Molecular Docking Workshop with DOCK Blaster

John Irwin

Monday 3pm

Outline

- 1. Very Brief Introduction to docking
- 2. A DOCK Blaster run
- 3. A hit picking party
- 4. Example presentation
- 5. Introduction to set problems

Screening for Novel Inhibitors by Molecular Docking

dock

Test high-scoring molecules

Why is docking so difficult?

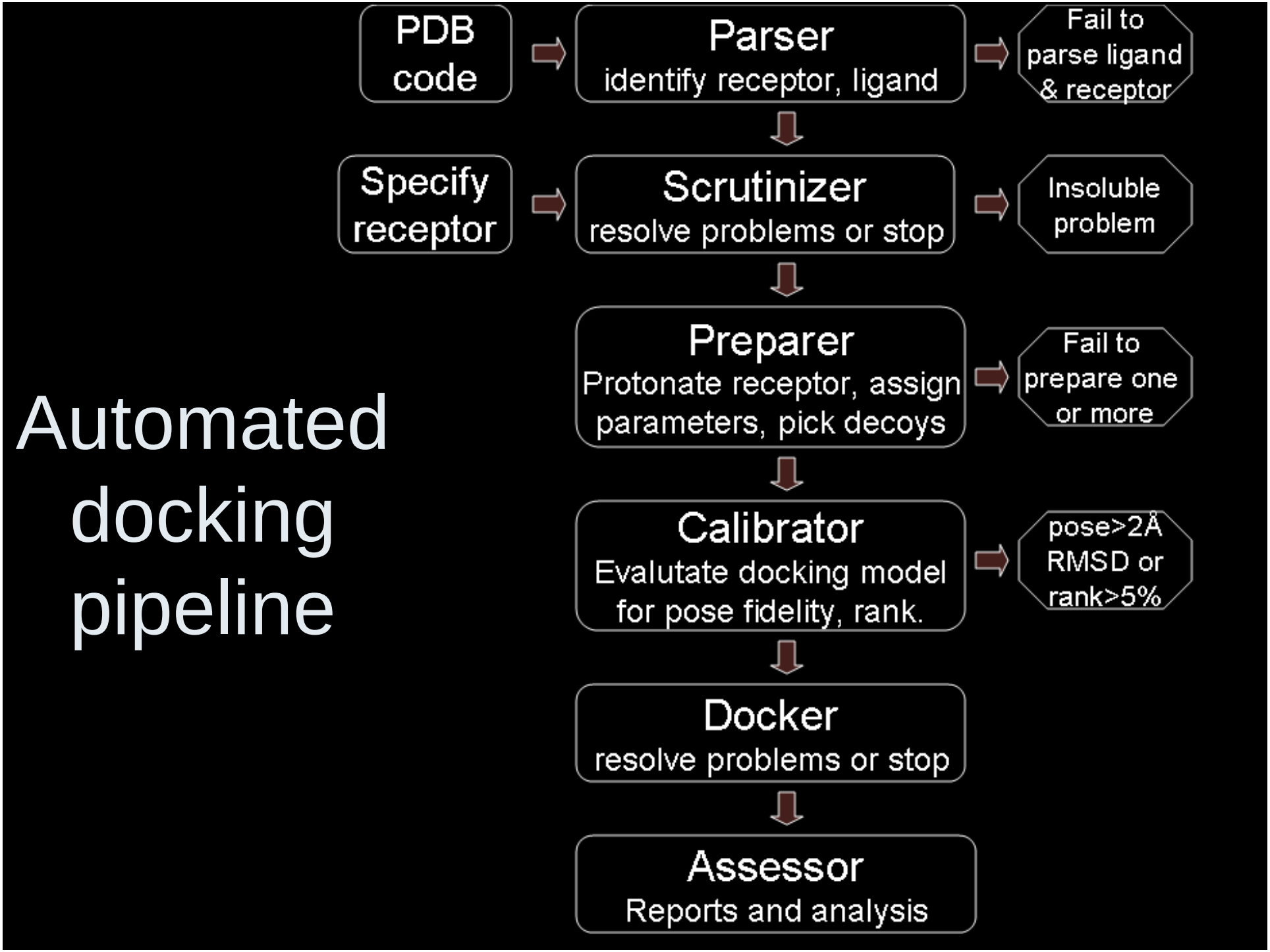
Binding sites are complicated
Lots of interactions to consider
Everything in competition with water

$$K_d = e^{-\Delta G/RT}$$

$$\Delta G_{bind} = \Delta G_{inter} - \Delta G_{solv}$$

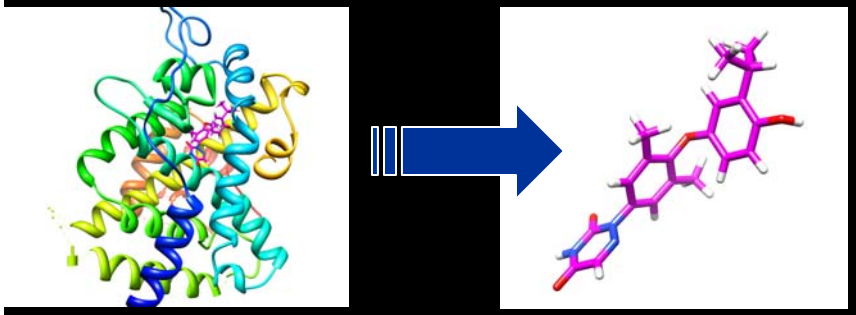
small large large

Automated docking pipeline

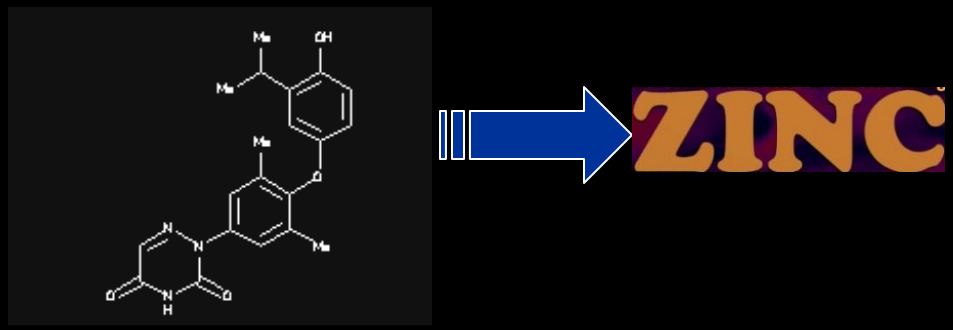


Automatic self-assessment

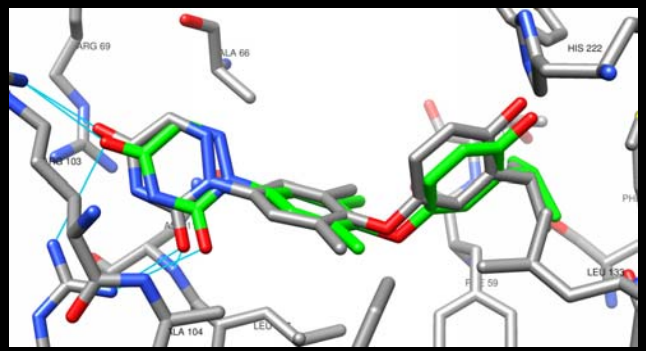
1. Remove ligand from receptor



2. Rebuild ligand without bias



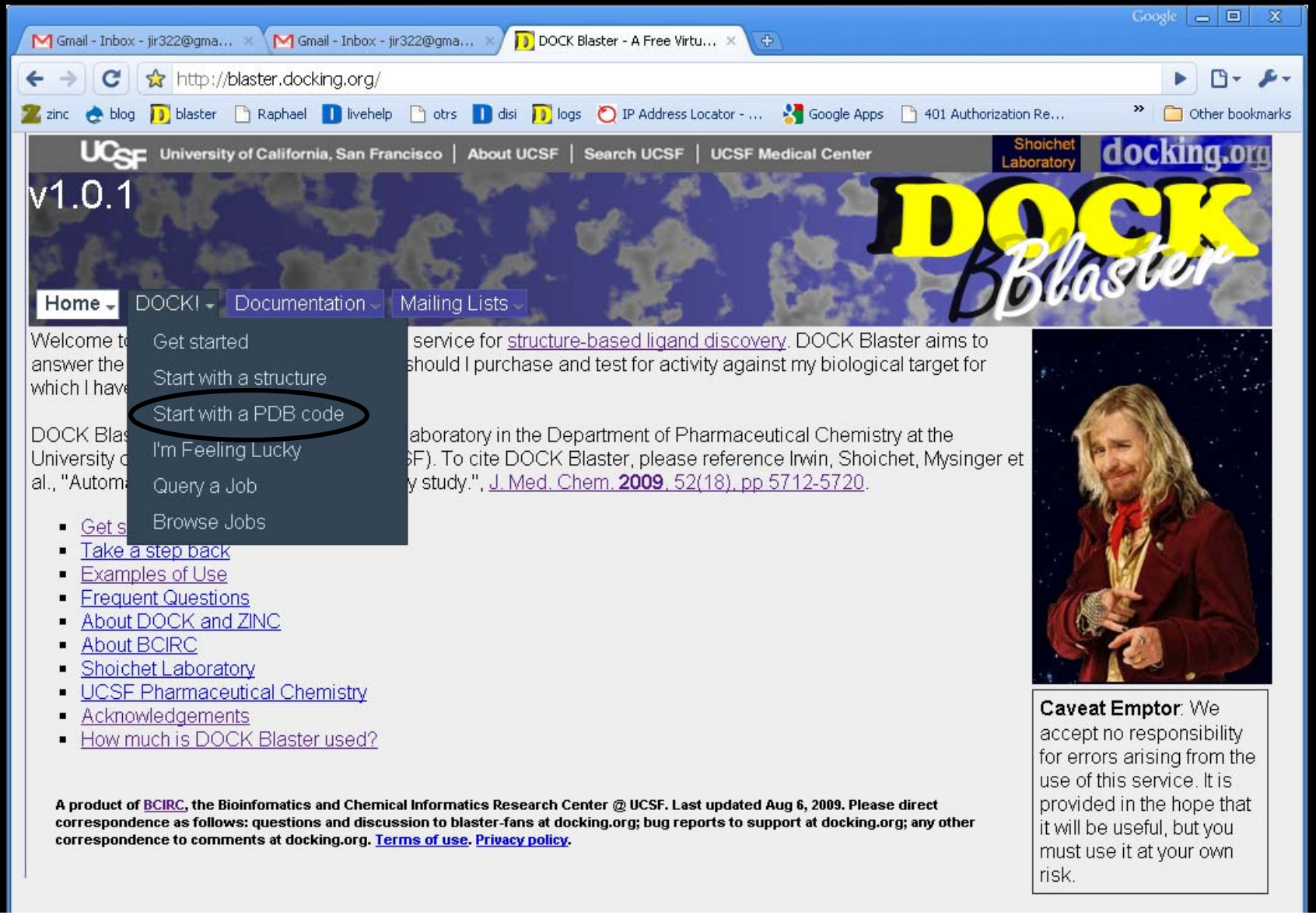
3. Dock ligand and 100 phyisically-matched decoys using 4 parameter sets



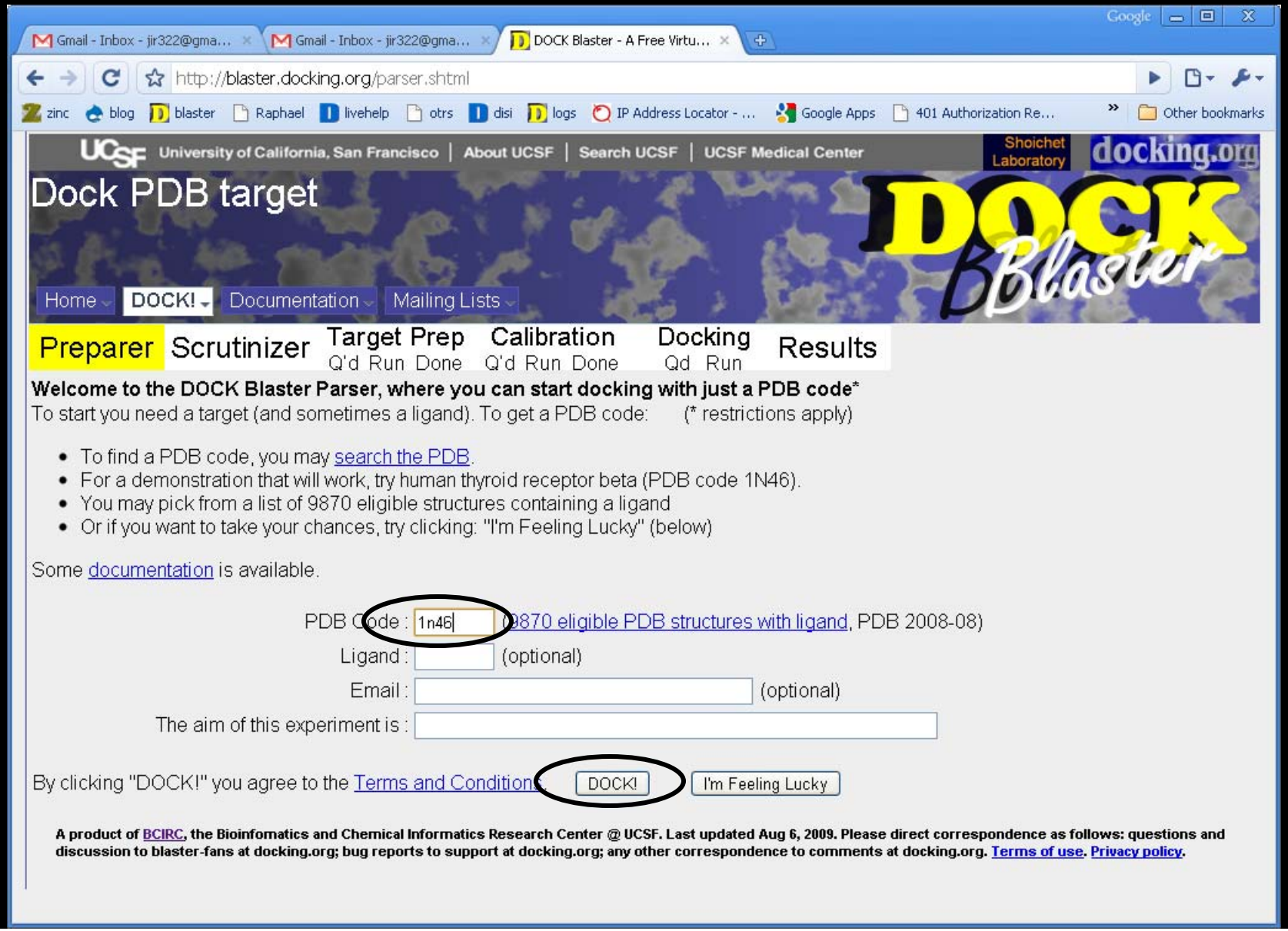
4. Evaluate pose-fidelity, enrichment

		Scoring	
		Polarized	*Normal*
Sampling	*Coarser*	3.61 Å / 1%	1.32 Å / 9%
	Finer	1.32 Å / 2 %	2.02 Å / 3%

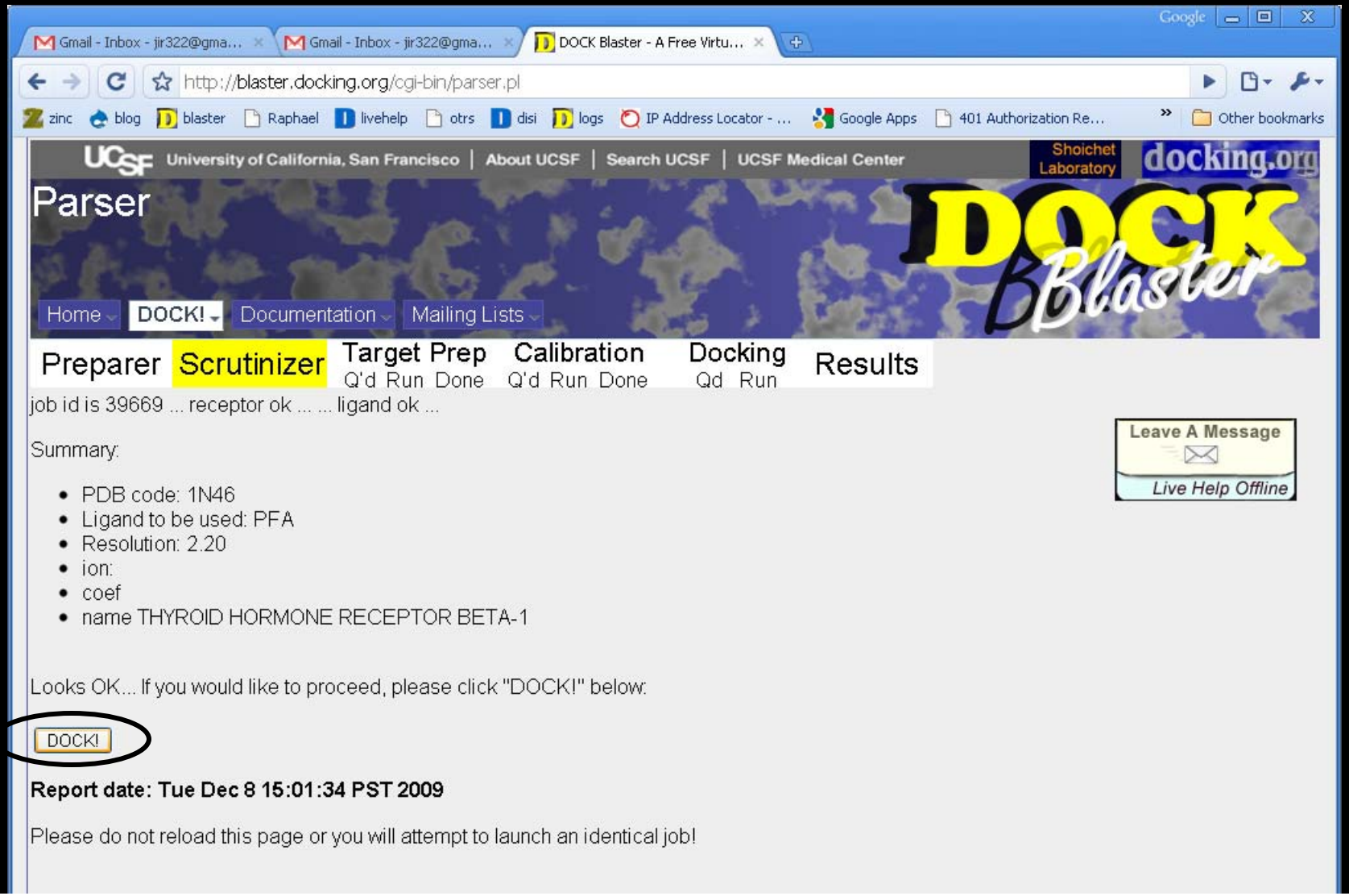
Starting point: http://blaster.docking.org
Choose: Start with a PDB code



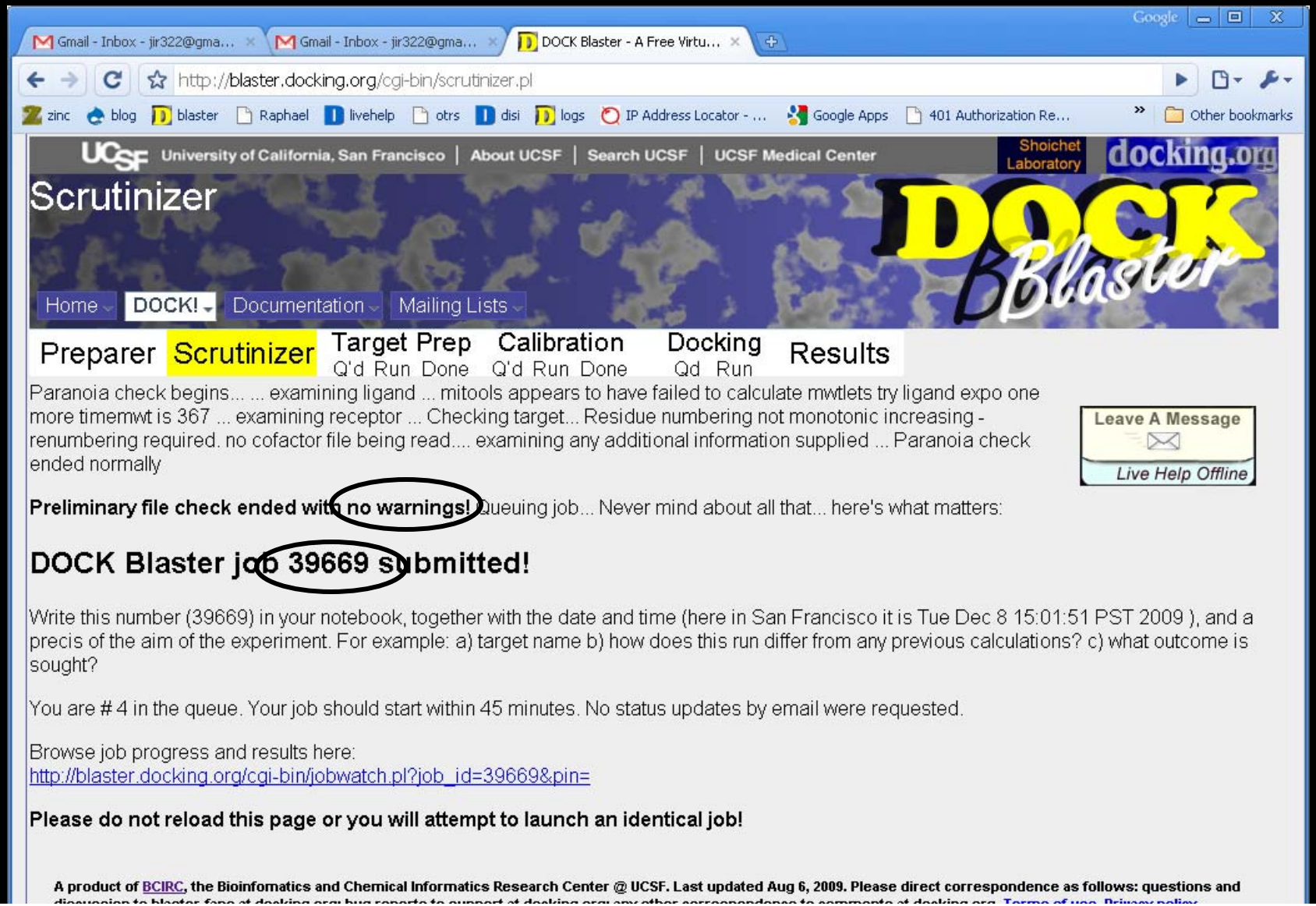
Pick a PDB Code for docking. Click DOCK! We will give you a list of codes to try



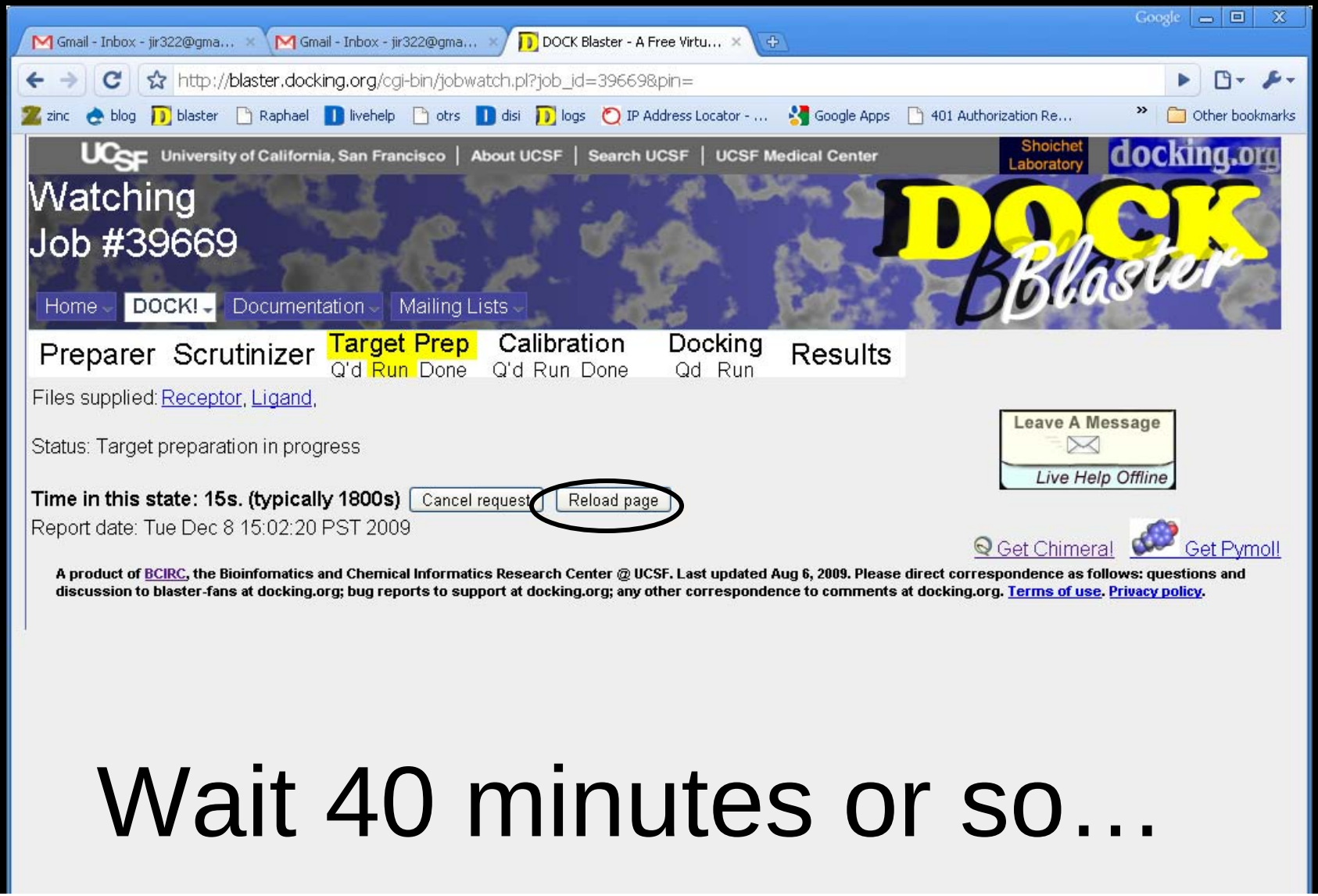
Check OK, and click DOCK! to confirm



The preliminary calculation has started. Take a note of the Job number. Wait.

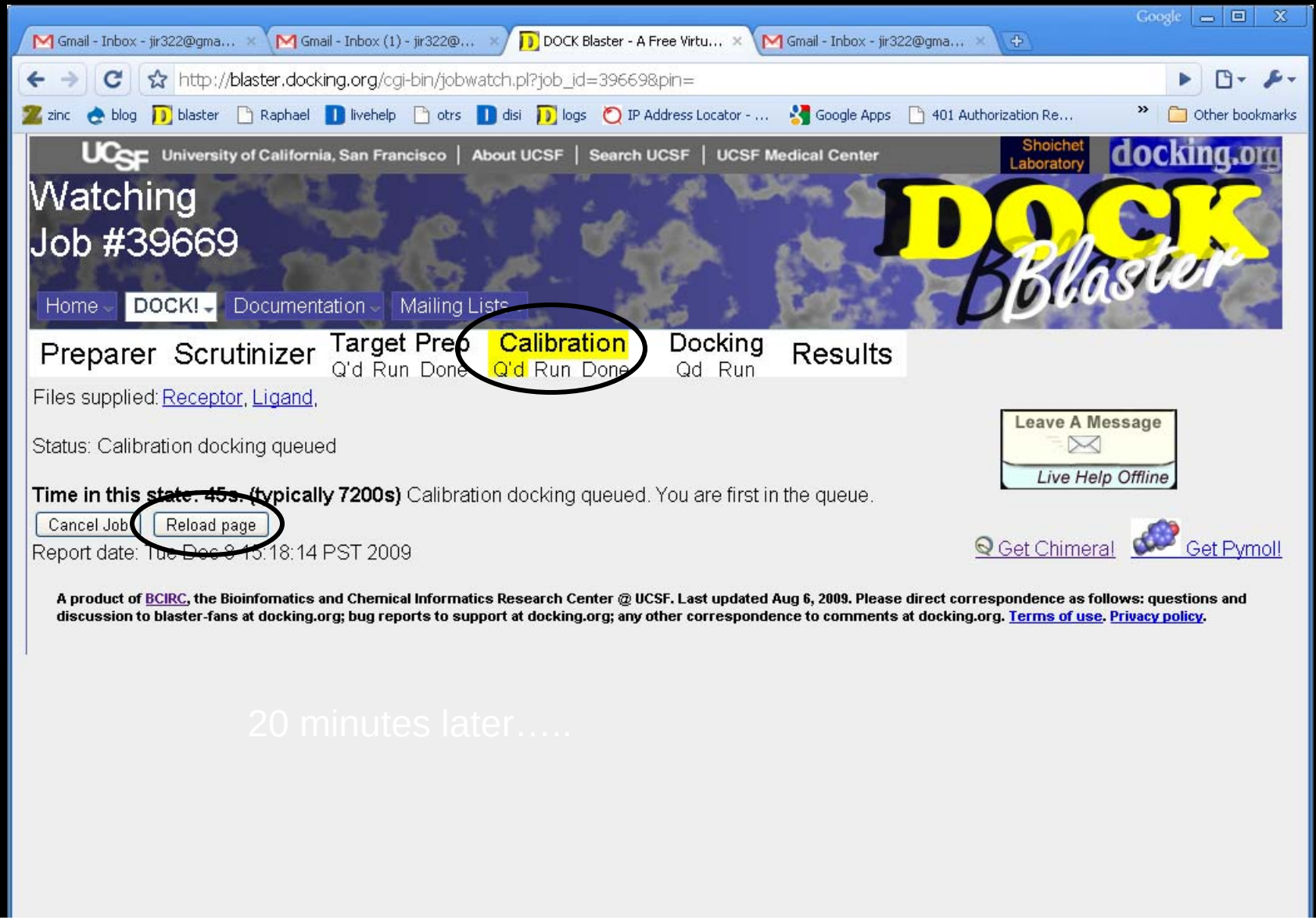


Still running… Wait 40 minutes or so….
(if everything looks ok, perhaps try SEA while waiting…)



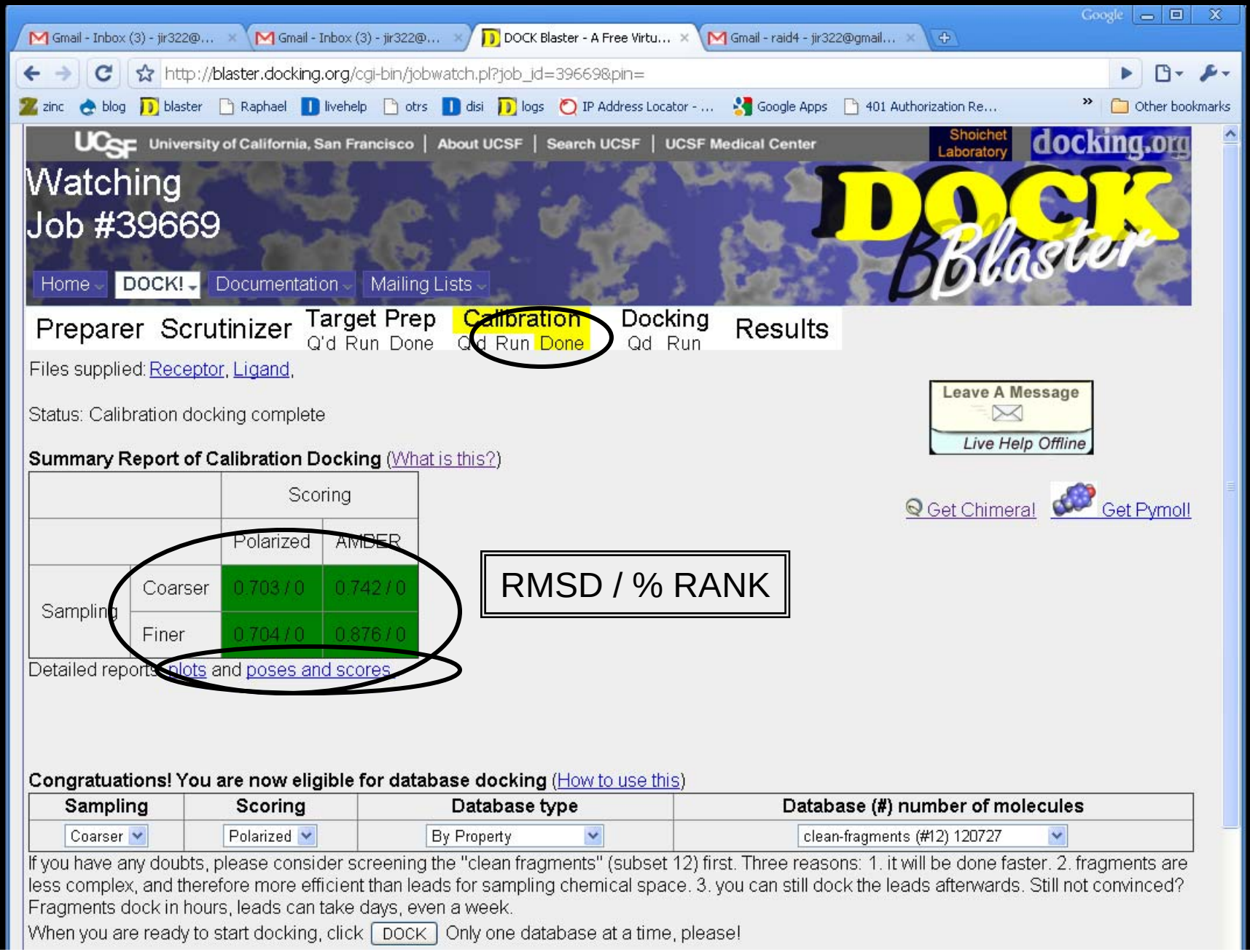
Wait 40 minutes or so…

Target preparation finished, now doing calibration (watch the yellow highlight move right…)

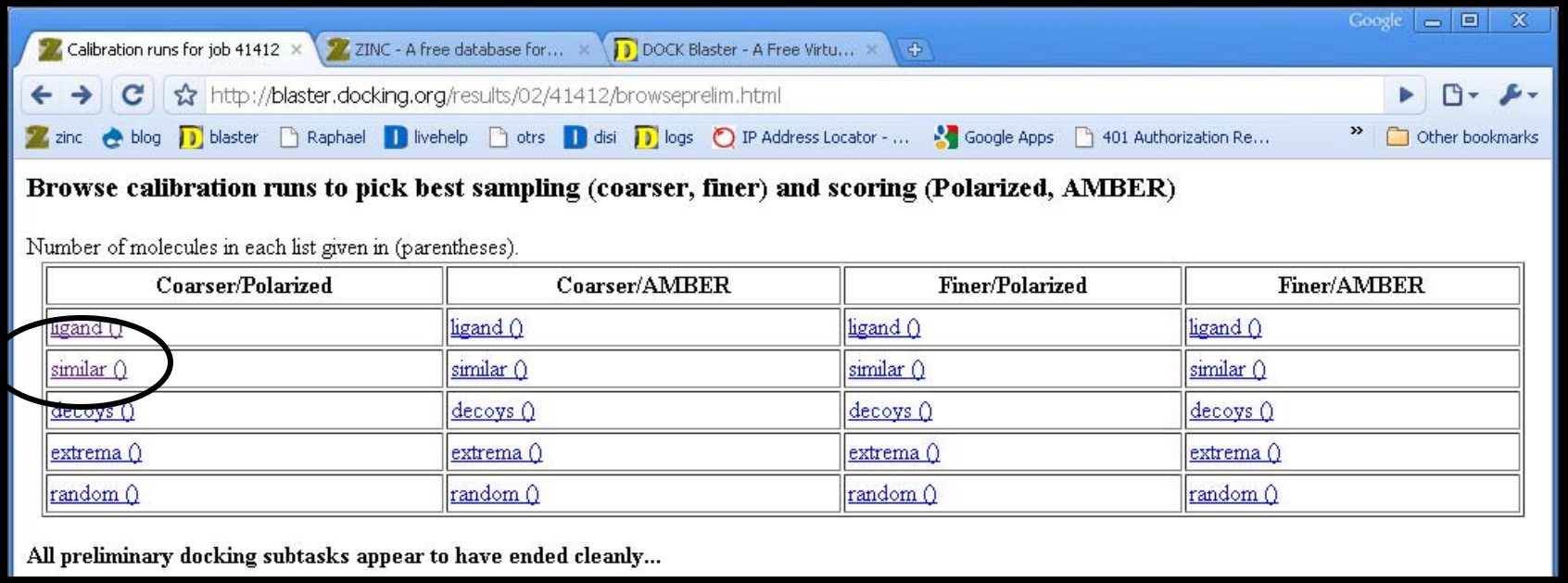


20 minutes later…..

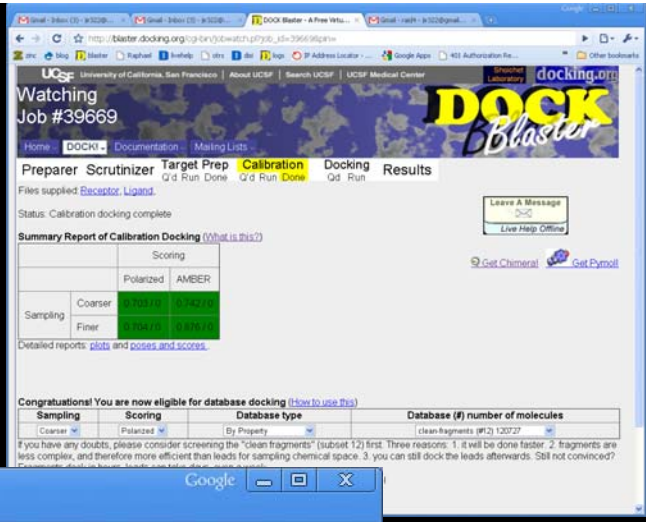
Calibration done. Are the results any good?

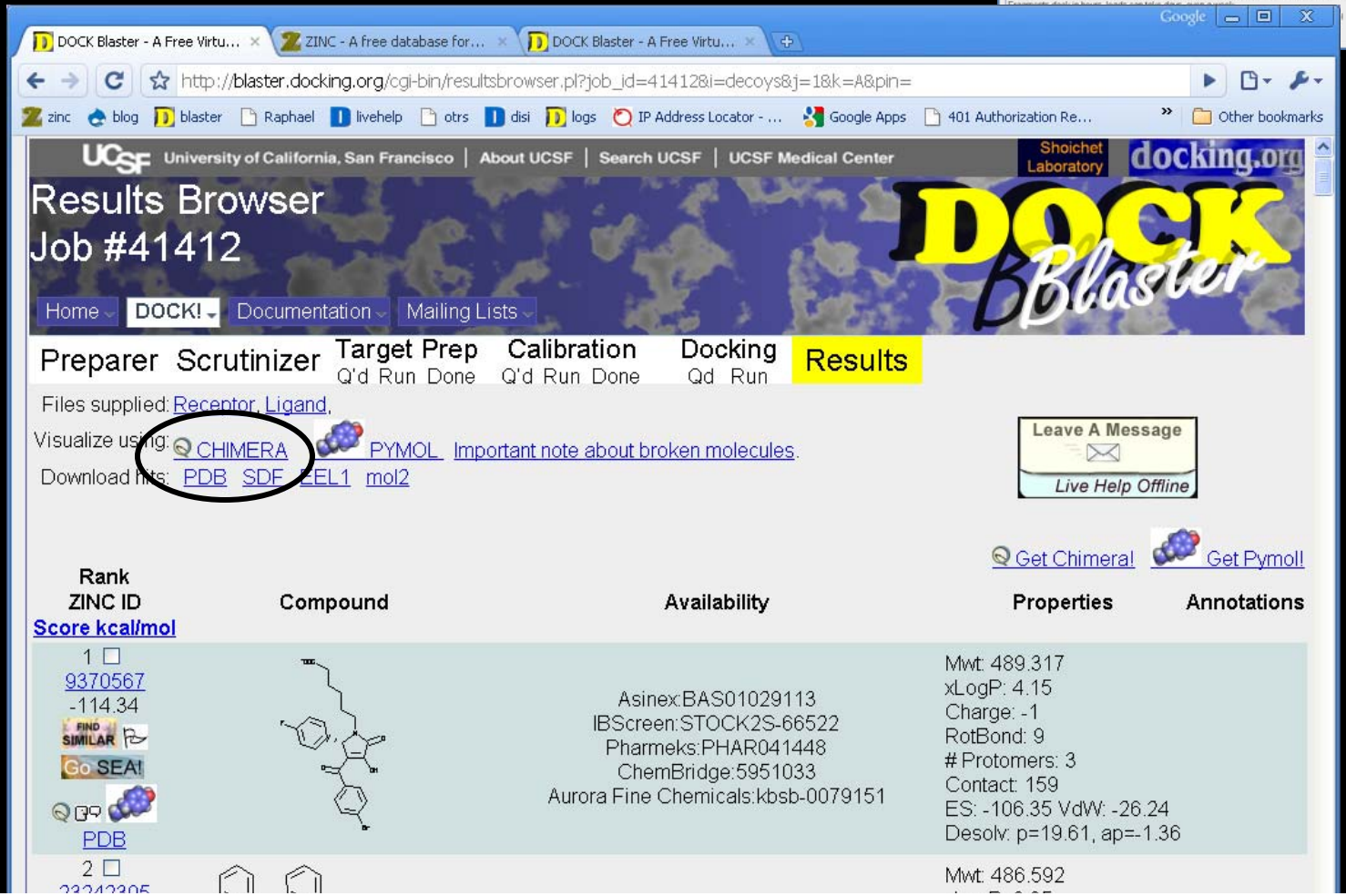


4 ways to dock: which one is best?

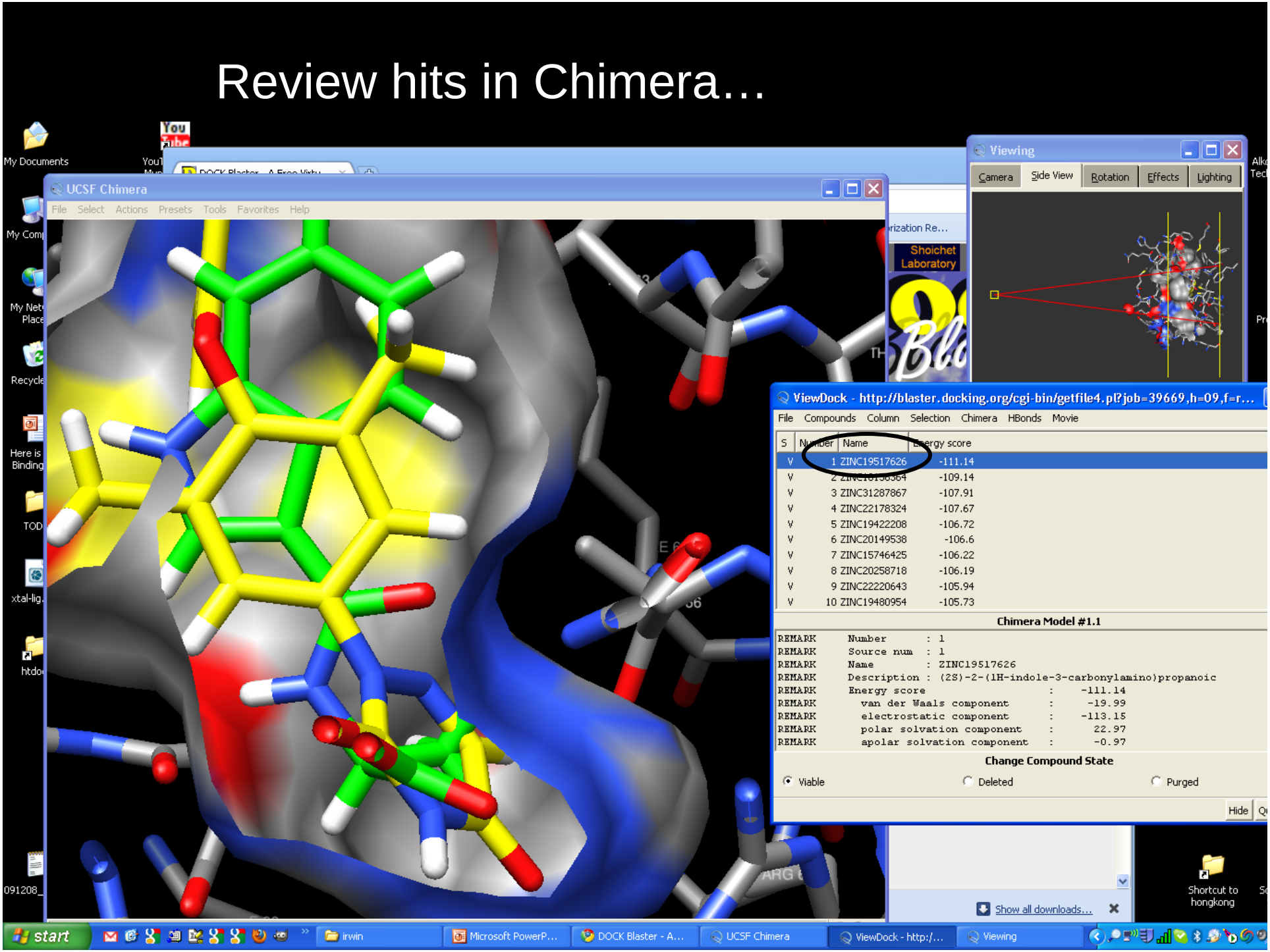


Review calibration data

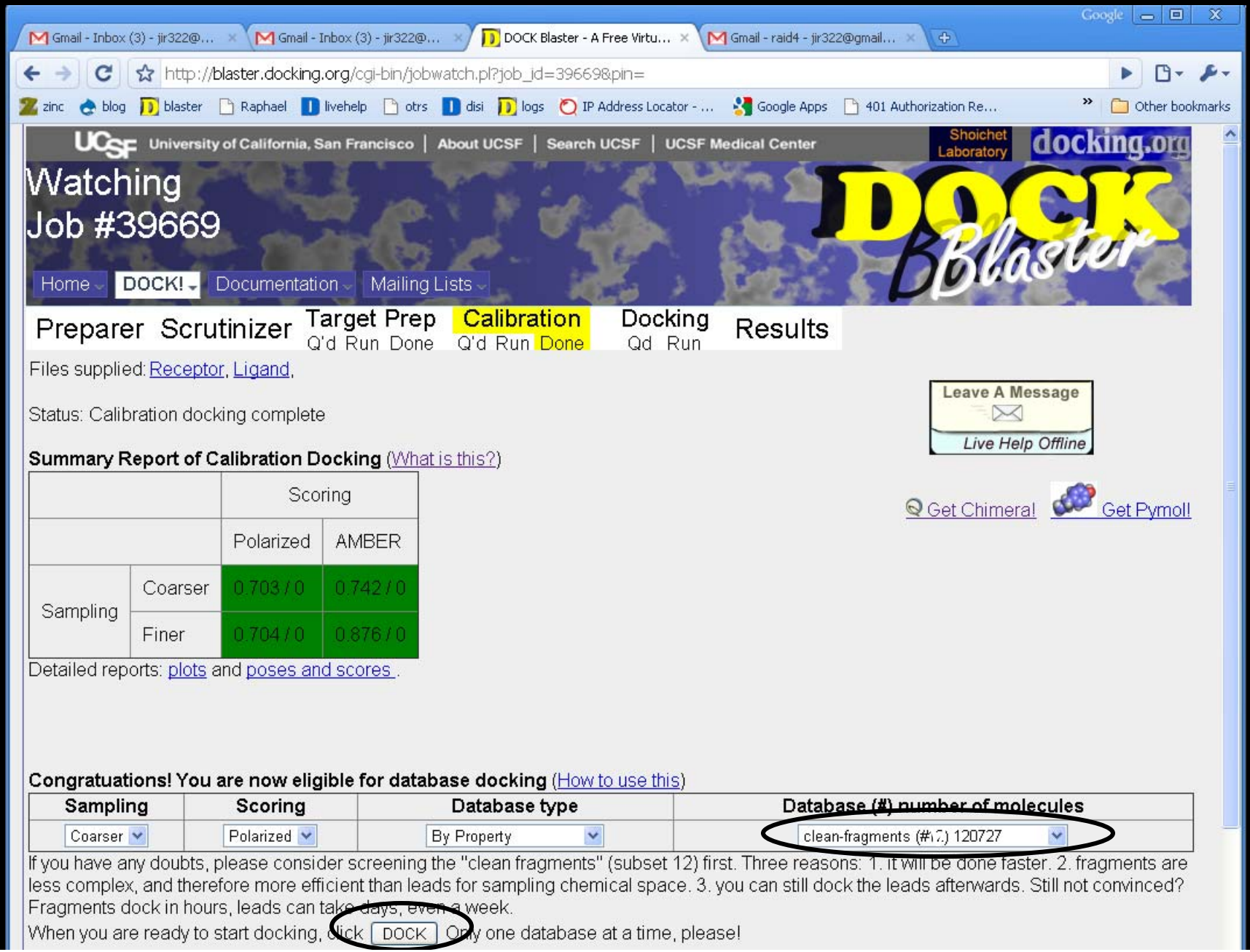




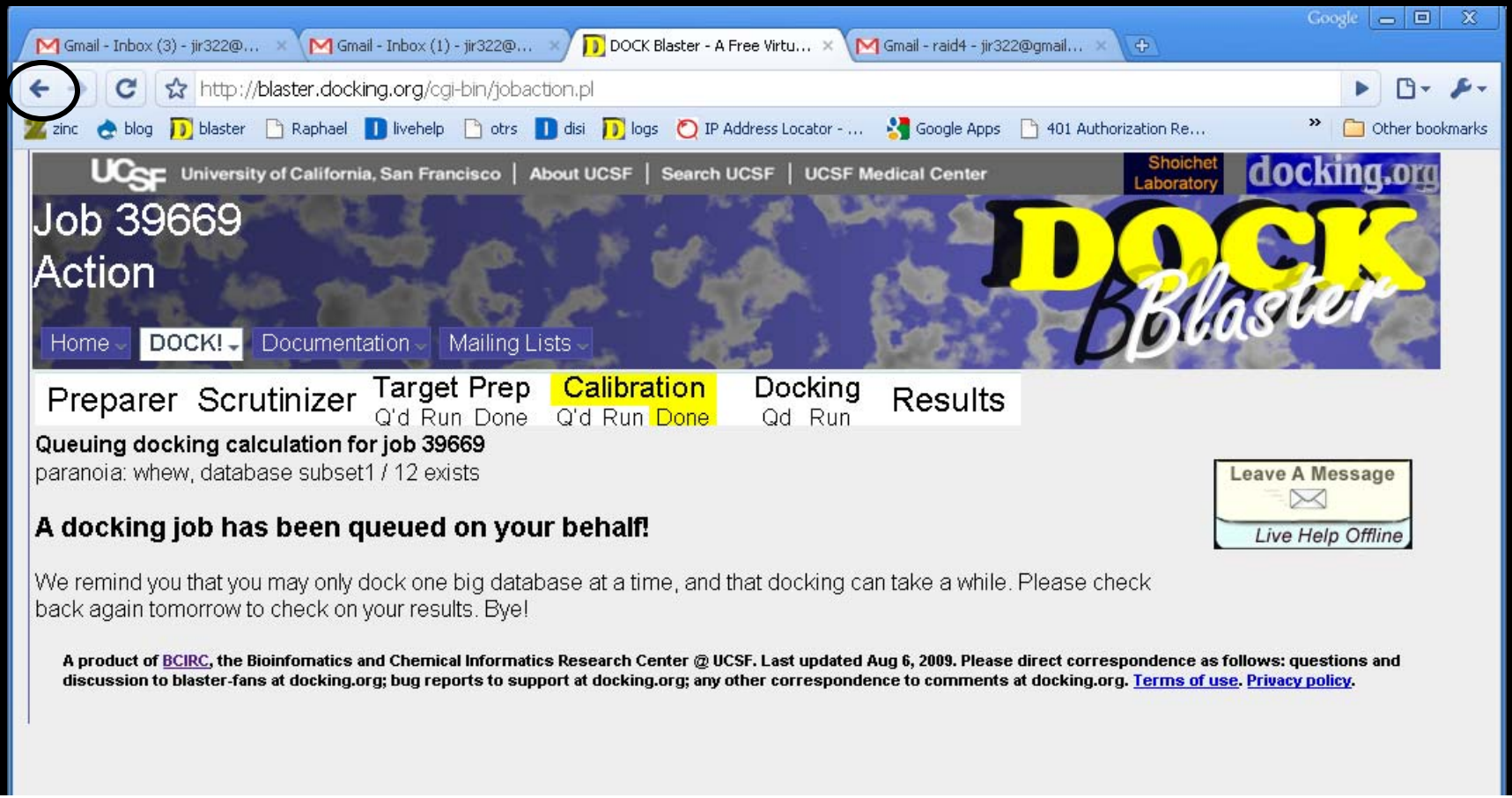
Review hits in Chimera…



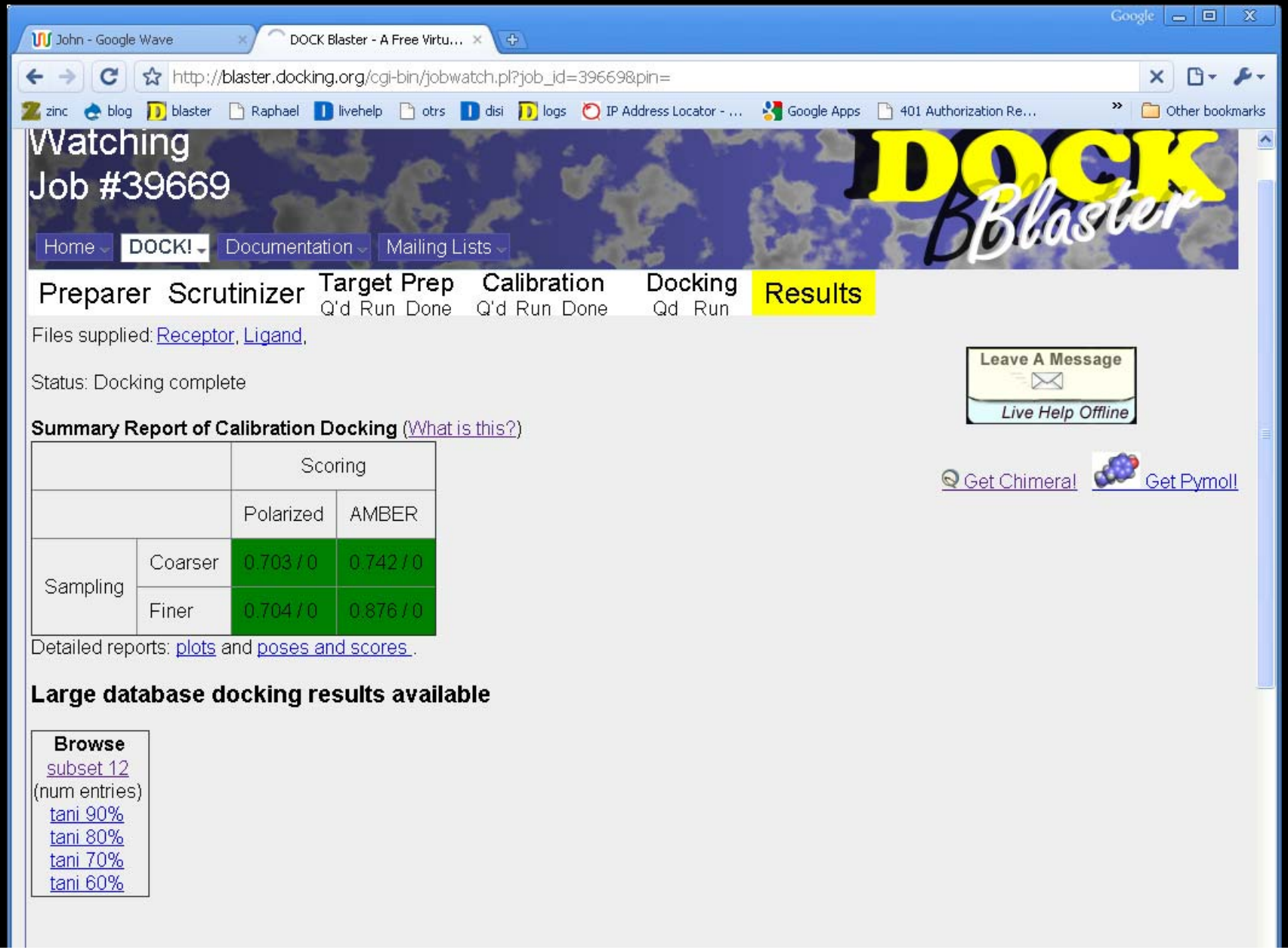
Calibration done. Are the results any good?



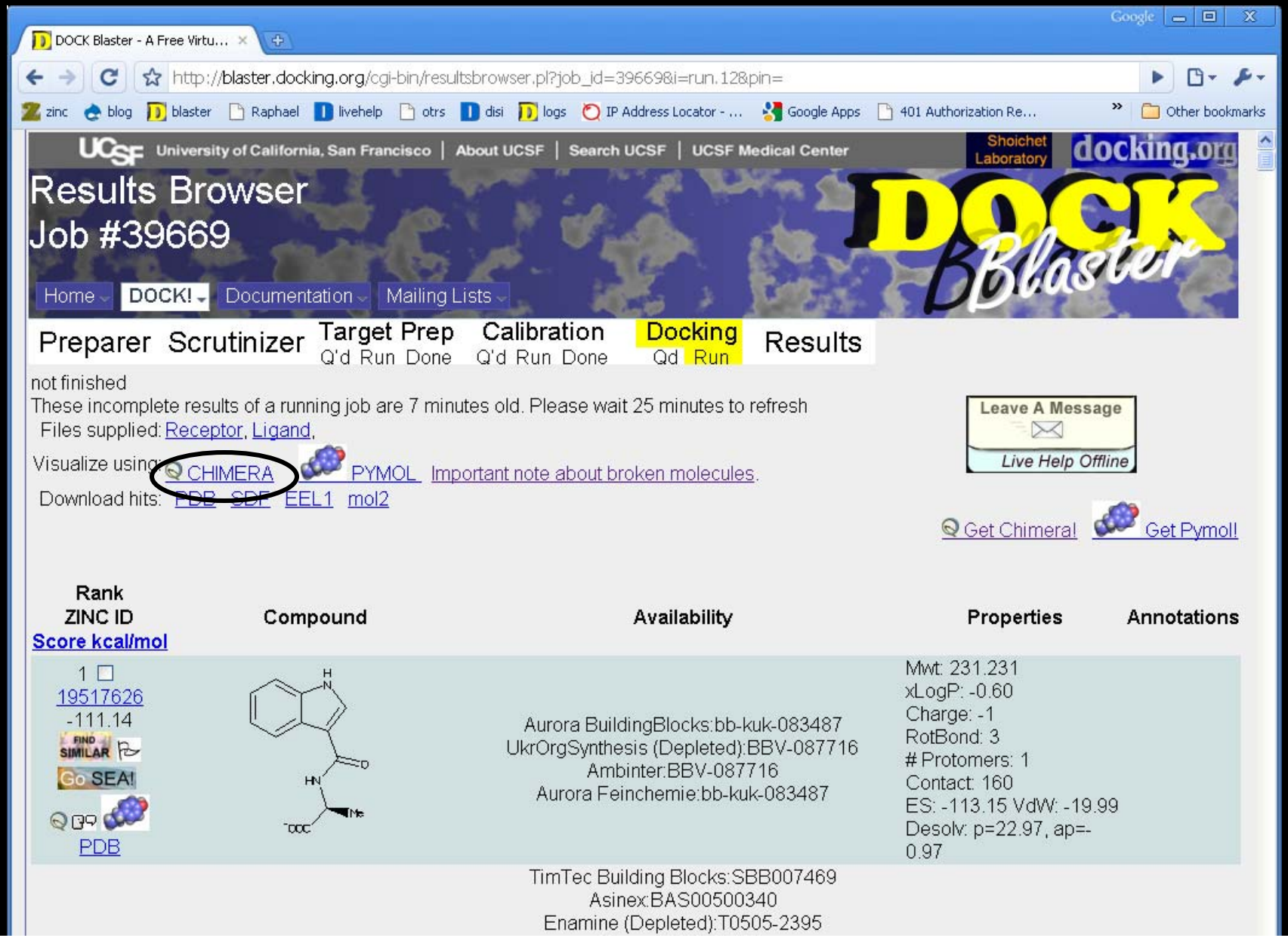
Click on DOCK to run a docking calculation. This may take 8 hours or so, depending… So it would be ideal to launch docking no later than Wednesday at 4pm.



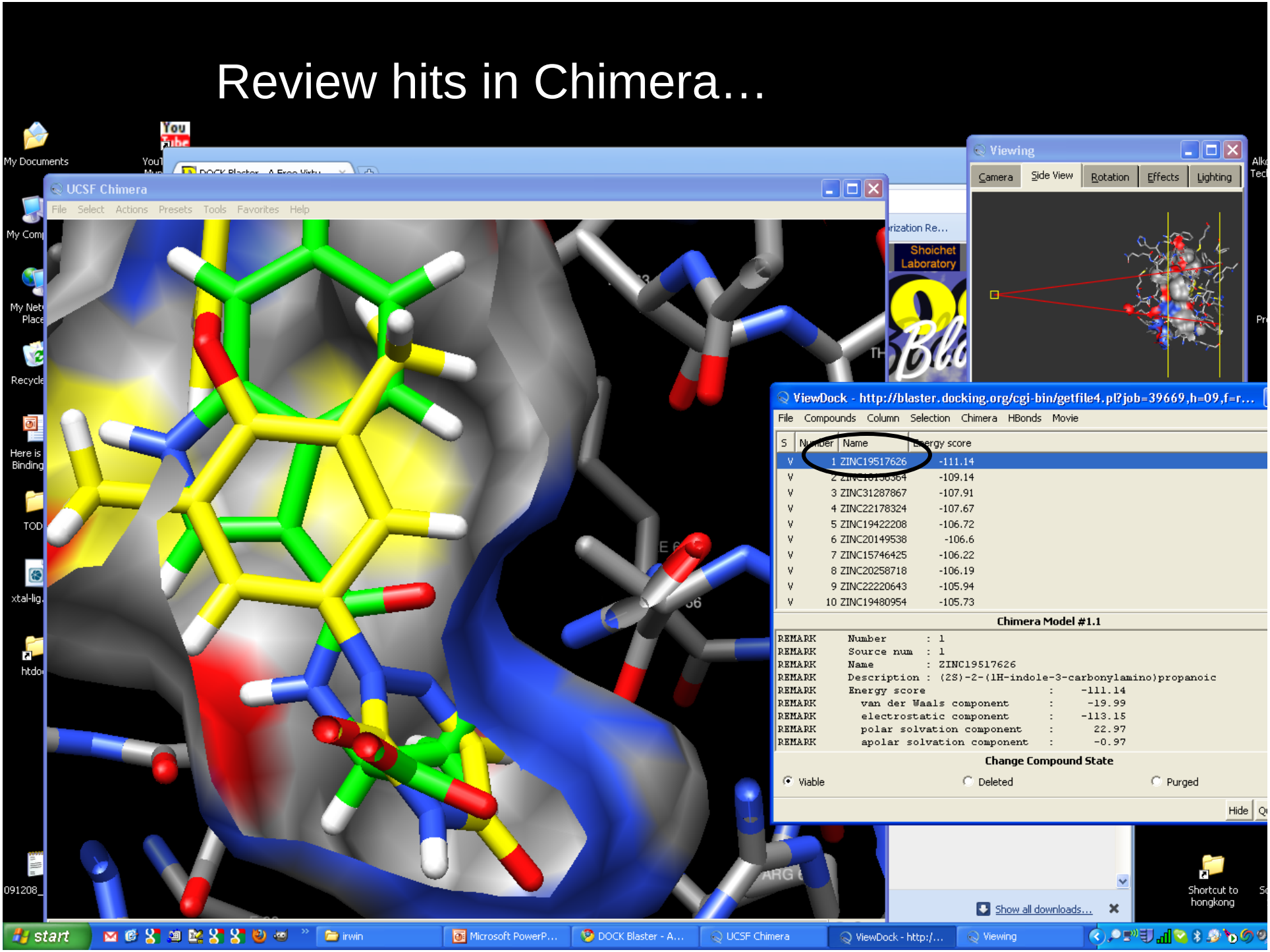
This is what it looks like when done.



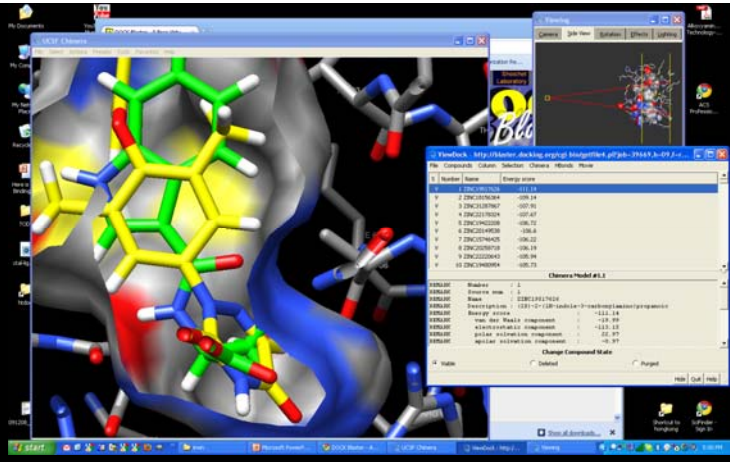
Review docking hits, use CHIMERA



Review hits in Chimera…



How to run a hit picking party



- How ligand docks & in crystal structure
- How actives dock - common interactions, missed opportunities
- Look at the top 10. (watch out for brokens)
- Look through the top 200 or so. Use A,B,C to classify your enthusiasm.
- Do this first with one other person, then with a group.

Types of Ligand-Protein Interactions

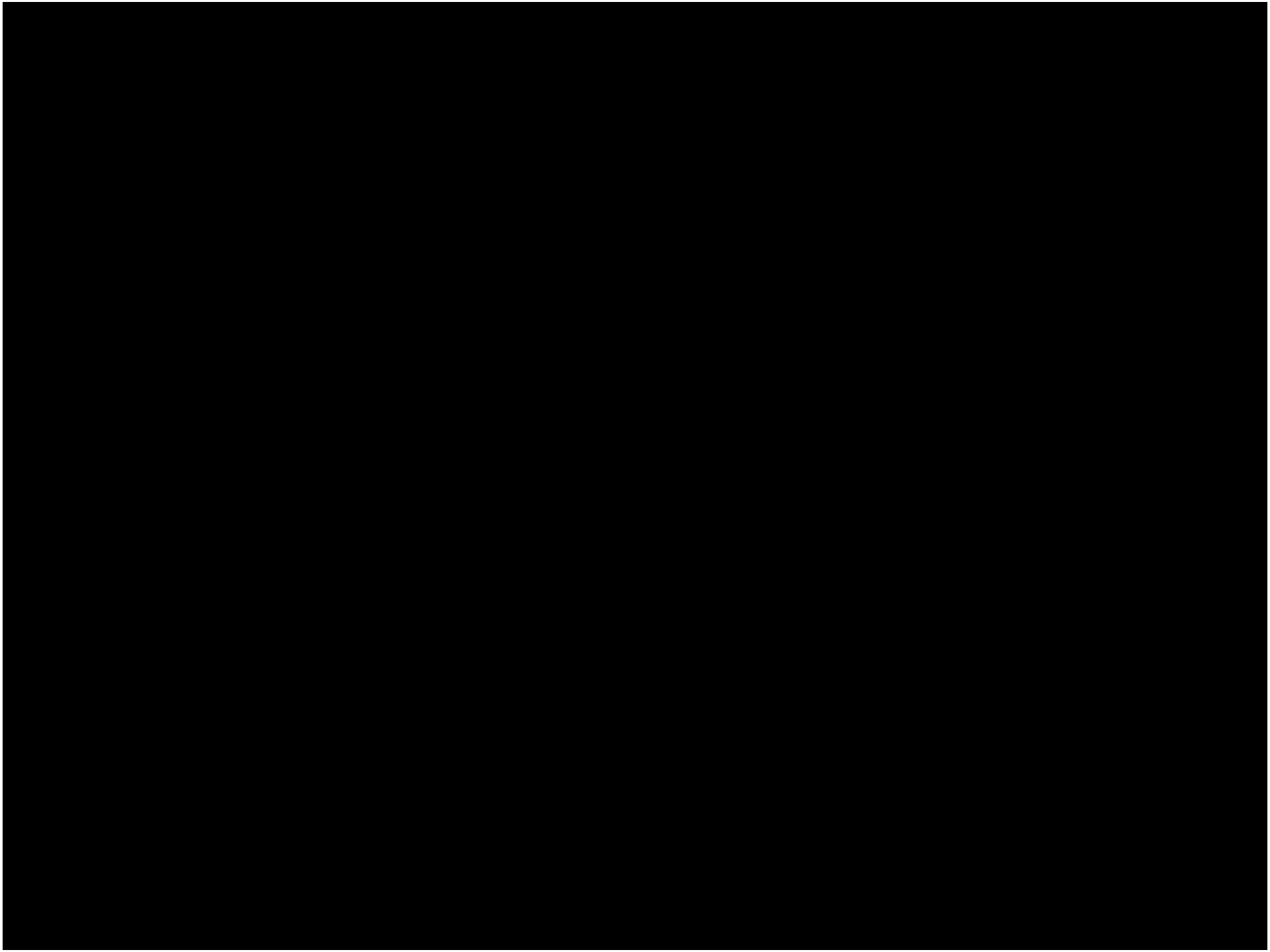
Types of Interaction	Strength	Effect of Distance
Covalent	V. Strong	long range
Ionic	V. Strong	1/r, long range
Ion-Dipole	Strong	$1/r^2$, short range
Dipole-Dipole	Moderate	$1/r^3$, short range
Hydrogen Bond	Moderate	$1/r^3$ (?) short range
Ion-Induced Dipole	Weak	$1/r^4$, v. short range
Dispersion	V. Weak	$1/r^6$, ext. short range
Repulsion	Ext. Strong	$1/r^{12}$, ext. short range
“Hydrophobic”	Weak	??

Example final presentation

- 1: Introduce the protein and binding site
- 2: Show the ligand, discuss how it binds
- 3: Calibration? Controls?
- 4-7. Show the four compounds you liked best. How different are they from precedented compounds? Show in 2D and 3D. Rotate if possible. Purchasable? Properties? likes/dislikes

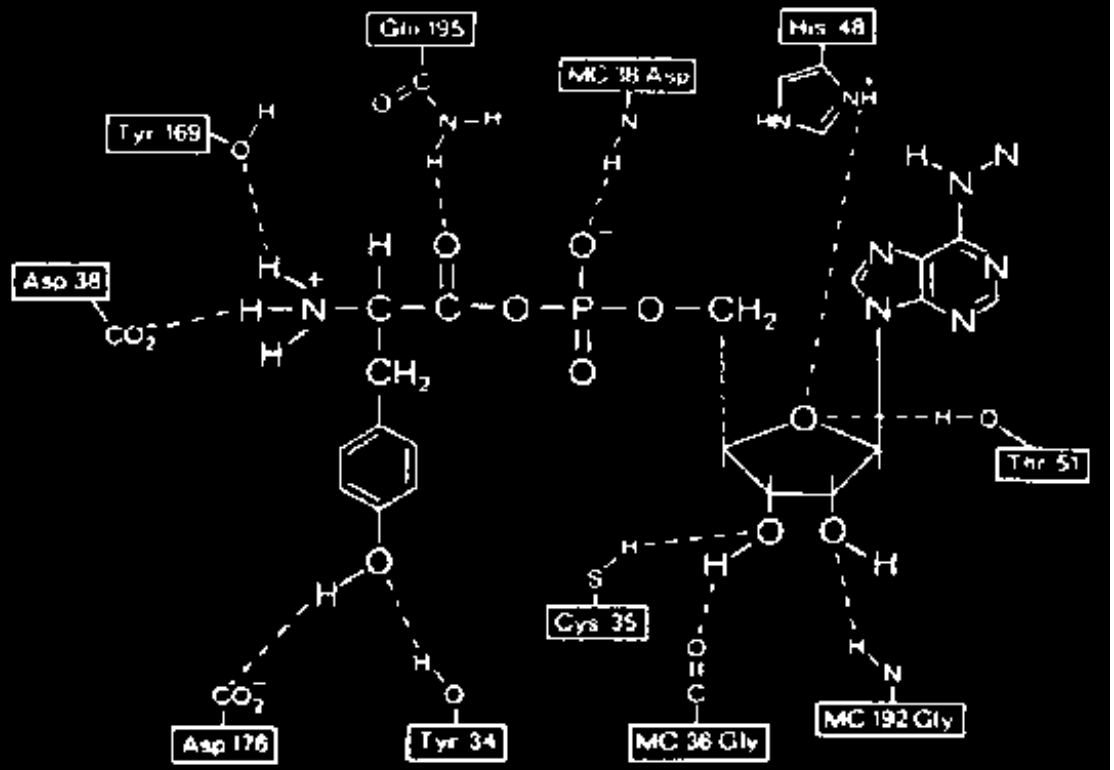
Now it is your turn….

- Monday evening
  - DOCK Blaster Set problems.
  - Work on at most 2 (to avoid overloading the server)
  - Work in groups of 1 or 2
- Wednesday
  - Dock to your own target.
  - Pick something that
    - A. you are interested in / know about
    - B. works with DOCK Blaster
- Thursday
  - Hit picking parties
  - Group presentations



Non-covalent Interactions in Proteins

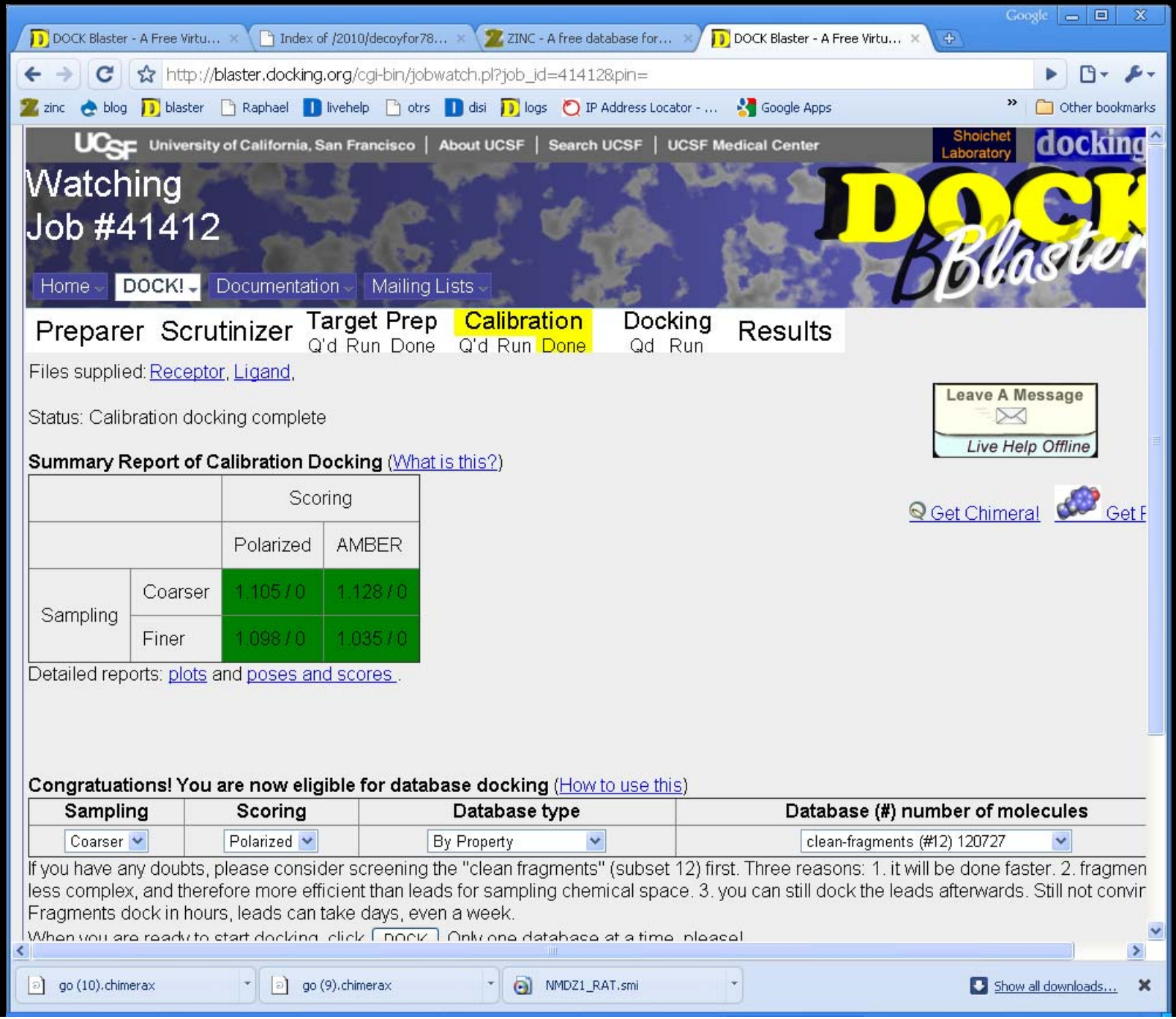
A.R Fersht, *Nature* (1985)



Energies in Vacuo			Energies in Protein Complexes (binding sites)		
donor	acceptor	energy kcal/mol	donor	acceptor	energy kcal/mol
dipole	dipole	~ -6.5	dipole	dipole	-0.5 to -1.5
dipole	induced dipole	~ -3	dipole	induced dipole	~ 1
charged	dipole	-13 to -20	charge	dipole	-3 to -5
charged	charged	~ -50	charge	charge	-3 to -5

How to run a group hit picking party

- Same as for 1 or 2, except only show specific molecules, not all molecules
- Solicit explanations for why people prefer one molecule or another.
- Disagreements can be interesting, and didactic.


DOCK Blaster - A Free Virtu...
Index of /2010/decoyfor78...
ZINC - A free database for...
DOCK Blaster - A Free Virtu...
http://blaster.docking.org/cgi-bin/jobwatch.pl?job_id=41412&pin=
zinc
blog
blaster
Raphael
livehelp
otrs
disi
logs
IP Address Locator - ...
Google Apps
Other bookmarks
UCSF University of California, San Francisco | About UCSF | Search UCSF | UCSF Medical Center
Shoichet Laboratory
docking
Watching
Job #41412
DOCK Blaster
Home
DOCK!
Documentation
Mailing Lists
Preparer
Scrutinizer
Target Prep
Q'd Run Done
Calibration
Q'd Run Done
Docking
Qd Run
Results
Files supplied: Receptor, Ligand,
Status: Calibration docking complete
Leave A Message
Live Help Offline
Summary Report of Calibration Docking (What is this?)
Scoring
Polarized
AMBER
Sampling
Coarser
1.105 / 0
1.128 / 0
Finer
1.098 / 0
1.035 / 0
Get Chimera!
Get F
Detailed reports: plots and poses and scores .
Congratuations! You are now eligible for database docking (How to use this)
Sampling
Scoring
Database type
Database (#) number of molecules
Coarser
Polarized
By Property
clean-fragments (#12) 120727
If you have any doubts, please consider screening the "clean fragments" (subset 12) first. Three reasons: 1. it will be done faster. 2. fragmen
less complex, and therefore more efficient than leads for sampling chemical space. 3. you can still dock the leads afterwards. Still not convir
Fragments dock in hours, leads can take days, even a week.
When you are ready to start docking, click DOCK. Only one database at a time, please!
go (10).chimerax
go (9).chimerax
NMDZ1_RAT.smi
Show all downloads...

esults Browser
b #41412

DOCK Blaster

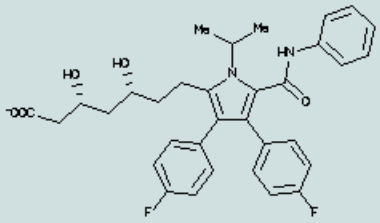
s supplied: Receptor, Ligand,

alize using: CHIMERA PYMOL Important note about broken molecules.

wnload hits: PDB SDF EEL1 mol2

Leave A Message
Live Help Offline

Get Chimera! Get Pymol!

Rank ZINC ID re kcal/mol	Compound	Availability	Properties	Annotations
1 ☐ 6052413 -139.01 FIND SIMILAR Go SEA! PDB		Individual Suppliers:882_1_3CD7 Individual Suppliers:UNNAMED00000089 Individual Suppliers:882 Individual Suppliers:385219	Mwt: 575.632 xLogP: 5.75 Charge: -1 RotBond: 12 # Protomers: 1 Contact: 248 ES: -122.64 VdW: -37.27 Desolv: p=23.40, ap=-2.50	

HPP (1) How ligand looks

Ligand poses well

e.G ligand poses badly

HPP (2) How actives look

Actives look good

Actives look bad

HPP (3) Look at the top 10

Examples of good

Examples of bad, broken

Actual example (7 slides)

- So, here it goes....