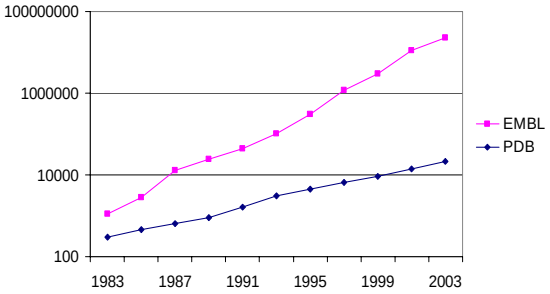
Structural Genomics

Iosif Vaisman

Email: ivaisman@gmu.edu

Dynamics of Database Growth



PDB Current Holdings

		Molecule Type				
		Proteins	Nucleic Acids	Protein/ NA Compl	Other	**Total**
Exp. Meth.	X-ray	37254	1000	1726	24	**40004**
	NMR	5948	789	136	7	**6880**
	EM	109	11	40	0	**160**
	Other	83	4	4	2	**93**
	Total	**43394**	**1804**	**1906**	**33**	**47137**

PDB Redundancy

Method	Description	# of Clusters
blast	95% identity (one chain)	18106
blast	90% identity (one chain)	17367
blast	70% identity (one chain)	15507
blast	50% identity (one chain)	13201
blast	40% identity (one chain)	11457
blast	30% identity (one chain)	9458

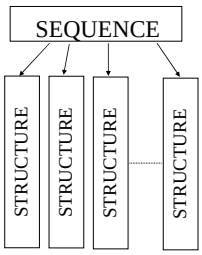
Representative sets of known structures

Filtering by parameters:
Resolution
R-factor
Sequence similarity
Experimental technique

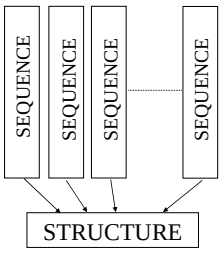
PDB-REPRDB http://mbs.cbrc.jp/pdbreprdb-cgi/reprdb_menu.pl

PISCES http://dunbrack.fccc.edu/PISCES.php

Protein modeling



Sequence-structure compatibility (fold recognition)



Structure-sequence compatibility (inverse folding)

Sequence-structure correlations

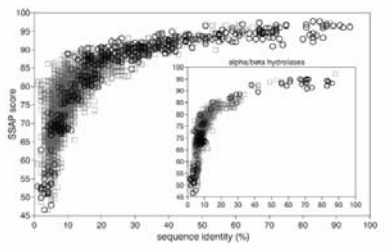
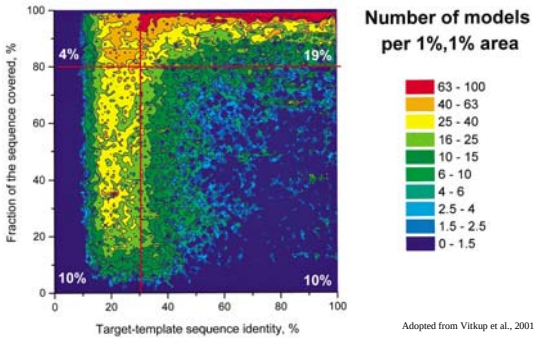


Fig. 1. Correlation between structure similarity (measured by the SSAP structure comparison algorithm, 0–100) and sequence similarity (measured by sequence identity) for all pairs of homologous domain structures in the CATH domain database.

Redfern and Orengo, 2005

Model structure coverage in sequence space



Adopted from Vitkup et al., 2001

Genome sequencing projects statistics

Organism	Complete	Draft assembly	In progress	total
Prokaryotes	590	402	460	1452
Archaea	47	4	31	82
Bacteria	543	398	429	1370
Eukaryotes	23	129	186	338
Animals	4	53	90	147
Mammals	2	21	26	49
Birds		1	2	3
Fishes		3	6	9
Insects	1	19	20	40
Flatworms		1	3	4
Roundworms	1	3	13	17
Amphibians			2	2
Reptiles			2	2
Other animals		6	19	25
Plants	3	3	34	40
Land plants	2	2	27	31
Green Algae	1	1	7	9
Fungi	10	52	31	93
Ascomycetes	8	46	21	75
Basidiomycetes	1	4	6	11
Other fungi	1	2	4	7
Protists	6	19	27	52
Apicomplexans	1	10	6	17
Kinetoplasts	1	2	6	9
Other protists	4	7	14	25
total:	**613**	**531**	**646**	**1790**

Structural Genomics Project

- Organize known protein sequences into families.
- Select family representatives as targets.
- Solve the 3D structure of targets by X-ray crystallography or NMR spectroscopy.
- Build models for other proteins by homology to solved 3D structures.

History of Structural Genomics

1995 **SG** project proposed in Japan

1997 Apr. **SG** pilot project starts at RIKEN Inst.

1997 **SG** studies initiated through DOE, NIGMS in US

1998/99 Initial **SG** projects start in Canada, Germany, US

1999 June Call for **SG** pilot projects issued by NIGMS/NIH

2000 Jan. OECD Committee for Scientific and Technological Policy (CSTP) proposes to initiate **SG** studies

2000 Apr. 1st International **SG** Meeting, Hinxton, UK

2000 June OECD/Global Science Forum (GSF) and **SG** Workshop, Florence, Italy

2000 Sep. **SG**: From Gene to Structure to Function, Cambridge, UK

2000 Sep. NIGMS Protein Structure Initiative starts in US with 7 Centers

2000 Nov. International Conference on **SG** (ICSG 2000), Yokohama, Japan / International SG Task Force Meeting / OECD/GSF Meeting

2001 Jan. OECD/CSTP/GSF, Paris, France – Further Study on **SG**

2001 Apr. 2nd International **SG** Meeting, Airlie House, US – Start of ISGO

2001 Sep. NIGMS Protein Structure Initiative adds 2 new centers

2002 Mar. European Commission announces funding of Structural Proteomics in Europe (SPINE)

2002 Apr. National project on Protein Structural and Functional Analyses starts in Japan

2002 Oct. ISGO International Conference on **SG** (ICSG 2002), Berlin, Germany

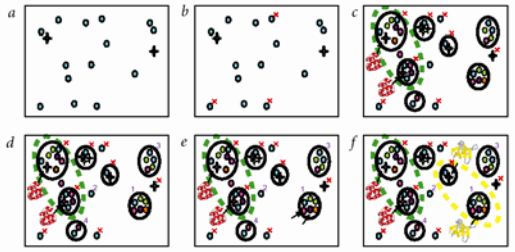
Heinemann, 2002

Goals of structural genomics

•Provision of enough structural templates to facilitate homology modeling of most proteins
•Structures of all proteins in a complete proteome
•Structural elucidation of a complete biological pathway
•Structural elucidation of a complete disease

Phil Bourne, 2005

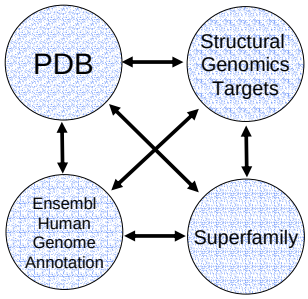
Target selection



a) realm of interest
b) family exclusion - impossible
c) family exclusion - known
d) prioritization
e) selection
f) analysis and interpretation

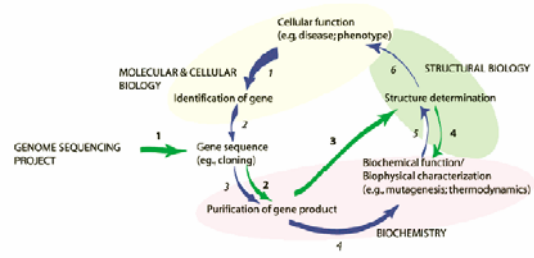
S.Brenner, 2000

Coverage of the Human Genome By Structure



Xie and Bourne, 2005

Structural genomics shortcuts



Yee et al., *Acc. Chem. Res.* **2003,** 36, 183-189

NIGMS Protein Structure Initiative

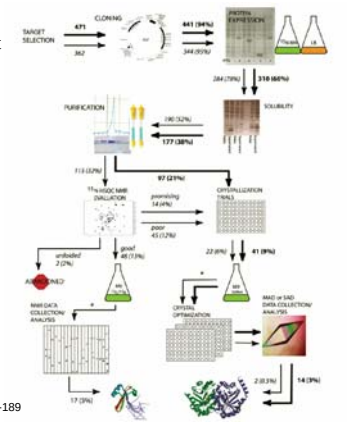
	12/2001	12/2002	12/2003	12/2004	11/2007
Selected	11214	21872	42726	74637	148735
Cloned	5465	11277	23237	45353	104366
Expressed	2860	6115	13602	25536	66458
Purified	1505	2823	5291	8398	25989
Crystallized	336	1161	1876	3199	9578
Diffraction	96	438	767	1651	4919
Crystal structure	87	314	545	1260	3781
PDB	76	247	569	1488	5235

Targets by genome

Organism	Number of targets	% Of all targets
Caenorhabditis elegans	4674	17.4
Arabidopsis thaliana	3900	14.5
Homo sapiens	3257	12.1
Pyrococcus furiosus	2179	8.1
Thermotoga maritima	1860	6.9
Mycobacterium tuberculosis	1476	5.5
Escherichia coli	1272	4.7
Saccharomyces cerevisiae	1254	4.7
Bacillus subtilis	1220	4.5
Bacillus stearothermophilus	764	2.8

Adopted from O'Toole et al., 2004

M. thermoautotrophicum structural genomics project



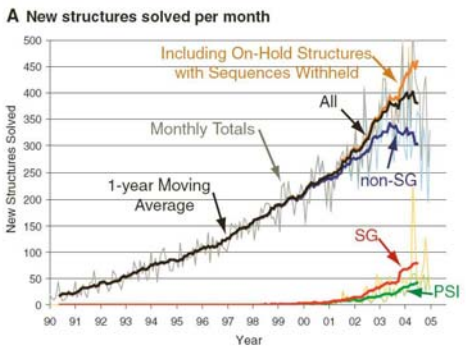
Yee et al., *Acc. Chem. Res.* **2003,** 36, 183-189

Current results

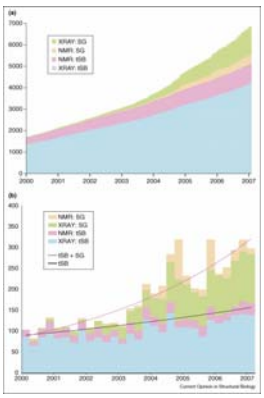
Group or SG center	Targets and nonidentical chains	New Pfam families (total family size)	Novel structures (30% ID)	New SCOP folds	New SCOP fold or superfamily
SG centers					
Berkeley Structural Genomics Center (BSGC)	57 (57 chains)	22 (5757)	41	4	6
Center for Eukaryotic Structural Genomics (CESG)	48 (48 chains)	7 (387)	28	0	0
Joint Center for Structural Genomics (JCSG)	186 (187 chains)	32 (4875)	92	3	4
Midwest Center for Structural Genomics (MCSG)	224 (229 chains)	55 (5512)	163	18	25
Northeast Structural Genomics Consortium (NESGC)	159 (159 chains)	52 (4811)	108	15	26
New York Structural Genomics Research Consortium (NYSGRC)	166 (171 chains)	27 (3982)	90	6	9
Southeast Collaboratory for Structural Genomics (SECSG)	67 (67 chains)	6 (1079)	25	0	1
Structural Genomics of Pathogenic Protozoa Consortium (SGPP)	26 (26 chains)	1 (19)	8	2	2
TB Structural Genomics Consortium (TB)	99 (99 chains)	9 (3938)	42	0	1
PSI centers (total of 9 centers above)	1032 (1043 chains)	211 (30,340)	597	48	74
Japanese center (RIKEN)	486 (718 chains)	50 (6860)	289	10	20
Other international SG (total, excluding all centers above)	169 (183 chains)	33 (5877)	69	6	9
Non-SG groups (since 2000)					
Non-SG structural biology (total)	17,096 (23,747 chains)	928 (249,171)	2,521	269	478
Steitz group	46 (559 chains)	23 (4190)	31	7	12
Huber group	185 (273 chains)	8 (679)	38	5	10
Iwata group	14 (54 chains)	14 (7960)	20	2	3

Structural genomics target database

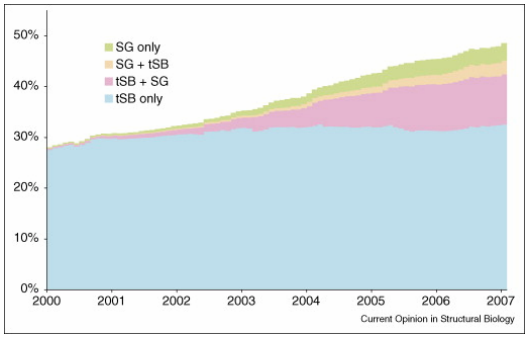
Current results



Current results



Structural coverage of the Swiss-Prot database



Grabowski et al., 2007

Practical applications of structural genomics

Fig. 3 Mis-annotation of the Rv3853 gene from *M. tuberculosis*. Originally annotated as the terminal SAM-dependent methyltransferase of menaquinone biosynthesis (MenG), Rv3853 has a monomer fold (left) that is completely different from that of a typical SAM-dependent methyltransferase such as CmaA1 (right)