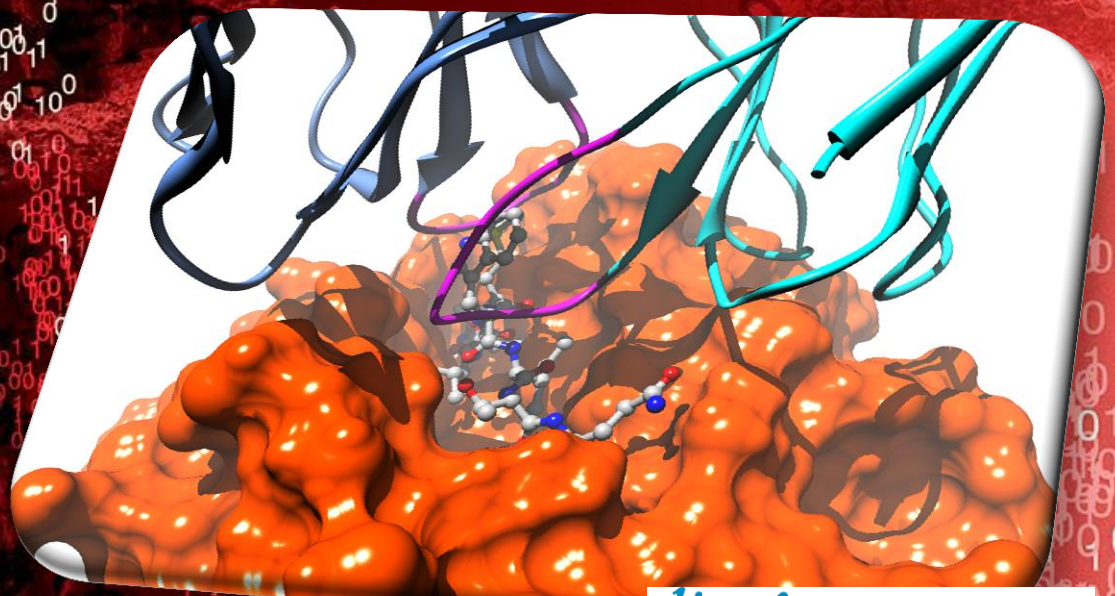
From molecular modeling to personalized medicine



Vincent Zoete, Forum Teratec 2017

June 27, 2017

UNIL | Université de Lausanne
Faculty of Biology and Medicine

CHUV

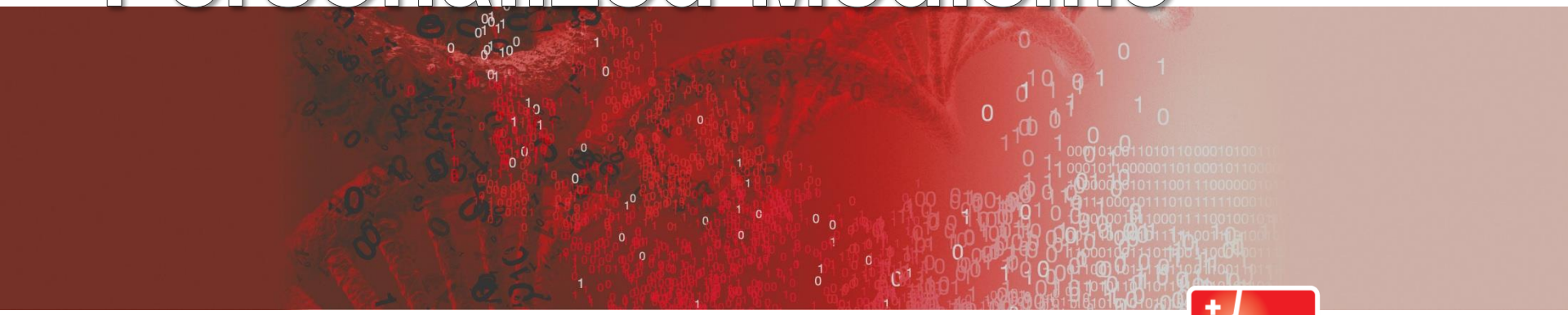
SIB
Swiss Institute of Bioinformatics

elixir SWITZERLAND

Protein Engineering

Drug Design

Personalized Medicine

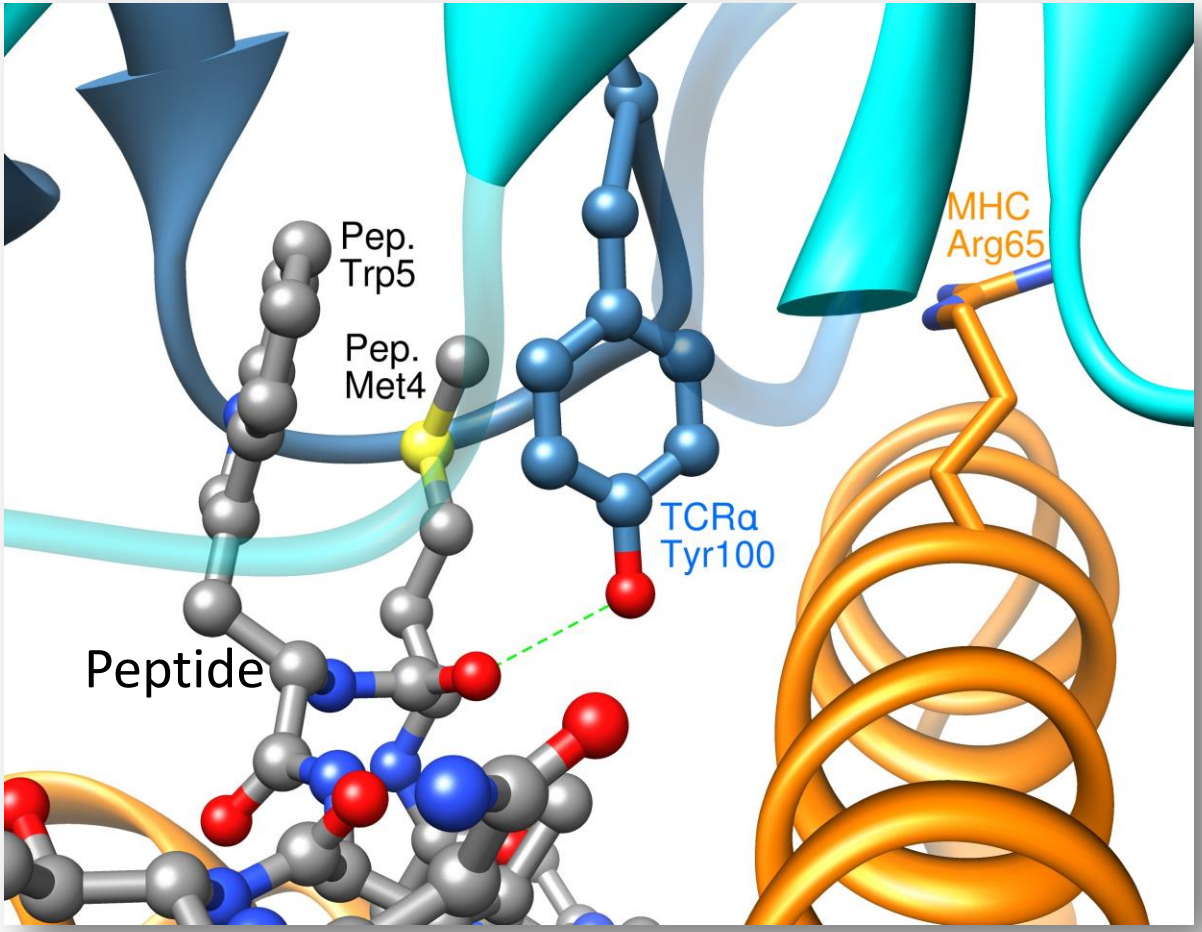


SIB
Swiss Institute of Bioinformatics

elixir SWITZERLAND

Structure-based Protein Engineering

How to use molecular mechanics for *in silico* protein engineering?

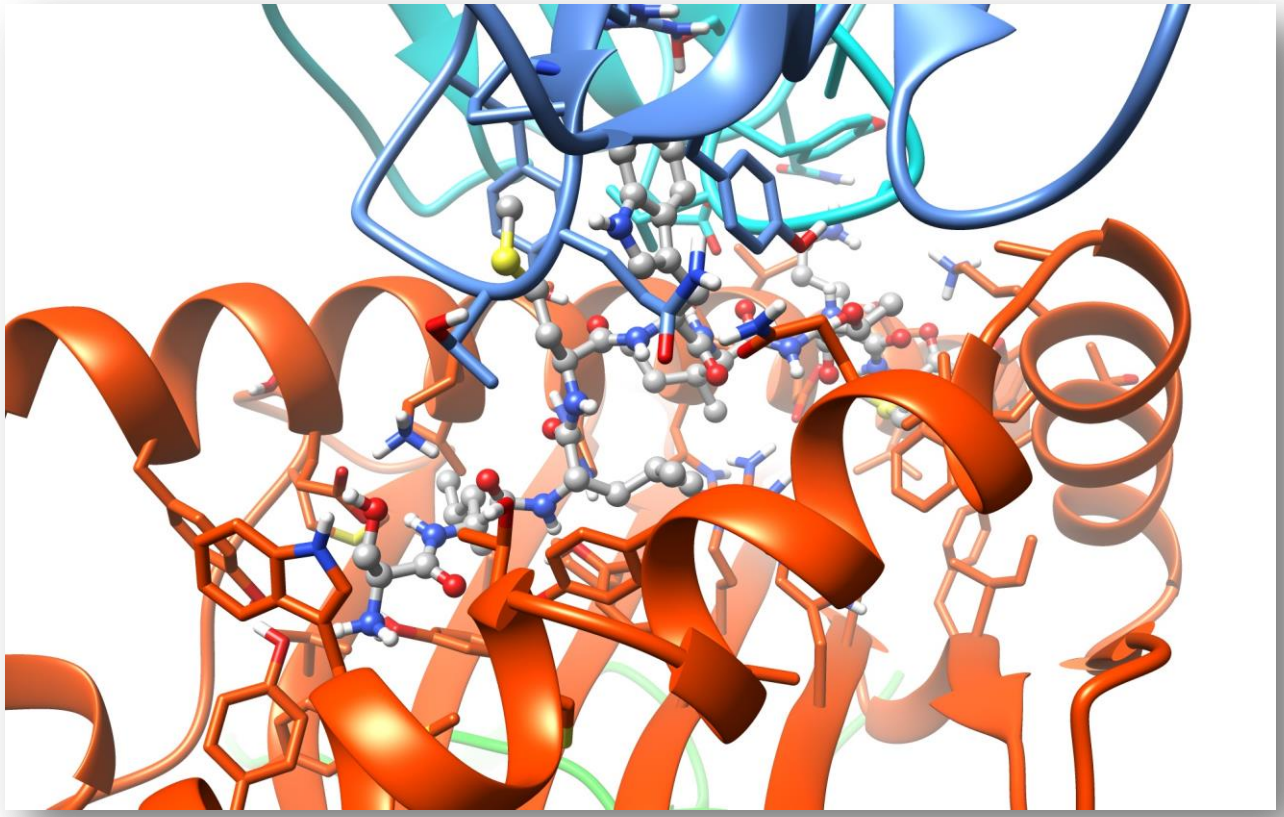


T-cell receptor (TCR)

Major histocompatibility complex (MHC)

Structure-based Protein Engineering

How to use molecular mechanics for *in silico* protein engineering?

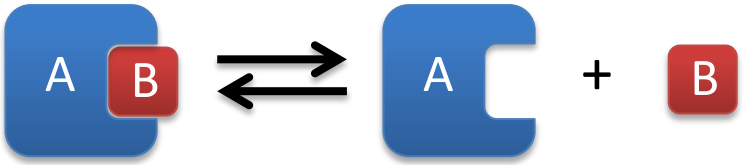


Visually: apparently “important” interactions everywhere

Need for a physics-based method to quantitatively estimate the importance of each residue/interaction

Structure-based Protein Engineering

Link between experiment and modeling

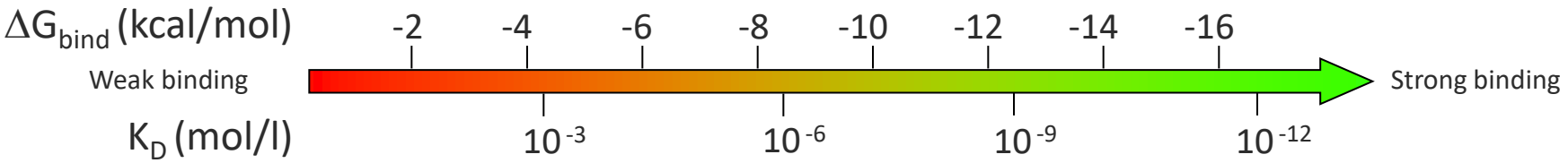


$$K_D = \frac{[A]\ [B]}{[AB]}$$

K_D : dissociation constant

Accessible by computer-aided methods

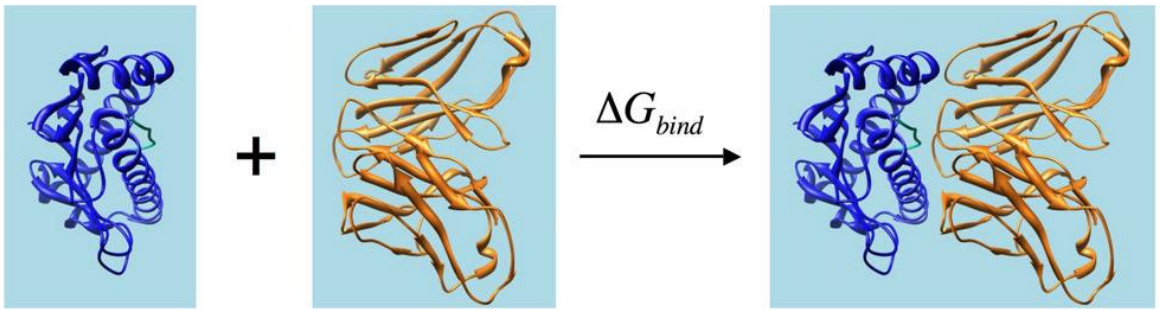
$$\Delta G_{bind} = RT \ln(K_D) = \Delta H - T\Delta S$$



Structure-based Protein Engineering

Calculating ΔG_{bind} by Molecular Mechanics – Generalized Born Surface Area

MM-GBSA:

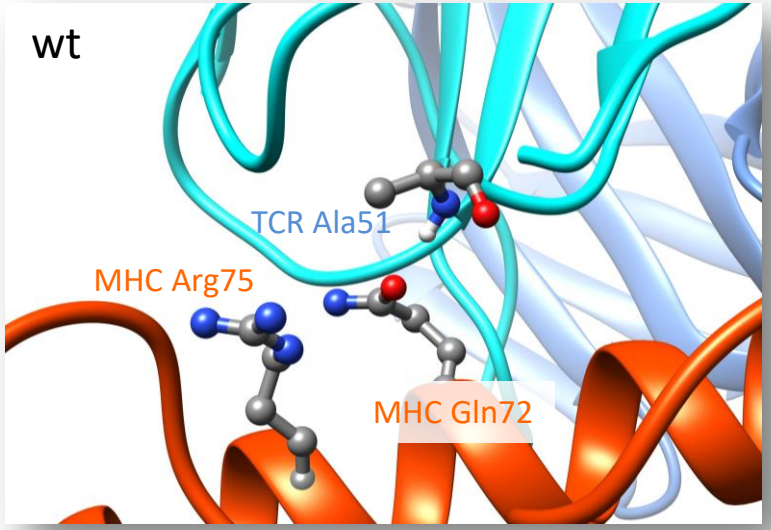


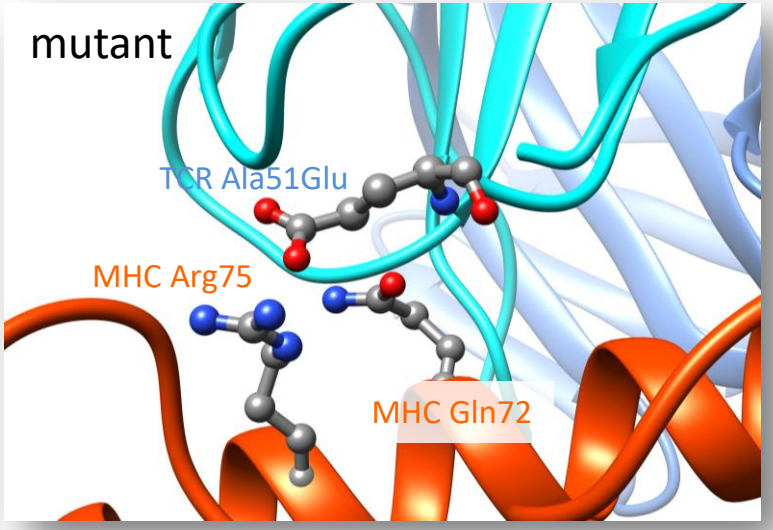
Zoete, V., Meuwly, M., & Karplus, M. *Proteins*, **2005**, *61*, 79–93.

Zoete, V.*, Meuwly, M.* *J. Comput. Chem.*, **2006**, *27*, 1843–1857.

Structure-based Protein Engineering

Using ΔG_{bind} to select mutations for experimental assay





MM-GBSA → DG_{bind}^{wt}

MM-GBSA → DG_{bind}^{mutant}

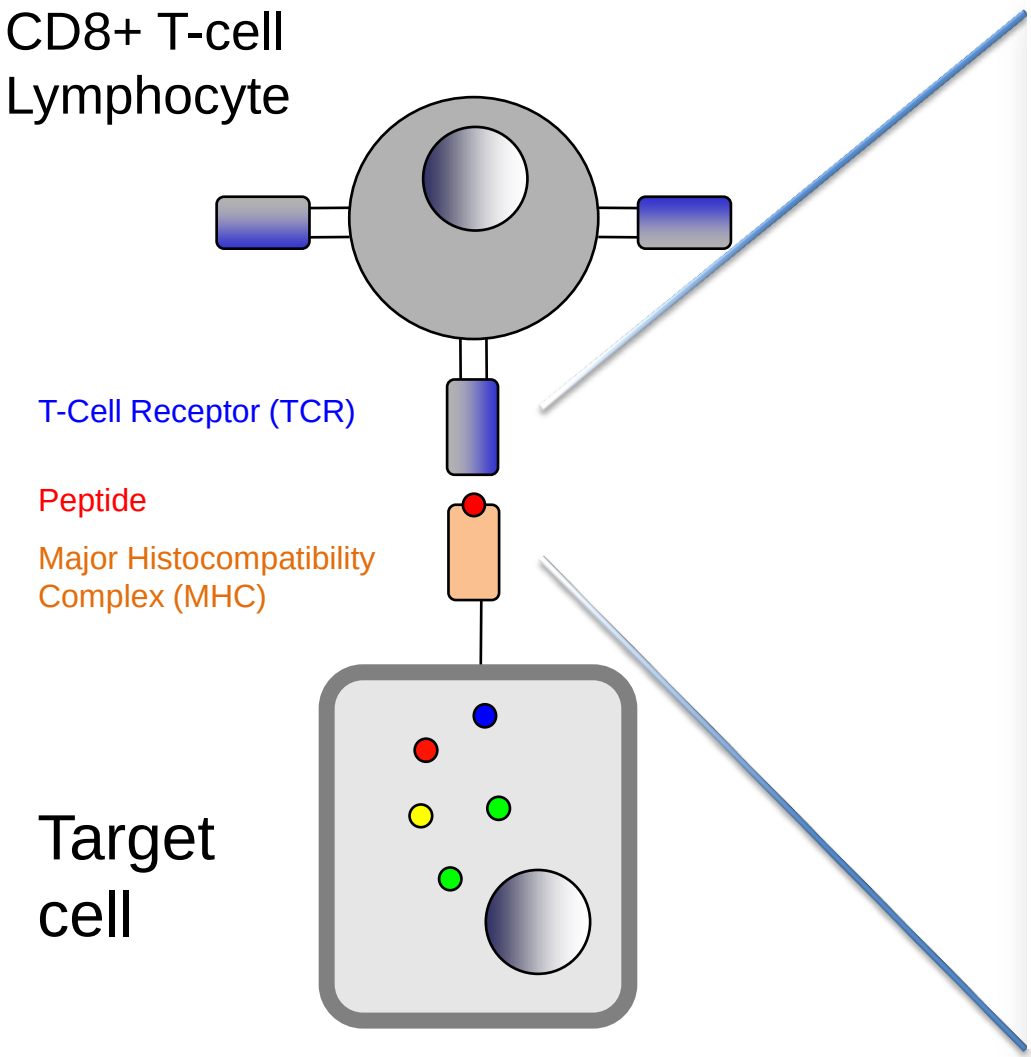
$$DDG_{bind} = DG_{bind}^{mutant} - DG_{bind}^{wt}$$

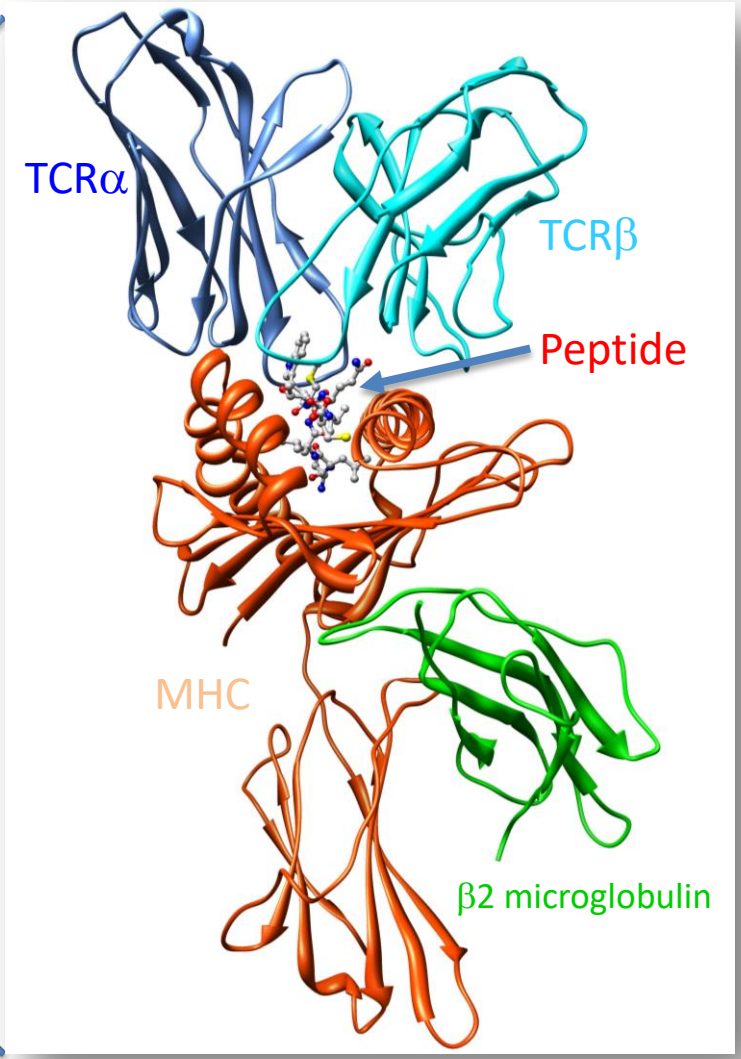
< 0 : selected for experiment

> 0 : rejected

Zoete, V., Irving, M. B., & Michielin, O. MM-GBSA binding free energy decomposition and T cell receptor engineering. *J. Molec. Rec.*, **2010**, *23*, 142–152.

Computer-aided Protein Engineering of TCR

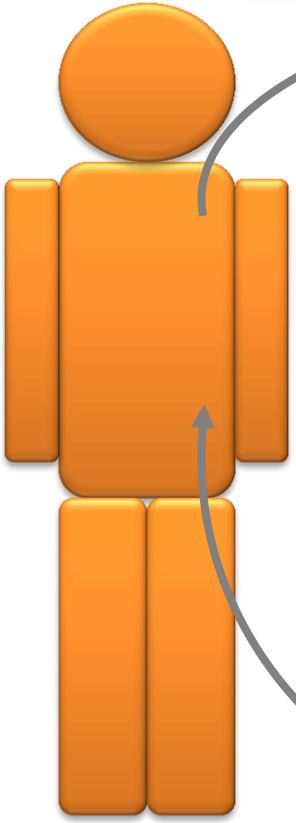




Computer-a f TCR

ive cell therapy

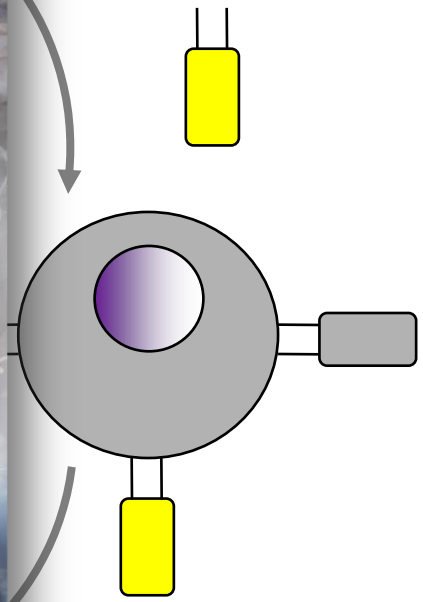
T lymph
extracti



Promis
Morgar
Johnso
Robbin
Phan, G
Hinrich
Rosenb
~ 45%
~ 20%

Reinfus

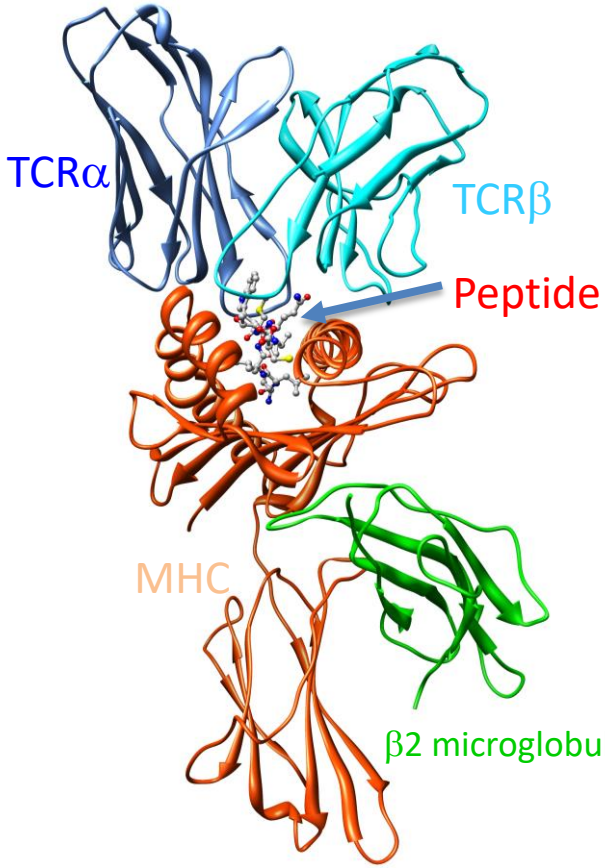
Transfection of efficient TCR

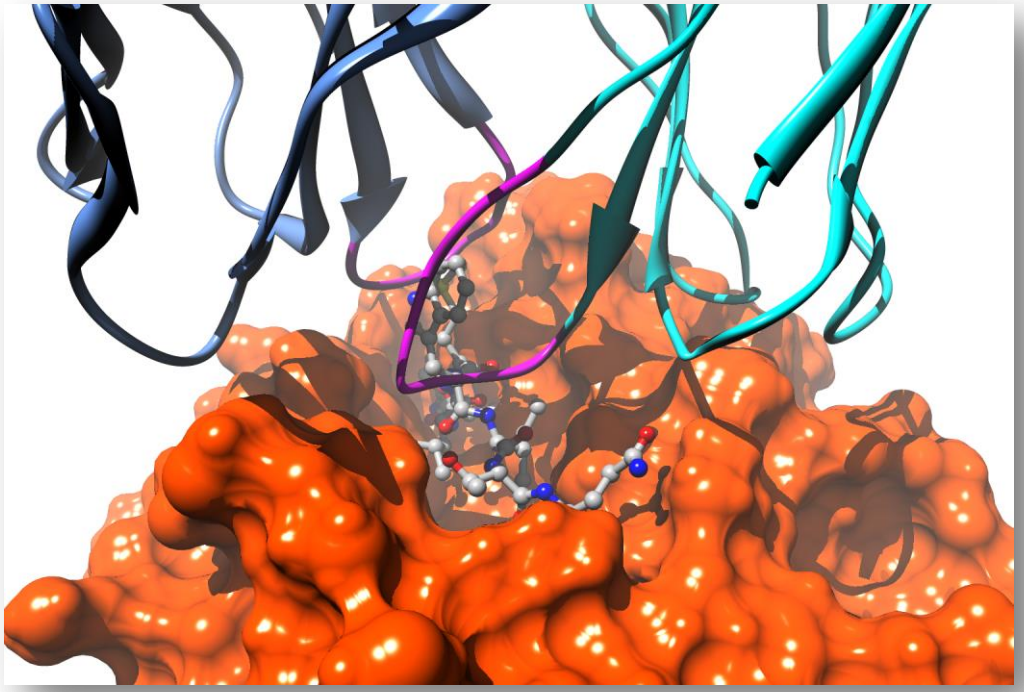


vitro expansion

Computer-aided Protein Engineering of TCR

Sequence modifications targeting CDR3

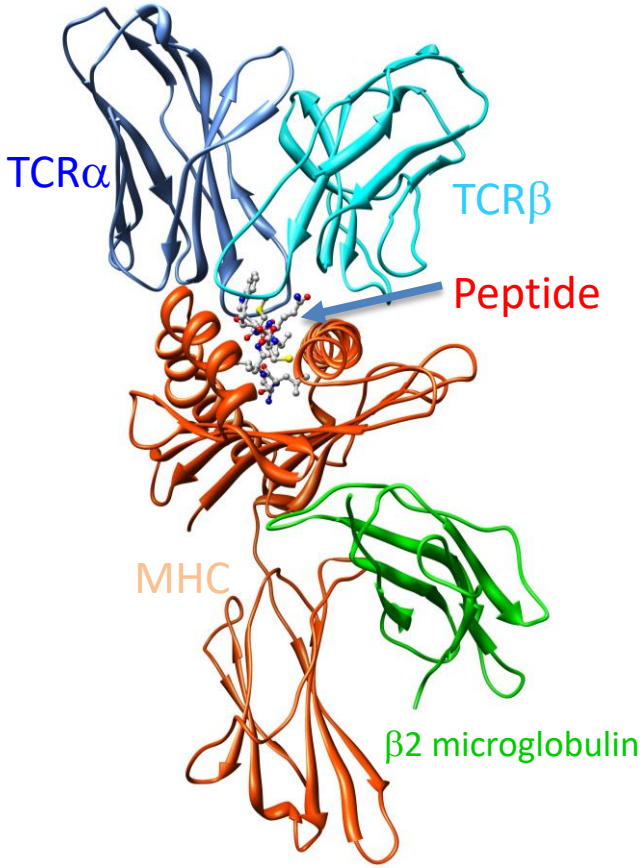


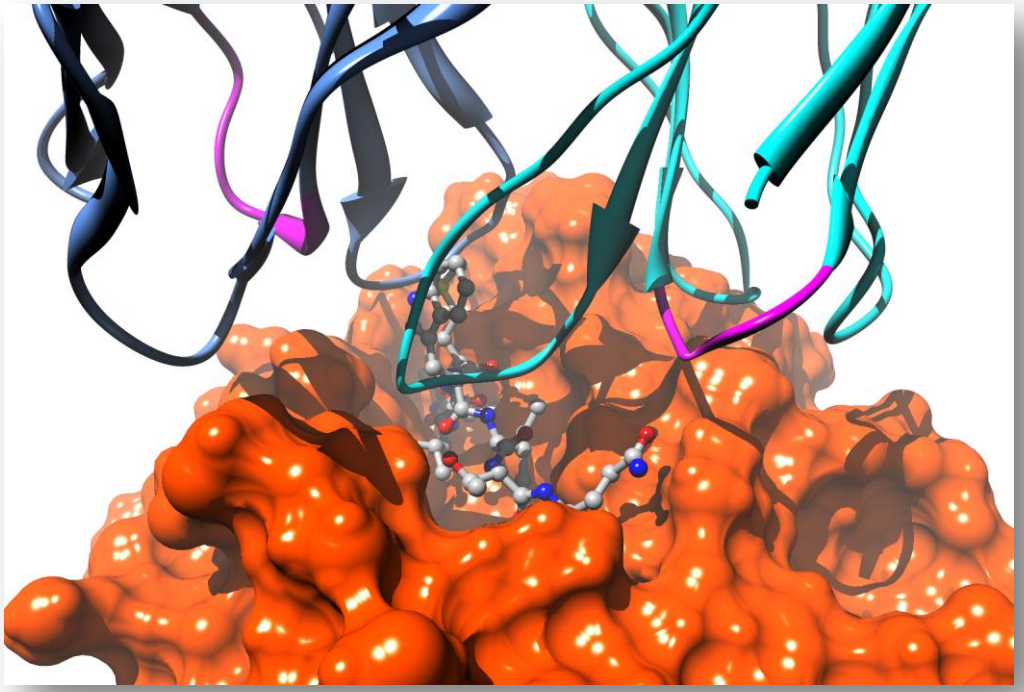


CDR3, in contact with MHC and peptide

Computer-aided Protein Engineering of TCR

Sequence modifications targeting CDR3, CDR1



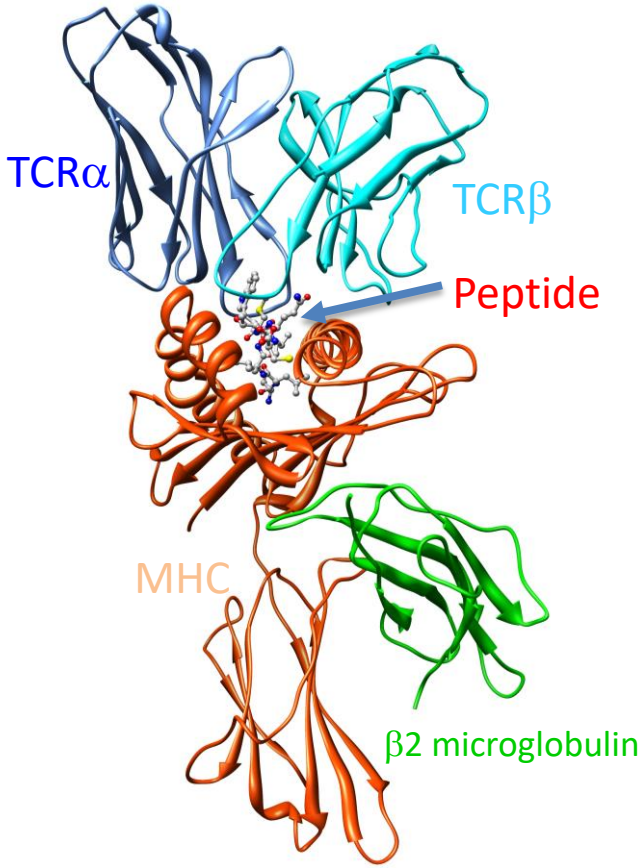


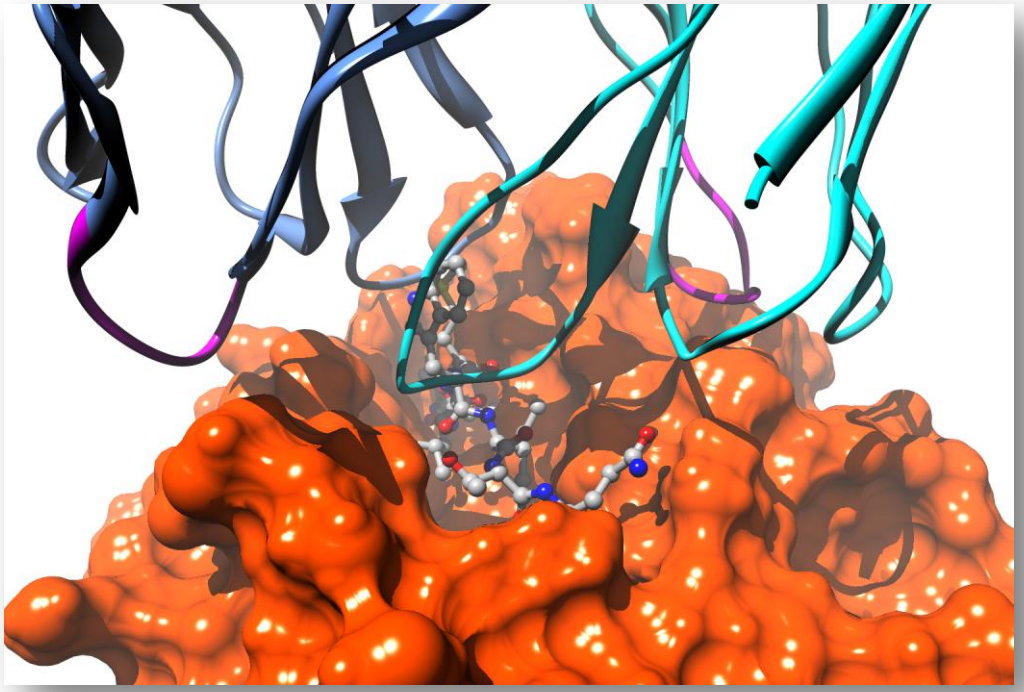
CDR3, in contact with MHC and peptide

CDR1, mainly in contact with MHC

Computer-aided Protein Engineering of TCR

Sequence modifications targeting CDR3, CDR1 and CDR2





CDR3, in contact with MHC and peptide
CDR1, mainly in contact with MHC
CDR2, mainly in contact with MHC

Computer-aided Protein Engineering of TCR

3D structure of the wild-type TCR-pMHC complex

MD simulation
MM-GBSA

DG_{bind} for wt TCR
& structural data

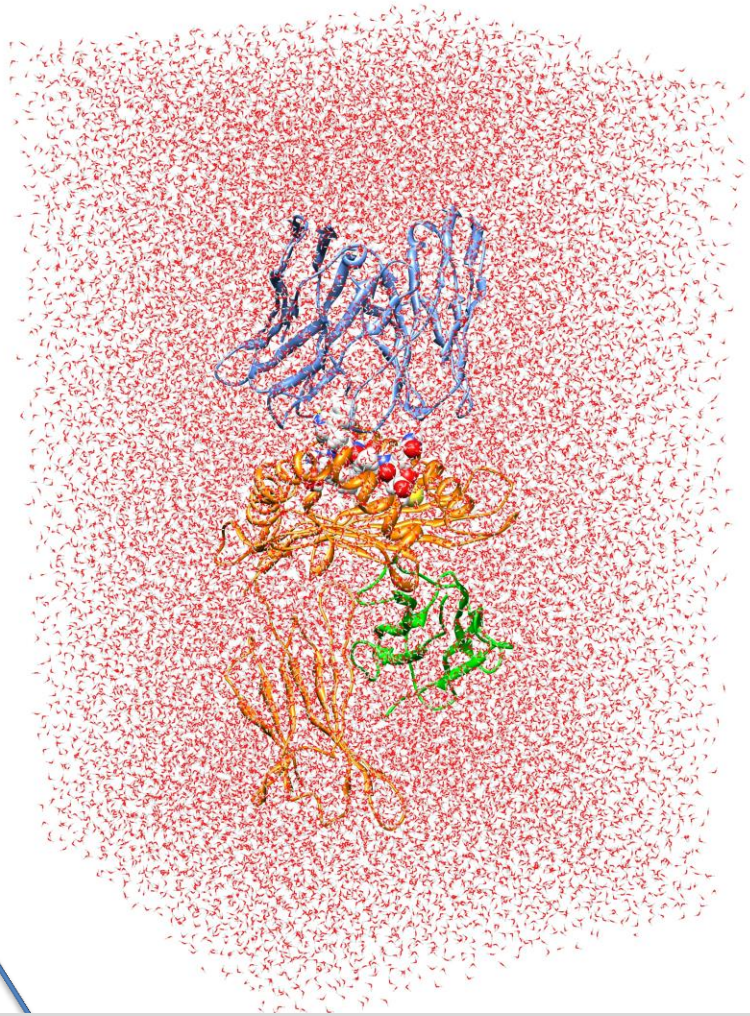
Rotamer library

3D structural models of possible TCR mutations

MD simulation
MM-GBSA

DDG_{bind} for TCR mutations

Mutations selected for expression, purification and experimental testing



Zoete, V.*, & Michielin, O.* *Proteins*, **2007**, *67*, 1026–1047.
Zoete, V., Irving, M. B., & Michielin, O., *J. Molec. Rec.*, **2010**, *23*, 142–152.

Computer-aided Protein Engineering of TCR

3D structure of the wild-type TCR-pMHC complex

MD simulation
MM-GBSA

DG_{bind} for wt TCR
& structural data

Rotamer library

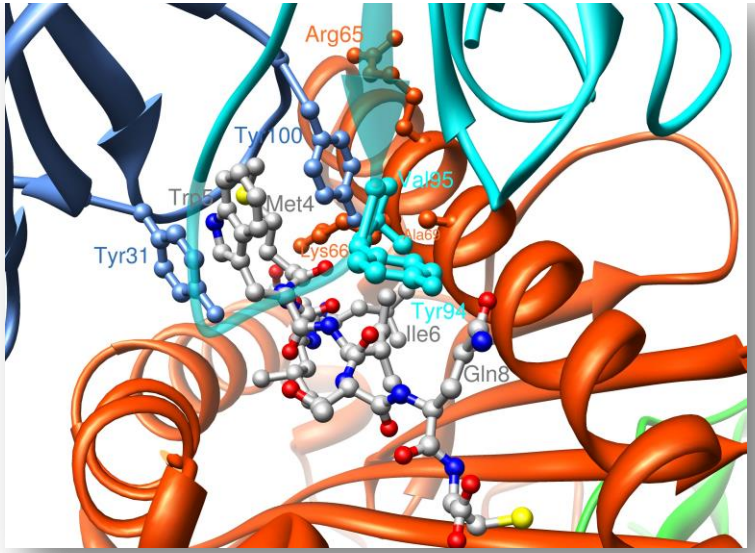
3D structural models of possible TCR mutations

MD simulation
MM-GBSA

DDG_{bind} for TCR mutations

Mutations selected for expression, purification and experimental testing

Residue	E_{vdW}	E_{elec}	$\Delta G_{desolv,elec}$	$\Delta G_{desolv,np}$	ΔG_{bind}^{res}
Glu29	-2.12	-58.92	71.25	-0.50	9.72
Asp55	-0.34	-56.52	59.24	-0.19	2.18
Arg93	-1.25	34.05	-30.60	-0.07	2.13
Gln95	-2.56	-4.37	8.26	-0.52	0.81
…					
Gly96	-2.30	-0.25	0.76	-0.20	-2.00
Ile53	-1.94	1.83	-1.77	-0.51	-2.39
Ser53	-1.22	-5.01	4.28	-0.47	-2.43
Gly98	-2.29	-5.26	5.28	-0.42	-2.69
Gln51	-2.09	-3.04	2.66	-0.29	-2.77
Tyr94	-1.84	1.02	-2.00	-0.18	-3.01
Val95	-3.18	-3.09	2.86	-0.39	-3.81
Tyr31	-5.25	-0.52	1.52	-0.54	-4.80
Tyr100	-5.07	-4.74	5.29	-0.72	-5.24



Computer-aided Protein Engineering of TCR

3D structure of the wild-type TCR-pMHC complex

MD simulation
MM-GBSA

DG_{bind} for wt TCR
& structural data

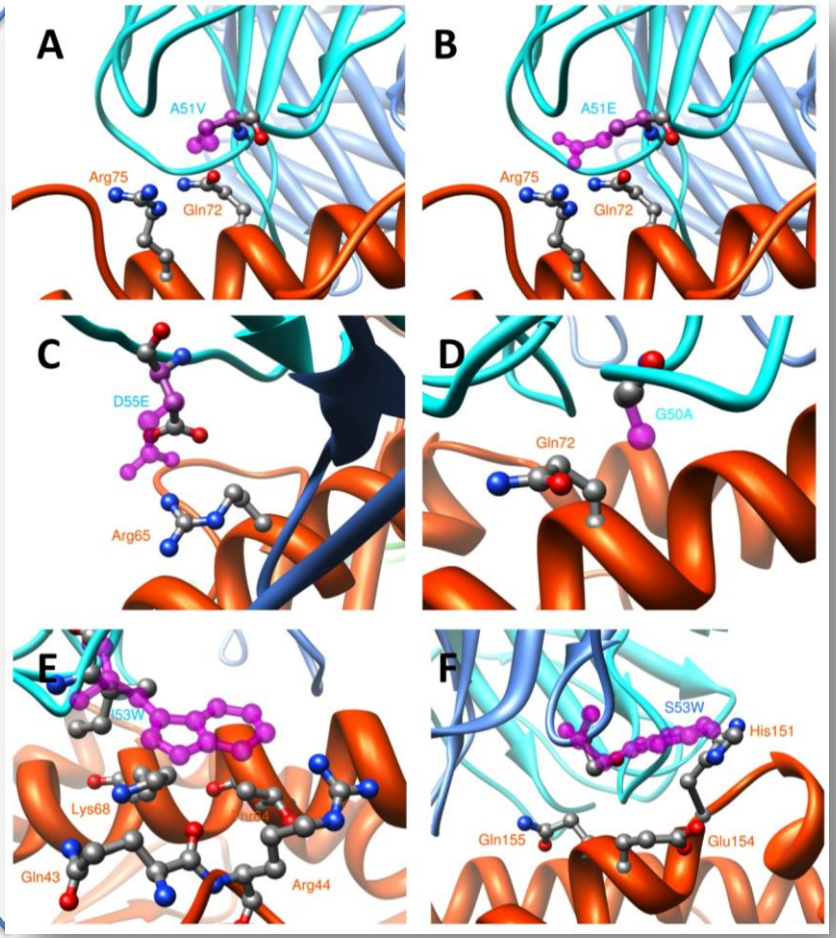
Rotamer library

3D structural models of possible TCR mutations

MD simulation
MM-GBSA

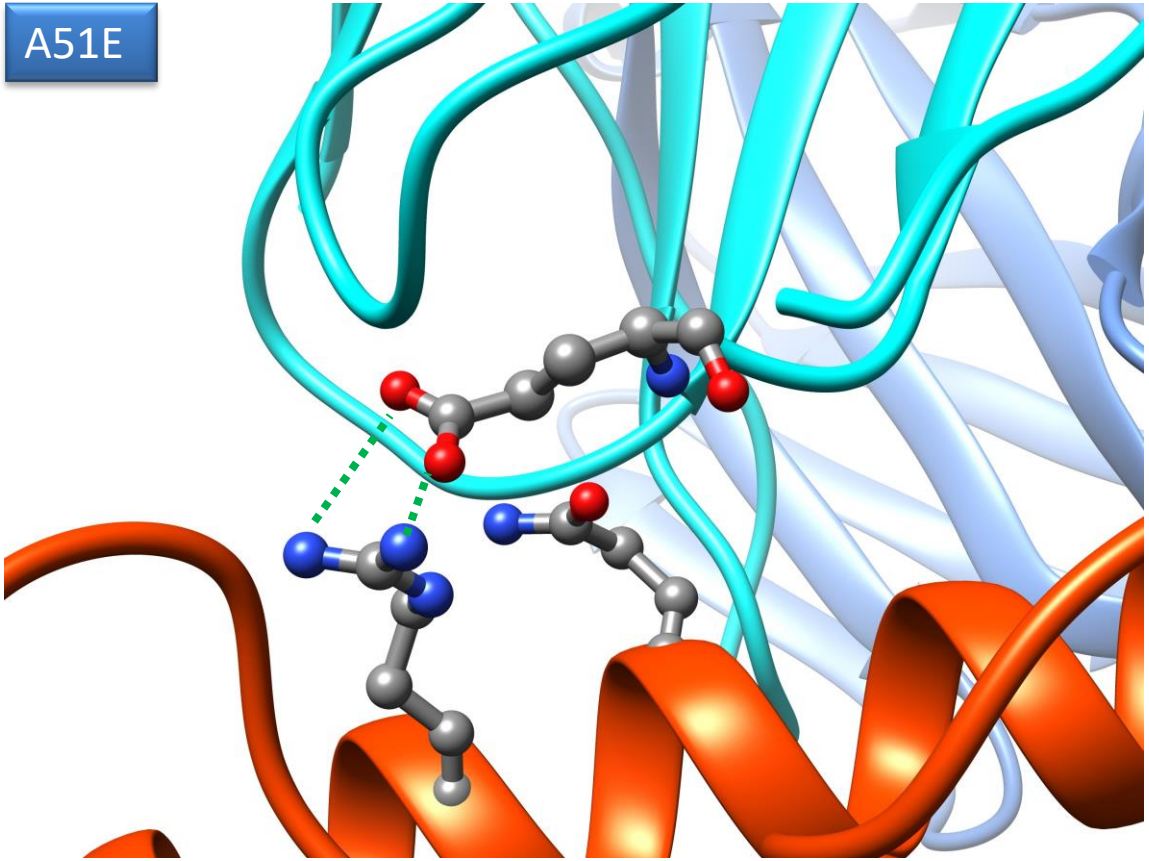
DDG_{bind} for TCR mutations

Mutations selected for expression, purification and experimental testing



Targeting Melanoma Epitope NY-ESO1/HLA-A2

Increasing affinity



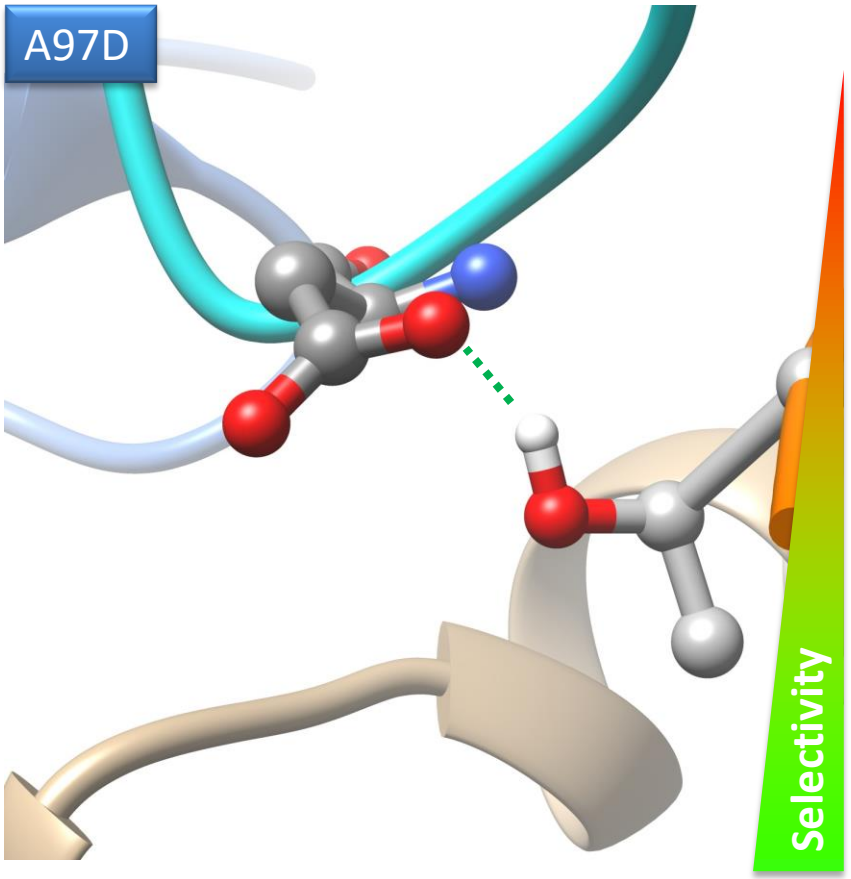
Gain in binding free energy:
-7.3 kcal/mol

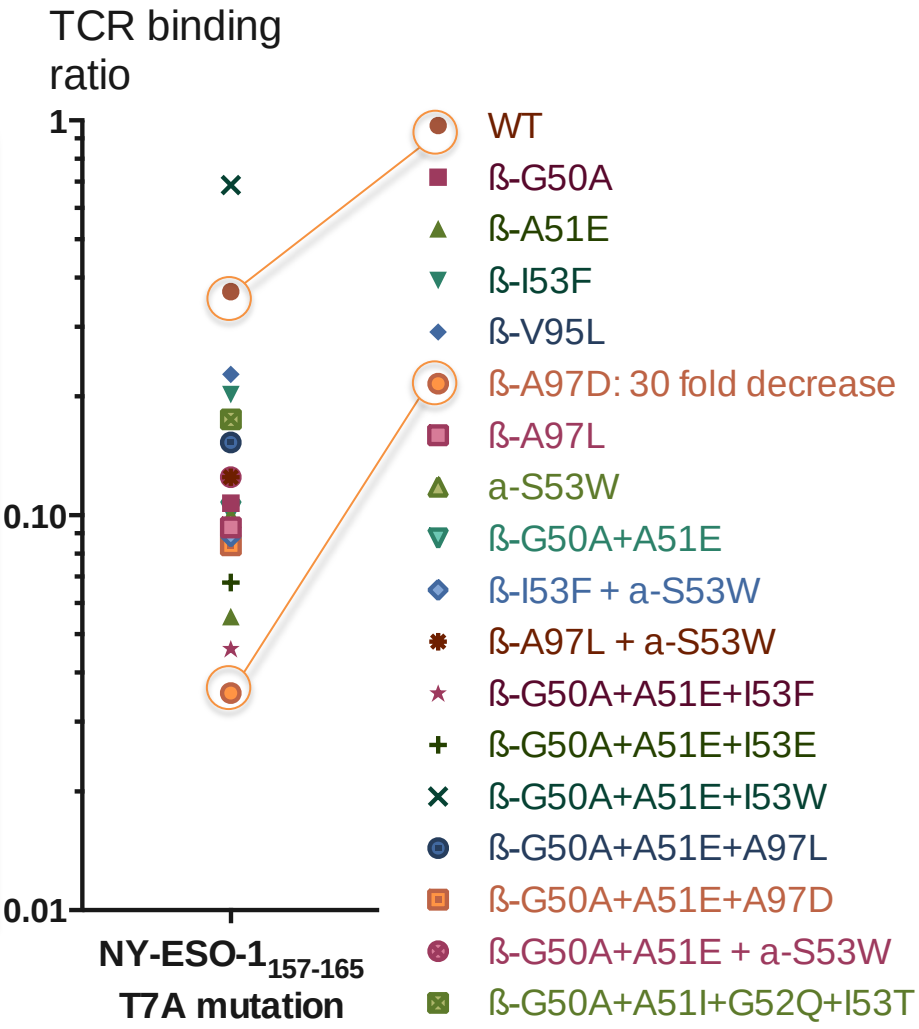
Irving, M.[1], Zoete, V.[1], Hebeisen, M.[1], Schmid, D., Baumgartner, P., Guillaume, P., Romero, P., Speiser, D., Luescher, I., Rufer, N., Michielin, O. *J. Biol. Chem.*, **2012**, *287*, 23068–23078.

Zoete, V., Irving, M., Ferber, M., Cuendet, M. A., & Michielin, O. *Frontiers in Immunology*, **2013**, *4*, 268.

Targeting Melanoma Epitope NY-ESO1/HLA-A2

Increasing selectivity





Computer-aided Protein Engineering of TCR

3D structure of the wild-type TCR-pMHC complex

MD simulation
MM-GBSA

DG_{bind} for wt TCR
& structural data

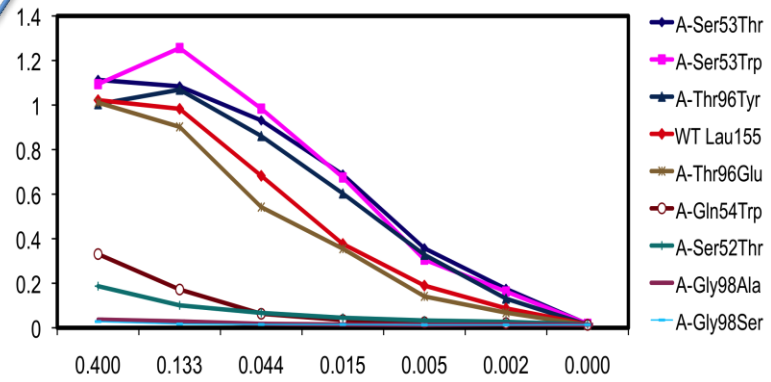
Rotamer library

3D structural models of possible TCR mutations

MD simulation
MM-GBSA

DDG_{bind} for TCR mutations

Mutations selected for expression, purification and experimental testing



	CDR2								CDR3				
	48	49	50	51	52	53	54	55	93	94	95	96	97
	S	V	G	A	G	I	T	D	S	Y	V	G	A
VAL49ILE	S	I	G	A	G	I	T	D	S	Y	V	G	A
GLY50VAL	S	V	V	A	G	I	T	D	S	Y	V	G	A
GLY50ALA	S	V	A	A	G	I	T	D	S	Y	V	G	A
ALA51GLU	S	V	G	E	G	I	T	D	S	Y	V	G	A
50ALA51GLU	S	V	A	E	G	I	T	D	S	Y	V	G	A
ALA51ASP	S	V	G	D	G	I	T	D	S	Y	V	G	A
ALA51VAL	S	V	G	V	G	I	T	D	S	Y	V	G	A
50ALA51ASP	S	V	A	D	G	I	T	D	S	Y	V	G	A
GLY52GLN	S	V	G	A	Q	I	T	D	S		V	G	A
ILE53PHE	S	V	G	A	G	F	T	D	S	Y	V	G	A
ILE53TRP	S	V	G	A	G	W	T	D	S	Y	V	G	A
ILE53GLU	S	V	G	A	G	E	T	D	S	Y	V	G	A
ASP55GLU	S	V	G	A	G	I	T	E	S	Y	V	G	A
TYR94ASN	S	V	G	A	G	I	T	D	S	N	V	G	A
VAL95LEU	S	V	G	A	G	I	T	D	S	Y	L	G	A
GLY96SER	S	V	G	A	G	I	T	D	S	Y	V	S	A
ALA97VAL	S	V	G	A	G	I	T	D	S	Y	V	G	V
ALA97LEU	S	V	G	A	G	I	T	D	S	Y	V	G	L

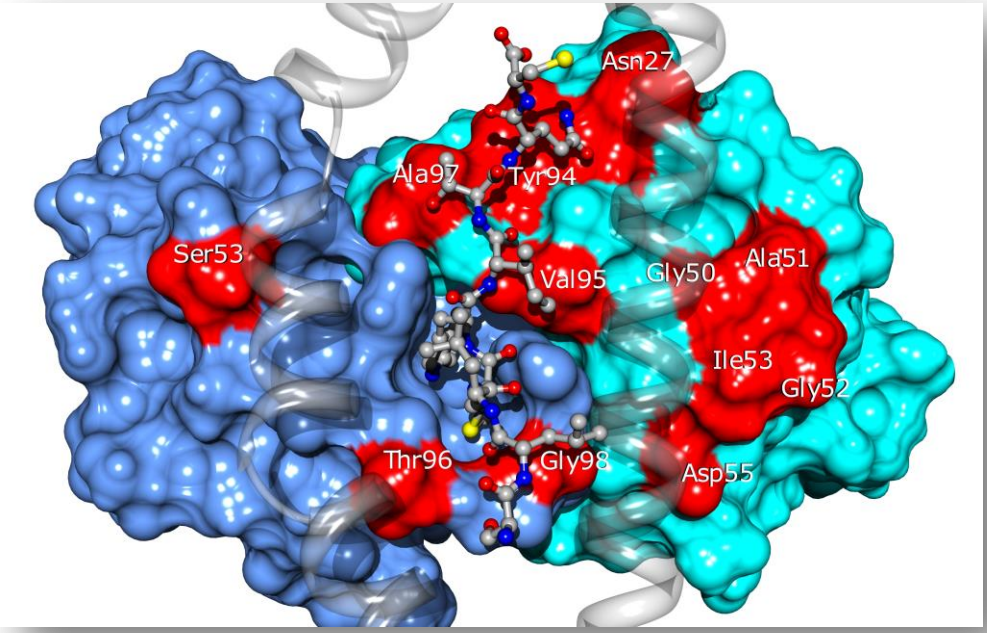
Outcome – Targeting Melanoma Epitope NY-ESO1/HLA-A2

- 24 single/double mutants tested (M. Irving)

- 13 (54 %) were more active than the wt TCR

- up to 56-fold increase for single mutations

- 150-fold increase for TCR Vβ G50A/A51E/A97L + Vα S53W



Outcome – Targeting Melanoma Epitope NY-ESO1/HLA-A2

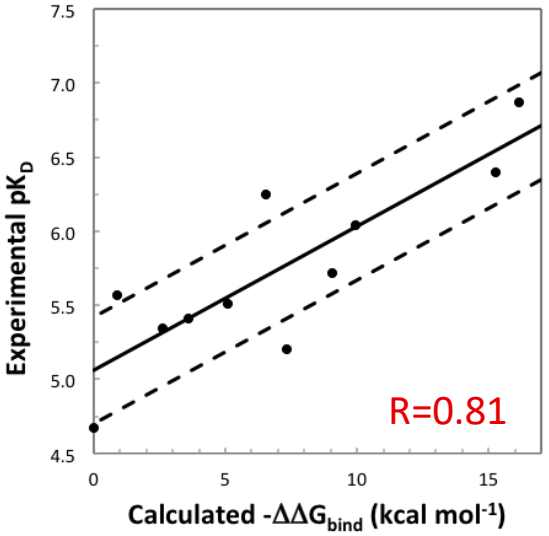
- 24 single/double mutants tested (M. Irving)

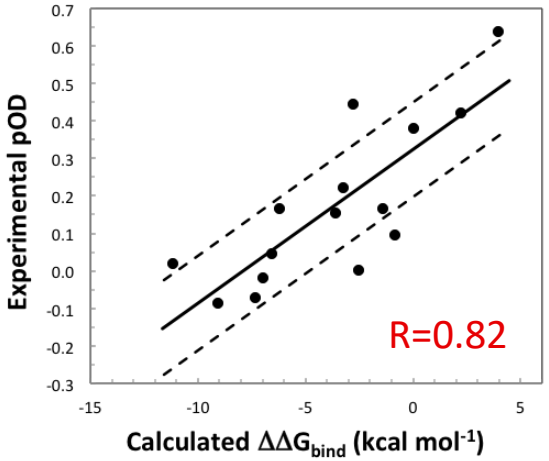
- 13 (54 %) were more active than the wt TCR

- up to 56-fold increase for single mutations

- 150-fold increase for TCR Vβ G50A/A51E/A97L + Vα S53W

- good correlation between calculated binding free energies and experimental results





Irving, M.[1], Zoete, V.[1], Hebeisen, M.[1], Schmid, D., Baumgartner, P., Guillaume, P., Romero, P., Speiser, D., Luescher, I., Rufer, N., Michielin, O. Interplay between T cell receptor binding kinetics and the level of cognate peptide presented by major histocompatibility complexes governs CD8+ T cell responsiveness. *J. Biol. Chem.*, **2012**, *287*, 23068–23078.

Zoete, V., Irving, M., Ferber, M., Cuendet, M. A., & Michielin, O. Structure-Based, Rational Design of T Cell Receptors. *Frontiers in Immunology*, **2013**, *4*, 268.

Outcome – Targeting Melanoma Epitope NY-ESO1/HLA-A2

- 24 single/double mutants tested (M. Irving)

- 13 (54 %) were more active than the wt TCR

- up to 56-fold increase for single mutations

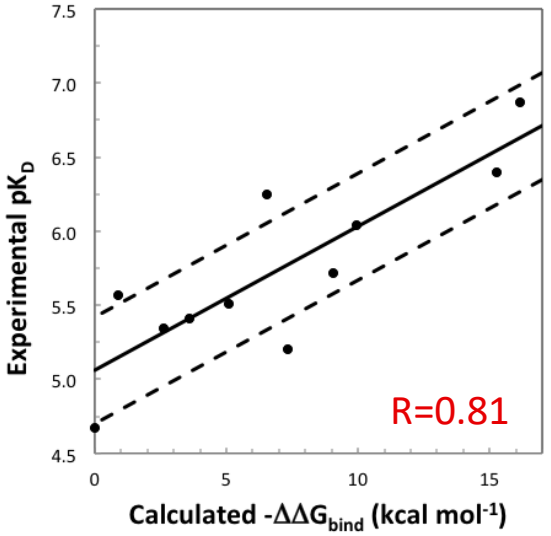
- 150-fold increase for TCR Vβ G50A/A51E/A97L + Vα S53W

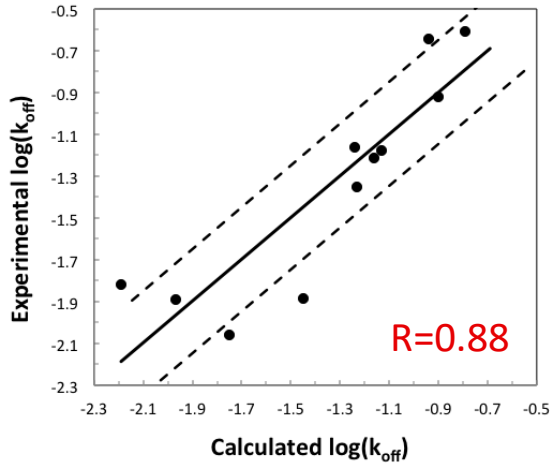
- good correlation between calculated binding free energies and experimental results

- good correlation between calculated energies and experimental k_{off} (R=0.88)

- **unfitted approach**: can be applied to other systems

  e.g. applied to TCR recognizing Melan-A antigen with 73% success rate

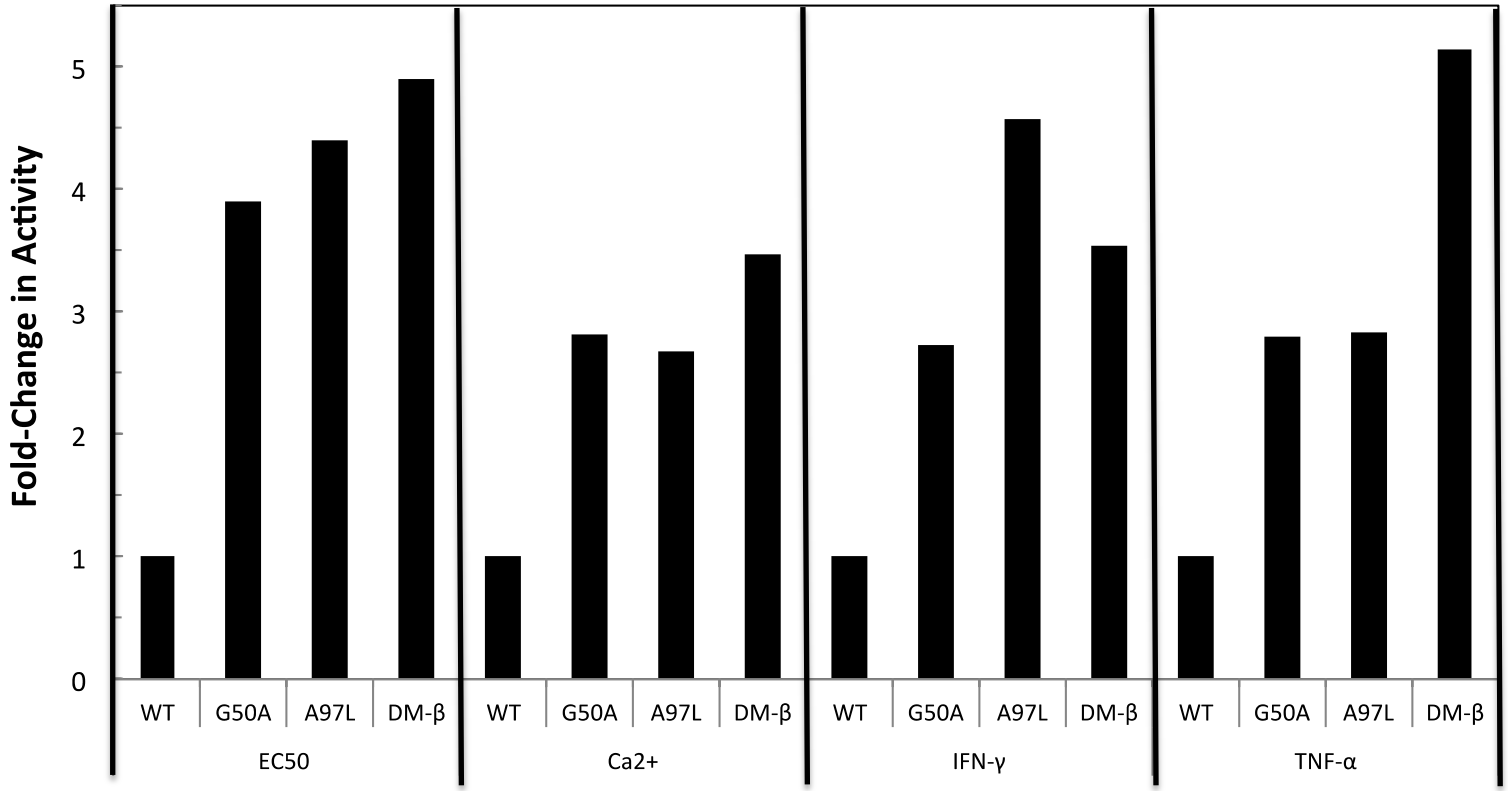




Outcome – Targeting Melanoma Epitope: NY-ESO1/HLA-A2

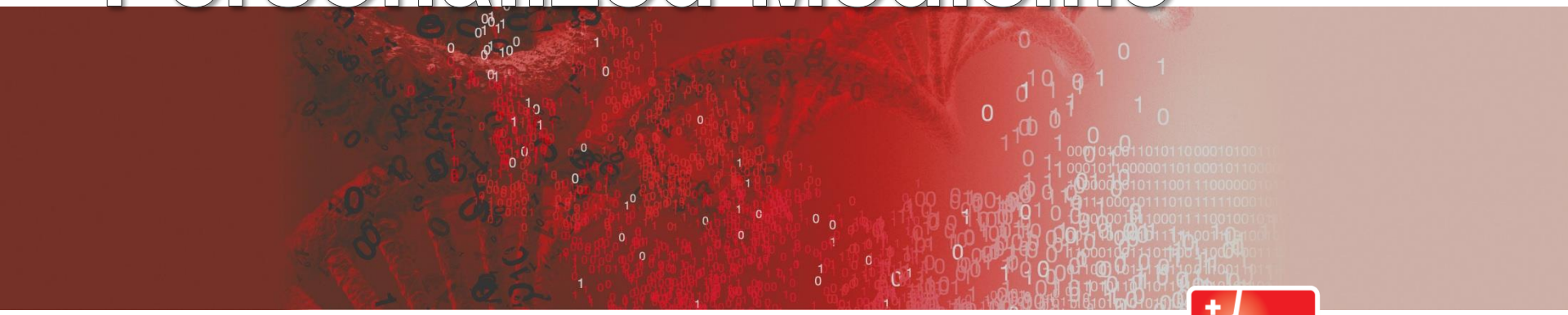
Both T-cell proliferation after antigenic challenge and tumor cell killing were significantly improved

Irving, M.[1], Zoete, V.[1], Hebeisen, M.[1], […] Michielin, O. *J. Biol. Chem.*, **2012**, *287*, 23068–23078.



Mouse model / Clinical trial at CHUV

Protein Engineering
Drug Design
Personalized Medicine



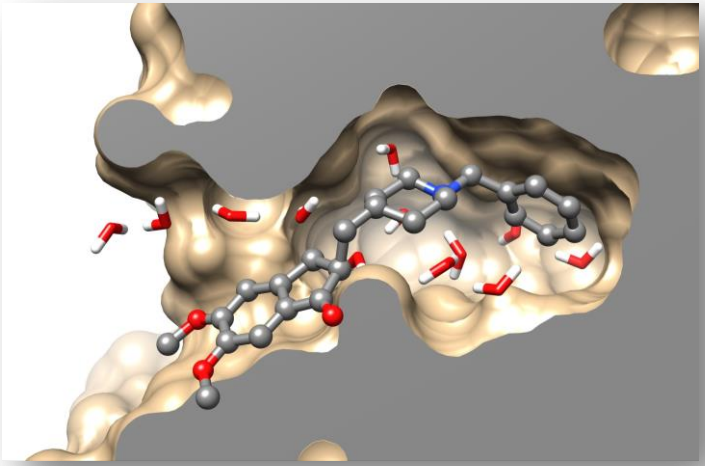
SIB
Swiss Institute of Bioinformatics

elixir SWITZERLAND

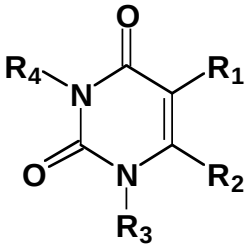
Computer-aided Drug Design

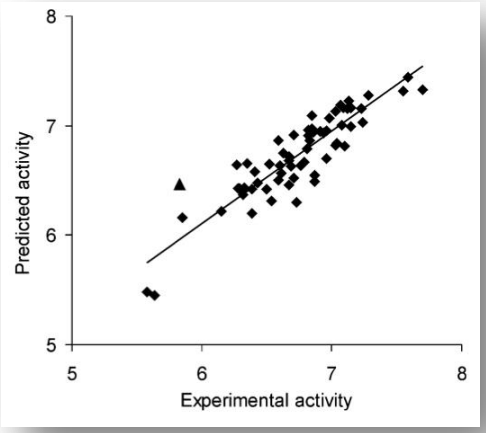
Two main categories of approaches to discover, create, optimize and evaluate active molecules:

- Structure-based approaches. Use the 3D structure of the targeted macromolecule. Ex: Molecular docking.



- Ligand-based approaches. Use the information derived from known ligands. Ex: Quantitative Structure-Activity Relationships (QSAR, machine learning), bioisosteric replacements.

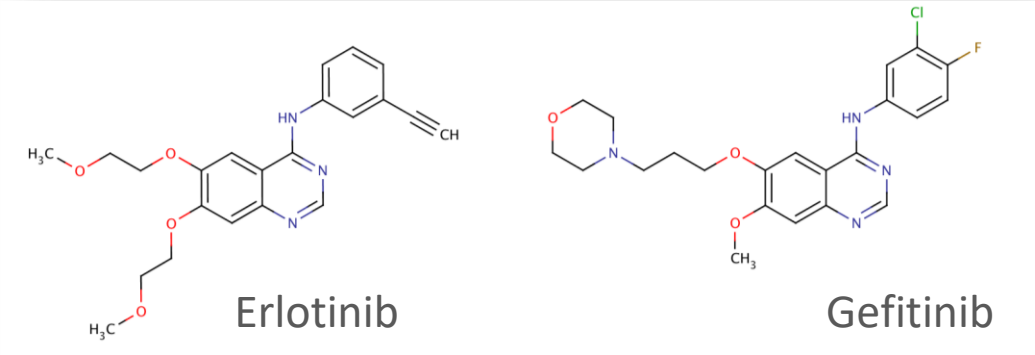




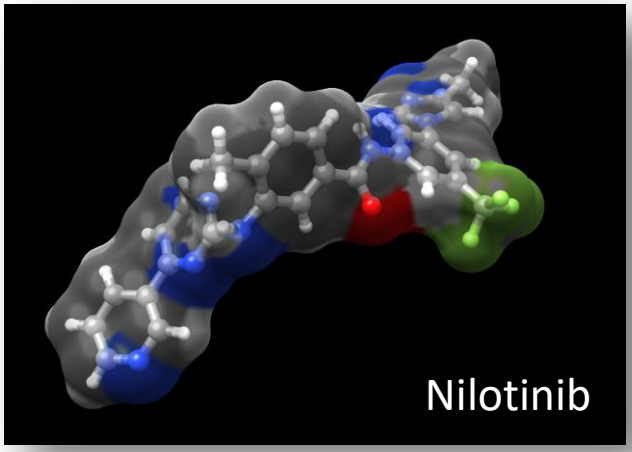
Ligand-based Drug Design

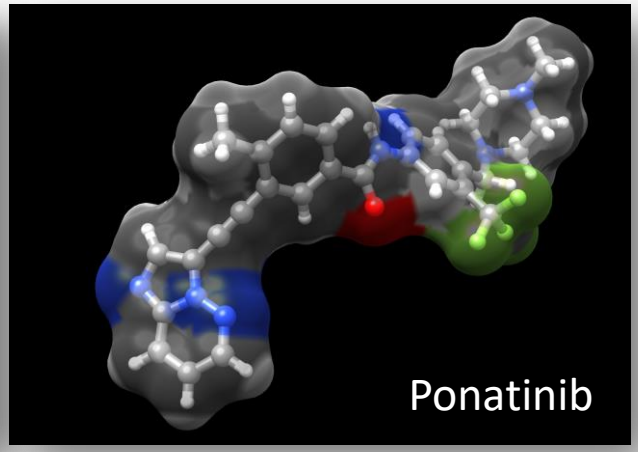
Assumption: if two molecules are very similar, they are likely to be active on the same target

- 2D: Similar by chemical structure



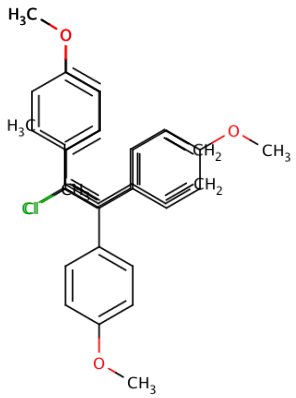
- 3D: Similar by shape (electrostatics and lipophilicity)

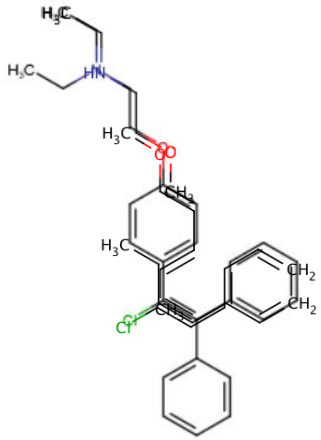




Molecular Similarity

Chemical similarity (2D fingerprints)





Identify molecular features

A=(0, 1 , 0, 1 , 0, 0, 1 , 0, 0, …)

B=(0, 1 , 0, 1 , 0, 0, 1 , 0, **1** , …)

Molecular Similarity

Chemical similarity (2D fingerprints)

The similarity value between molecules A and B is given by the **Tanimoto coefficient** T:

$$T = \frac{c}{a+b+c}$$

, where

a is the count of bits at 1 in molecule A **but not** in molecule B

b is the count of bits at 1 in molecule B **but not** in molecule A

c is the count of bits at 1 in both molecules A **and** B

A=(0, 1, 0, 1, 0, 0, 1, 0, 0, …)

T ranges from 0 for totally different molecules to 1 for identical molecules

B=(0, 1, 0, 1, 0, 0, 1, 0, **1**, …)

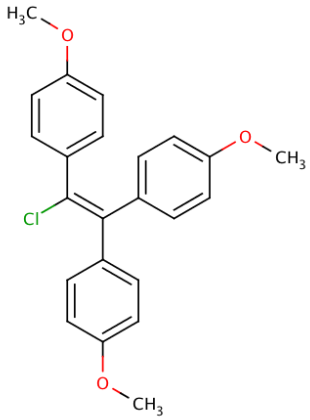
Molecular Similarity

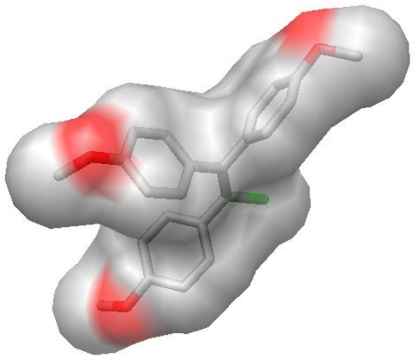
3D similarity (ROCS)

Grant, J.A., Gallardo, M.A., Pickup, B., *J. Comp. Chem.*, **1996**, *17*, 1653.

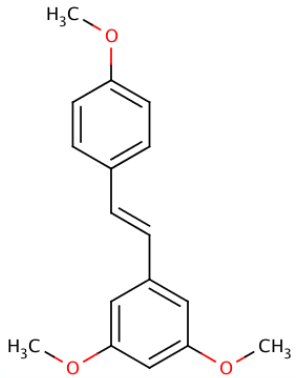
Molecules have similar shape if their volumes overlay well and any volume mismatch is a measure of dissimilarity.

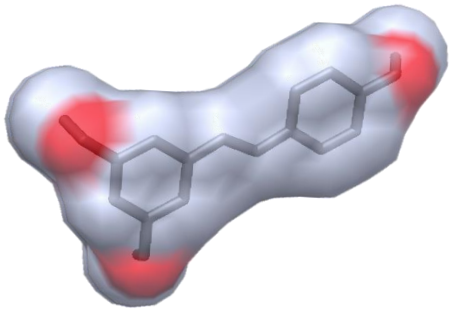
ROCS uses a smooth Gaussian function to represent the molecular volume, so it is possible to rapidly minimize to the best global match.





20 to 40 overlays per second





Similar 3D shape

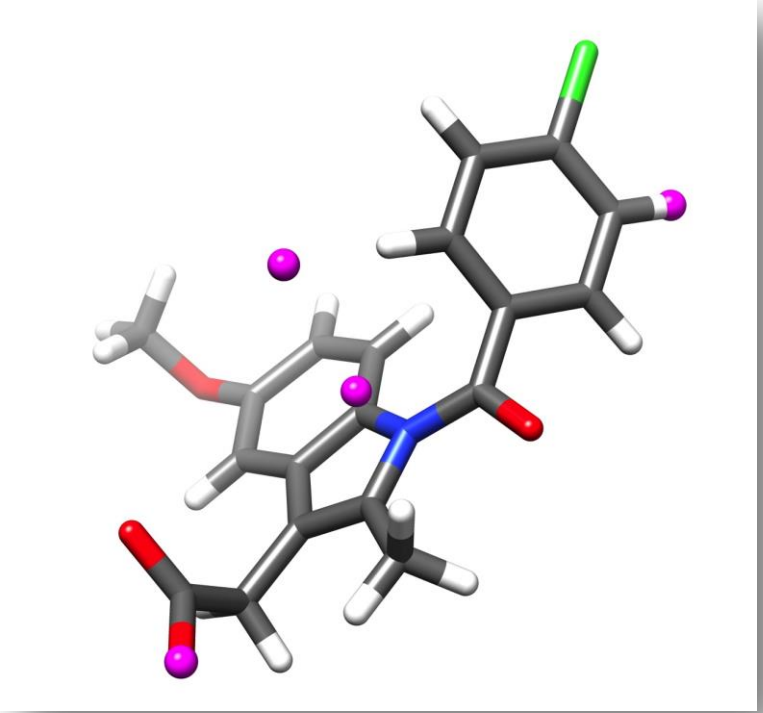
Courtesy of Prof. David Gfeller

Molecular Similarity

3D similarity (Electroshape)

M. S. Armstrong et al., *J. Comput.-aided Mol. Des.*, **2010**, 24, 789-801

Idea: transform a 3D conformation into a 1D vector



1. Place important points (centroids) around the molecule:
- C1, baricenter of all atoms
- C2, furthest atom from C1
- C3, furthest atom from C2
- C4, C5 and C6 are defined by vector cross products

2. Calculate 3 values for each centroid:
- Average of the distance to each atom
- Standard deviation of the distance
- Third moment of the distance

(5.987,

Molecular Similarity

3D similarity (Electroshape)

M. S. Armstrong et al., *J. Comput.-aided Mol. Des.*, **2010**, 24, 789-801

20 conformers, and thus 20 vectors, are calculated for each molecule

Vectors of both compounds are compared using Manhattan distance score

$$\text{Score} = \left(1 + \frac{1}{n}\sum_{1 \le i \le n} \left| x_i^{molA} - x_i^{molB} \right| \right)^{-1}$$

Score ranges from 0 (totally different shapes) to 1 (perfect match)

Advantages:

- independent of molecular orientation
- does not need molecular superposition

Speed: 10,000 comparisons per second

(20 conformers of the first compound against 20 conformers of second compound)

Molecular Similarity

Example of application

Virtual Screening:

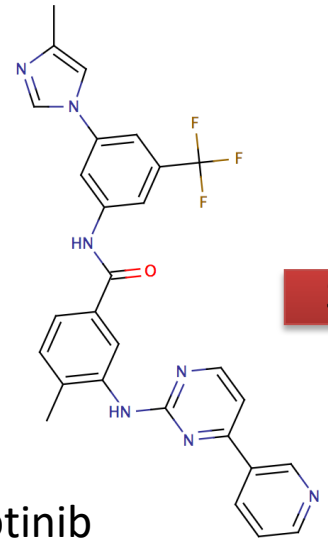
Molecule with **known** activity

Similarity

Library of molecules with **unknown** activities

List of **molecules** possibly active on the same target

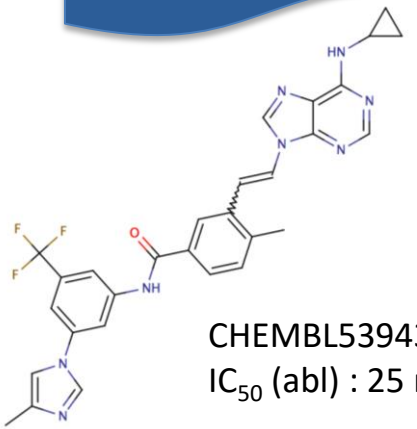
Ex:



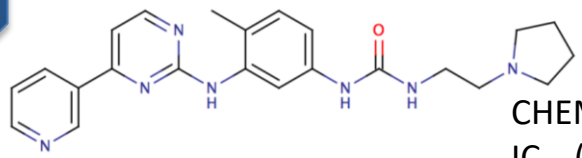
Nilotinib

Similarity

2,000,000 molecules from ChEMBL



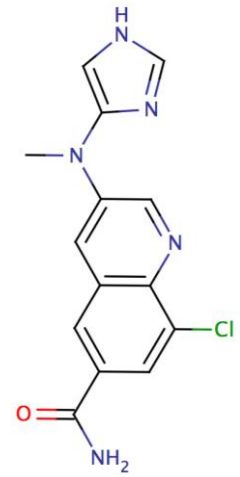
CHEMBL539433
IC_{50} (abl) : 25 nM



CHEMBL363926
IC_{50} (abl) : 8900 nM

Ligand-based CADD – SwissSimilarity.ch

A web tool to perform ligand-based virtual screening



User compound

www.SwissSimilarity.ch

750,000 Bioactive compounds

7,000 Drugs

2D and 3D ligand-based screening approaches

25,400,000 Commercial compounds

205,000,000 Virtual synthesizable compounds

Hits

Online tools

SwissTargetPrediction
SwissADME
…

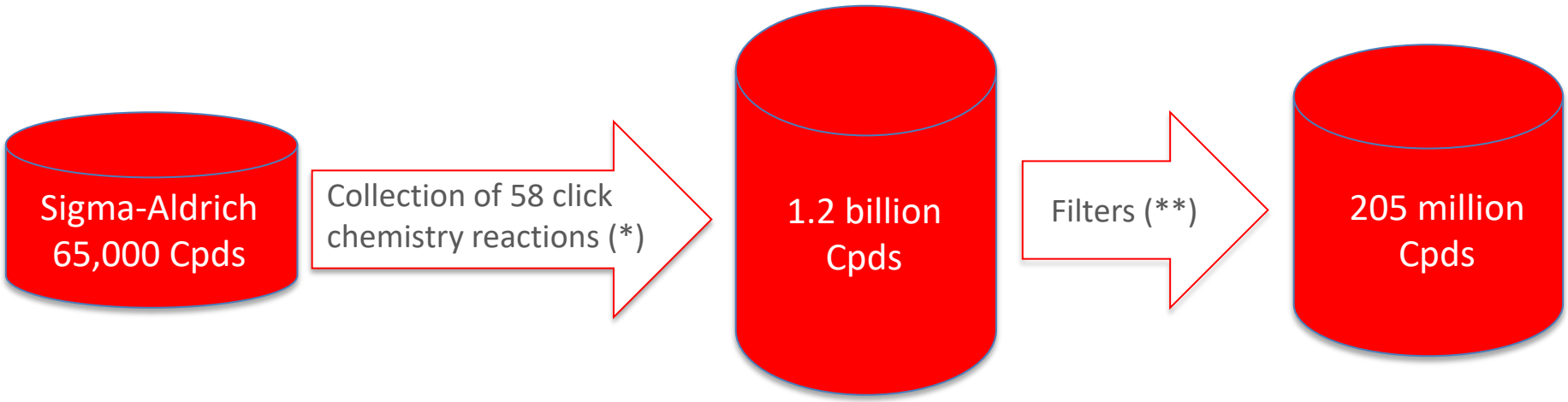
Databases

DrugBank, ChEMBL, ChEBI, ZINC, Vendors
…

Ligand-based CADD – SwissSimilarity.ch

Library of virtual compounds: 205'000'000 **molecules accessible by click chemistry from commercially available reactants**, and filtered for problematic compounds

Zoete V.*, Daina A., Bovigny C. and Michielin O.* SwissSimilarity. A web tool for low to ultra high-throughput ligand-based virtual screening. Under revision in *J. Chem. Inf. Model.*



(*) Hartenfeller, M., Eberle, M., Meier, P., Nieto-Oberhuber, C., Altmann, K.-H., Schneider, G., et al. *J. Chem. Inf. Model.*, **2011**, *51*(12), 3093–3098.

(**) Filters:

- Baell, J. B., & Holloway, G. A. *J. Med. Chem.*, **2010**, *53*(7), 2719–2740.
- Brenk, R., *et al*. *ChemMedChem*, **2008**, *3*(3), 435–444.

Ligand-based CADD – SwissSimilarity.ch

Choose a reference small molecule

Paste a SMILES in this box, or draw the reference molecule

Examples: Clear

Choose a method and a library to screen

Choose a library of small molecules to screen and the screening methods in the list below.

Perform the screening

Submit

(Provide a SMILES before submitting)

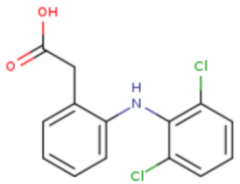
	#	FP2 fingerpri
Approved	1'516	◉
Experimental	4'788	○
Investigational	504	○
Withdrawn	161	○
Nutraceuticals	78	○
Illicit	169	○
Bio		
Ligands from the PDB	19'500	○
ChEMBL (activity<10μM)	177'000	○

Run parameters

Library screened	FDA approved drugs
Screening method	Electroshape
Date	Wed Sep 16 14:41:10 2015

If you publish these results, please cite the SwissSimilarity website.

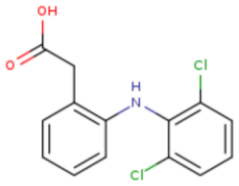
Query Molecule



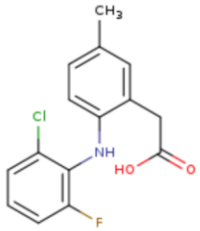
Results

Retrieve data:

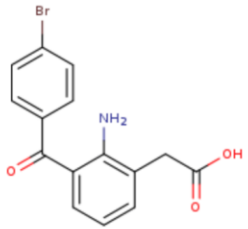
DB00586, Diclofenac
Score : 0.987



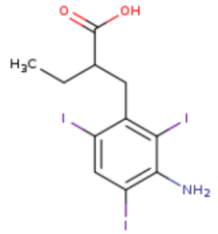
DB01283, Lumiracoxib
Score : 0.918



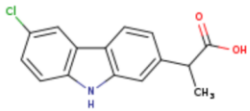
DB00963, Bromfenac
Score : 0.896



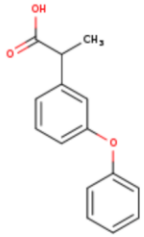
DB08946, Iopanoic acid
Score : 0.885



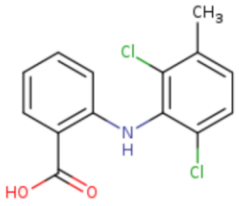
DB00821, Carprofen
Score : 0.882



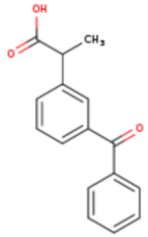
DB00573, Fenoprofen
Score : 0.882



DB00939, Meclofenamic acid
Score : 0.869

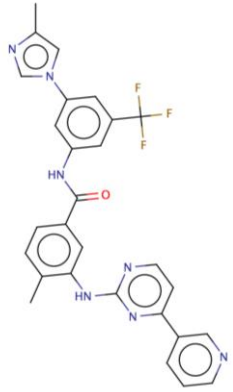


DB01009, Ketoprofen
Score : 0.865

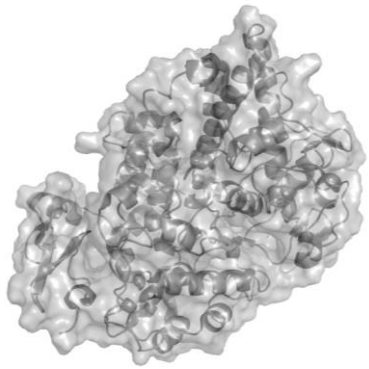


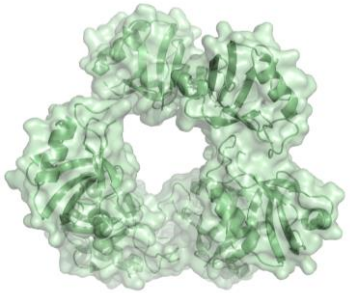
Ligand-based CADD – SwissTargetPrediction.ch

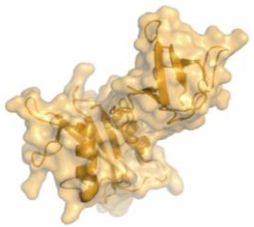
Usual vision: "The effect of a drug is explained by its interaction with one well-identified target". But…

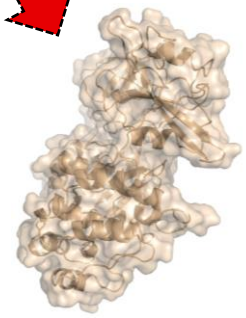


On average 6 targets for FDA approved drugs
Mestres, J. *et al*. Mol Biosyst 2009, 5, 1051–1057.









Primary target

~17% of bioactive small molecules and 10% of FDA approved drugs without known target (ChEMBL, DrugBank)

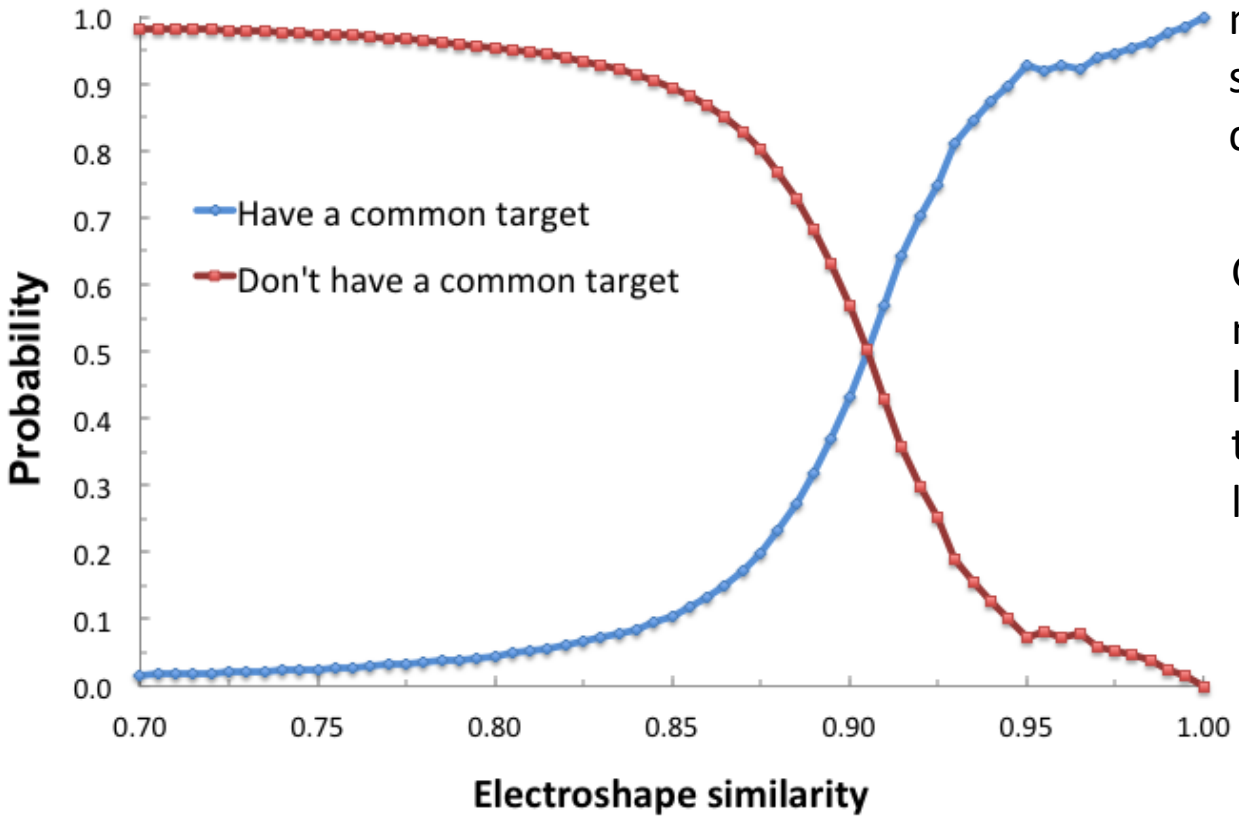
Secondary targets

- Side-effects
- Toxicity
- Drug repurposing

Courtesy of Prof. David Gfeller

Ligand-based CADD – SwissTargetPrediction.ch

Assumption: if two molecules are very similar, they are likely to be active on the same target



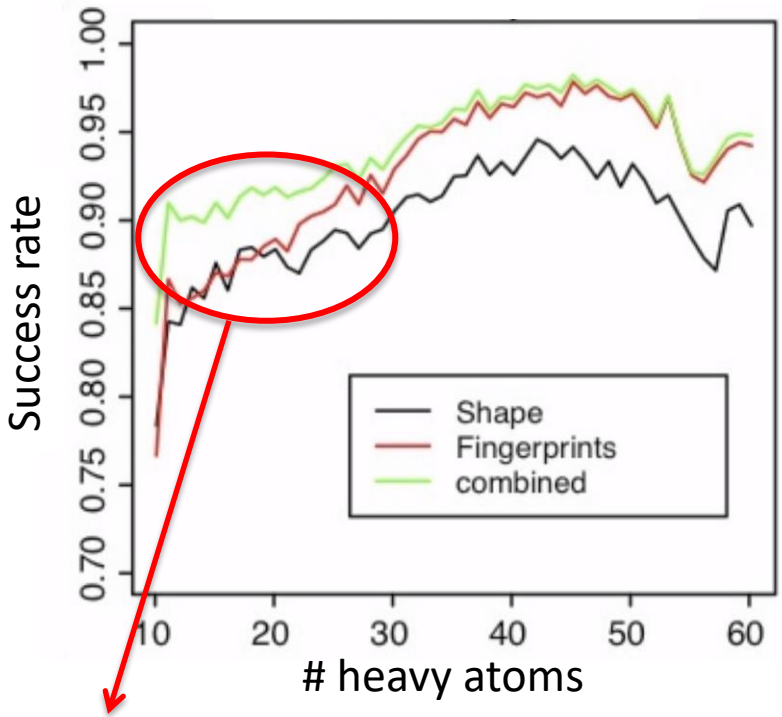
Probability, for a pair of molecules with a given similarity, to be active on a common target

Calculated on 350,000 small molecules having an activity lower than 10 μM on one of the 1654 human targets listed by ChEMBL.

Ligand-based CADD – SwissTargetPrediction.ch

- Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics.* **2013**, *29*, 3073–3079.
- Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: a Web Server for Target Prediction of Bioactive Small Molecules. *Nucleic Acids Res.* **2014**, *42(Web Server issue)*, W32-8.
- Gfeller D, Zoete V. Protein homology reveals new targets for bioactive small molecules. *Bioinformatics*. **2015**, *31*, 2721-7.

Predictions based on comparisons
excluding similar molecules



Dual scoring function helps making predictions for drug-like first-in-class compounds

Ligand-based CADD – SwissTargetPrediction.ch

- Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics.* **2013**, *29*, 3073–3079.
- Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: a Web Server for Target Prediction of Bioactive Small Molecules. *Nucleic Acids Res.* **2014**, *42(Web Server issue)*, W32-8.
- Gfeller D, Zoete V. Protein homology reveals new targets for bioactive small molecules. *Bioinformatics*. **2015**, *31*, 2721-7.

Choose an organism

- (•) Homo sapiens
- ( ) Mus musculus
- ( ) Rattus norvegicus
- ( ) Bos taurus
- ( ) Equus caballus

Paste a SMILES in this box, or draw a molecule

COC1=CC=C(C=C1)C(Cl)=C(C1=CC=C(OC)C=C1)C1=CC=C(OC)C=C1

Chlorotrianisene | Clear

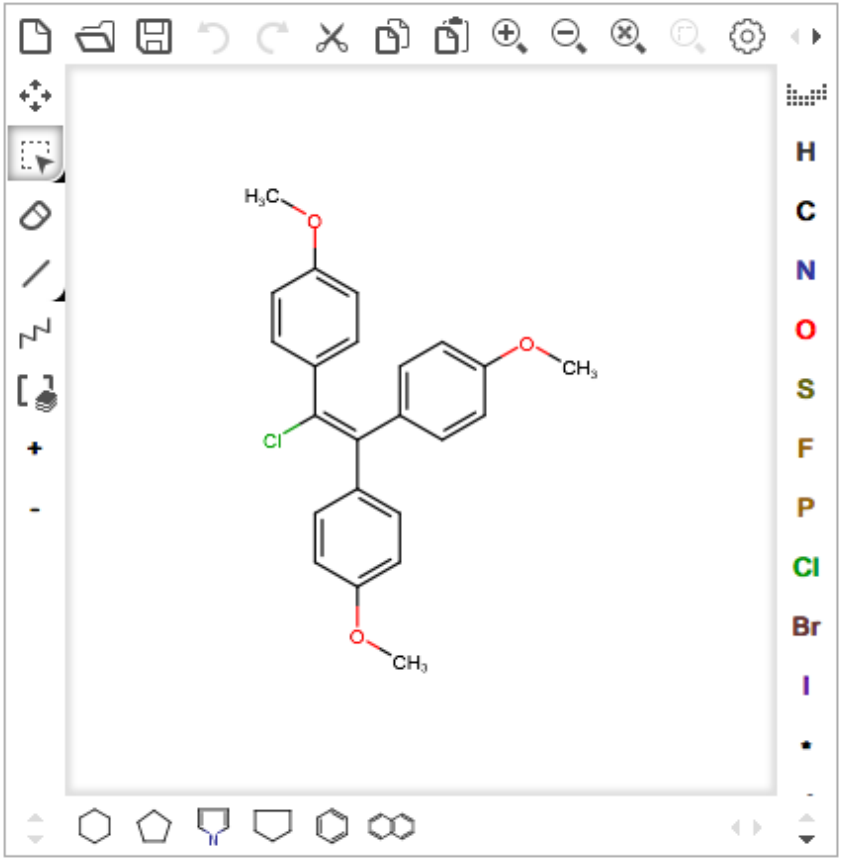
Examples:
Bisphenol-A
Chlorotrianisene

Predict the target

Submit

(Can take up to one minute)

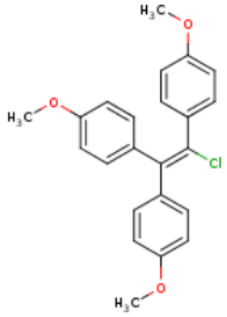
=



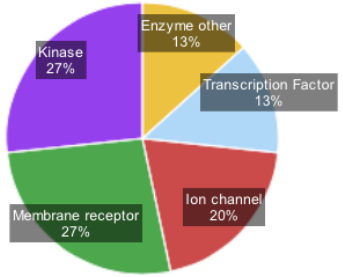
Ligand-based CADD – SwissTargetPrediction.ch

Reference:
Gfeller D., Michielin O. & Zoete V.
Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



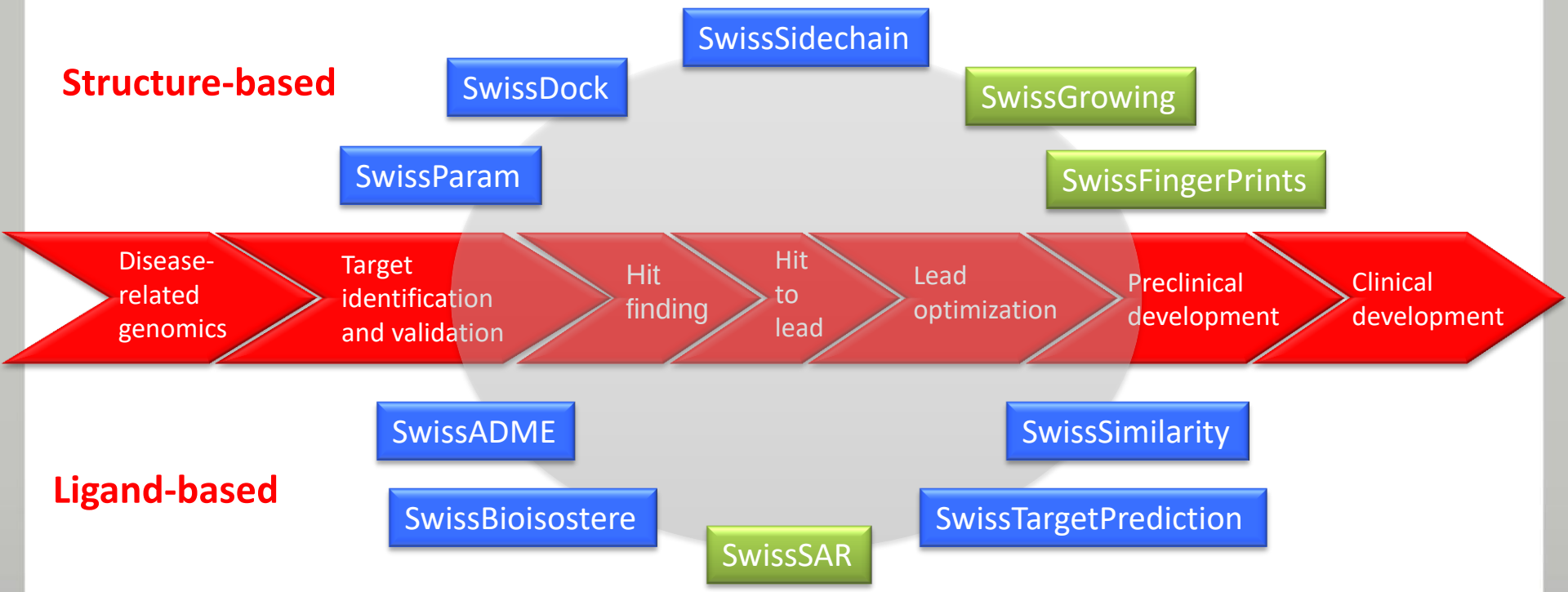
General Target Classes



Retrieve data:

Target	Common name	Uniprot ID	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Prostaglandin G/H synthase 1	PTGS1	P23219	CHEMBL221		68 / 31	Enzyme
Prostaglandin G/H synthase 2	PTGS2	P35354	CHEMBL230		68 / 31	Enzyme
Estrogen receptor	ESR1	P03372	CHEMBL206		8 / 32	Transcription Factor
Estrogen receptor beta *(by homology)*	ESR2	Q92731	CHEMBL242		7 / 32	Transcription Factor
Potassium voltage-gated channel subfamily H member 2	KCNH2	Q12809	CHEMBL240		39 / 2	Ion channel
Potassium voltage-gated channel subfamily H member 6 *(by homology)*	KCNH6	Q9H252			39 / 2	Ion channel
Potassium voltage-gated channel subfamily H member 7 *(by homology)*	KCNH7	Q9NS40			39 / 2	Ion channel
5-hydroxytryptamine receptor 6	HTR6	P50406	CHEMBL3371		14 / 5	Membrane receptor
Epidermal growth factor receptor	EGFR	P00533	CHEMBL203		83 / 5	Tyr Kinase
Receptor tyrosine-protein kinase erbB-2	ERBB2	P04626	CHEMBL1824		83 / 5	Tyr Kinase
ERBB4 intracellular domain *(by homology)*	ERBB4	Q15303	CHEMBL3009		83 / 5	Tyr Kinase

The SwissDrugDesign project – Current status



: in development

: online

Proteins, **2007**, *67*(4), 1010–1025.
J. Comput. Chem., **2009**, *30*(13), 2021–2030.
J. Comput. Chem., **2009**, *30*(14), 2305–2310.
J. of Cell. Molec. Med., **2009**, *13*(2), 238–248.
J. Mol. Recog., **2010**, *23*(5), 457–461.
J. Comput. Chem., **2011**, *32*(11), 2359–2368.
Nucleic Acids Res., **2011**, *39*(suppl 2), W270–W277.
J. Comput. Chem., **2011**, *32*(10), 2149–2159.
J. Comput. Chem., **2012**, *33*(18), 1525–1535.
Bioinformatics, **2013**, *29*(23), 3073–3079.
Nucleic Acids Res., **2013**, *41*(D1), D1137–43.
Nucleic Acids Res., **2013**, *41*(D1), D327–D332.
Nucleic Acids Res., **2014**, *42* (WS), W436–41.
J. Chem. Inf. Mol. Mod., **2014**, *54*(12), 3284–3301.
Nucleic Acids Res., **2014**, *42*(WS), W32–8.
Bioinformatics, **2015**, *31*(16), 2721–2727.
J. Comput. Chem., **2016**, *37*(4), 437–447.
Chemmedchem, **2016**, *11*(11), 1117–1121.
J. Chem. Inf. Mol. Mod, **2016**, *56*(8), 1399–1404.
J Chem Inf Model. **2017** , 57(1):73-84
Sci. Rep. **2017**, 7:42717
J. Chem. Educ **2017**, 94(3):335–344

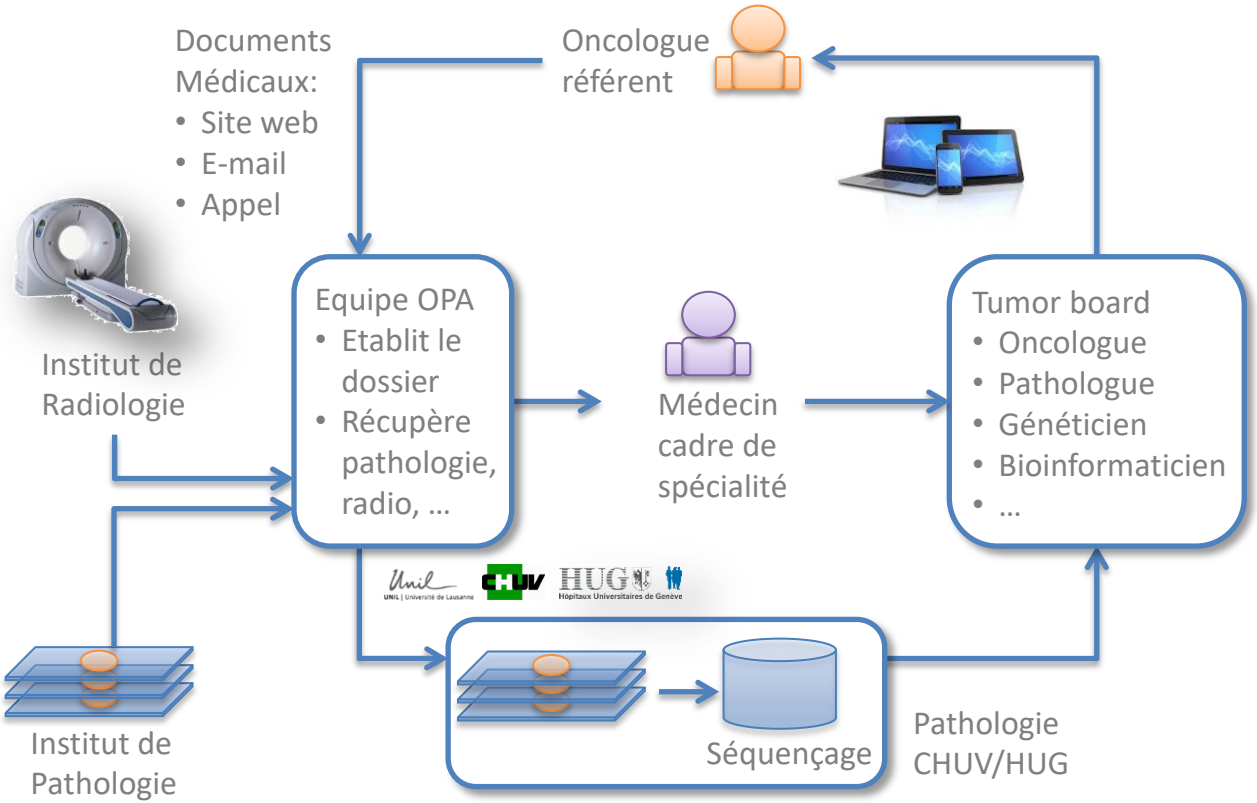
Protein Engineering
Drug Design
Personalized Medicine

SIB
Swiss Institute of Bioinformatics

elixir SWITZERLAND

Personalized Medicine

Réseau Romand d'Oncologie - Organisation interne:



L'oncologue référent reçoit

1. Un accusé de réception du cas dans la journée
2. Une invitation à se connecter au TB moléculaire
3. Dès le TB moléculaire terminé, toutes les propositions thérapeutiques (< 2h)
4. Un rapport médical et un rapport de pathologie la semaine suivante

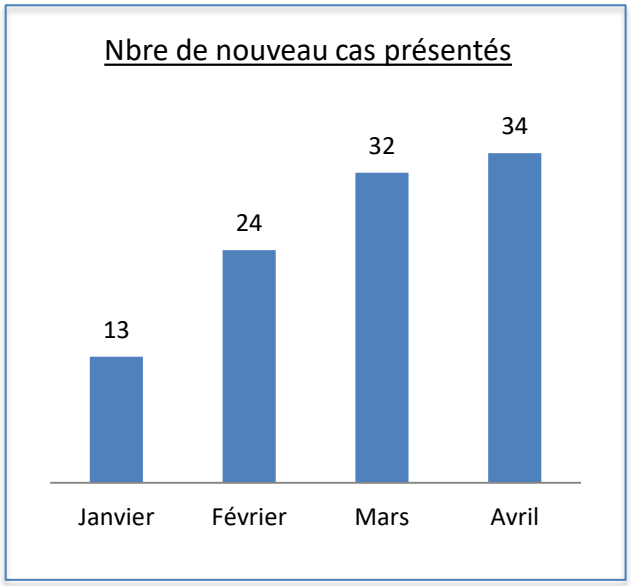
Participants: hôpitaux (universitaires) de Lausanne, Genève, Fribourg, Montreux, Neuchâtel, cliniques privées, etc… Bassin de 2 millions d'habitants

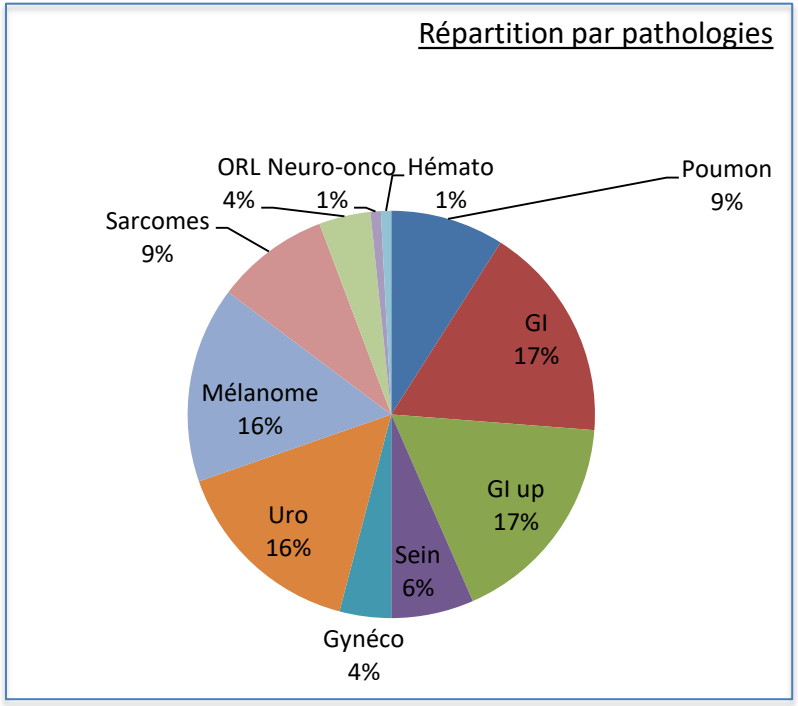
Personalized Medicine

Ex.: teleconference with Lausanne, Geneva, Fribourg and several private institutions

Personalized Medicine

Molecular Tumor Board, CHUV (Lausanne), 2017





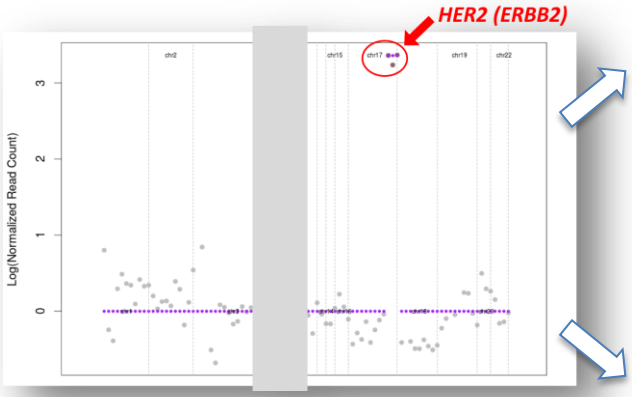
Augmentation de 161 % entre Janvier et Avril

103 patients présentés entre Janvier et Avril 2017
(+ 18 patients en 2016)

Personalized Medicine

Premiers bénéfices du Réseau Romand

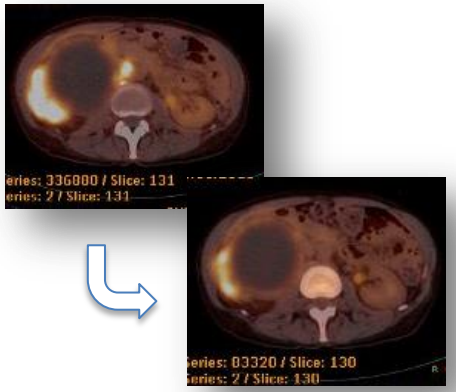
- De nombreux cas sont discutés toutes les semaines avec les HUG
- Des bénéfices cliniques sont obtenus régulièrement
- Toutes les statistiques de réponse et survie sont collectées
- Bénéfices additionnels:
  - Les analyses moléculaires concluent souvent à ***ne pas*** donner un traitement inutile
  - Meilleure rationalisation



Carcinome urothélial ayant épuisé les lignes de thérapie standard
(cas soumis au Réseau par nos collègues de la Clinique de Genolier)

Essai clinique potentiel:
- NCT02675829

Traitement off label:
- Trastuzumab Emtansine

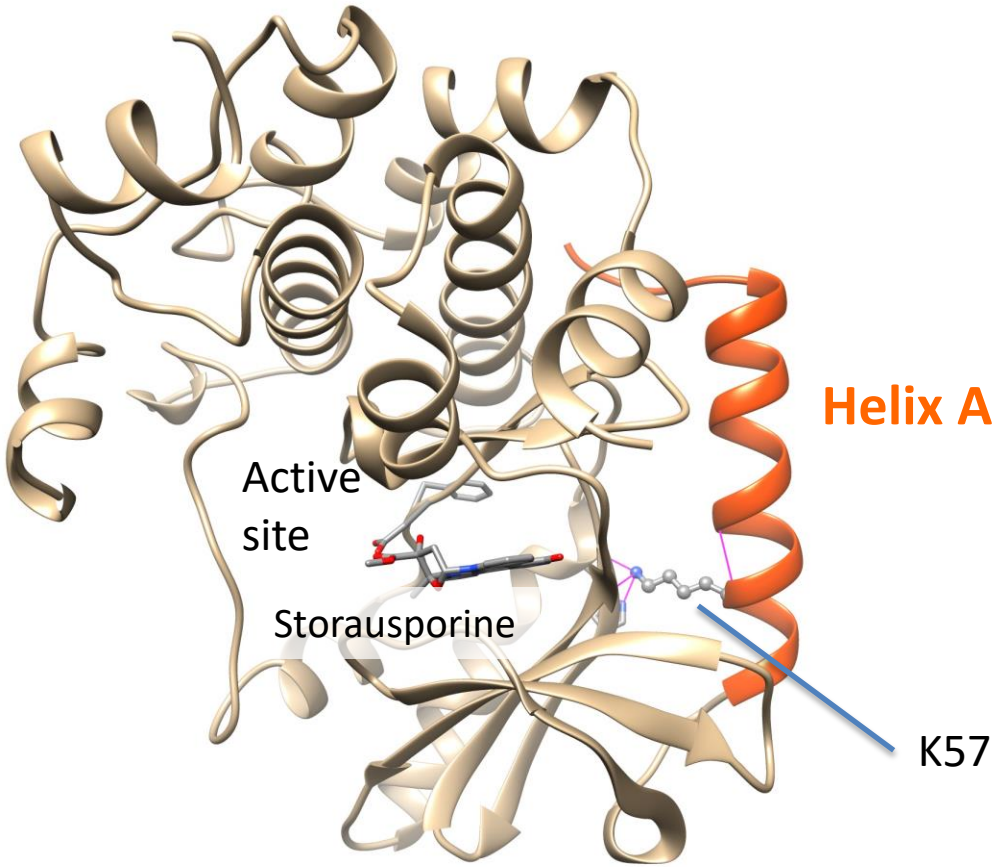


Personalized Medicine – What Modeling brings

MAP2K1 p.K57N

- Lys57 is not situated in the kinase domain, and is far from the kinase active site

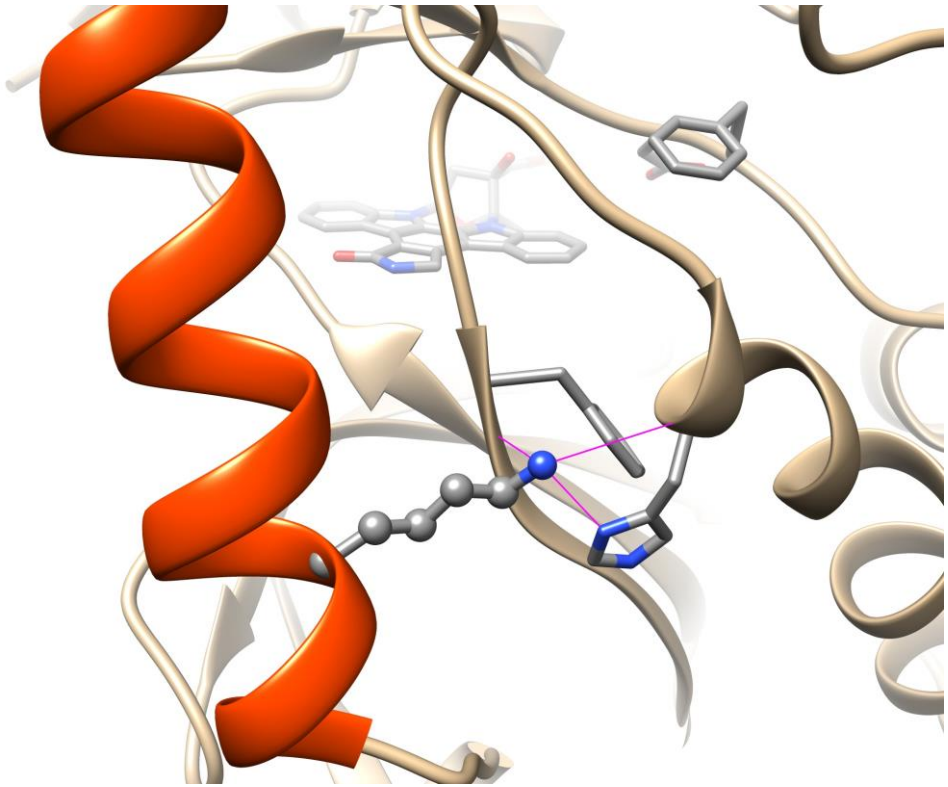
- Lys57 belongs to Helix A, known to be an activity switch of the kinase domain (i.e. unbinding of helix A from the kinase domain activates the kinase)



Personalized Medicine – What Modeling brings

MAP2K1 p.K57N

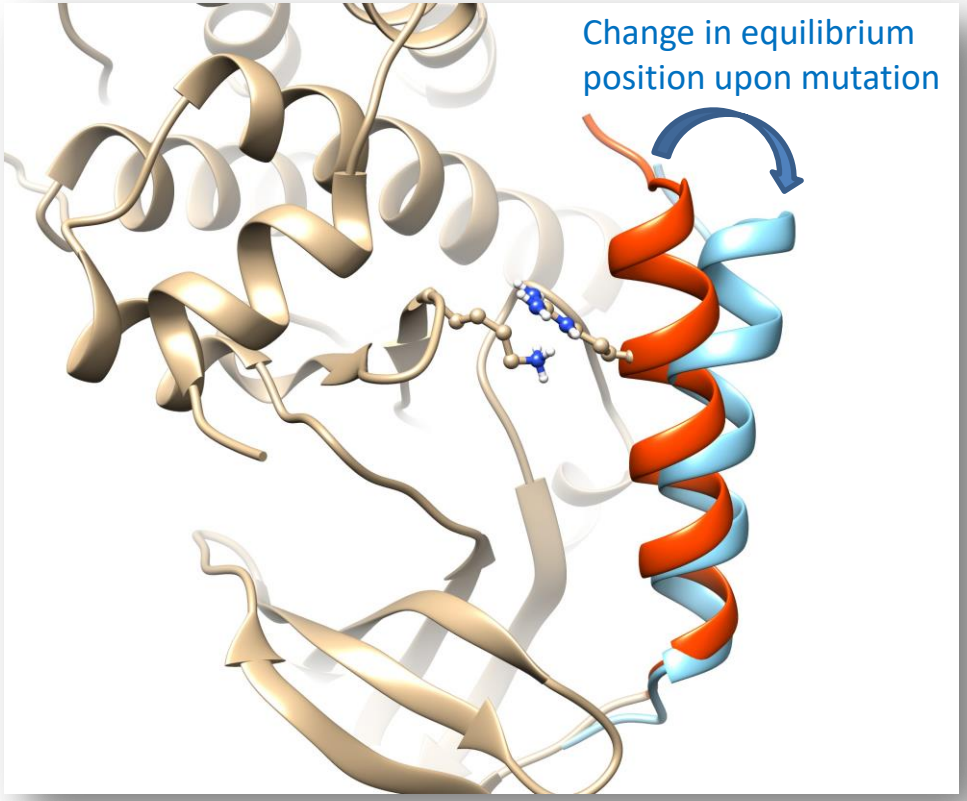
- Lys57 is not situated in the kinase domain, and is far from the kinase active site
- Lys57 belongs to Helix A, known to be an activity switch of the kinase domain (i.e. unbinding of helix A from the kinase domain activates the kinase)
- Lys57 makes hydrogen bonds with the kinase domain, which stabilizes Helix A in the inactive form



Personalized Medicine – What Modeling brings

MAP2K1 p.K57N

Analogy with the previously studied mutation **E203K**, which affects the kinase domain and destabilizes the inactive position of Helix A, resulting in a constitutive activation of MEK1



Obtained by Molecular-Mechanics based simulations:

- Molecular Dynamics simulations
- Normal mode analysis

Nikolaev, S. I., Rimoldi, D., Iseli, C., Valsesia, A., Robyr, D., Gehrig, C., Zoete, V. Michielin, O. et al. (2012). Exome sequencing identifies recurrent somatic MAP2K1 and MAP2K2 mutations in melanoma. *Nature Genetics*, *44*(2), 133–139.

Personalized Medicine – What Modeling brings

MAP2K1 p.K57N

- Lys57 is a conserved residue. The entire Helix A is well conserved

Helix A

Human	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Pan troglodytes	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Macaca mulatta	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Mus musculus	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Rattus norvegicus	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Canis lupus	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Bos taurus	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Gallus gallus	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Danio Rerio	K L E E	L E L D E Q Q K K R	L E A F L T Q K Q K	V G E L K D D D F E	K I S E L G A
Xenopus tropicalis	K L E E	L E L D E Q Q R K R	L E A F L T Q K Q K	V G E L K D D D F E	K V S E L G A

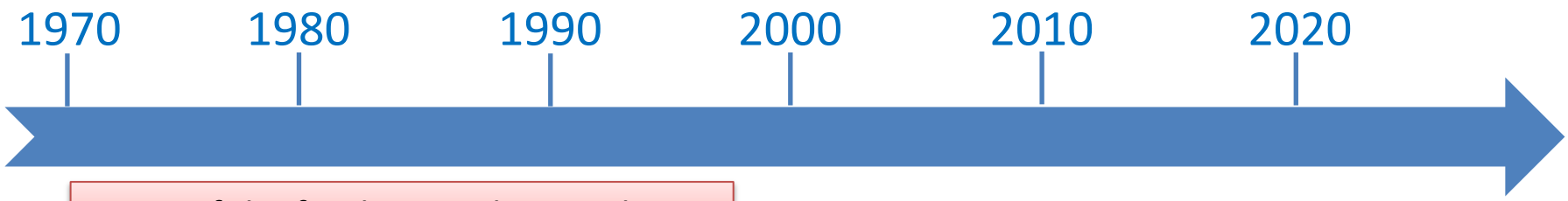
Human Lys57

- K57N was detected in patients with lung cancer, and was found to activate MAP2K1

Marks, J. L., et al. (2008). Novel MEK1 mutation identified by mutational analysis of epidermal growth factor receptor signaling pathway genes in lung adenocarcinoma. *Cancer Research*, *68*(14), 5524–5528.

Recommandation: treat patient with MAP2K1 inhibitor

Conclusion



Setup of the fundamental principles

Explaining biological mechanisms *a posteriori*

Prediction of biological phenomena.
Protein engineering

Contribution to personalized medicine

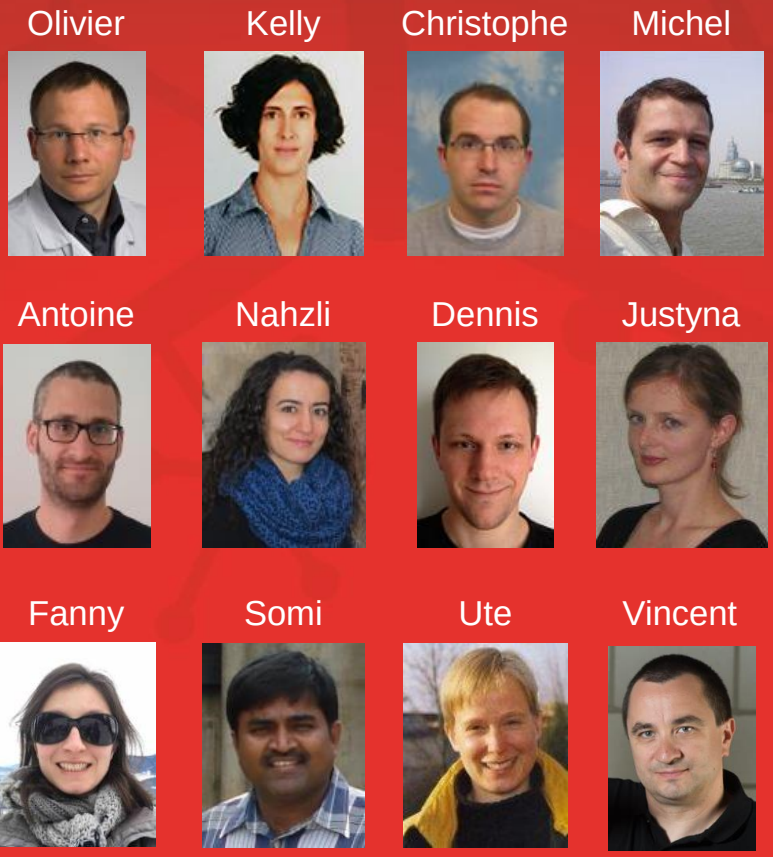
Factors:

- increasing computational power at lower cost
- increasing number of available experimental 3D structures (more then 130’000 today)
- availability of open access data (ChEMBL, Uniprot, etc.)
- acceptance of molecular modeling as a useful and functional tool for biology & medicine

Molecular Modeling Group

Head:
Olivier Michielin
Vincent Zoete

Team:
Kelly Ascencao
Christophe Bovigny
Michel Cuendet
Antoine Daina
Nahzli Dilek
Dennis Haake
Justyna Iwaszkiewicz
Fanny Krebs
Somi Reddy Majjigapu
Ute Röhrig



UNIL | Université de Lausanne
Faculty of Biology and Medicine

CHUV

SIB
Swiss Institute of Bioinformatics

Funding

SIB

UNIL | Université de Lausanne

FNSNF

LUDWIG CANCER RESEARCH

SystemsX.ch
The Swiss Initiative in Systems Biology

Research for Life

KTI/CTI

oncosuisse

SEVENTH FRAMEWORK PROGRAMME

Polish-Swiss Research Programme

Fondation Solidar-Immun

Thank you

UNIL | Université de Lausanne
Faculty of Biology and Medicine

Swiss Institute of Bioinformatics