

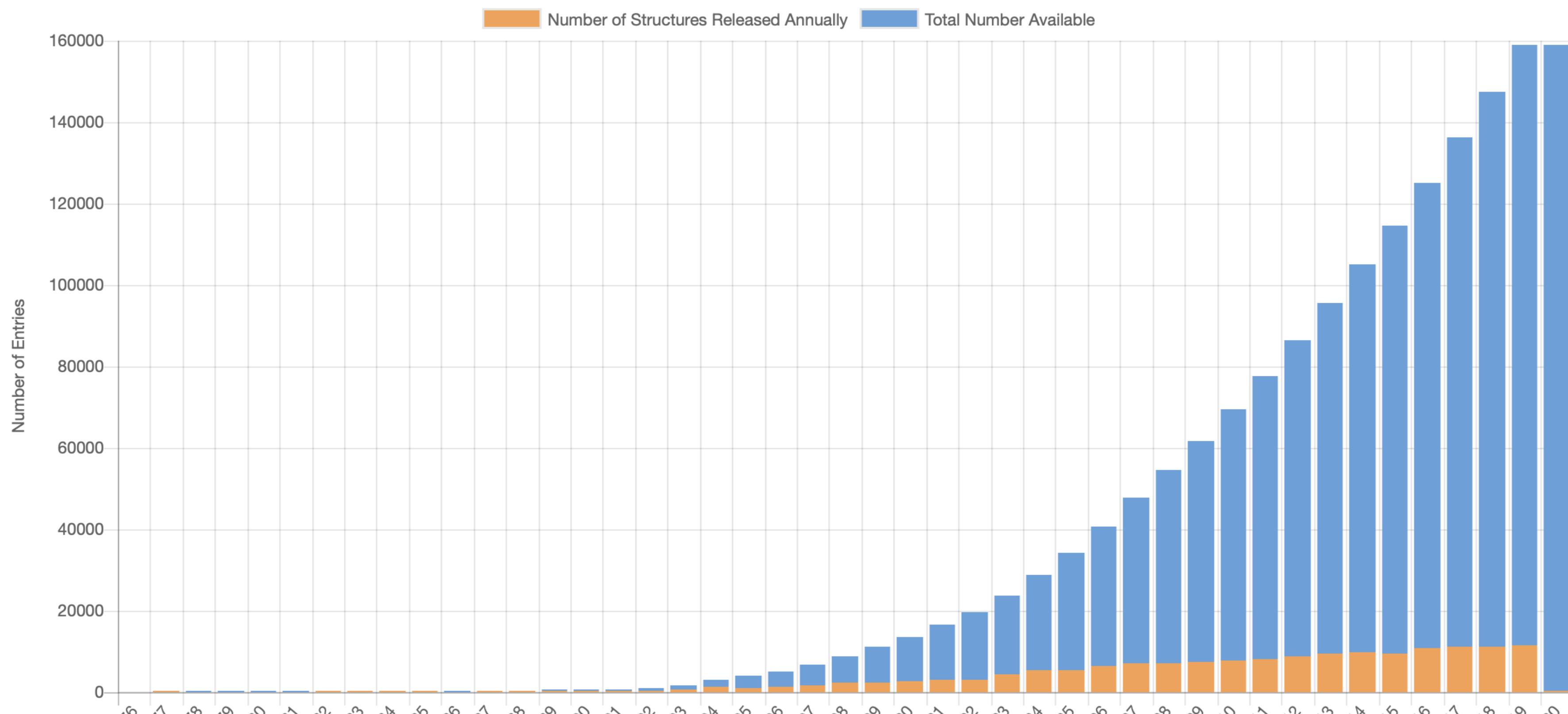
# 9/7/2022 Target Selection

- 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>

# Homology modeling further expands the range of accessible targets



In homology modeling, a protein model is built based on the structure of a similar protein

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## About MODELLER

MODELLER is used for homology or comparative modeling of protein three-dimensional structures (1,2). The user provides an alignment of a sequence to be modeled with known related structures and MODELLER automatically calculates a model containing all non-hydrogen atoms. MODELLER implements comparative protein structure modeling by satisfaction of spatial restraints (3,4), and can perform many additional tasks, including de novo modeling of loops in protein structures, optimization of various models of protein structure with respect to a flexibly defined objective function, multiple alignment of protein sequences and/or structures, clustering, searching of sequence databases, comparison of protein structures, etc. MODELLER is [available for download](#) for most Unix/Linux systems, Windows, and Mac.

Several graphical interfaces to MODELLER are commercially available. There are also many other resources and people using Modeller in graphical or web interfaces or other frameworks

1. B. Webb, A. Sali. Comparative Protein Structure Modeling Using Modeller. Current Protocols in Bioinformatics 54, John Wiley & Sons, Inc., 5.6.1-5.6.37, 2016.
  2. M.A. Marti-Renom, A. Stuart, A. Fiser, R. Sánchez, F. Melo, A. Sali. Comparative protein structure modeling of genes and genomes. Annu. Rev. Biophys. Biomol. Struct. 29, 291-325, 2000.
  3. A. Sali & T.L. Blundell. Comparative protein modelling by satisfaction of spatial restraints. J. Mol. Biol. 234, 779-815, 1993.
  4. A. Fiser, R.K. Do, & A. Sali. Modeling of loops in protein structures, Protein Science 9, 1753-1773, 2000.

The current release of Modeller is **9.23**, which was released on Oct 29th, 2019. Modeller is currently maintained by [Ben Webb](#).

**UCSF** MODELLER (copyright © 1989-2019 Andrej Sali) is maintained by [Ben Webb](#) at the Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, and California Institute for Quantitative Biomedical Research, Mission Bay Byers Hall, University of California San Francisco, San Francisco, CA 94143, USA. Any selling or distribution of the program or its parts, original or modified, is prohibited without a written permission from Andrej Sali. This file last modified: Tue Oct 29 10:42:12 PDT 2019.

**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<sup>+</sup>/K<sup>+</sup>-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

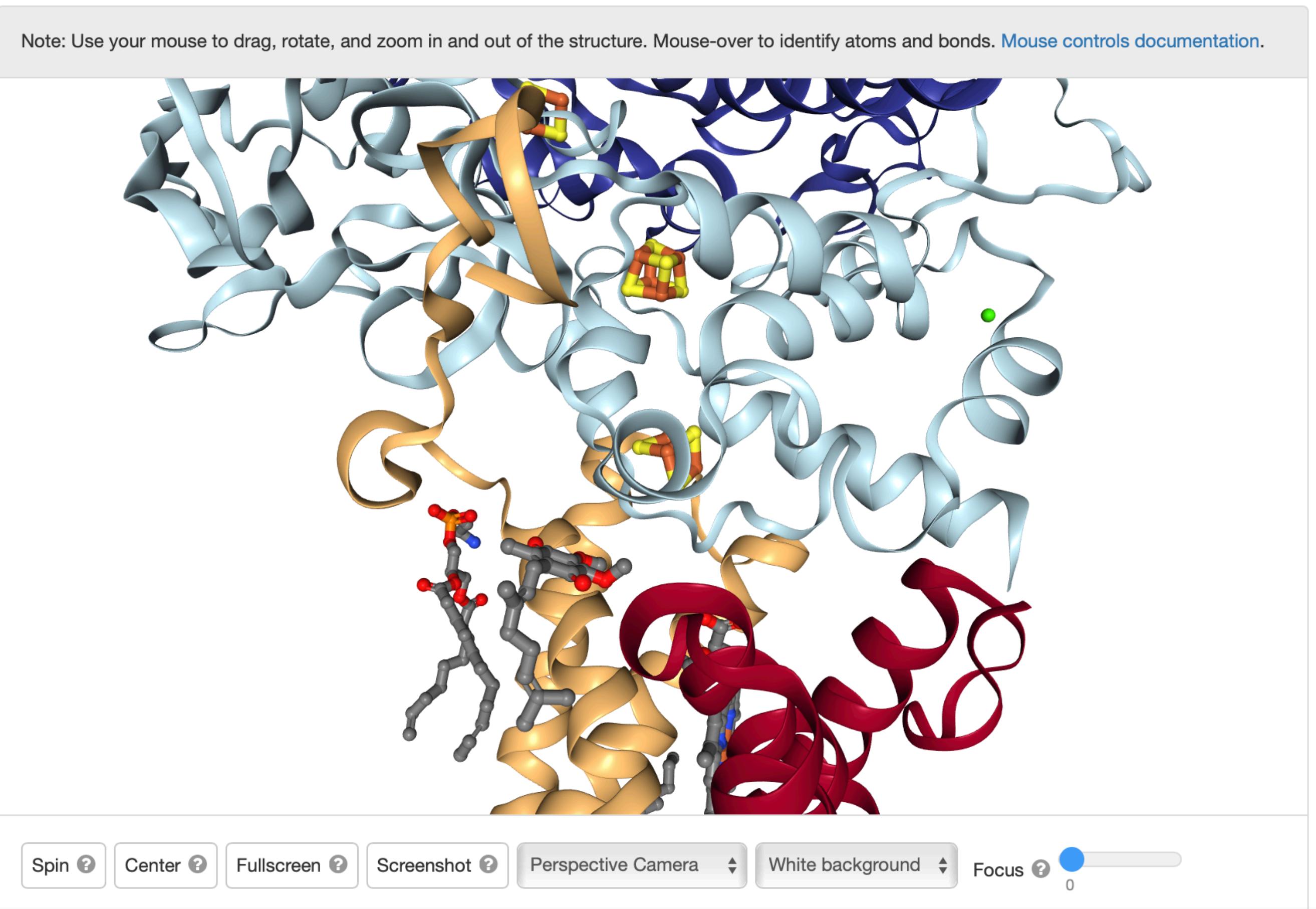
- The Special Programme for Research and Training in Tropical Diseases (TDR) Targets (<https://tdrtargets.org/>) - A database that allows you to apply various filters to identify drug targets. Focuses on neglected tropical diseases.
- Therapeutic target database (<http://idrblab.net/ttd/>) - “A database 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 protein considered to be drug-targets with small, drug-like molecules.” BindingDB can help you determine whether a any small molecule (not necessarily a drug) has been found that binds to a target.
- PocketDB (<http://proline.biochem.iisc.ernet.in/PocketDB/index.php>) - Databases of pockets in Protein Data Bank structures

# **Interactive Database Exercise**

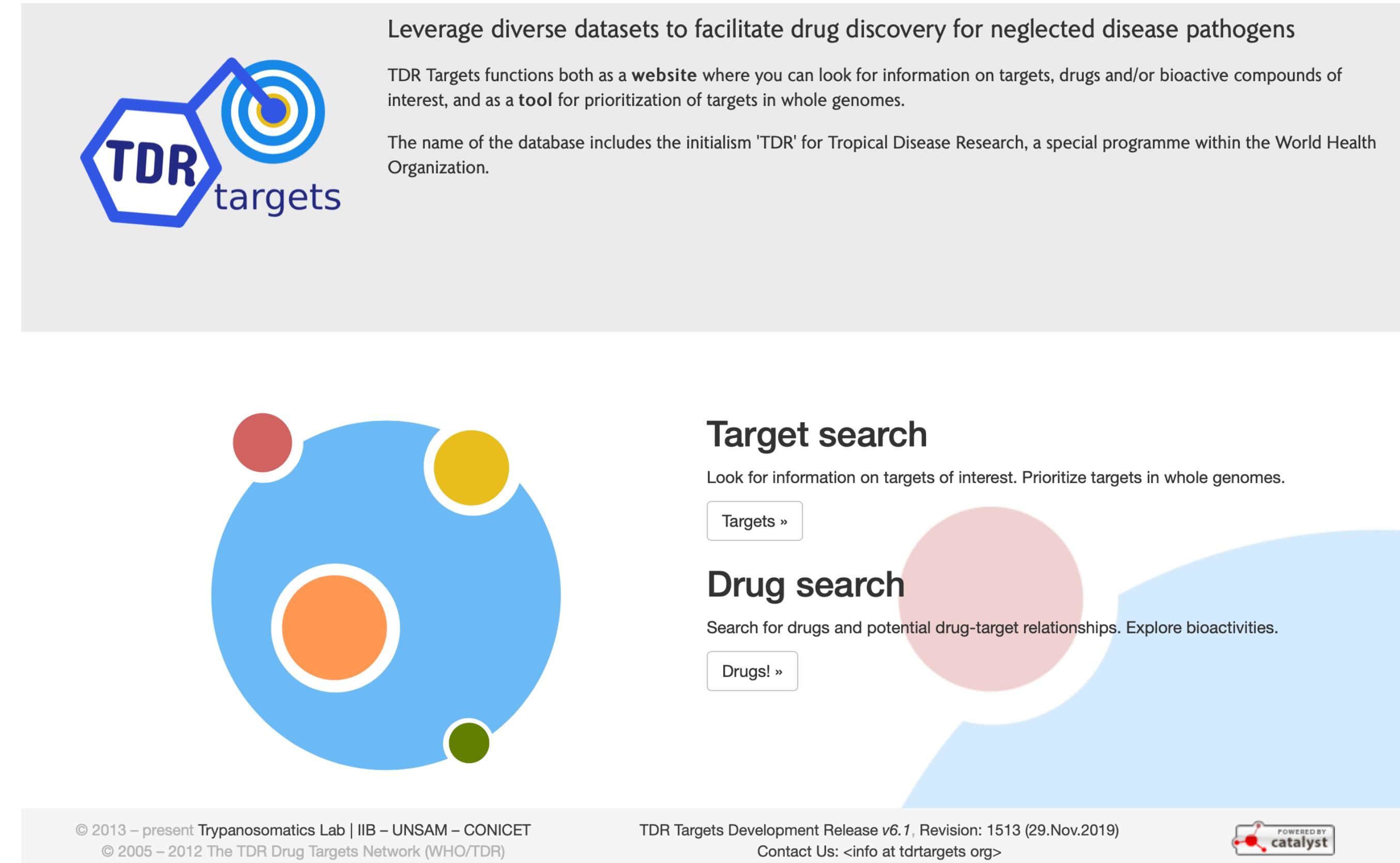
- I've been working with Oscar Juarez on discovering inhibitors for Complex II, a.k.a. Succinate Dehydrogenase (SDH), from *Pseudomonas aeruginosa*
- The structure of E. Coli SDH has been solved at a resolution of 2.6 Å
- Subunit B (cyan) has Iron-Sulfur centers
- We are targeting the ubiquinone site 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.



The screenshot shows the TDR Targets homepage. At the top, there is a logo consisting of a blue hexagon containing the letters 'TDR' and a blue circle containing a target symbol with the word 'targets' next to it. To the right of the logo is a text block: 'Leverage diverse datasets to facilitate drug discovery for neglected disease pathogens'. Below this, it says '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.' and 'The name of the database includes the initialism 'TDR' for Tropical Disease Research, a special programme within the World Health Organization.' Below this text is a large graphic of a blue circle with three smaller colored circles (red, yellow, green) inside it, representing a target or molecule. To the right of the graphic are two sections: 'Target search' (with a 'Targets »' button) and 'Drug search' (with a 'Drugs! »' button). At the bottom of the page, there is copyright information: '© 2013 – present Trypanosomatics Lab | IIB – UNSAM – CONICET © 2005 – 2012 The TDR Drug Targets Network (WHO/TDR)' and 'TDR Targets Development Release v6.1, Revision: 1513 (29.Nov.2019) Contact Us: <info at tdrtargets.org>'. A 'POWERED BY catalyst' logo is also present.

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>

POWERED BY catalyst

- 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>	<a href="#">Bm1_17325</a>	<a href="#">OG5_126927</a>	succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
<i>B. malayi</i>	<a href="#">Bm1_17330</a>	<a href="#">OG5_126927</a>	succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial
<i>B. malayi</i>	<a href="#">Bm1_17690</a>	<a href="#">OG5_126893</a>	succinate dehydrogenase [ubiquinone] iron-sulfur protein, mitochondrial
<i>B. malayi</i>	<a href="#">Bm1_30090</a>	<a href="#">OG5_129614</a>	Succinate dehydrogenase cytochrome b560 subunit, mitochondrialprecursor
<i>B. malayi</i>	<a href="#">Bm1_35660</a>	<a href="#">OG5_129488</a>	Succinate dehydrogenase
<i>C. trachomatis</i>	<a href="#">CT_591</a>	<a href="#">OG5_126893</a>	succinate dehydrogenase iron sulfur subunit
<i>C. trachomatis</i>	<a href="#">CT_592</a>	<a href="#">OG5_126927</a>	succinate dehydrogenase flavoprotein subunit
<i>E. granulosus</i>	<a href="#">EgrG_000416000</a>	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			
<b>Tb927.8.3380 has direct evidence of essentiality</b>			
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 <span style="background-color: orange; border: 1px solid black; padding: 2px;">this record</span>	Trypanosoma brucei	significant loss of fitness in bloodstream forms (3 days)	alsford
Tb927.8.3380 <span style="background-color: orange; border: 1px solid black; padding: 2px;">this record</span>	Trypanosoma brucei	significant loss of fitness in bloodstream forms (6 days)	alsford
Tb927.8.3380 <span style="background-color: orange; border: 1px solid black; padding: 2px;">this record</span>	Trypanosoma brucei	significant loss of fitness in procyclic forms	alsford
Tb927.8.3380 <span style="background-color: orange; border: 1px solid black; padding: 2px;">this record</span>	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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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	<a href="#">1zoy</a> (B)	16	151	46.00	0	1	0.950829	0.33
32	156	<a href="#">4ysx</a> (B)	40	175	46.00	0	0.99	0.956829	0.26
168	229	<a href="#">5i9f</a> (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)

- The structure we have used as a basis for modeling studies has been 1NEK. I tried this in the PockeTome (<http://ablab.ucsd.edu/POCKETOME/>). (Was down on 7/6). There was no record for it.
- Try a search for “succinate”. Did you find SDH?

**PockeTome**

Search for  
1nek  
in  
PDB codes  
Go

Search for  
succinate  
in  
Pocketome  
Go

About  
Browse All  
Find chemical  
Access and format  
Downloads  
Citation

About  
Browse All  
Find chemical  
Access and format  
Downloads  
Citation  
Contact

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Disclaimer  
© 2011–2020 Abagyan  
Lab

Search Results

Show only:  Human;  Other mammals;  Gram-positive bacteria;  Gram-negative bacteria;  Archaea;  Virus;  Other.

ARLY2\_ANAPL\_4\_468 Argininosuccinate lyase [Lyase 1 family. Argininosuccinate lyase subfamily]  
  
 Domains/regions: [R] Substrate binding  
 PDB: 1auw, 1dcn, 1hy1, 1k7w, 1tju, 1tjv, 1tjw  
 HET: as1

ASSY\_THET8\_1\_400 Argininosuccinate synthase [Argininosuccinate synthase family. Type 1 subfamily]  
  
 Domains/regions: [R] Substrate binding  
 PDB: 1j1z, 1j20, 1j21, 1kh1, 1kh2, 1kh3, 1kor  
 HET: amp, anp, as1, atp, cir

PURA\_ECOLI\_2\_432 Adenylosuccinate synthetase [Adenylosuccinate synthetase family]  
  
 Domains/regions: [R] IMP binding  
 PDB: 1ade, 1adi, 1cg0, 1cg1, 1cg3, 1cg4, 1ch8, 1cib, 1gim, 1gin, 1hon, 1hoo, 1hop, 1juy, ...  
 HET: amp, doi, dpo, gcp, gdp, gnh, gnp, gpx, h5p, hda, imo, imp, pgs, rpd, rpl

DRAA\_ECOLX\_22\_160 Dr hemagglutinin structural subunit [Dr-adhesin family]  
  
 Domains/regions: [R] Receptor-binding  
 PDB: 1usq, 1ut1, 2jkl, 2jkl, 2jkn, 2w5p  
 HET: brx, cl8, clm

GTR3\_HUMAN\_1\_489 Solute carrier family 2, facilitated glucose transporter member 3 [Major facilitator superfamily. Sugar transporter (TC 2.A.1.1) family. Glucose transporter subfamily]  
  
 Domains/regions: [R] Important for selectivity against fructose, [R] Monosaccharide binding  
 PDB: 4zw9, 4zwb, 4zwc, 5c65  
 HET: y01

NCZS\_STRCZ\_35\_147 Neocarzinostatin [Neocarzinostatin family]  
  
 Domains/regions: [R] Substrate binding  
 PDB: 1nco, 1noa, 2cbm, 2cbo, 2cbq, 4jw3  
 HET: chr, mrd, th2

TRY1\_BOVIN\_66\_246 Cationic trypsin [Peptidase S1 family]  
  
 Domains/regions: [D] Peptidase S1, [R] Substrate binding  
 PDB: 1aq7, 1auj, 1az8, 1bju, 1bjv, 1btp, 1btv, 1btw, 1btz, 1btz, 1c1n, 1c1o, 1c1p, 1c1q, 1c1r, 1c...  
 HET: 0ca, 0cb, 123, 124, 12u, 132, 13u, 169, 22m, 23m, 312, 334, 3yh, 49u, 607, 623, 653, 655...

- 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 for 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: "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 BID (Bioinformatics and Drug Design group) and IDRB. 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 text "Search Whole Database". Below the search bar is a smaller input field labeled "Search for Targets:" containing "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 ...

- 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 <a href="#">🔗</a>
Sequence	MAVLWRLSAVCAGALGGRALLRTPVVRPAHISAFLQDRPIPEWCVGQHIHLSPSHSGSK AASLHWTSERVVSVLLGLPAAYLNPCSAMDYSLAAALTGHGWLGQVVTDYVHDAL QKAAKAGLLALSALTFAGLCYFNYHDVGICKAVMLWKL

### References

REF 1	Succinate dehydrogenase is a direct target of sirtuin 3 deacetylase activity. PLoS One. 2011;6(8):e23295. <a href="#">🔗</a>
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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

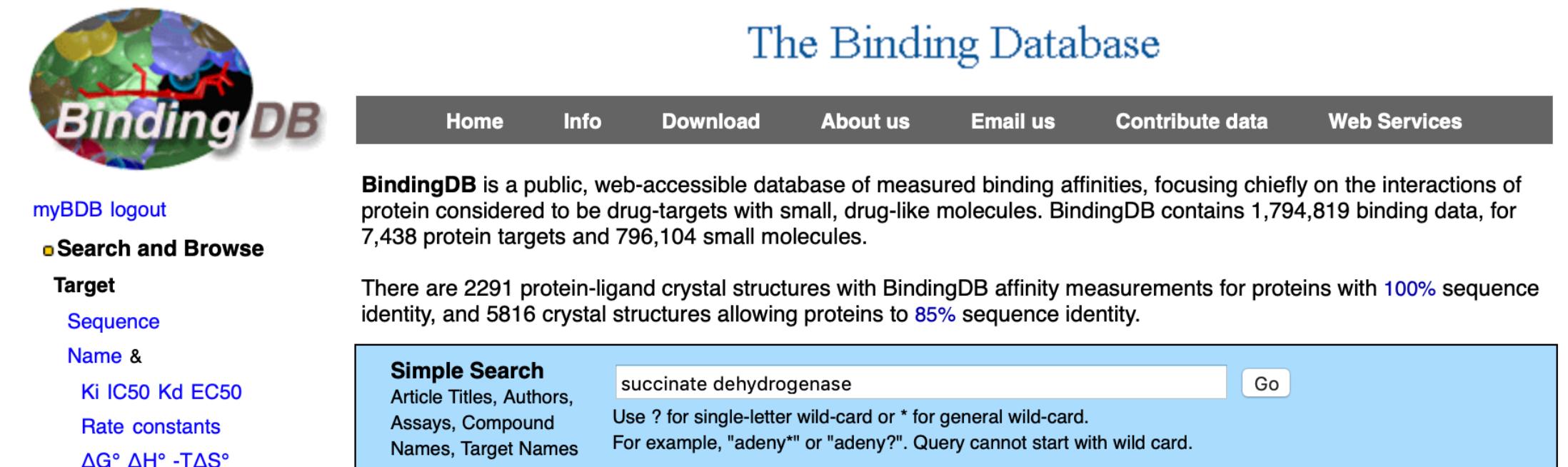
Target General Information	
Target ID	T39811 (Former ID: TTDI01376)
Target Name	Succinate dehydrogenase (SDHD)
Synonyms	Succinate-ubiquinone reductase membrane anchor subunit; Succinate-ubiquinone oxidoreductase cytochrome b small subunit; Succinate dehydrogenase complex subunit D; Succinate dehydrogenase [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 <a href="#">🔗</a>
Sequence	MAVLWRLSAVCAGALGGRALLRTPVVRPAHISAFLQDRPIPEWCVGQHIHLSPSHSGSK AASLHWTSERVVSVLLGLPAAYLNPCSAMDYSLAAALTGHGWLGQVVTDYVHDAL QKAAKAGLLALSALTFAGLCYFNYHDVGICKAVMLWKL

### References

REF 1	Succinate dehydrogenase is a direct target of sirtuin 3 deacetylase activity. PLoS One. 2011;6(8):e23295. <a href="#">🔗</a>
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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”. Then click on “mitochondrial complex ii; succinate dehydrogenase”.
- How many hits do you get?



The screenshot shows the main page of The Binding Database. At the top right is a blue header bar labeled "BindingDB News". Below it is a dark navigation bar with links: Home, Info, Download, About us, Email us, Contribute data, and Web Services. The main content area has a title "The Binding Database" and a logo featuring a globe with a red ribbon and the text "Binding DB". On the left, there's a sidebar with links: myBDB logout, Search and Browse (with sub-links Target, Sequence, Name &, Ki IC50 Kd EC50, Rate constants, ΔG° ΔH° -TΔS°), and a "Simple Search" form. The search form contains the query "succinate dehydrogenase" and a "Go" button. To the right of the search form, there's explanatory text about protein-ligand crystal structures and sequence identity. A sidebar on the right is titled "Novemeber 2017" and discusses a new download file for purchasable compounds.

- Finally let's try BindingDB (<http://www.bindingdb.org/bind/index.jsp>)
- Search for “succinate dehydrogenase”. Then click on “succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial”.
- How many hits do you get?
- I see 57!

The Binding Database

Compile Data Set for Download or QSAR

E-MAIL

Found 57 hits

Target/Host (Institution)	Ligand	Target/Host Links	Ligand Links	Trg + Lig Links	Ki nM	$\Delta G^\circ$ kJ/mole	IC50 nM	Kd nM	EC50/C50 nM	$k_{off}$ s <sup>-1</sup>	$k_{on}$ M <sup>-1</sup> s <sup>-1</sup>	pH	Temp °C
Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial ( <i>Septoria tritici</i> )	 <b>BDBM50191588</b> ((2R,3S,6S,7R,8R)-3-[(3-formamido-2-hydroxybenzoyl)...] Show SMILES Show InChI	UniProtKB/SwissProt GoogleScholar	Purchase CHEBI CHEMBL KEGG PC cid PC sid PDB UniChem	Article PubMed	n/a	n/a	2	n/a	n/a	n/a	n/a	n/a	
Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial ( <i>Septoria tritici</i> )	 <b>BDBM50411095</b> (CHEMBL439507) Show SMILES Show InChI	UniProtKB/SwissProt GoogleScholar	CHEMBL PC cid PC sid UniChem	Article PubMed	n/a	n/a	5	n/a	n/a	n/a	n/a		
Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial ( <i>Septoria tritici</i> )	 <b>BDBM50411096</b>	UniProtKB/SwissProt GoogleScholar	CHEMBL PC cid PC sid UniChem	Article PubMed	n/a	n/a	26	n/a	n/a	n/a	n/a		
<b>Assay Description</b>													
Inhibition of <i>Septoria nodorum</i> succinate dehydrogenase and Qi site of mitochondrial respiratory chain complex 3 by FMET2-3 assay													
<i>J Med Chem</i> 49: 4762-6 (2006)													
Article DOI: <a href="https://doi.org/10.1021/jm060408s">10.1021/jm060408s</a> BindingDB Entry DOI: <a href="https://doi.org/10.7270/Q2TD9ZJC">10.7270/Q2TD9ZJC</a>													
<b>More data for this Ligand-Target Pair</b>													
<b>Assay Description</b>													
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<b>More data for this Ligand-Target Pair</b>													
<b>Assay Description</b>													
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<i>J Med Chem</i> 49: 4762-6 (2006)													

# 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 two studies, one that tested inhibition for a bacterium *Septoria tritici*, and another 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?