MATEMAATIKA-LOODUSTEADUSKOND
INTEGREERITUD SÜSTEEMIDE BIOLOOGIA KESKUS
TEADUS- JA ARENDUSTEGEVUSE AASTAARUANNE 2012

1. Keskuse struktuur

Integreeritud süsteemide bioloogia keskus, Centre for Biology of Integrated Systems
Keskuse juhataja Madis Metsis
Integreeritud süsteemide bioloogia keskus on omaette struktuuriüksus matemaatika-loodusteaduskonna koosseisus. Keskuse juhataja oli 2012 aastal TTÜ bioinformaatika professor Madis Metsis. Keskuse nõukogusse kuulusid 2011/2012 õppeaastal Prof. Madis Metsis (nõukogu esimees), Prof. Toomas Neuman (töötajate valitud esindaja), Tuuli Käämbre (Keemilise ja Bioloogilise Füüsika Instituut, kutsutud välisliige), Prof. Ruth Sepper (Kliinilise Meditsiini Instituut, kutsutud välisliige). Alates 2012/2013 õppeaastast kuulusid keskuse nõukogusse Prof. Madis Metsis (nõukogu esimees), Ranno Rätsep (töötajate valitud esindaja), Mati Koppel (Jõgeva Sordiaretuse Instituut, kutsutud välisliige), Prof. Ruth Sepper (Kliinilise Meditsiini Instituut, kutsutud välisliige).
Keskuses oli 1. jaanuari 2012 seisuga 15 töötajat:
- Keskuse juhataja, bioinformaatika professor
- süsteemibioloogia professor
- 3 vanemteadurit
- projekti koordinaator
- 4 teadurit
- 4 spetsialisti
- 1 tehnik.

2012. aasta lõpu seisuga oli töösuhe keskusega lõppenud:
- süsteemibioloogia professoril
- 1 vanemteaduril
- projekti koordinaatoril
- 3 teaduril
- 2 spetsialistil.

2. Keskuse teadus- ja arendustegevuse (edaspidi T&A) iseloomustus

(NB! punktid 2.1- 2.6 täidab struktuuriüksus)

2.1 struktuuriüksuse koosseisu kuuluvate uurimisgruppide

2.1.1 teadustöö kirjeldus *(inglise keeles*);

On the year 2012 following scientific projectes were continued:
- Hormon-dependent gene regulation analysis on a genome wide level;
- Soil microbiome analysis and modelling, including for forensic applications;
- Protein-protein interaction networks in cardiac cells development;
- Development of bioinformatic tools for metagenome database analysis and OTUs identification;
- Development of new tools for human identification through skin microbiome analysis;
- Development tools for algae (Chara) identification at species, population and individual level.

2.1.2 aruandeaastal saadud tähtsamad teadustulemused *(inglise keeles).*

To provide a better understanding about the steroid-hormone NR-mediated regulation of the genes needed for implantation, ChIP-Seq and RNA-Seq methods employing next-generation sequencing (NGS) approaches were adopted and used on several steroid-responsive cell lines. An overview of methodological approaches has been published in a review article (Tamm et al, 2012, Chapter Review in Steroids - Basic Science). A line of new ligands for steroid receptors were also introduced, including clinically well-established tamoxifen (TAM) and mifepristone (RU486).

Gene expression profiling of the human endometrial Ishikawa cancer cell line treated with E2 & P4, TAM and RU486 was performed using RNA-seq. The transcriptome data provided valuable information about the potential biomarkers related to endometrial receptivity, and also facilitated an understanding of the molecular changes that take place in the endometrium in the early stages of breast cancer treatment and during contraceptive use (Tamm-Rosenstein *et al*, 2013; submitted PLOS ONE). A total of 82 and 93 gene biomarkers for endometrial receptivity were identified among E2 and P4 responsive genes, respectively. Identified biomarkers included: *EZH2, MDK, MUC1, SLIT2,* and *IL6ST*, which are genes previously associated with endometrial receptivity and embryo implantation. The cell cycle regulator cyclin D1 *(CCND1)* showed significant up-regulation following treatment with TAM; and is likely responsible for the onset of endometrial carcinoma as a side-effect of TAM treatment for breast cancer. Functional analysis of RU486 responsive genes identified genes related to adhesion and apoptosis. Specifically, these included *CTNND1, JUP, CDH2, IQGAP1,* and *COL2A1*, which have been associated with cell-cell contacts and adhesion, and were down-regulated following RU486 treatment.

During the studies on the human ovarian follicle as the environment of oocyte maturation linked to the success of controlled hormonal stimulation and IVF pregnancy, the patterns of active mRNA and non-coding RNA expression in the follicular somatic cells were identified (Kõks et al., 2010, Velthut et al., 2012a). In addition the indicators of oxidative stress, immune response and apoptosis that can be measured from the follicular fluid were analysed (Sarapik et al., 2012, Velthut et al., 2012b).
As a result was shown that several factors measured from the follicular fluid differentiate between patient groups according to the aetiology of infertility and correlate either with stimulation efficiency, number and fertilization rate of retrieved oocytes or pregnancy outcome. As an example, chemokines IL-8 and MIP1-beta and pro-inflammatory cytokine IL-18 pervade in higher concentration in the follicular fluid of women that achieved successful clinical pregnancy (Sarapik et al., 2012). According to gene expression studies, proteins involved in immune response are secreted from mural granulosa cells or immune cells outside the follicle or between the mural granulosa (Kõks et al., 2010).
In addition new associations between the efficiency of controlled ovarian stimulation and the level of oxidative stress in the follicle were determined (Velthut et al., 2012b). It appeared that the number of retrieved oocytes positively correlated with the level of oxidative stress, indicating elevated active metabolism during multiple follicle maturation. At the same time, higher oxidative stress was observed in those women, for whom less follicle stimulation hormone (FSH) was necessary for maturing one oocyte. This result refers to the fact that cellular metabolism and FSH signalling pathways are intertwined. It was found that the level of follicular antioxidants has considerably decreased in women with endometriosis.
For detecting the active signalling pathways in follicular somatic cells both mRNA chips (Kõks et al., 2010) as well as next-generation sequencing of mRNA and small RNA molecules was used (Velthut et al., 2012a). As an example, new miRNA molecules were found to be transcribed from the intronic regions of FSH receptor and aromatase genes. Both of these play an important role in

folliculogenesis and steroid hormone synthesis and are known to be highly expressed in the ovary. The target genes of identified miRNA-s have been so far studied by bioinformatic methods. Cumulus and mural granulosa cells can be clearly differentiated by their expressed mRNA content. The genes expressed in mural granulosa cells are involved in immune response (interleukins, toll-like receptor family genes), tissue remodelling (matrix metalloproteinases 9, 10 and 15) and cell division (EGR family of transcription factors). The genes expressed in cumulus granulosa cells, on the other hand, are concentrated into pathways responsible for inter-cellular adhesions (ASAM and gap junction protein-encoding genes) and the transport of low-molecular components (solute carrier family genes). Several ligand-receptor pairs between mural and cumulus granulosa cells were also determined providing evidence of communication between these cell populations (as an example, interleukins are expressed in mural compartment and interleukin receptors in cumulus population).

The implementation of the metagenomic approach on the estimation of composition of microbial communities in different body parts of healthy and diseased individuals focused on describing the bacterial and fungal composition of normal and abnormal microbiota at first in vaginal environment. On January 23rd 2013 paper on this subject was published in PLoS ONE titled "Characterization of the Vaginal Micro- and Mycobiome in Asymptomatic Reproductive-Age Estonian Women" and it analyzed the composition of normal microbiota based on samples collected from approximately 500 women.

2.2 Uurimisgrupi kuni 5 olulisemat publikatsiooni läinud aastal.

Drell, T.; Tummeleht, L.; Simm, J.; Aaspõllu, A.; Väin, E.; Saarma, I.; Salumets, A.; Donders, G.; Mertsis, M. (2012). Characterization of the Vaginal Micro- and Mycobiome in Asymptomatic Reproductive-age Estonian Women. PLoS ONE, xx - xx. [ilmumas]

Velthut, A., Simm, J., Metsis, M. & Salumets, A. 2012a. miRNA profile of granulosa cell populations of human antral ovarian follicle *PLoS One,* submitted.

Tamm, K.; Suhorutshenko, M.; Rõõm, M.; Simm, J.; Metsis, M. (2012). The Tissue Specific Role of Estrogen and Progesterone in Human Endometrium and Mammary Gland. Abduljabbar, H. (Toim.). Steroids - Basic Science (35 - 64).InTech - Open Access Publisher.

2.3 Loetelu struktuuriüksuse töötajate rahvusvahelistest tunnustustustest.

2.4 Loetelu struktuuriüksuse töötajatest, kes on välisakadeemiate või muude oluliste T&A-ga seotud välisorganisatsioonide liikmed.

Anu Aaspõllu - EUROFORGEN – Network of Execellence (FP7) National Contact Point

2.5 Aruandeaasta tähtsamad T&A finantseerimise allikad.

VEU445, Uue metagenoomse keskkonnamonitooringu meetodi arendus, Metsis Madis (1.01.2010 - 30.06.2012).

2.6 Soovi korral lisada aruandeaastal saadud T&A-ga seotud tunnustusi (va punktis 2.3 toodud tunnustused), ülevaate teaduskorralduslikust tegevusest, teadlasmobiilsusest ning anda hinnang oma teadustulemustele.

Doktorant Agne Velhut sai 2012/2013. aastaks Artur Linnu geenitehnoloogia stipendiumi

Keskuse töötajate osalemine ettekannetega rahvusvahelistel üritustel:

16. – 17. 04.2012 Tallinn, Eesti; LifePlus seminar
A. Aaspõllu, L. Lilje, J. Simm, E. Kägo, S. Sipp Kulli, M. Moora, M. Zobel, M. Metsis. Soil metagenome DNA typing in Forensic Sceince (suuline ettekanne).

14.-16.05.2012 Tartu, Eesti; ENFSI Scene of Crime Working Group annual meeting 2012 Crime Scene 2.0
A. Aaspõllu, T. Lillsaar, J. Simm L. Lilje, E. Kägo, M. Moora, M. Zobel, M. Metsis. Metagenome DNA Typing as an additional tools for forensics (suuline ettekanne).

20.08-24.08.2012 Haag, Holland; EAFS - 6th European Academy of Forensic Science Conference
A. Aaspõllu, T. Lillsaar, J. Simm, M. Metsis. Human skin microbiome as new player in forensic (suuline ettekanne).

15.09.2012 München, Saksamaa; EUROFORGEN – Network of Execellence National Contact Point Meeting
A. Aaspõllu. Forensic genetics in Estonia (suuline ettekanne).

2.7 Keskuse teadus- ja arendustegevuse teemade ja projektide nimetused *(Eesti Teadusinfosüsteemi, edaspidi ETIS, andmetel)*

- Haridus- ja Teadusministeerium

– sihtfinantseeritavad teemad:
– baasfinantseerimise toetusfondist rahastatud projektid (sh TTÜ tippkeskused):
– riiklikud programmid:

- Teiste ministeeriumide poolt rahastatavad riiklikud programmid:

- Uurija-professori rahastamine:

- SA Eesti Teadusfond/Eesti Teadusagentuur

– grandid:
ETF7823, Raku energiaühikutemoodustumise dünaamika tüvirakkude diferentseerumise protsessis lihasrakkudeks ja nende degradatsioon vananemise käigus, Metsis Madis (2009 – 2012)

– ühisgrandid välisriigiga:
– järeldoktorite grandid (SA ETF ja Mobilitas):
– tippteadlase grandid (Mobilitas):

- Ettevõtluse Arendamise SA

– eeluuringud:
– arendustoetused:

- SA Archimedesega sõlmitud lepingud

– infrastruktuur (nn „mini-infra“, „asutuse infra“):
Teekaardi objekt
AR11087, Eesti teadusarvutuste infrastruktuur (1.06.2011 - 31.12.2013)

– Eesti tippkeskused:
– riiklikud programmid:
– muud T&A lepingud:

- SA Keskkonnainvesteeringute Keskusega sõlmitud lepingud:
- Siseriiklikud lepingud:
- EL Raamprogrammi projektid:
- Välisriiklikud lepingud:

VEU445, Uue metagenoomse keskkonnamonitooringu meetodi arendus, Metsis Madis (1.01.2010 - 30.06.2012)

2.8 Struktuuriüksuse töötajate poolt avaldatud eelretsenseeritavad teaduspublikatsioonid *(ETIS klassifikaatori alusel 1.1, 1.2, 1.3, 2.1, 2.2, 3.1, 3.2, 3.3, 4.1 ja 5.1).*

1.1

Drell, T.; Tummeleht, L.; Simm, J.; Aaspõllu, A.; Väin, E.; Saarma, I.; Salumets, A.; Donders, G.; Mertsis, M. (2012). Characterization of the Vaginal Micro- and Mycobiome in Asymptomatic Reproductive-age Estonian Women. PLoS ONE, xx - xx. [ilmumas]

Davison, J.; Öpik, M.; Zobel, M.; Vasar, M.; Metsis, M.; Moora, M. (2012). Communities of arbuscular mycorrhizal fungi detected in forest soil are spatially heterogeneous but do not vary throughout the growing season. PLoS ONE, 8, e41938

Sepper, R.; Prikk, K.; Metsis, M.; Sergejeva, S.; Pugatsjova, N.; Bragina, O.; Marran, S.; Fehniger, T. (2012). Mucin5B expression by lung alveolar macrophages is increased in long-term smokers. Journal of Leukocyte Biology, 92(2), 319 - 324.

Hiiesalu, I.; Öpik, M.; Metsis, M.; Davison, J.; Vasar, M.; Moora, M.; Zobel, M.; Wilson, S.; Pärtel, M. (2012). Plant species richness belowground: higher richness and new patterns revealed by next generation sequencing. Molecular Ecology, 21(8), 2004 - 2016.

Sarapik, A., Velthut, A., Haller-Kikkatalo, K., Faure, G. C., Bene, M. C., De Carvalho Bittencourt, M., Massin, F., Uibo, R. & Salumets, A. 2012. Follicular proinflammatory cytokines and chemokines as markers of IVF success. *Clin Dev Immunol,* 2012**,** 606459.

Velthut, A., Simm, J., Metsis, M. & Salumets, A. 2012a. miRNA profile of granulosa cell populations of human antral ovarian follicle *PLoS One*, submitted.

Velthut, A., Zilmer, M., Zilmer, K., Kaart, T., Karro, H. & Salumets, A. 2012b. Elevated blood plasma antioxidant status is favourable for achieving IVF-ICSI pregnancy. *Reproductive BioMedicine Online,* (ilmumas).

1.2

1.3

Tamm, K.; Suhorutšenko, M.; Talving, E.; Kaljas, A.; Metsis, M. (2012). Suguhormoonide östradiooli ja progesterooni koespetsiifiline roll inimese endomeetriumis ja rinnanäärmes. Eesti Arst, 91(4), 182 - 189.

2.1

2.2

3.1

3.2

Tamm, K.; Suhorutshenko, M.; Rõõm, M.; Simm, J.; Metsis, M. (2012). The Tissue Specific Role of Estrogen and Progesterone in Human Endometrium and Mammary Gland. Abduljabbar, H. (Toim.). Steroids - Basic Science (35 - 64).InTech - Open Access Publisher

3.3

4.1

5.1

Pazouki, Leila; Suhorutšenko, Marina; Niinemets, Ülo (2012). Genetic Variability of Natural Scots Pine (Pinus sylvestris L.) Populations in Different Habitats . Molecular ecology, Vienna international plant conference association, Vienna, February 4-7. , 2012.

2.9 Struktuuriüksuses kaitstud doktoriväitekirjade loetelu *(NB! struktuuriüksus lisab struktuuriüksuse töötaja juhendamisel mujal kaitstud doktoriväitekirjade loetelu)*

2.10 Struktuuriüksuses järeldoktorina T&A-s osalenud isikute loetelu *(ETIS-e kaudu esitatud taotluste alusel)*

2.11 Struktuuriüksuses loodud tööstusomandi loetelu

3. Struktuuriüksuse infrastruktuuri uuendamise loetelu