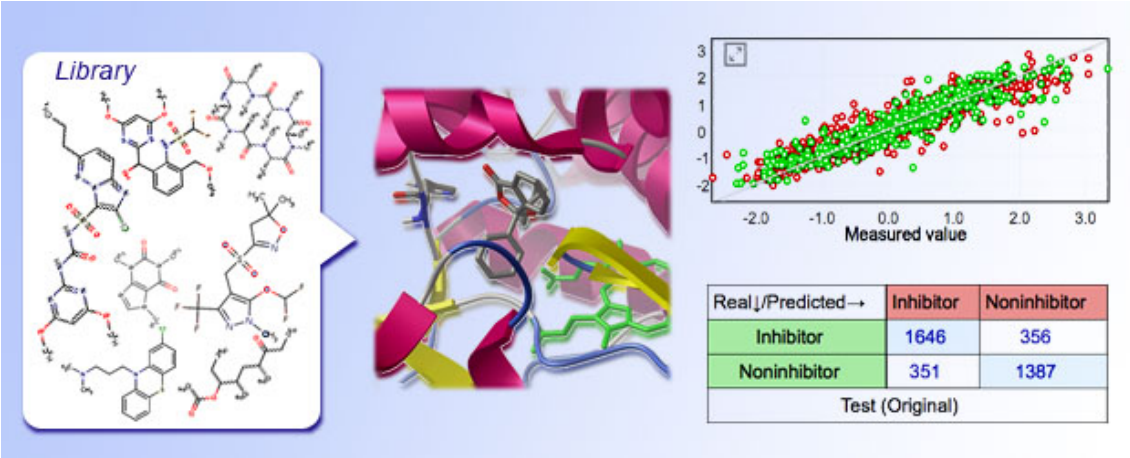


Helmholtz Zentrum München

Dr. Igor V. Tetko

Institute of Structural Biology, HelmholtzZentrum München & BIGCHEM GmbH

Wednesday, January 26, 2021

Institute of Structural Biology

HelmholtzZentrum münchen
German Research Center for Environmental Health

big chem

Helmholtz Association: Key Figures

Germany´s largest research organization

- 18 research centres
- Budget: 3.8 billion €, more than 36,000 staff

Mission

- We contribute to solving grand challenges
- We research systems of great complexity with large scale facilities
- We contribute to shaping our future

Research fields

- **Health**, Energy, Earth and Environment, Structure of Matter, Key Technologies, Transport and Space

Health Research Centers

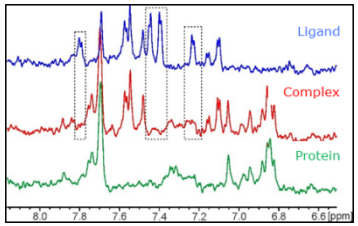
- Budget: 550 million €, about 5.500 staff
- Common Diseases: cancer, cardiovascular diseases, metabolic diseases, lung diseases and allergies, neurodegenerative diseases, infectious diseases
- Contribution to diagnosis, treatment, prevention
- Education and training of the next generation of scientists
- Move into the field of Precision Medicine

Helmholtz Zentrum München (HMGU): Key Figures

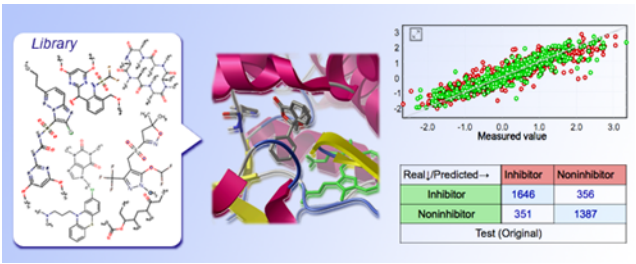
> 2 300	**Employees** (60% female, 70 nations)
21	**Young Investigator Groups**
49	**Institutes / Research Units**
31	**Appointments with universities**
1 448	**Publications**
26	**ERC Grants (total)**
3	**Translational centers**
> 40	**Clinical research projects** with partners
274	**Million € total budget**
45,7	**Million € third-party funding**
20	**Spin-off companies (since 1997)**
5	**Products**

Helmholtz Zentrum München
Structure-based drug discovery & technology platforms

Fragment Based Screening NMR hit validation
Grzegorz Popowicz, Ana Messias
Michael Sattler

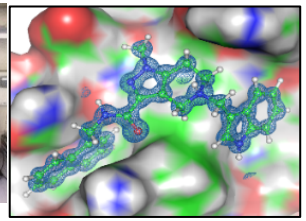


Chemoinformatics
Igor Tetko



Institute of Medicinal Chemistry
Oliver Plettenburg

X-ray Crystallography
Robert Janowski/Niessing



Protein Expression & Purification Facility
Arie Geerlof

- Protein production & support for structural biology & drug discovery
- Know-how, training, resources, i.e. expression vectors, general use proteins: TEV, precision, Cas9, …

Funding

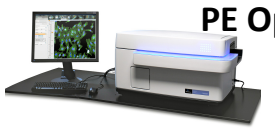
EU Horizon 2020 ITN "AEGIS"
EU Horizon 2020 ITN "*BIGCHEM*"
EU Horizon 2020 ITN "*AIDD*"
EU Horizon 2020 ITN "*RNAct*"
Novel methods in SBDD: BMWi-ZIM, TV, VIP+

Publications

Dawidowski *Science* (2017)
Jagtap *J Med Chem* (2016)
Riebold *Nature Medicine* (2015)
Gilsbach *J Med Chem* (2015)
Piccoli *Mol Cell Biol (*2014),
Zierer *Angew Chem (*2014)

Assay Development & Screening Platform
Kamyar Hadian

- In-house compound library
- Biochemical screening
  - AlphaScreen, FP, …
- Cell-based assays and screening



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http://www.helmholtz-muenchen.de/stb

Accelerated Early staGe drug dIScovery

AEGIS

Accelerated Early staGe drug dIScovery

EC HORIZON 2020 Marie Skłodowska-Curie
Innovative Training Network (ITN)

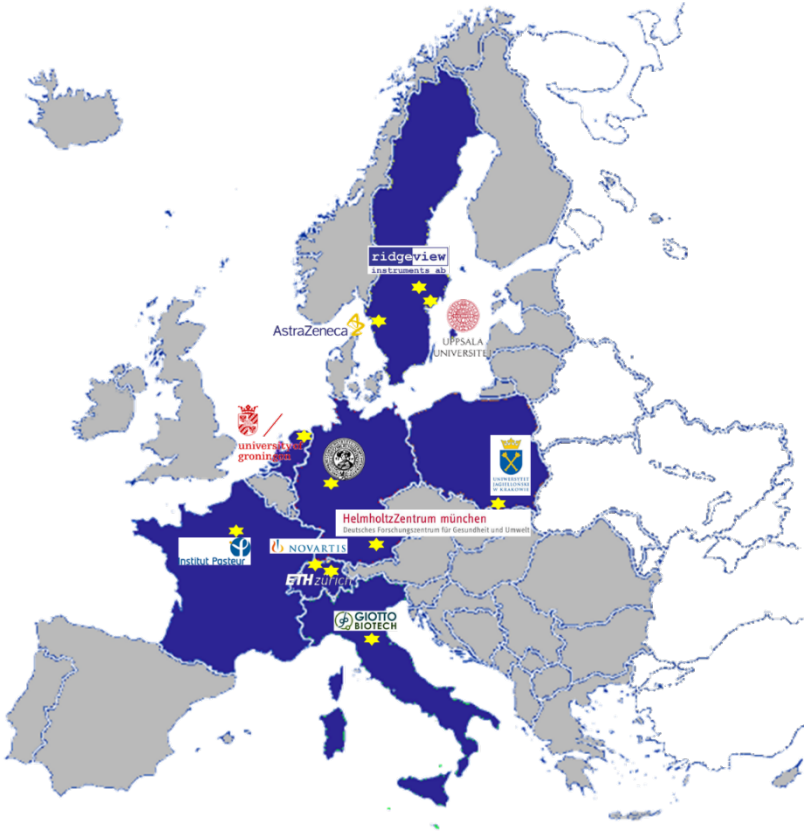
Coordination:
Michael Sattler, Helmholtz Zentrum München

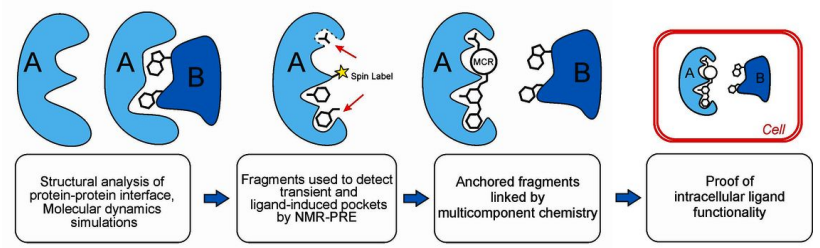
NOVARTIS

AstraZeneca

ridgeview instruments ab

GIOTTO BIOTECH





BigChem http://bigchem.eu

big data in chemistry + informatics = chemoinformatics

The **increasing volume of biomedical data** in chemistry and life sciences requires development of **new methods and approaches for their analysis**.

The BIGCHEM project will provide **innovative education in large chemical data analysis**. The innovative research program will be implemented with the target users, **large pharma companies and SMEs**, which generate and analyze large chemical data as well as will promote technology transfer from academy to industrial applications.

Marie Skłodowska-Curie Innovative Training Network
European Industrial Doctorate

BIGCHEM project publications http://bigchem.eu

BIGCHEM publications

FOLLOW

Horizon2020 Marie Skłodowska-Curie Innovative Training Network European Industrial Doctorate

Verified email at bigchem.eu

big data chemoinformatics cheminformatics

TITLE	CITED BY	YEAR
The rise of deep learning in drug discovery H Chen, O Engkvist, Y Wang, M Olivecrona, T Blaschke Drug discovery today 23 (6), 1241-1250	520	2018
Molecular de-novo design through deep reinforcement learning M Olivecrona, T Blaschke, O Engkvist, H Chen Journal of cheminformatics 9 (1), 48	325	2017
Automating drug discovery G Schneider Nature Reviews Drug Discovery 17 (2), 97	233	2018
Application of Generative Autoencoder in *De Novo* Molecular Design T Blaschke, M Olivecrona, O Engkvist, J Bajorath, H Chen Molecular informatics 37 (1-2), 1700123	175	2018
BIGCHEM: challenges and opportunities for big data analysis in chemistry IV Tetko, O Engkvist, U Koch, JL Reymond, H Chen Molecular informatics 35 (11-12), 615-621	71	2016
On the integration of in silico drug design methods for drug repurposing E March-Vila, L Pinzi, N Sturm, A Tinivella, O Engkvist, H Chen, G Rastelli Frontiers in pharmacology 8, 298	69	2017
QSAR without borders EN Muratov, J Bajorath, RP Sheridan, IV Tetko, D Filimonov, V Poroikov, ... Chemical Society Reviews	51	2020
Exploring the GDB-13 chemical space using deep generative models J Arús-Pous, T Blaschke, S Ulander, JL Reymond, H Chen, O Engkvist Journal of cheminformatics 11 (1), 1-14	51	2019
Randomized SMILES strings improve the quality of molecular generative models J Arús-Pous, SV Johansson, O Prykhodko, EJ Bjerrum, C Tyrchan, ... Journal of cheminformatics 11 (1), 1-13	45	2019
A de novo molecular generation method using latent vector based generative adversarial network O Prykhodko, SV Johansson, PC Kotsias, J Arús-Pous, EJ Bjerrum, ... Journal of Cheminformatics 11 (1), 74	34	2019
Chemical space: big data challenge for molecular diversity M Awale, R Visini, D Probst, J Arus-Pous, JL Reymond CHIMIA International Journal for Chemistry 71 (10), 661-666	27	2017

Cited by

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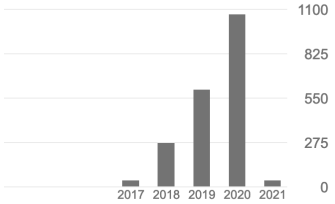
Citations	2035	2032
h-index	16	16
i10-index	29	29



Co-authors VIEW ALL

- Ola Engkvist, AstraZeneca R&D Gothenburg O…
- Hongming Chen, Astrazeneca R&D Mölndal
- Jürgen Bajorath, Professor of Life Science Inform…
- Thomas Blaschke, Phd student, AstraZeneca/Unive…
- Igor V. Tetko, Group Leader at Helmholtz Zentr…
- Jean-Louis Reymond, University of Bern
- Josep Arús-Pous, University of Bern
- Esben Jannik Bjerrum, Principal Scientist - Machine lear…
- Raquel Rodríguez-Pérez, Senior Scientist, Novartis Institut…
- Alexandre Varnek, Professor of Chemistry, Universit…
- Michael Withnall, Apheris AI

Up to now ~ 70 articles, including five highly cited articles according to the Web of Science

ICANN19

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Fabian Theis, Helmholtz Zentrum München (GmbH), Germany

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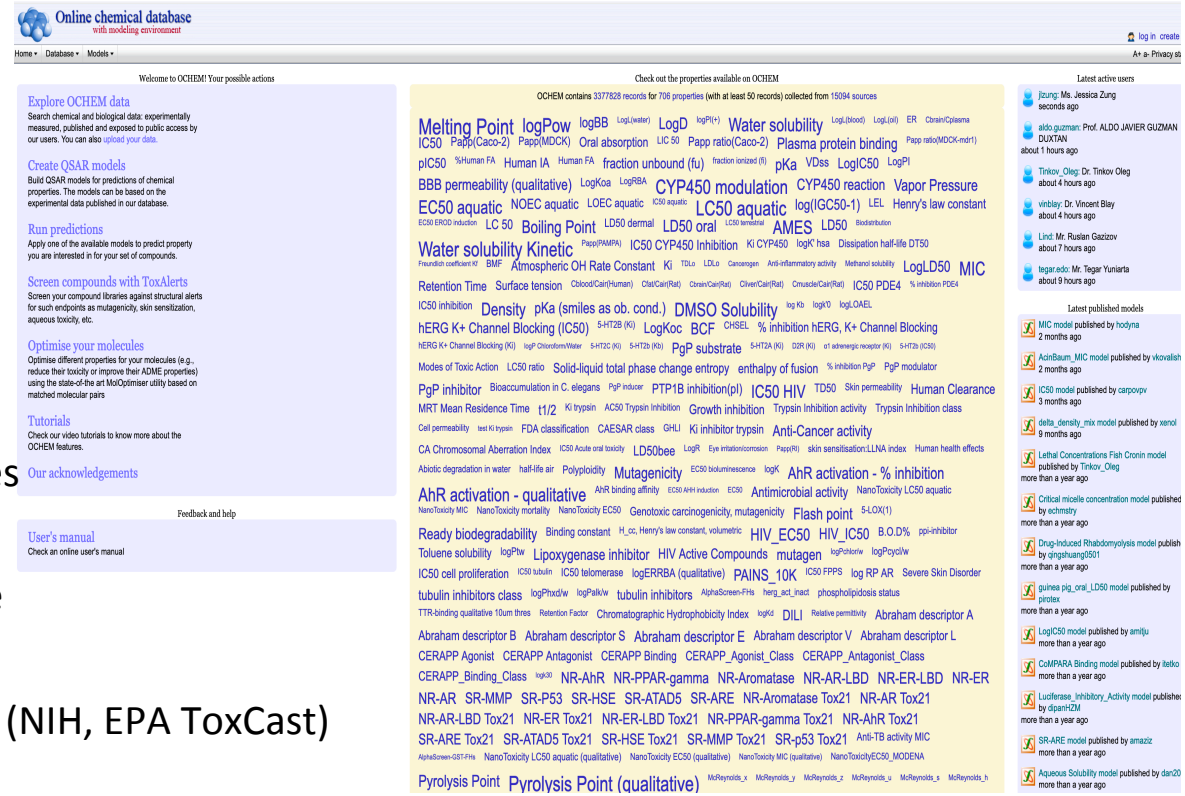
Jérémie Cabessa, Université Paris 2 Panthéon-Assas, France

Maxim Fedorov, Skoltech, Russia

OCHEM http://ochem.eu overview

- **Physico-chemical properties:** logP, water solubility, melting point, pyrolysis, vapor pressure, ODT, etc.
- **Biological activity:** estrogen receptors; endocrine disruptors; AMES mutagenicity; *in vivo* toxicity
- **Environmental endpoints:** ready biodegradability; fish toxicity; environmental toxicity, daphnia, etc.

- In total 162 published models*
- 7375 registered users
  - 600 commercial
  - 450 governmental
- ca 37M tasks were executed
- ca 3.4M data points for 692 properties
- >25M uploaded private data points
- Academic groups regularly contribute
- OCHEM is used for teaching
- Top-performing models in challenges (NIH, EPA ToxCast)



* As from 18.01.2021

OCHEM modeling

- Comprehensive modeling
- Multitask learning (up to 100 properties)
- >20 descriptor blocks
- Feature net (“model in model”)
- Consensus models
- GPU + CPU modern methods (~20)
- Supports models
  - >1,000,000 compounds
  - >200,000,000,000 descriptors*
  - >1,000 servers
  - up to 1GB in size (Java limit)
- Model private/publishing
- Export, import, web/REST services
- Conditions, external descriptors
- ToxAlerts

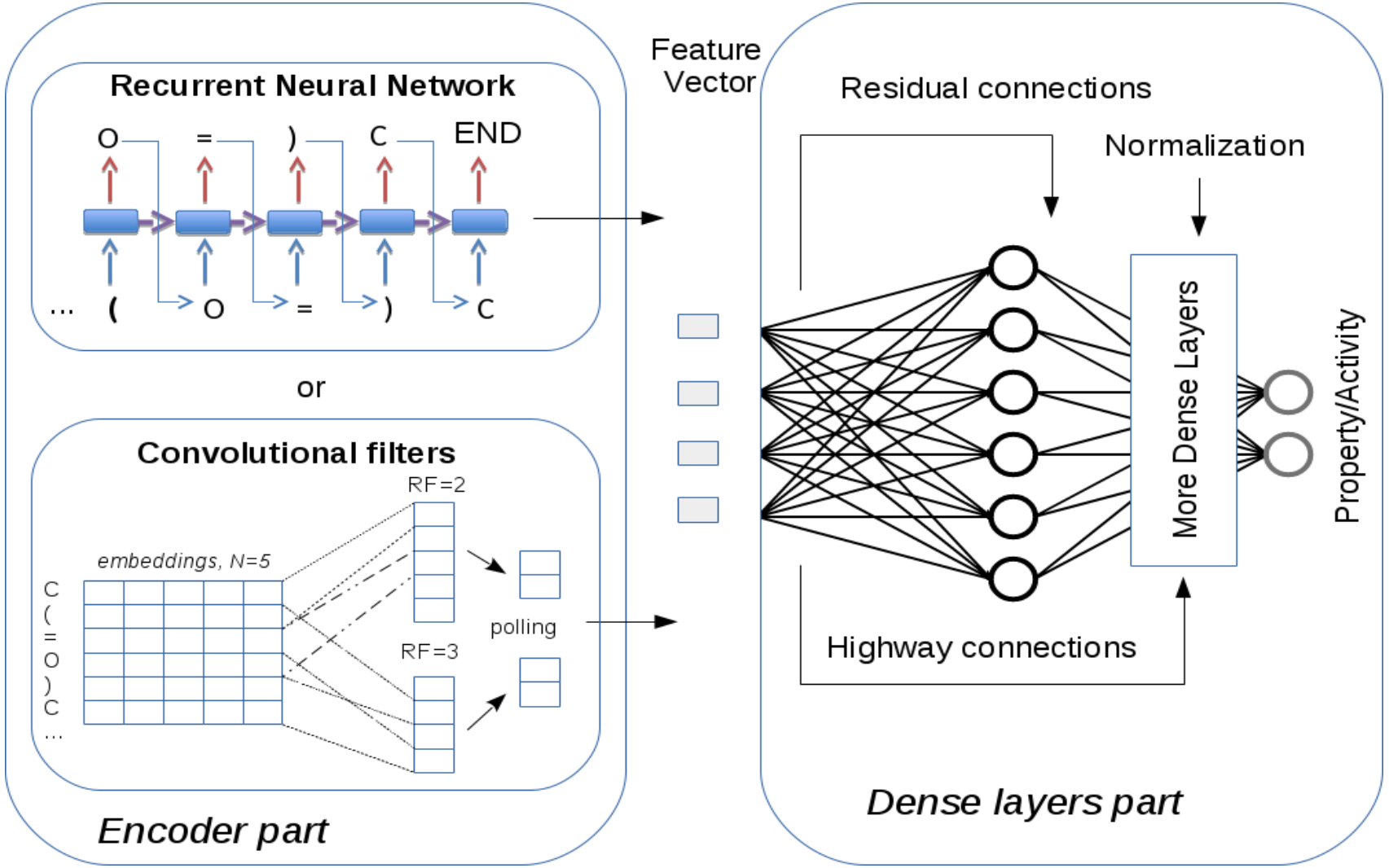
Predicted property: LLNA skin sensitization
Training set: TRAINING-SARpy-SKIN-SENS-giugno20 OK.xlsx

Metrics AUC for Training set Validation: Cross-Validation (84 models)

	LSSVMG	ASNN	PLS	KNN
ALogPS, OEstate	0.74	0.68	0.61	0.64
CDDD	0.8	0.74	0.75	0.71
CDK2 (cons,topol,geom,elec,hybrid) 3D:corina	0.75	0.71	0.56	0.71
ChemaxonDescriptors (pH 0 - 14:1) 3D:corina	0.76	0.7	0.59	0.68
Dragon6 (2D blocks: 1 28)	0.64	0.66	0.59	0.65
Dragon6 (3D blocks: 1-29) 3D:corina	0.76	0.72	0.57	0.65
Fragmentor (length:2 - 4)	0.72	0.7	0.59	0.63
GSFrag (F + L)	0.69	0.69	0.61	0.61
InductiveDescriptors 3D:corina	0.69	0.71	0.57	0.67
JPlogP	0.73	0.74	0.59	0.67
MAP4	0.71	0.65	0.59	0.67
MORDRED (All) 3D:corina	0.77	0.73	0.57	0.68
Mera, Mersy 3D:corina	0.73	0.69	0.55	0.67
OEstate	0.74	0.67	0.63	0.68
PyDescriptor 3D:corina	0.71	0.71	0.7	0.67
QNPR (length:1 - 3)	0.68	0.62	0.58	0.58
RDKIT (3D blocks: 1-11 15-16) 3D:corina	0.77	0.72	0.56	0.65
SIRMS (labels:charge+logp+hb+refractivity)	0.76	0.73	0.59	0.67
Spectrophores (accuracy=20) 3D:corina	0.68	0.6	0.52	0.6
StructuralAlerts	0.67	0.64	0.58	0.51
alvaDesc (3D blocks: (only) 1-30) 3D:corina	0.75	0.71	0.57	0.68

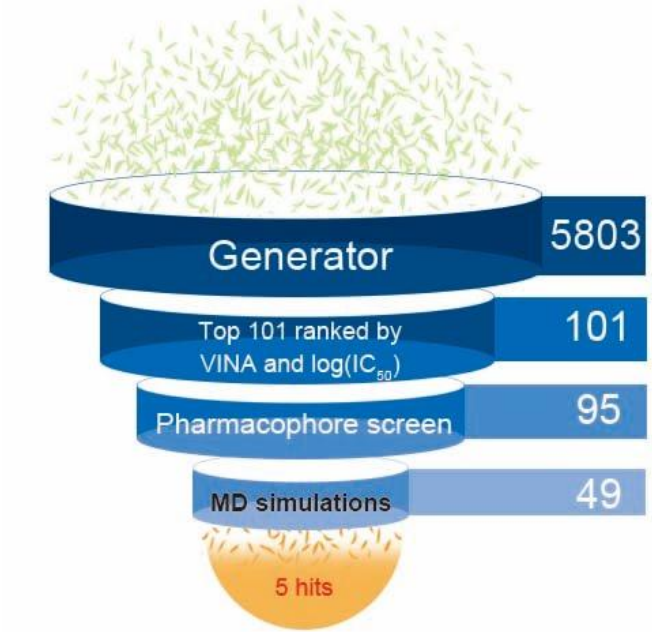
* Sparse format, DOI:10.1186/s13321-016-0113-y

Machine Learning directly from chemical structures



Karpov, P.; Godin, G.; Tetko, I.V. Transformer-CNN: Swiss knife for QSAR modeling and interpretation. *J. Cheminform.* **2020**, *12*, 17, doi:10.1186/s13321-020-00423-w.

Computer aided drug design of Mdmx inhibitors

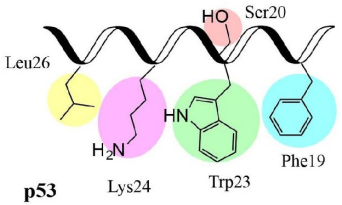


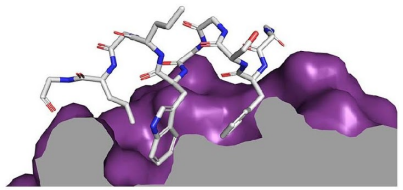
	RMSD				-*log*(IC_{50})	ΔG (kcal/mol)
Compound	**avg[a]**	**std[b]**	**min[c]**	**max[d]**		
WK298	2.183	0.662	0.543	4.227	-4.7	-4.1
3021	4.675	0.379	0.627	5.947	-5.2	-13.0
92	1.605	0.454	0.506	3.711	-7.7	-10.8
100	1.738	0.680	0.480	5.831	-7.9	-6.9
34	2.789	0.696	0.668	5.176	-7.9	-6.7
39	4.407	1.184	0.778	7.960	-7.6	-6.7

a. avg = the average; b. std = standard deviation; c. min = the minimum; d. max = the maximum

Xia, Z.; Karpov, P.; Popowicz, G.; Tetko, I.V. Focused Library Generator: case of Mdmx inhibitors. *J. Comput. Aided. Mol. Des.* **2020**, *34*, 769-782.

a)





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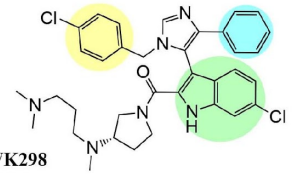

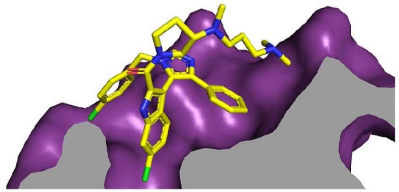

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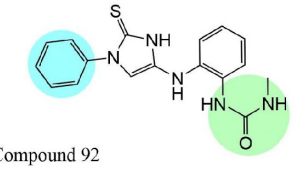
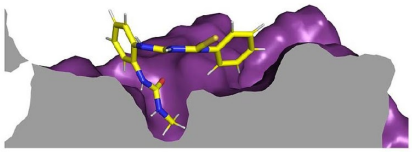
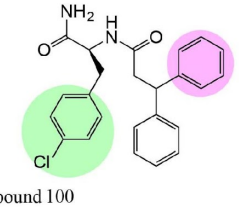
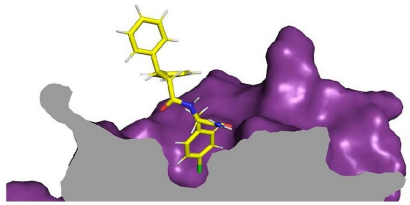
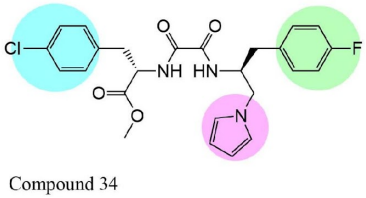
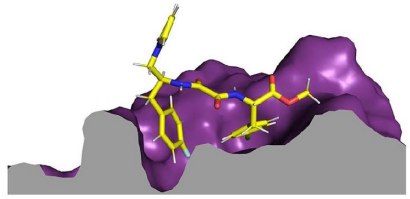


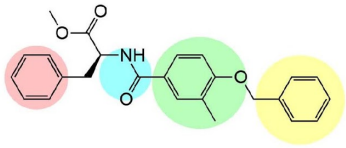




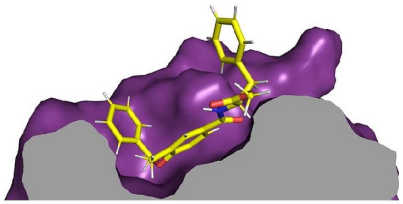






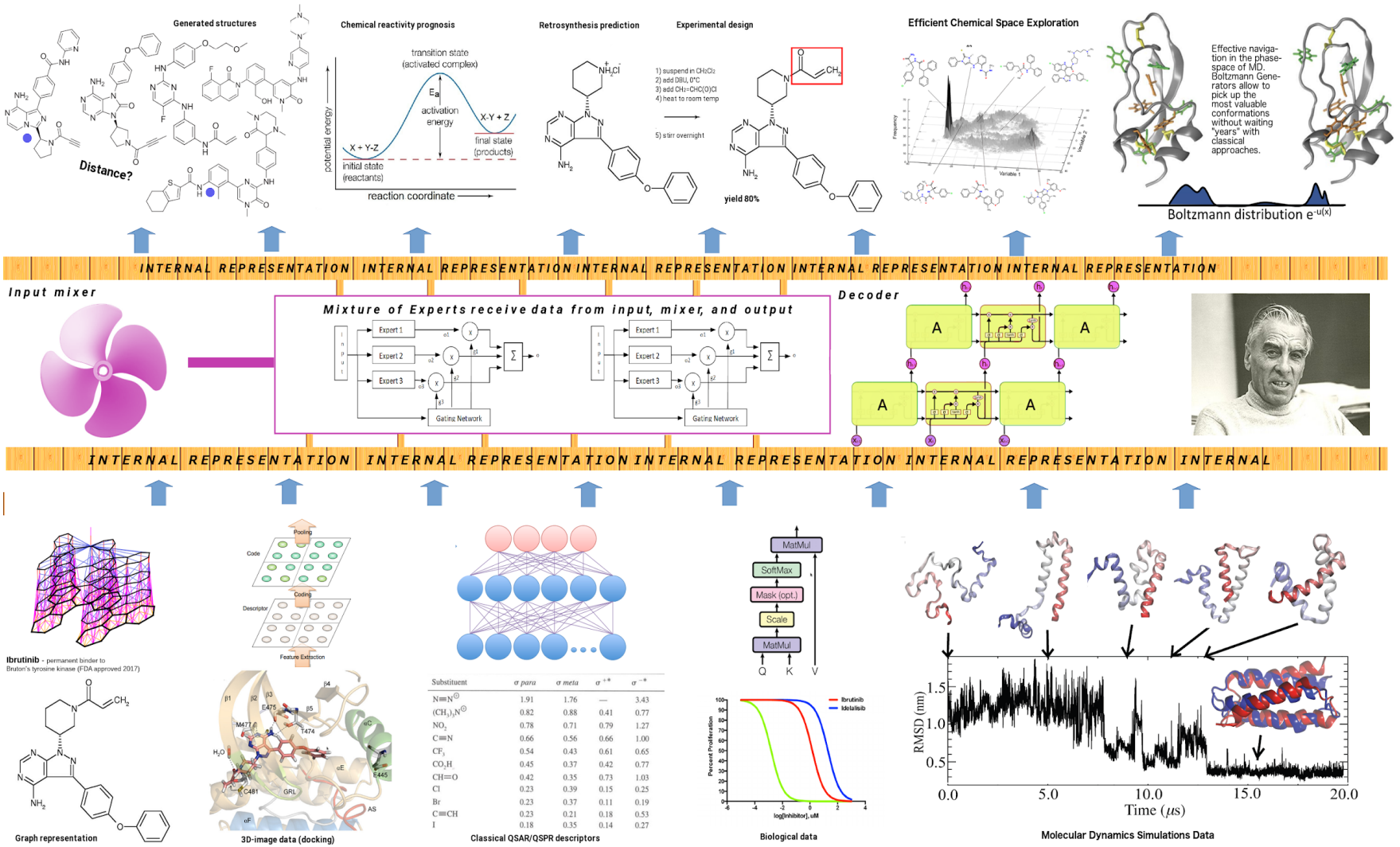


f)



Tetko, I.V.; Karpov, P.; Van Deursen, R.; Godin, G. State-of-the-art augmented NLP transformer models for direct and single-step retrosynthesis. *Nat. Comm.* **2020**, *11*, 1-11, doi:10.1038/s41467-020-19266-y.

AI "One Chemistry" model for drug discovery



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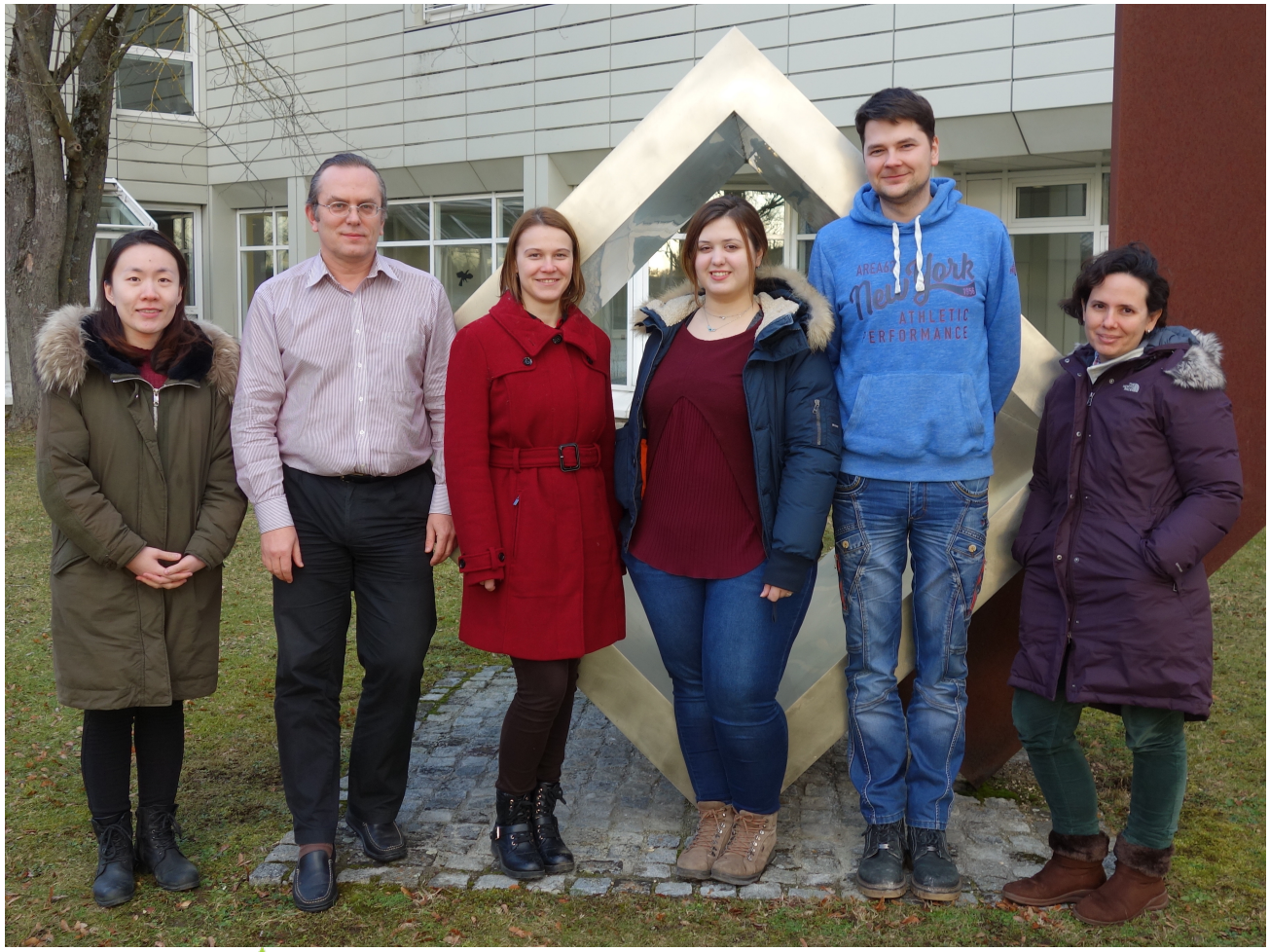

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MARIE CURIE ACTIONS

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environmental chemoinformatics
marie curie initial training network

BigChem