NSFT

Norsk Selskap for Farmakologi og Toksikologi
Norwegian Society of Pharmacology and Toxicology

Member of EPHAR, IUPHAR, EUROTOX and IUTOX **www.nsft.net**

Vintermøtet på Beitostølen

2019

Sponsor av NSFTs vintermøte 2019

Norsk Selskap for Farmakologi og Toksikologi

Program

Torsdag 24. januar	
13:00 - 14:30	**Lunsj**
14:30	Velkommen v/ NSFTs leder *Mohammad Nouri Sharikabad* BEITOHALLEN
	Drugs of abuse Fellessymposium *Møteleder: Mohammad Nouri Sharikabad (FHI)* BEITOHALLEN
14:40 - 15:10	The Pharmacology and Toxicology of Novel Psychoactive Substances *Inger Lise Bogen (OUS)*
15:10 - 15:40	How does maternal use of drugs of abuse affect the fetus? *Marte Handal (FHI)*
Pause	
Priser for årets beste artikler Fellessymposium *Møteledere*: *Hubert Dirven (FHI)/Lise Roman Moltzau (UiO)* BEITOHALLEN	
16:00 - 16:20	Limited Sampling Strategy to Estimate Whole Blood and Intra-lymphocyte Exposure of Everolimus in Renal Transplant Recipients using Population Pharmacokinetic Modeling and Bayesian Estimators *Ida Robertsen (UiO) (Årets artikkel i farmakologi)*
16:20 - 16:40	Deciphering the Combined Effects of Environmental Stressors on Gene Transcription: A Conceptual Approach *You Song (NIVA) (Årets artikkel i toksikologi)*
Kaffe	

Toksikologi: The dCod 1.0 project: decoding the systems toxicology of Atlantic cod *Møteleder*: *Anders Goksøyr (UiB)* Besseggen 1		Farmakologi: Cancer in children; disease, treatment and late effects *Møteleder*: *Mohammad Nouri Sharikabad (FHI)* Besseggen 2
17:10 - 17:15	Introduction *Anders Goksøyr (UiB)*	Cancer in children; an overview *Heidi Glosli, Chief physician* *Oslo University Hospital (Rikshospitalet)*
17:15 - 17:40	The chemical defensome of Atlantic cod (Gadus morhua): how does it differ from gene networks in human and zebrafish? *Marta Eide (UiB)*	
17:40 - 18:05	Toxicogenomic responses in Atlantic cod (Gadus morhua): *in vivo* and *in vitro* studies reveal possible new roles of FGF3 and FGF4 *Fekadu Yadetie (UiB)*	Late effects after cancer and its treatment *Heidi Glosli, Chief physician* *Oslo University Hospital (Rikshospitalet)*
18:05 - 18:30	A draft metabolic reconstruction of Atlantic cod (Gadus morhua) liver: how to and what for? *Eileen M. Hanna (UiB)*	New treatment Principles *Heidi Glosli, Chief physician* *Oslo University Hospital (Rikshospitalet)*
19:30	**Samling i baren**	
20:00	**Middag**	

Fredag 25. januar

12:30 - 14:00	**Lunsj**

Mikro / Nano
Fellessymposium
Møteleder: Hubert Dirven (FHI)
BEITOHALLEN

14:00 - 14:30	Macro, micro, nano: What we know and should know about plastic pollution *Martin Wagner (NTNU)*
14:30 - 15:00	Ultrasound-mediated delivery of nanomedicine for improved treatment of cancer and brain diseases *Marieke Olsman (NTNU)*

Kaffe

Frie foredrag

Toksikologi *Møteleder: Odd André Karlsen (UiB)* Besseggen 1		Farmakologi *Møteleder:Kristine Hole (Diakonhjemmet)* Besseggen 2	
15:30	Subchronic dietary exposure to ethoxyquin dimer induces microvesicular steatosis in male BALB/c mice *Annette Bernhard (IMR)*	Betydningen av SLC6A4-genotype for terapisvikt av escitalopram *Kristine Alm (Diakonhjemmet)*	15:30
15:40	Nutrients, dioxins and dioxin-like PCBs in Norwegian fatty fish; risk or benefit? *Ole Jakob Nøstbakken (IMR)*	Efficacy and Safety of Empagliflozin in Renal Transplant Recipients with Post-Transplant Diabetes Mellitus *Kine Eide Kvitne (UiO)*	15:40
15:50	The effect of selenomethionine on methylmercury accumulation in BALB/c mice Ragnhild Marie Mellingen *(IMR)*	Farmakodynamikk og arteriovenøs forskjell av intravenøs nalokson i friske frivillige som får remifentanil TCI *Ida Tylleskär (NTNU)*	15:50
16:00	Health effects and toxicokinetics of deoxynivalenol and ochratoxin A in dietary exposed Atlantic salmon (Salmo salar) *Aksel Bernhoft (NVI)*	Kombinert betydning av CYP2C19- og CYP2D6-genotype for individuell variasjon i serumkonsentrasjon av escitalopram – en retrospektiv observasjonsstudie basert på data fra over 3000 pasienter *Jenny Tran (Diakonhjemmet)*	16:00

16:10	High-dimensional immune cell profiling reveals functional immune signatures for patients with unknown mechanisms of allergic reactions to food *Friederike Sonnet (FHI)*	CNP increases titin phosphorylation and decreases passive tension in cardiomyocytes *Lise Román Moltzau (UiO)*	16:10
16:20	HEMA affect IL-1β release and phagocytosis in THP-1 macrophages *Bergitte P Olderbø (NIOM)*	Dose intensity of antidepressants in older persons 2007-2017 – a study based on therapeutic drug monitoring data *Kristine Tveit (HVL)*	16:20
16:30	Toxicity of combined exposure of HEMA and nicotine in PE/CA-PJ49 cells *Solveig Uvsløkk (NIOM)*	Tacrolimus concentrations measured in capillary micro samples *Rolf Klaasen (OUS)*	16:30
16:40	Biomagnification of PFAS in the Antarctic breeding south polar skua *Laura Andrea Alfaro Garcia (UiO)*	Pharmacokinetics of a novel, approved, 1.4 mg intranasal naloxone formulation for reversal of opioid overdose- a randomised controlled trial *Arne Skulberg (NTNU)*	16:40
Pause			
17:00	Using diet to explain the bioaccumulation of organic contaminants in Norwegian populations of killer whale (Orcinus orca) *Clare McEnally (UiO)*	Effect of CYP2C19 genotype on serum concentration of sertraline *Line S. Bråten (Diakonhjemmet)*	17:00
17:10	How well do herring gull or eider duck represent pollution status in an urban fjord? *Helene Thorstensen (UiO)*	Role of early changes in cardiac performances caused by calcineurin inhibitors in organs toxicities *Bernadin Ndongson-Dongmo (UiO)*	17:10
17:20	Environmental contaminants in herring gull from two colonies in the Oslofjord, and maternal transfer to eggs *Nina Cathrine Knudtzon (UiO)*	Antiepileptikabruk assosiert med økt risiko for terapisvikt av klozapin *Katrine Mathisen (Diakonhjemmet)*	17:20
17:30	DNA damage in dragonfly nymphs (Odonata, Anisoptera) living in highway runoff sedimentation ponds is correlated with pollution level *Merete Grung (NIVA)*	Contactless quantification of tacrolimus-specific tremor *Markus H. Hovd (UiO)*	17:30

17:40	Contaminant accumulation and biological responses in Atlantic cod (Gadus morhua) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances *Karina Dale (UiB)*	
17:50	Towards more relevant exposure scenarios; transformation and ecotoxicological effects of Ag and TiO2 nanoparticles transformed through wastewater treatment processes *Anastasia Georgantzopoulou (NIVA)*	
18:00	In vitro assessment of estrogenic and androgenic effects of bisphenols on Atlantic cod (Gadus morhua) *Siri Ø. Goksøyr (UiB)*	
18:10	Accumulation of clothianidin, a neonicotinoid pesticide, in bumblebees (Bombus terrestris) *Malin Røyset Aarønes (UiB)*	
18:20	The Effects of Environmental Contaminants on Northern Crested Newt (Triturus Cristatus) and Smooth Newt (Lissotriton Vulgaris) Exposed to Road Water Runoff in Sedimentation Ponds *Sofie Lindman (UiO)*	

Postervisning

Toksikologi *Møteleder: Hubert Dirven (FHI)* Besseggen 1 (kl. 18:30)	Farmakologi *Møteleder: Lise Roman Moltzau (UiO)* Besseggen 2 (kl. 17:45)
In vitro assessment of estrogenic effects of bisphenols on Atlantic cod (Gadus morhua) *Christine T. Johansen (UiB)* Biological effects in Atlantic cod (Gadus morhua) and haddock (Melanogrammus aeglefinus) exposed to crude oil with and without UV radiation. *Zhanna Tairova (UiO)* Mercury, cadmium and lead in trout (Salmo trutta) from Norwegian lakes. *Vidar Berg (NMBU)* Toxicity of PMMA nanoplastics in the marine microalgae Rhodomonas salina *Anastasia Georgantzopoulou (NIVA)*	Effekt av uremiske toksiner på intestinal og hepatisk CYP3A-aktivitet i pasienter med terminal nyresvikt *Fahiza Arifi (UiO)* A search for an allosteric binding site on the natriuretic peptide receptor A *Henriette Andresen (UiO)* Characterization of extracellular vesicles from human skeletal muscle cells *Misbah Hussain (NTNU)*

Adverse effects related to plastic additives exposure in Atlantic cod (Gadus morhua) *Hilde Andersen (NMBU)* Aktivering av aryl hydrokarbon reseptor (Ahr) signalveien hos egg og larve fra Atlanterhavstorsk etter råoljeeksponering med og uten UV- bestråling *Lars Eirik Myklatun (UiB)* Uptake and effects of microplastics from feed in Atlantic cod (Gadus morhua) *Syver Hauge (UiO)* Effects of Ag and TiO2 nanoparticles before and after wastewater treatment processes: an in vitro approach using Eisenia fetida coelomocytes *Anastasia Georgantzopoulou (NIVA)* How do different environmental contaminants effect the activity of transcriptional factors in blue whales (Balaenoptera musculus)? *Karoline Viberg (UiB)* Results from the Norwegian human biomonitoring study in the EuroMix project: Exposure to the pesticides boscalid and imazalil from the diet in Norway *Friederike Sonnet (FHI)* Maternal exposure to a mixture of persistent organic pollutants have long-lasting effects on gut metabolite composition but not on colorectal cancer. *Silje Modahl Johanson (NMBU)* Cardiopulmonary effects of acute inhalation exposure of rats to exhaust emissions with and without particle filter - The PrevenTap project *Anna J. Lauvås (FHI)* A mouse model for Acute Myeloid Leukemia reveals a dose rate response after ionizing radiation *Dag Eide (FHI)*	Behandling av humane skjelettmuskelceller med selektive hemmere for diacylglyserol acyltransferase 1 og 2 viser at de har ulike roller i glukosemetabolismen *Ali Afshar (UiO)* Effekten av kjønnshormoner på differensiering av stamceller til osteoblaster og regulering av cysteinproteasene legumain og cathepsin B *Mustafa Awale (UiO)*
20:00	**Middag**
22:00 - 22:30	**Kveldsnytt** Besseggen 2

Lørdag 26. januar		
Generalforsamling og årsmøter		
09:00 - 09:30	Årsmøte Seksjon for toksikologi Besseggen 1	Årsmøte Seksjon for farmakologi Besseggen 2
09:30 - 10:30	Generalforsamling Norsk Selskap for Farmakologi og Toksikologi Besseggen 2	
12:30 - 14:00	**Lunsj**	
Beitoforelesningen 2019 (BCPT-sponsored) *Møteleder: Hubert Dirven (FHI)* BEITOHALLEN		
14:00 - 14:45	Science and society – nice to know or need to know? *Alan Boobis (Imperial College, London)*	
Nordic symposium (BCPT-sponsored) The Immune system: from therapy to toxicology Fellessymposium *Møteleder: Mohammad Nouri Sharikabad (FHI)* BEITOHALLEN		
14:50 - 15:20	The CGRP Pathway in Migraine as a Viable Target for Therapies *Prof Lars Edvinsson (Lund Universitet)*	
Kaffe		
15:50 - 16:20	Immunotoxicology – the youngster in toxicology but with a bright future *Unni C. Nygaard (FHI)*	
16:20 – 16:50	Manipulating the immune system to treat cancer, how does it work and who is doing what in Oslo Cancer Cluster? *Øyvind Kongstun Arnesen (Ultimovacs AS)*	
Pause		

Toksikologi Hazard and exposure assessments of mixtures of chemicals for human health *Møteleder: Hubert Dirven (FHI)* Besseggen 1		Farmakologi Treatment of psychotic disorders *Møteleder*: Ida Robertsen (UiO) Besseggen 2	
17:10 - 17:40	Strategies for exposure and hazards assessment of mixtures as developed in the H2020 EuroMix project *Trine Husøy (FHI)*	The complexity of psychotic disorders and treatments *Nils Eiel Steen (UiO)*	17:10 - 17:30
		Personalized medicine in antipsychotic treatment *Espen Molden (Senter for Psykofarmakologi/UiO)*	17:30 - 17:50
17:40 - 18:10	Effect studies with human relevant mixtures of persistent organic pollutants (POPs) *Erik Ropstad (NMBU)*	The Norwegian prednisolone in early psychosis study *Rune Kroken (HUS/UiB)*	17:50 - 18:10
20:00	**Festmiddag**		

Søndag 27. januar

08:00 - 12:00	**Brunsj**

Innholdsfortegnelse

NSFTs vintermøte nr. 47

Norsk Selskap for Farmakologi og Toksikologi (NSFT) har arrangert vintermøter hvert år siden 1973, det vil si at årets møte er nummer 47 i rekken. Selskapets styre gikk i 1972 sterkt inn for å få i gang nasjonale møter, som både kunne bli et kontaktforum og en faglig arena for selskapets voksende antall medlemmer fra de ulike deler av landet.

I det programmet leveres til trykking er det påmeldt 107 deltakere til årets møte (ledsagere og barn ikke inkludert), og det er 20 inviterte foredragsholdere fordelt på 9 symposier. Til sammen er det meldt inn 29 frie foredrag og 19 postere fordelt på farmakologi og toksikologi.

I år har NSFT mottatt økonomisk støtte fra Basic & Clinical Pharmacology & Toxicology (BCPT) for å invitere flere utenlandske foredragsholdere og holde et nordisk symposium. Støtten har også gjort det mulig å opprettholde stipendtildelingen for studenter som presenterer poster eller frie fordrag.

Styret i NSFT takker for året som har gått og håper at deltakerne får både faglig og sosialt påfyll på årets vintermøte.

Vennlig hilsen
Styret

Oversikt over styremedlemmer i NSFT

NSFTs hovedstyre
Leder: Mohammad Nouri Sharikabad
Sekretær: Jan Tore Samuelsen
Kasserer: Kristine Hole
Styremedlem: David Eidsvoll
Representant for bedriftsmedlemmer: Lars Erik Eng Eibak
Representanter fra seksjonsstyrene: Ida Robertsen og Hubert Dirven
Varamedlemmer: Rigmor Solberg, Birgitte Lyrån og Aina Westrheim Ravna

Seksjon for farmakologi
Leder: Ida Robertsen
Styremedlemmer: Sigrid Narum, Lise Román Moltzau, Kristin Nordal og Ingvild Holdø

Kontaktpersoner for seksjon for farmakologi
Bergen: Jon Andsnes Berg
Trondheim: Ola Dale
Tromsø: Aina Westrheim Ravna

Seksjon for toksikologi
Leder: Hubert Dirven
Styremedlemmer: Merete Grung, Dag Marcus Eide, Marit Nøst Hegseth, Nina Landvik, Pål Amdal Magnusson og Odd Andre Karlsen. Varastyremedlem: Vidar Berg.

Velkommen til NSFTs vintermøte 2019

Kjære medlemmer, deltagere og ledsagere, velkommen til Norsk Selskap for Farmakologi og Toksikologi sitt førtisyvende vintermøte. Vintermøtet er en årlig hovedaktivitet i Norsk Selskap for Farmakologi og Toksikologi (NSFT) og har vært organisert og holdt siden 1973.

Norsk Farmakologisk Selskap ble stiftet i 1936 og etter hvert ble fagområde toksikologi innlemmet og selskapet skiftet navn til NSFT i 1981. Medlemmer i NSFT og deltagere på våre arrangementer dekker mange fagfelt, og arbeider med tema som spenner fra eksperimentell forskning til klinisk arbeid, arbeider i offentlige institusjoner, sykehus, akademia og farmasøytisk industri. NSFT sitt vintermøte er dermed en meget god arena for å treffe kollegaer fra basal og klinisk farmakologi samt human- og miljø- toksikologi og få oppdatering og ikke minst danne nye kontakter på tvers av kompetanse og fagfelt. Vi må erkjenne at NSFT ikke kan konkurrere med store internasjonale kongresser og møter hverken i størrelse eller økonomi. Vi håper og tror likevel at vintermøtene tilbyr et variert og godt faglig program i fine rammer her på fjellet. For å oppnå dette er vi avhengige av våre medlemmers deltagelse, innsats og faglig bidrag, noe NSFT setter veldig stor pris på. Jeg vil samtidig bruke anledningen å takke alle styremedlemmer og varamedlemmer for deres meget gode innsats i 2018 som gjør det mulig å arrangere dette vintermøtet.

Vi har i år en variert og godt program med flere meget spennende tema fra inviterte foredragsholdere. Programmet inneholder som vanlig felles sesjoner og separate sesjoner i farmakologi og toksikologi. Utdeling av pris til beste poster i begge fagfeltene er en fast post i programmet. Vi er utrolig glad og takknemlig for den økonomiske støtten vi mottar fra vår hovedsponsor «Basic and Clinical Pharmacology and Toxicology, BCPT» for dette vintermøte i likhet med forhenværende årene. Uten BCPT sin støtte hadde selskapet hatt store utfordringer med å kunne arrangere vintermøtet. Samtidig er muntlige presentasjoner og posterer innfor både farmakologi og toksikologi en sentral og uunnværlig del av vintermøtene. Dette er en spesielt godt egnet arena for yngre forskere og studenter til å få presentert sine forskningsresultater.

Et av årets høydepunkter for NSFT er den årlig utdeling av Poulssonmedaljen som har fått sitt navn etter den store norske farmakologen professor Poul Edvard Poulsson (1858- 1935). Poulssonmedaljen 2018 ble tildelt i toksikologi til professor Juliette Legler, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Nederland. Polussonseminaret ble holdt for ca. 60 tilhørere ved Staten arbeidsmiljøinstitutt, et vellykket seminar av høy faglig kvalitet. Professor Legler holdt følgende foredrag «Unravelling the role of environmental chemicals in disease with toxicology and epidemiology».

Jeg håper at alle får tre lærerike dager og at dere bruker formiddagene til å lade batteriene og at dette fører til et produktivt 2019. Her er alle forholdene lagt til rette for en fin tur på ski eller bena i storslått natur, en tur i slalåmbakken eller et deilig bad med badstue. Snakk med oss i arrangementskomiteen hvis du lurer på noe. Jeg vil også bruke anledningen til å oppfordre alle medlemmer til å delta på årsmøter og generalforsamling på lørdag morgen. Gi oss gjerne tilbakemelding på hva du syns om arrangementet og forbedringsforslag enten direkte eller i evaluering av arrangementet som dere får elektronisk etter vintermøte.

Med vennlig hilsen
Mohammad Nouri Sharikabad
Leder, NSFT

Praktisk informasjon

Hotelloversikt

Første gang en er på Beitostølen høyfjellshotell (Radisson Blu Resort Beitostølen) kan det være vanskelig å vite i hvilken retning en skal gå for å få med seg de første foredragene.

Dersom det ikke er en folkemengde å følge etter foreslås følgende:
Beitohallen: Andre etasje, ta til venstre. Beitohallen er i enden av korridoren.
Konferanseavdelingen: Andre etasje, gå rett fram gjennom glasshallen. Her finner du rommene Besseggen 1 og Besseggen 2.

Vintermøtet er godkjent som etter- og videreutdanningskurs

Farmasøyters etter- og videreutdanning (FEVU) er et poengsystem for registrering av deltakelse i faglige etterutdanningsaktiviteter. NSFTs vintermøte 2019 tildeles FEVU-poeng. Farmasøyter som er medlemmer av Norges Farmaceutiske Forening (NFF) kan selv registrere deltakelse på vintermøtet ved å logge inn på «*Min side*» på www.farmaceutene.no i etterkant av arrangementet. For mer informasjon om FEVU-poeng, se: http://www.farmaceutene.no/fevu-hva-er-det.

Vintermøtet er også godkjent av Den norske legeforening som valgfritt kurs (16 timer) innen klinisk farmakologi.

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Årsberetning 2018

1. Styrets sammensetning

Generalforsamlingen i NSFT ble holdt 27. januar 2018 på Radisson BLU Resort Beitostølen.

Styrets sammensetning etter valget på generalforsamlingen har vært som følger:
- Leder: Mohammad Nouri Sharikabad (2017-2019)
- Sekretær: Jan Tore Samuelsen (2016-2018. 2018-2020)
- Kasserer: Kristine Hole (2017-2018. 2018-2020)
- Styremedlem: David Eidsvoll (2017-2019)

Vararepresentanter:
- Rigmor Solberg (2018-2020)
- Birgitte Lyrån (2016-2018. 2018-2020)
- Aina Westrheim Ravna (2012-2014, 2014-2016. 2016-2018 og 2018-2020)

Seksjonene har utpekt følgende representanter til styret:
- Toksikologi: Hubert Dirven
- Farmakologi: Ida Robertsen

Representant for industrien:
- Lars Erik Eng Eibak (2017-2019)

Valgkomité for 2019:
- Jørn A. Holme (2017-2019)
- Vigdis Aas (2017-2019)
- Sara Bremer (2018-2020)

Revisor:
- Vigdis Aas (2018-2020)

2. Styrets arbeid

Det har vært avholdt 6 møter i hovedstyret. Deler av styrets arbeid har vært utført via e-post.
Styret har i perioden jobbet med:
- Organisering av NSFTs faglige virksomhet (vår-, høst- og vintermøte)
- Planlegging og organisering av utdeling av Poulssonprisen og pris for beste publikasjon
- Organisering av styrets arbeid og møter
- Rekruttering av nye medlemmer
- Formidling av informasjon på NSFTs nettsider, i nyhetsbrev og via Facebook
- Europeisk registrert toksikolog (ERT)-registreringer
- Finansiering av Selskapets aktiviteter

3. Økonomi

Økonomien til NSFT vurderes som tilfredsstillende. Medlemskontingenten er kr 400,- for vanlige medlemmer og kr 150,- for studenter. Medlemskontingenten for bedriftsmedlemmer er fortsatt kr 3500,-.

NSFT har i 2018 mottatt økonomiske støtte fra Basic & Clinical Pharmacology & Toxicology (BCPT) til NSFTs vintermøte 2018 som gikk til forelesere, da spesielt Beitoforelesningen, Nordisk symposium og støtte til studenter.

For Vintermøtet 2019 er det satt av 19.600,- til stipend for studenter som presenterer poster eller fritt foredrag. Stipend, Beitoforelesningen, årets artikkel og Nordisk symposium støttes i år av BCPT.

4. Faglig virksomhet

Vintermøtet

Vintermøtet 2018 ble holdt på Radisson Blu Resort Beitostølen 25. januar – 28. januar. Det var påmeldt 105 deltakere (ledsagere og barn ikke inkludert) og det var invitert 20 foredragsholdere fordelt på 9 symposier. Symposiene hadde følgende hovedtema:

- *Alzheimer – causes and new targets* (felles)
- *Årets artikkel (Farmakologi & toksikologi, felles)*
- *Perfluorerte forbindelser* (toksikologi)
- *Antidepressiva og barn* (farmakologi)
- *Real-World Evidence* (felles)
- *Developmental neurotoxic effects of environmental toxicants and pharmaceutical drugs and the contribution of in vitro systems* (Beitoforelesningen, felles)
- *Toxicology and pharmacology without animal experiments: will it be possible in the next 10 years?* (Nordic symposium, felles)
- *Hot topics in risk assessment* (toksikologi)
- *Dagens behandling - for mye, for lenge?* (farmakologi)

Kveldsnytt, *«Diamanter, toksikologi og tannkrem»*, ble holdt av Jon E. Dahl, Nordisk Institutt for Odontologiske Materialer.

Til sammen var det meldt inn 28 frie foredrag og 21 postere fordelt på farmakologi og toksikologi.

Vårmøte

Focus on pesticides and effects on humans and the environment.
Tid og sted: 19. april 2018, Folkehelseinstituttet, Oslo.
Arrangør: NSFT

Høstmøte

Seminar på Lab 18 med følgende tema:
- *Epigenetikk og NGS*
- *Doping*

Tid og sted: 18. oktober 2018, Norges Varemesse, Lillestrøm.
Arrangør: NSFT

Poulssonforelesning og seminar:

Poulssonmedaljen 2018 innen humantoksikologi ble tildelt professor Juliette Legler ved Utrecht University, Nederland.
Medaljeoverrekkelsen og Poulssonseminar ble holdt 10. oktober i Auditoriet på STAMI, Oslo
Arrangør: NSFT

NSFTs publikasjonspris
NSFT opprettet i 2014 en ny pris for beste publikasjon fra norske fagmiljøer innen hhv. farmakologi og toksikologi. De første prisene ble delt ut på vintermøtet 2015.

Vinner av årets publikasjonspris innen farmakologi er Ida Robertsen (UiO) og medarbeidere for artikkelen *«Limited Sampling Strategy to Estimate Whole Blood and Intra-lymphocyte Exposure of Everolimus in Renal Transplant Recipients using Population Pharmacokinetic Modeling and Bayesian Estimators»*, Clinical Pharmacokinetics, 2018. Styret mottok til sammen 6 nominasjoner innen farmakologi og komiteen for vurderingen av publikasjonene har bestått av Lise Roman Moltzau (UiO), Kristin Nordal (OUS) og Rigmor Solberg (UiO).

Vinner av publikasjonsprisen innen toksikologi er You Song (NIVA) for artikkelen *«Deciphering the Combined Effects of Environmental Stressors on Gene Transcription: A Conceptual Approach»*, Environmental Science and Technology, 2018. Styret mottok til sammen 9 nominasjoner innen toksikologi, og komiteen for vurderingen har bestått av Dag Marcus Eide (FHI), Asbjørn Nilssen (NTNU) og Marit Nøst Hegseth (UiT)

5. Medlemmer
Selskapet har 294 medlemmer (per 1.1.2019). Av disse har 79 medlemmer oppgitt tilhørighet til farmakologiseksjonen, 125 til toksikologiseksjonen og 36 medlemmer har tilhørighet til begge seksjonene. De resterende medlemmene har ikke valgt seksjonstilhørighet.

Det er fortsatt mange medlemmer som ikke har betalt medlemskontingent. Ved utgangen av 2018 hadde 39 % av medlemmene betalt medlemskontingenten for 2018. Medlemmer uten funksjonell e-postadresse og manglende medlemskontingent vil etter hvert fjernes automatisk fra databasen.

6. Formidling av faglig informasjon i nyhetsbrev og på nettsider
NSFT har i løpet av 2018 sendt ut 9 elektroniske nyhetsbrev til samtlige medlemmer. Nyhetsbrevene inneholder bl.a. informasjon om kommende kurs og arrangementer innen farmakologi og toksikologi. Faglig informasjon har også blitt publisert på NSFTs nettsider og på NSFTs Facebook-side.

7. Toksikologen
Elektronisk versjon av medlemsbladet «Toksikologen» har blitt lagt ut på NSFTs nettsider i mars (nr. 1). Lenke til bladet har også blitt publisert i nyhetsbrev og på NSFTs Facebook-side.

8. Registreringsordningen for Europeisk-registrerte toksikologer (ERT)
Registreringsordningen er underlagt NSFT og er administrert gjennom en nasjonal godkjenningskomité. Komitéen har bestått av: Birgitte Lindeman (leder), FHI - Folkehelseinstituttet, Oslo (valgt til 2019); Christine Bjørge, Miljødirektoratet, Oslo (valgt til 2019); Espen Mariussen, NILU-Norsk institutt for luftforskning, Kjeller (valgt til 2019); Hege Stubberud, Glencore Nikkelverk AS, Kristiansand (valgt til 2017); Åse Krøkje, Norges teknisk-naturvitenskapelige universitet, Trondheim (valgt til 2021); Ketil Hylland, Universitetet i Oslo, Oslo (valgt til 2021); Marie Bjørgan, Yara International ASA, Oslo (valgt til 2021); Elise Rundén-Pran, NILU-Norsk institutt for luftforskning, Kjeller (valgt til 2019), Shan Zienolddiny, Statens Arbeidsmiljøinstitutt (Stami), (valgt til 2019). Mer informasjon om ordningen finnes på NSFTs nettsider: http://nsft.net/registrert-toksikolog

9. Registreringsordning for Europeisk sertifisert farmakolog (EuCP)

En komité bestående av Hege Thoresen (UiO), Harald Thidemann Johansen (UiO), Aina Westrheim Ravna (UiT), Laila Sortvik Nilssen (SLV), Janne K. Sund (NTNU), Siri Amundsen (UNN) og Tone Otterhaug (PCI Biotech) har utarbeidet et forslag til nasjonale retningslinjer for EuCP som tilfredsstiller de internasjonale retningslinjene fra The Federation of European Pharmacological Societies (EPHAR). Søknad om å opprette ordningen ble sendt til EPHAR i 2017, men den er ikke ferdigbehandlet.
Mer informasjon om ordningen finnes på: www.ephar.org/eucp/

Styret for 2018 takker for seg og ønsker det nye styret lykke til i det videre arbeidet.

Oslo, januar 2019

Mohammad Nouri Sharikabad (leder)
Jan Tore Samuelsen (sekretær)
Kristine Hole (kasserer)
David Eidsvoll (styremedlem)
Ida Robertsen (leder, Seksjon for farmakologi)
Hubert Dirven (leder, Seksjon for toksikologi)
Lars Erik Eng Eibak (industrirepresentant)
Rigmor Solberg (vara)
Birgitte Lyrån (vara)
Aina Westrheim Ravna (vara)

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til generalforsamling i NSFT
Beitostølen, 26. januar 2019, kl. 09:30

DAGSORDEN:

1. Konstituering av generalforsamlingen ved sekretær Jan Tore Samuelsen
    a. Godkjenning av møteinnkalling og dagsorden
    b. Valg av ordstyrer og referent

2. Årsberetning for 2018 - gjennomgang ved Jan Tore Samuelsen

3. Økonomi - gjennomgang ved kasserer Kristine Hole
    a. NSFTs regnskap for 2018 og budsjett for 2019

4. Valg ved valgkomiteen.
    a. Nytt styre
    b. Ny valgkomité

5. Innmeldte saker
    a. Forslag om å etablere æresmedlemskap i NSFT (innmeldt sak til generalforsamlingen 2018; se vedlegg)
    Styret synes dette er et godt forslag, men foreslår likevel at vi foreløpig ikke etablerer dette. Mange medlemmer ville sannsynligvis oppfylle kravene til et slikt æresmedlemskap, noe som ville svekke en allerede presset økonomi i selskapet.
    b. Forslag om at NSFT blir med som søker om å få IATDMCT-kongressen til Oslo (se vedlegg)
6. Eventuelt

Oslo, 4. januar 2019
Hovedstyret i NSFT

Forslag om å etablere æresmedlemskap i NSFT

Det er foreslått at medlemmer som har gjort en ekstraordinær innsats i styrearbeid over lengre tid kan belønnes med æresmedlemskap i NSFT. Det foreslås at styret hvert tredje år vurderer om det er aktuelle kandidater for utnevnelse til æresmedlem og at disse ikke trenger å betale årskontingent til NSFT.

(Innmeldt sak til generalforsamlingen 2018)

NSFT

Fra: Stein Bergan <stein.bergan@farmasi.uio.no>
Sendt: fredag 4. januar 2019 08.58
Til: nsft@nsft.net
Kopi: Anders Åsberg; Nils Tore Vethe
Emne: Saker til generalforsamling

Undertegnede har sammen med Anders Åsberg og Nils Tore Vethe søkt to ganger om å få kongressen IATDMCT til Oslo. Vi har ikke nådd opp, men fått "hederlig omtale", mange tilbakemeldinger fra enkeltmedlemmer rundt i verden og vært nære på. Vi ønsker derfor å søke en gang til, selv om vi nå er i fare for å havne litt ned på lista siden Europa har to av de kommende kongressene
-se mer info på IATDMCT sin webside
https://iatdmct.org/events/iatdmct-congress.html

Flere (de fleste?) av kongressene har vært arrangert i samarbeid med nasjonale organisasjoner med lignende 'scope' og sammensetning av profesjoner. Derfor hadde jeg tenkt å foreslå samarbeid med NSFT når vi forhåpentlig hadde klart å få kongressen, men fra påtroppende president har jeg noen hint som tyder på at det vil styrke søknaden om dette er etablert på forhånd.

Derfor er mitt forslag at NSFT blir med som søker om å få kongressen til Oslo, neste frist er i juli og det gjelder kongressen for 2023. (Websiden er ikke helt oppdatert, kongressen for 2022 er allerede tildelt Praha).
Vi har gjort mye av jobben allerede, har kontakt med Visit Oslo og Congress Conferences som har hjulpet oss mye. Det er ikke til å legge skjul på at hotellprisene i Norge er en utfordring –sammen med det å skaffe tilstrekkelig sponsorstøtte. De seneste kongressene som jeg kjenner til, har imidlertid gått i solid pluss, som har blitt delt mellom nasjonal organisasjon og IATDMCT.

Det er allerede en del NSFT-medlemmer som også er medlem av IATDMCT, og flere av oss er medlemmer i IATDMCT sine scientific committees. Foruten dette med søknad om kongress, er disse to organisasjonene på mange måter parallelle –nasjonalt og internasjonalt- og jeg tror det kunne være stimulerende også for NSFT å etablere mer samarbeid med IATDMCT. For klinisk toksikologi sin del tror jeg ikke organisasjonen er så kjent i Norge, så hittil har dette vært mest aktuelt for klinisk farmakologi.

Dersom det skulle være støtte i NSFT for å søke om IATDMCT-kongressen, er det vel noe som styret kan bestemme, ville jeg tro. Men uansett ville det være greit å ha diskutert det på generalforsamlingen først, derfor dette forslag. Jeg kan i så fall påta meg å orientere litt nærmere og svare på spørsmål om IATDMCT og kongressene.

Vennlig hilsen
Stein Bergan.

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Stein Bergan
Professor,
Department of Pharmacology,
Oslo University Hospital;
and School of Pharmacy, Univ of Oslo, Norway

Årsberetning 2018 - seksjon for farmakologi

Dette er styrets beretning om aktiviteter i perioden fra 1. februar 2018 til 26. januar 2019. Årsberetningen legges fram for godkjenning på årsmøtet i Seksjon for farmakologi på Beitostølen 26. januar 2019.

Styret har hatt følgende sammensetning:
Leder: Ida Robertsen (2015-2019)
Sekretær: Ingvild Holdø (2017-2019)
Styremedlem: Sigrid Narum (2011-2019)
Styremedlem: Lise Román Moltzau (2016-2019)
Styremedlem: Kristin Nordal (2016-2019)

Kontaktpersoner utenfor Oslo har vært:
Bergen: Jon Andsnes Berg
Trondheim: Ola Dale
Tromsø: Aina Ravna

Representant for seksjonen i NSFTs hovedstyre har vært Ida Robertsen.
Valgkomiteen har bestått av Kjetil Wessel Andressen, Gunhild Heide og Maria Ulvestad.

Styret har i perioden avholdt 4 styremøter, og har ellers hatt fortløpende kontakt via e-post og telefon om aktuelle saker. Seksjonen har pr 1.1.2019 115 medlemmer. Av disse er 36 også medlem av Seksjon for toksikologi. Totalt registrerte medlemmer i NSFT er 294.

EPHAR (www.ephar.org)
Neste EACPT-møte:
The 14th congress of the European Association for Clinical Pharmacology and Therapeutics
Stockholm, Sweden, June 29- July 2 2019
http://www.eacpt2019.org/

IUPHAR (www.iuphar.org)
Neste IUPHAR-møte:
19th World Congress of Basic and Clinical Pharmacology 2022
Glasgow, Scotland, July 16 - 22, 2022
NSFT kan ha en representant på generalforsamlingen.

NSFTs publikasjonspris innen farmakologi 2018
Vinner av årets publikasjonspris innen farmakologi er Ida Robertsen og medarbeidere for artikkelen "*Limited Sampling Strategy to Estimate Whole Blood and Intra-lymphocyte Exposure of Everolimus in Renal Transplant Recipients using Population Pharmacokinetic Modeling and Bayesian Estimators",* Clinical Pharmacokinetics, 2018. Styret mottok til sammen 6 nominasjoner innen farmakologi og komiteen for vurderingen av publikasjonene har bestått av Lise Roman Moltzau (UiO), Kristin Nordal (OUS) og Rigmor Solberg (UiO).

Begrunnelse:
Prisen for beste publikasjon innenfor fagfeltet farmakologi går til: Ida Robertsen og medarbeidere for artikkelen «Limited Sampling Strategy to Estimate Whole Blood and Intra-lymphocyte Exposure of Everolimus in Renal Transplant Recipients using Population Pharmacokinetic Modeling and Bayesian Estimators». Artikkelen er publisert i det anerkjente tidsskriftet Transplantation. Dette er et samarbeidsprosjekt mellom Farmasøytisk institutt, Universitet i Oslo, Avdeling for transplantasjonsmedisin, Oslo Universitetssykehus og Farmakologisk institutt/INSERM, Universitetet i Limoges, Frankrike.

Robertsen og medarbeidere hadde som mål i denne studien å utvikle en farmakokinetisk populasjonsmodell og et Bayesian-estimat basert på begrenset prøvetaking for å estimere eksponering av immunsuppressivet everolimus i fullblod og lymfocytter hos nyretransplanterte. 12-timers farmakinetikkprofil fra 12 pasienter ved to ulike tidspunkt ble gjort og analysert ved hjelp av LC-MS/MS. En farmakokinetisk modell ble utviklet ved hjelp av ikke-parametrisk modellering. Forfatterne viser at den nye farmakokinetikkmodellen tillater nøyaktig bestemmelse av everolimuskonsentrasjon i både fullblod og lymfocytter. Studien kan samtidig danne grunnlag for lignende modeller for andre immunsuppressiva.

Publikasjonen er godt skrevet, har en klar farmakologisk problemstilling og er klinisk relevant. Komiteen trekker spesielt frem som positivt at studien er meget fremtidsrettet og at det er et internasjonalt samarbeid.

Lab18
Seksjon for farmakologi har deltatt i utformingen av programmet til NSFTs sesjon på labmessen Lab18 som ble avholdt 16-18 oktober i Norges Varemesse, Lillestrøm.

Program Lab18
Velkommen ved NSFTs leder Mohammad Nouri Sharikabad

Del 1 - Epigenetikk og NGS
- Toxico-epigenetics and potential applications of NGS in toxicology
  Nur Duale, Folkehelseinstituttet

Del 2 - Doping
- Farmasi- relevant kunnskap i kampen mot doping?
  Astrid Gjelstad, UiO/Antidoping Norge
- Doping i idrett - metoder for påvisning og analytiske utfordringer
  Yvette Dehnes, Dopinglaboratoriet, OUS

Vintermøtet 2018
Seksjonen har deltatt i utformingen av programmet for NSFTs vintermøte.

Regnskap
Regnskapet for seksjonen har i 2018 vært håndtert sammen med regnskapet for NSFT som helhet. For en formell økonomisk oversikt henvises det derfor til NSFTs regnskap.

Avslutning
Seksjonsstyret for 2018 takker for seg og ønsker det nye styret lykke til med det videre arbeidet.

Ingvild Holdø	Sigrid Narum	Lise Román Moltzau	Kristin Nordal
(Sekretær)	(Styremedlem)	(Styremedlem)	(Styremedlem)

Ida Robertsen
(Leder)

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til årsmøte i seksjon for farmakologi

NSFT

Beitostølen, 26. januar 2019, kl. 09:00-09:30

DAGSORDEN

1. Konstituering av årsmøtet
    a. Godkjenning av møteinnkalling og dagsorden
    b. Valg av ordstyrer og referent

2. Årsberetning for farmakologiseksjonen 2018

3. Godkjenning av budsjett for seksjon for farmakologi

4. Valg
    a. Nytt styre i farmakologiseksjonen
    b. Ny valgkomité

5. Orienterings- og diskusjonssaker
    a. Vår/høstmøte 2019
    b. Innspill til vintermøte 2020

6. Eventuelt

Oslo, januar 2019
Styret i farmakologiseksjonen NSFT

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Årsberetning 2018 – seksjon for toksikologi

1. Styrets sammensetning

Årsmøtet for toksikologiseksjonen ble avholdt på Vintermøtet 27. januar 2018 på Radisson BLU Resort Beitostølen.

Styrets sammensetning for toksikologiseksjonen i året 2018 har vært som følger:

Leder - Hubert Dirven (2016-2019) – FHI, Oslo
Merete Grung (2016-2019) – NIVA/UiO, Oslo
Dag Marcus Eide (2016 - 2020) – FHI, Oslo
Odd Andre Karlsen (2016-2020) – UiB, Bergen
Marit Nøst Hegseth (2017-2019) – UiT, Tromsø
Nina Landvik (2018-2020) – Miljødirektoratet, Oslo (før 15. august 2018: STAMI, Oslo)
Pål Amdal Magnusson (2018-2020) – Miljødirektoratet, Oslo

Varamedlemmer:

Vidar Berg (2016-2019) – NMBU

Valgkomiteen for 2019: Shan Zienolddiny, Yke Arnoldussen og Gunnar Sundstøl Eriksen

2. Styrets arbeid

Styret har i perioden avholdt 4 møter og har hatt omfattende kommunikasjon via epost.

Styret har i perioden jobbet med:
- Organisering av seksjonens faglige virksomhet (vår-, høst- og vintermøter)
- Organisering av Poulsson-pris og seminar
- Organisering av pris for beste publikasjon
- Rekruttering og utdanning av toksikologer (inkludert støtte til Fagrådet for humantoksikologi)
- Utgivelse av seksjonens tidsskrift "Toksikologen"
- Formidling av informasjon på NSFTs nettsider og i nyhetsbrev
- Europeisk registrert toksikolog (ERT)-registreringer
- Hubert Dirven deltok i Eurotox business council meeting i Brussels (september 2018)

3. Faglig virksomhet

Vintermøtet 2018

Pris for beste poster gikk til Alexandra I.S. Treimo (NIOM): Are nanoparticles used in dental materials neurotoxic?

Pris for beste frie foredrag gikk til Vegard Sæter Grytting (FHI): Di-n-butyl phthalate enhances PMA-induced macrophage differentiation of THP-1 monocytes via PPARγ.

Anna Price fra EU Joint Research centre holdt Beito-forelesning om *in vitro* systemer for å studere Developmental neuroTox.

Vårmøtet 2018

Møtet fant sted 19. april i Auditoriet, Folkehelseinstituttet

Tema: Focus on pesticides and effects on humans and the environment

Agenda

13:00 Welcome – **Hubert Dirven** (NSFT)
13:05 Glyphosate: Hazard assessment regarding carcinogenicity by IARC, EFSA and ECHA
Anna Mehl, Mattilsynet, Ås
13:45 Sublethal effects and learning outcomes of imidacloprid on bumblebees
Julie Sørli Paus-Knudsen, UiO
14:15 Coffee break
14:40 How to reduce transport of mobile pesticides in the environment to water sources?
Trine Eggen (NIBIO, Ås)
15:05 Occurrence of pesticides in Norwegian environment
Marianne Stenrød (NIBIO, Ås)
15:30 Mixture toxicity of pesticides in Norwegian environment
Karina Petersen (NIVA, Oslo)
15.55 Questions/comments

Rundt 50 personer deltok på dette vårmøtet.

Høstmøtet/Poulsson-seminaret 2018

Onsdag 10. oktober hadde toksikologiseksjonen æren av å organisere Poulsson-forelesning i auditoriet, STAMI.

Poulsson Lecture and award ceremony:
Prof Dr Juliette Legler, Professor of Toxicology and Environmental Health and Chair of Toxicology. Institute for Risk Assessment Sciences, Utrecht University, The Netherlands

13:00 Welcome – **Hubert Dirven** (chair tox section NSFT)

13:05 Introduction of Prof Dr Juliette Legler – **Mohammad Sharikabad** (Chair NSFT)

Award ceremony

13.15 Poulsson lecture

Unravelling the role of environmental chemicals in disease with toxicology and epidemiology
Juliette Legler

14.15 Coffee break

14.45 Transgenerational effects of environmental stress via epigenetic inheritance in zebrafish
Jorke Kamstra (NMBU)

15.15 What's the potential role of environmental factors in the obesity epidemic?

Merete Eggesbø (FHI)

15.45 Environmental contaminants in animals, food and humans - **Jan Ludvig Lyche** (NMBU)

16:15 End of meeting

Rund 70 personer deltok på dette Poulsson-seminaret.

Lab18
Seksjon for toksikologi har deltatt i utformingen av programmet til NSFTs sesjon på labmessen Lab18 som ble avholdt 16-18 oktober i Norges Varemesse, Lillestrøm.

Program Lab18

Velkommen ved NSFTs leder Mohammad Nouri Sharikabad

Del 1 - Epigenetikk og NGS

- Toxico-epigenetics and potential applications of NGS in toxicology
  Nur Duale, Folkehelseinstituttet

Del 2 - Doping

- Farmasi- relevant kunnskap i kampen mot doping?
  Astrid Gjelstad, UiO/Antidoping Norge
- Doping i idrett - metoder for påvisning og analytiske utfordringer
  Yvette Dehnes, Dopinglaboratoriet, OUS

Nominasjon av NSFT's publikasjonspris innen toksikologi for 2018

Siden 2014 har NSFT tildelt pris for årets beste publikasjon fra norske fagmiljøer innen hhv. farmakologi og toksikologi (akseptert for publikasjon i perioden 1. november året før til 31. oktober inneværende år).

I 2018 har komiteen for vurderingen bestått av Dag Markus Eide (FHI), Asbjørn Nilssen (NTNU) og Marit Nøst Hegseth (UiT).

Toksikologiseksjonen fikk inn 9 nominasjoner til denne prisen.

Vinner av publikasjonsprisen innen toksikologi er: Song, Y., Asselman, J., De Schamphelaere, K. A. C., Salbu, B., & Tollefsen, K. E. (2018). Deciphering the Combined Effects of Environmental Stressors on Gene Transcription: A Conceptual Approach. Environmental Science and Technology, 52(9), 5479–5489.

Artikkelen ble nominert med følgende begrunnelse:
Artikkelen vinner fordi den tar opp tre brennhete temaer i toksikologien:

- Adverse outcome pathways / Mode of Action
- Blandingseffekter - ioniserende stråling er en veldefinert og grundig studert miljøeffekt velegnet for modellstudier. Utarmet uran er et meget aktuelt stoff for toksikologiske studier, men med en mer kompleks virkningsmekanisme.
- Genekspresjon - vurdering av uttrykksnivåer som endepunkt i en pathway analyse

Komiteen mener at artikkelen er klart skrevet. Metoden og tankegangen er lett å følge for forskere som jobber med tilsvarende problemstillinger, og vil være nyttig også for forskere utenfor økotoksikologi-, strålings- og toksikologimiljøet. Konklusjonene virker plausible, selv om forfatterne kanskje tillegger genekspresjon en noe optimistisk rolle i utvikling av AOPs. Kombinert med mer standard endepunktseksperimenter vil genekspresjon være meget viktige verktøy for mekanisme-forståelse også framover.

Europeisk registrerte toksikologer (ERT)-komiteen
Registreringsordning for toksikologer: Den norske komiteen for godkjenning av Europeiskregistrerte toksikologer (ERT) har etter Vintermøtet 2018 bestått av: Birgitte Lindeman (leder), Folkehelseinstituttet, Oslo (valgt til 2019); Christine Bjørge, Miljødirektoratet, Oslo (valgt til 2019);

Espen Mariussen, Norsk institutt for luftforskning, Kjeller (valgt til 2019); Hege Stubberud, Glencore Nikkelverk AS, Kristiansand (valgt til 2020); Åse Krøkje, Norges teknisk-naturvitenskapelige universitet, Trondheim (valgt til 2018); Ketil Hylland, Universitetet i Oslo, Oslo (valgt til 2018); Marie Bjørgan, Yara International ASA, Oslo (valgt til 2018); Elise Rundén-Pran, Norsk institutt for luftforskning, Kjeller (valgt til 2019), Shan Zienolddiny, Statens arbeidsmiljøinstitutt (valgt til 2019).

Informasjon om ERT-ordningen finnes på NSFTs nettsider: http://nsft.net/registrert-toksikolog

Oppsummering av ERT-komitéens arbeid i 2018
Komiteen mottok høsten 2018 gledelig nok hele 9 søknader om førstegangs-registrering og 8 søknader om re-registrering. Søknadene blir behandlet i ERT-komitéen i januar 2019. Det er per 2018 omtrent 80 registrerte toksikologer på den norske listen.

Det var ikke deltagelse fra den norske ERT-komiteen på EUROTOX' ERT-møte i 2018.

Den norske ERT-komiteen jobber med utvidelse av informasjon til søkere om registeringsprosedyrene og oppbevaring/sletting av data ift til de nye personvernskravene.

Vintermøtet 2019

Styret har foreslått en del temaer til symposia (dCOD-prosjektet, mikro-/nanomaterialer, Beito-forelesning med Alan Boobis (Science and society: nice to know or need to know), The immune system and mixtures) til vintermøte og har invitert foredragsholdere til toks-symposia.

Toksikologiseksjonen fikk inn 17 abstrakter for orale presentasjoner og 14 abstrakter for postervisninger til Vintermøtet 2019. Alle som presenterte postere fikk tilbud om en 3 minutters speed presentasjon.

For å lage mer plass til frie foredrag har vi også i 2019 byttet ut et toks-symposium med en frie foredrag-seksjon.

4. Utgivelse av "TOKSIKOLOGEN"- Toksikologiseksjonens fagtidsskrift
Fagbladet «Toksikologen» har blitt sendt ut (elektronisk versjon) til samtlige medlemmer i mars (nr. 1). På grunn av tidspress rakk redaksjonen ikke å lage flere utgaver.

Redaksjonen i Toksikologen i 2018 besto av: Thomas Aga Legøy (redaktør), Gunhild Rogne Halland, Pernille Kvernland, Marie Dahlberg Persson.

Det nye toks-styret må finne ut om det fortsatt er hensiktsmessig med utgivelse av Toksikologen. Hvis svaret er ja, må miljøet kommer med kandidater til redaksjonen. Primært er MSc og PhD studenter aktuelle som redaksjonsmedlemmer, så universitetsmiljøene må bidra til rekrutteringen.

5. Andre aktiviteter
De siste årene er utdanningen innen humantoksikologi og muligheter til å søke penger for humantoksikologisk forskning blitt svekket. Spesielt bekymringsfullt er at NFR og departementene ikke prioriterer eksperimentell forskning relatert til humantoksikologi i strategi og programdokumenter. Dette er bekymringsfullt, da både forskning og forvaltning har et stort behov for humantoksikologer med spisskompetanse. Miljøgifter, kjemikalier og forurensning truer helsa vår, og det kreves både gode forskningsmiljøer og solid faglig kompetanse for å dekke forvaltningens behov innenfor regulering av kjemikalier. Humantoksikologer med god kompetanse er nødvendig for

å utføre risikovurderinger i et sykdomsforebyggende perspektiv for en rekke departementer som er ansvarlige for regulering og forvaltning av blant annet matvarer, kjemikalier, lokal luftkvalitet, arbeidsmiljø, landbruk og havbruk. Et svekket utdanningstilbud innen toksikologi og sterk reduserte muligheter til å drive med eksperimentelt forskning vil få store konsekvenser for rekruttering av humantoksikologer til forvaltningen, næringslivet og internasjonale organisasjoner som EFSA, ECHA og WHO, og vil på sikt også kunne true etablerte humantoksikologiske forskningsmiljøer i instituttsektoren og ved enkelte universiteter. Norsk selskap for farmakologi og toksikologi (NSFT) og det humantoksikologiske miljøet i Norge er derfor sterkt bekymret for situasjonen rundt utdanning og forskning innenfor fagområdet humantoksikologi.

Fagrådet for humantoksikologi
Mange miljøer er bekymret for utdanningstilbudet på MSc, PhD og post-doc nivå innen humantoksikologi. FHI har opprettet et fagråd for humantoksikologi som Hubert Dirven leder. Toks-styret i NSFT støtter aktivt fagrådets arbeid.

6. Medlemmer

125 NSFT-medlemmer har oppgitt tilhørighet til toksikologiseksjonen og 36 medlemmer har tilhørighet til begge seksjonene.

Oslo, januar 2019
Styret for Toksikologiseksjonen

NSFT

Norsk Selskap for Farmakologi og Toksikologi

Innkalling til årsmøte i Seksjon for toksikologi, NSFT Beitostølen, 26. januar 2019, kl. 09:00-09:30

DAGSORDEN:

1. Konstituering av årsmøtet
    a. Godkjenning av møteinnkalling og dagsorden
    b. Valg av ordstyrer og referent

2. Årsberetning for toksikologiseksjonen 2018. Leder av seksjonen går gjennom årsberetning

3. Valg
    a. Nytt styre i toksikologiseksjonen
    b. Ny valgkomité

4. Etablering av en ærespris (Poulsson-pris) for økotoksikologer

5. Møter 2019 – nye forslag og videreføring av idéer
    a. Vår- og høstmøte 2019
    b. Innspill til vintermøte 2020

6. Eventuelt

Oslo, januar 2019
Styret i toksikologiseksjonen NSFT

Inviterte foredrag (IF)

IF-1

The Pharmacology and Toxicology of Novel Psychoactive Substances

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During the last decade the illicit drug market has changed dramatically with a rapid increase in the number of new substances. The novel psychoactive substances (NPS), also known as designer drugs, legal highs, spice or bath salts, are synthetic analogues of traditional drugs of abuse (e.g. heroin, cocaine, cannabis, and amphetamine) or pharmacotherapeutic agents, created to circumvent existing drug laws. Since 2010, more than 500 new substances have been reported on the European drug market. The wide availability for purchase on the internet has contributed to the rapid and global changes in recreational drug trends. In general, the pharmacological effects of NPS resemble those of traditional drugs which they are intended to mimic; however, NPS are often more potent and appear to exhibit more severe adverse effects. Furthermore, the purity and composition of NPS containing products are highly variable. As a rule, the consumers do not know what substance they are taking or in what concentration, and are exposing themselves to incalculable health risks and consequences. Synthetic stimulants and cannabinoids have been the most common types of NPS, but more recently an increasing number of highly potent synthetic opioids have appeared. The number of NPS related deaths has increased dramatically, with synthetic opioids being involved in more than 28 000 fatal intoxications in the United States in 2017. Increased knowledge of the pharmacology and toxicology of NPS is needed to raise awareness of the health consequences posed by different NPS on the recreational drug market.

IF-2

How does maternal use of drugs of abuse affect the fetus?

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Use of illicit drugs is most frequent among young adults; and about 30% of these are women in reproductive age. Illicit drugs can easily cross the placenta and may affect the fetus. Different trends in illicit drug use patterns in Europe increases the concern that more fetuses will be affected by maternal use of illicit drugs. Knowledge of the associations between use of illicit drugs during pregnancy and adverse outcomes in the newborn is scares and several of the previous studies have methodological weaknesses. Many of the studies were conducted in selected populations in countries where the quality of health care differs for different patient populations making a comparison between groups difficult.
In several studies, we have tried to use a new research approach by using the unique nationwide health registry data available in both Norway and the Czech Republic. Linkage of registry data by use of personal identification numbers makes it possible to address several of the limitations from earlier studies. We have for instance been able to study large, unselected study populations and identify relevant comparison groups.
The outcomes we have focused on are adverse neonatal outcomes captured in the birth registries and childhood morbidity captured as ICD-10 diagnosis in the patient registries. We have performed comparisons with different relevant comparison groups as well as the unexposed population of pregnant women.
Results from the different studies will be presented and discussed. There will be a focus on associations between cannabis, methamphetamine, opioids and opioid maintenance treatment and adverse neonatal outcomes and childhood morbidity.
Taken together the studies indicate that prenatal exposure to illicit drugs results in quite similar neonatal outcomes in the newborns and these outcomes are more unfavorable than what is observed in the unexposed newborns. The results might indicate that life-style, morbidity and socioeconomic factors common to pregnant drug dependent women play a large role for the observed adverse outcomes.

IF-3

A Limited Sampling Strategy to Estimate Exposure of Everolimus in Whole Blood and Peripheral Blood Mononuclear Cells in Renal Transplant Recipients using Population Pharmacokinetic Modeling and Bayesian Estimators

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Aim
Intracellular exposure of everolimus may be a better marker of therapeutic effect compared to trough whole-blood concentrations. We aimed to develop pharmacokinetic population models and Bayesian Estimators based on a limited sampling strategy for estimation of dose interval exposures of everolimus in whole-blood and peripheral blood mononuclear cells (PBMC) in renal transplants.

Methods
Full whole-blood and PBMC concentration-time profiles of everolimus were obtained from 12 stable renal transplants on two different occasions, 4 weeks apart. The dataset was treated as 24 individual profiles and split into a development dataset (n=20) and a validation dataset (n=4). The pharmacokinetic model was developed using non-parametric modeling and its performances and those of the derived Bayesian estimator were evaluated in the validation set.

Results
A structural two-compartment model with first-order elimination and two absorption phases described by a sum of two gamma distributions were developed. None of the tested covariates (age, gender, albumin, hematocrit, fat-free mass and genetic variants as *CYP3A5*1*, *ABCB1* haplotype, *PPARA*42*, *PPARA*48* and *POR*28*) were retained in the final model. A limited sampling schedule of two whole-blood samples at 0 and 1.5 hours and one PBMC sample at 1.5 hours post dose provided accurate estimates of the AUC in comparison with the trapezoidal reference AUC (relative bias±SD= -3.9±10.6% and 4.1±12.3% for whole-blood and PBMC concentrations, respectively).

Conclusion
The developed model allows simultaneous and accurate prediction of everolimus exposure in whole-blood and PBMC, and supplies a base for a feasible exploration of the relationships between intracellular exposure and therapeutic effects in prospective trials.

IF-4

Deciphering the combined effects of environmental stressors on gene transcription: a conceptual approach

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Background
Use of classical mixture toxicity models to predict the combined effects of environmental stressors based on toxicogenomics (OMICS) data is still in its infancy. Although several studies have made attempts to implement mixture modeling in OMICS analysis to understand the low-dose interactions of stressors, it is not clear how interactions occur at the molecular level and how results generated from such approaches can be better used to inform future studies and cumulative hazard assessment of multiple stressors. The present work was therefore conducted to propose a conceptual approach for combined effect assessment using global gene expression data, as illustrated by a case study on assessment of combined effects of gamma radiation and depleted uranium (DU) on Atlantic salmon (*Salmo salar*).

Methods
Implementation of the independent action (IA) model in re-analysis of a previously published microarray gene expression data was performed to describe gene expression patterns of combined effects and identify key gene sets and pathways that were relevant for understanding the interactive effects of these stressors.

Results
A total of 3120 differentially expressed genes (DEGs) were caused by additive effects, whereas 279 (273 synergistic, 6 antagonistic) were found to deviate from additivity. Functional analysis further revealed that multiple toxicity pathways, such as oxidative stress responses, cell cycle regulation, lipid metabolism and immune responses were enriched by DEGs showing synergistic gene expression. A key toxicity pathway of excessive reactive oxygen species (ROS) formation leading to enhanced tumorigenesis signaling is highlighted and discussed in detail as an example of how to take advance of the approach. Furthermore, a conceptual workflow describing the integration of combined effect modeling, OMICS analysis and bioinformatics is proposed.

Conclusion
The present study presents a conceptual framework for utilizing OMICS data in combined effect assessment and may provide novel strategies for dealing with data analysis and interpretation of molecular responses of multiple stressors.

IF-5

Toxicology: The dCod project

The chemical defensome of Atlantic cod (*Gadus morhua*): how does it differ from defensome networks in human and zebrafish?

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Background
The chemical defensome comprises an integrated network of gene families and pathways that together function to metabolize and eliminate harmful compounds[1,2]. It is critical for survival and highly conserved from invertebrates to fish and mammals. The chemical defense genes of Atlantic cod (*Gadus morhua*), a commercially and ecologically important species, are poorly studied. The object of this investigation is to assess the chemical defensome network of cod and compare it with the defensome networks of zebrafish (*Danio rerio*) and human (*Homo sapiens*).
Methods
Using HMMER searches and Pfam profiles, the newly curated Atlantic cod proteome assembly was searched for chemical defensome proteins. Orthologs of the cod proteins was found through reciprocal best hit BLASTP searches in the zebrafish proteome. Human and zebrafish defensome genes were identified based on previous studies[3]. Using the protein-protein interactions covered by the STRING database, we were able to model and visualize the chemical defensome networks in Cytoscape.
Results
The genes involved in the chemical defensome of Atlantic cod were identified and compared to human and zebrafish defensome networks. Using network analysis and graph theory methods, we have identified central nodes and protein-protein interactions and processes within the defensome networks. Moreover, the cod defensome network was used in analysis of toxicogenomic data in order to look for patterns beyond individual pathway enrichment analyses.
Conclusion
The identification and modelling of fish and human chemical defensome genes enables a dynamic visualization of these complex networks. A better knowledge of the genes and proteins involved in the chemical defensome networks will benefit toxicogenomic studies of the individual species, as well as the extrapolation of results from model animals to other species.

The study is part of dCod 1.0, part of Centre for Digital Life Norway (project no. 248840), and iCod 2.0 (project no.244564), funded by the Research Council of Norway and the University of Bergen.

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IF-6

Toxicology: the dCod project

Toxicogenomic responses in Atlantic cod (*Gadus morhua*) after treatment with selected environmental contaminants *in vivo* and *ex vivo* in liver slices.

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Background
The Atlantic cod (*Gadus morhua*) is an emerging model organism in environmental toxicology. The sequencing and annotation of its genome (Star *et al*., Nature 2011) facilitated toxicogenomics studies aimed at mapping the molecular targets, biomarker candidates and pathways affected by environmental contaminants.
Methods
Exposure experiments to selected environmental contaminants were performed in Atlantic cod, *in vivo* as well as *ex vivo* in precision-cut liver slices (PCLS) previously developed in our lab (Eide *et al*., Aquat Tox 2014). Using transcriptomics (mainly RNA-seq) and proteomics methods, we mapped differentially expressed genes and proteins followed by bioinformatics analysis to identify pathways affected.
Results
Hundreds of genes responding to selected contaminants were mapped, which helped to predict pathways affected and possible mechanisms involved. In our recent study, genes in the aryl hydrocarbon receptor (Ahr) and estrogen receptor pathways were mapped using RNA-seq, after treatment of PCLS by benzo[a]pyrene (BaP) and 17α-ethynylestradiol (EE2), respectively. Up-regulated genes include novel estrogen and xenoestrogen target genes such as fibroblast growth factor (fgf) genes *fgf3* and *fgf4*. Further experiments in liver slices and *in vivo* were performed to investigate possible perturbations of the FGF signaling pathway. Our recent results show that after treatment of PCLS by estrogens and xenoestrogens, the *fgf3* and *fgf4* genes are transcriptionally activated early and transiently. After 12-24h peak levels, the mRNA levels of the two genes gradually fall to background levels in PCLS culture. However, less pronounced induction of the *fgf3* and *fgf4* genes was observed by *in vivo* estrogen exposure studies (1-3 days). The transcriptional activation of these genes could be blocked by co-treatment of PCLS with EE2 and the estrogen receptor antagonist tamoxifen, indicating that their induction is dependent on ligand-activated estrogen receptor. Some FGF receptor (FGFR) downstream target genes were also induced suggesting activation of the FGF signaling pathway in estrogen treated liver slices.
Conclusions
Estrogens transcriptionally activate the *fgf3* and *fgf4* genes early and transiently in cod liver slices. Considering the importance of the FGF signaling pathway in processes such as embryonic development, differentiation and carcinogenesis, its possible perturbation by estrogens and xenoestrogens warrants further investigation.

The study was supported by the iCod 2.0 (244564) and the dCod 1.0 (248840) projects which belong to the Center for Digital Life Norway (DLN), funded by the Research Council of Norway.

IF-7

Toxicology: The dCod project

A draft metabolic reconstruction of Atlantic cod (*Gadus morhua*) liver: how to and what for?

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Background

The availability of genome sequences, annotations and the knowledge of the biochemistry underlying metabolic transformations have paved the way towards metabolic network reconstructions of many organisms. These networks can depict the form and function of genes in a target organism. When modeled using mathematical representations, a reconstruction can thus simulate the corresponding genotype-phenotype relationships. Accordingly, genome-scale models (GEMs) can help understand and predict the reactions of organisms to genetic and environmental variations. The interdisciplinary aspect and activities of the dCod project motivate our efforts to assemble existing knowledge on the Atlantic cod (*Gadus morhua*) into a metabolic reconstruction that can greatly support its evolving role as a model organism in environmental toxicology and other areas of biology.

Methods

Reaching a refined bottom-up metabolic reconstruction requires a long and strenuous process that typically consists of four main phases [1]. In the first stage, a draft reconstruction is generated from available sequences and annotations by retrieving reactions involving metabolic genes. Then, a refinement procedure follows to curate and balance the covered metabolic reactions. In the third phase, the refined reconstruction is converted to a constraint-based and condition-specific mathematical format. Finally, subsequent simulations and iterative validations can be performed using various datasets related to the target organism.

Results

We are currently exploring the RAVEN (Reconstruction, Analysis and Visualization of Metabolic Networks) Toolbox 2 [2] which allows semi-automated reconstruction of GEMs, based on protein homology and using existing template GEMs and KEGG database. We focus on the Atlantic cod liver and use as template an existing curated human liver GEM that emphasizes lipid metabolism. Our preliminary draft model shows favorable retrieval of reactions from the template model to the draft Atlantic cod GEM, based on protein homology.

Conclusion

The generated draft reconstruction will be subject to further enhancement at the first phase in terms of input GEMs and at succeeding refinement and simulation phases, as described above.

The study is funded through the dCod 1.0 project which is part of the Center for Digital Life Norway (DLN) granted by the Research Council of Norway (248840).

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IF-8

Cancer in children and adolescents – overview, late effects and new treatment modalities

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Each year approximately 200 children and adolescents (below 18 years of age) are diagnosed with cancer in Norway. The main groups of oncological disease are leukaemia, brain/central nervous system tumours and solid tumours outside the central nervous system. More than 30 different diagnoses are described. Luckily, the overall survival rate exceeds 80%.

Oncology treatment in patients below 18 years of age is usually conducted according to international treatment protocols. The need for international collaboration is immense due to small numbers of patients. This is, of course, especially important for small countries like Norway. The recommended treatment differs according to tumour type, localisation and dissemination of the disease. The treatment can be uni- or multimodal. The most common modalities are chemotherapy, surgery and/or irradiation. Lately, immunotherapy has been an option for patients with refractory or relapsing disease. Sequencing of tumour to discover new targets for therapy is increasing. Personalized treatment is probably the future for these patients.

The promising treatment results come with a price. Old fashioned treatment with chemotherapy, surgery and irradiation is associated with different kinds of late effects. Organ function failure, hormonal deficiencies, malfunction and cognitive challenges are among the most common late effects.

Some late effects appear immediately, whereas others tend to emerge later on. To avoid excessive late effects, surveillance of vulnerable structures is performed up front and during treatment. Surveillance is performed after cessation of treatment as well, to cope with appearing late affects as early and efficiently as possible. Personalized facilitation may be necessary.

The new and increasing immunotherapy may be associated with different kinds of inflammation and special efforts have to be undertaken to avoid excessive and disabling late effects.

IF-9

Macro, micro, nano: What we know and should know about plastic pollution

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Plastic pollution has become a prominent environmental issue. Microplastics in particular are the pollutants *du jour* attracting massive academic, public and political attention. This "attractiveness" is certainly a product of our attention economy which heavily draws upon the visibility of plastics pollution. However, there is a mismatch between the public perception and the actual scientific knowledge of the environmental risks of (micro)plastics. Thus, I will take a look at the state-of-the-science with regard to the abundance and the toxicity of microplastics, using aquatic ecosytems as a case study. I will use the available data to approach the key question of whether microplastics represent an environmental risk or not. I will supplement this with own, unpublished data on the human toxicology of nano- and microplastics. As the answer will not be clear-cut, I will also highlight the limitations of our current risk assessment framework.
To put plastic pollution in a larger societal context, I will critically reflect on the question why we (as researchers) are so obsessed with microplastics and inevitably touch on perverse incentives in academia. Finally, I will explore the role of plastic pollution in the larger Anthropocene discourse to discuss potential impacts on societies.

IF-10

Ultrasound-mediated delivery of nanomedicine for improved treatment of cancer and brain diseases

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Nanotechnology has started a new era in engineering multifunctional nanoparticles (NPs) to improve diagnosis and therapy of various diseases, incorporating both contrast agents for imaging and drugs for therapy into so called theranostic NPs. In cancer therapy, encapsulating the drugs into NPs improves the pharmacokinetics and reduces the systemic exposure due to the leaky capillaries in tumours. NPs might also have a potential of treating diseases in the central nervous system (CNS) if the blood-brain barrier (BBB) could be opened. The access of molecules to the CNS is strictly controlled by the specialized and tight junction between the endothelial cells forming the blood vessels constituting the BBB.

A prerequisite for successful therapy is that the therapeutic agents reach their targets and limit the exposure to normal tissue. The delivery depends on the vasculature, the transport across the capillary wall, through the extracellular matrix, and across the cell membrane. Although the NPs may pass the tumour capillaries, the uptake of drug-loaded NPs is low and they are heterogeneously distributed in the tumour tissue. In order to improve the uptake and distribution of NPs into diseased tissue, the administration of NPs should be combined with a treatment facilitating the delivery. Therefore, new designs of NP based drug delivery systems are needed to secure efficient drug release within tumors.

Focused ultrasound in combination with microbubbles has shown to both improve the delivery of NPs to tumors and to temporarily open the BBB. In the presence of ultrasound, microbubbles oscillate and produce biomechanical forces on the blood vessel wall, facilitating transport across the capillary wall and into the extracellular matrix.

Different types of these ultrasound mediated drug delivery systems have been developed by our group and have shown to significantly improve the delivery of drugs to tumors and to enhance the therapeutic efficacy[1,2]. Furthermore, we were able to temporarily open the BBB making delivery of nanomedicine across the BBB possible[3]. An overview of these drug delivery systems and tumor models used to assess these systems will be given just as a general introduction in ultrasound mediated drug delivery.

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IF-11

Science and society – nice to know or need to know?

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On balance, whilst there are some caveats, science has served society well. Over the last century there have been dramatic improvements in health at both ends of the age spectrum, with increased longevity and decreased infant mortality. Nutrition has similarly benefited. However, as many of the diseases of a hundred years ago were overcome, they were replaced by new diseases, or at least diseases that were not of major concern a century ago. These include neurobehavioral conditions, neurodegenerative diseases, allergy and obesity-related conditions. The reasons for these trends are not straightforward. For example, as fatal diseases of earlier life are overcome, diseases of older age will increase. Diagnostic techniques are improving, so detection limits will increase. However, there is real concern that, at least in part, the causes are chemical in origin, i.e. that exposure to synthetic chemicals used for industrial purposes, as pesticides, as food additives, in food packaging, is at levels sufficient to cause adverse effects. And certainly, there are numerous publications that would support this. But, there are also numerous publications that argue the opposite. The continuing debate over the safety of bisphenol A is an example of this. There is both a qualitative and a quantitative problem. For example, on the one hand, how do we assess the potential of a chemical to cause neurobehavioral effects in animal models and on the other, what levels of a chemical causing obesogenic effects in a test system are of concern in exposed individuals?

Advances is science and technology are providing an unparalleled opportunity to develop a novel approach to assessing the safety of chemicals, utilising computational and in vitro methods. This would enable chemical effects on any, and all, biological processes in humans to be evaluated. However, confidence in the reliability of the methods used needs to be established, and the adequacy of the range of biological effects assessed needs to be determined. Approaches are being developed to address these concerns, but international agreement has yet to emerge. The move from in vivo studies will place more reliance on interpretation of perturbations of basic biology than on identification of adverse outcomes. This has important implications for method verification, where comparisons with results of conventional tests will not be appropriate, and will need to be replaced by consideration of basic biology. For example, when does perturbation of a biochemical pathway result in progression to adversity? The Adverse Outcome Pathway approach has the potential to underpin this strategy, but only if due consideration is given to the above aspects.

Risk assessment is part of the risk analysis paradigm, which underlies many policy and risk management decisions. Whilst risk assessment needs to be science and evidence-based, it is only one of the factors that determine policy. Others include benefit, socio-economic cost, public acceptability. It is therefore important that risk assessment provides information not only on potential concerns to human health, but also on the levels at which these are likely to occur and on the associated uncertainty. It would be easy to ensure safety from a vaccine by not administering it, but the consequential increase in childhood deaths due to otherwise preventable viral infection would be a heavy societal cost. The risk assessor needs therefore to distinguish between the conceivable and the probable. If science-based advances in public health are to continue, we need to recognise that there is no zero-risk option and risk-benefit comparison has an important role to play.

IF-12

The CGRP Pathway in Migraine as a Viable Target for Therapies
Prof Lars Edvinsson (Lund Universitet)

IF-13

Immunotoxicology – the youngster in toxicology but with a bright future

Unni C. Nygaard, Senior scientist, Norwegian Institute of Public Health

Up to one in five people of the Western population suffers from immune-mediated diseases including asthma/allergy and autoimmune diseases. Furthermore, it has been claimed that in roughly half of all disorders that are not primarily classified as immune mediated disorders, inflammatory processes also play a central role (cardiovascular diseases, diabetes, cancers, neuron, infectious diseases etc). In view of this, immunotoxic exposures leading to a misbalanced immune system may have a huge economic and societal impact, by promoting adverse effects like immune suppression, -stimulation, hypersensitivity and autoimmunity. Since a number of these diseases have an early life onset, developmental immunotoxicity is of particular concern.

Immunotoxicology is one of the youngest fields in toxicology. Although considerable work was performed during the 1970 and 1980, progress in immunotoxicity testing and inclusion of functional immune endpoints in regulatory guidelines has been limited, probably hampered by the complexity of this fine-tuned system and its adverse outcomes. Presently, the only OECD guideline tests assessing functional immunotoxicity are for skin sensitization and when triggered, developmental immunosuppression in the extended one-generation reproductive toxicity study (EOGRTS).

It is increasingly clear, however, that the environment affects and shapes immune function during foetal development and throughout life. Recent technological and biostatistical advances allow for high dimensional assessment of immune function and systems immunology approaches. Such approaches hold promise for future advancements in identifying mechanisms and causal relationships in toxicology. We are currently applying mass cytometry (cytometry time of flight, CyTOF) methodology and subsequent unbiased/unsupervised mathematical algorithms for toxicology studies on cells from human cohort studies and experimental models. Mass cytometry permits simultaneous detection of 40-50 metal isotope-tagged antibody specificities in a single sample. Thus, classification of cell subtypes and their activation status, and simultaneous detection of functional markers like intracellular cytokines, signaling pathways and proliferation is possible. This approach is particularly powerful in identifying new combinations of characteristics that are easily overlooked in traditional (supervised) analyses. Preliminary results from the PhenAll and Euromix projects will be presented. Combined with advanced in vitro and organioid systems, we expect such results to contribute to development of AOPs and novel, sensitive and specific immunotoxicity tests. The combination of experimental and epidemiological studies is expected to be important for future immune toxicity evaluations.

IF-14

Manipulating the immune system to treat cancer, how does it work and who is doing what in Oslo Cancer Cluster?

Øyvind Kongstun Arnesen (Ultimovacs AS)

There is no longer any reasonable doubt that the immune system can recognise and kill cancer cell to the extent that patients benefit. There are established treatments where manipulation of the immune system is the mode of action. The Nobel Prize in medicine and physiology 2018 was awarded to James P. Allison and Tasuku Honjo for their contribution in this field. The immune system responds to almost all types of cancer but is unable to clear cancer cells from a growing tumour. Normal tissues have mechanisms to protect themselves from an activated immune system and a growing tumour has similar mechanisms. New treatments of cancer are based on manipulation of the tumour microenvironment and/or activation of immune cells. Norwegian academic institutions and companies are in the forefront of this research.

IF-15

Strategies for exposure and hazards assessment of mixtures as developed in the H2020 EuroMix project

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Problem formulation

The Horizon 2020 EuroMix project aims to provide validated test strategies for the hazard and exposure assessments of chemical mixtures. The main approaches as developed in the project will be presented. A web-based toolbox, including Monte Carlo Risk Assessment (MCRA) modelling tools, is developed for performing risk assessments of chemical mixtures. In order to examine source-to-dose calculations, a human biomonitoring (BM) study was performed.

Method

For two 24-hour study periods separated by 2-3 weeks, adult volunteers (44 males and 100 females) in Norway kept detailed diaries on food consumption (type/brand, weight, time and packaging material) and the usage of personal care products (PCPs) (type/brand of product, time and number of applications, and number of showers and hand washes). The participants also registered the number of thermal papers (TP) handled. In parallel, 24 hours urine samples were collected. Bisphenol A (BPA), bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB) and bisphenol AF (BPAF) as well as parabens, triclosan (TRCS), triclocarban (TRCB) and oxybenzone (OXB) were analysed in the urine samples of the first day. Exposures to BPA, BPS and BPF from foods, PCPs, and TP were modeled for the study population. The risk assessment tool MCRA (EuroMix toolbox) was used for calculating individual external exposure from foods, aggregating dietary with non-dietary exposure from PCPs and TP, converting external to internal exposure, and for the comparison with BM data.

Results

BPA was found above LOD in 96% of the urine samples, BPS in 29% and BPF in 4% of the urine samples. OXB, TRCS, methylparaben (MePA) and ethylparaben (EtPA) were detected in 90-100% of the urine samples and propylparaben (PrPA) and butylparaben (BuPA) in 65% and 50%, respectively. BPB, BPAF and TRCB were not detected. Modeled aggregate internal exposures covered the full range of measured urinary amounts for all BP analogs. Individual-based medians of modeled BPA exposures were in very good agreement with the respective measurements. However, BPS and BPF levels in participants with positive measurements of the respective BP were mostly underestimated by modeled exposures. Urinary measurements did not reveal a significant correlation between the amount of canned food, the number of PCPs used, or the number of TP handling events and levels of BPA, BPS, or BPF.

Conclusion

The good agreement between modeled and measured BPA exposure shows that the exposure situation is realistically captured by the considered exposure sources and source concentrations. However, for BPS and BPF, source concentrations are partly missing and/or might not be up-to-date, which mostly leads to too low predictions of exposures.

IF-16

Effect studies with human relevant mixtures of persistent organic pollutants (POPs)

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The term persistent organic pollutants (POPs) is used to define chemical compounds that are toxic to humans and wildlife, resistant to degradation and have the potential to bioaccumulate and biomagnify in living organisms. Most experimental studies investigating effects of POPs use single compounds. Studies focusing on effects of POP mixtures are limited, and often conducted using extracts from collected specimens. Confounding effects of unmeasured substances in such extracts may bias the estimates of presumed causal relationships being studied. We describe the use of an environmentally relevant mixture of POPs, containing 29 different chlorinated, brominated and perfluorinated compounds. POPs listed under the Stockholm Convention on Persistent Organic Pollutants and reported to occur at the highest levels in Scandinavian food, blood or breast milk prior to 2012 were selected, and two different mixtures representing different exposure scenarios constructed. The *in vivo* mixture, contained POP concentrations based on human estimated daily intakes, whereas the *in vitro* mixture was based on levels in human blood. In addition to the total *in vitro* mixture, 6 sub-mixtures containing the same concentration of chlorinated + brominated, chlorinated + perfluorinated, brominated + perfluorinated, or chlorinated, brominated or perfluorinated compounds only were constructed. Using sub-mixtures allows studying the effect of adding or removing one or more chemical group. We used the mixtures to make realistic exposures of environmental contaminants for toxicity studies, based on relative levels of POPs to which we are exposed. Effects related to endocrine disruption, cancer and reproductive defects as well as effects on the nervous- and immune systems were investigated using different animal and cell models.

IF-17

The complexity of psychotic disorders and treatments

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Objective
Psychotic disorders comprise a range of phenotypes characterized by psychotic and affective symptoms with schizophrenia and bipolar disorder as prototypes of the respective symptom clusters. There is a large variation in course and outcome of psychotic disorders, indicating subphenotypes and diversity of mechanisms. Large international collaborative efforts are needed to describe the genetic architecture and lay the basis for individualized treatment.

Method
The talk will give a brief introduction to the complexity of psychotic phenotypes and recent genetic findings, indicating potential avenues for developing more personalized treatments.

Results
Psychiatric diagnoses are syndromal descriptions based solely on signs and symptoms. The current psychotic disorders are broad categories with overlapping characteristics encompassing individuals with one brief illness episode to chronic conditions in need for long term hospitalization, care and support. The huge effort for establishing diagnostic biomarkers has so far been unsuccessful, and it is unlikely that the diagnoses correspond to specific underlying mechanisms. The poorly defined pathophysiology, diversity and broad diagnostic descriptions is reflected in the lack of tools for predicting treatment response. Patients are often subjected to a lengthy trial and error approach based on lack of response and side-effects. The last years have seen a major increase in large international collaborations for describing the genetic architecture of psychotic disorders, indicating overlapping genetics across diagnoses and with brain structures and somatic conditions. The talk will present novel findings with specific focus on associations with metabolic and immunological genetics, illustrating current research strategies for improved understanding of psychotic disorders which may form the basis for future individualized treatment.

Conclusion
Predicting treatment response and individualizing treatment in psychotic disorders is a major challenge in current psychiatric research. Huge samples and novel statistical models are needed to describe the genetic underpinnings and pathophysiology of these complex disorders. The last decade has seen a large increase in these efforts with identification of a substantial amount of novel genetic loci, showing overlap across psychiatric and somatic conditions and laying the basis for new diagnostic schemes and individualized treatment.

IF-18

Personalized medicine in antipsychotic treatment

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Topic: Today, treatment of schizophrenia and other psychotic disorders is characterized by trial-and-error until an 'acceptable' symptom improvement is obtained. This approach often leads to treatment failure, polypharmacy, side effects and/or non-compliance. Thus, there is a need of alternative approaches to optimize antipsychotic drug therapy. However, due to the limited and stagnated knowledge about disease mechanisms underlying psychotic disorders, which likely vary between patients with similar symptom traits, development of innovative and targeted antipsychotic drugs appears unlikely. Instead, individualized dosing of existing drugs seems to be the realistic concept of personalized medicine in antipsychotic treatment.
Methods: Mainly based on research during the last decade at Center for Psychopharmacology, the presentation will provide an overview of factors being important for individual dose requirements and treatment success focused on the antipsychotics risperidone, olanzapine and clozapine. Furthermore, the potential value of preemptive pharmacogenetic testing and therapeutic drug monitoring (TDM) as tools for preventing therapeutic failure will be highlighted.
Results: While concurrent use of interacting agents is a predominant factor to account for when prescribing olanzapine and clozapine, pharmacogenetic variability is of foremost importance for risperidone. For all drugs, individual variability in metabolism is associated with risk of therapeutic failure. Our research supports that TDM may prevent therapeutic failure, including non-compliance, which differs significantly between risperidone, olanzapine and clozapine. In the case of risperidone, knowing *CYP2D6* genotype may preemptively avoid failure by adjusting initial dosing.
Conclusion: Implementing current knowledge on genetic or non-genetic factors that determine pharmacokinetic variability and individual dose requirements may improve personalized treatment of antipsychotic drugs. TDM and pharmacogenetic analyses should be used as tools to facilitate treatment success.

IF-19

The Norwegian Prednisolone in Early Psychosis Study (NorPEPS)

Rune A. Kroken

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Background. Medical treatment of schizophrenia are mainly antipsychotics with moderate to good effect sizes on positive symptoms. The effects on negative symptoms and cognitive dysfunction are low to poor, and the overall effect of antipsychotics is to treat psychosis rather than to improve the trajectory of schizophrenia. Novel treatment principles must be explored.

As a consequence of elevated immune-related proteins – cytokines – in serum/plasma from patients with schizophrenia, and an association of immune-coding genes with schizophrenia in large GWAS studies immune-influencing drugs are tried in several on-going studies. We choose prednisolone to conduct a proof-of-concept study.

Method. Randomized double-blind placebo-controlled add-on design with 6 weeks of prednisolone/ placebo, 1 year follow-up. 90 participants with schizophrenia-spectrum disorders will be included from study sites in Bergen, Trondheim, Stavanger and Oslo.

PI. Erik Johnsen, Haukeland university hospital and University of Bergen.

Status. Assigned PhD candidates and research nurses in Bergen and Stavanger. Including patients.

Frie foredrag

De frie foredragene er på 10 minutter hver, hvorav 8 minutter er til foredraget og 2 minutter er til spørsmål og diskusjon.

NSFTs pris for beste frie foredrag 2019
En priskomité vil vurdere alle bidrag og finne en vinner innen henholdsvis farmakologi og toksikologi. Hver vinner får tildelt diplom og en vandreplakett under festmiddagen lørdag 26. januar. Priskomiteen for frie foredrag i toksikologi 2019 består av Jason Matthews og Ketil Hylland. Priskomiteen for frie foredrag i farmakologi 2019 består av Stein Bergan, Monica Hermann, Vigdis Aas og Kristine Hole.

Vinnere av pris for beste frie foredrag 2018 var: Erlend Johannesen Egeland, Farmasøytisk institutt, Universitetet i Oslo (Farmakologi) og Vegard Sæter Grytting, Folkehelseinstituttet (Toksikologi).

Frie foredrag i toksikologi (TF)

TF-1

Subchronic dietary exposure to ethoxyquin dimer induces microvesicular steatosis in male BALB/c mice

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Background
Ethoxyquin (EQ) is a synthetic antioxidant, which has routinely been added to fishmeal in order to prevent auto-oxidation and ignition under storage and long distance sea transport. Fishfeed for salmon aquaculture that contains fishmeal, will also contain EQ, which can be transferred to the edible parts of the salmon. Once taken up by the fish, EQ from fish feed is quickly metabolized to other compounds, and is mainly found in the fillet as ethoxyquin dimer (EQDM). In their most recent risk assessment of EQ as a feed additive, the European Food Safety Authority (EFSA) identified knowledge gaps and called for data related to target animal- and consumers safety, and safety for the environment.
This project investigated potential risks of dietary EQDM exposure to consumers of farmed Atlantic salmon fillet using mice as a surrogate model.

Method
Male BALB/c mice were exposed to one of six doses ranging from 0.015 to 518 mg EQDM/kg bodyweight/dag (n=10/group) for 90 days. The toxicity and dose-response of EQDM was investigated taking a «systems toxicology» approach; Liver metabolomic and proteomic profiling was performed as an initial screening for EQDM-induced changes, and the identified target pathways were validated through biochemical measurements of classic physiological endpoints and histopathology.
The potential risk to consumers was assessed using benchmark dose modelling of the critical effect found in the study.

Results
Following 90 days dietary exposure, doses above 10 mg/kg body weight/day affected whole body lipid metabolism resulting in increased liver weights and decreased adipose tissue mass. Metabolomic screening of livers revealed alterations indicating incomplete fatty acid beta-oxidation and hepatic oxidative stress. Histopathological evaluation and biochemical analyses of the liver confirmed the development of microvesicular steatosis and activation of the glutathione system.
Hepatic protein profiling and pathway analyses suggested a likely mediation of EQDM-induced responses through activation of CAR/PXR nuclear receptors and an induction of a NRF2-mediated oxidative stress response.

Conclusion
The development of microvesicular steatosis was considered the critical endpoint of the study, from which a Reference Point for dietary EQDM exposure was established at 1.1 mg/kg body weight/day using benchmark dose modelling. Applying an uncertainty factor of 200, an Acceptable Daily Intake of 0.006 mg EQDM/kg body weight was proposed.

Reference
Bernhard, A., Rasinger, J. D., Wisløff, H., Kolbjørnsen, Ø., Myrmel, L. S., Berntssen, M. H., ... & Madsen, L. (2018). Subchronic dietary exposure to ethoxyquin dimer induces microvesicular steatosis in male BALB/c mice. *Food and Chemical Toxicology*.

TF-2

Nutrients, dioxins and dioxin-like PCBs in Norwegian fatty fish; risk or benefit?

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Problemstilling
In a recent risk assessment performed by the European Food Safety Authority (EFSA), the tolerable weekly intake (TWI) for dioxins (PCDD+PCDF) and dioxin-like PCBs (dl-PCBs) was reduced considerably, from 14 to 2 pg WHO-05 TEQ/ kg bw per week. Fatty fish are a major exposure route of dioxin and dl-PCBs, but are also the main sources of marine omega 3 fatty acids and vitamin D, which are important nutrients in the human diet. By assessing a large dataset on both nutrient and contaminants in three important fatty fish species, Atlantic mackerel, Atlantic herring and farmed Atlantic salmon, we aimed to describe the congener distribution, the levels of total dioxin and dl-PCBs, as well as the levels of marine n-3 fatty acids and vitamin D. We further aimed to evaluate these data in a food benefit/risk context.
Metode
Herring, mackerel, and farmed salmon fillets have been sampled between 2006 and 2017, and from 4000 of these samples data on concentrations of 29 different dioxins and dl-PCBs were assessed. Further, we assessed another 996 samples analysed for the marine omega 3 fatty acids DHA and EPA, and 962 samples analysed for vitamin D. The levels of dioxin and dl-PCB were compared to the new TWI, while the levels of nutrients were compared to the recommended adequate intakes (AI) established by the EFSA.
Resultater
Mean total upper bound dioxin and dl-PCB levels ranged from 0.51 ng/kg WHO-05 TEQ in farmed Atlantic salmon to 0.82 ng/kg WHO TEQ in Atlantic herring. PCB 126 accounted for approximately 50% of the total TEQ in all three species. Excluding other sources, one meal of 150 g of herring or mackerel exceeded the TWI for ∑dioxins and dl-PCBs, while one meal of Atlantic salmon corresponds to 53% of the TWI.
Median level of the marine omega 3 DHA and EPA ranged from 11.9 mg/g fat in farmed Atlantic salmon to 51.9 mg/g fat in mackerel, while the median of vitamin D ranged from 0.04 mg/kg in mackerel to 0.23 mg/kg in herring. For all three species, one meal of 150 g provided the weekly AI for EPA and DHA. Atlantic salmon provided 103% of the weekly requirement, while herring and mackerel contributed with 178% and 422% respectively. For vitamin D, herring provided 50% of weekly AI, while salmon and mackerel provided 14% and 8% respectively.
Konklusjon
Although a weekly meal of Norwegian fatty fish provides the recommended intake of marine fatty acids, and is a good source of vitamin D, it contain dioxins and dl-PCBs sufficient to exceed or contribute substantially to the TWI.
A new risk-benefit assessment of fatty fish consumption is recommended

TF-3

The effect of selenomethionine on methylmercury accumulation in BALB/c mice

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Background
Methylmercury (MeHg) is a highly toxic compound that is released into the biosphere and atmosphere through natural and anthropogenic sources. The main exposure route of MeHg in humans is through consumption of seafood. MeHg is highly bioavailable and accumulates in all tissues, including the brain. The toxicity of MeHg is dependent on the dose ingested and the accumulated levels in tissues. However, seafood also contains nutrients, such as selenium, that potentially ameliorate the toxic effects of MeHg. In fish, supplementary Se has been shown to reduce the accumulated levels of Hg and increase the elimination of Hg in tissues (1). Therefore, the objective of this study was to investigate how the marine nutrient selenium (in the form of selenomethionine (SeMet)) can influence mercury (Hg) accumulation in mice.

Method
Thirty-six male BALB/c mice were included in a fractional factorial study design. The mice were assigned to 6 groups and fed standard rodent diets containing either a low dose MeHg (0.25 mg Hg kg^{-1} feed), a high dose MeHg (3.40 mg Hg kg^{-1} feed) or no MeHg, each either supplemented with 2.5 mg SeMet kg^{-1} feed or no SeMet. Feed intake and physiological parameters, such as body weight and body composition were assessed during the trial. Hg and Se accumulation were analyzed *post mortem* following 11 weeks of exposure.

Results
No differences were observed in feed intake, total weight gain and total body mass following 11 weeks dietary exposure. A lower fat mass was observed in the groups that received the high dose of MeHg. Lower accumulated levels of Hg were observed in the mice exposed to a low dose MeHg compared to the high dose MeHg-exposed mice. Supplementation of SeMet in the feed reduced the accumulation of Hg in cortex, gastrocnemius and tibialis in mice exposed to the high dose MeHg. The same effect was not seen in mice that received the low dose MeHg. No effects of dietary SeMet supplementation were seen on Hg accumulation in kidneys. A positive correlation between Se and Hg concentration was detected in liver.

Conclusion
Dietary SeMet supplementation reduced accumulation of Hg in cortex and muscles of male BALB/c mice.

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TF-4

Health effects and toxicokinetics of deoxynivalenol and ochratoxin A in dietary exposed Atlantic salmon (*Salmo salar*)

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Background:
The increased use of plant ingredients in fish feed implies possible contamination with mycotoxins, which could harm fish health and lead to mycotoxin residues in edible parts of the fish.

Method:
Post-smolt Atlantic salmon were fed with standard feed added one of five concentrations of either pure deoxynivalenol (DON; 0.5-6 mg/kg) or pure ochratoxin A (OTA; 0.2-2.4 mg/kg), or no added toxins for up to eight weeks.

Results:
Effects on performance (i.e. feed intake and –efficiency, weight gain, length and condition), various clinical biochemical parameters, packed cell volume and vaccination response against *Aeromonas salmonicidae* were all inversely correlated with DON dose, whereas relative liver weight increased with DON dose. DON was also found to impair the epithelial barrier (decreased relative expression of markers for three tight junction proteins) and modulate the cytokine signalling in the intestine. For DON, a BMDL20 of 0.3 mg/kg feed for reduced total protein in plasma, a BMDL5 of 0.5 mg/kg feed for reduced condition factor, and a NOAEL of 1 mg/kg feed based on reduced packed cell volume and clinical chemical effects were derived. In fish fed OTA, the health effects were rather small, and a BMDL or NOAEL could not be derived.
DON was distributed to various tissues including muscle, and the concentrations increased significantly from three to eight weeks of exposure. OTA was mainly found in liver and kidney, and the concentrations in liver decreased significantly from three to eight weeks. OTA was eliminated faster than DON from various tissues. The levels observed do not suggest any risk to consumers of salmon fed diets containing maximum recommended levels of these toxins.
Conclusion:
The salmon showed rather high sensitivity to DON and low sensitivity to OTA. Whereas the maximum recommended levels of these mycotoxins in feed in Norway and the EU seem to protect consumers, they do not protect post-smolt salmon against adverse effects of DON.

TF-5

High-dimensional immune cell profiling reveals functional immune signatures for patients with unknown mechanisms of allergic reactions to food

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Background
Food allergy has emerged as a considerable public health concern. Yet, the underlying immunological mechanisms of these adverse reactions are still not fully understood. Food allergic reactions are mediated either by allergen-specific Immunoglobulin E (sIgE), by distinct pathways in the absence of sIgE in serum, or may show etiologies of both.
The diagnosis of food allergy, in particular in absence of food-specific IgE, is difficult, and diagnostic biomarkers for the different allergy phenotypes are either lacking or have limited accuracies.
The aim of this study was to identify functional and/or phenotypical immune cell signatures characteristic for food allergy with an IgE-positive and an IgE-negative serology, with the overarching goal to obtain new insight in the underlying mechanisms of food allergy. Identification of such signatures/mechanisms will facilitate an accurate clinical diagnosis of food allergy phenotypes and may contribute to build adverse outcome pathways (AOPs) and identify key events (KE) applicable in future development of immunotoxicity tests.

Methods
For this purpose, we performed high-dimensional profiling of peripheral blood mononuclear cells (PBMC) from adult sIgE-positive food allergy patients, sIgE-negative food allergy patients and healthy controls by mass cytometry/CyTOF (cytometry by time of flight). A combination of conventional gating strategies and unsupervised algorithm-guided analysis approaches was used to identify all major immune cell populations in PBMC and simultaneously determine their activation status, proliferation status, and cytokine expression patterns.

Results
We identified several cell populations where the combination of marker expression was significantly different between individuals with severe adverse reactions to food with a sIgE-positive or sIgE-negative serology, and healthy controls.
Interestingly, most of these cell subpopulations were similar in the two groups of food allergics, suggesting that several immune cell mechanisms may be common for food allergic patients with a sIgE-positive and a sIgE-negative serology.
The most striking observation was a reduction in polyfunctional $CD4^+$ and $CD8^+$ T cells after in vitro stimulation, in both food allergy groups compared to the healthy controls.

Conclusion
Our results provide a basis for further studies on mechanistic, KE and diagnostic biomarker studies and illustrate the great potential of mass cytometry as a sensitive tool for identification of biomarkers and/or mechanistic knowledge.

TF-6

HEMA affect IL-1β release and phagocytosis in THP-1 macrophages

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Introduction
Resin-based biomaterials used in dentistry consist of methacrylate monomers that are polymerized *in situ*. The conversion to polymer is never complete and this causes leakage and patient exposure to electrophile monomers such as 2-hydroxyethyl methacrylate (HEMA). In addition, dental personnel that handle these materials are exposed on a daily basis. Lipopolysaccharide (LPS) is commonly used in studies investigating inflammatory macrophage responses to bacteria. HEMA has been shown to decrease LPS-induced cytokine release of interleukin (IL)-1β and tumor necrosis factor (TNF)-α in murine macrophages (RAW 264.7). In this study, we aim to investigate if HEMA reduces live bacteria-induced cytokine release in human macrophages. In addition, the effects of HEMA on phagocytosis of live bacteria were investigated to study macrophage functionality.

Methods
The human monocytic cell line THP-1 was differentiated to macrophages by phorbol myristate acetate (PMA). THP-1 macrophages were subsequently exposed to HEMA and LPS from *E. coli* or to HEMA and live *S. aureus* bacteria. *S. aureus* was chosen as a cytokine inducer as it is present in the oral cavity and known to induce a strong IL-1β release. Cytokine levels of IL-1β, IL-8 and TNF-α were measured by enzyme-linked immunosorbent assay (ELISA) in the experiments involving live *S. aureus* bacteria, while only IL-1β was measured in the LPS experiments. In addition, the effect of HEMA on THP-1 macrophages ability to phagocytose live S. aureus was investigated.

Results
HEMA reduced the LPS-induced cytokine release of IL-1β, as previously shown in RAW 264.7 macrophages. Furthermore, HEMA similarly reduced the *S. aureus*-induced release of IL-8 and TNF-α. Phagocytosis is important for elimination of bacteria. In contrast to the reduced cytokine release, THP-1 macrophages exposed to HEMA increased phagocytosis of *S. aureus* bacteria.

Conclusion
HEMA reduced LPS and *S. aureus*-induced release of IL-1β from human macrophages, while increasing phagocytosis of *S. aureus* bacteria. Consequently it appears that HEMA may affect the macrophage immune response.

TF-7

Toxicity of combined exposure of HEMA and nicotine in PE/CA-PJ49 cells

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Introduction

Tobacco as well as nicotine replacement therapy products contain relative high levels of nicotine. Research on the toxicity of nicotine has mainly focused on the interaction with nicotinic cholinergic receptors, but a lysosomotropic response of nicotine is also reported. The latter may explain recent research that indicates that nicotine interact with the autophagy response in cells. The monomer 2-hydroxyethylmethacrylate (HEMA) found in resin-based dental materials is known to leak after curing, thereby causing patient exposure. HEMA has a cytotoxic potential *in vitro,* and it is suggested that cellular defence against HEMA-induced damage involves autophagy. For nicotine-addicted patients treated for dental decay with resin-based dental materials, combined exposure to nicotine and HEMA is likely to occur.

The aim of this study was to investigate the individual and combined effect of nicotine and HEMA exposure on cell viability and autophagy.

Methods

For this in *vitro study,* a human tongue squamous carcinoma cell line (PE/CA-PJ49) was used as a model. Cells were cultured and exposed to HEMA and nicotine individually and in combination. Cells were also treated with an inhibitor of lysosomal proteins. Cell viability was measured using MTT assay in addition to phase-contrast microscopy pictures to map morphological changes. Specific antibody was used to detect changes in levels of the autophagy related protein SQSTM1/p62 after different exposures. Data was quantified using western blot and Odyssey CLx Infrared System.

Results

Results showed that exposure to nicotine or HEMA alone had no effect on cell viability. However, combined exposure to nicotine and HEMA showed reduction of the viability in cells with increasing concentrations. Results showed that HEMA induced both synthesis and degradation of p62. This imply increased autophagy flux. Further, cells exposed to nicotine showed significant increased level of p62. Results indicates that this increase was caused by decreased lysosomal degradation, implying inhibition of autophagy.

Conclusion

This study has shown that combined exposure to nicotine and HEMA affects the cell viability in a synergistic manner. The results support that autophagy protects cells against HEMA-induced toxicity. The impairment of autophagy pathway may explain the observed synergistic toxicity of combined exposure to nicotine and HEMA.

TF-8

Biomagnification of PFAS in the Antarctic breeding south polar skua

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Introduction: A previous study on south polar skuas (*Catharacta maccormicki*) found increasing per- and polyfluoroalkyl substances (PFAS) concentrations in blood during the breeding season at the colony of Svarthamaren [(1)]. The present study compares biomagnification (using stable isotopes $\delta^{13}C$ and $\delta^{15}N$) in two food webs: at Svarthamaren (continental Antarctica), where skuas prey almost exclusively upon eggs and chicks of Antarctic petrels (*Thalassoica antarctica*), and petrels prey on fish and marine invertebrates; and Dumont D'Urville (DDU, peripheral Antarctica), where skuas prey almost exclusively upon eggs and chicks of Adélie penguins (*Pygoscelis adeliae*).

Materials and methods: LC/MS was used to measure PFAS in stomach samples and eggs from Antarctic petrels, and in blood samples from south polar skuas, Adélie penguin chicks, and Antarctic petrel adults and chicks. Stable isotopes were also analysed. Results were merged with those of previous studies [(1,2)] to form a database for Svarthamaren and DDU, which we used to calculate biomagnification factors (BMF) and Trophic Magnification Factors (TMF) for detected PFAS within the two contrasted ecosystems.

Results: At Svarthamaren, PFUnA was above detection limit in all matrices, but not all samples. Other PFAS included PFOS, PFNA, PFDcA, PFTriA and PTFeA. Concentrations increased along the food web, south polar skuas having the highest. At DDU, concentrations were lower, but the pattern was comparable to Svarthamaren. Branched PFOS were quantified in skua samples at DDU, but absent in other matrices. Prey items contained more PFAS above detection limit at Svarthamaren than DDU. We calculated BMF and TMF for all detected PFAS at Svarthamaren, but only for PFOS, PFNA, PFDcA and PFUnA at DDU. BMF for PFOS was generally high in both colonies, indicating another, unidentified major source. For other PFAS, values were variable, but comparable between colonies.

Conclusion: PFAS concentrations in south polar skuas from both colonies and Antarctic petrels at Svarthamaren probably reflect exposure outside Antarctica during winter. The concentrations detected in Adélie penguins are not high enough to explain the PFAS levels in skuas at DDU. Thus at DDU, PFAS levels are due to other prey either within the region or more likely outside Antarctica [(3)].

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TF-9

Using diet to explain the bioaccumulation of organic contaminants in Norwegian populations of killer whale (*Orcinus orca)*

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Research question

As apex marine predators, the killer whale (*Orcinus orca*) is one of the most heavily contaminated animals in the world. In addition to gender, location and age, the strongest explanatory variable for contaminant levels in killer whales is often diet. Whilst generalist as a species, the killer whale tends to specialise on a narrow range of prey at the group and/ or population level, frequently spanning trophic levels. Previous research of Norwegian killer whales has assumed Atlantic herring (*Clupea harengus)* to be the primary prey. However, there is new evidence that some groups have specialised on a diet of marine mammals such as seals. The aim of this project is to quantify the levels of contaminants in Norwegian killer whales across and within groups. With support from stable isotope analysis, and observation records, diet will be explored as an explanatory variable for varying contaminant levels.

Methods

Fieldwork was conducted from 2017-2018 in Northern Norway, and 38 biopsy samples were collected using lightweight darts. All sampled individuals were photographically identified and linked to a database of prior observations. Contaminant analysis of 29 samples was conducted at the Environmental Toxicology Laboratory at the Norwegian University of Life Sciences (NMBU) - Campus Adamstuen. Organic contaminants (including polychlorinated biphenyls and pesticides), brominated flame-retardants, and their hydroxy- metabolites were analysed for. Stable isotope ratios of nitrogen ($\delta^{15}N$) and carbon ($\delta^{13}C$) were analysed in 38 skin samples. Samples were lipid extracted prior to $\delta^{13}C$ analysis, due to the bias lipids introduce by $\delta^{13}C$ depletion. Non-lipid-extracted samples were used for $\delta^{15}N$ analysis due to the unpredictable effects of chemical lipid extraction on $\delta^{15}N$ values. Preparation and analysis of $\delta^{15}N$ and $\delta^{13}C$ were both conducted at the University of Oslo.

Results

Results are expected at the end of December, with preliminary statistical analysis to be conducted in January. We expect higher levels of contaminants in males than females, due to efficient reproductive transfer of contaminants in female marine mammals, and higher levels in adult males than juvenile males due to age accumulation. If dietary reconstruction indicates some groups to have specialised on a marine mammal prey (higher $\delta^{15}N$ values), we expect to find higher contaminant levels in those groups than in groups with a primary herring diet.

Conclusion

Diet is expected to be the primary explanatory variable in the varying contaminant levels in Norwegian killer whales. The project will not only give information on the current contaminant burden, but also assist in resolving potential diet specialisation. This will provide an important baseline for the management and conservation of the Arctic marine ecosystem.

TF-10

How well do herring gull or eider duck represent pollution status in an urban fjord?

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Research question

Environmental monitoring is performed across the world for determination of contamination status of ecosystems. For coastal marine ecosystems, seabirds are commonly used as indicators of contaminant levels high in the food web. A species that is used for this purpose is the herring gull, *Larus argentatus.* The herring gull is well suited to be a monitoring species for many reasons, including a wide and Holarctic distribution and high trophic position. The herring gull is a species with a broad ecological niche, foraging from both marine and anthropogenic sources. This poses the question of how well the herring gull is suited for its role as indicator of the status of marine food webs. This will be addressed by comparing contaminant levels in relation to carbon source and trophic position of herring gull and the marine benthic-feeding eider duck, *Somateria molissima*.

Methods

Blood and eggs of herring gull and eider duck were collected from the inner Oslofjord area during the breeding season in late May 2017. A total number of 60 samples were collected; 15 blood samples and 15 eggs from each species. The samples were analysed for a range of legacy and emerging environmental contaminants in the laboratories at the Norwegian Institute for Water Research (NIVA), the Norwegian Institute for Air Research (NILU) Kjeller and NILU Tromsø, and $\delta^{15}N$ and $\delta^{13}C$ stable isotopes at Institute for Energy Technology (IFE). In addition, determination of lipid content was performed at NILU. Results from laboratory analyses were treated for missing and censored values to ensure a high-quality dataset, and statistical analysis is on-going. Methods used include constrained and unconstrained ordination as well as correlation tests and box plots.

Results

The lower $\delta^{15}N$ and $\delta^{13}C$ can indicate a more terrestrial diet in herring gulls than eider duck. After quality control, only hexachlorobenzene (HCB) and a range of polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and perfluorinated alkyl substances (PFAS) were included in the statistical analysis. Eider duck blood is the matrix with the highest concentrations of the lipophilic organochlorides and organobromides, while PFAS concentrations show less differences between matrixes.

C*onclusions*

The low $\delta^{15}N$ of herring gull is contradictory to general food web assumptions, but in light of the strong terrestrial signal supports the claim that eider duck is a better indicator of contamination in the Oslofjord.

TF-11

Environmental contaminants in herring gull from two colonies in the Oslofjord, and maternal transfer to eggs

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Research question

The Oslofjord contains a range of contaminants (Ruus et al., 2017). Urbanfjord is a monitoring program conducted for several years, and has quantified the levels of various contaminants in a range of species representing the Oslofjord community. The European herring gull (*Larus argentatus*) has been used as a biomarker for the inner fjord contaminant status. However, it is not clear how well the studies of these gulls represent the status of the marine ecosystem, as dietary markers indicate a diet that is not representative of the Oslofjord (Keilen, 2017). To address this question, the contaminant and stable isotope values from adult herring gulls and their eggs will be compared between two locations in the Oslofjord.

Method

The fieldwork at Søndre Skjælholmen (inner fjord) and Store Revlingen (outer fjord) was conducted in late May 2017. From each location, body measurements, blood samples from 15 adult female gulls as well as one associated egg from each nest were collected. In both matrices (whole-blood and egg), analyses of perfluorinated alkyl substances (PFAS) at NIVA and polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), pesticides, brominated flame-retardants (PBDEs), siloxanes and 11 different metals at NILU were performed. To investigate dietary markers, stable isotopes of nitrogen ($\delta^{15}N$) and carbon ($\delta^{13}C$) were analysed. Statistical analyses were performed on contaminants with >75% of the values above limit of detection. Principal Component Analysis (PCA) was conducted on $\log_{10}$-transformed contaminant concentrations to investigate the variation in adult gulls and the maternal transfer, as well as the association with location, $\delta^{15}N$ and $\delta^{13}C$.

Results

The $\delta^{13}C$ and $\delta^{15}N$ values differed between locations and between matrices within each location. The concentrations of lipophilic contaminants were highest inn gull eggs and lowest in adult gulls, where lead, iron, cadmium, and nickel dominated. The levels of PFASs, mercury, and arsenic were highest in outer compared to inner Oslofjord gulls.

Conclusion

The $\delta^{13}C$ values showed a more marine signal for the gulls from the outer fjord, compared to the inner fjord which seem more influenced by scavenging on garbage and left overs. The higher $\delta^{15}N$ value in eggs compared to blood might be due to matrix composition differences, or as a result of dietary changes before and after egg laying. Higher concentrations of lipophilic contaminants than metals in eggs suggest more maternal transfer of the former.

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TF-12

DNA damage in dragonfly nymphs (Odonata, Anisoptera) living in highway runoff sedimentation ponds is correlated with pollution level

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Scope
The main objective of the present study was to assess whether organisms living in highway sedimentation ponds are subjected to genotoxic effects due to their exposure to traffic related pollutants with special emphasis on PAHs. This was performed by assessing DNA damage by use of the Comet assay in dragonfly nymphs (Anisoptera) from the genus *Aeshna*, collected from highway sedimentation ponds and natural ponds.

Method
Three highway sedimentation ponds (Skullerud, Nøstvedt and Vassum) and two natural ponds (Svarta and Båntjernveien) were included in the study. Skullerud, Nøstvedt and Vassum receive runoff from the four-lane highway E6. In addition, the Vassum pond receives regularly tunnel wash water from three tunnels (Nordby tunnel, Smiehagen tunnel and Vassum tunnel). Sediment samples were analysed for PAHs, alkylated PAHs and metals. Dragonfly nymphs were collected, and the haemolymph analysed for DNA damage by the Comet assay.

Results
The sediments from the sedimentation ponds contained high levels of PAHs (up to 10 000 µg/kg dw), while the two natural ponds contained much lower levels. The alkylated PAHs contributed more than 70 % to the total PAHs in sedimentation ponds, but much lower contribution to the total PAH in natural ponds. This can be interpreted as a petrogenic source to PAHs in sedimentation ponds. The dragonfly nymphs were mainly *Aeshna cyanea* (72 %), but also *A. juncea* (23 %) and *A. grandis* (3 %) were collected. An optimised method for cell extraction from haemolymph was developed. DNA strand breaks was significant between ponds ($p=0.0012$), with the highest percentages of DNA fragment in the Comet tails in nymphs from Vassum sedimentation pond, followed by Skullerud and Nøstvedt. The % tail DNA in nymphs from Nøstvedt was however, not statistically different from % tail DNA in nymphs from natural ponds. The relationship between the sum of PAHs and alkylated PAHs in the sediments and mean % tail DNA showed a positive correlation ($R2$ adj. 0.96, $p=0,013$).

Conclusion
DNA damage in sedimentation ponds were closely correlated with pollution levels, measured here by PAH levels. However, the metals and other contaminants will also likely contribute to the environmental hazard.

TF-13

Contaminant accumulation and biological responses in Atlantic cod (*Gadus morhua*) exposed to polycyclic aromatic hydrocarbons and perfluoroalkyl substances

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Background and aim
Studying effects of environmental contaminants in mixtures is crucial to understand their toxic behavior. The objective of the present study was to investigate the biological responses of mixtures of six polycyclic aromatic hydrocarbons (PAHs) and/or four perfluoroalkyl substances (PFASs), at low (L) or high (H=20xL) doses, in juvenile Atlantic cod (*Gadus morhua*).
Methods
We performed a two-week *in vivo* experiment, with intraperitoneal (IP) injections of farmed, juvenile cod at day 0 and day 7. In total, 10 groups, each consisting of 21-22 fish were included in the experiment, with two control groups, separate groups of PAH mix (L, H) and PFAS mix (L, H), and four groups combining PAH and PFAS mixes (L/L, H/L, L/H, H/H, respectively). To assess chemical accumulation, PFAS concentrations were determined in cod liver, and concentrations of PAH metabolites were determined in bile. Several biological effects were investigated by measuring various biomarkers at transcript and protein levels in the liver. These analyses were complemented with precision-cut liver slices (PCLS) exposed to the same compounds at similar concentrations.
Results
Chemical analyses showed significantly higher concentrations of PAHs and PFASs in cod tissues for the H groups compared to the controls and the L groups. Several changes were observed for various gene transcripts, e.g. significant downregulation and upregulation of *cyp1a* and *ahrrb*, respectively, for the H-PAH group. In contrast, ELISA analyses showed a significant increase in Cyp1a levels for the L-PAH, H-PAH and H/H groups. In PCLS experiments, the H-PAH and H/H groups showed significant induction of *cyp1a* and *ahrrb* transcripts.
Conclusion
In summary, accumulation of contaminants and effects on several biological responses were observed in cod, demonstrating biological effects of PAH and PFAS mixtures, both alone and combined. We plan to further investigate responses of single compounds using PCLS.
The study was funded by dCod 1.0 (Project no. 248840), a large project linked to Center for Digital Life Norway (DLN), financed by the Research Council of Norway (NFR).

TF-14

Towards more relevant exposure scenarios; transformation and ecotoxicological effects of Ag and TiO_2 nanoparticles transformed through wastewater treatment processes

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Problem description. The increase in production and use of Ag and TiO_2 nanomaterials has led to their release in wastewater streams and subsequently in the environment. Nanoparticles (NPs) can undergo transformations in environmental media such as domestic wastewater, leading to an alteration in behavior and toxicity that may differ from their pristine counterparts and make predictions challenging. The overall goal of this study was to elucidate the behavior of Ag and TiO_2 NPs in realistic matrices such as wastewater effluents and activated sludge, and investigate the subsequent effects of transformed particles relative to their pristine counterparts.
Methods. A laboratory-scale wastewater treatment system was established and combined with a battery of ecotoxicological assays and characterization techniques. The system was based on activated sludge treatment with a pre-denitrification system and fed with synthetic wastewater spiked daily with 10 µg Ag NPs/L (PVP coated, 25 nm, nanoComposix) and 100 µg TiO_2 NPs/L (5 nm, NM-101, JRC) over a 5-week period. Effluent samples and samples from all reactors were collected weekly and analyzed by sequential filtration and ICP-MS to determine the NP fractionation and partitioning. Transmission electron microscopy (TEM) and sp-ICP-MS were performed on selected samples. The effects of transformed particles present in the effluents were assessed using a battery of bioassays including freshwater and marine algae (growth inhibition, reactive oxygen species -ROS- formation), crustaceans and *in vitro* models of relevance for NP toxicity assessment (RTgill-W1 cell line, metabolic activity, epithelial integrity, ROS formation, gene expression).
Results. Sequential filtration and ICP-MS analysis of the different fractions of the effluent showed that above 80% of Ag and Ti was associated with residual colloidal material. TEM revealed the presence of TiO_2 aggregates in the effluent while Ag NPs were associated with S, Cu and Zn. Increased toxicity was observed during the first weeks of the system operation with effects being species-dependent; marine epibenthic copepods and algae were more sensitive. Increased ROS levels were observed *in vitro* (RTgill-W1 cell model) followed by increased epithelial permeability and increased zonula occludens-1 (ZO-1) mRNA levels.
C*onclusion*. The combination of a laboratory-scale wastewater treatment system with characterization techniques and a battery of bioassays allowed for tracking the NP aging and effects of the aged particles present in the effluent. The extent of the observed effects was dependent on the organisms exposed, with bottom feeding organisms and algae being more sensitive, while the *in vitro* model proved to be a good tool for realistic and complex environmental samples. Through a relevant exposure scenario, this study adds useful pieces to our still fragmentary understanding of the environmental fate of transformed NPs.

TF-15

In vitro assessment of estrogenic and androgenic effects of bisphenols on Atlantic cod (*Gadus morhua*)

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Bisphenol A (BPA) is a high production volume chemical often used in manufacturing polycarbonate plastics and epoxy resins, which is utilized in food storing articles. Due to its endocrine-mimicking properties BPA was banned in 2010 for its use in baby bottles in the US, Canada, and Denmark among others. Recently, several other bisphenols (BPs) have been developed and used as BPA substitutes for producing plastics with similar properties. However, limited knowledge exists about the potential endocrine disrupting effects of these bisphenol analogs. In this study, 12 different bisphenols (BPA, BPB, BPC, BPE, BPF, BPG, BPS, BPZ, BPAF, BPFL, BADGE, and BPTMC) were tested for their endocrine-disrupting properties towards the estrogen- (ER) and androgen (AR) receptor of Atlantic cod (*Gadus morhua*). A luciferase reporter gene assay was developed to investigate the BPs ability to bind to the ligand binding domain and trans-activate the receptors *in vitro*. Our findings showed that eight of the compounds (BPB, BPC, BPE, BPF, BPS, BPZ, BPAF, BPTMC) produced agonistic effects similar to BPA on ER, while three BPs activated the AR. To complement the *in vitro* results, precision cut liver slices (PCLS) were exposed *ex vivo* to a selection of BPs to investigate the effects on the estrogen receptor target gene, vitellogenin (Vtg), and analysed with qPCR and ELISA. Seven of the eight BPs tested produced increasing Vtg levels with increasing concentration of BP. In summary, the results indicate that several of the substitute BPs have the ability to act as endocrine disruptors on ER and AR similar to, and possibly even stronger, than BPA.

Acknowledgement: The work is part of the dCod 1.0 project (decoding the systems toxicology of Atlantic cod (*Gadus morhua*)), funded by the Research Council of Norway (248840), linked to Center for Digital Life Norway.

TF-16

Accumulation of clothianidin, a neonicotinoid pesticide, in bumblebees (*Bombus terrestris*)

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Research question
Bumblebees are important and effective pollinators in temperate habitats, largely due to their isolated hairy bodies and endothermic abilities. The neonicotinoid insecticide clothianidin has negative, sub-lethal, impacts on bee pollinators as it, among other things, affects the brain's centre for memory and learning. This has led to a recent ban on three neonicotinoids, including clothianidin, in the EU and Norway. Neonicotinoids generally have low bioaccumulation factors, but show accumulation in some animals, for example, earthworm (*Eisenia andrei*) and partridges (*Alectoris rufa*). The aim of this study was to investigate clothianidin accumulation in bumblebees (*Bombus terrestris*) and accumulation in different parts of their body: head, the digestive channel, and rest of the body.

Method
Bumblebees were exposed to five different dosages of clothianidin through artificial nectar (sugar water), all in a range of field realistic concentrations (1µg/kg – 13.1µg/kg) in a chronic exposure regime lasting 9 days. Prior to the chemical analysis, each bumblebee was divided into three compartments: head, stomach/intestine/rectum, and rest of the body. Analysis will be performed at the Norwegian Institute of Water Research, on three dosages and an unexposed control.

Results
The last chemical analysis will be performed in January/February 2019. We expect to find an accumulation of clothianidin and/or its main metabolites in the head and the digestive channel.

Conclusion
This is an ongoing study. A conclusion will be reached after chemical and statistical analysis is completed.

TF-17

The Effects of Environmental Contaminants on Northern Crested Newt (*Triturus Cristatus)* and Smooth Newt (*Lissotriton Vulgaris)* Exposed to Road Water Runoff in Sedimentation Ponds.

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The road network in Norway is under constant development by construction and expansion of new roads and tunnels. The expansion of roads contributes to increased traffic volume which has several environmental impacts. Pollutants originating from traffic are released to the environment causing pollution of air, soil and water. Sedimentation ponds has been constructed approximate to heavy traffic roads to treat contaminated road runoff and tunnel wash water as a measure to reduce negative impacts on receiving waterbodies. The main treatment process in such systems are sedimentation of particle bound pollutants which will be retained in the sediment. Additionally, these sedimentation ponds are rapidly colonized by aquatic organisms including amphibians. Amphibians are especially vulnerable to pollutants due to their highly permeable skin and multiple life stages in both water and on land. Aquatic species inhabiting the sedimentation ponds are affected both by contaminated sediment and runoff water, especially during acute discharge of tunnel wash water. Hence, there may be an apparent conflict between the effective cleaning function of the ponds and the species inhabiting them.

The first aim of the study was to determine whether sedimentation ponds are inhabited by the red listed amphibian species Northern crested newt (*Triturus Cristatus*) and Smooth newt (*Lissotriton Vulgaris*). A survey of 27 sedimentation ponds along E6 and E18 in Akershus, Østfold and Vestfold county was conducted. The survey included presence of the species as well as measurement of several ecological and chemical variables such as water quality and oxygen level which are critical for the species survival. In addition, sediment samples were collected and measured for concentrations of polycyclic aromatic hydrocarbons (PAHs) and heavy metals to establish the degree of pollution in the sedimentation ponds. These measurements will help to determine which factors potentially influence the species presence in the sedimentation ponds. The survey showed that 13 out of 27 sedimentation ponds were inhabited by at least one of the two species, five of which also contained the red listed Northern crested newt.

The second aim of the study was to assess any ecotoxicological impacts related to road associated contaminants on the two amphibian species. Several biomarkers, based on gene expression, was included. In addition, PAH metabolites was measured, using high performance liquid chromatography, to assess a link between levels of PAHs in the sediment and biomarkers. Results obtained showed a gradient of PAH-metabolites, probably allowing to use these as a biomarker of exposure. To quantify the effect of exposure, qPCR was conducted using 10 biomarkers to measure relative gene expression of antioxidants and DNA repair genes. The results obtained from this study will clarify whether the amphibian species are affected by road-associated contaminants deriving from road runoff.

Frie foredrag farmakologi (FF)

FF1 Klinisk farmakologi

Betydningen av SLC6A4-genotype for terapisvikt av escitalopram

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Problemstilling

Serotonintransportøren (SERT) er kodet av SLC6A4-genet. De mest karakteriserte genetiske variasjonene i promotorregionen til SLC6A4 er 5-HTTLPR ('serotonin transporter gene-linked polymorphic region') og singel nukleotidpolymorfismen, rs25531 A>G, hvor samlet genotype av disse forklarer om man har lavt, intermediært eller høyt uttrykk av SERT. Enkelte studier tyder på at pasienter med redusert SERT-uttrykk er mer utsatt for bivirkninger og nedsatt effekt av selektive serotoninreopptakshemmere. Det finnes derimot en del motstridende funn. Dette kan skyldes at de fleste studier ikke har inkludert både mutasjonen „„„„5-HTTLPR og rs25531 A>G. Hensikten med denne studien er å undersøke forekomsten av SLC6A4-genotype, i en norsk naturalistisk studiepopulasjon og undersøke hvordan predikert SERT-fenotype er forbundet med terapisvikt av escitalopram.

Metode

Studien er basert på eksisterende data fra utførte analyser og reanalyserte biobankede prøver ved Senter for psykofarmakologi, Diakonhjemmet sykehus. Det ble hentet ut data fra pasienter som hadde utført serumkonsentrasjonsmålinger av escitalopram i perioden 01.2005-10.2018, samt historikk om andre antidepressiva som var blitt målt i samme periode. I tillegg ble det hentet ut samlet genotype av 5-HTTLPR, CYP2C19 og CYP2D6 (tilgjengelig fra 01.2011). Det primære endepunktet på terapisvikt var om escitaloprambrukere (dose- og/eller serumpositive pasienter) hadde byttet til et annet antidepressiva innen 1 år etter siste escitaloprammåling (testgruppen). Pasienter som haddet byttet, samt en randomisert, stratifisert kontrollgruppe (n=98 pasienter) som ikke hadde byttet, ble deretter sammenliknet. Byttegrad og type antidepressiva det ble byttet til blant pasienter med lavuttrykks SERT-fenotype, ble sammenliknet med intermediær og høyuttrykksfenotype.

Resultat

Totalt 2484 unike escitaloprambrukere med samlet genotype av 5-HTTLPR, CYP2C19 og CYP2D6 ble ekstrahert fra databasen. Av disse opplevde 293 av pasientene (11,8%) terapisvikt (testgruppen), og majoriteten av disse byttet til bupropion (35,5%), venlafaksin (19,5%) og fluoksetin (13,3%). Frekvensen av lavuttrykks, intermediær og høytuttrykks SERT-fenotype var henholdvis 25,8%, 47,7% og 26,5% i testgruppen mot henholdvis 21,4%, 48,0% og 30,6% i kontrollgruppen. Selv om det var 4,4% høyere lavuttrykks SERT-fenotype i testgruppen enn i kontrollgruppen var ikke forskjellen signifikant (p=0,39). Alder og kjønn var heller ikke assosiert med bytte. CYP2C19-genotype var derimot assosiert med bytte ($p<0,05$).

Konklusjon

Foreløpige resultater indikerer at det ikke er en sammenheng mellom lavuttrykks, intermediær og høyuttrykksfenotype av SERT og terapisvikt av escitalopram, målt som bytte til et annet antidepressiva innen 1 år. Dette kan tyde på at det kan være andre faktorer som som påvirker terapiresponsen hos disse pasientene, som f.eks. farmakokinetiske faktorer, depresjonstype og/eller -alvorlighet.

FF2 Klinisk Farmakologi

Efficacy and Safety of Empagliflozin in Renal Transplant Recipients with Post-Transplant Diabetes Mellitus

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Objective

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have lately become recommended treatment in patients with type 2 diabetes and high cardiovascular risk. Patients with post-transplant diabetes mellitus (PTDM) also have high cardiovascular risk. The aim of this study was to investigate safety and efficacy of empagliflozin in renal transplant recipients (RTRs) with PTDM.

Research design and methods

From November 2016 to January 2018, 49 RTRs were included in an investigator-initiated, single-center, prospective, double blind study, and randomized to receive either 10 mg empagliflozin or placebo once daily for 24 weeks. RTRs transplanted >1 year ago, diagnosed with PTDM, with stable renal function (estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2) and with stable immunosuppressive therapy were eligible for inclusion.

Results

In total 44 RTRs (22 empagliflozin/22 placebo, 34 males) completed the study. Median (IQR) change in HbA1c and fasting plasma glucose were significantly reduced after 24 weeks of empagliflozin treatment compared to placebo; -0.2% (-0.6, -0.1) (-2.0 mmol/mol (-6.5, -1.0)) vs 0.1% (-0.1, 0.4) (1.0 mmol/mol (-0.75, 3.8)) (P=0.002) and -0.7 mmol/L (-1.2, -0.13) vs 0.3 mmol/L (-0.45, 0.55) (P=0.02) respectively. The treatment also resulted in a significant median (IQR) reduction in body weight of -2.5 (-4.0, -0.05) kg compared to an increase of 1.0 (0.0, 2.0) kg in the placebo group (P=0.001). There were no significant differences between the groups in adverse events, trough levels of immunosuppressive drugs or eGFR after 24 weeks of treatment.

Conclusions

Empagliflozin treatment appeared safe and improved glycemic control in RTRs with PTDM compared to placebo. A concomitant reduction in body weight was seen.

FF3 Klinisk farmakologi

Farmakodynamikk og arteriovenøs forskjell av intravenøs nalokson i friske frivillige som får remifentanil TCI

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Innledning

I Norge dør ca 250 personer årlig av opioidoverdose. Så langt har ikke-godkjente nesesprayer med motgiften nalokson vært et lavterskel tiltak for å få ned dødeligheten. Nå er to sprayer med markedsføringstillatelse i Europa, én fra dne-pharma, Oslo, i samarbeid med NTNU og én fra Mundipharma. Godkjenningene er basert på måling av blodkonsentrasjoner i friske frivillige. Vi har utviklet en steady state modell for å studere sammenhengen mellom nalokson-konsentrasjon og nalokson-virkning i friske frivillige. Opioid-agonisten remifentanil gis med target controlled infusion (TCI) slik at steady state oppnås etter 12 min når nalokson blir gitt. Opioideffekt måles med pupillometri. Vi undersøkte også blodkonsentrasjoner av nalokson og remifentanil i både arterielt og venøst blod.

Metode

Studien er godkjent av REK og Legemiddelverket. 12 friske frivillige fikk remifentanil med Minto TCI model til plasma target konsentrasjon på 1,3 ng/ml) i 102 min. Infusjonen ble gitt med Alaris PK Guardrail syringe pumps (CareFusion Cooperation, UK). 1 mg nalokson intravenøst (iv) ble gitt etter 12 min TCI. Opioideffekt ble målt med pupillometri (Neuroptics VIP 200 Pupillometer). Blodkonsentrasjoner av nalokson og remifentanil ble kvantifisert med validerte høytrykksvæske-massespektrometri-metoder.

Resultater

Blodprøver av remifentanil bekreftet TCI prediksjonene, dog var de reelle blodkonsentrasjonene litt lavere enn innstilt på pumpen. 1 mg iv nalokson opphevet effekten av remifentanil i løpet av 4 min. Estimert varighet av naloksoneffekten var 118 min. Da var nalokson-konsentrasjonen 0,5 ng/ml, dvs at vi har etablert naloksons laveste effektive konsentrasjon i friske frivillige. Siden nye preparat godkjennes på blodkonsentrasjoner er dette viktig. Det var ingen arteriovenøs forskjell i blodkonsentrasjoner for nalokson, i motsetning til for remifentanil.

Konklusjon

Vår modell kan bli et nyttig verktøy for sammenligning av virkningsprofiler for nye nalokson-preparater.

FF4 Klinisk farmakologi

Kombinert betydning av CYP2C19- og CYP2D6-genotype for individuell variasjon i serumkonsentrasjon av escitalopram – en retrospektiv observasjonsstudie basert på data fra over 3000 pasienter

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Problemstilling
Escitalopram metaboliseres hovedsakelig via enzymet CYP2C19, men også sekundært via CYP2D6. Nylig ble det vist at CYP2C19-genotype predikerer variasjon i serumkonsentrasjon og risiko for terapisvikt av escitalopram. Hensikten med denne studien er å undersøke hvilken betydning CYP2D6-kombinert med CYP2C19-genotype har for individuell variasjon i serumkonsentrasjonen av escitalopram i en populasjon på over 3000 pasienter.

Metode
Studien benyttet retrospektive serumkonsentrasjonsdata av escitalopram fra pasienter med kjent CYP2D6/2C19-genotype basert rutineanalyser utført ved Senter for Psykofarmakologi, Diakonhjemmet sykehus. Data ble hentet ut fra laboratoriedatabasen (Swisslab Roche II) i perioden 2005-2018. For å tillate inklusjon av flere serumkonsentrasjonsmålinger per pasient ble linear mixed model-analyser benyttet (IBM SPSS Statistics 25.0). I de statistiske analysene ble betydningen av CYP2D6-genotype estimert ved å sammenligne estimert dosejustert serumkonsentrasjon (CD-ratio) av escitalopram hos pasienter med ulik CYP2C19-genotype. Det ble justert for forskjeller i kjønn, alder og tid etter siste doseinntak.

Resultater
Det ble inkludert 3099 genotypede pasienter med minst en serumkonsentrasjonsanalyse av escitalopram (totalt 6007 analyser). Innad i alle CYP2C19-genotyper var det signifikant økt escitalopram CD-ratio blant intermediære (IM) (9-18%, $p<0,027$) og langsomme CYP2D6 omsettere (PM) (20-34%, $p<0,001$) sammenlignet med normale omsettere (NM) av CYP2D6. Hos pasienter som var både 2C19 og 2D6 PM var estimert CD-ratio 3,3 ganger høyere enn for pasienter som var NM via begge enzymene.

Konklusjon
CYP2D6-genotype er av signifikant betydning for individuell variasjon i serumkonsentrasjon av escitalopram uavhengig av CYP2C19-genotype, men den kliniske relevansen er størst blant pasienter som er CYP2C19 PM. Studien viser derfor at man ved å kombinere CYP2C19- og CYP2D6-genotype kan predikere en fornuftig startdosering av escitalopram til den enkelte pasient.

FF5 Basal farmakologi

CNP increases titin phosphorylation and decreases passive tension in cardiomyocytes

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Background and aims:

Diastolic heart failure, often referred to as heart failure with preserved ejection fraction (HFpEF), accounts for about 50% of heart failure cases. Currently there exist few treatment options for this condition. Typically, HFpEF patients have a stiff heart with reduced diastolic filling. In cardiomyocytes, titin is the most important protein involved in regulating passive tension and it is important for structural integrity of the myofibrils. In cardiomyocytes, titin is the most important protein involved in regulating passive tension and it is important for the structural integrity of the myofibrils. In cardiomyocytes, cGMP activates protein kinase G (PKG) that phosphorylates titin and decrease passive tension. The receptor responsible for this cGMP remains unknown. In this study the aim was to determine which cGMP-dependent signaling pathways, activating PKG, induce titin phosphorylation and reduce passive tension development.

Methods

Cardiomyocytes were isolated from male Wistar rat hearts. Cyclic GMP production was induced by activating the natriuretic peptide receptor (NPR)-A, NPR-B and soluble guanylyl cyclase (sGC). Intracellular cGMP levels, titin phosphorylation and passive tension of single cardiomyocytes were measured in ventricular cardiomyocytes. Mapping specific phosphorylation sites on titin after stimulation was done using LC-MS/MS.

Results

Stimulation of NPR-B by CNP increased titin phosphorylation and reduced passive tension, whereas stimulation of NPR-A and sGC did not significantly modify phosphorylation or passive tension. Titin phosphomapping revealed several novel phosphosites in the A- and M-band after stimulation with CNP.

Conclusion

NPR-B stimulation enhanced titin phosphorylation and reduced passive tension, whereas NPR-A and sGC activation did not. Thus, the intracellular effects measured trough NPR-B stimulation could therefore potentially lead to reduced ventricular wall stiffness and improve LV filling which would be beneficial in HFpEF patients.

FF6 Klinisk farmakologi

Dose intensity of antidepressants in older persons 2007-2017 – a study based on therapeutic drug monitoring data

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Background:
Older patients are at increased risk of side-effects from psychotropic drugs, both due to higher serum concentrations and increased vulnerability. We have previously shown that individuals > 65 years obtain a 1.5- 2 fold higher serum concentration of most antidepressant when given equal doses as younger patients (Waade, 2012). Also, dose reductions in older patients were not sufficient to compensate for the increased exposure and twice as many older patients had serum concentrations above the upper level of the reference range compared with younger individuals (Waade, 2012, Hermann, 2015). The aim of the present study was to investigate if the dose intensity of antidepressants in older persons has been reduced over the last 10 years by using data from a therapeutic drug monitoring (TDM) database. The benefit by using TDM data and not registry data is that the latter only gives information about the drug dispensed at the pharmacy and no information about compliance or exposure.

Method:
Drug doses and serum concentrations from all patients treated with at least one antidepressant (escitalopram, citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, mirtazapine, venlafaxine or duloxetine) in 2007 and 2017 were withdrawn from a routine TDM database. In total, 14350 samples (3255 samples from individuals ≥65 years) were included in the study (time of sampling ≥10 and ≤ 30 hours after drug intake, information about drug dosage, serum concentrations at or above the lower limit of quantification). Antidepressant doses and fraction of samples above reference range for individuals ≥65 years for 2017 were compared with 2007. Antidepressants with n<50 in one of the age groups for 2007 and/or 2017 were not included in the analysis (paroxetine, fluoxetine, fluvoxamine and duloxetine).

Results:
For most antidepressants there was a tendency towards lower average doses for individuals ≥65 years in 2017 compared with 2007. The fraction of samples above the upper limit of reference range was increased in older individuals from 2007 to 2017 for three of the antidepressants, escitalopram (14.3% vs 21.3%), sertraline (3.2% vs 6.5%) and venlafaxine (3.4% vs 16.9%).

Conclusion:
The study shows that treatment intensity of antidepressants in older individuals has not decreased from 2007 to 2017.

References:
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FF7 Klinisk farmakologi

Tacrolimus concentrations measured in capillary micro samples

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Background

Routine therapeutic drug monitoring (TDM) of tacrolimus (Tac) is currently performed in venous bloods samples drawn at the hospital. The novel volumetric absorptive microsampling (VAMS™) devices allow the patients themselves to collect a finger prick capillary blood sample suitable for tacrolimus monitoring. In the present study we have validated a commercial product (Mitra tip®, Neoteryx, USA) compared to simultaneously drawn venous samples in stable kidney transplant recipients.

Methods

Two 12-hour Tac pharmacokinetic investigations (13 samples each), separated by at least one week, were performed in 27 renal transplant recipients with target Tac trough 4-7 µg/L. Patients were included 3 ± 1 weeks after transplantation and received mycophenolate mofetil and prednisolone in addition to twice daily tacrolimus as maintenance immunosuppressive therapy. At each sampling point 2 venous and 2 capillary samples (10 µL) were obtained; one pair (venous/capillary) went directly to the lab while the second pair was sent via ordinary mail service. Tacrolimus was analyzed using the standard mass spectrometry assay at the hospital and the microsampling method was validated according to the guideline on bioanalytical method validation of the European Medicines Agency (EMA).

Results

A total of 682 pairs of venous and microsampled specimens from patients were assayed for Tac concentrations. Mean Tac dose and trough concentration were 3.5 ± 1.5 mg and 6.6 ± 1.5 µg/L, respectively. The micro sample concentrations were on the average 4.2% (95% CI: -5.1% to -3.4%) lower than the venous samples. All results of the method validation were within the criteria of the EMA guideline. Range of Tac concentrations tested was from 0.7 to 57 µg/L, the accuracy ranged from 88% to 98% and imprecision was below 5% (except for the 0.7 µg/L where CV was 11%). The Mitra tip® micro samples were stable for at least 30 days in room temperature and was not influenced by postal service shipment.

Conclusion

Measurement of whole blood tacrolimus concentrations in 10 µL capillary blood from renal transplant recipients can be reliably and safely performed using the VAMS™ technique. Following a minimum of training, this also provides an option for self-collection by patients.

FF8 Klinisk farmakologi

Pharmacokinetics of a novel, approved, 1.4 mg intranasal naloxone formulation for reversal of opioid overdose- a randomised controlled trial.

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Introduction

Intranasal (IN) naloxone is an established treatment of opioid overdose. Anyone likely to witness an overdose should have access to the antidote. This study presents data on a new formulation of naloxone for this use, recently approved in 12 European countries.

Methods

Open, randomised four-way crossover trial in human volunteers (n=22). One and two doses of IN 1.4 mg naloxone compared to intramuscular (IM) 0.8 mg and intravenous (IV) 0.4 mg naloxone. Quantification of plasma naloxone was performed by liquid chromatography tandem mass spectrometry. Pharmacokinetic non-compartment analyses were used for the main analyses. A non-parametric pharmacokinetic population model was developed for Monte Carlo simulations of different dosing scenarios.

Results

$AUC_{0\text{-}last}$ for IN 1.4 mg and IM 0.8 mg were 2.62 ±0.94 and 3.09 ±0.64 h*ng/mL, respectively (p=0.33). C_{max} was 2.36 ±0.68 ng/mL for IN 1.4 mg, and 3.73 ±3.34 for IM 0.8 mg (p=0.72). Two IN doses showed dose linearity, and achieved a C_{max} of 4.18 ±1.53 ng/mL. T_{max} was reached after 20.2 ±9.4 min for IN 1.4 mg and 13.6 ±15.4 min for IM (p=0.098). The absolute bioavailability for IN 1.4 mg was 0.49 (±0.24), while the relative IN/IM bioavailability was 0.52 (±0.25).

Conclusion

IN 1.4 mg naloxone provides adequate systemic concentrations compared to IM 0.8 mg, without statistical different maximum plasma concentration, time to maximum plasma concentration or area under the curve. Simulations support that it has a place both as peer administered antidote and for titration of treatment by professionals.

FF9 Klinisk farmakologi

Effect of *CYP2C19* genotype on serum concentration of sertraline

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Objectives
Sertraline is a selective serotonin reuptake inhibitor (SSRI) metabolized mainly in the liver by the polymorphic enzyme CYP2C19. The aim of this study was to investigate the effect of *CYP2C19* genotype on serum concentrations of sertraline in a large population of psychiatric patients.

Methods
Patients who had performed both serum concentration measurements of sertraline and *CYP2C19* genotyping were retrospectively retrieved from a therapeutic drug monitoring (TDM) database at Center for Psychopharmacology, Diakonhjemmet Hospital. Inclusion criteria were information about the prescribed sertraline dose on the requisition forms and blood sampling for sertraline TDM 10-30 hours after the last dose intake. Patients treated with sertraline were divided into four subgroups based on their *CYP2C19* genotype; i) PM, homozygous carriers of *CYP2C19 null* alleles, i.e. **2*, **3* or **4*, ii) intermediate metabolizers (IM), heterozygous carriers of *null* alleles, iii) extensive metabolizers (EM), absence of variant alleles (**1/*1*) and iv) ultra rapid metabolizers (UM), carriers of *the *17* allele. To allow the inclusion of multiple TDM measurements of sertraline per patient over time, dose-adjusted serum concentrations (C/D ratios) were compared between the subgroups by linear mixed model analysis using EM as reference. Age and gender were included as possible covariates in the multivariate statistical analysis.

Results
Overall, a total of 1208 patients representing 2248 TDM measurements, were included in the study. Mean C/D ratios of sertraline in PM, IM, EM and UM were 1.95 nM/mg, 1.09 nM/mg, 0.82 nM/mg, 0.74 nM/mg, respectively. Compared to EMs, the mean C/D ratio of sertraline was increased 137% in the PM subgroup and 33% in the IM subgroup ($p<0,001$). Among *CYP2C19* UMs, the mean C/D ratio of sertraline was decreased with 10% compared with the EM subgroup ($p<0,05$). A 14% higher C/D ratio of sertraline was also detected for women compared with men ($p<0.001$), while patients ≥65 years had a 10% higher C/D ratio of sertraline than younger patients ($p<0.05$).

Conclusion
This study shows that *CYP2C19* genotype is of significant importance for the individual variability in dose-adjusted serum concentration of sertraline. Thus, dose requirements in *CYP2C19* PM, IM and UM are different compared to EM, which should be considered as an important factor for the clinical response of sertraline treatment

FF10 Basic Pharmacology

Role of early changes in cardiac performances caused by calcineurin inhibitors in organs toxicities.

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Problem

The calcineurin inhibitors (CNI) cyclosporine and tacrolimus are the basis of most immunosuppressive protocols for the prevention of graft rejection following organ transplantation and in various autoimmune diseases. But CNI therapies are also known to ultimately damage the organs they are intended to protect or prevent from rejection as well as other organs, making their use mostly tolerated due to their impressive ability to improve short-term outcomes. In fact, the identification of calcineurin inhibitor-related toxicity as one of the main reasons for the long-term failures has been established. Therefore, because the early detection of drugs adverse effects is important to prevent progression to end-stage failure, this study aimed to evaluate a possible causal relationship between early cardiac dysfunction during the initial phase of CNI therapy and organs toxicities.

Methods

The cardiac performance was measured using a pressure-volume-conductance approach. Responses were evaluated in mice 5h after intra-peritoneal injection of CNI in WT, PI3Kgamma KD ("kinase dead"; lacking PI3Kgamma kinase function) and in WT treated with selective inhibitor of PI3Kgamma. Thereafter, several organs including heart, kidney, liver, lung, spleen and pancreas were collected after similar treatment as mentioned above for histological analysis. Finally, underlying mechanisms associated with observed effects were studied in primary cells and plasma using several biochemical approaches.

Results

Cardiac output (CO) was significantly reduced (~30%) in mice 5h after CNI injection indicating an early effect of CNI on cardiac performance. This reduction of cardiac performance was at least partly explained by the reduction of cardiac contractility (ESPVR), but also by the reduction of the end diastolic volume (EDV) that was potentially due to the intravascular volume depletion given the positive response to the volume expansion test. The histological analysis of organs from mice treated similarly with CNI revealed a significant higher level of cell death/stress and infiltration of neutrophils likely mediated (at least in part) by the reduced CO. Interestingly, the CO after the same treatment in transgenic mice with inhibited enzymatic function of PI3Kgamma (PI3Kgamma “kinase dead”), and in mice treated simultaneously with PI3Kgamma selective inhibitor was normal and the tissue damages was concomitantly (cell death and neutrophils infiltration) limited in those mice.

Conclusion

Our study suggests the early CO assessment as a potential tool (marker) to determine the risk of CNI-related organs toxicities and proposes a potential strategy to reduce the progression of long-term site effects of CNI.

FF11 Klinisk farmakologi

Antiepileptikabruk assosiert med økt risiko for terapisvikt av klozapin

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Problemstilling

Klozapin er det mest effektive legemiddelet i behandling av schizofreni. På grunn av risiko for alvorlige bivirkninger, som epilepsilignende anfall og agranulocytose, er bruken av klozapin begrenset til pasienter med behandlingsresistent schizofreni. Antiepileptika brukes ofte i kombinasjon med klozapin, men potensielle interaksjoner kan medføre terapiproblemer. Hensikten med denne retrospektive, longitudinelle studien er å undersøke i hvilken grad kombinert bruk av antiepileptika øker risiko for terapisvikt av klozapin.

Metode

I studien ble det hentet ut dose- og serumkonsentrasjonsdata fra pasienter med TDM-målinger av ulike antipsykotika og antiepileptika i perioden 2005-2017 fra databasen ved Senter for Psykofarmakologi, Diakonhjemmet sykehus. En antipsykotika- og antiepileptikabruker ble definert som en pasient med positiv serumkonsentrasjon og/eller oppgitt dose av det aktuelle antipsykotikumet/antiepileptikumet. Avbrutt klozapinbehandling ble brukt som primært endepunkt på terapisvikt. Dette ble analysert i relasjon til kombinasjonsbehandling med antiepileptika. Oppstart av minst ett annet antipsykotikum innen ett år etter siste TDM-analyse av klozapin ble definert som terapisvikt (testgruppe), og ble sammenlignet med pasienter som ikke hadde avbrutt klozapinbehandlingen i studieperioden (kontrollgruppe).

Resultater

Det ble identifisert 2499 klozapinbrukere (43925 klozapinmålinger), hvorav 983 var kvinner (39,3 %). Gjennomsnittsalder i populasjonen var 46,2 år (14,5 SD). Det ble registrert 851 personer med samtidig bruk av antiepileptika (34,1 %). Det ble i studieperioden identifisert 166 personer (6,60 %) som hadde avbrutt klozapinbehandlingen og startet opp med ett eller flere antipsykotika innen ett år etter siste klozapinanalyse. Det var signifikant flere antiepileptikabrukere (46,4 %) og valproatbrukere (21,7 %) i testgruppen enn i kontrollgruppen (33,2 % antiepileptikabrukere, p=0,001; 13,3 % valproatbrukere, p=0,002). Det var ingen signifikant forskjell i lamotriginbrukere mellom test- (15,7 %) og kontrollgruppen (12,1 %, p=0,176).

Konklusjon

Studien viser at kombinert bruk av antiepileptika, og da i særlig grad valproat, er assosiert med økt risiko for terapisvikt av klozapin. Dette kan skyldes uheldige interaksjoner mellom klozapin og antiepileptika, hvor valproat er spesiell med en selektiv påvirkning på den aktive klozapin-metabolitten (N-demetylklozapin).

FF12 Klinisk farmakologi

Contactless quantification of tacrolimus-specific tremor

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Background

Tremor is a common side effect of tacrolimus therapy that may significantly influence transplanted patients' daily life. The aim of the present study was to develop a method for contactless quantification of tacrolimus-specific tremor in renal transplant recipients

Method

Using a Leap Motion Controller®, the three-dimensional position of each joint in the hands can be obtained every 20 milliseconds with a precision of <1 millimeter. The patient is asked to perform a series of exercises with the hand approximately 20 centimeter above the device. Exercises include holding the hand still with the arm outstretched, with and without a 225 g weight on the wrist, pointing at a target with the index finger, and moving the hand in a circular motion. The function of the exercises is to estimate the contribution of postural and intentional tremor, respectively.

The signals are de-trended and subjected to a Welch's power spectral density estimate analysis to provide the X-Y-Z motion of respective joints in the hand at different frequencies. This enables evaluation of individual frequencies' contribution to the tremor, where the dominant tacrolimus-induced tremor is suspected to be in the range of 10-12 Hz in literature. This is considerably higher than e.g. Parkinson's tremor, for which the dominant frequency is in the range of 4-6 Hz.

Tremor was investigated before tacrolimus treatment, i.e. the day before transplantation, and at different days over the first weeks after transplantation in several patients. Pre-transplantation observations formed the baseline readings for the individual patient, enabling assessment of change in tremor after initiation of tacrolimus treatment. In addition, tremor was also investigated at different time points following the ingestion of the morning tacrolimus dose of twice daily dosed tacrolimus (Prograf®) in 20 patients. Patients were observed for 5-8 hours after dose intake.

Results

Preliminary results from the method development indicate a tacrolimus-specific tremor in the area 9-12 Hz. This is observed through an increase in the power density spectra in this area after starting on tacrolimus. A concomitant change is not seen for the lower band of 4-6 Hz. Correlation to tacrolimus whole blood concentrations within a dose interval will be presented during the conference.

Conclusion

Tacrolimus-induced tremor is shown to have a higher frequency than parkinsonian and essential tremor, as indicated by literature. Moreover, its unique high frequency allows for fast and easy detection of tremor-type. It remains to show the degree of correlation to the concentration of tacrolimus in blood.

Postere

Toksikologi
Postere henges opp på anvist plass i **Besseggen 1.** Postervisningen ledes av: Hubert Dirven (FHI).

Farmakologi
Postere henges opp på anvist plass **i «glasshallen» utenfor Besseggen.** Postervisningen ledes av: Lise Roman Moltzau (UiO)

Hver poster får plass tilsvarende en plakat på rundt 80 x 120 cm (bredde x høyde). Alle postere må henges opp med tape. Tape vil bli lagt ut ved de merkede plassene.

Presentasjon
Posternepresentasjonene skjer som en 3-minutters PowerPoint-presentasjon med 3-4 lysbilder, hvorav ett tittellysbilde. Unngå bruk av animasjoner.
Pek på hovedpoengene og få frem:

- Problemstilling
- Hvordan studien er utført
- Hovedfunn
- Konklusjon

Ta opp hovedtrekkene og unngå detaljer. Dette er ikke et vanlig foredrag og målet er at tilskuerne skal få lyst til å studere posteren nærmere etterpå. Postersesjonen avsluttes med en fri posterdiskusjon. Her går man tilbake til de enkelte posterne og utfolder seg sammen med spesielt interesserte.

For postere inne toksikologi er det ingen PowerPoint-presentasjon, bare diskusjon ved posterne

NSFTs posterpris 2019
En posterpriskomité vil vurdere alle bidrag og finne en vinner innen henholdsvis toksikologi og farmakologi. Hver vinner får tildelt diplom og en vandreplakett under festmiddagen lørdag 26. januar. Komiteen for bedømming av postere i toksikologi består av Merete Grung og Erik Ropstad. Komiteen for bedømming av postere i farmakologi består av Anders Åsberg, Espen Molden og Lise Roman Moltzau.

Posterprisvinnere fra 2018: Alexandra I.S. Treimo, NIOM (Toksikologi) og Marie-Victoire Louise Augusta Cosson, UiO (Farmakologi)

Postere i toksikologi (TP)

TP-1

In vitro assessment of estrogenic effects of bisphenols on Atlantic cod (Gadus morhua)

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Background: The estrogen receptor (ER) is a steroid hormone receptor involved in growth, development, reproduction and homeostasis. ER belongs to the nuclear receptor super family which are ligand activated-transcription factors that can be activated by both endogenous- and exogenous compounds, such as industrial chemicals. Bisphenol A (BPA) is a chemical produced in large quantities, and it is used in the manufacture of polycarbonate plastics and epoxy resins. Polycarbonate plastics are commonly used as food and drink packaging, and non-food applications such as toys and pacifiers. Since BPA has been reported to act as a teratogen and an endocrine disruptor in vertebrate animals, public concern has been raised about the safety of BPA in consumer products. As a result, many manufacturers have removed BPA from their products. However, many of these "BPA-free" products are manufactured with bisphenols substitutes including bisphenol S (BPS) and bisphenol F (BPF). In this study, BPA and 11 BPA analogues were tested for their ability to activate the ERα in Atlantic cod (*Gadus morhua).* Atlantic cod is an important teleost in North-Atlantic fisheries, and have in recent years emerged as a model species in environmental toxicology studies. The BPA analogue that have been assessed were BPB, BPC, BPF, BPAF, BPFL, PBS, BADGE, BPE, BPG, BPZ and BPTMC.
Methods: A luciferase reporter gene assay (LRA) with the Atlantic cod ERα ligand-binding domain (LBD) has recently been established in our research group. In short, Cos-7 cells were co-transfected with an effector plasmid containing the LBD ERα fused to the Gal4-DNA binding domain (DBD), and a luciferase reporter gene plasmid. Ligand activation of ERα was measured as luciferase activity in bisphenol-exposed cells, which was quantified by the amount of light emitted from the oxidation of luceferint to oxyluceferin. Cytotoxicity was followed with Alamar blue and CFDA-AM. Activation of ER was also assessed *ex vivo* with precision cut liver slices (PCLS). Activation of ER was determined by measuring induction of vitellogenin and ERα transcripts using quantitative real-time PCR and by measuring vitellogenin in the culture medium using ELISA. Ethynylestradiol (EE2) was used as a positive control for ERα activation in both *in vitro* and *ex vivo* assays.
Results: Among the 12 bisphenols tested in LRA, eight bisphenols were able to activate the Atlantic cod ERα (BPA, BPE, BPB, BPF, BPS, BPZ, BPAF and BPTMC). Highest activation of Atlantic cod ERα was found in Cos-7 cells exposed to BPA, PBE, BPF, BPB and BPAF. Generally similar activation patterns were observed in cell culture LRA and ex vivo PCLS assays.
Conclusion: BPA and many of the BPA analogues tested were able to activate cod ERα. This indicates that these compounds may act as xenoestrogens in Atlantic cod and warrants further studies with *in vivo* experiments.

Acknowledgement: The work is part of the iCod 2.0 and dCod 1.0 project (decoding the systems toxicology of Atlantic cod (*Gadus morhua*)), funded by the Research Council of Norway (248840), and is part of the Center for Digital Life Norway.

TP-2

Biological effects in Atlantic cod (*Gadus morhua*) and haddock (*Melanogrammus aeglefinus*) exposed to crude oil with and without UV radiation.

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The main goal of this study is to understand the underlying biological mechanisms of crude oil toxicity on embryo development of cod and haddock. These data will aid the development of new and better methods for risk modeling in relation to future offshore oil spills. As phototoxicity can increase the sensitivity of pelagic fish eggs to oil contamination, this study assessed different biological effects, such as chorionic alterations and profiles of vitamin A and E, in embryo and larvae of cod and haddock exposed to crude oil and UV radiation (UV-A and UV-B) during early developmental stages. Vitamins A and E are critical to normal fish embryo development. Disruption of vitamin A signaling due to environmental exposure to pollutants, including oil compounds, can be one of the underlying mechanisms behind abnormal embryo development. Therefore, in this study, different forms of vitamin A (retinol, retinal, retinyl esters and retinoic acid) and vitamin E (tocopherol) in eggs and larvae of cod and haddock from different exposure groups were identified and quantified. Haddock embryos are particularly sensitive to dispersed crude oil due to direct interaction with crude oil droplets, which adhere to the chorion. Therefore, different chorionic properties between cod and haddock eggs were investigated.

The eggs were exposed (with and without UV) to low levels of oil for 3 days during the early embryonic stages and then transferred to clean water prior to hatching. Vitamin analyses were conducted on embryos exposed for 72h, and 3 dph larvae using high-performance liquid chromatography with photo-diode array detector (HPLC/UV). Scanning electron microscopy (SEM) was used to assess chorionic alterations.

The levels and the interrelationship patterns between the identified vitamins, in both embryo and larvae, and the degree of chorionic damages in eggs, differed between the exposure groups. The present study shows that the combination of environmentally relevant levels of crude oil exposure and UV radiation can disturb vitamin A and E balance in developing embryo, and cause phototoxic effects, especially on chorion, which may be detrimental for early life stages of cod and haddock.

The present study is a collaboration between «dCod 1.0: Decoding the systems toxicology of Atlantic cod» (NFR project 248840) and «Eggtox: Unraveling the mechanistic effects of crude oil toxicity during early life stages of cold-water marine teleosts» (NFR project 267820).

TP-3

Mercury, cadmium and lead in trout (*Salmo trutta*) from Norwegian lakes.

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Introduction
Heavy metal toxicity may be threat to both human health and to wildlife. Humans and wild animals are exposed through food to metals that are unnecessary for body functions, such as cadmium, mercury and lead. In the present study, these metals were analysed in freshwater trout (*Salmot trutta*) liver for the Norwegian Environment Agency.

Methods
Livers from three to five individual fish were pooled into three to five samples from each lake (the number were reduced if sufficient number were not available). In total 34 lakes were sampled. The samples were decomposed using HNO_3, and analysed on an Agilent 8800 QQQ ICP-MS against standards for each element, and including international reference material. The analyses were performed at the Laboratory for Soil and Water analysis, Faculty of Environmental Sciences and Natural Resource Management (MINA), NMBU.

Results
Large differences were measured between lakes. The ratio between the levels in the lake with highest/lowest levels were 23, 160 and 2 800 for mercury, lead and cadmium respectively. The lakes with highest levels of contaminants were mostly in the southern part of Norway, but not all lakes from the southern parts of the country had fish with high levels of metals. For mercury, increasing concentrations was seen with increasing weight when data from all lakes were included. This was not seen for cadmium or lead. Further, in each lake, the ratio between the metal concentrations in samples from the fish with highest and lowest weight, exceeded 1 in 21 of 28 lakes for mercury, 15 of 27 for cadmium and 14 of 28 for lead, suggesting that only for mercury increasing concentrations is found with increasing weight within lakes. The three metals were not correlated to each other, suggesting that different sources contributes to the metals. Fish from some of the lakes have remarkably high concentrations of one or more metals compared to other lakes. It is however, not easy to identify any obvious source, and the lakes are not close to dense populated areas.

Conclusion
The high concentrations found in some lakes are not easy to explain. To increase the understanding of metal accumulation in these lakes, similar studies should be performed in other lakes in the same areas to reveal possible local sources from industries or waste deposits.

TP-4

Toxicity of PMMA nanoplastics in the marine microalgae *Rhodomonas salina*

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Scope

Plastics entering the aquatic environment can degrade into different sized particles due to mechanical, chemical and biological processes. Plastic particles <1 mm are denominated microplastics, while those <100 nm are designated as nanoplastics (NPLs). NPLs possess specific properties due to their small size, which can increase their potential toxicity towards aquatic organisms. Still, their presence and behaviour in the aquatic environment, as well as toxic mechanisms are still largely unknown. Accordingly, this study aims to evaluate the effects caused by plain and carboxylated PMMA (PMMA and PMMA-COOH, 50 nm) in the marine microalgae *Rhodomonas salina*.

Methods

After 72 hours exposure to both PMMA particles, algal cells were analysed for growth rate, natural pigments content, cell size, cell complexity, cell viability, cell cycle, reactive oxygen species (ROS) formation, mitochondrial membrane potential, lipid peroxidation (LPO) and DNA content using flow cytometry. Additionally, photosystem II (PSII) performance was analysed by PAM fluorometry, to provide further information on the absorption, distribution and use of energy in photosynthesis. PMMA behaviour in exposure media was also evaluated using dynamic light scattering (DLS) and nanoparticle tracking analysis (NTA).

Results

Results obtained showed a different behaviour of PMMA NPLs in exposure media over time, with PMMA forming micro-scale aggregates (2266 ± 260 nm) while PMMA-COOH maintained its nominal size range (57.1 ± 0.4 nm). Several differences were detected in *R. salina* exposed to both PMMA NPLs in terms of toxic effects. Plain PMMA caused a significant effect in cell viability, ROS formation, LPO, pigment content and photosynthetic performance, probably associated with particle interaction with algal cells. On the other hand, a higher impact of PMMA-COOH was observed in terms of algal growth, photosynthetic performance, cell viability and metabolic activity, with minor effects seen in terms of ROS formation and pigment content.

Conclusion

Overall, surface chemistry and size seem to be key parameters for the impact of PMMA NPLs in microalgae. Future experiments focusing on the in-depth characterization of the mode of action of these particles are underway.

TP-5

Adverse effects related to plastic additives exposure in Atlantic cod (*Gadus morhua*)

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Aims
A vast amount of the plastic we use end up in the ocean and estimates suggest a doubling of plastic in the ocean, to 250 million tonnes by 2025 (Jambeck et al. 2015). Plastic contain additives such as phthalates, and these are known to have adverse health effects on living organisms. The additives may leach from products into the environment. Fish liver is a target organ for contaminants, due to its crucial role in biological functions such as metabolic homeostasis and detoxification processes. Precision cut liver slices (PCLS) is a promising ex vivo system that is utilized within toxicology, using slices of complete liver tissue (Eide et al. 2014). The overall aim of the present study is to determine if exposure to plastic additives, such as phthalates, Bisphenol A (BPA) and Benzotriazoles, have the potential to promote adverse effects in Atlantic cod. Our study is a part of the dCod project on the systems toxicology of Atlantic cod, which aims to generate a deeper understanding of the responses of cod to environmental pollutants, and to create tools for environmental monitoring and risk assessment by combining environmental toxicology, biology, bioinformatics and mathematics.

Methods
PCLS from six male juvenile Atlantic cod (*G. morhua*) from ILAB, Bergen, were exposed to 4 concentrations of mono-(2-ethylhexyl)-phthalate (MEHP), BPA and Benzotriazole (BT) both singly and in mixtures ranging from 0.1-100 µM (MEHP), 0.022-22 µM (BPA) and 0.042-42 µM (BT). Histology and transmission electron microscopy (TEM) were used to assess pathological changes and ultrastructure of the exposed liver tissue. Vitellogenin produced by the hepatic tissue were analysed using ELISA and the transcription levels of some biomarker genes (*vtg1, esr1, cyp1a, scdb, aclya, fabp1a* and *acox1*) were measured using qPCR.

Results
Histological evaluation did not show any pathological changes. TEM, vitellogenin ELISA and qPCR are ongoing, and results will be presented at the conference.

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TP-6

Aktivering av aryl hydrokarbon reseptor (Ahr) signalveien hos egg og larve fra Atlanterhavstorsk etter råoljeeksponering med og uten UV- bestråling

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Bakgrunn: Et kontroversielt tema de siste årene har vert oljeutvinning i kystområdene utenfor Lofoten, Vesterålen og Senja (Krumsick and Rose, 2018). Feltene som er oppe til vurdering overlapper sterkt med gyteområdene til flere nordlige fiskearter, blant annet Atlanterhavstorsk (*Gadus morhua*). Et potensielt utslipp vil kunne eksponere egg og larver for råolje på det mest sårbare stadiet av livssyklusen (Olsen *et al.*, 2010). Råolje inneholder polysykliske aromatiske hydrokarboner (PAH) som har vist å gi toksiske effekter hos en rekke marine organismer, inkludert fisk. PAH'er som er tilstede øverst i vannsøylen kan i tillegg absorbere UV-stråling fra sollys og bli fotooksidert til quinion-forbindelser, som kan forårsake oksidativt stress i egg og larver (Lee, 2003). Enzymet cytokrom P450 1A (Cyp1a) er en kjent biomarkør for PAH eksponering. Dette enzymet blir indusert ved ligand-aktivering av aryl hydrokarbonreseptor (Ahr) som binder planare aromatiske hydrokarboner. Etter aktivering diffunderer ligand-reseptorkomplekset inn i cellekjernen der det dimeriserer med partneren aryl hydrokarbon reseptor kjerne translokator (ARNT) og binder til xenobiotisk respons element (XRE) på DNA som igjen aktiverer transkripsjon av *cyp1a* genet (Goksøyr, 1994). Kvantifisering av *cyp1a* induksjon vil gi innsikt i hvilken grad embryo til Atlanterhavstorsk er eksponert for PAH forbindelser.
Metode: I dette forsøket ble befruktede egg fra Atlanterhavstorsk eksponert for relevante konsentrasjoner av råolje (3-600 ug/l) med og uten bestråling av UV-lys (UV-B og UV-C) over en periode på 72 timer. Prøvetakning ble gjennomført etter 12, 24, 48 og 72 timer, hvor egg ble samlet, telt under mikroskop, og deretter lagt i prøverør på tørris (-80°C). Tre dager etter klekking (3dph) ble det tatt bilde og video av larvene for å avdekke eventuelle deformiteter som følge av eksponeringen. Uttrykking av *cyp1a, cyp1b, cyp1c, cyp1d, ahr1a* og *ahr2a* ble kvantifisert ved bruk av qPCR med LightCycler® 480 SYBR® Green 1 Master fra Roche og C1000™ Thermal Cycler fra BioRad. Uttrykkingen av *cyp1a, ahr1a* og *ahr2a* blir visualisert spatialt og temporalt i egg og larver ved bruk av "whole-mount" *in situ* hybridisering. Det blir gjort deformitetsanalyse av bilde og video av larver 3 dph ved bruk av programmet ImageJ. I tillegg blir RNA fra egg i den høyeste eksponeringsgruppen (600 ug/l og 200 ug/l) RNA sekvensert og det vil bli gjort videre bioinformatisk analyse for å identifisere forandringer i genekspresjon av behandlingen.
Resultat: RNA gelelektroforese indikerer god integritet på RNA isolert fra torskeeggene. Prober for ahr1a, ahr2a og cyp1a til whole mount in situ hybridisering er syntetisert, testet og har gitt signal (farging) i embryo og larve.

Denne studien har blitt finansiert av Forskningsrådet via EGGTOX prosjektet (prosjekt nr. 267820), iCod 2.0 (prosjekt nr. 244564) and dCod 1.0 (prosjekt nr. 248840).

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TP-8

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Uptake and effects of microplastics from feed in Atlantic cod (*Gadus morhua*)

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Issue

In recent years there has been a focus on environmental research on microplastics. Microplastics, plastic particles <5mm, have been found in oceans worldwide. Particles are present in fish collected in nature. The aim of this study was to quantify microplastic uptake, translocation, and effect of polyethylene and polystyrene particles in Atlantic cod.

Methods

90 cod were distributed into 30 water tanks. The tanks were randomly divided into five treatment groups: receiving pellet with coconut oil only, with 0.20 μm PS added, with 4-6 μm PE added, with 20-25 μm PE added and 125-500 μm PE added. After two weeks the fish were terminated, and samples of blood, blood plasma, brain, muscle, and liver were collected.

TP-9

Effects of Ag and TiO_2 nanoparticles before and after wastewater treatment processes: an *in vitro* approach using *Eisenia fetida* coelomocytes

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Problem description. The majority of nanomaterials (NMs) used in commercial applications are likely to enter the wastewater stream and reach wastewater treatment plants (WWTPs). In many countries, wastewater effluent and sewage sludge are discharged in aquatic environments or applied on agricultural land, however, the transformation of the particles and the potential hazard they pose in these compartments are poorly understood. Recent studies have shown high association of NMs with sewage sludge[1], therefore soils can be a sink for NM pollution making terrestrial organisms vulnerable. The aim of the study is to understand the transformation of NMs during wastewater treatment processes and to evaluate the potential environmental hazard of aged particles through biosolid application.
Methods. An *in vitro* approach using *Eisenia fetida* coelomocytes as a model for invertebrate immune responses was taken in the present study to investigate the effects of Ag and TiO_2 NPs present in either municipal or sludge obtained from a lab-scale WWTP. Initial investigations focus on Ag (PVP coated, 25 nm, nanoComposix) and TiO_2 particles (uncoated anatase, nominal primary size of 5 nm, NM-101, JRC) and their mixture. A lab-scale wastewater treatment system is used to study the transformation of Ag and TiO_2 NPs through biological wastewater treatment processes[1], and the potential effects of the aged particles through biosolids application is evaluated. Extensive characterization of the particles in exposure media is performed with dynamic light scattering (DLS), single particle-Inductively Coupled Plasma Mass Spectrometry (sp-ICP-MS) and transmission electron microscopy (TEM), while sequential filtration/ICP-MS, sp-ICP-MS and TEM are performed on the sludge containing Ag and TiO_2 NPs. The effects of the pristine and aged particles on the metabolic activity, lysosomal integrity, reactive oxygen species (ROS) formation, immune response and coelomocyte population are assessed. Nanoparticle uptake and intracellular localization are evaluated with sp-ICP-MS.
Results. Exposure to biosolids from a municipal wastewater treatment plant led to a cell population change (eleocyte:amoebocyte ratio) which was dose and time-dependent. Increased ROS levels and decreased lysosomal integrity was observed at the highest dose (3 times the recommended application rate). According to ICP-MS analysis the municipal sludge contained 2300 mg/kg Ti and 4 mg/kg Ag while the lab-scale sludge contained 324 mg/kg Ti and 14 mg/kg Ag. Samples from soil, porewater, whole earthworms and coelomocytes are currently being analyzed while methods for the extraction of NPs from soil are under development for sp-ICP-MS analysis.
C*onclusion*. This study presents a more relevant exposure scenario through the application of biosolids containing transformed nanomaterials. Preliminary results show effects at the cellular level of *E. fetida* at high doses. Ongoing studies focus on the evaluation of the immune responses and the presence of NPs in different matrices with sp-ICP-MS
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TP-10

How do different environmental contaminants effect the activity of transcriptional factors in blue whales (Balaenoptera musculus)?

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Transcription factors are known to regulate the expression of several enzymes involved in biotransformation phase one and phase two. For example, the Aryl Hydrocarbon Receptor (AhR) regulates the expression CYP1A. This receptor is a ligand-activated transcription factor that can alter transcription by tethering to the transcription factors, or binding to their cognate response element. AhR is a member of a protein family that has a basic helix loop (bHLH) and a Per-ARNT-Sim (PAS) domain. Many of the AhRes ligands are halogenated aromatic hydrocarbons or polycyclic aromatic hydrocarbons. The most potent exogenous ligand in human AhR identified so far is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which has often been used as an agonist in experiments with AhR (1). AhR is involved with an organism`s response to environmental contaminants, making research on AhR important in a world with increasing amounts of emerging contaminants. AhR has been shown to be involved in physiological processes, such as cell development and immunity (3) in some animals, but little is known about AhR's role in marine mammals. The receptor complex has never been characterized in blue whales before and therefore AhR's response to contaminants thus unknown in these animals.
The aim of this study was to investigate the transcriptional activity of blue whale nuclear receptors and AhR, when exposed to Persistent Organic Pollutants (POPs) present in blue whale blubber. AhR, ARNT and nuclear receptors have been amplified from blue whale blubber; these will be used to establish a luciferase gene reporter assay that in turn will be used to study the activation of the receptor with different ligands (2).

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TP-11

Results from the Norwegian human biomonitoring study in the EuroMix project: Exposure to the pesticides boscalid and imazalil from the diet in Norway

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Background
The fungicides boscalid and imazalil were among the most frequently detected pesticides in the national food monitoring programs 2013-2017 from the Norwegian food safety authority (Mattilsynet).
The aim of the present study was to estimate the daily intake of these two pesticides, compare the estimated exposure with measured concentrations in urine, and evaluate if the daily intake of boscalid and imazalil through fruit and vegetable consumption is a cause for public health concern.

Methods
A human biomonitoring study was performed to study the exposure to chemicals present in food and personal care products. In two 24 h periods two-three weeks apart, 144 participants (100 women and 44 men) kept detailed diaries about all foods consumed and collected all urine excreted.
Individual-specific consumption data from both 24 h periods were used to estimate boscalid and imazalil exposure deterministically. A sensitive ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS-MS) method was developed to measure imazalil and boscalid residues in 24 h urine pools.

Results
Overall, the estimated exposure of boscalid and imazalil was comparable between males and females. In different exposure scenarios, the estimated exposure of boscalid ranged from 0-2.2 ng/kg bw and the estimated exposure of imazalil ranged from 0-1.5 ng/kg bw. Correspondingly, expressed as percentage of the acceptable daily intake (ADI), the estimated intake ranged between 0-6 % ADI for both pesticides.
Primary comparisons with measured pesticide concentrations in urine may indicate good convergence with the estimated intake.

Conclusion
Preliminary results suggest that the estimated intake of boscalid and imazalil from the diet is well below the acceptable daily intake values set by the European Food Safety Authority (EFSA).

References
www.mattilsynet.no

TP-12

Maternal exposure to a mixture of persistent organic pollutants have long-lasting effects on gut metabolite composition but not on colorectal cancer.

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Problemstilling

The incidence rate of colorectal cancer (CRC) in the Norwegian population is among the highest in the world. Persistent organic pollutants (POPs) have been associated with the risk of cancer, a connection that could be attributed to maternal pollutant transfer and exposure during sensitive developmental stages. A mixture of POPs has previously been shown to increase the number of colonic lesions in A/J Min/+ mice after 10 weeks of dietary exposure (Hansen *et al.* 2018). This mixture was designed to resemble the composition and concentrations of POPs detected in the Scandinavian diet. The present study aimed to investigate 1) how maternal exposure to a mixture of POPs affected the development of CRC, 2) if maternal exposure changed the gut metabolite composition, and 3) if direct exposure caused a similar change in metabolite composition as maternal exposure.

Metode

The A/J Min/+ mouse is a model for CRC and was used in the present study. Dams were exposed to the mixture of POPs throughout mating, gestation and lactation. Offspring were sacrificed at 20 weeks of age, 17 weeks after ended exposure. In the study by Hansen *et al.* (2018), A/J Min/+ mice were exposed directly through feed for 10 weeks. Intestines were scored for lesions and gut metabolite composition was characterized by ^{1}H nuclear magnetic resonance (NMR) spectroscopy on cecum content and tissue.

Resultater

Maternal exposure to the mixture of POPs increased the average size of small lesions in the colon. However, Control mice had a marginally larger area covered with large lesions than the Exposed mice. Direct exposure did not affect the metabolite composition in cecum tissue or content. Interestingly, maternal exposure significantly changed the metabolites present in cecum tissue. The same difference was not found in cecum content.

Konklusjon

1) Maternal exposure to a mixture of POPs did not affect the development of CRC in A/J Min/+ mice. 2) However, maternal exposure caused a long-lasting change in the metabolites of the gut wall. 3) This change was not evident after direct exposure.

Referanser

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TP-13

Cardiopulmonary effects of acute inhalation exposure of rats to exhaust emissions with and without particle filter - The PrevenTap project

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Background: Air pollution is a major health problem worldwide and a leading cause of death and diseases from environmental exposure. In Norway, the annual death rate from polluted air is 300-1900[1], with the majority being related to cardiopulmonary effects. Increased use of emerging biofuels raises concerns about health effects of new emissions. New emission reduction technologies for removal of PM and NO_x have been developed to reduce adverse health effects. Acute effects from diesel engine exhaust (DEE) may be the most relevant to immediate cardiopulmonary effects.
Methods: We analyzed cellular and molecular effects in lungs, pulmonary vein, aorta and the heart in Fisher 344 rats exposed to 1st and 2nd generation DEE, gasoline and bioethanol emissions and NO_2 from a Euro 5-classified diesel engine both with and without diesel particle filter (DPF) technology. The 1st generation biodiesel contained 7% (B7) or 20% (B20) rapeseed methyl esters, and the 2nd generation biodiesel were made from hydrogenated vegetable oil (HVO) (SHB20). The rats were exposed for 6 h (6h/day, both with and without DPF, n = 9/treatment) in whole body exposure chambers.
Results: Flow cytometry of Broncho alveolar lavage fluid (BALF) revealed inflammatory effects in lungs. mRNA expression of genetic markers of inflammation and oxidative stress was assessed in tissue from lungs, aorta, pulmonary vein and heart. Genetic markers of cardiovascular effects including endothelial dysfunction, thrombosis and cellular adhesion were analyzed in aorta, pulmonary vein and the heart.
Conclusion: Work is still in progress and conclusions will follow.

References

1. NIPH (2016) Burden of Disease in Norway 1990 – 2013

TP-14

A mouse model for Acute Myeloid Leukemia reveals a dose rate response after ionizing radiation

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Radiation and chemicals induce leukaemia in mice as well as humans. In the inbred CBA mouse model, two molecular 'hits' have previously been identified as part of acute myeloid leukemia (AML) development. The first is the well characterised dose-dependent chromosome 2 deletion with loss of one copy of the essential haematopoietic transcription factor Sfpi1. In addition, we developed a unique mouse model, CBASpm, engineered to contain the second hit, a point mutation occurring on the undeleted Sfpi1 allele making mice highly sensitive to environmentally induced leukaemia.
CBASpm mice has been engineered with a point mutation in the PU.1 DNA binding domain. Heterozygous deletion of the SPI1 locus and mutation of the -14kb SPI1 upstream regulatory element were described previously in human primary AML. The Spi1 mutation model can be exploited to understand the molecular mechanisms of any leukaemogenesis and to study sporadic and experimentally induced leukaemias. This makes the mice a model of choice for low dose and dose-rate studies in radiation biology.
We present data that sheds new light on how radiation dose rate, as well as dose, affect AML development.
Studies of the effects of low dose/low dose rate ionizing radiation in reproducible animal models are very important for human risk assessment, both regarding accidental and routine exposures. The model could also be useful in other mutagenicity / carcinogenicity studies

Postere i farmakologi (FP)

FP1 Klinisk farmakologi

Effekt av uremiske toksiner på intestinal og hepatisk CYP3A-aktivitet i pasienter med terminal nyresvikt

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Problemstilling

Kronisk nyresvikt er et økende globalt folkehelseproblem. Noen pasienter vil utvikle terminal nyresvikt. Legemidler som elimineres via nyrene må ofte dosejusteres i disse pasientene. Det er også blitt vist at aktivitet av legemiddelmetaboliserende enzymer i tarm og lever kan bli påvirket ved terminal nyresvikt, men årsaken til dette eller hvor stor effekten er på ulike legemidler er ikke fullstendig klarlagt. I HEMMER-studien skal den akutte effekten av uremiske toksiner på CYP3A-aktivitet i pasienter med terminal nyresvikt studeres ved å bruke midazolam som probe. Studiens hensikt er å bestemme CYP3A-aktivitet dagen før og dagen etter hemodialyse i pasienter med terminal nyresvikt.

Metode

En 8-timers farmakokinetisk undersøkelse av midazolam ble utført dagen før og dagen etter hemodialyse i pasienter med terminal nyresvikt. Pasientene fikk 1,5 mg midazolam oralt og 1 mg intravenøs dose med 4-timers mellomrom. Blodprøver ble tatt 0, 0,25, 0,5, 1, 1,5, 2, 3, 4, 4,1, 4,25, 4,5, 5, 5,5, 6, 7 og 8 timer etter den orale dosen. Blodprøvene ble prøveopparbeidet ved hjelp av væske-væske ekstraksjon, og konsentrasjoner av midazolam ble bestemt ved en validert UPLC-MS/MS metode. Standard non-kompartment metoder ble anvendt for å bestemme farmakokinetiske parametere, og den absolutte biotilgjengeligheten av midazolam ble beregnet.

Resultater og diskusjon

Tolv pasienter med en median alder på 68 (47-78) år ble inkludert i studien og gjennomgikk begge undersøkelsesdager. Seks av pasientene var kvinner og seks var menn. På den uremiske undersøkelsesdagen hadde pasientene en median S-kreatinin på 622 (371-1144) µmol/L sammenliknet med 436 (272-1042) µmol/L på den non-uremiske undersøkelsesdagen. Farmakokinetisk profil og absolutt biotilgjengelighet av midazolam både før og etter hemodialyse er hittil blitt bestemt i tre av pasientene. De foreløpige resultatene indikerer at aktiviteten av CYP3A ikke endrer seg fra dagen før til dagen etter dialyse hos pasienter med terminal nyresvikt. Flere pasienter vil bli inkludert i analysen, og oppdaterte resultater vil bli presentert på møtet.

FP2 Basal farmakologi

A search for an allosteric binding site on the natriuretic peptide receptor A

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Introduction

Enhancement of the natriuretic peptide (NP) system has become an attractive therapeutic target since NPs and their receptors are central regulators of cardiovascular and renal homeostasis. Atrial NP (ANP) and brain type NP (BNP) activate NP receptor (NPR)-A and C-type NP (CNP) activates NPR-B. NPRs are membrane bound guanylyl cyclases (GCs) that catalyse the production of cGMP upon activation. These receptors consist of an extracellular ligand-binding domain, a transmembrane domain and intracellular kinase homology domain (KHD), coiled-coil domain (CCD) and GC domain (GCD). We have previously identified small molecular allosteric enhancers of NPR-A, which showed selectivity towards NPR-A with no effects towards NPR-B. In order to optimize our compounds further, we want to elucidate the localisation of the allosteric binding site.

Method

Chimeric NPR-A/NPR-B receptors were constructed using In-Fusion HD plus cloning kit. Compounds ability to modulate the efficacy of BNP and CNP in chimeric NPR-A/NPR-B receptors were investigated in transiently transfected cells and the cGMP production was measured using AlphaScreen assay for cGMP. Modulation of the enzyme activity of the GCD was investigated in substrate-velocity assays in membranes from NPR-A expressing cells and cGMP production was measured by ELISA.

Results

Using chimeric receptor consisting of the extracellular part of NPR-A and the intracellular part of NPR-B abolished the compounds ability to increase BNP-mediated cGMP production. However, the opposite a chimeric receptor consisting of the extracellular part of NPR-B and the intracellular part of NPR-A caused an increase in the CNP-mediated cGMP production and/or a shift in the EC_{50}-value of CNP. Further studies showed that our compounds most likely bind to the KHD in NPR-A, however the CCD also seems to be involved. None of the compounds were able to increase the efficacy of the GCD in substrate-velocity assays. This supports our findings that the compounds do not bind to the GCD.

Conclusion:

The allosteric binding site is located at the intracellular KHD, however the CCD seems to be involved in propagating the efficacy of the compounds. Further studies are needed to find the exact location for this novel allosteric binding site on NPR-A and to understand the modulation action of the compounds.

FP3 Basal farmakologi

Characterization of extracellular vesicles from human skeletal muscle cells

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Background and aims

Extracellular vesicles (EV) are circulating, cell-derived nanoparticles containing proteins, lipids and nucleic acids that interact with and modify local and distant cellular targets. It has become increasingly clear that cells release EVs that reflect their cell of origin. These EVs are of different types, including exosomes, microvesicles and apoptotic bodies. The purpose of this project was to isolate and characterize EVs from human skeletal muscle cells (myotubes) by their size, concentration, surface markers and cargo components. Further, we want to study possible differences between EVs from type 2 diabetic (T2DM) and normal glucose tolerant (NGT) muscle biopsy donors.

Methods

Primary human skeletal muscle cells from extremely obese donors diagnosed with and without T2DM were used in this project. Muscle biopsies was taken during bariatric surgery with informed consent from the patients. EVs were derived from the cell culture medium from myotubes by different centrifugation and filtration techniques. NanoSight was used to measure size and concentration of EVs. Specific EV surface markers like CD9, CD63 and CD81 were detected by flow cytometry. Transmission electron microscopy (TEM) was used to investigate morphology/structure of EVs. Large-scale analysis of protein content are being performed by proteomics and miRNAs by RT-PCR.

Results and Conclusions

So far, EVs from 8 different cell cultures have been isolated, 5 T2DM and 3 NGT. The myotubes produced both exosomes and microvesicles at about the same concentration. The average size of the exosomes and microvesicles were 112 nm and 162 nm, respectively. Preliminary data imply that the distribution between exosomes and microvesicles might be different between T2DM and NGT. The EV surface markers CD63 and CD81 were found on both exosomes and microvesicles, while the level of CD9 was very low. Proteomic analysis of EV from one donor showed in total about 1000 different proteins contained in either exosomes or microvesicles, and among these 140 proteins were unknown. The protein cargo of exosomes and microvesicles were also clearly different. In total EV from 6 donors with T2DM and 6 NGT will be analysed. The results will provide important information about the role of EVs as biomarkers and signalling components.

FP4 Basal farmakologi

Behandling av humane skjelettmuskelceller med selektive hemmere for diacylglyserol acyltransferase 1 og 2 viser at de har ulike roller i glukosemetabolismen

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Problemstilling

Diacylglyserol acyltransferase (DGAT) 1 og 2 katalyserer det siste trinnet i triglyserid-syntesen, dannelsen av triacylglyserol (TAG) fra diacylglyserol. Selv om enzymene katalyserer samme reaksjon, kommer de fra ulike proteinfamilier og tidligere studier har vist at de kan ha ulike roller i lipidmetabolismen i forskjellige vev. Vi ønsker å studere om DGAT1 og DGAT2 også har spesialiserte roller i lipid- og glukosemetabolismen i humane skjelettmuskelceller (myotuber) ved å bruke selektive hemmere av DGAT1 og DGAT2.

Metode

Humane satelittceller ble isolert fra skjelettmuskelbiopsier, dyrket og differensiert til myotuber som ble behandlet med hemmere av DGAT1 (A922500) eller DGAT2 (JNJ-DGAT2-A). For å studere enzymenes rolle i glukosemetabolismen ble [^{14}C]glukose og [^{14}C]acetat benyttet som radioaktive tracere.

Resultater

Glukosemetabolismen ble studert i nærvær av DGAT1 og DGAT2 hemmere, med og uten oljesyre. Det viste seg at DGAT2 hemmer reduserte opptak og oksydasjon av glukose, samt glykogensyntese, mens DGAT1 ikke ga noen endringer i glukosemetabolismen. Denne effekten ble sett etter 4 timers behandling med DGAT hemmere. Glykogensynteseforsøket viste ingen signifikant endring av insulineffekt etter behandling med DGAT1 eller DGAT2 hemmere.

Konklusjon

Selv om de katalyserer samme reaksjon synes DGAT1 og DGAT2 å ha spesialiserte roller for både lipid- og glukosemetabolismen i humane skjelettmuskelceller. Foreløpige resultater indikerer at DGAT2 ser ut til å ha større påvirkning av glukosemetabolismen enn DGAT1.

FP5 Basalfarmakologi

Effekten av kjønnshormoner på differensiering av stamceller til osteoblaster og regulering av cysteinproteasene legumain og cathepsin B

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Problemstilling

Den viktigste årsaken til osteoporose hos kvinner etter overgangsalderen (klimakteriet) er mangel på kjønnshormonet østrogen. Legumain (asparaginyl endopeptidase, AEP), er en lysosomal cysteinprotease og identifisert som en viktig faktor for differensieringen av stamceller til osteoblaster. Vår forskningsgruppe har nylig vist økt nivå av legumain hos postmenopausale osteoporotiske pasienter og at legumain hemmer differensiering av osteoblaster og *in vivo* beindannelse via degradering av beinmatriksproteinet fibronektin. Cathepsin B er også en lysosomal cysteinprotease og har viktig rolle ved flere sykdomstilstander, som inflammasjon og kreft. Det er kjent at også cathepsin B degraderer fibronektin ved både sur og nøytral pH i normalt vev og svulstvev. Det er ikke kjent om kjønnshormoner har cellulære effekter på regulering av cysteinproteaser. Det var derfor interessant å studere om kjønnshormoner (østrogen, progesteron og testosteron) har effekter på regulering av legumain og cathepsin B under differensiering av stamceller til osteoblaster.

Metoder

Det ble benyttet en cellelinje av hBMSC («human bone marrow-derived multipotent stromal (skeletal or mesenchymal) stem cells») som var stabilt transfektert med katalytisk subenhet av human telomerase revers transkriptase. Cellene ble dyrket i 3, 7, 14 eller 21 dager i osteoblast induksjonsmedium, med eller uten kjønnshormoner alene eller i kombinasjon (1 nM 17β-østradiol, 1 µM progesteron eller 0,06 µM testosteron). Etter høsting av cellelysat ble det målt totalprotein og aktivitet av legumain og cathepsin B ved spalting av spesifikke fluorescerende peptidsubstrater. Sekresjon av legumain ble målt i kondisjonerte medier ved ELISA, mens proteinuttrykk i cellelysat ble analysert ved hjelp av immunoblotting. Aktivitet av cellulær alkalisk fosfatase (ALP) og beinmineralisering ved hjelp av BoneTag® ble brukt som osteoblastmarkører.

Resultater

Foreløpige resultater antyder at kjønnshormoner har stimulerende effekt på osteoblastdifferensiering ved å øke ALP-aktivitet og beinmineralisering. Østradiol og testosteron så ikke ut til å endre legumain-aktiviteten i løpet av 21 dager, mens progesteron viste tendens til å være stimulerende. Cathepsin B-aktivitet ble derimot redusert etter behandling med progesteron i 21 dager, men viste tendens til økning med østradiol eller testosteron.

Konklusjon

Nåværende data har vist at kjønnshormoner stimulerer differensiering av stamceller til osteoblaster ved å øke aktivitet eller uttrykk av osteoblastmarkører, men effekten på cysteinproteasene legumain og cathepsin B ser ut til å være forskjellig.

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Mottakere av stipend må sende kontonummer og adresse til nsft@nsft.net innen 15. februar 2019.