University of Helsinki, Faculty of Pharmacy (UH-PHAR)

http://www.helsinki.fi/pharmacy/bio/en/Research/index.html

Check out the University of Helsinki Youtube Video

FINLAND

specialist screening site

HELSINKI

an official partner site of eu openscreen

This partner site provides specialized screening and supporting chemoinformatics facility that complements the high throughput site (UH-FIMM) in Helsinki. In addition, to the generic skills, equipment and expertise the UH-PHAR partner site hosts specific fields of expertise in the fields of antimicrobial screens, natural product screening and pharmacokinetic extension of ADME profiles.

THE PEOPLE

Prof. Arto Urtti (arto.urtti@helsinki.fi)

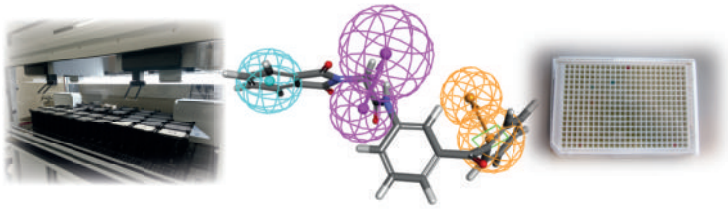
Dr. Päivi Tammela *Dr. Henri Xhaard* *Dr. Heidi Kidron*

THE PROJECTS

Integrated in vitro – in silico screening approach...

...in discovering novel antibacterials

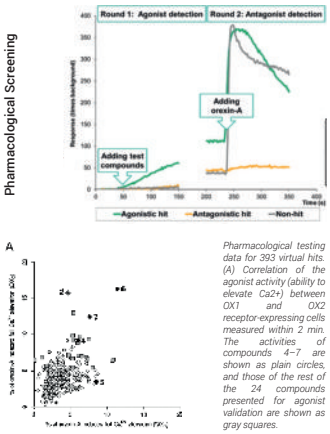
Multidrug-resistant bacterial infections are an increasing source of healthcare problems, and in this project, we developed a screening strategy that integrates cell-based HTS with in silico analogue search for antimicrobial small molecule drug discovery. We performed a HTS on a diverse chemical library by using an assay based on a bioluminescent E. coli K-12 (pTetLux1) strain. The HTS yielded eight hit compounds with >50% inhibition. These hits were then used for structural similarity- based virtual screening, and out of 29 analogues selected for in vitro testing, four compounds displayed potential activity in the pTetLux assay. The 11 most active compounds from combined HTS and analogue search were further assessed for antimicrobial activity against clinically important strains of E. coli and S. aureus and for in vitro cytotoxicity against human cells.



Pharmacophore model...

...to discover orexin receptor agonists

Orexin receptors are G protein-coupled receptors involved in sleep/wake regulation as well as other physiological functions such as metabolic regulation. Up to recently, only antagonists of these receptors were known and developed as a new class of compounds to treat insomnia. Agonists, useful as attention-altering agents or potentially to treat narcolepsy, had proven difficult to develop. Using a pharmacophore in silico screening combined with the testing of 400 compounds from the FIMM library obtained through DDCB, we discovered weak agonists of the Orexin receptors. We are now conducting follow-up studies searching for analogues of our hit compounds to test. In addition we are involved in discussions with the pharmaceutical industry about compound development.



Pharmacological testing data for 393 virtual hits. (A) Correlation of the agonist activity (ability to elevate Ca2+) between OX1 and OX2 receptor-expressing cells measured within 2 min. The activities of compounds 4–7 are shown as plain circles, and those of the rest of the 24 compounds presented for agonist validation are shown as gray squares.

THE HARDWARE

<u>*HTS screening systems:*</u>

- *Automated liquid handling (Biomek i7)*
- *Plate readers/imagers: Cytation 5, Varioskan LUX, Victor, Multiskan GO*

<u>*Readouts/ Screening technologies:*</u>

- *LUM, FI, TRF, ABS, HCS/Imaging*

<u>*Other instruments and infrastructure:*</u>

- *Biosafety level 2 microbiology and cell culture facilities*
- *96-well zeta sizer for particle size analyser (detection of precipitates)*
- *Analytical services: triple quadruple LC/MS instrument and Q-TOF MS*

Specialised on antimicrobial targets, efflux transporters and ADME profiling

THE SOFTWARE

<u>Software tools:</u>
We have access to academic licences to commercial software such as Scrödinger Maestro, Accelrys Discovery Studio, Volsurf+. Computational services include include: 1) Chemical library design; 2) Predictive computational ADME profiling; 3) Virtual screens, follow-up screens including both ligand- and structure- based methods; 4) Hit-to-lead compound design, bioisosteric replacements; 5) Data integration, KNIME workflows. Computational tools are being developed and made freely available to the scientific community; for example, predictive ADME models, and drug data mining tools. A web site has been developed in 2015 and published in 2016 and has already received considerable visibility (ADME/Tox and Adverse effects Predictive modelling, http://idaapm.helsinki.fi.

<u>Data analysis tools:</u>
Chem-/bioinformatics resources high performance supercomputing facilities are accessible both through the Finnish IT Center for Science. CSC-IT furthermore organize access to commercial software licences as a national consortia https://www.csc.fi/home.

THE OUTPUT

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2. *Wissel G, Kudryavtsev P, Ghemtio L, Tammela P, Wipf P, Yliperttula M, Finel M, Urtti A, Kidron H, Xhaard H. Exploring the structure-activity relationships of ABCC2 modulators using a screening approach. Bioorg. Med. Chem., 2015, 23:3513-25. http://dx.doi.org/10.1016/j.bmc.2015.04.029*
3. *Turku A, Borrel A, Leino TO, Karhu L, Kukkonen JP, Xhaard H. Pharmacophore model to discover OX1 and OX2 orexin receptor ligands. J. Med. Chem., 2016, 59:8263-75. doi: 10.1021/acs.jmedchem.6b00333*
4. *Legehar A, Xhaard H, Ghemtio L. IDAAPM: integrated database of ADMET and adverse effects of predictive modeling based on FDA approved drug data. J. Cheminform., 2016, 8, 33. doi: 10.1186/s13321-016-0141-7. eCollection 2016.*
5. *Sjöstedt N, Holvikari K, Tammela P, Kidron H. Inhibition of breast cancer resistance protein and multidrug resistance associated protein 2 by natural compounds and their derivatives. Mol. Pharm., 2017, 14(1):135-146. http://dx.doi.org/10.1021/acs.molpharmaceut.6b00754*

THE FUTURE

<u>Collaborations (academic/industrial):</u>
FIMM, Institute for Molecular Medicine Finland, Institute of Biotechnology, University of Helsinki, Neuroscience Centre, University of Helsinki, University of Eastern Finland

<u>Networks:</u>
Drug Discovery and Chemical Biology Network (national)
Nordic Chemical Biology Consortium

<u>Training capacities:</u>
Training for BSc, MSc, and PhD students in screening technologies and computational methods

- Development of phenotypic 3D-cell culture models and multispecies co-culture assays, and tools for their analyses
- Aiming to develop our computational activities as web-based services that use our own data and tools and will both provides visibility and access to customers

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