Creating an academia-based platform to discover substances acting on serotonergic or glutamatergic systems as potential new antidepressant or anxiolytic drugs

The Institute of Pharmacology, Polish Academy of Sciences was formed in 1974 in the city of Kraków. The Institute carries out research works in the fields of neuropharmacology, neurochemistry and neurobiology. One of the main topics of research is: the design and search for new antidepressant and anxiolytic agents. The Institute also deals with: drug addiction and dependence; learning and memory; neurodegenerative diseases, epilepsy, pain. In the years 1955–2009, 5173 papers were published (of which 2979 were original) and 20 patents were granted to the Institute's scientists. Currently the Institute employs over 160 full time staff, (of whom 100 are research scientists) and trains about 25 PhD students. Recently the Institute became a Center of Excellence in Neuropsychopharmacology "FRAM" and is the leading Polish scientific institution in the field of neuropharmacology.

Molecular Modelling Group, Medical Pharmacology and Toxicology, Department of Medical Biology, Faculty of Health Science, University of Tromsø, headed by professor Ingebrigt Sylte, uses molecular modelling and structural bioinformatics to gain insight into protein structure, function and interactions of drug target proteins. Sequence and structure analysis and homology modelling are used to construct three dimensional (3D) protein models. Automatic docking and molecular dynamics simulations are used to predict binding affinities and to study time dependent structural changes following protein-drug or protein-protein complexation. The molecular modelling group provides tools for molecular modelling of proteins, ligands, protein-protein and protein-ligand interactions.

National Medicines Institute exists since 1951. It is a state owned (Ministry of Health) research based unit whose activity is concerned with medicines control and health protection. It employs ca. 270 employees, among them ca. 90 scientists (10 professors). Scientific research concerns medicines quality and mechanisms of activity, state medicines control as well as reference, consulting and educational activity form the basic platform of the Institute expertise. The Institute activity is interdisciplinary and encloses such fields as pharmacy, pharmacology, chemistry, biochemistry, biophysics, microbiology, molecular biology, epidemiology and vaccinology.

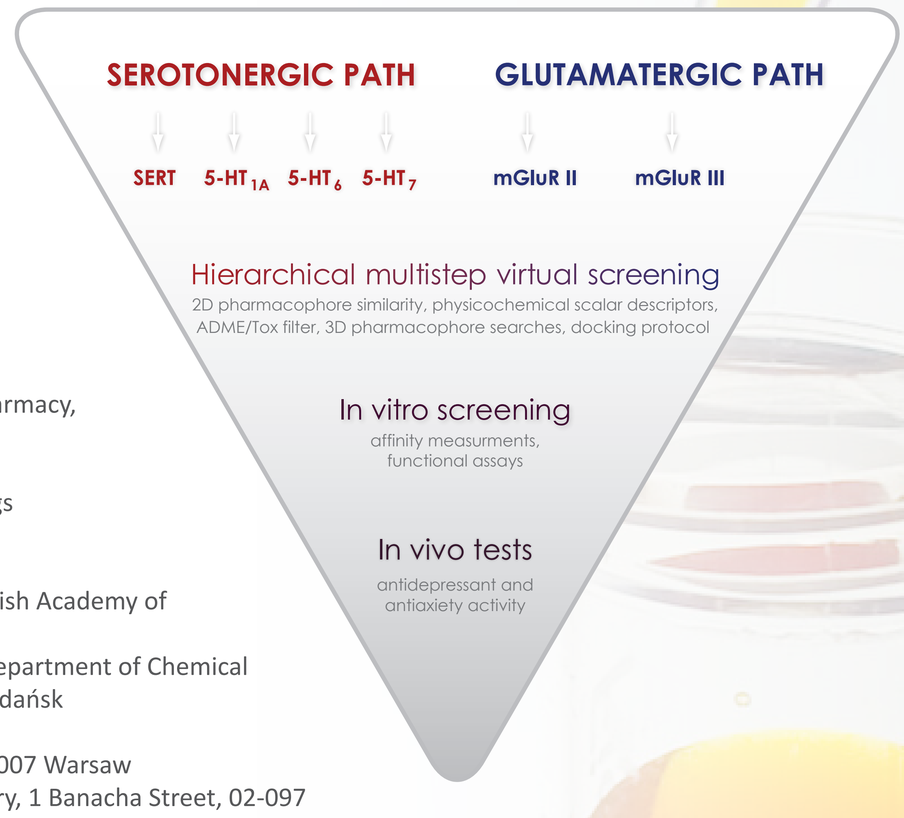
DATABASES					
		Enamine	ChemBridge	ChemDiv	SUMMARY
	# of drug-like compounds	approx. 1.2 mill	approx. 680.000	approx. 600.000	approx. 2.5 mill
	# of building blocks	approx. 31.000	approx. 10.500	approx. 5.000	
2D FINGERPRINT-BASED SCREENING					
Path 1	SSRIs	1877/1309[a]	3012/666[a]	3214/1813[a]	
	TCAs	661	936	568	
	3-Phenyltropanes	1511	1626	2615	
	Radioligands	1408	1199	684	
	Mazindols	400	466	627	
	(*S*)-citalopram	1477	1103	2517	
	Sertraline	297	433	436	
	Fluoxetine/Venlafaxine	1039	900	674	
	Fluvoxamine	190	271	79	
	SSRI general hypothesis	1780	4764	3327	
Path 2	General hypothesis	4935	3156	2615	
	Total # of compounds	**15007**	**15520**	**15955**	**46482**
PHYSIOCHEMICAL PROPERTY FILTERING					
Path 1	SSRIs	822	2112	1495	
	TCAs	217	488	270	
	3-Phenyltropanes	337	466	181	
	Radioligands	56	651	302	
	Mazindols	174	263	299	
	(*S*)-citalopram	539	354	897	
	Sertraline	139	250	211	
	Fluoxetine/Venlafaxine	360	555	257	
	Fluvoxamine	103	223	38	
Path 2	General hypothesis	1461	1302	1220	
	Total # of compounds	**4208**	**6664**	**5170**	**16042**
ADME/TOX FILTERING					
Path 1	SSRIs	630	1479	1055	
	TCAs	196	424	240	
	3-Phenyltropanes	267	397	154	
	Radioligands	206	585	277	
	Mazindols	134	190	200	
	(*S*)-citalopram	368	190	437	
	Sertraline	128	211	179	
	Fluoxetine/Venlafaxine	232	429	184	
	Fluvoxamine	45	118	22	
Path 2	General hypothesis	1315	1114	901	
	Total # of compounds	**3521**	**5137**	**3649**	**12307**
3D PHARMACOPHORE-BASED SCREENING					
Path 1	SSRIs	96	474	290	
	TCAs	44	92	63	
	3-Phenyltropanes	38	42	17	
	Radioligands	38	45	6	
	Mazindols	72	117	111	
	(*S*)-citalopram	33	56	75	
	Sertraline	22	48	23	
	Fluoxetine/Venlafaxine	13	25	24	
	Fluvoxamine	1	1	0	
Path 2	General hypothesis	173	334	234	
	Total # of compounds	**530**	**1234**	**843**	
	Overlap analysis	**423**	**919**	**620**	**1962**
	Stereoisomerisation	927	1923	1894	4744
	# of clusters	78	86	69	
FLEXIBLE DOCKING					
	# of compounds (score < -10)*	150	269	241	
	# of compounds (score < -12)*	95	183	124	
	# of compounds (score < -15)*	40	100	43	
VISUAL INSPECTION					
	D98-interaction**	73[b]	77[c]	62[d]	**212**
	In stock	67	68	47	**182**
BIOLOGICAL EVALUATION					
	Binders	10	18	9	**37**

As an example of Academic Screening Platform application, a scheme of the multi-step virtual screening protocol designed for identification of new serotonin transporter (SERT) inhibitors is presented. The filtering procedure is based on two-dimensional (2D) pharmacophore similarity, physicochemical scalar descriptors, an ADME/Tox filter, three-dimensional (3D) pharmacophore searches and a docking protocol. Numbers indicate the quantity of compounds at the output of each step. Finally, 182 virtual hits were biologically evaluated, and 37 novel SERT binders were identified.

Main objective: on the basis of the accumulated knowledge, experience and validated experimental methods developed by the above-mentioned scientific institutions, we have re-scaled the existing research capabilities to a multi-level screening platform which facilitates the process of antidepressant and anti-anxiety drug discovery. Using molecular modeling techniques, we perform a virtual screening of compound libraries on the basis of our own pharmacophores and receptor models. In order to examine a broad range of chemical structures, the compound acquisition system is being constantly developed. The therapeutic potential of both in-house and externally synthesized compounds is first evaluated *in vitro* and subsequently by *in vivo* tests.

The screening program is directed to research institutions from Poland and Norway, and compounds are tested free of charge. In the Project we focus on two main molecular targets which are recognized as important in antidepressant/anxiolytic mechanism of action:

- *the serotonergic system – compounds with dual SERT/5-HT$_{1A}$ antagonistic activity, and ligands of 5-HT$_6$ and 5-HT$_7$ receptors;*
- *the glutamatergic system – in which we concentrate mainly on groups II and III of metabotropic glutamate receptors (mGluR).*



Institutions participating in the Screening Program

1. Jagiellonian University Medical College, Faculty of Pharmacy, 9 Medyczna Street, 30-688 Kraków
   - Department of Medicinal Chemistry
   - Department of Technology and Biotechnology of Drugs
   - Department of Physicochemical Drug Analysis
   - Department of Organic Chemistry
2. Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 112 Sienkiewicza Street, 90-363, Łódź
3. Medical University of Gdańsk, Faculty of Pharmacy, Department of Chemical Technology of Drugs, Al. Gen. J. Hallera 107, 80-416 Gdańsk
4. Medical University of Warsaw
   - Department of Medical Chemistry, 3 Oczki Street, 02-007 Warsaw
   - Faculty of Pharmacy, Department of Physical Chemistry, 1 Banacha Street, 02-097 Warsaw
5. Medical University, Department of Synthesis and Chemical Technology of Pharmaceutical Substances, 6 Stasica Street, 20-081 Lublin
6. Poznan University of Medical Sciences, Faculty of Pharmacy, 10 Fredry Street, 61-701 Poznań
7. Technical University of Lodz, Faculty of Chemistry, 116 Żeromskiego Street, 90-924 Łódź
8. Department of Chemistry Norwegian University of Science and Technology, Trondheim, Norway
9. School of Pharmacy University of Oslo, Norway

PROJECT LEADER

Prof. Andrzej Pilc
Institute of Pharmacology
Polish Academy of Sciences
Department of Neurobiology
12 Smętna Street
31-343 Kraków, Poland
tel.: +4812 6623-284
fax: +4812 6374-500
e-mail: nfpilc@cyf-kr.edu.pl

POLISH PARTNER

Prof. Zdzisław Chilmonczyk
National Medicines Institute
Department of Cell Biology
30/34 Chełmska Street
00-725 Warsaw, Poland
tel.: +4822 851 43 69
e-mail: chilmon@il.waw.pl

NORWEGIAN PARTNER

Prof. Ingebrigt Sylte
Medical Pharmacology
and Toxicology
Department of Medical Biology
Faculty of Health Science
University of Tromsø
Breivika MH, N-9037 Tromsø, Norway
tel.: +47 77644 705
e-mail: ingebrigt.sylte@uit.no

CONTACT PERSON

Prof. Andrzej Bojarski
Institute of Pharmacology
Polish Academy of Sciences
Department of Medicinal Chemistry
12 Smętna Street
31-343 Kraków, Poland
tel.: +4812 6623 365
fax: +4812 6374 500
e-mail: bojarski@if-pan.krakow.pl

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