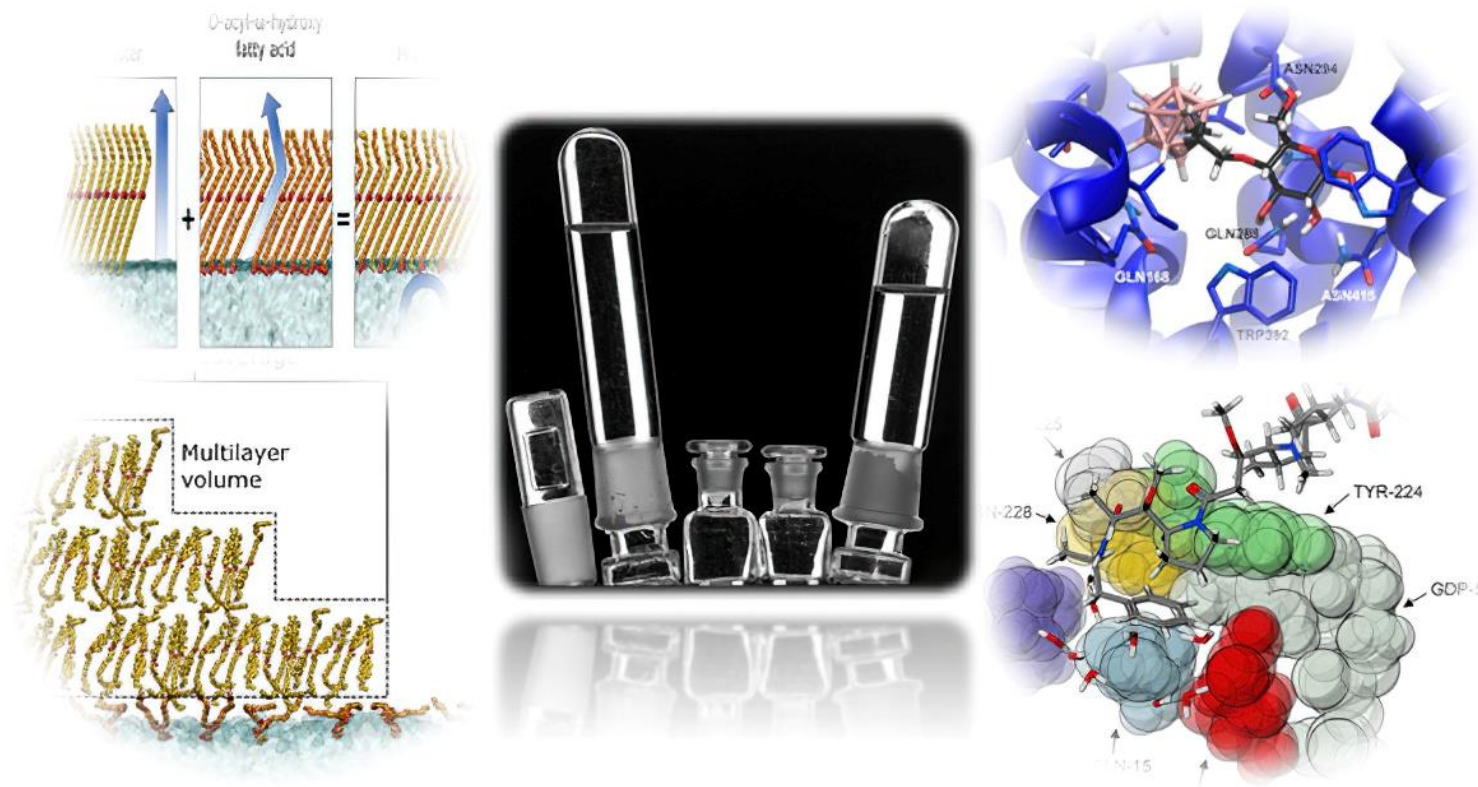




Lessons Learned from Developing a “Sweet” Delivery Strategy to BNCT

Assoc. Prof. PhD. Filip Ekholm
Head of the Biomolecular Chemistry Group
Department of Chemistry, University of Helsinki

The Biomolecular Chemistry group



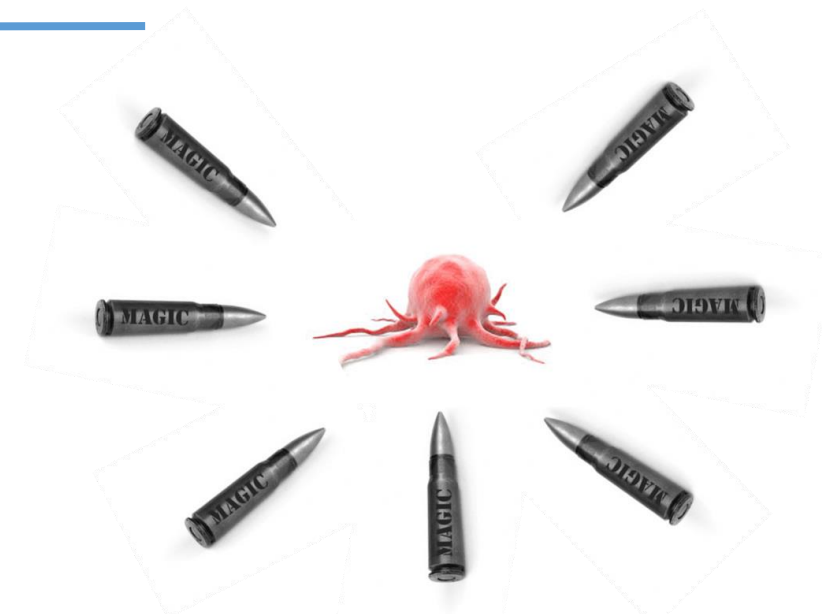
The Biomolecular Chemistry group was founded in 2017 at the Department of Chemistry, University of Helsinki. We belong to the sustainable chemistry for Health and Environment program. Our expertise resides in the synthesis, structural elucidation and profiling of biomolecules. We focus on application-oriented research topics at the interface of chemistry, medicine and biology.

Outline of Today's Presentation

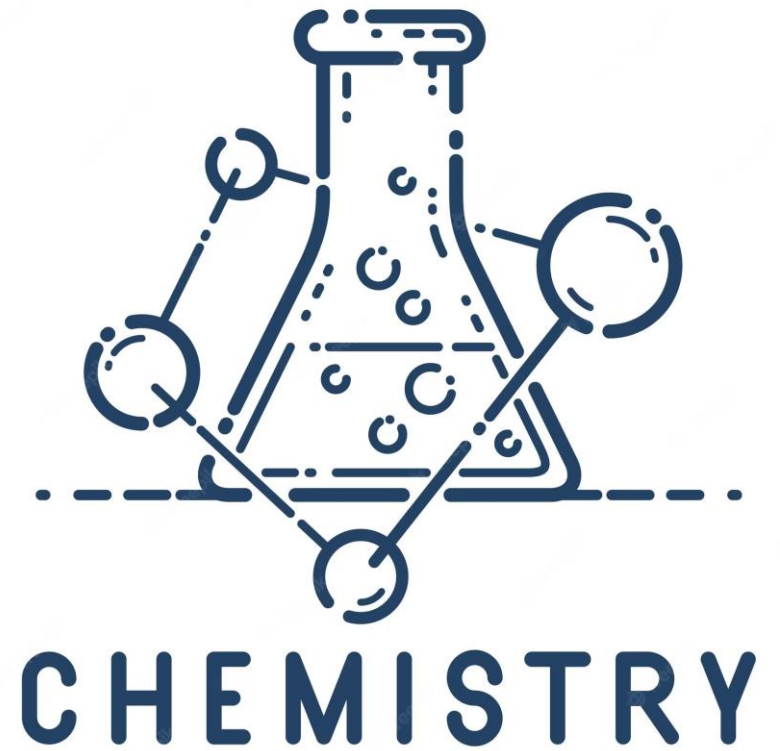
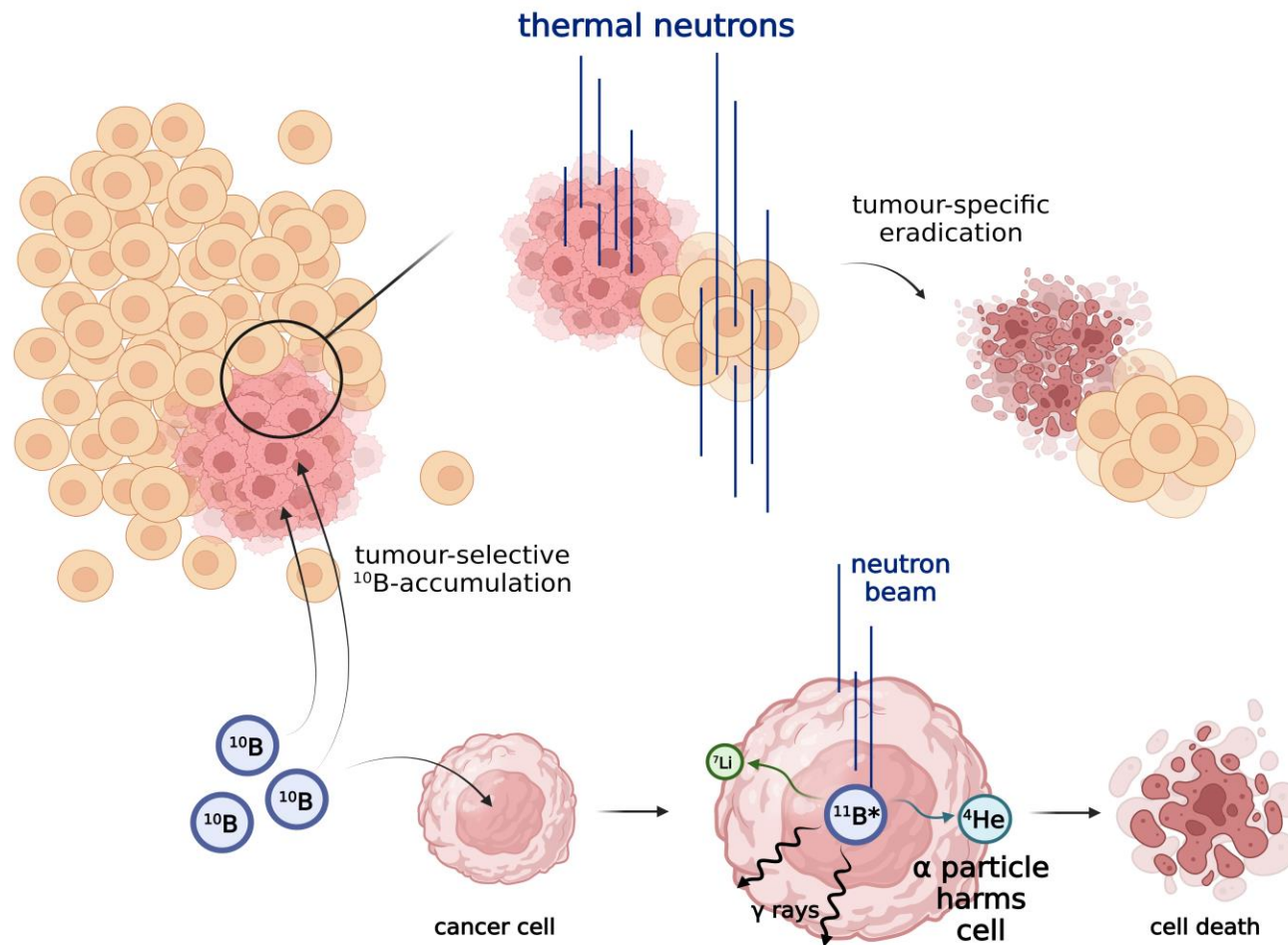
- BNCT and Chemistry
- Design of Medicinal Chemistry Projects in BNCT

- Stage I: Design of a GLUT-Targeting Approach to BNCT
- Stage II: Synthesis and Structural Characterization
- Stage III: *In Vitro* Profiling of Substrates

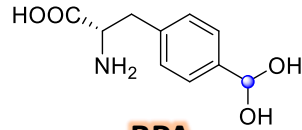
- Conclusions and Future Outlook



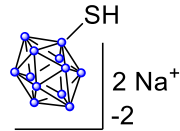
BNCT and Chemistry



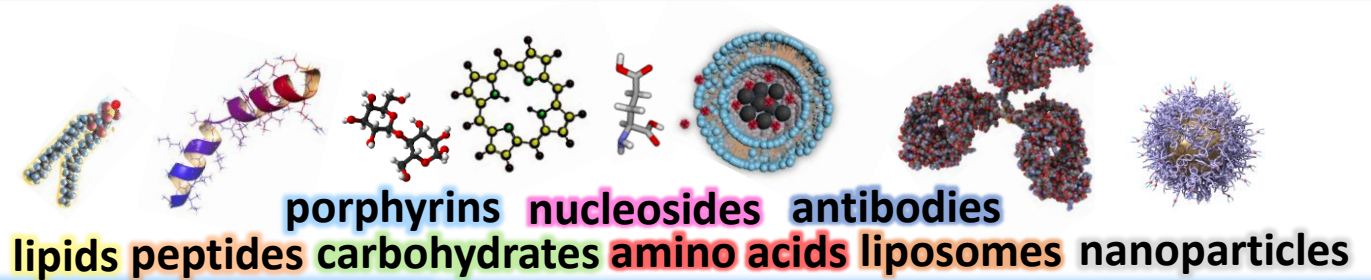
BNCT and Chemistry



BPA

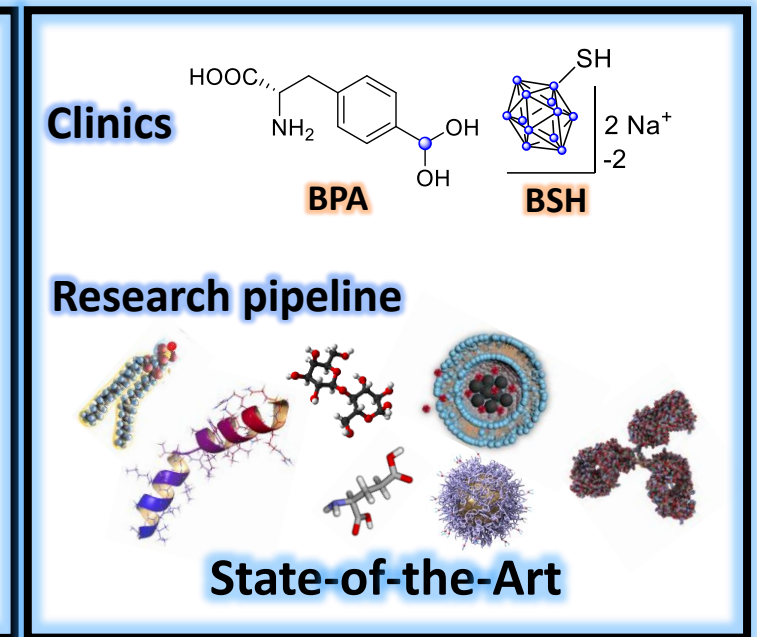
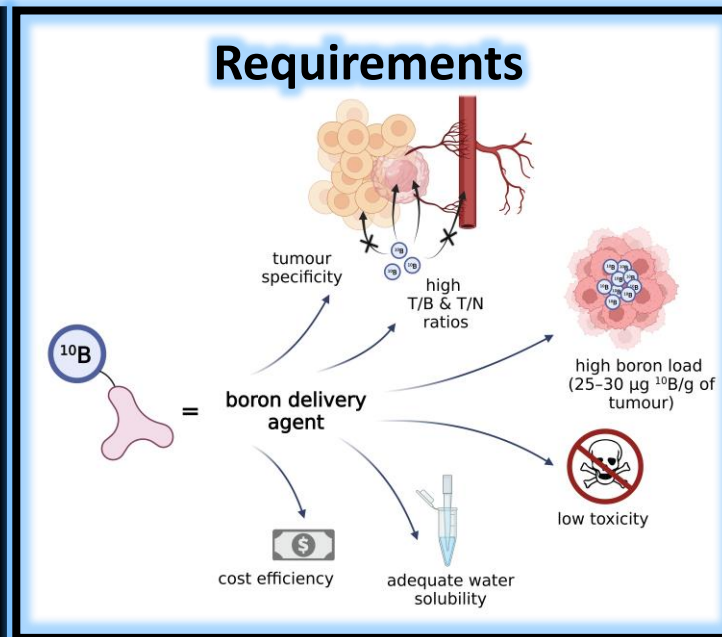
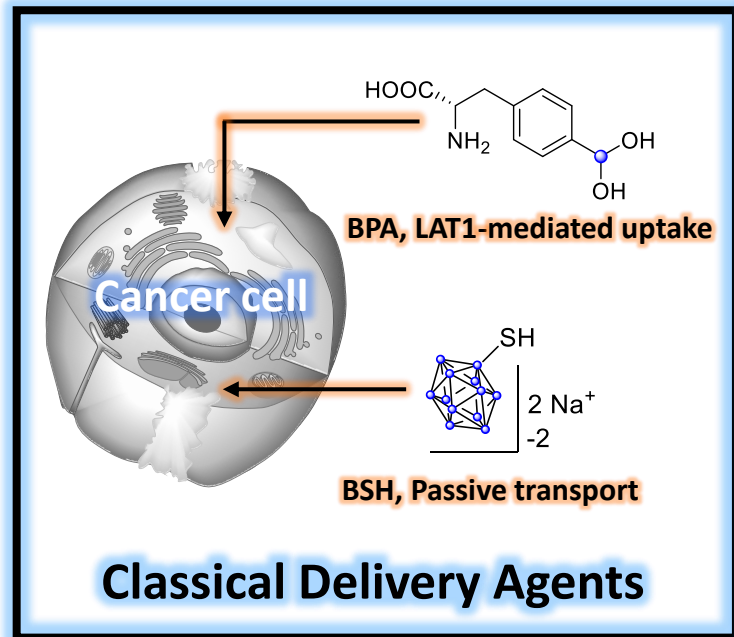


BSH

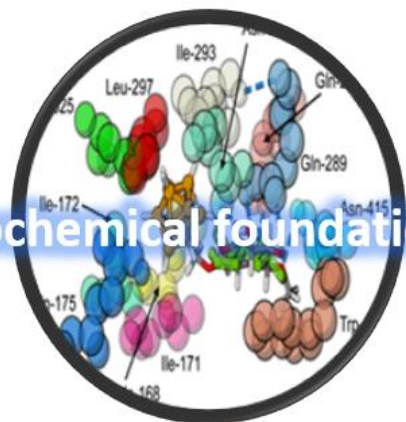


porphyrins nucleosides antibodies

Locher, 1936 *JACS* 1958 *J.Med.Chem.* 1967 *Chem. Rev.* 1998 *Cancer Commun.* 2018 *Coordin. Chem. Rev.* 2020



Design of Medicinal Chemistry Projects in BNCT



Molecular libraries

Biochemical foundations

Biological assessment

Labeling and imaging

Preclinical BNCT

Stage 1

Stage 2

Stage 3

Chemistry: Design and synthesis of new delivery agents

Molecular biology: Early-stage *in vitro/in vivo* assessment of delivery agents

Pharmacy: Formulation development

Radiopharmaceutical chemistry: Diagnostics and imaging platforms

Preclinical BNCT: Proof-of-concept *in vitro/in vivo* studies

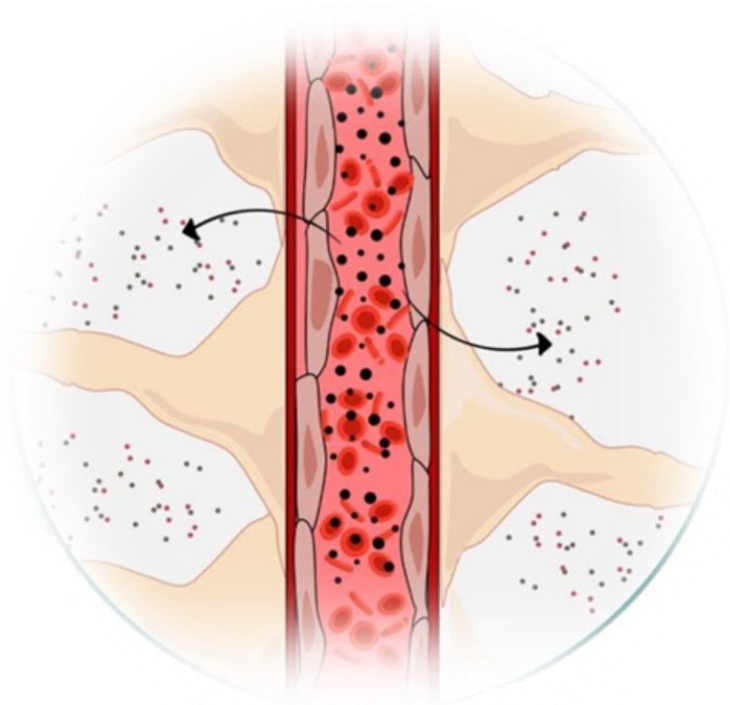
GMP-compliant manufacturing: Partnering with pharmaceutical companies/CMOs

Clinical BNCT-trials: Proof-of-concept in human

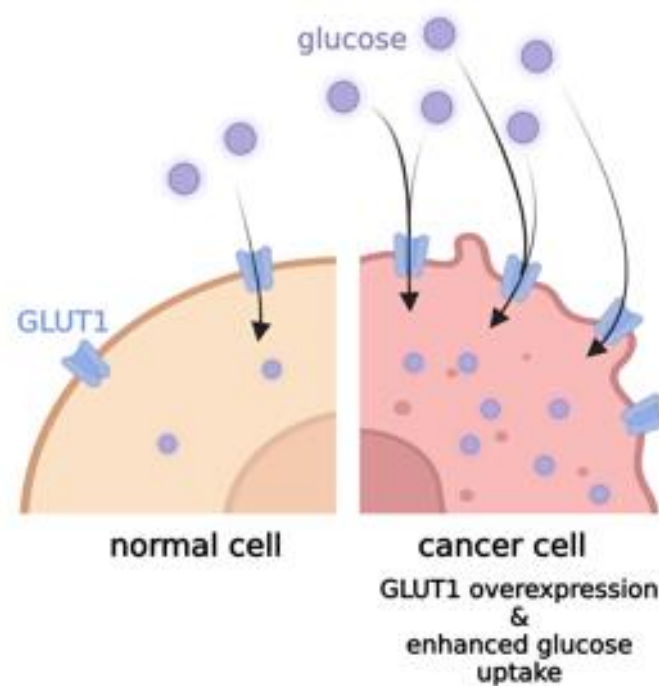


Scientists

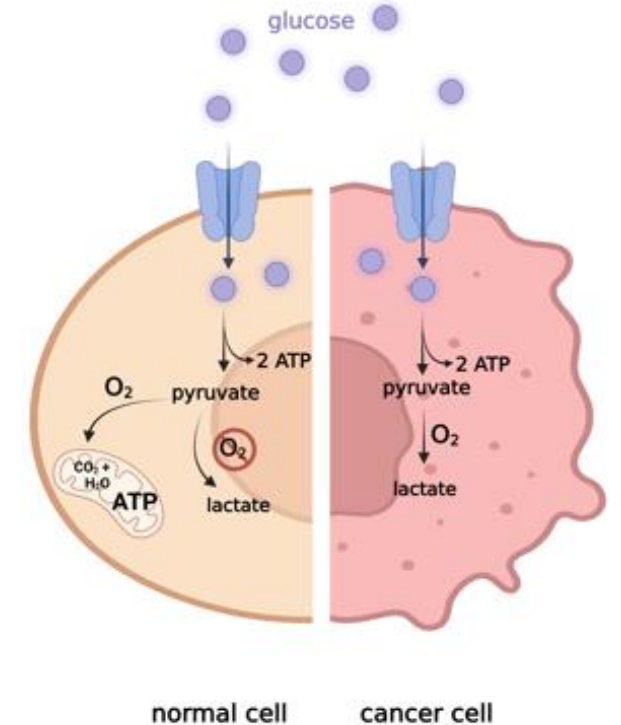
Stage I: Design of a GLUT-Targeting Approach to BNCT



Glucose and the BBB



GLUT-transporters & cancers



Impaired metabolism increases demand

Selected work on carbohydrates

Hawthorne, 1988 Adams, 1992 Tietze, 2003 Hosmane, 2012 Our team, 2020

Hawthorne, *Organometallics* **1988**, 7, 2519; Adams, *J. Med. Chem.* **1992**, 35, 1628; Tietze, *Chem. Eur. J.* **2003**, 4, 1179; Hosmane, *Dalton Trans.* **2012**, 31, 8982.

Stage I: Design of a GLUT-Targeting Approach to BNCT



Monni



Sarparanta



Laakkonen



Airaksinen



Rautio



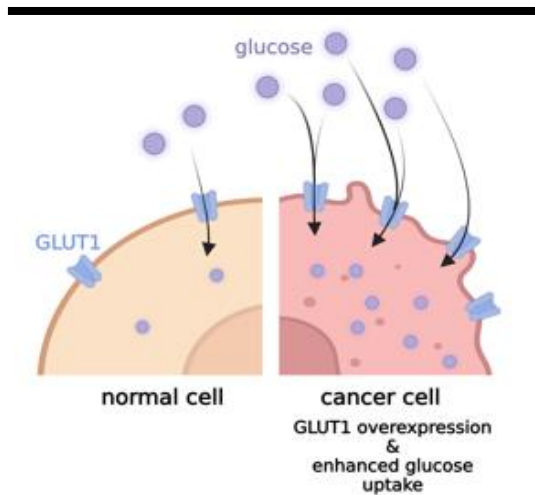
Hey-Hawkins



Johansson



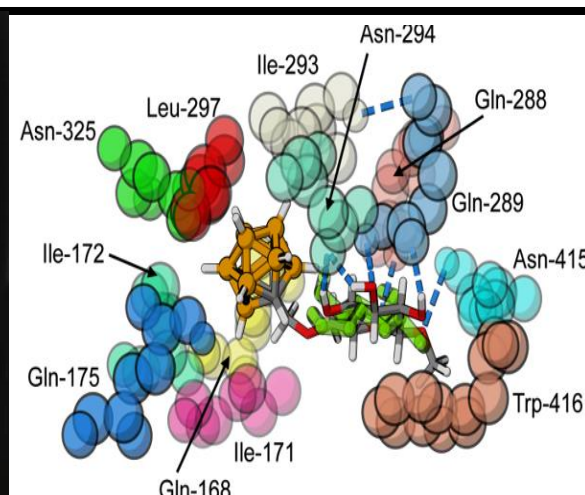
Maaheimo



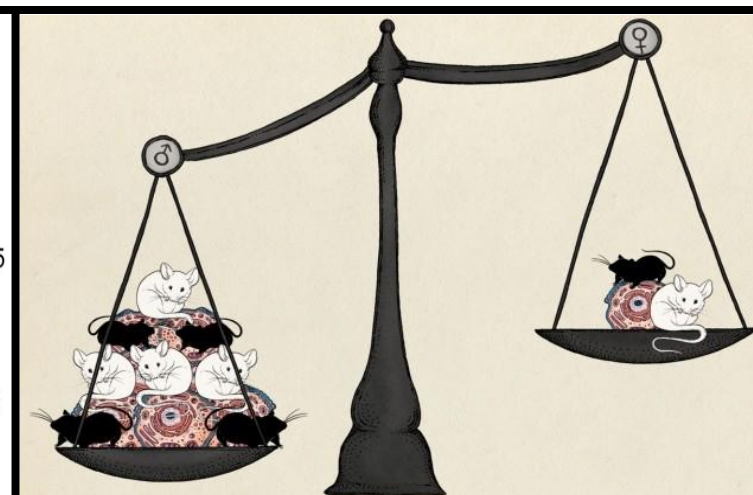
Selection of Target



Chemistry

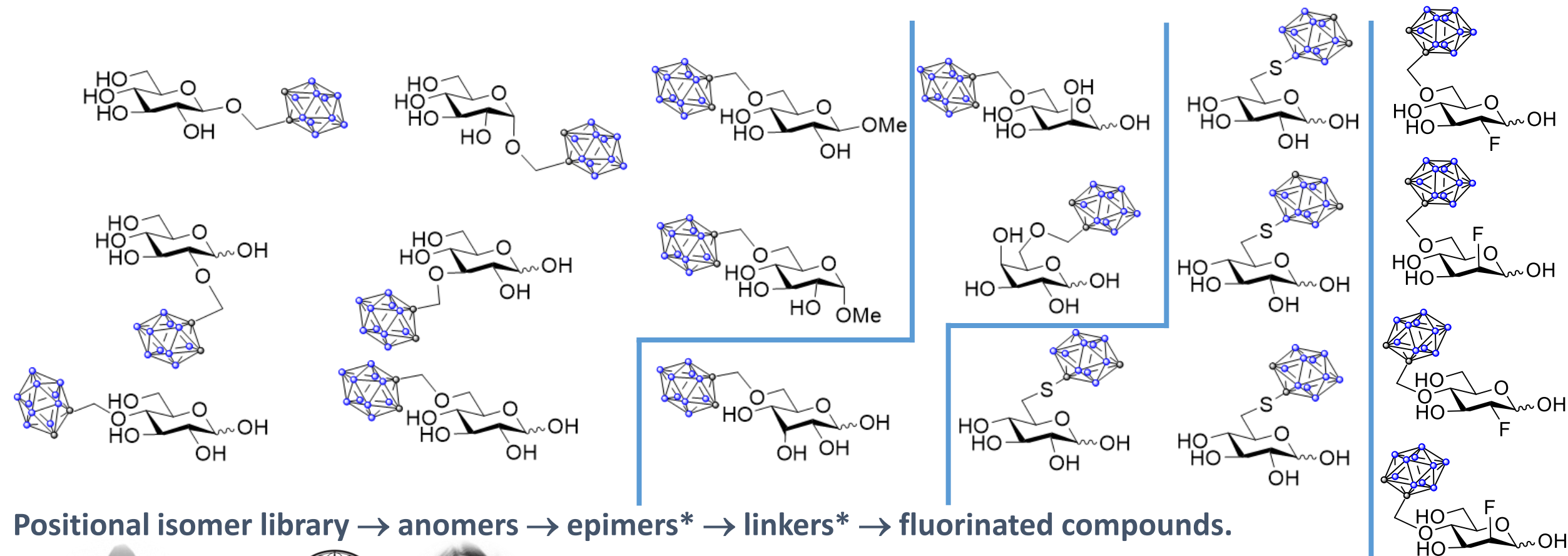


Molecular Biology



Preclinical Assessment

Stage II: Synthesis and Structural Characterization of Delivery Agents



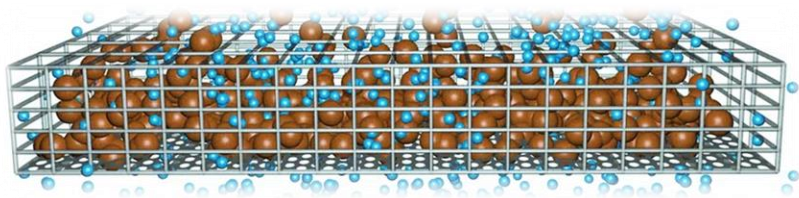
Matović



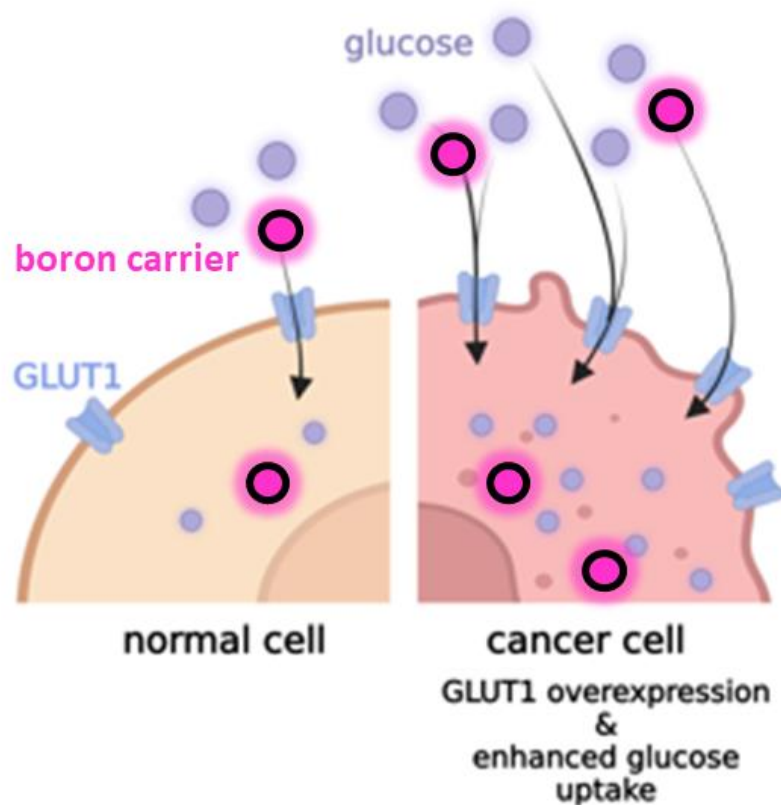
Team Hey-Hawkins

Mol. Pharmaceutics **2020**, *17*, 3885; *Mol. Pharmaceutics* **2021**, *18*, 285; *ACS Omega* **2022**, *7*, 30375; *Mol. Pharmaceutics* **2023**, *20*, 3127; *Molecules* **2024**, *29*, 4263. PhD-thesis of Jelena Matović.

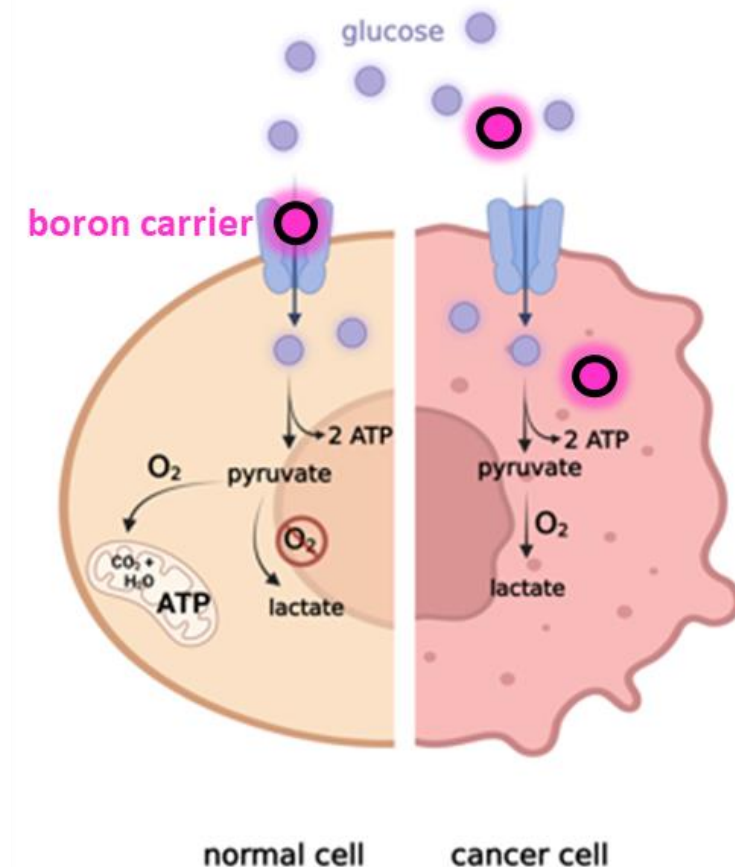
Stage III: *In Vitro* Profiling of Substrate Libraries



In vitro cytotoxicity
Stability/Protein Binding

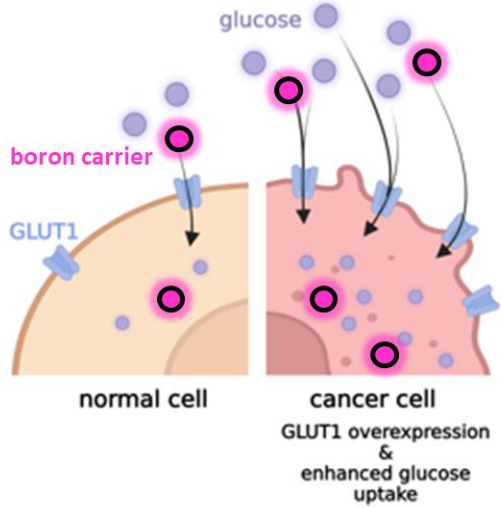


Transporter Affinity &
Boron Delivery Capacity



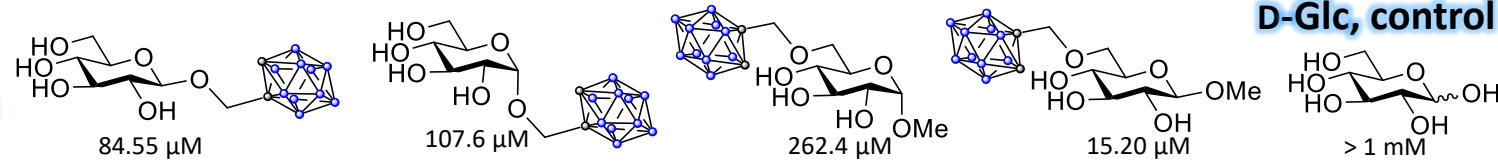
Metabolic Routes

Stage III: *In Vitro* Profiling of Substrate Libraries

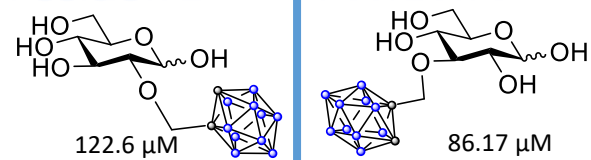


GLUT-Affinity

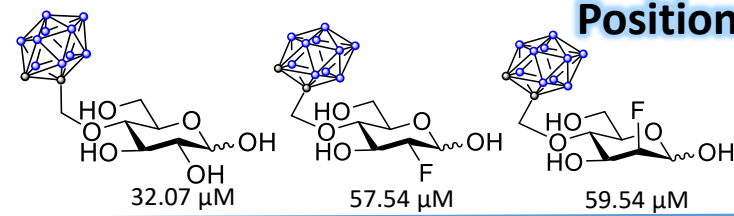
Position 1/glycosides



Position 2

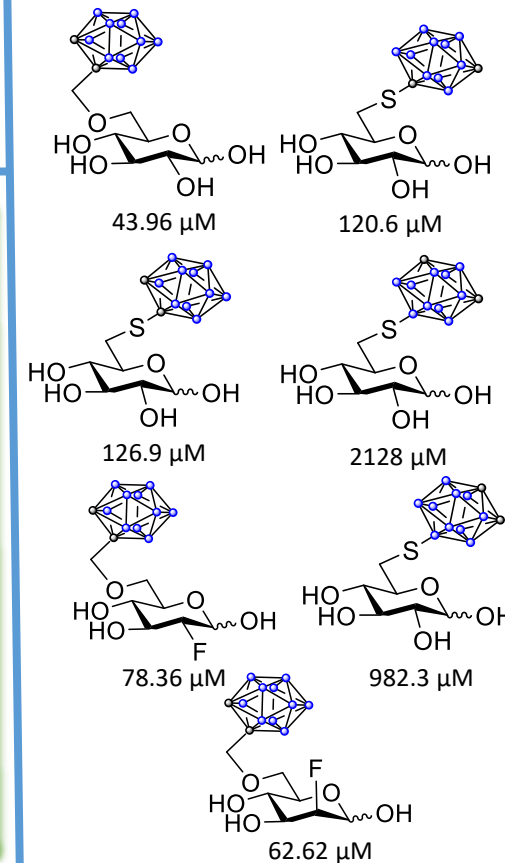


Position 3

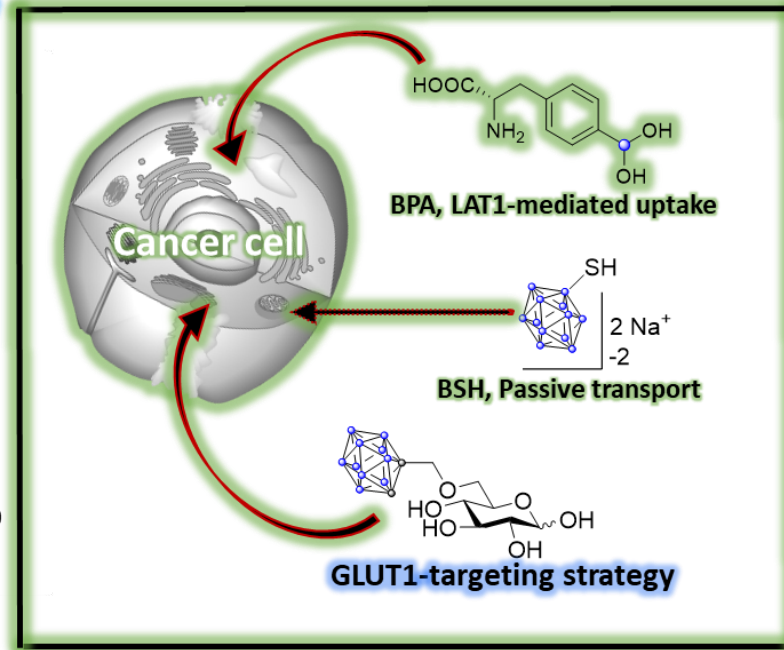
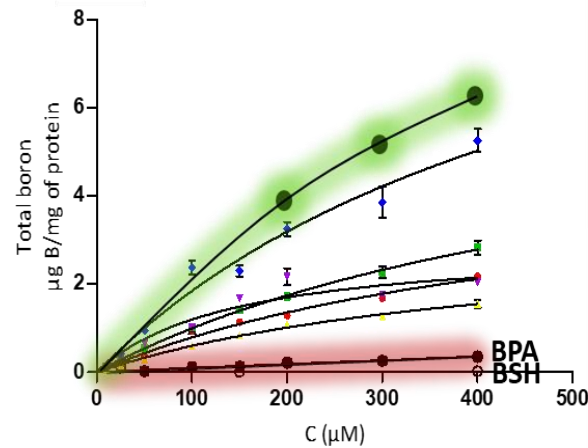


Position 4

Position 6



Boron Delivery Capacity



Transport Affinity & Boron Delivery Capacity



Team Rautio Team Johansson

Conclusions & Future Outlook

GLUT-Targeting Approach to BNCT

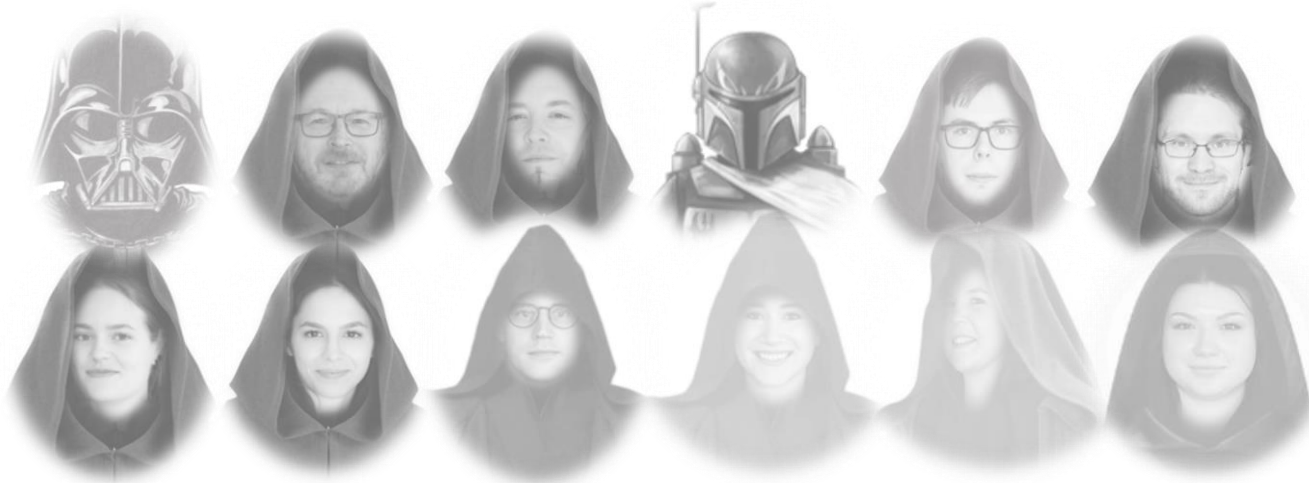
- Library of systematically modified glycoconjugate delivery agents
 - New insights on the requirements/substrate scope of the GLUTs
 - Excellent *in vitro* performance
 - *In vivo* manuscript under preparation (comparison to BPA-F)
 - The GLUT-targeting approach is probably not the future of clinical BNCT
-

Lessons Learned

- Setting up a medicinal chemistry program for BNCT is challenging
- Larger consortia would be beneficial for increasing the future prospects of BNCT
- From a chemists point-of-view: BPA is a very good delivery agent (clinics vs. mfg cost)
- Our team has continued working with other delivery strategies and are open to collaborative ventures

Acknowledgments

The Biomolecular Chemistry group:



Funding:



Collaborators on BNCT:



Sarparanta Rautio Monni Airaksinen Hey-Hawkins Johansson Maaheimo Laakkonen



Research project:

