Closing remarks

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LADME

	Key message	Note
LA	Understanding all LA parameters (pH dependent solubility, in stomach, precipitation in intestine, effect of micronization, efflux) is needed for right formulation strategy.	Betain HCLtransiently restores pH and helps stomach pH dependent solubility
A	Precision-cut intestinal slices are good models to study P-gp	
D	Spheroid model > applicable for screening for CPPs and stapling enhances brain delivery	Calibration is needed for prediction of brain penetration
D	Good concordance between in vitro and in vivo approaches to predict brain exposure	Not applicable for zwitterions and acids (yet)
D	MDCKII-MDR1, MDCKII-BCRP monolayers are widely applied tools to predict brain penetration of drugs	
D	Specific inhibitors (Valspodar, Ko143) can be used to set-up chemical knock-out models for P-gp and BCRP	Ko143 is unstable in plasma so samples should be collected into chilled tubes containing NaF
(M) E	Good understanding of role of sinusoidal uptake by OATPs	Role of OAT2 and OCT1 is emerging

DDI and Tox

	Key messages	Notes
DDI	Extensive understanding of P-gp-based tDDI	The ideal test system for DE is still investigated
DDI	Biomarkers > early DDI assessement	Full complexity should be looked at
DDI	Improved protocols (preincubation, calibration) provide more relevant data	Preincubation has an effect on IC50 data of multiple trps
DDI	Automation, high-speed bioanalysis and LIMS makes early application of ADME profiling possible	
DDI	HEK-BCRP membranes are superior to other BCRP-overexpressing membranes	
DDI	Accurate prediction of low fu values is possible	Current guidelines lead to overprediction of clinical DDI
Tox	High pos pred value (PPV) of hPTEC and high NPV of animal testing is best combination for nephrotox	Primary PTC cultures preserves expression of trps, including OATs
Tox	rBsep KD > best to monitor T3-BA and TCA-d4 in plasma	rBsep KD model > complex phenotype due to comp mech
Tox	ABCG2 inhibition (by SJ000831433?) may improve prognosis of high MYCN pediatric AML	Porhyrin inducing drugs > toxicity in patients with impaired ABCB6
Tox	DILISym predicts liver injury > increasingly used in	

Highlighted topics

Microbiota

- Role in producing new metabolites (EPAC M11)
- Role in deconjugation of glucuronide conjugates of EPAC/metabolites
- Role in deconjugation (deamidation) and reduction of of bile salts
- MoA of antibiotics induced DDI

Exosomes

- Communication between cells / organs
- Rich pool of biomarkers (represent protein, miRNA, etc profile of donor organs)
- Transfer of drug resistance is possible
- Way of tissue sampling

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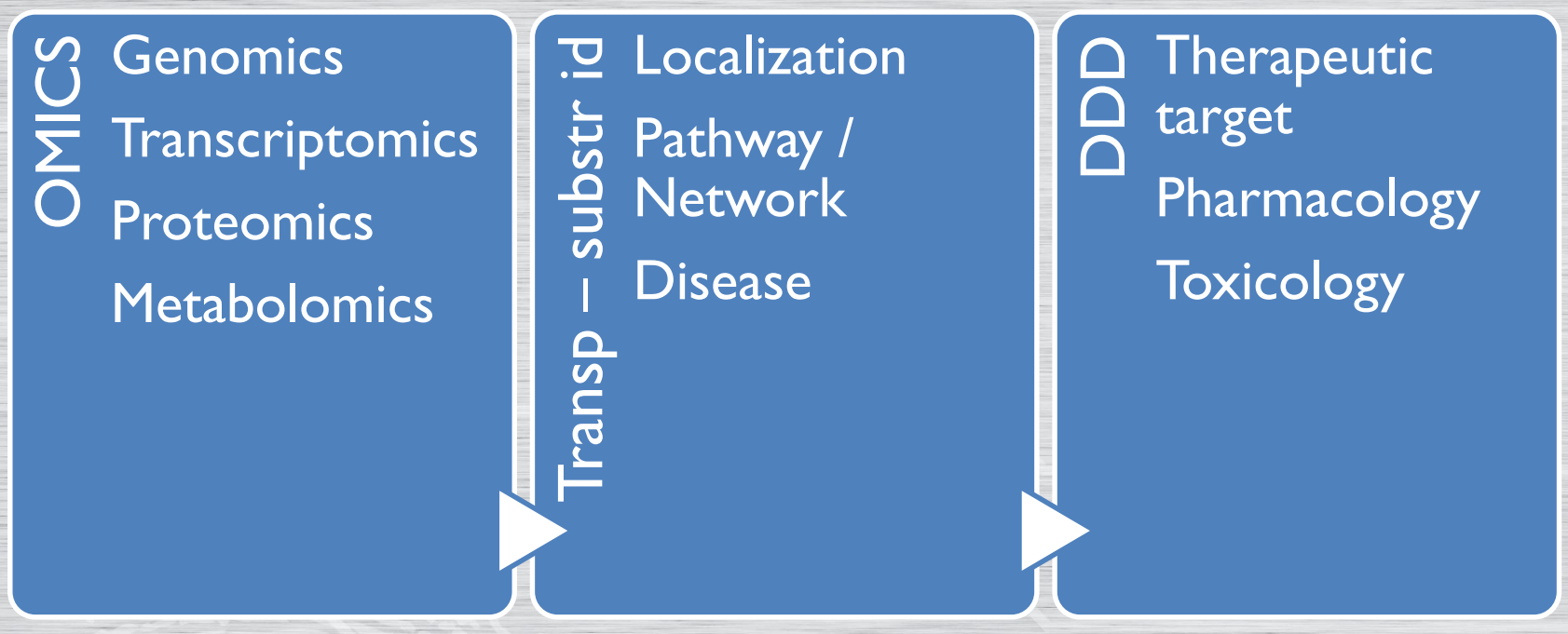
Technology and applications



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Therapeutic target

Influx

- BBB OATPs transport statins through BBB > reduce ischemic damage
- LAT1 and ASCT2 > BBB penetration, cancer
- SLC30A10 > ameliorates excess of Mn
- Updated version of BDDCS illuminates druggable targets

Efflux

- ABCG2 inhibition potential cure for MYCN AML

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Pharmacology – regulation of transporter activity

Inhibition

- **Non-covalent inhibitors (glifozins, urads, etc.)**
- Modulators of gene expression / activity (Crawford 2018 DMD)

Activation

- **Correctors (lumacraftor)**
- **Potentiators (ivacaftor)**
- Modulators of gene expression (ALK5 antagonists, ALK1 agonists > increased Oatp1a4 exp)
- Pathway modulators
  - GalNAc antisense to Tmprss6 > increased hepcidin > decreased Mn

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Subcellular localization of drug targets

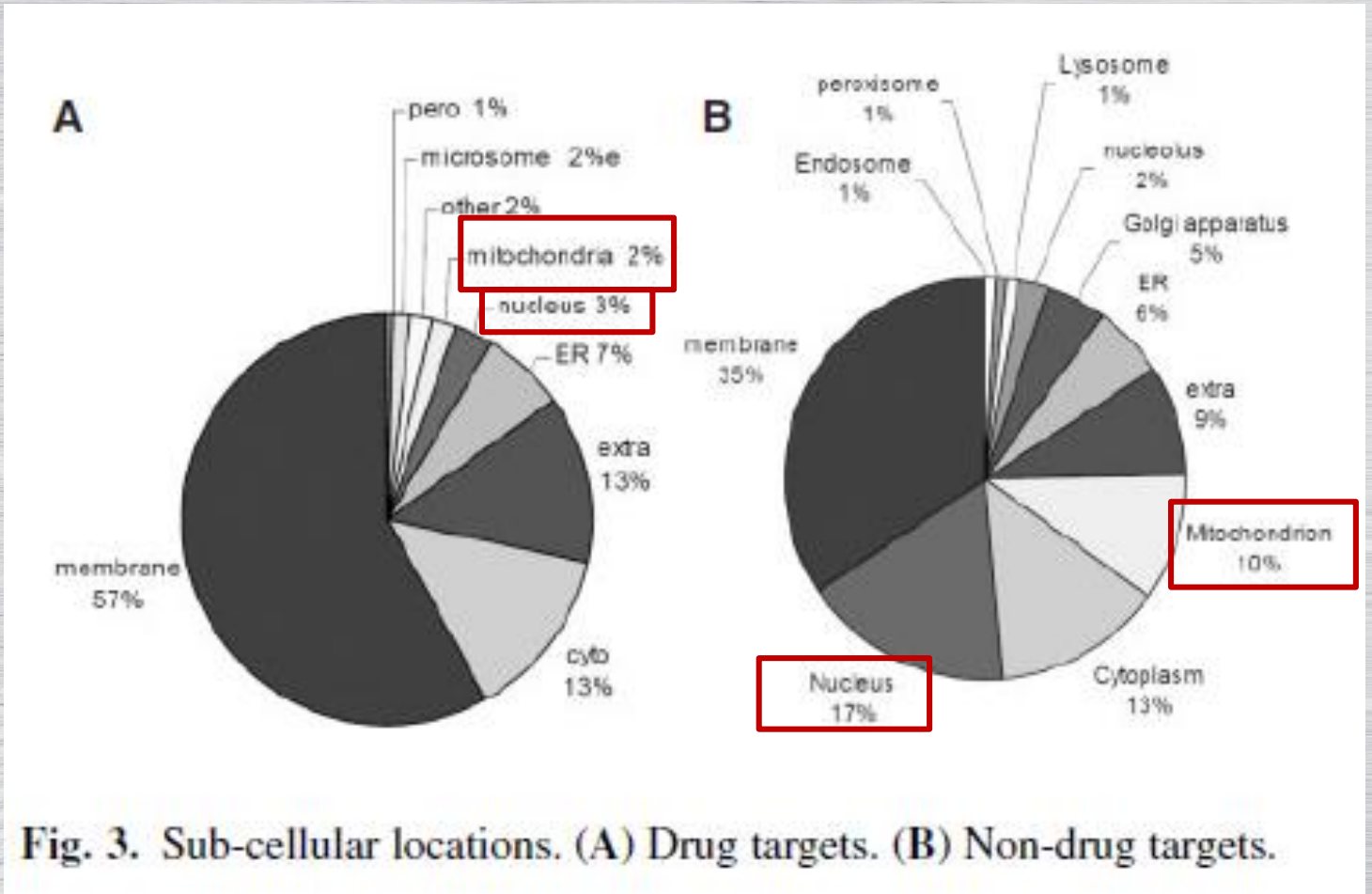

Fig. 3. Sub-cellular locations. (A) Drug targets. (B) Non-drug targets.

Bakheet 2009 Bioinf

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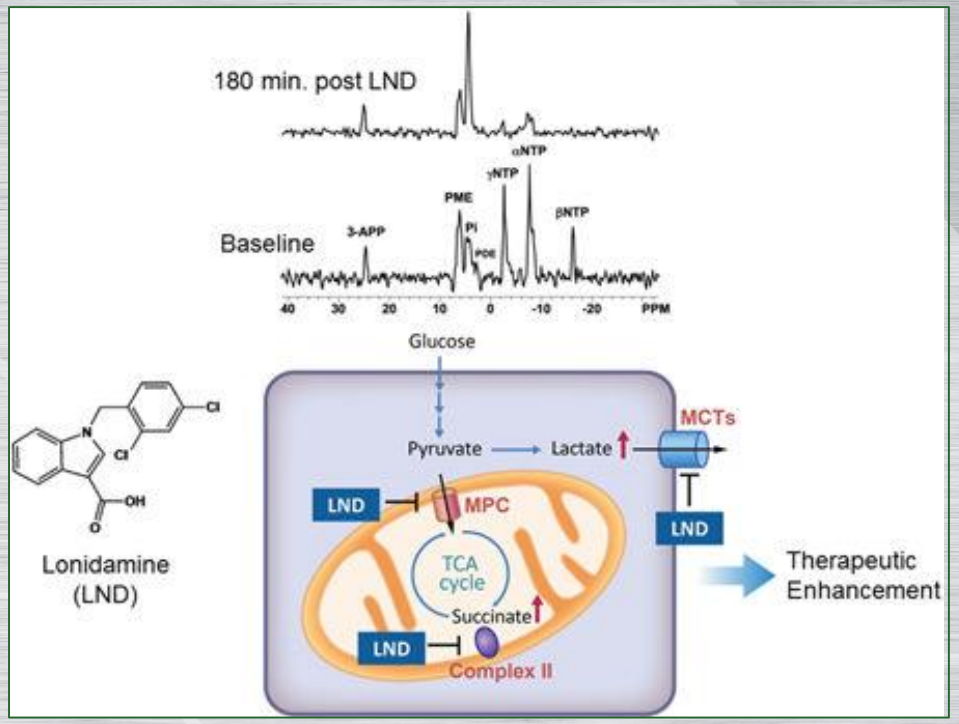
Toxicity /Adverse effects

Physiological substrate

- Modulation of transport
- Modulation of metabolism

Impaired homeostasis

- Toxicity
- Adverse events



- Greater availability of data for plasma membrane transporters > plasma levels go up (bile acids/salts, urate, bilirubin, etc.)
- Fewer examples for intracellular transporters
  - Pb2+, Mn2+, Cd2+ enter mitochondria via Ca2+ channels > replace Ca2+ > toxicity
  - Lonidamine toxicity – not toxic to normal cells

Nath 2016 BBA

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Transporter issues

Disease

- Transporters as therapeutic targets (BCRP, LAT1, ASCT2, Slc30a10)
- Transporters as determinants of PK of dugs (CNS drugs (P-gp, BCRP, Oatp1a4)
- Transporters as tissue/cell targeting of drugs (OCTN2, LAT1)

Preclinical testing

- in vitro / in vivo with reference to PK/PD properties (BBB models (transfectants, spheroids, in vivo), absorption (transfectants, precision cutslices)) excretion (kidney)
- tDDI tests (P-gp, OATPs, OCTs), biomarkers (cynos)
- Tox profile (BSEP, ABCB6, various kidney transporters, serotonin reuptake)
- Modeling / simulations (docking studies (LAT1, ASCT2), IVIVE (BBB), PBPK

Clinical testing

- tDDI (P-gp) / PGx / biomarkers
- Toxicity (hepatotoxicity, nephrotoxicity)
- PK / PD (plasma vs tissue levels)

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Thanks for attending
Special thanks to presenters

Have a safe trip home

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SW

Strength

- Understanding LADME parameters>right formulation strategy
- Extensive understanding of P-gp with regard DDI
- High positive predictive value (PPV) of hPTEC and high NPV of animal testing
- rBsep KD > best to monitor T3-BA and TCA-d4 in plasma
- Spheroid model > applicable for screening for CPPs
- Good concordance between in vitro and in vivo approaches to predict brain exposure
- Understanding role of sinusoidal uptake
- Improved protocols (preincubation, calibration) provide more relevant data

Weakness

- rBsep KD model > complex phenotype due to comp mech
- BBB spheroids>low dynamic range for efflux trp effects
- Not applicable for zwitterions and acids
- Preincubation has an effect on IC50 data of multiple trps

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OT

Opportunities

- Tools available to study molecular details of ADMETox (EPAC)
- Biomarkers > early DDI assessement
- Potentiation of Oatp-mediated uptake of statins > stroke treatment
- A selection of 1B1/1B3 probes / inhibitors offer greater relevance of DDI studies
- Accurate prediction of fu values is possible
- ABCG2 inhibition>potential to cure MYCN driven AML
- In silico LAT1 and ASCT2 work tools to study reprogramming metabolic networks and developing leads
- Targeting NPs to $ATB^{0,+}$ and OCTN2 increased uptake of nanoparticles
- DILISym predicts liver injury > increasingly used in reg submissions
- Automatipon, high-speed bioanalysis and LIMS makes early application of ADME profiling possible

Threats

- Potential interference with homeostasis of endogenous substrate (was not the case for EPAC)
- Current guidelines tend to overpredict clinical DDI
- Porhyrin inducing drugs>toxicity in patients with reduced/inhibited ABCB6 function

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