CENTRE FOR INTEGRATIVE SEQUENCING

PROGRAMME
iSEQ MIDTERM MEETING
11–12 DECEMBER 2014
AT FUGLSØCENTRET

AARHUS
UNIVERSITY

WELCOME TO THE
iSEQ MIDTERM MEETING
11-12 DECEMBER 2014

Dear iSEQ employee or collaborator.

Welcome to the iSEQ Midterm Meeting 2014.

The aim of our meeting is to discuss and develop our scientific plans and the related activities in iSEQ, and enjoy scientific and social interactions.

We are very pleased that the programme features distinguished speakers from some of our main collaborators in addition to a selection of internal iSEQ speakers.

We are looking forward to spending time with you in the beautiful surroundings of Fuglsøcentret.

Best regards,
iSEQ PIs

Mikkel Schierup
Torben Ørntoft
Torben Heick Jensen
Jørgen Kjems
Wang Jun
Preben Bo Mortensen
Anders Børglum

The idyllic Fuglsøcentret

PROGRAMME
THURSDAY 11 DECEMBER

11.45-13.00	Arrival and lunch
13.00-13.05	Anders Børglum: Welcome
13.05-14.05	Anders Lund: *Non-coding RNA in cancer*
14.05-15.05	Albin Sandelin: *Systematic characterization of enhancer RNA dynamics in cellular response*
15.05-15.35	Coffee/tea break
15.35-16.35	Richard Sallari: *Convergence of dispersed regulatory mutations reveals candidate driver genes in prostate cancer*
16.35-17.35	Kasper Lage: *Functional interpretation of genomes using biological networks*
18.30-	Dinner

PROGRAMME
FRIDAY 12 DECEMBER

08.00-09.00	Breakfast
09.00-10.40	Two parallel tracks, 5 internal speakers in each See page 8-9
10.40-11.00	Coffee/tea break
11.00-12:00	Plenary discussion, ideas for iSEQ future focus points, evaluation
12.00-13.00	Lunch
13.00	Departure

PARALLEL SESSION 1
RNA AND CANCER

CHAIR: TORBEN ØRNTOFT AND JØRGEN KJEMS

09.00-09.20 Jørgen Kjems:
Characterization of miRNA controlling stem cell differentiation

09.20-09.40 Søren Lykke-Andersen:
Human nonsense-mediated RNA decay initiates widely by endonucleolysis and targets snoRNA host genes

09.40-10.00 Henrik Hornshøj:
ncDriver: detection of non-coding cancer drivers from whole-genome mutations

10.00-10.20 Marat Lloret Llinres:
Role of the RNA exosome and the NEXT complex during differentiation

10.20-10.40 Mathilde Thomsen:
Cellular populations that define the heterogeneity of bladder cancer

PARALLEL SESSION 2
CNS AND BIOINFORMATICS

CHAIR: MIKKEL SCHIERUP AND ANDERS BØRGLUM

09.00-09.20 Ditte Demontis:
Whole-exome sequencing reveals increased burden in ADHD cases of rare functional and disruptive variants in candidate risk genes

09.20-09.40 Morten Venø:
Non-coding RNA expression in fetal developing pig brain and epilepsy

09.40-10.00 Rune Friborg:
Scaling computing resources with the increase in genome sequences

10.00-10.20 Mads Engel Hauberg:
Dissecting the role of microRNA in the etiology of schizophrenia

10.20–10.40 Søren Besenbacher:
The rate and pattern of germline mutations in humans

EXTERNAL **SPEAKERS**

Professor Anders Lund

Anders H. Lund graduated from the University of Aarhus, Denmark, in 1996. He worked initially as a postdoc at the University of Aarhus (1996-1999) studying murine leukemia viruses before moving to the Netherlands Cancer Institute as a postdoctoral researcher (1999-2004) where he worked on the identification of novel oncogenes. He was appointed associate professor at the Biotech Research and Innovation Centre, University of Copenhagen, in 2004 and became full professor in 2009. At the University of Copenhagen his group focuses on the identification and functional characterization of non-coding RNAs and epigenetic modifiers in cancer.

NON-CODING RNA IN CANCER

THURSDAY 11 DECEMBER 2014, 13.05–14.05

Non-coding RNAs constitute a very diverse group of molecules, the majority of which remain uncharacterized. Nevertheless, non-coding RNAs have been found to influence a multitude of cellular pathways and to play important roles in human pathologies.

Using a custom microarray approach we have profiled the expression of non-coding RNAs in 5 major cancers and a range of cancer-related cell culture model systems. The seminar will provide examples of functional follow-up studies.

EXTERNAL **SPEAKERS**

Professor Albin Sandelin

Albin Sandelin is a Professor at the Department of Biology and BRIC, Copenhagen University. He obtained his MSc in Molecular Biology in 2000 from Stockholm University and his PhD from Karolinska Institute in 2004. His most noted work from that period was the JASPAR DNA motif database, now a standard tool in bioinformatics. During his postdoctoral period at RIKEN, he was one of the key analysts of 5' end data from the FANTOM project. As a principal investigator at Copenhagen University, he has used the same technique in combination with computational methods to investigate the biology of gene regulation, and is now extending this into inflammatory disease. A recent highlight was an atlas of enhancer regions and their usage over the human body.

SYSTEMATIC CHARACTERIZATION OF ENHANCER RNA DYNAMICS IN CELLULAR RESPONSE

THURSDAY 11 DECEMBER 2014, 14.05–15.05

Changes to cell phenotype, via differentiation programs or transient responses to external stimuli, are coordinated by dynamic gene regulatory programs. Systematic analyses are needed to elucidate what regulatory features and mechanisms that are shared and distinct between the diverse transition events in mammalian cells. Within the FANTOM5 consortium, we used 5' end RNA-seq (CAGE) to measure coordinated enhancer activation by enhancer RNA(eRNA) transcription and gene expression across 34 human and mouse cell time courses covering a wide range of diverse cell types and biological states, providing an unprecedented, high-resolution overview of dynamic gene regulation in transitioning cells.

The large number of dynamically regulated TSSs and enhancers detected enabled us to make a systematic comparison of the transcriptional programs and regulators between transitioning cells. Regardless of cell type, most dynamically regulated TSSs and enhancers follow a limited number of generic response patterns in the first six hours. Enhancers dominate the patterns characterized by rapid early changes in expression occurring already after 15-30 minutes. TSS associated with transcription factors dominate the second wave responses peaking at 100 min followed by a late response wave dominated by other genes.

Remarkably, while the trajectories are used in all cell types investigated, the overlap in enhancers and TSSs following a given trajectory across two or more cells is small. The data set also allows for detailed investigation of the temporal dynamics of interacting enhancers and TSSs. We find that eRNAs are typically expressed before the TSS linked to the enhancer is transcribed, and that the lag is dependent on both the dynamic expression pattern for the eRNAs and gene type; in particular, transcription factors genes TSSs respond faster than other genes.

EXTERNAL **SPEAKERS**

Postdoctoral Associate Richard Sallari

Richard Sallari investigates the genomic mechanisms of cancer emergence and evolution. His research addresses both the inherited variants that initiate the transformation of normal cells and the somatic mutations that drive tumor formation.

Specifically, he has shown that cancer-associated variants act primarily through affinity modulation of key transcription factors at distal enhancers and that cancer genes need not be mutated themselves but can instead harbor highly frequent convergent mutations in their sets of proximal and distal regulators.

He is currently affiliated with the MIT Computer Science and Artificial Intelligence Laboratory (CSAIL) and the Broad Institute of MIT and Harvard, past affiliations include Dartmouth College and the University of Toronto. He has thrived under the mentorship of Jason Moore, Kevin Peterson, Mathieu Lupien and Manolis Kellis.

CONVERGENCE OF DISPERSED REGULATORY MUTATIONS REVEALS CANDIDATE DRIVER GENES IN PROSTATE CANCER

THURSDAY 11 DECEMBER 2014, 15.35–16.35

Cancer genome sequencing has revealed cancer-associated genes based on recurrent mutations across independent tumors, but has been largely restricted to protein-coding alterations. Here, we extend recurrence analysis to dispersed regulatory mutations, based on transcriptome and genome sequencing of cancer-normal sample pairs in prostate cancer. We infer the regulatory plexus of each gene in healthy prostate, defined as its three-dimensional neighborhood of regulatory regions, combining chromosome looping and epigenomic annotations. Cancer-dysregulated genes show an increased mutation rate in non-coding regions, enriched in predicted enhancers active in prostate and diverse other tissues, suggesting out-of-context de-repression. Controlling for mutational heterogeneity across tumors, genomic regions, and chromatin states, we identify 15 genes showing significant regulatory recurrence, with roles in androgen-insulin signaling, immune system evasion, and mitochondrial function, suggesting higher-order pathway-level convergence. Our results provide a model for both cancer and personal genome regulatory analysis, by coalescing low-frequency scattered mutations into high-frequency regulatory events.

EXTERNAL **SPEAKERS**

Director, Ass. Professor Kasper Lage

Kasper Lage is the Director of Bioinformatics of the Massachusetts General Hospital (MGH) Department of Surgery where he leads a research group. He holds an academic appointment as Assistant Professor at Harvard Medical School and is an Associate Member of the Broad Institute of MIT and Harvard.

Kasper has a Ba. in Biochemistry and an M. Sc. in Health Sciences, both from the University of Copenhagen. He did his Ph.D. at the Technical University of Denmark in the area of bioinformatics and systems biology of human genetic diseases under the supervision Center Director Søren Brunak. He moved to Boston in 2008 to do his postdoc at MGH, Harvard and the Broad Institute, and joined the Harvard faculty in 2010.

His research revolves around computational analyses of very large genomic datasets and the integration of these data with functional genomics networks with the aim of disease prediction, diagnostics, and to gain a higher resolution insight into the biological underpinnings of a variety of diseases. His analyses and methods have led to the identification of specific genes and networks in many different cancers as well as autism, diabetes, and cardiovascular disorders.

Kasper serves on a number of boards and committees for example the Research Computation Oversight Committee of Partners HealthCare and he has been involved in several biotech startups in translational genetics and bioinformatics which together have raised > 24 MUSD in funding.

FUNCTIONAL INTERPRETATION OF GENOMES USING BIOLOGICAL NETWORKS

THURSDAY 11 DECEMBER 2014, 16.35–17.35

The recent explosion in genome-wide association studies, exome-sequencing projects, and epigenetic data sets, have revealed many genetic variants likely to be involved in disease processes, but the composition and function of the molecular systems they affect remain largely obscure. This limits our progress towards biological understanding and therapeutic intervention. Computational analyses that systematically integrate biological networks (i.e., networks in which genes are connected if they are functionally associated in some experimental system) with genetic data have emerged as a powerful scalable approach to functionally interpret large genomic data sets by enabling the identification of de novo pathways perturbed in disease. This talk will highlight approaches and methods being developed in this area, and exemplify how different network-based methods have been used to analyze common and rare genetic variants to deduce the molecular networks perturbed by genetics and environment in a wide range of diseases. Furthermore, as a general model for how in silico networks can be expanded, consolidated and validated, I will show how cardiac ion-channel networks involved in human arrhythmia were elucidated and validated by combining, GWAS, quantitative interaction proteomics, and model organisms through rigorous statistical frameworks.

The idyllic Fuglsøcentret

PRACTICAL **INFORMATION**

WHERE
Fuglsøcentret
Dragsmurvej 6
DK-8420 Knebel

TRANSPORTATION
Thursday 11 December
Departure at 10.30 from
Aarhus University,
Wilhelm Meyers Allé 4,
8000 Aarhus C
in front of the Bartholin Building (1242)

Departure at 10.40 from
Molekylær Medicinsk Afdeling,
Science Center Skejby,
Brendstrupgårdsvej 21,
8200 Aarhus N.

Friday 12 December
Departure at 13.00 from Fuglsøcentret

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