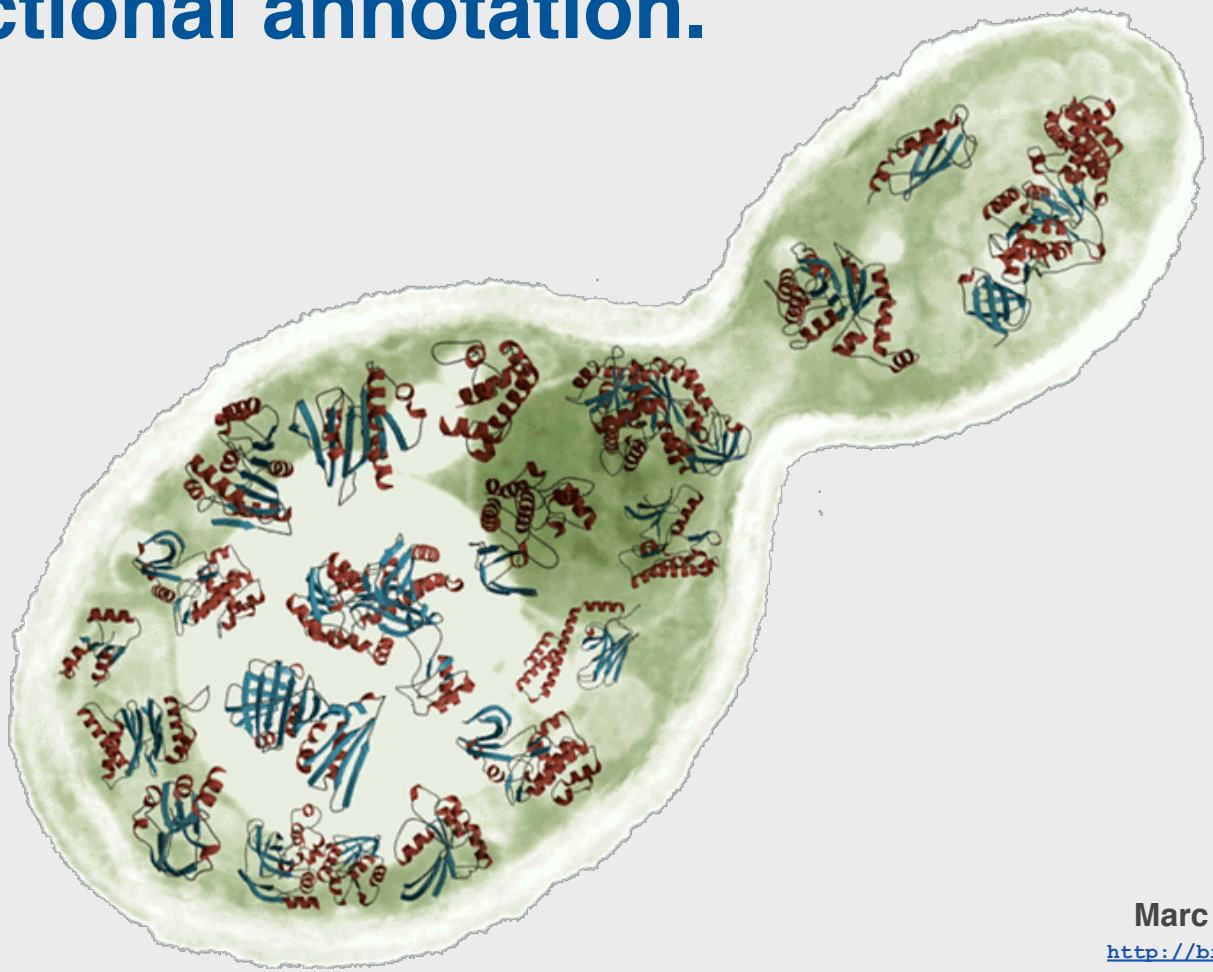
Comparative protein structure models for functional annotation.



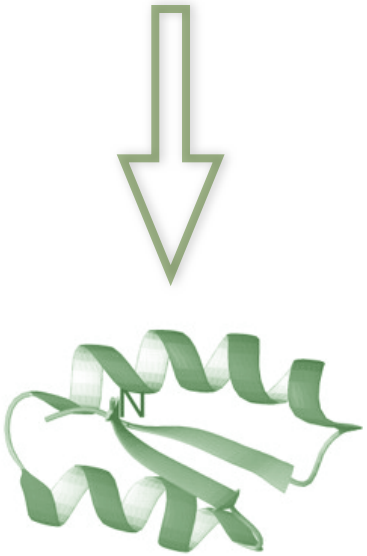
Marc A. Marti-Renom
http://bioinfo.cipf.es/sgu/

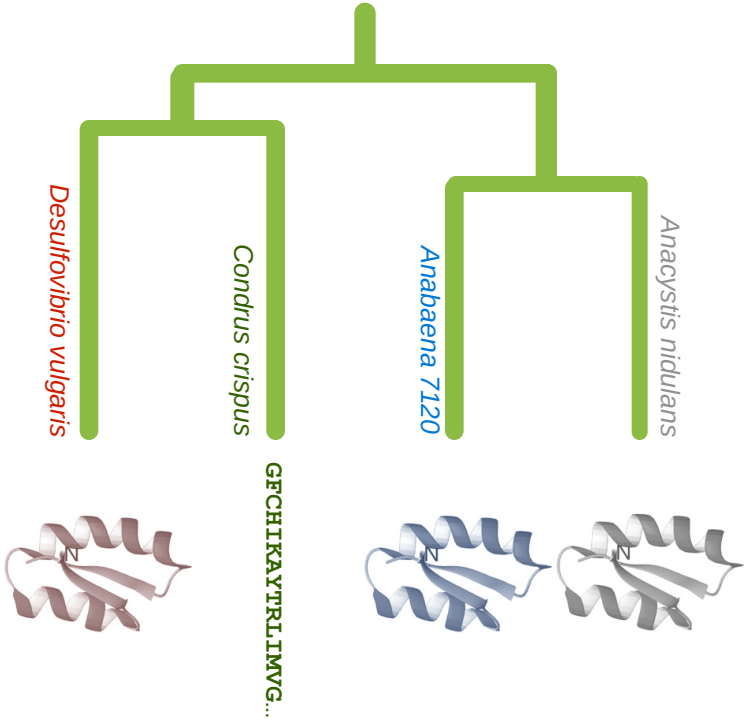
Structural Genomics Unit
Bioinformatics Department
Prince Felipe Resarch Center (CIPF), Valencia, Spain

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Principles of protein structure

GFCHIKAYTRLIMVG...





Folding (physics)

Ab initio prediction

Evolution (rules)

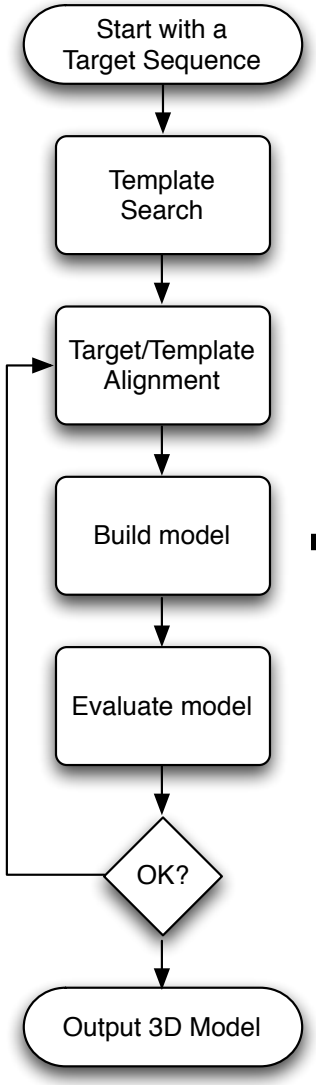
Threading

Comparative Modeling

D. Baker & A. Sali. Science 294, 93, 2001.

Comparative modeling by satisfaction of spatial restraints

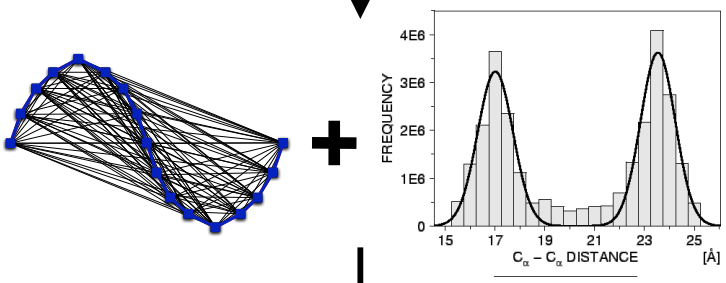
MODELLER



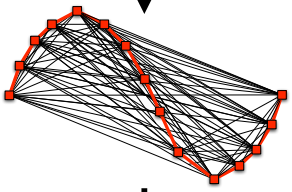
Given an alignment...

MSVIPKR--GNCEQTSE
ASILPKRLFGNCEQTSD

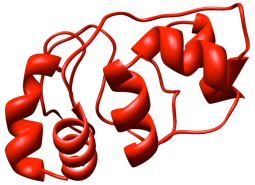
extract spatial features from the template(s) and statistics from known structures



apply these features as restraints on your target sequence



optimize to find the best solution for the restraints to produce your 3D model



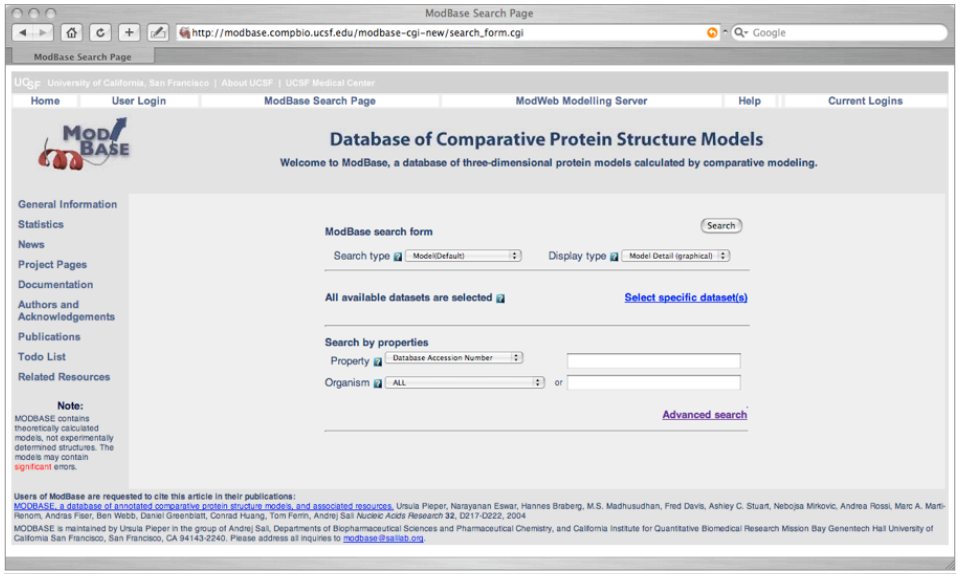
A. Šali & T. Blundell. J. Mol. Biol. 234, 779, 1993.
J.P. Overington & A. Šali. Prot. Sci. 3, 1582, 1994.
A. Fiser, R. Do & A. Šali, Prot. Sci., 9, 1753, 2000.

ModBase Statistics

Large-scale modeling of the TrEMBL-SWISSPROT databases

http://www.salilab.org/modbase/

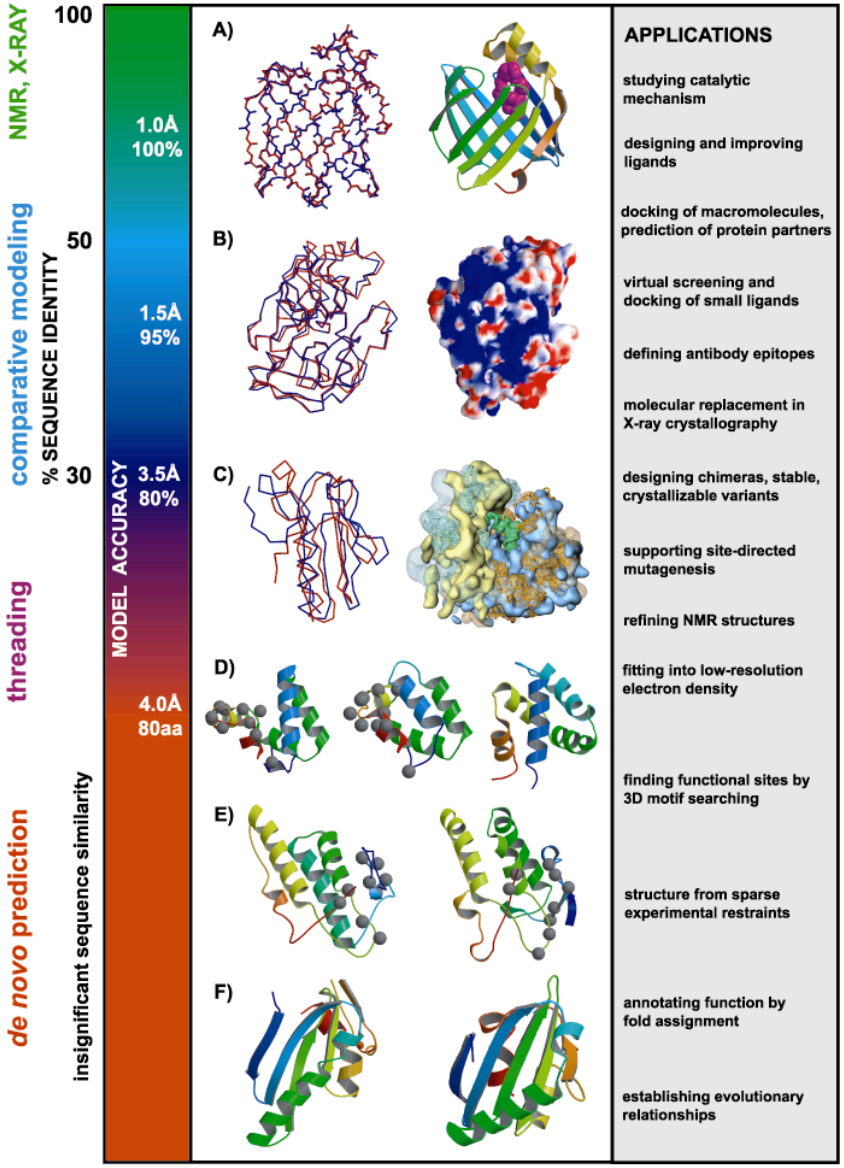
Sequences (total)	1,930,692
Sequences (modeled)	1,084,784
Models	3,094,542

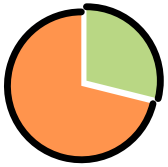


UCSF
University of California
San Francisco

Pieper et al. NAR 34, D291 (2006)

Utility of protein structure models, despite errors





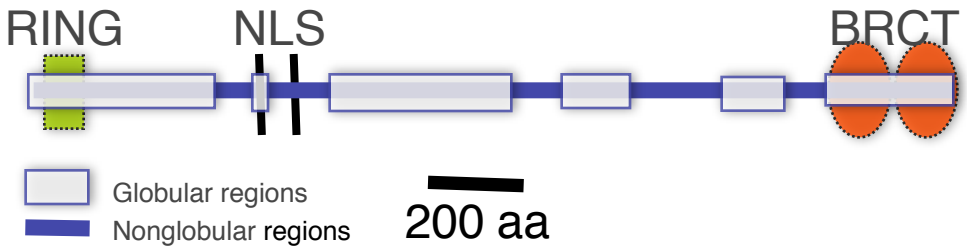
D. Baker & A. Sali. Science 294, 93, 2001.

Structural analysis of missense mutations in human BRCA1 BRCT domains

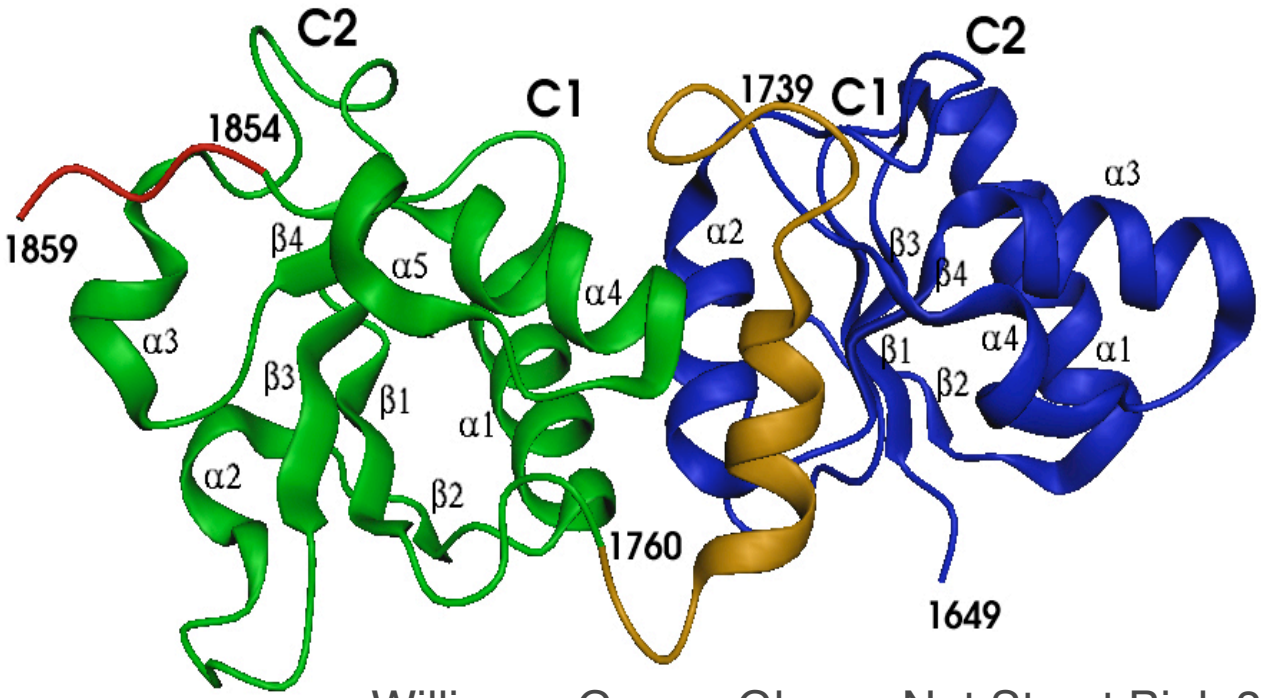
Cannot measure the functional impact of every possible SNP at all positions in each protein! Thus, prediction based on general principles of protein structure is needed.

N. Mirkovic, **M.A. Marti-Renom,** B.L. Weber, A. Sali, and A.N.A. Monteiro
Structural analysis of missense mutations in juman BRCA1 BRCT domains
Cancer Research (2004). **64**:3790

Human BRCA1 and its two BRCT domains



BRCA1 BRCT repeats, 1jnx



Williams, Green, Glover. Nat.Struct.Biol. 8, 838, 2001

CONFIDENTIAL

MYRIAD

BRACAnalysis™

Comprehensive BRCA1-BRCA2 Gene Sequence Analysis Result

Niecee Singer, MS Strang Cancer Prevention Center 428 E 72nd St New York, NY 10021	**SPECIMEN** Specimen Type: Blood Draw Date: n/a Accession Date: Oct 27, 2000 Report Date: Nov 17, 2000	**PATIENT** Name: Date of Birth: Feb 02, 1953 Patient ID: Gender: Female Accession #: 00019998 Requisition #: 56694

Physician: Fred Gilbert, MD

Test Result

Gene Analyzed	Specific Genetic Variant
BRCA2	H2116R
BRCA1	None Detected

Interpretation

GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE

The BRCA2 variant H2116R results in the substitution of arginine for histidine at amino acid position 2116 of the BRCA2 protein. Variants of this type may or may not affect BRCA2 protein function. Therefore, the contribution of this variant to the relative risk of breast or ovarian cancer cannot be established solely from this analysis. The observation by Myriad Genetic Laboratories of this particular variant in an individual with a deleterious truncating mutation in BRCA2, however, reduces the likelihood that H2116R is itself deleterious.

Authorized Signature:

Brian E. Ward, Ph.D.
Laboratory Director

Thomas S. Frank, M.D.
Medical Director

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members. It is strongly recommended that these results be communicated to the patient in a setting that includes appropriate counseling. The accompanying Technical Specifications summary describes the analysis, method, performance characteristics, nomenclature, and interpretive criteria of this test. This test may be considered investigational by some states. This test was developed and its performance characteristics determined by Myriad Genetic Laboratories. It has not been reviewed by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

CONFIDENTIAL

MYRIAD

BRACAnalysis™

Comprehensive BRCA1-BRCA2 Gene Sequence Analysis Result

Niecee Singer, MS Strang Cancer Prevention Center 428 E 72nd St New York, NY 10021	**SPECIMEN** Specimen Type: Blood Draw Date: n/a Accession Date: Oct 27, 2000 Report Date: Nov 17, 2000	**PATIENT** Name: Date of Birth: Feb 02, 1953 Patient ID: Gender: Female Accession #: 00019998 Requisition #: 56694
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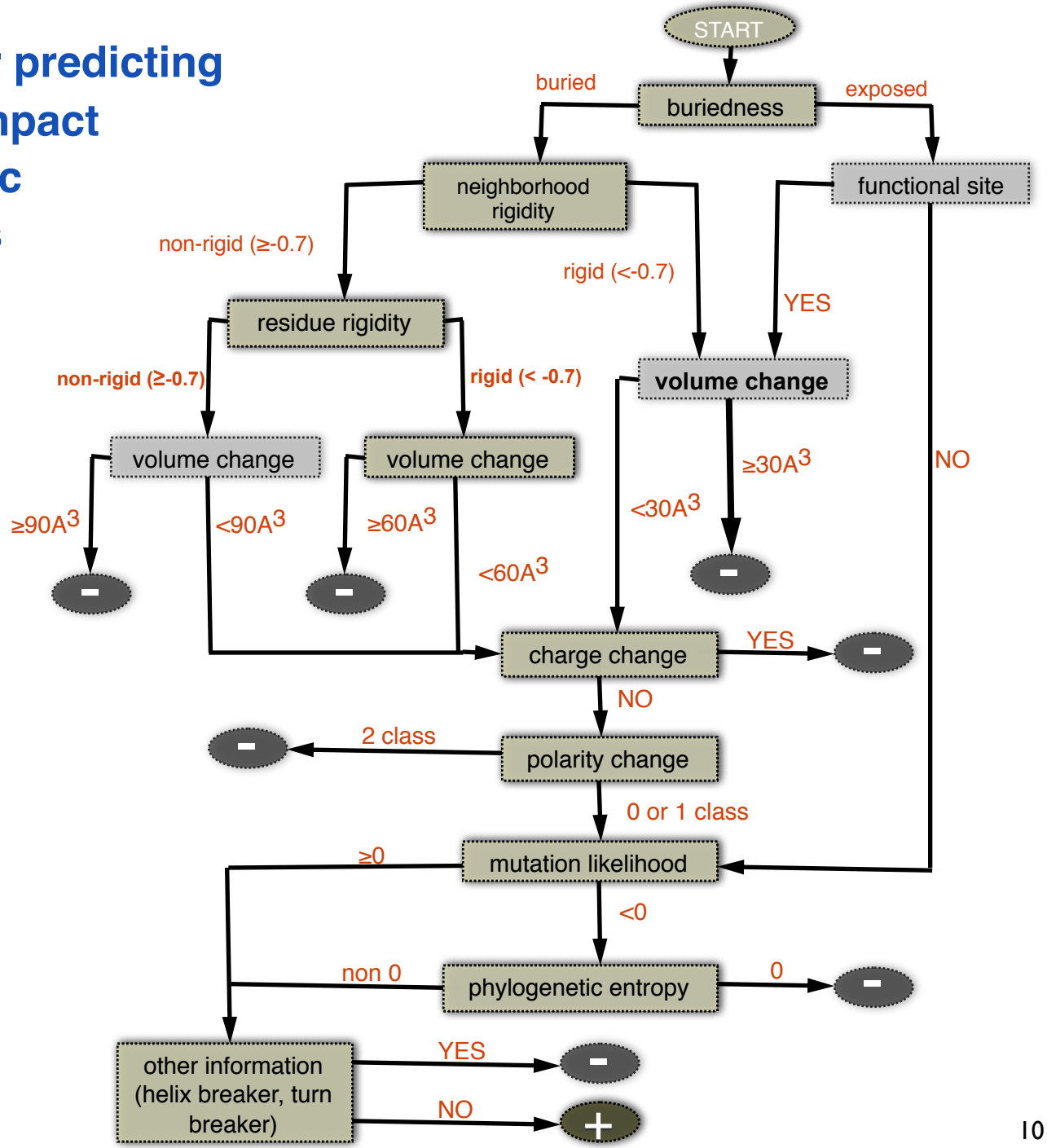
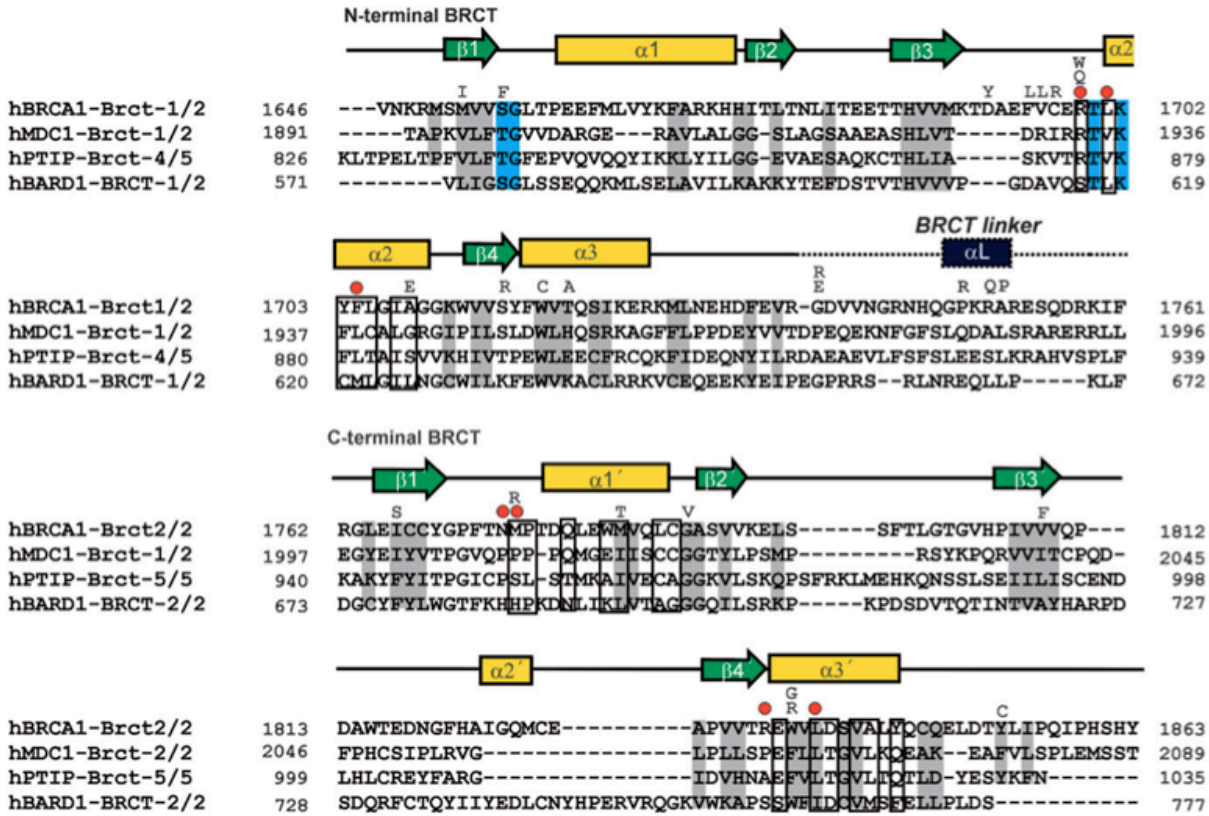
Missense mutations in BRCT domains by function

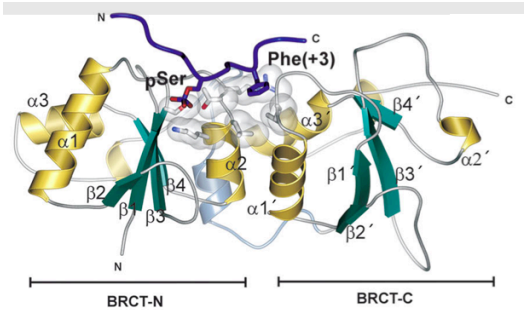
	cancer associated	not cancer associated	?
no transcription activation	C1697R R1699W A1708E S1715R P1749R M1775R		M1652K L1657P E1660G H1686Q R1699Q K1702E Y1703HF 1704S L1705PS 1715NS1 722FF17 34LG173 8EG174 3RA175 2PF1761 I F1761S M1775E M1775K L1780P I1807S V1833E A1843T
transcription activation		M1652I A1669S	V1665M D1692N G1706A D1733G M1775V P1806A
?			M1652T V1653M L1664P T1685A T1685I M1689R D1692Y F1695L V1696L R1699L G1706E W1718C W1718S T1720A W1730S F1734S E1735K V1736A G1738R D1739E D1739G D1739Y V1741G H1746N R1751P R1751Q R1758G L1764P I1766S P1771L T1773S P1776S D1778N D1778G D1778H M1783T C1787S G1788D G1788V G1803A V1804D V1808A V1809A V1809F V1810G Q1811R P1812S N1819S A1823T V1833M W1837R W1837G S1841N A1843P T1852S P1856T P1859R

"Decision" tree for predicting functional impact of genetic variants



Putative binding site on BRCA1

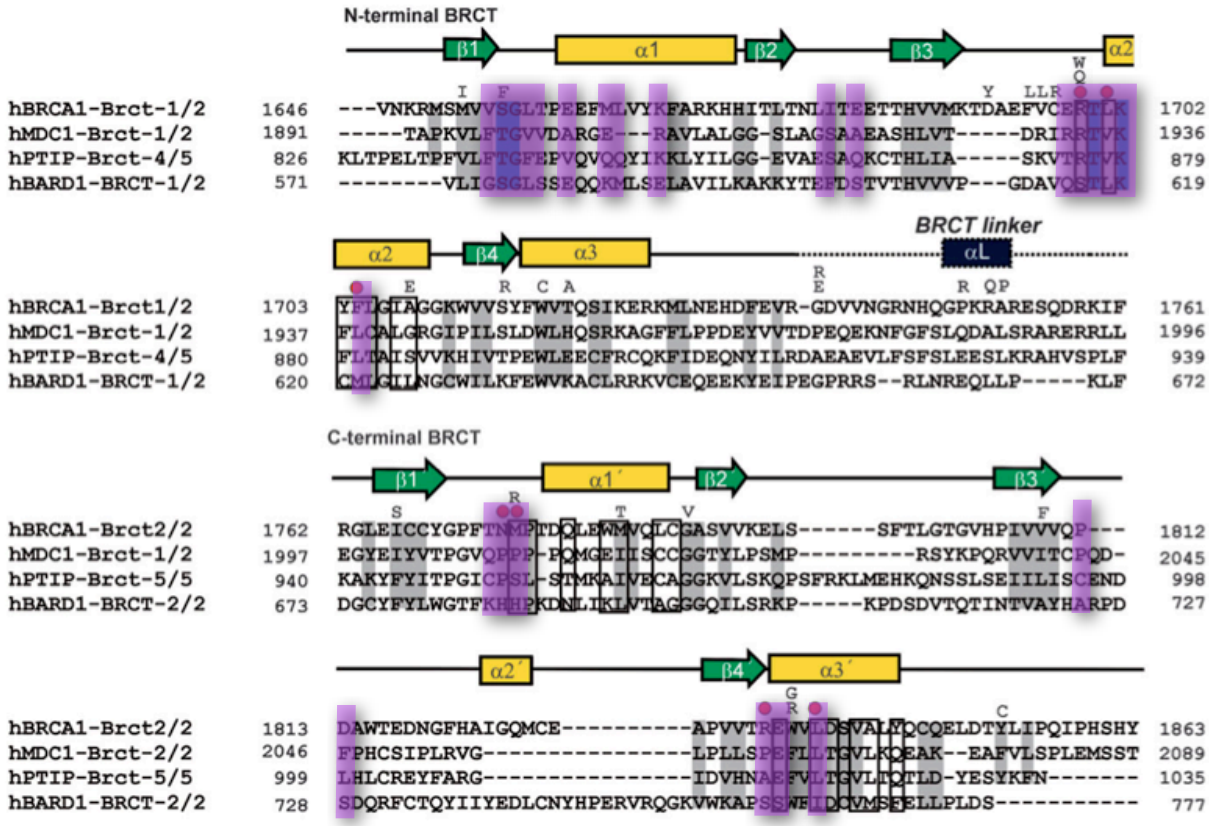


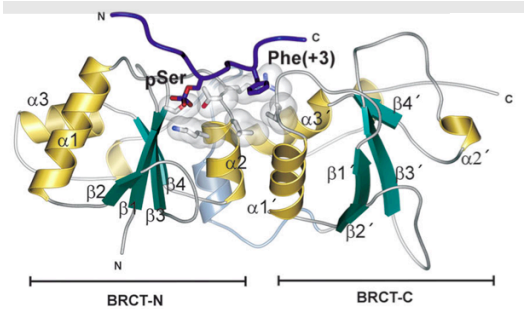


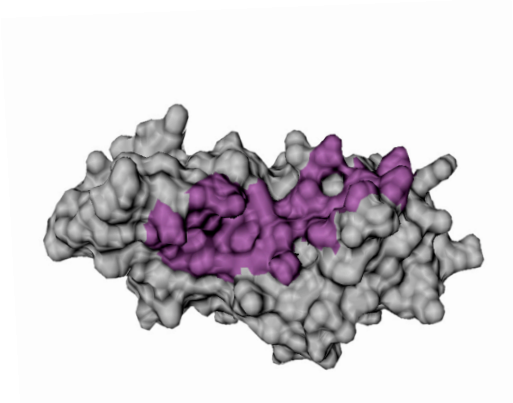
Williams *et al.* 2004 Nature Structure Biology. **June 2004 11**:519

Mirkovic *et al.* 2004 Cancer Research. **June 2004 64**:3790

Putative binding site on BRCA1



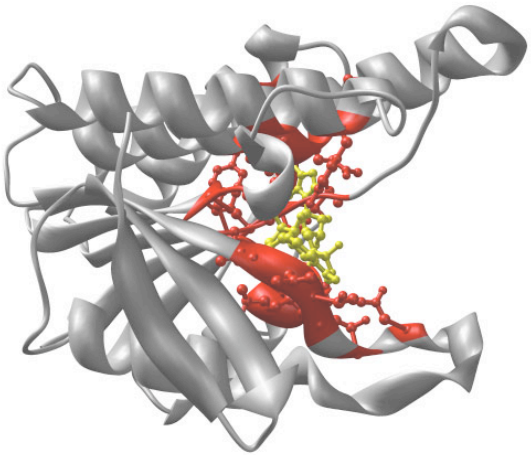




Putative binding site predicted in 2003 and accepted for publication on March 2004.

Williams *et al.* 2004 Nature Structure Biology. **June 2004 11**:519

Mirkovic *et al.* 2004 Cancer Research. **June 2004 64**:3790



Comparative annotation

The AnnoLite and AnnoLyze programs

Marti-Renom et al. BMC Bioinformatics (2007) Suppl. 8 S4.

Marti-Renom et al. NAR Special Web Servers (2007) in press

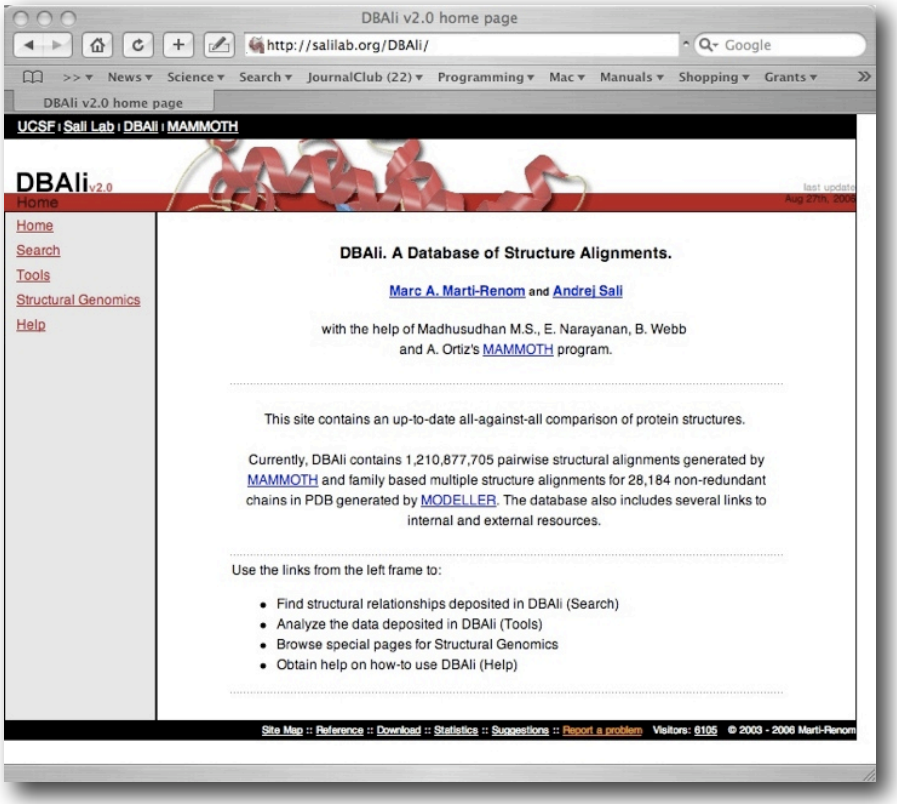
For 20% protein structures function is *unknown*

	Structural Genomics*	Traditional methods
Annotated**	654	28,342
Not Annotated	506 (43.6%)	6,815 (19,4%)
Total deposited	1,160	35,157

** annotated as STRUCTURAL GENOMICS in the header of the PDB file*
***annotated with either CATH, SCOP, Pfam or GO terms in the MSD database*
36,317 protein structures, as of August 8th, 2006

DBAli$_{v2.0}$ database

http://bioinfo.cipf.es/squ/services/DBAli/
http://www.salilab.org/DBAli/



- ✓ Fully-automatic
- ✓ Data is kept up-to-date with PDB releases
- ✓ Tools for "on the fly" classification of families.
- ✓ Easy to navigate
- ✓ Provides tools for structure analysis

Does not provide a stable classification similar to that of CATH or SCOP

Pairwise structure alignments	
Last update:	June 21st, 2007
Number of chains:	92,806
Number of structure-structure comparisons:*	1,600,024,693
Multiple structure alignments	
Last update:	March 22nd, 2007
Number of representative chains:	31,848
Number of families:	11,900

Uses MAMMOTH for similarity detection

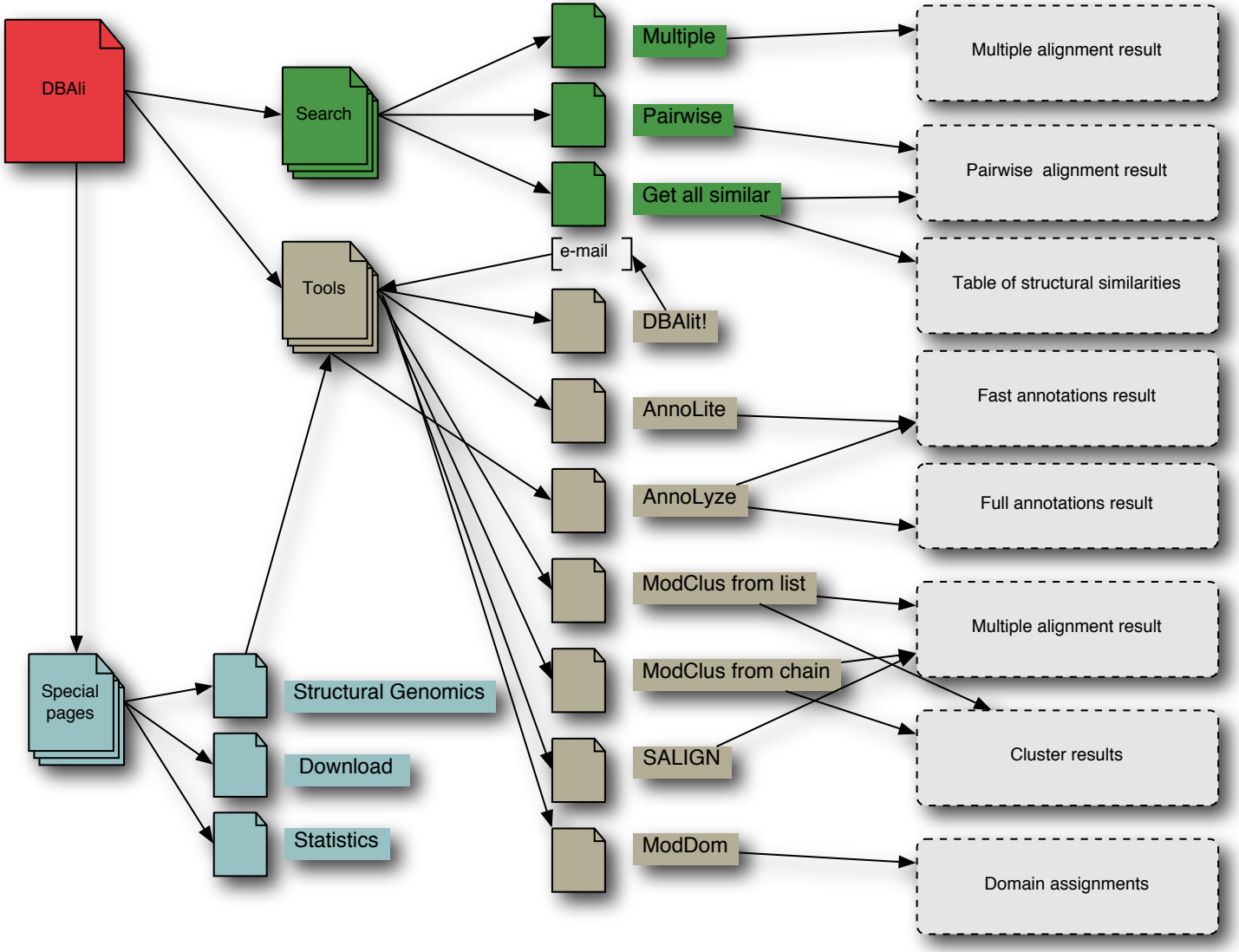
- ✓ **VERY FAST!!!**
- ✓ **Good scoring system with significance**

Ortiz AR, (2002) Protein Sci. 11 pp2606

Marti-Renom et al. 2001. Bioinformatics. 17, 746

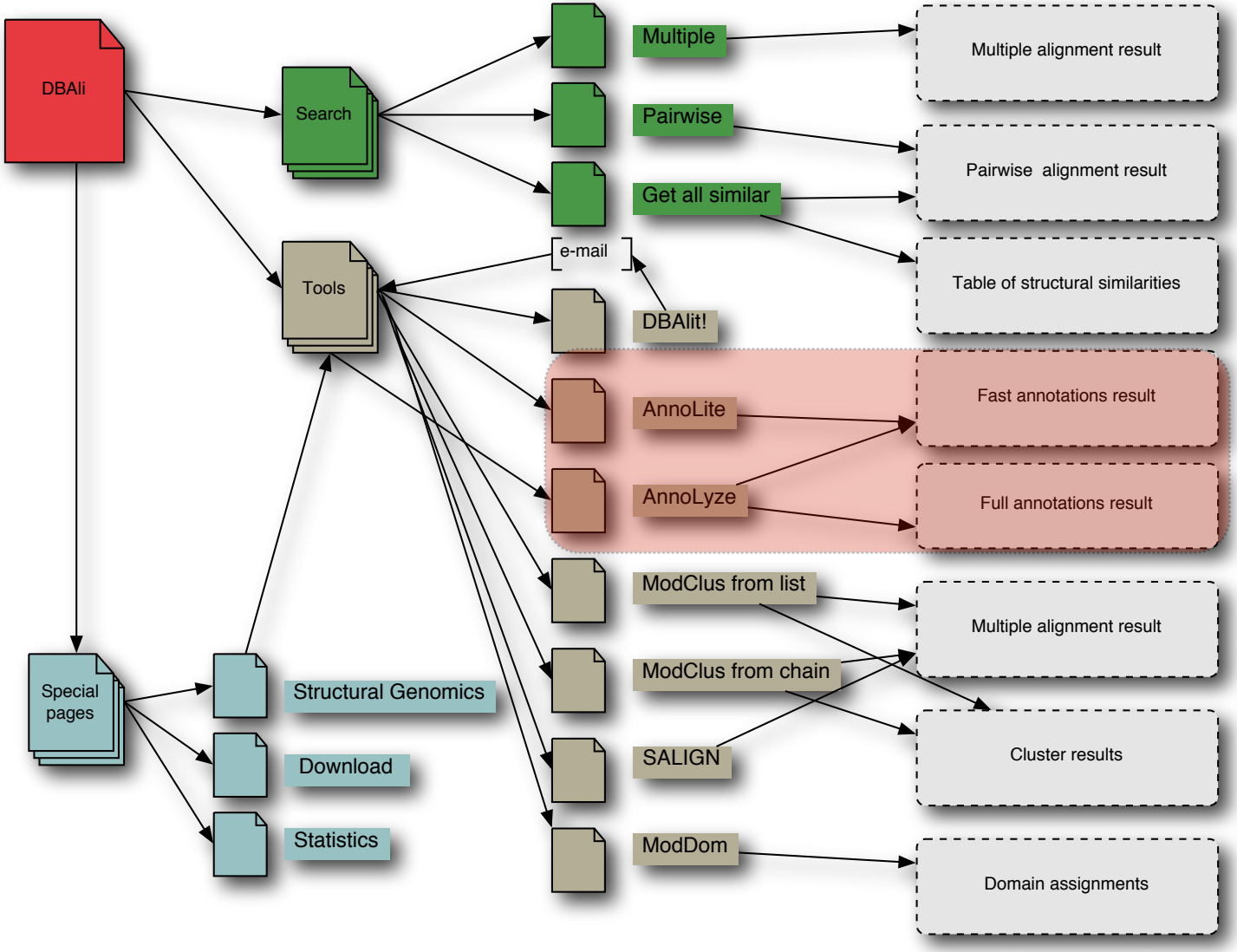
DBAli$_{v2.0}$ database

http://bioinfo.cipf.es/squ/services/DBAli/
http://www.salilab.org/DBAli/



DBAli$_{v2.0}$ database

http://bioinfo.cipf.es/squ/services/DBAli/
http://www.salilab.org/DBAli/



AnnoLite

	Conf.	P-value	Link	Description
CATH:		7.5e-99	2.70.100.10	1,4-Beta-D-Glucan Cellobiohydrolase I, subunit A
SCOP:		0.00	b.29.1.10	Glycosyl hydrolase family 7 catalytic core
PFAM:		0.00	PF00840	Glycosyl hydrolase family 7
InterPro:		1.3e-99	IPR001722	Glycoside hydrolase, family 7
		6.0e-51	IPR008985	Concanavalin A-like lectin/glucanase
		1.0e-42	IPR000254	Cellulose-binding region, fungal
EC Number:		1.2e-44	3.2.1.91	Cellulose 1,4-beta-cellobiosidase.
		6.0e-41	3.2.1.4	Cellulase.
GO Molecular Function:		6.0e-36	0030248	cellulose binding
		8.4e-36	0016162	cellulose 1,4-beta-cellobiosidase activity
		1.0e-35	0004553	hydrolase activity, hydrolyzing O-glycosyl compounds
		1.4e-30	0008810	cellulase activity
		3.1e-20	0016798	hydrolase activity, acting on glycosyl bonds
		1.0e+0	0016787	hydrolase activity
GO Biological Process:		1.1e-63	0030245	cellulose catabolism
		1.2e-54	0000272	polysaccharide catabolism
		3.6e-20	0005975	carbohydrate metabolism
GO Cellular Component:		1.2e-23	0005576	extracellular region

Information annotated in the MSD database.

High, medium and low confidence annotations not annotated in the MSD database.

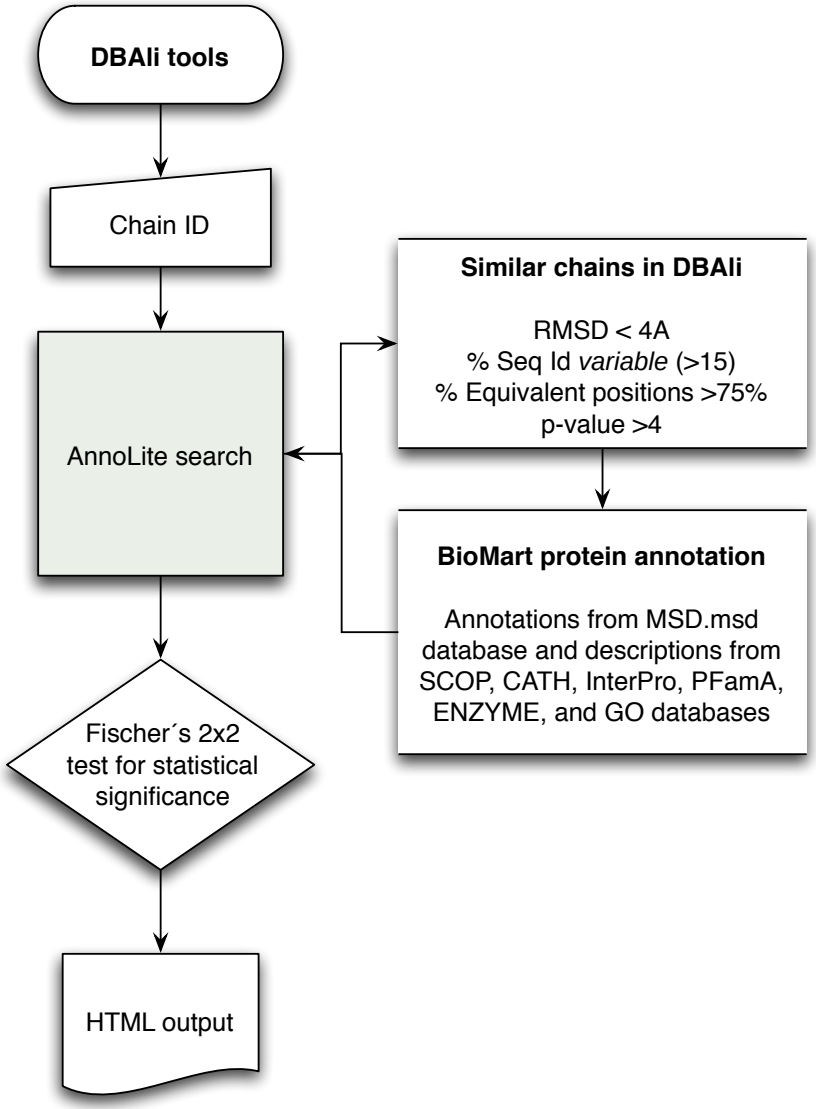
High, medium and low confidence annotations already annotated in the MSD database.

Benchmark set

	Number of chains
Initial set*	50,223
FULL annotation**	10,997
Non-redundant set***	1,879

**data from BioMart MSD.3 (release February 2005)*
***annotated with CATH, SCOP, Pfam, EC, InterPro, and GO terms in the MSD database*
***not two chains can be structurally aligned within 2A, superimposing more than 60% of their Cα atoms and have a length difference inferior to 30aa*

Method



AnnoLite results for chain 1gpi:A based on 44 structural similar chains.

	Conf.	P-value	Link	Description
CATH:		7.5e-99	2.70.100.10	1,4-Beta-D-Glucan Cellobiohydrolase I, subunit A
SCOP:		0.00	b.29.1.10	Glycosyl hydrolase family 7 catalytic core
PFAM:		0.00	PF00840	Glycosyl hydrolase family 7
InterPro:		1.3e-99	IPR001722	Glycoside hydrolase, family 7
		6.0e-51	IPR008985	Concanavalin A-like lectin/glucanase
		1.0e-42	IPR000254	Cellulose-binding region, fungal
EC Number:		1.2e-44	3.2.1.91	Cellulose 1,4-beta-cellobiosidase.
		6.0e-41	3.2.1.4	Cellulase.
GO Molecular Function:		6.0e-36	0030248	cellulose binding
		8.4e-36	0016162	cellulose 1,4-beta-cellobiosidase activity
		1.0e-35	0004553	hydrolase activity, hydrolyzing O-glycosyl compounds
		1.4e-30	0008810	cellulase activity
		3.1e-20	0016798	hydrolase activity, acting on glycosyl bonds
		1.0e+0	0016787	hydrolase activity
GO Biological Process:		1.1e-63	0030245	cellulose catabolism
		1.2e-54	0000272	polysaccharide catabolism
		3.6e-20	0005975	carbohydrate metabolism
GO Cellular Component:		1.2e-23	0005576	extracellular region

Information annotated in the MSD database.
High, medium and low confidence annotations not annotated in the MSD database.
High, medium and low confidence annotations already annotated in the MSD database.

Scoring function

Fisher's 2x2 contingency test

	Non-similar	Similar	Total
Annotated	a	b	a+b
Not Annotated	c	d	c+d
Total	a+c	b+d	n

1b78A SCOP c.51.4.1	Similar	Not similar	Total
Annotated	4	2	6
Not Annotated	0	71,096	71,096
Total	4	71,098	71,102

$$p = \binom{a+b}{a}\binom{c+d}{c} \Big/ \binom{n}{a+c}$$

$$= \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!a!b!c!d!}$$

$$p = 1.78e^{-19}$$

Sensitivity .vs. Precision

	Optimal cut-off	Sensitivity (%) Recall or TPR	Precision (%)
SCOP fold	1e-6	92.7	88.4
CATH fold	1e-3	95.7	90.1
InterPro	1e-3	88.4	78.2
PFam family	1e-4	90.5	82.8
EC number	1e-4	93.3	79.7
GO Molecular Function	1e-1	84.3	80.9
GO Biological Process	1e-3	85.5	74.8
GO Cellular Component	1e-2	77.6	58.6

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Precision} = \frac{TP}{TP + FP}$$

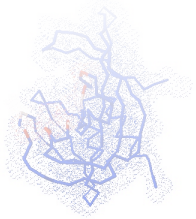
AnnoLyze

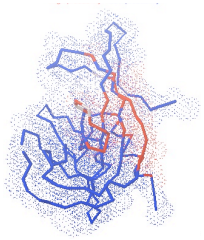
Inherited ligands: 4

Ligand	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
MO2	59.03	0.185	48 49 52 62 63 66 67 113 116
CRY	20.00	0.111	23 29 31 37 44 48 49 83 85 94 96 103 121
BOG	20.00	0.111	19 20 21 48 49 51 96 98 136
ACY	15.87	0.163	23 29 31 37 44 45 81 83 85 94 96 98 103 121 135

Inherited partners:1

Partner	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
d.113.1.1	23.68	0.948	19 20 50 51 52 53 54 55 56 57 58 77 78 79 80 81 82 83 84 85 93 95 97 99 134 135 138 142 145





Benchmark

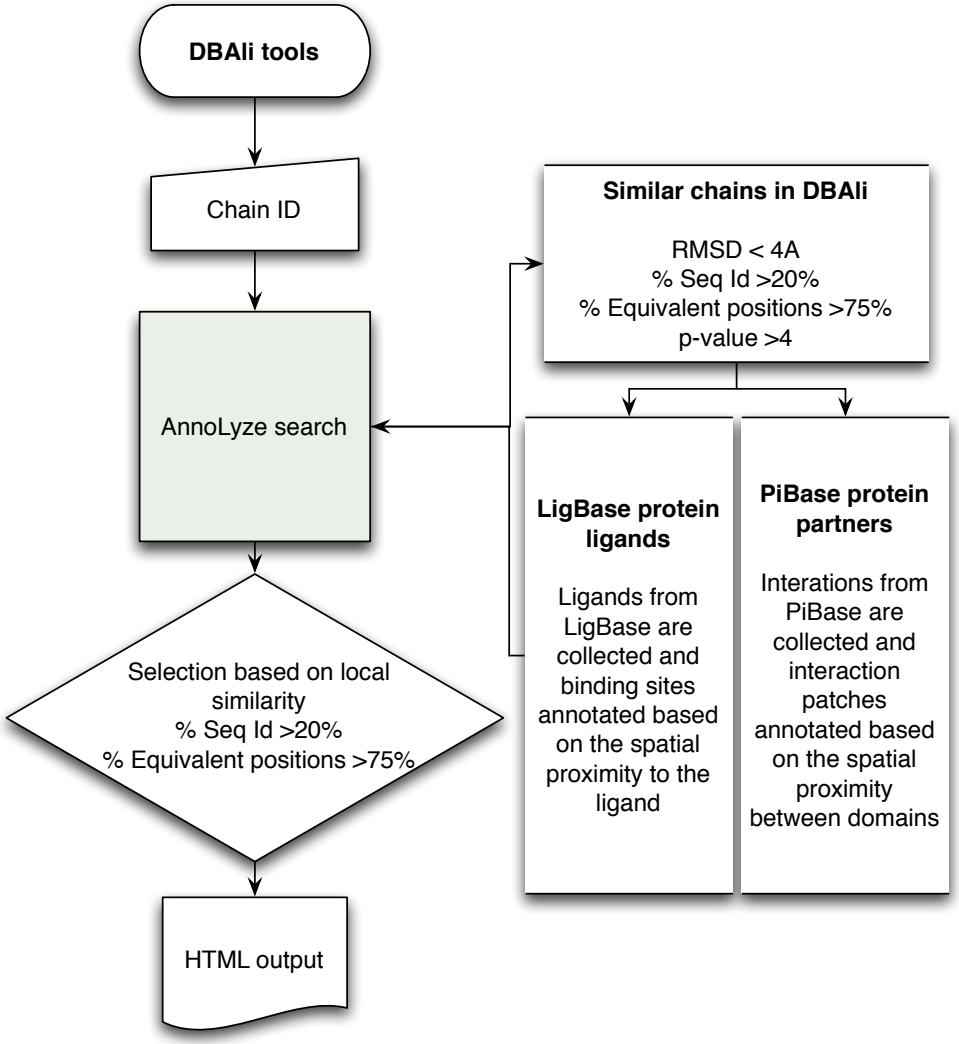
	Number of chains
Initial set*	78,167
LigBase**	30,126
Non-redundant set***	4,948 (8,846 ligands)

*all PDB chains larger than 30 aminoacids in length (8th of August, 2006)
**annotated with at least one ligand in the LigBase database
***not two chains can be structurally aligned within 3A, superimposing more than 75% of their Cα atoms, result in a sequence alignment with more than 30% identity, and have a length difference inferior to 50aa

	Number of chains
Initial set*	78,167
πBase**	30,425
Non-redundant set***	4,613 (11,641 partnerships)

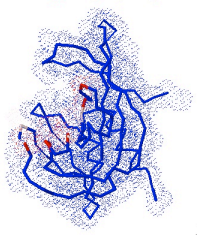
*all PDB chains larger than 30 aminoacids in length (8th of August, 2006)
**annotated with at least one partner in the πBase database
***not two chains can be structurally aligned within 3A, superimposing more than 75% of their Cα atoms, result in a sequence alignment with more than 30% identity, and have a length difference inferior to 50aa

Method



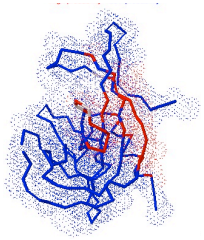
Inherited ligands: 4

Ligand	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
MO2	59.03	0.185	48 49 52 62 63 66 67 113 116
CRY	20.00	0.111	23 29 31 37 44 48 49 83 85 94 96 103 121
8OG	20.00	0.111	19 20 21 48 49 51 96 98 136
ACY	15.87	0.163	23 29 31 37 44 45 81 83 85 94 96 98 103 121 135



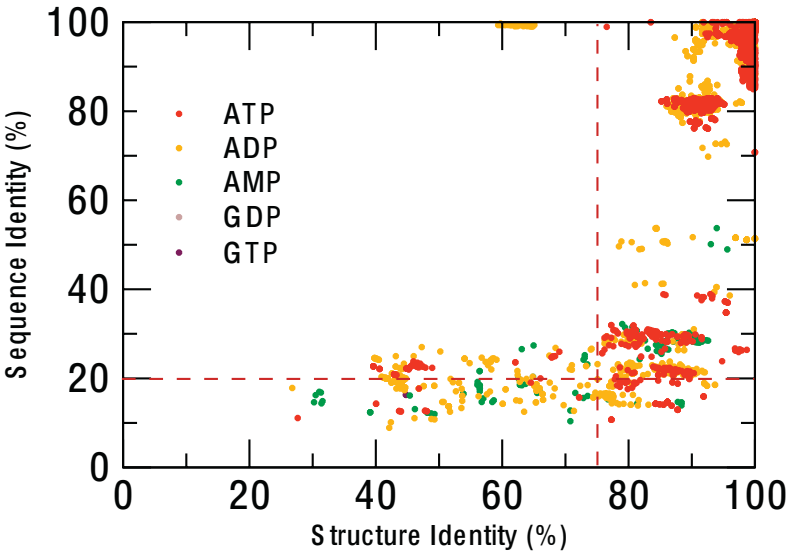
Inherited partners:1

Partner	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
d.113.1.1	23.68	0.948	19 20 50 51 52 53 54 55 56 57 58 77 78 79 80 81 82 83 84 85 93 95 97 99 134 135 138 142 145

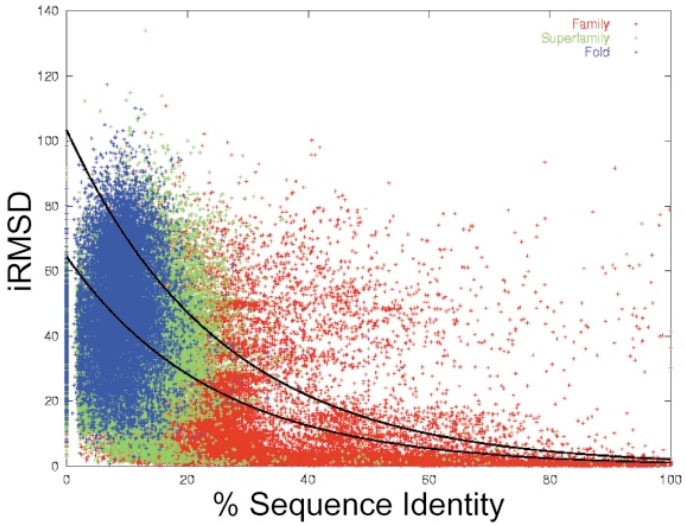


Scoring function

Ligands



Partners



Aloy *et al.* (2003) J.Mol.Biol. 332(5):989-98.

Sensitivity .vs. Precision

	Optimal cut-off	Sensitivity (%) Recall or TPR	Precision (%)
Ligands	30%	71.9	13.7
Partners	40%	72.9	55.7

$$\text{Sensitivity} = \frac{TP}{TP + FN} \qquad \text{Precision} = \frac{TP}{TP + FP}$$

Example (2azwA)

Structural Genomics Unknown Function

Molecule: MutT/nudix family protein

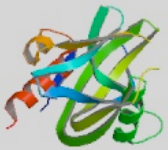
PDB ID: 2azw:A

Header:
STRUCTURAL GENOMICS, UNKNOWN FUNCTION

Compound:
MOL_ID: 1; MOLECULE: MUTT/NUDIX FAMILY PROTEIN; CHAIN: A; ENGINEERED: YES

Source:
MOL_ID: 1; ORGANISM_SCIENTIFIC: ENTEROCOCCUS FAECALIS V583; ORGANISM_COMMON: BACTERIA; EXPRESSION_SYSTEM: ESCHERICHIA COLI; EXPRESSION_SYSTEM_COMMON: BACTERIA; EXPRESSION_SYSTEM_STRAIN: BL21(DE3); EXPRESSION_SYSTEM_VECTOR_TYPE: PLASMID; EXPRESSION_SYSTEM_PLASMID: PET15B

Resolution: 1.90Å



Links: none

SCOP: none

CATH: none

Sequence:
Md5: 09b13d23ceae0fdfcaddec636e2ddfa6KTPTAAAS
Length: 146

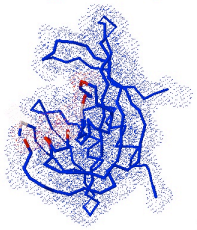
```
KTPTFGKREE TLTYQTRYAA YIIVSKPENN TMVLVQAPNG AYFLPGGEIE
GTETKEEAIH REVLEELGIS VEIGCYLGEA DEYFYSNHRQ TAYYNPGYFY
VANTWRQLSE PLRTNTLHWV APEEAVRLLK RGSHRWAVEK WLAAAS
```

Ligands: none

Interacting partners: none

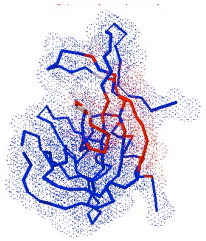
Inherited ligands: 4

Ligand	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
MO2	59.03	0.185	48 49 52 62 63 66 67 113 116
CRY	20.00	0.111	23 29 31 37 44 48 49 83 85 94 96 103 121
8OG	20.00	0.111	19 20 21 48 49 51 96 98 136
ACY	15.87	0.163	23 29 31 37 44 45 81 83 85 94 96 98 103 121 135



Inherited partners: 1

Partner	Av. binding site seq. id.	Av. residue conservation	Residues in predicted binding site (size proportional to the local conservation)
d.113.1.1	23.68	0.948	19 20 50 51 52 53 54 55 56 57 58 77 78 79 80 81 82 83 84 85 93 95 97 99 134 135 138 142 145



Similar structures: 20
Similar sequences: 890

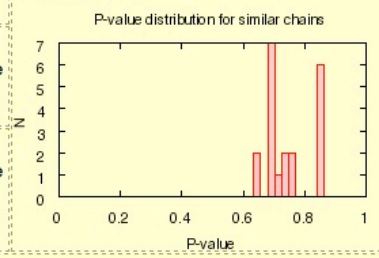
Most similar structure in DBAli:

Code	SeqId(%)	EqPos	RMSD	P-Value	See
1vc9:A	22.76	123	3.57	17.28	ali

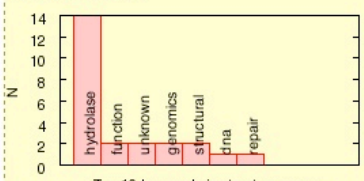
Most similar sequence in DBAli:

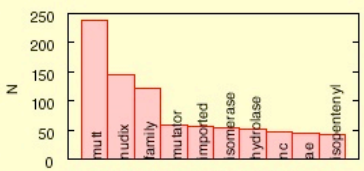
Code	SeqId(%)	EqPos	RMSD	P-Value	See
1vcd:B	24.59	122	3.47	17.00	ali

P-value diustribution:

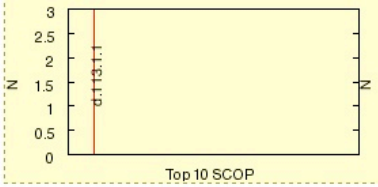


Keyword distribution:



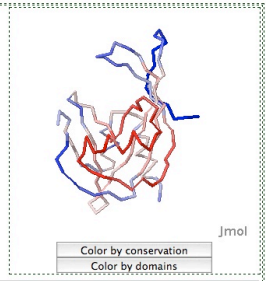


SCOP and CATH distribution for similar structures:



Chain: 2azwA
Equivalences selected: 6783
Coverage: 100.00 %
Number of domains: 1
Assignment score:0.5470
Alternative assignments: here

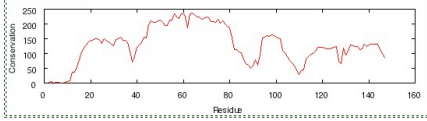
Highest score assignment:
Domain 1:
2-113,115-147
Length: 145
Conservation: 506.49



Protein sequence colored by conservation and underlined by domain color:

```
KTPTFGKREE TLTYQTRYAA YIIVSKPENN TMVLVQAPNG AYFLPGGEIE GTETKEEAIH REVLEELGIS
VEIGCYLGEA DEYFYSNHRQ TAYYNPGYFY VANTWRQLSE PLRTNTLHWV APEEAVRLLK RGSHRWAVEK
WLAAAS
```

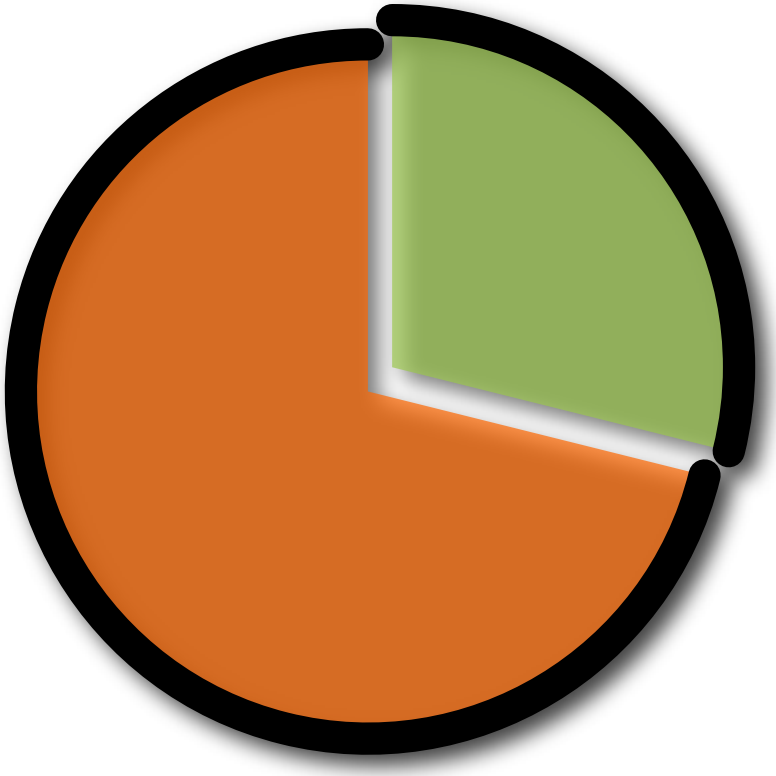
Conservation profile:



	Conf.	P-value	Link	Description
CATH:		1.1e-20	3.90.79.10	Nucleoside Triphosphate Pyrophosphohydrolase
SCOP:		4.2e-29	d.113.1.1	MutT-like
PFAM:		2.0e-74	PF00293	NUDIX domain
InterPro:		1.9e-65	IPR000086	NUDIX hydrolase
		2.7e-20	IPR003561	Mutator MutT
		2.9e-14	IPR002667	Isopentenyl-diphosphate delta-isomerase
EC Number:		1.7e-4	3.6.1.17	Bis(5'-nucleosyl)-tetraphosphatase (asymmetrical).
GO Molecular Function:		4.5e-19	0008413	8-oxo-7,8-dihydroguanine triphosphatase activity
		3.8e-13	0004452	isopentenyl-diphosphate delta-isomerase activity
		1.9e-6	0016787	hydrolase activity
		5.4e-3	0004081	bis(5'-nucleosyl)-tetraphosphatase (asymmetrical) activity
		1.9e-2	0000287	magnesium ion binding
GO Biological Process:		7.7e-11	0008299	isoprenoid biosynthesis
		1.5e-5	0006974	response to DNA damage stimulus
		1.7e-5	0006260	DNA replication
		2.4e-5	0006281	DNA repair

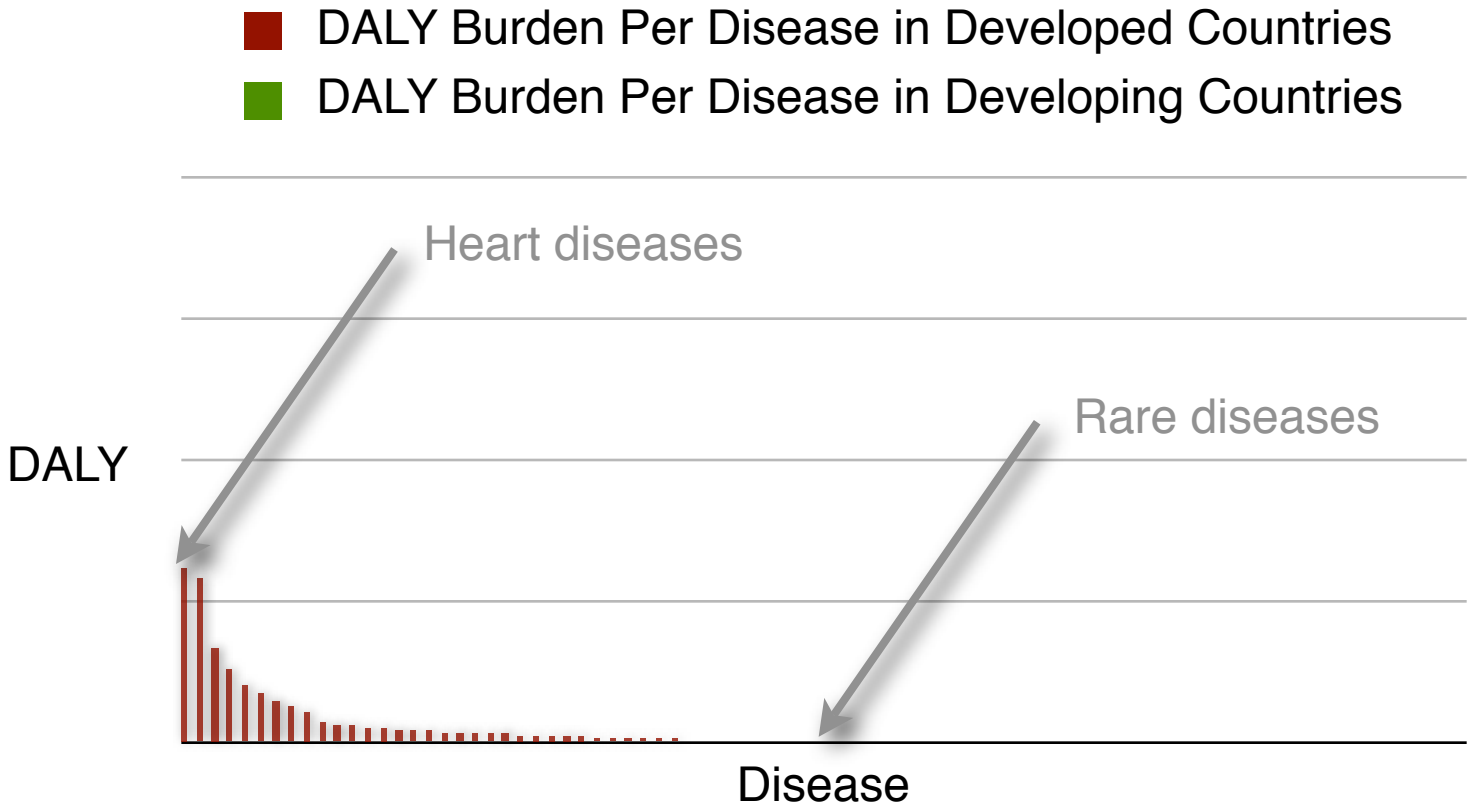
Tropical Disease Initiative (TDI)

Predicting binding sites in protein structure models.



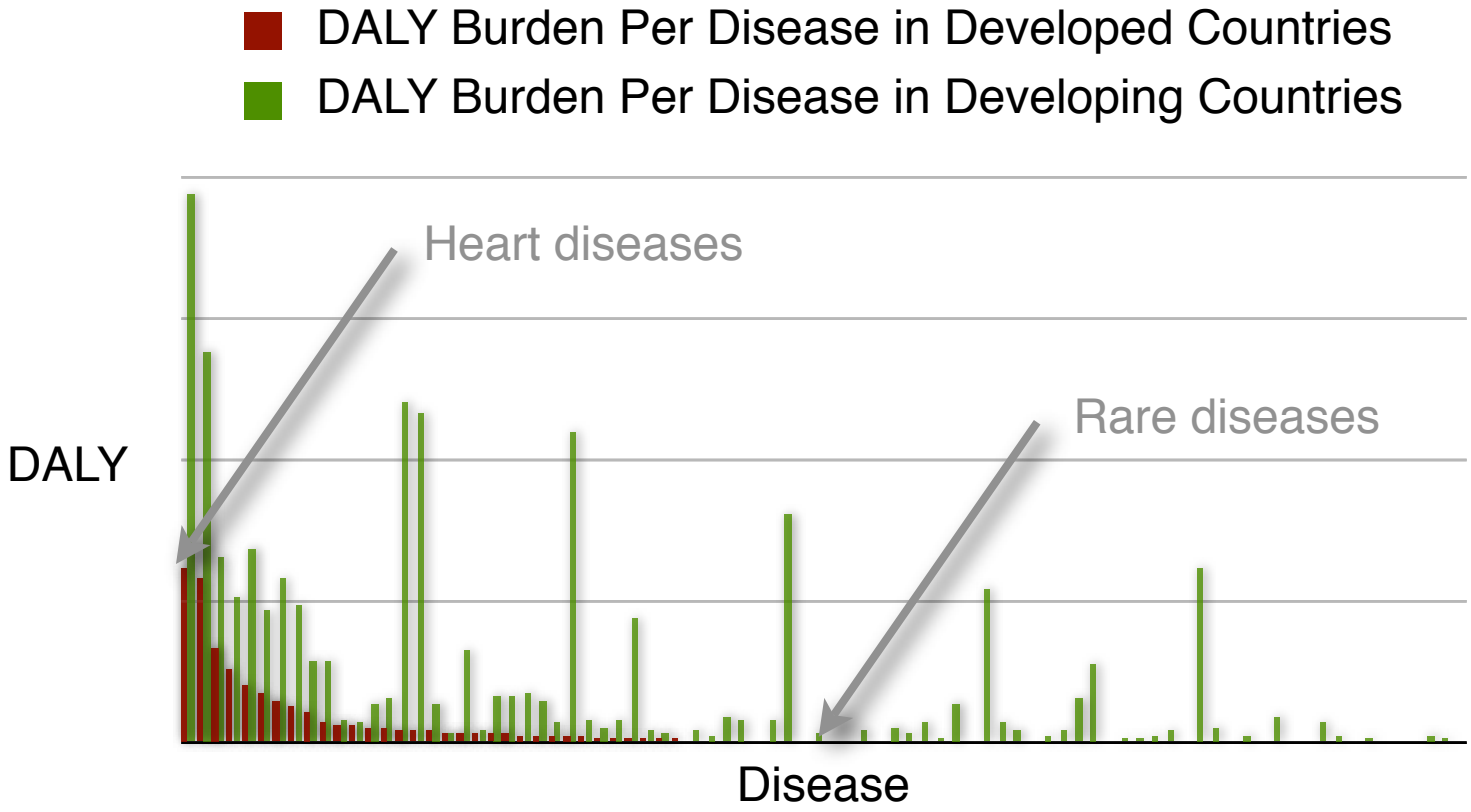
http://www.tropicaldisease.org

Need is High in the Tail



Disease data taken from WHO, *World Health Report 2004*
DALY - Disability adjusted life years
DALY is not a perfect measure of market size, but is certainly a good measure for importance.
DALYs for a disease are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition. The DALY is a health gap measure that extends the concept of potential years of life lost due to premature death (PYLL) to include equivalent years of 'healthy' life lost in states of less than full health, broadly termed disability. One DALY represents the loss of one year of equivalent full health.

Need is High in the Tail



Disease data taken from WHO, *World Health Report 2004*
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"Unprofitable" Diseases and Global DALY (in 1000's)

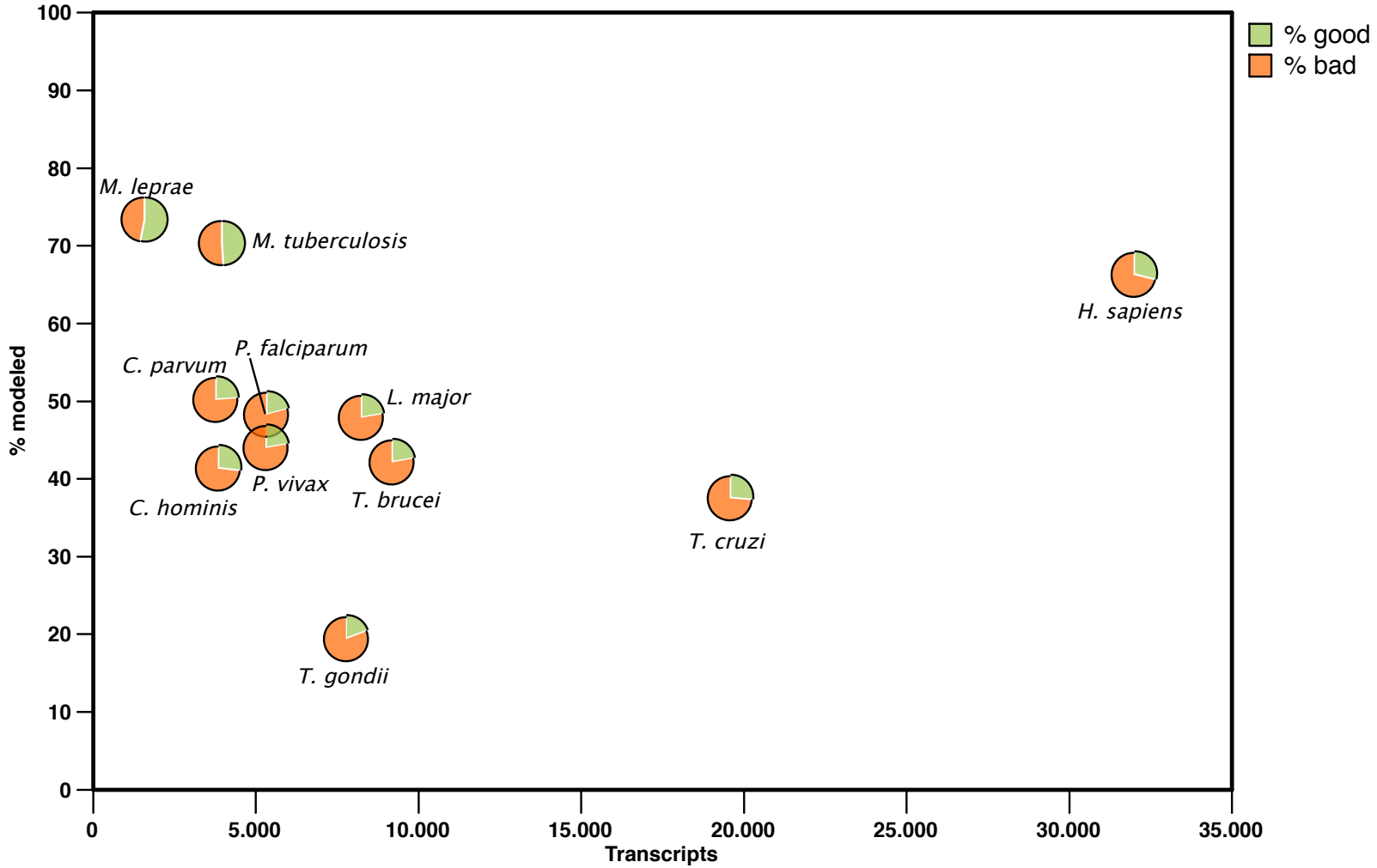
Malaria*	**46,486**
Tetanus	7,074
Lymphatic filariasis*	**5,777**
Syphilis	4,200
Trachoma	2,329
Leishmaniasis*	**2,090**
Ascariasis	1,817
Schistosomiasis*	**1,702**
Trypanosomiasis*	**1,525**

Trichuriasis	1,006
Japanese encephalitis	709
Chagas Disease*	**667**
Dengue*	**616**
Onchocerciasis*	**484**
Leprosy*	**199**
Diphtheria	185
Poliomyelitise	151
Hookworm disease	59

Disease data taken from WHO, *World Health Report 2004*
DALY - Disability adjusted life year in 1000's.
* Officially listed in the WHO Tropical Disease Research disease portfolio.

Modeling Genomes

data from models generated by ModPipe (Eswar, Pieper & Sali)

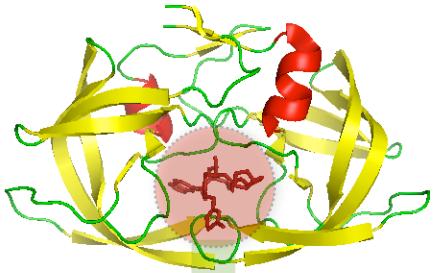


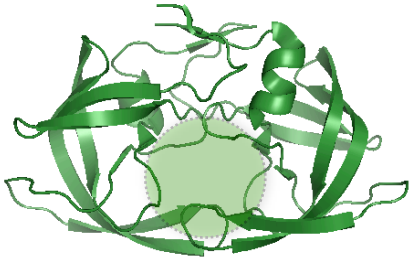
A good model has MPQS of 1.1 or higher

Comparative docking

1. Expansion

co-crystalized protein/ligand

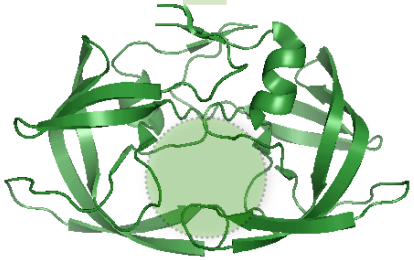




crystalized protein

2. Inheritance

model



template

Summary table

models with inherited ligands

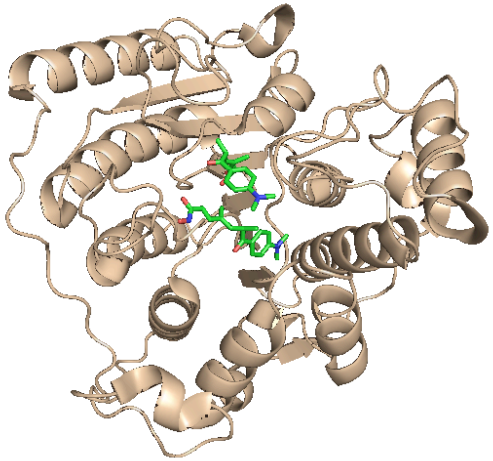
from 16,284 good models, 295 inherited a ligand/substance with at least one compound already approved by FDA and ready to be used from ZINC

	Transcripts	Good	Ligands	Lipinski	Lipinski+ZINC	FDA+ZINC
C. hominis	3,886	886	183	131	28	12 (10)
C. parvum	3,806	949	219	145	30	12 (10)
L. major	8,274	1,845	488	334	84	44 (34)
M. leprae	1,605	1,321	286	189	39	29 (25)
M. tuberculosis	3,991	2,887	404	285	71	44 (37)
P. falciparum	5,363	1,057	271	191	48	20 (16)
P. vivax	5,342	1,042	267	177	37	18 (15)
T. brucei	921	1,795	440	309	94	46 (36)
T. cruzi	19,607	3,915	730	493	127	62 (52)
T. gondii	7,793	587	174	124	28	8 (7)
TOTAL	**60,588**	**16,284**	**3,462**	**2,378**	**586**	**295 (242)**

Example of inheritance (expansion)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

Template 1t64A a human HDAC8 protein.



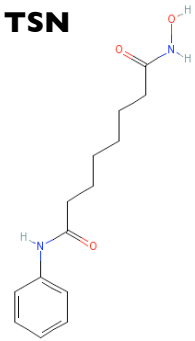
	Origen	Formula	Name	Cov.	Seq, Id. (%)
ZN	X-ray	Zn^{2+}	Zinc ion	--	--
NA	X-ray	Na^{+}	Sodium ion	--	--
CA	X-ray	Ca^{2+}	Calcium ion	--	--
TSN	X-ray	$C_{17}H_{22}N_2O_3$	Trichostatin A	--	--
SHH	Expanded	$C_{14}H_{20}N_2O_3$	Octadenioic acid hudroxyamide phenylamide	100.00	83.8

Example of inheritance (inheritance)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

	Formula	Name	Cov.	Seq, Id. (%)	Residues
TSN	$C_{17}H_{22}N_2O_3$	Trichostatin A	100.00	90.9	90 131 132 140 141 167 169 256 263 293 295
SHH	$C_{14}H_{20}N_2O_3$	Octadenioic acid hudroxyamide phenylamide	100.00	90.9	

TSN



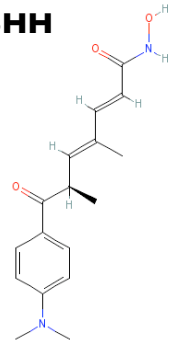
suberoylanilide hydroxamic acid

Pharmacological Action:

- Anti-Inflammatory Agents, Non-Steroidal
- Antineoplastic Agents
- Enzyme Inhibitors
- Anticarcinogenic Agents

Inhibits histone deacetylase I and 3

SHH



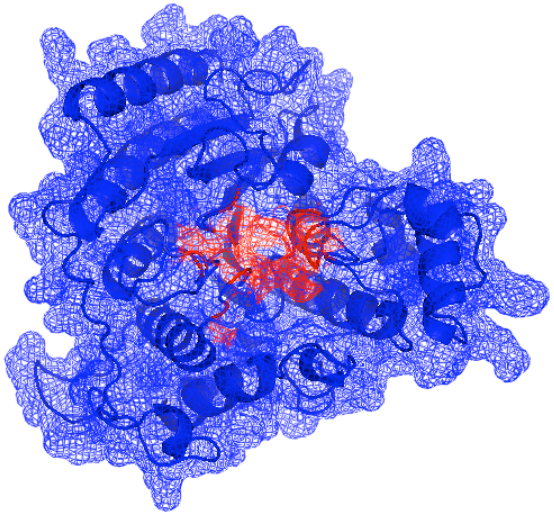
trichostatin A

Pharmacological Action:

- Antibiotics, Antifungal
- Enzyme Inhibitors
- Protein Synthesis Inhibitors

chelates zinc ion in the active site of histone deacetylases, resulting in preventing histone unpacking so DNA is less available for transcription

	LmjF21.0680.1.pdb
Template	1t64A
Seq. Id (%)	**38.00**
MPQS	1.47



Example of inheritance (CDD-Roos-literature)

LmjF21.0680 from L. major *"Histone deacetylase 2" (model 1)*

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 13143–13147, November 1996
Medical Sciences

Apicidin: A novel antiprotozoal agent that inhibits parasite histone deacetylase

(cyclic tetrapeptide/Apicomplexa/antiparasitic/malaria/coccidiosis)

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2004, p. 1435–1436 Vol. 48, No. 4
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.4.1435–1436.2004

Antimalarial and Antileishmanial Activities of Aroyl-Pyrrolyl-Hydroxyamides, a New Class of Histone Deacetylase Inhibitors

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Nebosja Mirkovic (RU)

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