MATEMAATIKA-LOODUSTEADUSKOND
KEEMIAINSTITUUT
TEADUS- JA ARENDUSTEGEVUSE ARUANNE 2014

1. Struktuur

Keemiainstituut, Department of Chemistry
Instituudi direktor prof Mihkel Kaljurand

- Analüütilise keemia õppetool, Chair of Analytical Chemistry, prof Mihkel Kaljurand
- Anorgaanilise keemia õppetool, Chair of Inorganic Chemistry, dotsent Toomas Tamm
- Bioorgaanilise keemia õppetool, Chair of Bioorganic Chemistry, prof Nigulas Samel
- Biotehnoloogia õppetool, Chair of Biotechnology, prof Raivo Vilu
- Molekulaartehnoloogia õppetool, Chair of Molecular Technology, prof Mati Karelson
- Orgaanilise keemia õppetool, Chair of Organic Chemistry, prof Margus Lopp
- Rohelise keemia õppetool, ERA Chair of Green Chemistry (alates 01.05.2014), prof Nicholas K.P. Gathergood (tööd alustab 01.01.2015)
- Keemilise analüüsi teadus- ja katselaboratoorium, Laboratory of Chemical Analysis, v-teadur Maria Kulp

2. Instituudi teadus- ja arendustegevuse iseloomustus

Chair of Analytical Chemistry. Analüütilise keemia õppetool - professor Mihkel Kaljurand

Research group A: **Computerized analytical separation methods.**
Komputeriseeritud analüütilised lahutusmeetodid – prof Mihkel Kaljurand

Three directions in research were aimed: determination chemical warfare agents and abused drugs in harsh environments and life signatures in the extra-terrestrial atmospheres using digital microfluidics. The research team lost financing from the Estonian Science Agency but thanks to the support from TTÜ (75 thousand Euros) and PECS grant from European Space Agency (ESA) „ Chemical analysis in shifting environments" the research was carried on in a satisfactory level. In addition the team participated in the NATO Science for Peace program which aimed to determination of dumped CWAs into the Baltic Sea (MODUM). Within the latter project the PhD student Heidi Lees was awarded stipend from the Ministry of Defence of Estonian Republic.

Publikatsioonid

Vaher, M.; Borissova, M.; Seiman, A.; Aid, T.; Kolde, H.; Kazarjan, J.; Kaljurand, M. (2014). Automatic Spot Preparation and Image Processing of Paper Microzone-Based Assays for Analysis of Bioactive Compounds in Plant Extracts. Food Chemistry, 143, 465 - 471.

Hyvärinen, S.; Mikkola, J.P.; Murzin, T. Yu.; Vaher, M.; Kaljurand, M.; Koel, M. (2014). Sugars and sugar derivatives in ionic liquids media obtained from lignocellulosic biomass: Comparizon of capillary electrophoresis and chromatographic analysis. Catalysis Today, 223, 18 - 24.

Levandi, T.; Püssa, T.; Vaher, M.; Ingver, A.; Koppel, R.; Kaljurand, M. (2014). Principal

component analysis of HPLC-MS/MS patterns of wheat (Triticum aestivum) varieties extracts Proceedings of the Estonian Academy of Sciences, 63(1), 86 - 92.

Kobrin, E-G.; Lees, H.; Fomitšenko, M.; Kubáň, P.; Kaljurand, M. "Fingerprinting postblast explosive residues by portable capillary electrophoresis with contactless conductivity detection." Electrophoresis, 2014, 35(8), 1165 - 1172.

Osalemised konverentsidel:
7th NoSSS Symposium – Nordic Separation Science. Society 7th Conference. 11–13 June, 2014 – osalesid M. Kaljurand, J. Gorbatsova, J. Mazina.
20th International Mass Spectrometry Conference, Geneva, Switzerland, August 24-29, 2014 – osalesid M.Vaher, M. Kuhtinskaja ja M. Kulp
MODUM Meeting , Helsingi, 15- 17. okt. 2014.a. – osalesid M. Vaher, M. Kuhtinskaja, H. Lees, P. Jõul
11th International Interdisciplinary Conference on Bioanalysis CECE 2014, October 20 - 22, 2014 – osales M. Kaljurand

Research group B: **New applications of supercritical CO_2 . Ülekriitilise CO_2 uusi rakendusi – Dr Mihkel Koel**

Grant from Estonian Research Council PUT 391(2014-16) Aerogels as materials for chemical analysis (ESTAG grant PUT-391 Aerogeelid materjalidena keemilise analüüsi jaoks)

Under the consideration are two types of aerogels: silica aerogel compositions, resorcinol-formaldehyde organic aerogels (RF) as raw material for carbon aerogels and modified carbon aerogels. Under the study are aerogel-based composite materials where cellulose could be the composite making polymer. Also the possibilities for modification of RF aerogels with metals using different methods for that is studied. Also:

- Finding exact correlations between important reaction parameters in aerogel processing steps and obtained nano-porous properties of aerogels;
- Development ways to combine inorganic (silica and carbon) aerogels with cellulosic material to obtain flexible porous materials;
- Development ways to incorporate different metals and metal complexes into the structure of aerogels;
- Obtained aerogels with different functional properties will be analysed against their physical, optical and electrochemical properties.

It is become evident that it is possible to tune the nanostructure of aerogel materials with determined particle size and surface area, which have suitable mechanical and chemical properties. Also aerogels together with ionic liquids can be used to obtain composite materials with properties useful to develop materials for sensors.

Publications:

S.Hyvärinen, J-P. Mikkola, D.Yu.Murzin, M.Vaher, M.Kaljurand, M.Koel, Sugars and sugar derivatives in ionic liquid media obtained from lignocellulosic biomass: Comparison of capillary electrophoresis and chromatographic analysis, Catalysis Today 223(2014)18-24.

K.Kreek, M.Kulp, M.Uibu, A.Mere, M.Koel, Preparation of metal-doped carbon aerogels from oil shale processing by-products, Oil Shale, 31,2(2014)185–194

Kristiina Kreek , Kadri Kriis , Birgit Maaten, Mai Uibu, Arvo Mere, Tõnis Kanger, Mihkel Koel, Organic and carbon aerogels containing rare-earth metals: Their properties and

application as catalysts, J. Non-Crystal. Solids, 404 (2014) 43–48

Korraldati rahvusvaheline konverents *EUCHEM2014 Molten Salts and Ionic Liquids*, Tallinn, 6-11 juuli 2014
Osaleti võrgustiku *Pohjoisen Itämeren alueen kestävä kemia ja prosessiteknologia* (POKE) töös, mille raames korraldati võrgustiku seminar Tallinnas ja osaleti võrgustiku teistel seminaridel ja suvekoolis.

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Chair of Organic Chemistry. Orgaanilise keemia õppetool – Professor Margus Lopp

Research projects:
1. IUT19-32 Directed asymmetric catalytic synthesis: an integrated approach; Suunatud asümmeetriline katalüütiline süntees: kompleksne integreeritud käsitlus (Prof. Margus Lopp)
2. TAR8103A Center of Excellence in Chemical Biology. Keemilise Bioloogia Tippkeskus (Prof. Margus Lopp)
3. AR12171 Development of Trk antagonists as drug candidates for the treatment of neuropathic pain. National R&D program „Biotechnology. Rahvuslik Biotehnoloogia programm. (Prof. Margus Lopp)

Main Scientific Results:
Projects 1 and 2. Investigations were carried out in three main directions:
a) new asymmetric reactions
b) synthesis of new compounds of bioactivity interest
c) computational chemistry to rationalize the obtained experimental results

Direction A: **New asymmetric reactions** (prof Margus Lopp, prof Tõnis Kanger)

- Sonogashira cross-coupling reaction of 3-bromo-1,2-diones with different alkynes was developed to open access to alkynylsubstituted 1,2-diketones – usefull starting compounds for many bioactive compounds [10]
- An asymmetric organocatalytic approach to spiro-cyclopropane oxindole derivatives was developed. Spiro-cyclopropanes were obtained in high enantiomeric purity and moderate to high yields. [2]
- The concept of remote activation of reactivity in organocatalytic alkylation of the isatin was discovered. The nucleophilicity of amide nitrogen was increased by using thiourea catalysts. [9]
- The mechanism of stereochemistry of the asymmetric transformation of Ti alkyl complexes in the cyclopropanation reaction was established. [7]

Direction B: **Synthesis of new compounds of bioactivity interest** (prof Margus Lopp)

- A general catalytic asymmetric method to obtain substituted lactone carboxylic acids was developed and described. The approach affords enantiomeric starting compounds for nucleoside analogues synthesis. [3]
- A general method to synthesize 5-S-functionalized pyrimidine nucleosides was developed. [1]
- Heterogeneous platinum catalytic oxidation of 1,2-diols was developed. [6]
- In the course of the total synthesis of 9,11-secosterols, asymmetric synthesis of 2,2,3-

trisubstituted cyclopentanone – D-ring fragment of the secosterol was developed. [4]

Direction C: **Computational chemistry** (prof Toomas Tamm)

- Computational studies of hemicucurbiturils were continued with modelling of the cavity of the 8-membered and larger macrocycles, and the binding modes of various guest molecules in it. The reaction mechanism of interconversion of 6- and 8- membered hemicucurbituril, including the re-cyclization, was studied in detail. The possible reaction pathways were determined and good agreement with experimental findings obtained. VCD spectra of the monomer used in synthesis of the hemicucurbiturils, was determined. Two papers have been published on these topics, with more in the pipeline. [13, 14]
- Reaction mechanisms of CO_2 fixation, as well as interconversion of the subsequent intermediates (formate, methanol), with use of on iridium-based catalysts were studied in additional detail. Several problems which were hindering progress in the area were successfully resolved. Two manuscripts are close to submission.
- Stability of different isomers anf conformers of complexes of Ti(OiPr)4 with cyclopentane-1,2-dione was established by using DFT calcualtions. [8]

Project 3. Development of Trk antagonists as drug candidates for the treatment of neuropathic pain. (Prof. Margus Lopp; project principal Prof. Tõnis Timmusk)
Indole-like TrkA inhibitors were synthesized and tested on TrkA inhibition

Project 4. **Design of heterogeneous metal catalysts supported on apatite** (Prof. Tõnis Kanger)
The following results were obtained:

- Synthesis and fully characterization of a new Cu modified hydroxyapatite was achieved;
- Cu modified apatite is an efficient catalyst for the Glaser Hay coupling reaction;
- The acetylenic homo-coupling occurs without additive bases and chelating ligands. The results of the project are presented in an article. [12]

2014 Publications of directions A, B and C:

1. Kananovich, D.G.; Reino, A.; Ilmarinen, K.; Rõõmusoks, M.; Karelson, M.; Lopp, M. A General Approach to the Synthesis of 5-S-functionalized Pyrimidine Nucleosides and their Analogues. Organic and Biomolecular Chemistry, 2014, 12, 5634 - 5644.
2. Ošeka, M.; Noole, A.; Žari, S.; Öeren, M.; Lopp, M.; Kanger, T. (2014). Asymmetric Diastereoselective Synthesis of Spirocyclopropane Derivatives of Oxindole. European Journal of Organic Chemistry, 2014, 17, 3599 - 3606.
3. Paju , Anne; Oja, Karolin; Matkevitš, Katharina; Lumi, Priit; Järving, Ivar; Pehk, Tõnis. Asymmetric synthesis of tertiary 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids. Heterocycles, 2014, 88(2), 981 - 995.
4. Kõllo, M.; Aav, R.; Tamp, S; Jarvet, J.; Lopp, M. Asymmetric synthesis of the 2,2,3-trisubstituted cyclopentanone, D-ring fragment of 9,11-secosterols. Tetrahedron, 2014, 70(38), 6723 - 6727.
5. Preegel, G.; Noole, A.; Ilmarinen, K.; Järving, I.; Kanger, T.; Pehk, T.; Lopp, M. Enantioselective Organocatalytic Michael Addition of Cyclopentane-1,2-diones to Nitroolefins. Synthesis, 2014, 46(19), 2595 - 2600.
6. Reile, Indrek; Kalle, Sigrid; Werner, Franz; Järving, Ivar; Kudrjashova, Marina; Paju, Anne; Lopp, Margus. Heterogeneous Platinum Catalytic Aerobic Oxidation of Cyclopentane-1,2-diols to Cyclopentane-1,2-diones . Tetrahedron, 2014, 70(22), 3608 - 3613.

7. Kulinkovich, O.G.; Kananovich, D.G.; Lopp, M.; Snieckus, V. Insight into the Mechanism and Stereochemistry of the Transformations of Alkyltitanium Ate-Complexes. An Enhanced Enantioselectivity in the Cyclopropanation of the Carboxylic Esters with Titanacyclopropane Reagents. Advanced Synthesis and Catalysis, 2014, 356(17), 3615 - 3626.
8. Osadchuk, I.; Pehk, T.; Paju, A.; Lopp, M.; Öeren, M.; Tamm, T.. Isomers and conformers of complexes of Ti(OiPr)4 with cyclopentane-1,2-dione: NMR study and DFT calculations. International Journal of Quantum Chemistry, 2014, 114(15), 1012 - 1018.
9. Žari, S.; Kudrjashova, M.; Pehk, T.; Lopp, M.; Kanger, T. Remote Activation of the Nucleophilicity of Isatin. Organic Letters, 2014, 16(6), 1740 - 1743.
10. Paju, A.; Kanger, T.; Müürisepp, A-M.; Aid, T.; Pehk, T.; Lopp, M. Sonogashira cross-coupling of 3-bromo-1,2-diones: an access to 3-alkynyl-1,2-diones. Tetrahedron, 2014, 70(35), 5843 – 5848
11. Kreek, K.; Kriis, K.; Maaten, B.; Uibu, M.; Mere, A.; Kanger, T.; Koel, M.. Organic and carbon aerogels containing rare-earth metals: Their properties and application as catalysts. Journal of Non-Crystalline Solids, 2014, 404, 43 - 48.
12. Maaten, B.; Moussa, J.; Desmarets, C.; Gredin, P.; Beaunier, P.; Kanger, T.; Tõnsuaadu, K.; Villemin, D.; Gruselle, M.. Cu-Modified Hydroxy-Apatite as Catalyst for Glaser-Hay C-C Homo- Coupling Reaction of Terminal Alkynes. Journal of Molecular Catalysis A: Chemical, 2014, 393, 112 - 116.
13. Oeren, M.; Shmatova, E.; Tamm, T.; Aav, R. Computational and ion mobility MS study of (all-S)-cyclohexylhemicucurbit[6]uril structure and complexes. Physical Chemistry Chemical Physics, 2014, 16(36), 19198-19205.
14. Fomitsenko, M.; Shmatova, E.; Oeren, M.; Jarving, I.; Aav, R. New homologues of chiral cyclohexylhemicucurbit[n]urils. Supramolecular Chemistry, 2014, 26(9), 698-703.

Research group D: **Molecular containers research group. Molekulaarsete mahutite uurimisgrupp – Dr Riina Aav**

The research in our supramolecular chemistry group focuses on development of new molecular containers, mainly chiral hemicucurbiturils. Development of methods for the synthesis of new chiral hemicucurbiturils is accompanied with the studies on their formation mechanism as well as host-guest and supramolecular properties. We consider that interplay between the fields of synthetic organic, physical and analytical chemistry is the bases for reaching new discoveries.

Main results in field of container molecules in year 2014:

- Existance of new chiral homologues of cyclohexylhemicucurbit[6]uril (cycHC6)were discovered and cycHC8 isolated. [1]
- Host-guest properties of cycHC6 were studied and formation of inclusion complexes with anions was confirmed. [2]
- Method for efficient syntheisis of cycHC8 was found.
- The formation mechanism of substituted hemicucurbiturils via dynamic combinatorial library is under study.

Publications of group members in 2014:

- Fomitšenko, M.; Shmatova, E.; Öeren, M.; Järving, I.; Aav, R. “New homologues of chiral cyclohexylhemicucurbit[n]urils” *Supramol. Chem.*, 2014 Vol. 26, No. 9, 698–703.
- Öeren, M.; Shmatova, E.; Toomas Tamm, Aav, R. “Computational and ion mobility MS

study of (all-S)-cyclohexylhemicucurbit[6]uril structure and complexes" *Phys.Chem.Chem.Phys*., 2014, 16, 19198 -19205.
- Kõllo, M.; Aav, R.; Tamp, S; Jarvet, J.; Lopp, M.. Asymmetric synthesis of the 2,2,3-trisubstituted cyclopentanone, D-ring fragment of 9,11-secosterols. *Tetrahedron,* 2014, 70(38), 6723 - 6727.
- Žari, S.; Metsala, A.; Kudrjashova, M.; Kaabel, S.; Järving, I.; Kanger, T. "Asymmetric Organocatalytic Aza-Michael Reactions of Isatin Derivatives" *Synthesis* 2015, 47, DOI: 10.1055/s-0034-1379956.
- Kobrin, E-G.; Lees, H.; Fomitšenko, M.; Kubáň, P.; Kaljurand, M. "Fingerprinting postblast explosive residues by portable capillary electrophoresis with contactless conductivity detection." *Electrophoresis*, 2014, 35(8), 1165 - 1172.

Chair of Bioorganic Chemistry. Bioorgaanilise keemia õppetool – prof Nigulas Samel

IUT 19-9 Structural and regulatory aspects of lipid and lipoprotein metabolism. Lipiidide ja lipoproteiinide metabolismi struktuursed ja regulatoorsed aspektid. Prof. Nigulas Samel (PI)

Lipids and lipoproteins have shown to play many dynamic roles in regulating a wide array of cellular activities including metabolic and gene regulation, energy production, and signalling pathways. Lipid mediators (prostaglandins, leukotrienes and other oxylipins) have been linked to the immune and inflammatory responses, cell proliferation and apoptosis, as well as shown to be essential determinants in many pathologies, including diabetes, cancer, cardiovascular and neurodegenerative disorders. Lipid and lipoprotein producing and metabolizing enzymes and lipid-regulating metabolic cascades have been targeted for drug development. The main goals of the project are: elucidation of fundamental structural, catalytic and regulatory aspects of enzymes responsible for biosynthesis of lipid mediators, and study of regulatory mechanisms of lipoprotein metabolism and endothelial lipolysis.

Research groups A, B and C:

A. Eicosanoids and eicosanoid metabolizing enzymes. Eikosanoidid ja neid metaboliseerivad ensüümid. Prof. Nigulas Samel (PI)

Research Description

We are interested in the mechanism of biosynthesis of oxygenated metabolites of arachidonic acid, and their role in homeostasis and survival of different organisms. The areas of our current interest are the following:

1. Structural and functional characterization of allene oxide – lipoxygenase fusion proteins (AOS-LOX). Structures of the metabolites and mechanisms of their formation. The role of the pathway in coral stress response;

2. Discovery and characterization of novel enzymes responsible for prostaglandin synthesis (cyclooxygenases (COX) and downstream isomerases) in lower organisms. Heterologous expression of human COXs in yeast culture;

3. Mutagenesis and X-ray crystallographic studies of calcium-mediated allosteric activation of lipoxygenases (LOX). Control mechanisms of oxygenation specificity of LOXs.

4. Mechanisms of platelet aggregation. Influence and synergetic effects of eicosanoids, antioxidants and glycose metabolites.

Main Findings in 2014

1. We showed that two AOS-LOX isoforms (AOS-LOXa and –b) which differ by their catalytic specificity and gene regulation exist in the soft coral *Capnella imbricata*. Our data suggest that the AOS-LOXa is involved in mediating early response to wound and temperature stress *in vivo*.

2. We cloned and characterized a novel membrane-associated prostaglandin E synthase-2 (mPGES-2) in two amphipod crustaceans. The amphipod enzymes are homologous with human mPGES-2, contain a conserved Cys110-x-x-Cys113 motif and have a very low heme-binding affinity. We assume that the amphipod mPGES-2, unlike its mammalian counterparts, is responsible for PGE_2 synthesis not only *in vitro* but also *in vivo*.

Human PGHS-1 and -2 were expressed in the yeast *Pichia pastoris*. Recombinant hPGHS-2 was catalytically active whereas hPGHS-1 was inactive. Characterization of N-glycosylation patterns by nano-LC/MS/MS showed that the isoforms exhibit similar N-glycosylation occupancy. Our results indicate that contrary to previous speculations, insufficient or improper N-glycosylation might not be the cause of COX-1 inactivity.

3. Mutagenesis studies of 11*R*-LOX showed that the π-cation bridge between Ca^{2+}–binding PLAT-domain and catalytic domain plays a crucial role in the Ca^{2+}–initiated allosteric regulation of LOX activity.

4. Glucose has been found to impair the inhibition of platelets with aspirin and alter the basal activity of nitric oxide synthase (NOS) in platelets. Our recent data obtained in studying the effects of glucose on the different inhibitory pathways in activated platelets support the suggestion that the effect of glucose on the inhibition of platelets by agents activating an NOS-dependent pathway is mediated by glucose metabolite lactate.

Publications in 2014

Teder, T.; Boeglin, W. E.; Brash, A. R. (2014). Lipoxygenase catalyzed transformation of epoxy fatty acids to hydroxy-endoperoxides: A potential P450 and lipoxygenase interaction. *Journal of Lipid Research*, 55(12), 2587 - 2596.

Hansen, K.; Varvas, K.; Järving, I.; Samel, N. (2014). Novel membrane-associated prostaglandin E synthase-2 from crustacean arthropods. *Comparative Biochemistry and Physiology. B-Biochemistry and Molecular Biology*, 174, 45 - 52.

Kukk, K.; Kasvandik, S.; Samel, N. (2014). N-glycosylation site occupancy in human prostaglandin H synthases expressed in *Pichia pastoris*. *SpringerPlus*, 3(436), 436.

Kobzar, G.; Mardla, V.; Samel, N. (2014). Lactate is a possible mediator of the glucose effect on platelet inhibition. *Platelets*, 25(4), 239 - 245.

Lõhelaid, H.; Teder, T.; Tõldsepp, K.; Ekins, M.; Samel, N. (2014). Up-Regulated Expression of AOS-LOXa and Increased Eicosanoid Synthesis in Response to Coral Wounding. *PLoS ONE*, 9(2), e89215.

B. Mechanisms of endothelial lipolysis. Endoteelse lipolüüsi mehhanismid. Uurimisgrupi juht juhtivteadur Aivar Lõokene

Teadustöö kirjeldus

Lipoproteins are noncovalent assemblies of lipids and proteins, a major function of which is to transport lipids through the vascular and extravascular body fluids. The lipoprotein

metabolism is under control of an intricate regulatory network that includes a number of proteins, lipids and proteoglycans. Patients at increased cardiovascular risk commonly display high levels of plasma triglyceride-rich lipoproteins, elevated LDL cholesterol, small dense LDL particles and low levels of HDL-cholesterol. Many remain at high risk even after successful lowering of LDL cholesterol, presumably because triglyceride levels remain high. Lipoprotein lipase (LPL) maintains triglyceride homeostasis in blood by hydrolysis of triglyceride-rich lipoproteins. The activity, stability and transport of LPL is influenced by a number of ligands such as apolipoproteins C-II, C-III and A-V, fatty acids, angiopoietin-like proteins 3 and 4, heparan sulfates and glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1). Of the above proteins, apolipoprotein A-V, angiopoietin-like proteins and GPIHBP1 were discovered only few years ago and their action is unknown yet. The main goal our group is to elucidate how metabolism of lipoproteins is regulated by molecular interactions between lipases, angiopoietin-like proteins, cell surface receptors, apolipoproteins and proteoglycans. The knowledge of these interactions in combination with available structural information provides the basis for the design of the drugs that could be used for the treatment of lipid metabolic disease.

Aruandeaastal saavutatud tähtsamad teadustulemused:
We have demonstrated that two regions of GPIHBP1, the acidic N-terminal domain and the central Ly6 domain, interact with LPL as two distinct binding sites. While LPL and the N-terminal domain formed a tight but short lived complex, characterized by fast on- and off-rates, the complex between LPL and the Ly6 domain formed more slowly and persisted for longer time. Unlike the interaction of LPL with the Ly6 domain, the interaction of LPL with the N-terminal domain was significantly weakened by salt. Heparin dissociated LPL from the N-terminal domain, and partially from wild type GPIHBP1, but was unable to elute the enzyme from the Ly6 domain. When LPL was in complex with the acidic peptide corresponding to the N-terminal domain of GPIHBP1, the enzyme retained its affinity for the Ly6 domain. Furthermore, LPL that was bound to the N-terminal domain was able to interact with lipoproteins, while LPL bound to the Ly6 domain was not. Our data suggest that the two domains of GPIHBP1 interact independently with LPL and that the functionality of LPL depends on its localization on GPIHBP1.
Given the central role of LPL in lipid metabolism we sought to find small molecules that could increase LPL activity and serve as starting points for drug development efforts against cardiovascular disease. Using a small molecule screening approach we have identified small molecules that can protect LPL from inactivation by the controller protein angiopoietin-like protein 4 during incubations in vitro. One of the selected compounds, 50F10, was directly shown to preserve the active homodimer structure of LPL, as demonstrated by heparin-Sepharose chromatography. On injection to hypertriglyceridemic apolipoprotein A-V deficient mice the compound ameliorated the postprandial response after an olive oil gavage. This is a potential leadcompound for the development of drugs that could reduce the residual risk associated with elevated plasma TGs in dyslipidemia.

Olulisemad publikatsioonid 2014:

Larsson, M.; Caraballo, R.; Ericsson, M.; Lookene, A.; Enquist, P.A.; Elofsson, M.; Nilsson, S.K.; Olivecrona, G. Identification of a small molecule that stabilizes lipoprotein lipase in vitro and lowers triglycerides in vivo. *Biochem Biophys Res Commun*. 2014, 450(2):1063-1069.

Reimund, M.; Larsson, M.; Kovrov, O., Kasvandik, S.; Olivecrona, G.; and Lookene, A. Evidence for Two Distinct Binding Sites for Lipoprotein Lipase on

Glycosylphosphatidylinositol-anchored High Density Lipoprotein-binding Protein 1 (GPIHBP1). *Journal of Biol. Chem*. In presss.

C. Research group for biocatalytic synthesis. Biokatalüütilise sünteesi uurimisgrup. Vanemteadur dr Omar Parve

Biocatalytic resolution of stereoisomers of 1,2-alkanediol and analogous tetrol compounds has been investigated. Biocatalytic stereoselective acylation and deacylation methods for the treatment of γ-hydroxycarboxylic acid sodium salts have been studied with the aim of stereoresolution of the corresponding γ-lactones, such as γ-valerolactone, Grieco lactone etc. A novel chiral derivatizing agent – [(1R)-1-[(2-chloroacetyl)oxymethyl]undecyl] benzoate for the stereochemical analysis of the γ-hydroxycarboxylic acid sodium salts which allows their trapping directly from the reaction mixture has been developed.

Tähtsamad teadustulemused:
1. Developing of the stereospecific lipase-catalytic acylation method for the treatment of Grieco lactone sodium salts in organic solvent for the resolution of enantiomers.
2. A novel chiral derivatizing agent – [(1R)-1-[(2-chloroacetyl)oxymethyl]undecyl] benzoate for the stereochemical analysis of the γ-hydroxycarboxylic acid sodium salts – which allows their trapping directly from the reaction mixture – has been developed.

Publikatsioonid:
1. Ly Villo, Andrus Metsala, Sven Tamp, Jaan Parve, Imre Vallikivi, Ivar Järving, Nigulas Samel, Ülo Lille, Tõnis Pehk, Omar Parve. Thermomyces lanuginosus Lipase with Closed Lid Catalyzes Elimination of Acetic Acid from 11-Acetyl-Prostaglandin E2. *ChemCatChem* 2014, 6, 1998-2010.
2. Andrus Metsala, Sven Tamp, Kady Danilas, Ülo Lille, Ly Villo, Sirje Vija, Tõnis Pehk, Omar Parve. An Assessment of Alternative Low Level Calculation Methods for the Initial Selection of Conformers of Diastereomeric Esters. *Journal of Theoretical Chemistry*, 2014, 1 - 10.
3. Jaan Parve, Lauri Vares, Indrek Reile, Tõnis Pehk, Ly Villo, Omar Parve (2015). Separation of (S)-1,2-Dodecanediol from Racemic Mixture by Lipase-Catalyzed Resolution and Simultaneous Selective Crystallization. Nuno Candeias (Toim.). Comprehensive Organic Chemistry Experiments for the Laboratory Classroom (1 - 7). London: Royal Soc Chemistry [ilmumas].
4. Jaan Parve, Indrek Reile, Tiina Aid, Marina Kudrjašova, Aleksander-Mati Müürisepp, Imre Vallikivi, Ly Villo, Riina Aav, Tõnis Pehk, Lauri Vares, Omar Parve Lipase-catalyzed stereoresolution of long-chain 1,2-alkanediols: a screening of preferable reaction conditions. *J. Mol. Cat. B: Enz*. 2015 [esitatud].

Hinnang oma teadustulemustele on hea, vt. eriti artikkel 1 ja artikkel 3.
Esimene töö, mis ilmus 2014 juunis kõrge reitinguga ajakirjas kirjeldab uut ensüüm-katalüüsiga seotud nähtust (milleks on kontsentratsioon-selektiivne süntees) ja selgitab teoreetiliselt selle mehhanismi.
Artikkel kolm on võetud vastu avaldamiseks raamatus, mis kujutab endast originaalsete uute meetodite – üliõpilastele sobivate praktikumitööde – kogumikku. Meie töö kirjeldab meie poolt väljatöötatud biokatalüütilist meetodit 1,2-dodekaandiooli (S)-enantiomeeri eraldamiseks ratsemaadist, milles ensüümkatalüütiline metanolüüs on täiendatud samaaegse kemo- ja stereoselektiivse kristallisatsiooniga otse reaktsioonisegust.

Chair of Biotechnology. Biotehnoloogia õppetool - prof Raivo Vilu

Food systems biology and physics. Toidu süsteemibioloogia ja füüsika. – prof Raivo Vilu

The key subjects of the study were: lactic acid bacteria, probiotics and yeast; development of single cell model of microorganisms; study of growth space of microorganisms; role of peptides and bioactive compounds as media components. The aims of the project were a) development of systems biology of microorganisms and food production processes using omics methods and mathematical modelling, and b) development of processes of anaerobic waste treatment, and biomethane production from different wastes including slaughterhouse solid wastes. .

Tulemused:
Single cell models (SCM) for the optimization of biotechnological processes of synthesis of biomass, ethanol, lactate etc. using recombinant E. coli and L. lactis based on the use of multi-omics data were developed . Models for aerobic growth of lactic acid bacteria were developed aand mutants for the study of regulation mechanisms were designed. Optimization of anaerobic processes of co-digestion of biodegradable wastes including solid slaughterhouse wastes was carried out. Evaluation of ecological efficiency of Estonian economy using multisector I/O models was carried out. Growth efficiency and amino acid metabolism of bacteria was evaluated using novel microcalorimetric methods for the study of lactic acid bacteria in milk and milk gels.

Publikatsioonid

Aller, Kadri; Adamberg, Kaarel; Timarova, Veronica; Seiman, Andrus; Feštšenko, Darja; Vilu, Raivo (2014). Nutritional requirements and media development for Lactococcus lactis IL1403. *Applied Microbiology and Biotechnology*, 98, 5871 - 5881.

Lahtvee, Petri-Jaan; Seiman, Andrus; Arike, Liisa; Adamberg, Kaarel; Vilu, Raivo (2014). Protein turnover forms one of the highest maintenance costs in Lactococcus lactis. *Microbiology-SGM*, 160, 1501 - 1512.

Pitk, P.; Kaparaju, P.; Palatsi, J.; Belen, F.; Vilu, R. (2014). Mesophilic co-digestion of dairy manure and lipid rich solid slaughterhouse wastes: process efficiency, limitations and floating granules formation. *Bioresource Technology*, 166, 168 - 177.

Peebo, K; Valgepea, K; Nahku, R; Riis, G; Õun, M; Adamberg, K; Vilu, R (2014). Coordinated activation of PTA-ACS and TCA cycles strongly reduces overflow metabolism of acetate in Escherichia coli. Applied Microbiology and Biotechnology, 5131 - 5143.

Abner, K.; Aaviksaar, T.; Adamberg, K.; Vilu, R. (2014). Single-cell model of prokaryotic cell cycle. *Journal of Theoretical Biology*, 341, 78 - 87.

Chair of Molecular Technology. Molekulaartehnoloogia õppetool - vanemteadur Mati Karelson

T031A - **Modeling of biomedically and environmentally important systems using computational chemistry. Uued arvutusmeetodid keerukate biomolekulide süsteemide kirjeldamiseks. – Dr Mati Karelson.**

The subject of the research has been the computational study of detailed mechanisms of interactions of chemical compounds with the living organisms and environment. The research has been carried out by the development of new computational methods and the respective software. The novel methodological approaches include development of (1) ab initio quantum-chemical descriptors for molecules in external fields; (2) new quantum molecular dynamics based molecular docking techniques; (3) new algorithms for the search of optimum conformational structure of flexible molecules; and (4) implementation of advanced mathematical methods for the structure-activity relationships. The methodology developed is applicable for the description and prediction of (1) physicochemical properties; (2) pharmacodynamic and pharmacokinetic data; (3) antiviral activity of compounds; (4) activity of mimetics of neurotrophic factors; (5) structure and properties of peptide delivery vectors.

Tähtsamad teadustulemused 2014:
The methodological work included a critical evaluation of the applicability of various machine-learning methods such as artificial neural networks (ANN), support-vector machines (SVM) and others for the prediction of novel biologically active compounds (e.g. drug candidates). The advances and limitations of these methods were extensively discussed. In another direction, new sets of effective molecular descriptors (topological fingerprints) were developed and tested for the virtual screening of large molecular libraries. The new descriptors enabled to predict novel scaffolds for the inhibitors of leucine-rich repeat kinase 2 (LRRK2), mutations of which have been associated with Parkinson's disease type 8. A dual inhibition of enzymes α-glucosidase and butyrylcholinesterase by small drug-like molecules, including 1,4-disubstituted-1,2,3-triazoles, chalcones, and benzothiazepines, was rationalized with the help of Molecular Field Topology Analysis. Quantitative structure-property relationships were developed for the cell-penetrating peptides that were instrumental for the rational design of new, more efficient compounds.

Olulisemad publikatsioonid 2014

Kahn, I.; Lomaka, A.; Karelson, M. (2014). Topological Fingerprints as an Aid in Finding Structural Patterns for LRRK2 Inhibition. Molecular Informatics, 33, 269-275.

Kananovich, D.G.; Reino, A.; Ilmarinen, K.; Rõõmusoks, M.; Karelson, M.; Lopp, M. (2014). A General Approach to the Synthesis of 5-S-functionalized Pyrimidine Nucleosides and their Analogues. Organic and Biomolecular Chemistry, 5634-5644.

Regberg, J.; Srimanee, A.; Erlandsson, M.; Sillard, R.; Dobchev, D.A.; Karelson, M.; Langel, Ü. (2014) Rational design of a series of novel amphipathic cell-penetrating peptides. Int. J. Pharmaceutics, 464, 111-116.

Dobchev, D.; Pillai, G.; Karelson, M. (2014). In Silico Machine Learning Methods in Drug Development. Current Topics in Medicinal Chemistry, 16, 1913-1922.

Välisorganisatsioonide liikmed: Mati Karelson – American Chemical Society; International Academy of Mathematical Chemistry

3.2.4 Olulisi sündmusi keemiainstituudis 2014

EL RP7 Horisont 2020 raames sai toetust TTÜ *rohelise keemia õppetooli asutamine* (projektijuht Mihkel Koel). TTÜ nõukogu otsused:

- Moodustada matemaatika-loodusteaduskonna keemiainstituudis alates 1. maist 2014 rohelise keemia õppetool.
- Moodustada matemaatika-loodusteaduskonna keemiainstituudi rohelise keemia õppetoolis rohelise keemia professori ametikoht .
- Tallinna Tehnikaülikooli nõukogu valis keemiainstituudi rohelise keemia õppetooli professoriks tunnustatud Iiri teadlase Dublini Linnaülikooli õppejõu Nicholas Gathergoodi, kes asus tööle 01.01.2015. Teadustöö põhisuund on: keskkonnasõbralikud kemikaalid ja protseduurid.

Orgaanilise keemia õppetooli sündmusi:

- Eesti Teaduste Akadeemia valis 3.12.2014 üldkogul järgmiseks 5-aastaseks perioodiks akadeemia peasekretäriks TTÜ orgaanilise keemia professor Margus Loppi.
- TTÜ nõukogu esitas Eesti Vabariigi aastapreemia kandidaadiks keemia ja molekulaarbioloogia valdkonnas matemaatika-loodusteaduskonna dekaani professor Tõnis Kangeri teadustöö „Asümmeetrilised organokatalüütilised ja kaskaadreaktsioonid” .
- 2014. a valmis Tõnis Kangeri eestvedamisel ja osalusel tõlge eesti keelde kaasaegsest kõrgkooli õpikust: Francis A. Carey ja Robert M. Giuliano, Orgaaniline keemia, Tallinna Raamatutrükikoda 2014, 1273 lk.
- Professor Margus Loppilt ilmus õpik kõrgkoolidele: Margus Lopp. Stereokeemia. Tallinna Tehnikaülikooli Kirjastus, 2014, 277 lk.
- TTÜ 2013. aasta teadusartikkel loodus-, täppis- ja terviseteaduste valdkonnas oli: K. Ausmees, K. Kriis, T. Pehk, F. Werner, I. Järving, M. Lopp, T. Kanger. Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds. J. Org. Chem. 2012, 77, 10680−10687.

Tallinna Tehnikaülikoolis loodi alates 01.04.2014 *kaitse- ja julgeoleku-uuringute keskus, mille juhiks sai dr. Katrin Idla* keemiainstituudist. Katrin Idla on kaitsealast teadus- ja arendustööd teinud üle kümne aasta, sh koostöö NATOga.

TTÜ 2013. *aasta õppejõuks valiti Aini Vaarmann* analüütilise keemia õppetoolist.