collection of COVID related data), and Try the BindingDB Browser Extension (with links to the Chrome webstore and Mozilla Firefox add-on). A note about the BDBFind browser extension is also present.

BindingDB

The first public molecular recognition database, BindingDB supports research, education and practice in drug discovery, pharmacology and related fields.

If BindingDB was of value to your research, please take a moment to donate to this nonprofit project. Your donation will let us provide you with more data and improved service.

Donate Now

Go

succinate dehydrogenase iron-sulfur

[Advanced Search](#)

Targets ▾

BindingDB Archive

BindingDB is archived quarterly at [UC San Diego Library Digital Collections](#).

Compounds ▾

Coronavirus Binding Data

BindingDB has accelerated collection of COVID related data. You can find the result [here](#).

Publications ▾

Try the BindingDB Browser Extension

Special Datasets ▾

Special Tools ▾

Other Databases ▾

Tutorials

myBDB

We are excited to share our new browser extension, **BDBFind**. Once installed in your browser, BDBFind automatically lets you know when BindingDB has the data from an article, PubMed Entry, or US Patent you are looking at online and provides direct links to view or download the data. Get BDBFind by searching for it in the Chrome webstore or in Firefox extensions or by following these links:

<https://chrome.google.com/webstore/search/bdbfind> (Once installed, click on the "jigsaw puzzle" icon to keep the BDB icon displayed.)

<https://addons.mozilla.org/addon/bdbfind>.

Watch BDBFind in action in this 1.5 minute video:

- Finally let's try BindingDB (<http://www.bindingdb.org/bind/index.jsp>)
- Search for “succinate dehydrogenase iron-sulfur”. Then click on “iron-sulfur subunit of complex ii”.
- How many hits do you get?
- I see 515!

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AND PHARMACEUTICAL SCIENCES

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Report error Found 515 Sort by Ki ▾

Targets▼	Compounds▼	Publications▼	Special Datasets▼	Special Tools▼	Other Databases▼	Tutorials	myBDB	Filter my 515 hits				
								<p>Targets 1▼</p> <p>Publications 3▼</p> <p>Institutions 3▼</p> <p>Affinity: 0.23 to 5.0E+5 nM▼</p> <p>Xtal structures: 0</p> <p>Docked structures: 0</p> <p>Catalog Cmpds: 5</p>				
								<p>Target Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial (Speckled leaf blotch fungus)</p> <p>Fmc Stine Research Center</p> <p>Curated by ChEMBL</p> <p>Ligand</p> <p>BDBM50191588 ((2R,3S,6S,7R,8R)-3-[(3-formamido-2-hydroxybenzoyl)...])</p> <p>Copy SMILES Copy InChI</p>	<p>Affinity Data</p> <p>IC50: 2nM</p> <p><u>Assay Description:</u> Inhibition of Septoria nodorum succinate dehydrogenase and Qi site of mitochondrial respiratory chain complex 3 by FMET2-3 assay More data for this Ligand-Target Pair</p>	<p>Target Info</p> <p>UniProtKB/SwissProt</p> <p>GoogleScholar</p>	<p>Ligand Info</p> <p>Purchase ChEBI</p> <p>CHEMBL KEGG</p> <p>PC cid PC sid PDB</p> <p>Similar</p>	<p>In Depth</p> <p>Details Article PubMed</p> <p>Copy BDB DOI</p>
								<p>Target Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial (Speckled leaf blotch fungus)</p> <p>Fmc Stine Research Center</p> <p>Curated by ChEMBL</p> <p>Ligand</p> <p>BDBM50411095 (CHEMBL439507)</p> <p>Copy SMILES Copy InChI</p>	<p>Affinity Data</p> <p>IC50: 5nM</p> <p><u>Assay Description:</u> Inhibition of Septoria nodorum succinate dehydrogenase and Qi site of mitochondrial respiratory chain complex 3 by FMET2-3 assay More data for this Ligand-Target Pair</p>	<p>Target Info</p> <p>UniProtKB/SwissProt</p> <p>GoogleScholar</p>	<p>Ligand Info</p> <p>CHEMBL PC cid</p> <p>PC sid Similar</p>	<p>In Depth</p> <p>Details Article PubMed</p> <p>Copy BDB DOI</p>
								<p>Target Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial (Speckled leaf blotch fungus)</p> <p>Fmc Stine Research Center</p> <p>Curated by ChEMBL</p> <p>Ligand</p> <p>BDBM50411094 (CHEMBL379116)</p> <p>Copy SMILES Copy InChI</p>	<p>Affinity Data</p> <p>IC50: 26nM</p> <p><u>Assay Description:</u> Inhibition of Septoria nodorum succinate dehydrogenase and Qi site of mitochondrial respiratory chain complex 3 by FMET2-3 assay More data for this Ligand-Target Pair</p>	<p>Target Info</p> <p>UniProtKB/SwissProt</p> <p>GoogleScholar</p>	<p>Ligand Info</p> <p>CHEMBL PC cid</p> <p>PC sid Similar</p>	<p>In Depth</p> <p>Details Article PubMed</p> <p>Copy BDB DOI</p>
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What do I learn from the BindingDB hits?

- The relatively large number of compounds that bind to SDH suggests that the site is druggable
- The results are from three studies, one that tested inhibition for a bacterium *Septoria tritici* and two for humans. The fact that many compounds bind to the human enzyme means that specificity could be an issue.
- It may be worth trying some of the compounds against *P. Aeruginosa*.

In the pharmaceutical industry, target selection is not only based on science, but also business

- How do pharmaceutical companies make money?
 - Costs
 - research and development is very expensive
 - manufacturing is relatively cheap
 - Income from drug sales
- In the current system, research and development (opposed to making old drugs) is incentivized by patents
 - must be novel, non-obvious, and useful. usually true for drugs.
 - provide monopoly on legal sales for a temporary period (in the U.S., 20 years from earliest filing)
 - need to be filed country-by-country
- In general, this system means that for a drug development campaign, the market must be
 - large enough
 - rich enough
 - not too competitive

Review questions

- What is necessary and what is desirable for a biological macromolecule to be a suitable target for structure-based drug design?
 - What is necessary/desirable about the physiological role?
 - What is necessary/desirable about the structural properties?
 - What are some business considerations that pharmaceutical companies use to decide whether to develop a drug for a particular target?
- What are some databases that you can use to help find a suitable target?