

Platinum

Protein-ligand affinity change upon mutation database



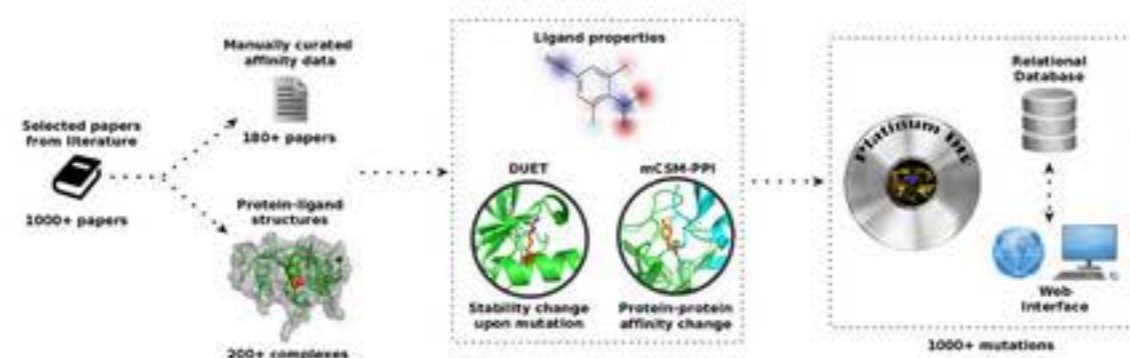
Platinum: a large-scale structural database of experimentally measured effects of mutations on protein-ligand complexes

Douglas E. V. Pires*, Tom L. Blundell, David B. Ascher*

High throughput sequencing initiatives are generating extensive data on non-synonymous single nucleotide polymorphisms (nsSNPs) in human and other genomes. The strong selective pressure imposed by small molecule drugs on many quickly evolving systems, including viruses, bacteria and human cancer, can cause the rapid development of resistance to these therapies.

In order to study and understand the impacts of missense mutations on the interaction of ligands with the proteome, as well as to guide protein engineering, we have developed **Platinum**. This manually curated, literature-derived database comprising over 1,000 mutations for the first time associates experimental information on changes in protein-ligand affinity with the three-dimensional structures of the complex. To minimise differences arising from experimental techniques and to be able to compare directly binding affinities, Platinum considers only changes measured by the same group and with the same amino-acid sequence used for structure determination, providing a direct link between protein structure, how a ligand binds and how mutations alter the affinity of the ligand for the protein.

We believe that Platinum will be an invaluable resource for understanding the effects of mutations that give rise to drug resistance, a major problem emerging in pandemics such those caused by the influenza virus, in infectious diseases such tuberculosis, in cancer and in many other life threatening illnesses.



About PLATINUM

PLATINUM is a manually curated, literature-derived database that associates experimental information on changes in protein-ligand affinity with the three-dimensional structures of the complex.

The current version of PLATINUM contains structural and affinity data reflecting the effects of mutations on protein-ligand complexes comprising:

- Over 1000 data points (approximately 80% of which are single-point mutations) with protein-ligand affinity data extracted from over 180 peer-reviewed manuscripts;
- More than 200 distinct ligands;
- Approximately 300 distinct PDB structures assigned to 140 different Uniprot entries.

Other information in the database include **ligand properties** and **predictions** of the effect of mutations on protein stability (calculated using **DUET**) and protein-protein affinity (calculated using **mCSM-PPI**).



Search page

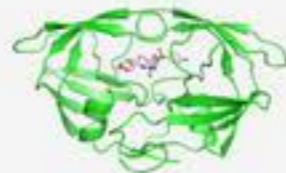
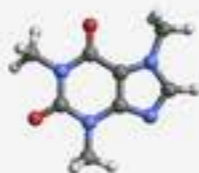
1

2

Platinum: protein-ligand affinity change upon mutation database



Search by ligand and protein properties



3

Ligand type

All ligand types

5

Mutation effect

All effects

7

Experimental method

All methods

9

Mutation type

All Single-point

11

Submit query

4

Organism category

All categories

6

Protein classification

All classes

8

Structure Resolution Range

All Below 2.5Å Below 2.0Å

10

Affinity constant

All (KD/Ki/Km) KD's only

How to query the database:

The complete set of mutations, structural and affinity data in PLATINUM can be browsed by clicking in (1). Alternatively, users can search (2) for specific categories using the following criterium:

- Ligand type (3), classified according to [PDBChem](#);
- Organism category (4), which is broadly grouped by phylogenetic kingdoms;
- Mutation effect (5), to select mutations that either decrease or increase protein-ligand affinity;
- Protein classification (6), as assigned by the PDB;
- Experimental method (7), to choose how the affinities were determined;
- Structure resolution range (8), which allows you to select data based upon the resolutions of the complex structures.
- Mutation type (9), which allows you to view only single-point mutations;
- Affinity constant (10), which allows you to view only KD measurements;

After selecting the desired options you can submit your query (11).

Database page

The screenshot shows the PLATIP database interface. At the top, there is a navigation bar with 'Browse' (1), 'Data' (2), 'Help', 'Contact', 'Acknowledgements', and 'Related Resources'. Below the navigation bar, there are four buttons: 'Show mutation properties', 'Show ligand properties', 'Show affinity details', and 'Show protein information'. A 'Column filtering' section contains input fields for 'Protein Name', 'Mutation', 'Ligand ID', and 'Uniprot ID'. A dropdown menu shows '10 records per page' (5) and a search box. The main table displays columns: Protein Name, Mutation, Is in binding site?, Ligand ID, Affinity Constant, Affinity Reference (nM), Affinity Mutant (nM), Reference PDB ID, Mutant PDB ID, DUET prediction, Uniprot, and PMID. The table contains 10 rows of data. At the bottom, there is a pagination bar showing 'Showing 1 to 10 of 133 entries' and a 'Download results' button (6). A 'New query' button is also visible.

Protein Name	Mutation	Is in binding site?	Ligand ID	Affinity Constant	Affinity Reference (nM)	Affinity Mutant (nM)	Reference PDB ID	Mutant PDB ID	DUET prediction	Uniprot	PMID
2-dehydropantoate 2-reductase	N98A	YES	APX	KD	232464.4969	137801.4935	1YON	None	-0.171	P0A9J4	17242510
2-dehydropantoate 2-reductase	N98A	YES	APX	KD	56875.6353	20806.0807	1YON	None	-0.171	P0A9J4	17242510
2-dehydropantoate 2-reductase	R31A	NO	APX	KD	232464.4969	197915.0761	1YON	None	-0.126	P0A9J4	17242510
2-dehydropantoate 2-reductase	R31A	NO	APX	KD	56875.6353	1959913.5494	1YON	None	-0.126	P0A9J4	17242510
4-hydroxybenzoyl-CoA Thioesterase	D17N	YES	4CO	KD	330	420	1LO7	None	-1.576	P56653	11997398
4-hydroxybenzoyl-CoA Thioesterase	D17N	YES	4CA	KD	1090	1000	1LO8	None	-1.59	P56653	11997398
Aminoglycoside N3-acetyltransferase	H183A	YES	ACO	KD	33350	3720	3IJW	3N0S	-2.06	Q81P86	21601576
Aminoglycoside N3-acetyltransferase	H183G	YES	ACO	KD	33350	6100	3IJW	3N0M	-2.69	Q81P86	21601576
ArtJ	E163Q	NO	ARG	KD	39	150	2Q2A	None	-0.963	D0VWX8	18022195
ArtJ	E35K	YES	ARG	KD	39	11000	2Q2A	None	-3.196	D0VWX8	18022195

Accessing the database

After clicking on **Browse** or performing a **Search** the database entries will be displayed in a tabulated format on this page.

The rows are coloured according to the effect of the mutation upon the binding affinity of the ligand. Red indicates that the mutant has a weaker affinity than the reference, while blue indicates that the mutant has stronger affinity.

Columns descriptions are available by hovering your cursor over the column headings (*tooltip function*). The headings of the hidden columns are coloured according to property they are linked to.

The information that is displayed can be adjusted according to your interests. Additional information regarding the following aspects can be shown or hidden:

- Residue properties (1), when reference structure is available;
- Ligand properties (2);
- Affinity experimental details (3) and
- Protein structural information (4).

The number of records displayed per page can be selected at (5) and the filtered results can be downloaded as a comma-separated .csv file (6), which can be easily imported by any spreadsheet program (e.g., LibreOffice, Microsoft Excel, Numbers, etc.) or any text editor.

Database page

PLATINUM [Browse](#) [Search](#) [Data](#) [Help](#) [Contact](#) [Acknowledgements](#) [Related Resources](#)

Visualization controls
[Show mutation properties](#) [Show ligand properties](#) [Show affinity details](#) [Show protein information](#)

Column filtering
Protein Name **2** Mutation **3** AS Ligand ID **4** GDP Uniprot ID **5** Q18014 **1**

10 records per page Search:

Protein Name	Mutation	Is in binding site?	Ligand ID	Affinity Constant	Affinity Reference (nM)	Affinity Mutant (nM)	Reference PDB ID	Mutant PDB ID	DUET prediction	Uniprot	PMID
Putative GDP-fucose protein o-fucosyltransferase 1	D244A	NO	GDP	KD	350	100	3ZY2	None	-0.215	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	D242A	NO	GDP	KD	350	90	3ZY2	None	-0.489	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	R40A	YES	GDP	KD	350	3100	3ZY2	None	-0.516	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	N43A	YES	GDP	KD	350	300	3ZY2	None	-0.791	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	F357A	YES	GDP	KD	350	26900	3ZY2	None	-2.706	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	F261A	YES	GDP	KD	350	120	3ZY2	None	-2.812	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	F199A	NO	GDP	KD	350	180	3ZY2	None	-3.228	Q18014	21966509
Putative GDP-fucose protein o-fucosyltransferase 1	W245A	YES	GDP	KD	350	1600	3ZY2	None	-3.295	Q18014	21966509

Showing 1 to 8 of 8 entries (filtered from 280 total entries) [-- Previous](#) [1](#) [Next -->](#)

[New query](#) [Download results](#)

Filtering query results

Once a query result is displayed users can select subsets of mutations of interest by either using a global search **(1)** or a field-specific filtering tools.

The supported fields are:

- Protein name **(2)**;
- Mutation **(3)**;
- Ligand ID **(4)** and
- Uniprot ID **(5)**.

The column filtering fields also support [regular expressions](#), and can therefore be used to build sophisticated selections.

For instance, the example shows the selection results considering the following options:

- Mutations affecting GDP binding (**Ligand ID: GDP**);
- For the *C. elegans* GDP-fucose protein O-fucosyltransferase 1 (**Uniprot ID: Q18014**) and
- Using a regular expression (**Mutation: A\$**, which denotes "last character of the field is A") to filter only alanine scanning mutations.

Data page

The screenshot shows the PLATINUM website interface. At the top is a navigation bar with links for 'Browse', 'Search', 'Data', 'Help', 'Contact', 'Acknowledgements', and 'Related Resources'. Below this is a large grey button labeled 'Database' with a purple circle containing the number '1' overlaid on it. To the left of the main content area is a folder icon with a downward arrow. To the right, there are two download options: 'Platinum database content in single tab-separated file:' with a purple circle containing the number '2' and a file icon, and 'Processed PDB files (biological assemblies) for complexes in Platinum DB:' with a purple circle containing the number '3' and a PDB file icon. The University of Cambridge logo is in the bottom left, and a footer note says 'Best viewed using Chrome on 1280x1024 resolution and above'.

Downloading the database

The data page (1) allows users to download the complete set of information available in PLATINUM:

- You can download PLATINUM as a single flat-file (comma-separated) by clicking on (2).
- Additionally, you can also download the full set of processed protein-ligand complexes in PDB format (3).



Contact page

Contact

1



Mailing address

[Dr. Douglas E. V. Pires](#)
[Dr. David B. Ascher](#)

University of Cambridge
Department of Biochemistry
80 Tennis Court Road
Cambridge UK
CB2 1GA

E-mail addresses

dpires@dcc.ufmg.br
dascher@svi.edu.au

2

Get in touch

Have you come across a problem on the website or have any requests or suggestions? Please report it here!

Name

Email address

(optional)

3

Submit

Getting in touch

In case you experience any trouble using PLATINUM or have any suggestions or comments, please do not hesitate in contacting us (1) either via e-mail (2) or through the online form (3).