FINAL REPORT

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PI: **Dr. Csilla Laczka**

Title: **Development of new tools for studying the function and drug interaction pattern of organic anion transporters**

I. BACKGROUND

Organic Anion Transporting Polypeptides (OATPs) are exchangers mediating the cellular uptake of large, organic, amphipatic molecules [1]. At least four members of the family, OATP1A2, 1B1, 1B3 and 2B1 are multispecific transporters that, besides their endogenous substrates including bilirubin, bile acids and estrone-3-sulphate, recognize various drugs (including statins, antivirals and chemotherapeutics). These OATPs are important in the **intestinal absorption, hepatic clearance and blood to brain penetration** of diverse molecules both with endogenous and exogenous origin [2-4]. Co-administration of OATP substrates and inhibitors may lead to altered pharmacokinetics or even toxicity, termed as OATP-mediated drug-drug (DDI) or food-drug interaction (FDI) [5-8]. Documented DDIs identify OATP1B1 and OATP1B3 as key factors determining hepatic elimination of statins (atorvastatin, cerivastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) [8, 9]. Therefore, if the hepatic elimination of a drug candidate is expected, investigation of the interaction with OATP1B1 and OATP1B3 during early drug development is recommended by regulatory agencies, FDA (U.S. Food and Drug Administration), EMA (European Medicines Agency) and PMDA (Pharmaceuticals and Medical Devices Agency, Japan) [10-12].

Besides these extensively studied OATPs, several poorly investigated members of the family, e.g. the brain-specific OATP1C1, a thyroid hormone transporter, are also **pharmacological targets** [13, 14]. Additionally, OATPs have altered expression in various **pathological conditions,** e.g., in various cancers [15]. However, the relevance of this mis-regulated expression or whether this can be exploited in targeted chemotherapy has not yet been clarified.

Finally, our knowledge about the relevance of various OATP isoforms, arising from alternative transcription start or alternative splicing is also scarce [16-18].

II. AIMS OF THE PROJECT

1) ESTABLISHMENT OF FLUORESCENCE-BASED TECHNIQUES FOR LARGE SCALE SCREEN OF OATP FUNCTION

Multispecific OATPs, 1A2, 1B1, 1B3 and 2B1 are proven sites of DDI and FDI that may result in unexpected toxicity. Therefore, the interaction of these OATPs with drugs is crucial to be monitored at early stages of drug development. In these studies radioactive probes are routinely used, however compared to these, fluorescent probes may provide more sensitive, safe and cost-effective alternatives [19]. One of the aims of the current project was the development of such fluorescence-based assays for OATP1A2, OATP1C1 and OATP3A1, the under-investigated OATPs of the central nervous system.

2) TEST OF THE INTERACTION OF THE FLUORESCENT SUBSTRATES WITH FURTHER TRANSPORTERS

Governed action of hepatic OATPs and ATP Binding Cassette transporters (ABCs) ensures efficient hepatobiliary elimination of their substrates. Inhibition of hepatobiliary clearance e.g., by co-administration of their drug substrates, can result in severe side effects. Cells co-expressing OATP and ABC transporters are routinely applied to measure the vectorial transport of common OATP ABC substrates, and to investigate drug-drug interactions (DDI) mediated by these transporters. Radioactively labeled substrates have been repeatedly used in such assays. To date, fluorescence-based methods allowing the simultaneous investigation of OATP1B1 and ABC transporters have not been identified. Hence Aim 2 of the research proposal was to find common fluorescent substrates of hepatic OATPs and ABCs allowing their simultaneous in vitro investigation.

3) CHARACTERIZATION OF THE ROLE OF DRUG-TRANSPORTING OATPs IN ANTICANCER DRUG TOXICITY

Although the ability of OATP1A2, 1B1, 1B3 and 2B1 to transport anticancer drugs has been demonstrated [15], the exact role of OATPs in cancer, and their contribution to drug response is not yet clarified. Hence one of our aims was to investigate whether the function of these OATPs can be exploited to kill cancer cells.

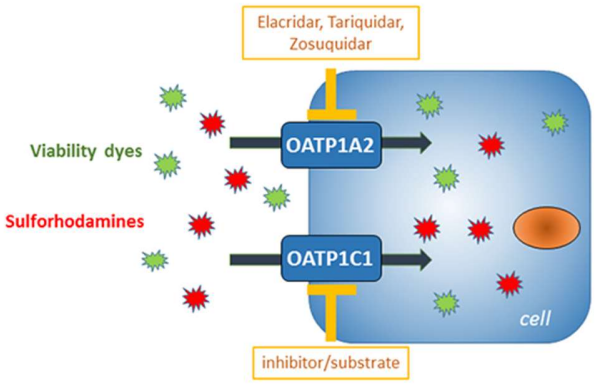
4) EVALUATION OF THE FUNCTIONAL/PHARMACOLOGICAL RELEVANCE OF OATP ISOFORMS

Besides the eleven major OATP protein variants, additional isoforms exist. These isoforms, e.g. the cancer-specific OATP1B3-V1, represent promising targets of pharmacology. However, a thorough analysis of their endogenous and exogenous substrates is still missing.

III. MAJOR ACHIEVEMENTS:

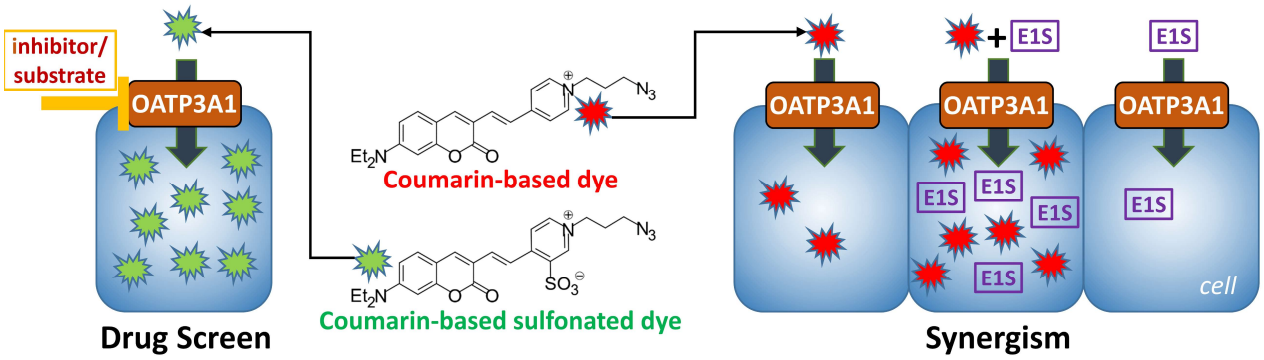
AIM 1:

- **Development of fluorescence-based assays for OATP1A2 and OATP1C1, OATPs of the central nervous system.** We identified sulforhodamines and a viability dye (Live/Dead Green) as excellent test substrates of OATP1A2 and OATP1C1. Using these dyes we set up a method suitable for sensitive detection of substrate/inhibitor interactions of these proteins. Moreover, the novel method allowed the identification of interaction between third generation P-glycoprotein (Multidrug resistance protein 1, member of the ATP Binding Cassette family, one of the key players of drug resistance) inhibitors, elacridar, tariquidar and zosuquidar and OATP1A2. Since OATP1A2 is abundantly expressed in the endothelial cells of the blood-brain barrier, our results indicate that OATP1A2-mediated uptake of these P-glycoprotein inhibitors may promote the accumulation of these compounds in the central nervous system and result in neurotoxicity. Indeed, we found that OATP1A2 results in increased cellular toxicity of elacridar (**V. Publication list, Bakos et al., 2020a**).

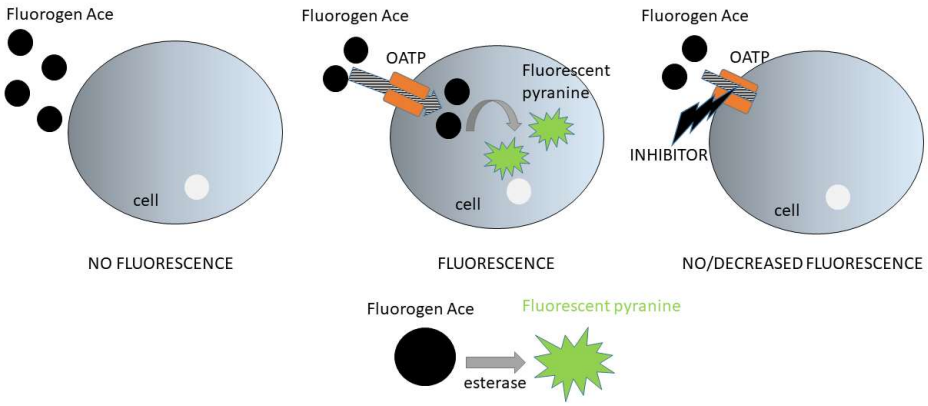


- **<u>Identification of coumarin-based dyes as sensitive probes and modulators of OATP3A1 function.</u>** We found that previously identified fluorescent probes of OATPs are not suitable to test OATP3A1 function. Hence, in the frame of the project additional fluorescent compounds were screened, and a series of dyes as high-capacity transported substrates of OATP3A1 were identified. We found that the novel probes are applicable to test drug interactions of OATP3A1. Moreover, the different inhibitory pattern of the probes and the reciprocal activation of the endogenous substrate estrone-3-sulfate and

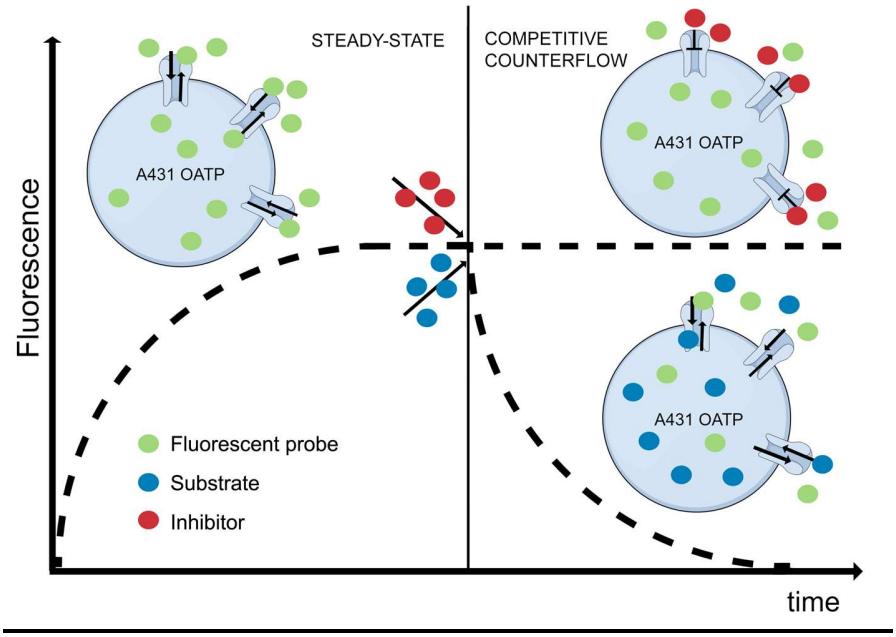
one of the coumarin-based dyes indicated the presence of multiple binding sites of OATP3A1. These results promote our understanding of the mechanism of OATP transport function and the design of pharmacological modulators (**V. Publication list, Bakos et al., 2020b**).



- **<u>Development of the first add-and-read method for the investigation of hepatic OATPs.</u>** Fluorescent probes provide a cheaper and more sensitive alternative to radioligands for the investigation of OATP drug interactions. However, since current probes (either radioactive or fluorescent) require the removal of the probe at the end of the experiment, they are not ideally suited for high-throughput screening. Hence, in the frame of the current work, we have tested a series of pyrene-based dyes, including a fluorogenic analog, acetoxy-pyranine that we identified as a substrate of hepatic OATPs, 1B1, 1B3 and 2B1. We showed that acetoxy-pyranine allows the simple, add-and-read assessment of OATP function, providing the first real time method for the investigation of hepatic OATPs (**V. Publication list, Ungvári et al., 2021**).



- **Development of an in vitro assay to discriminate OATP substrates and non-transported inhibitors.** Identification of transported substrates of OATPs requires the radioactive/fluorescent labeling of the candidate molecule, or HPLC and/or LC-MS/MS can be an alternative. Recently, an indirect assay based on the exchanger function of OATPs, termed as competitive counterflow (CCF) has been developed that discriminates transported and non-transported inhibitors of OATP2B1 and OATP1A2. However, no such assay has been available for the major hepatic OATPs, 1B1 and 1B3. In the current project we successfully applied acetoxy-pyranine in a CCF for OATP1B1 (**V. Publication list, Ungvári et al., 2021**). Since the method is unique, we have also handed in a patent application (**PCT/HU2020/050062**). Later, with the help of different fluorescent probes, we managed to set up the CCF method for all four multispecific OATPs, 1A2, 1B1, 1B3 and 2B1 (**V. Publication list, Ungvári et al., 2023**).



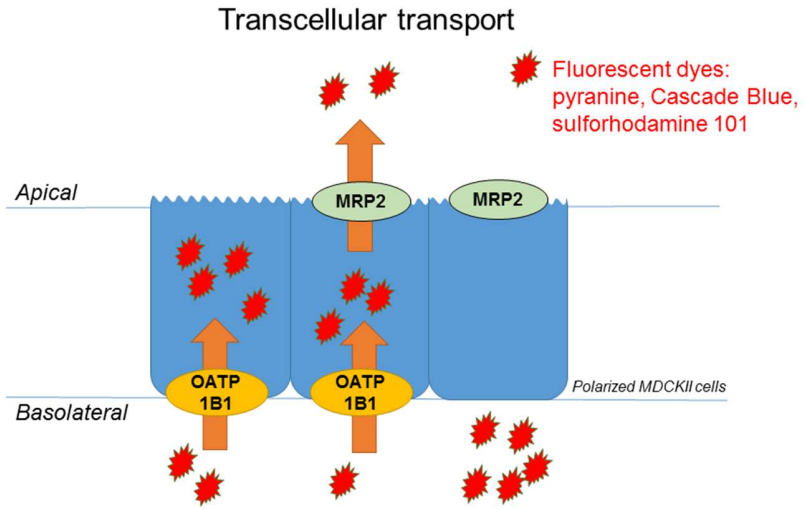
- **A review summarizing recent fluorescence-based assays for ABC and SLC (Solute carrier)-type drug transporters**, listing the various novel method developed in our laboratory was also prepared and published **(V. Publication list, Özvegy-Laczka et al., 2023).**

AIM 2:

- **A fluorescence method for assessing transport activity of OATPs and MRP2.** Governed action of hepatic OATPs and ABCs ensures efficient hepatobiliary elimination of their substrates. Inhibition of

hepatobiliary clearance e.g. by co-administration of their drug substrates, can result in severe side effects. Cells co-expressing OATP and ABC transporters are routinely applied to measure the vectorial transport of common OATP ABC substrates, and to investigate drug-drug interactions (DDI) mediated by these transporters. Radioactively labeled substrates have been repeatedly used in such assays. At the beginning of this project, fluorescence-based methods allowing the simultaneous investigation of OATP1B1 and ABC transporters have not been identified. In accordance with Aim 2 of the research proposal OATP1B/2B1 substrate dyes were investigated for interaction with other hepatic drug transporters of the ABC family, ABCC2/MRP2 and ABCG2. These studies lead to the identification of common OATP and ABC substrates and the establishment of the first fluorescence-based assay for the simultaneous investigation of the hepatic transporters OATP1B1 and MRP2. These data were compiled in a paper (**V. Publication list, Székely et al., 2020**). Moreover, an international patent application based on these novel findings was handed in (**PCT/HU2020/050014**).

Graphical abstract



AIM 3:

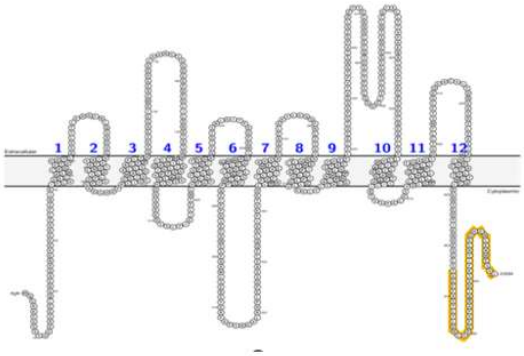
- **<u>OATPs in anticancer drug toxicity</u>.** In the frame of the current project using the previously established fluorescently labeled cell line overexpressing OATP2B1, a set of a 100-membered FDA-approved drug panel was screened. Compounds with an enhanced OATP2B1-mediated toxicity were looked for. We identified 13 compounds that kill OATP2B1 overexpressing cells with higher efficiency. These chemotherapeutics are potential OATP2B1 substrates. Indeed, in indirect transport measurements, their

interaction with OATP2B1 was proved. Our results indicate that OATP2B1 can be exploited to sensitize cells *in vitro* (**V. Publication list, Windt et al., 2019**).

- **OATPs in anticancer toxicity of estrone-based compounds.** In the current study, we have identified various 13α-estrone-based molecules as effective inhibitors of OATP2B1 (see **Chapter V. Publication list, Laczkó-Rigó et al., 2020 and 2021**). In order to investigate whether these estrone-based inhibitors can selectively be enriched in cells overexpressing OATP2B1, and hence result in increased cell killing, cytotoxicity measurements and direct transport of the best-performing compound were conducted. We demonstrated that 2-halogenated 13α-estrones can selectively inhibit the proliferation of OATP2B1-expressing cells most probably due to their increased OATP2B1-mediated cellular accumulation (**V. Publication list, Laczkó-Rigó et al., 2021**).

AIM 4:

- **Cloning and characterization of a novel OATP3A1 isoform.** OATP3A1 is a ubiquitously expressed protein mediating the uptake of estrone-3-sulfate, prostaglandins E1 and E2, and thyroxin. In the current study, based on protein database search, we identified a potential novel isoform of OATP3A1, that we named OATP3A1_V3. Based on qPCR data, we found that OATP3A1_V3 has highest expression in the human brain and testis. In order to characterize its function, we cloned the mRNA of OATP3A1_V3 from a brain mRNA library and expressed the corresponding protein in HEK-293 cells. Functional analysis of OATP3A1_V3 revealed that it is a functional transporter with similar substrate specificity as the previously characterized isoforms, OATP3A1_V1 and OATP3A1_V2. Localization studies performed on the polarized model cell line MDCKII engineered to overexpress OATP3A1_V1 or OATP3A1_V3 revealed distinct localization of the two isoforms. Moreover, by generating an anti-OATP3A1_V3 antibody, we have proven protein expression of this novel transporter variant in human brain and testis-derived tissue slices. Based on their overlapping substrate specificity but distinct localization, e.g., in choroid plexus cells, OATP3A1 isoforms may mediate transcellular movement of their substrates, e.g., that of neurosteroids (**V. Publication list, Bakos et al., 2022**).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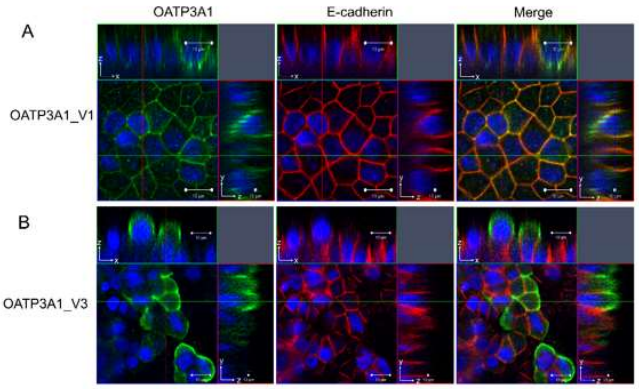
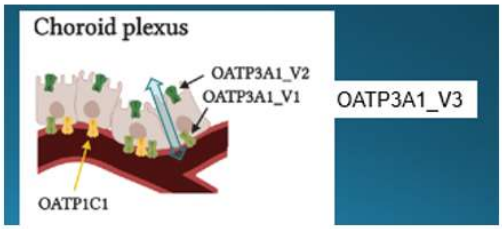

OATP3A1
E-cadherin
Merge
A
OATP3A1_V1
B
OATP3A1_V3


Choroid plexus
OATP3A1_V2
OATP3A1_V1
OATP1C1
OATP3A1_V3

IV. FURTHER ACHIEVEMENTS:

1) Identification of a novel class of OATP2B1 inhibitors

OATP2B1 is a multispecific transporter involved in ADME (absorption, distribution, metabolism and elimination) of various drugs. In addition, OATP2B1 is expressed in breast cancer cells. The substrate recognition of OATP2B1 is not fully understood. In our earlier work, we identified 13-epiestrones as potent inhibitors of OATP2B1. In the frame of the current project, with the help of our chemist collaborators, estrone-based molecules were systematically designed and synthesized in order to define molecular determinants of the interaction of 13α- and 13β-estrones with OATP2B1. A nanomolar OATP2B1 inhibitor was identified (**V. Publication list, Laczkó-Rigó et al., 2020 and Jójárt, Laczkó-Rigó et al., 2021**). In a further study, the specificity of estrone-based inhibitors was investigated, during which we identified several OATP2B1-selective inhibitors as well as general inhibitors of hepatic OATPs, 1B1, 1B3 and 2B1 (**V. Publication list, Tuerkova et al., 2021**). Finally, based on machine learning, 44 compounds were selected to dissect function of OATP1B1, OATP1B3 and OATP2B1. The in vitro activity profiling of these compounds was performed in our laboratory, by which we identified general and specific OATP1B and OATP2B1 inhibitors. These results helped the refining of the structural model of OATP1Bs and OATP2B1 which by the time of the study was not available (**V. Publication list, Tuerkova et al., 2022**).

2) Interaction of OATPs with antivirals

Maraviroc is regarded a safe anti-HIV agent with low toxicity and hence allowed for the treatment of pregnant women. However, the transport mechanism by which it crosses the placenta is still not clarified. When tested in the fluorescence-based assay, we detected interaction of maraviroc with OATPs, 1A2, 1B3 and 2B1. Further experiments revealed that maraviroc is a transported substrate of OATPs, 1A2 and 1B3, and hence these transporters are involved in the placental transport of maraviroc **(V. Publication list, Tupova et al., 2020)**.

3) Flavonoid metabolites may result in OATP-mediated food-drug interactions

Due to their wide-ranging positive health effects, flavonoids are widely marketed as dietary supplements. However, interaction of these ingredients with enzymes or transporters involved in drug absorption, distribution, metabolism or excretion may result in altered pharmacokinetics of co-administered medicines

or endogenous substrates. Although there is increasing literature of these food-drug interactions, flavonoid metabolites rapidly formed and present in the blood at high concentrations are poorly investigated in this regard. In our studies (**V. Publication list, Mohos et al., 2020a, Mohos et al., 2020b**), we show that chrysin, quercetin and isorhamnetin metabolites are high affinity inhibitors of hepatic, intestinal and central nervous system OATPs. Therefore, these interactions can be considered when co-applied with OATP drug substrates.

4)Analysis of the potential prognostic value of OATP4A1 SNPs in colorectal cancer

Overexpression of OATPs may influence the progression of tumors, as was earlier reported in the case of OATPs, 1B3, 2B1 and 4A1. However, the influence of OATP4A1 single nucleotide polymorphisms (SNPs) in tumor progression has not yet been investigated. In our work we generated various cellular models to investigate the two most common SNPs of OATP4A1, rs34419428, R70Q; rs1047099G, V78I, in regard of expression, localization and function. These studies revealed no major differences in the case of SNPs compared to the wild-type protein. Accordingly, analysis of colorectal cancer derived patient samples did not reveal any association between rs34419428 and rs1047099G and disease outcome. However, RFLP analysis revealed linkage equilibrium between rs34419428 and rs1047099G (**V. Publication list, Buxhofer-Ausch et al., 2020**).

5) **Interaction of OATPs with repurposed anti COVID-19 drugs**

The COVID-19 pandemic initiated the use of previously approved drugs (e.g. remdesivir, favipiravir) originally developed for the treatment of other diseases. However, since SARS-CoV-2 mostly affects(ed) co-morbid patients already on other medications, potential drug-drug interaction could not be thoroughly studied. With the help of the fluorescence-based methods developed in the frame of the current research grant, we contributed to the mapping of the interaction between several repurposed drugs and major drug transporters. This work resulted in three publications (**V. Publication list, Telbisz et al., 2021, Ambrus et al., 2021, Bakos et al., 2023).**

6) Identification of an FDA-approved drug as a novel OATP substrate

Using the novel fluorescence-based assays developed in the frame of the current project (Bakos et al., 2020a, Ungvári et al., 2021 and 2023) we have looked for novel drug-OATP interactions, in which we identified an FDA (the US Food and Drug Administration)-approved antiprotozoal agent, pentamidine as a specific and novel substrate of OATP1A2. Since OATP1A2 is highly expressed in blood-brain barrier

endothelial cells, it may promote the uptake of this drug into the central nervous system (**V. Publication list, Ungvári et al., 2023**).

7) <u>In vitro photodynamic activity of aza-BODIPY derivatives</u>

Photodynamic therapy offers a minimally invasive and specific treatment of cancer and various other diseases. The basis of PDT is that upon photoactivation, the light-sensitive dye generates reactive oxygen species (ROS) and hence results in cell death. It has been shown earlier, that cellular accumulation of various NIR dyes (near infrared dyes favourable for in vivo applications) suitable for PDT is mediated by OATPs. In the frame of the current study, we investigated the dark and light-induced toxicity of newly synthesized BODIPY derivatives (designed and synthesized by our chemist collaborators) on the cellular models generated earlier in our laboratory. Although we did not find enhanced toxicity of the dyes in OATP-expressing cells compared to their mock controls, we demonstrated that one of the new derivatives has enhanced light-induced toxicity (with IC_{50} in the nanomolar range) with no detectable dark toxicity even in the micromolar range (**V. Publication list, Hlogyik et al., 2023**).

V. PUBLICATIONS

with the support of the actual grant, 21 papers were published

1. Bakos É, Német O, Patik I, Kucsma N, Várady G, Szakács G, **Özvegy-Laczka C.** A novel fluorescence-based functional assay for human OATP1A2 and OATP1C1 identifies interaction between third-generation P-gp inhibitors and OATP1A2. FEBS J. 2020 Jun;287(12):2468-2485. doi: 10.1111/febs.15156. Epub 2019 Dec 17. PMID: 31770475
2. Windt T, Tóth S, Patik I, Sessler J, Kucsma N, Szepesi Á, Zdrazil B, **Özvegy-Laczka C.** , Szakács G. Identification of anticancer OATP2B1 substrates by an in vitro triple-fluorescence-based cytotoxicity screen. Arch Toxicol. 2019 Apr;93(4):953-964. doi: 10.1007/s00204-019-02417-6. Epub 2019 Mar 12. PMID: 30863990
3. Bakos É, Tusnády GE, Német O, Patik I, Magyar C, Németh K, Kele P, **Özvegy-Laczka C**. Synergistic transport of a fluorescent coumarin probe marks coumarins as pharmacological modulators of Organic anion-transporting polypeptide, OATP3A1. Biochem Pharmacol. 2020 Dec;182:114250. doi: 10.1016/j.bcp.2020.114250. Epub 2020 Sep 28. PMID: 32991865
4. Székely V, Patik I, Ungvári O, Telbisz Á, Szakács G, Bakos É, **Özvegy-Laczka C.** Fluorescent probes for the dual investigation of MRP2 and OATP1B1 function and drug interactions. Eur J Pharm Sci. 2020 Aug 1;151:105395. doi: 10.1016/j.ejps.2020.105395. Epub 2020 May 29. PMID: 32473861
5. Tupova L, Hirschmugl B, Sucha S, Pilarova V, Székely V, Bakos É, Novakova L, **Özvegy-Laczka C**, Wadsack C, Ceckova M Interplay of drug transporters P-glycoprotein (MDR1), MRP1, OATP1A2 and OATP1B3 in passage of maraviroc across human placenta. Biomed Pharmacother. 2020 Sep;129:110506. doi: 10.1016/j.biopha.2020.110506. Epub 2020 Jul 12. PMID: 32768979
6. Mohos V, Fliszár-Nyúl E, Ungvári O, Bakos É, Kuffa K, Bencsik T, Zsidó BZ, Hetényi C, Telbisz Á, **Özvegy-Laczka C**, Poór M. Effects of Chrysin and Its Major Conjugated Metabolites Chrysin-7-Sulfate and Chrysin-7-Glucuronide on Cytochrome P450 Enzymes and on OATP, P-gp, BCRP, and MRP2 Transporters. Drug Metab Dispos. 2020 Oct;48(10):1064-1073. doi: 10.1124/dmd.120.000085. Epub 2020 Jul 13. PMID: 32661014
7. Mohos V, Fliszár-Nyúl E, Ungvári O, Kuffa K, Needs PW, Kroon PA, Telbisz Á, **Özvegy-Laczka C,** Poór M. Inhibitory Effects of Quercetin and Its Main Methyl, Sulfate, and Glucuronic Acid Conjugates

on Cytochrome P450 Enzymes, and on OATP, BCRP and MRP2 Transporters.Nutrients. 2020 Jul 31;12(8):2306. doi: 10.3390/nu12082306.

8. Laczkó-Rigó R, Jójárt R, Mernyák E, Bakos É, Tuerkova A, Zdrazil B, **Özvegy-Laczka C.** Structural dissection of 13-epiestrones based on the interaction with human Organic anion-transporting polypeptide, OATP2B1. J Steroid Biochem Mol Biol. 2020 Jun;200:105652. doi: 10.1016/j.jsbmb.2020.105652. Epub 2020 Mar 6. PMID: 32147459
9. Buxhofer-Ausch V, Német O, Sheikh M, Andrikovics H, Reiner A, Ausch C, Mechtcheriakova D, Tordai A, Gleiss A, **Özvegy-Laczka C,** Jäger W, Thalhammer T. Two common polymorphic variants of OATP4A1 as potential risk factors for colorectal cancer.Oncol Lett. 2020 Nov;20(5):252. doi: 10.3892/ol.2020.12115. Epub 2020 Sep 17. PMID: 32994815
10. Ungvári O, Király L, Bakos É, **Özvegy-Laczka C.** 8-acetoxy-trisulfopyrene as the first activatable fluorogenic probe for add-and-read assessment of Organic anion-transporting polypeptides, OATP1B1, OATP1B3, and OATP2B1. FASEB J. 2021 Sep;35(9):e21863.
11. Laczkó-Rigó R, Bakos É, Jójárt R, Tömböly C, Mernyák E, **Özvegy-Laczka C.** Selective antiproliferative effect of C-2 halogenated 13α-estrones on cells expressing Organic anion-transporting polypeptide 2B1 (OATP2B1). Toxicol Appl Pharmacol. 2021 Aug 30;429
12. Tuerkova A, Ungvári O, Laczkó-Rigó R, Mernyák E, Szakács G, **Özvegy-Laczka C.** , Zdrazil B.J Data-Driven Ensemble Docking to Map Molecular Interactions of Steroid Analogs with Hepatic Organic Anion Transporting Polypeptides. Chem Inf Model. 2021 Jun 28;61(6):3109-3127.
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14. Telbisz Á, Ambrus C, Mózner O, Szabó E, Várady G, Bakos É, Sarkadi B, **Özvegy-Laczka C.** Interactions of Potential Anti-COVID-19 Compounds with Multispecific ABC and OATP Drug Transporters. Pharmaceutics. 2021 Jan 9;13(1):81.
15. Ambrus C, Bakos É, Sarkadi B, **Özvegy-Laczka C.**, Telbisz Á. Interactions of anti-COVID-19 drug candidates with hepatic transporters may cause liver toxicity and affect pharmacokinetics. Sci Rep. 2021 Sep 8;11(1):17810.
16. Bakos É, Német O, Kucsma N, Tőkési N, Stieger B, Rushing E, Tőkés AM, Kele P, Tusnády GE, **Özvegy-Laczka C.** Cloning and characterization of a novel functional organic anion transporting polypeptide 3A1 isoform highly expressed in the human brain and testis. Front Pharmacol. 2022 Sep 2;13:958023. doi: 10.3389/fphar.2022.958023. eCollection 2022. PMID: 36120371

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18. Bakos É, Temesszentandrási-Ambrus C, **Özvegy-Laczka C.** , Gáborik Z, Sarkadi B, Telbisz Á Interactions of the Anti-SARS-CoV-2 Agents Molnupiravir and Nirmatrelvir/Paxlovid with Human Drug Transporters. Int J Mol Sci. 2023 Jul 8;24(14):11237. doi: 10.3390/ijms241411237. PMID: 37510996
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VI. PATENT APPLICATIONS:

1. PCT/HU2020/050062 “A REAL-TIME, ADD-AND-READ FLUORESCENCE-BASED ASSAY FOR TESTING FUNCTION AND DRUG INTERACTIONS OF OATP TRANSPORTERS”
2. PCT/HU2020/050014 “Fluorescence method for assessing transport activity of OATPs and MRP2”

VII. FURTHER ACHIEVEMENTS 2.

- **PhD theses:** in total, 5 PhD students were involved in the project of which 3 students successfully completed their PhD studies: Izabel Patik (2020), Virág Székely (2021) and Réka Rigó (2022).

Writing of 2 more PhD theses is in progress: Orsolya Ungvári, expected defense in 2024 and Hana Kaci, expected defense in 2024.

- **Success of students involved in the project**

- 1st price at National Conference of Undergraduate Students Involved in Research (Virág Székely, 2019)
- Cooperative Doctoral Program (Orsolya Ungvári, 2021-2023)

- Csilla Laczka successfully applied for the **Doctor of Sciences title** of the Hungarian Academy of Sciences (2022).

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