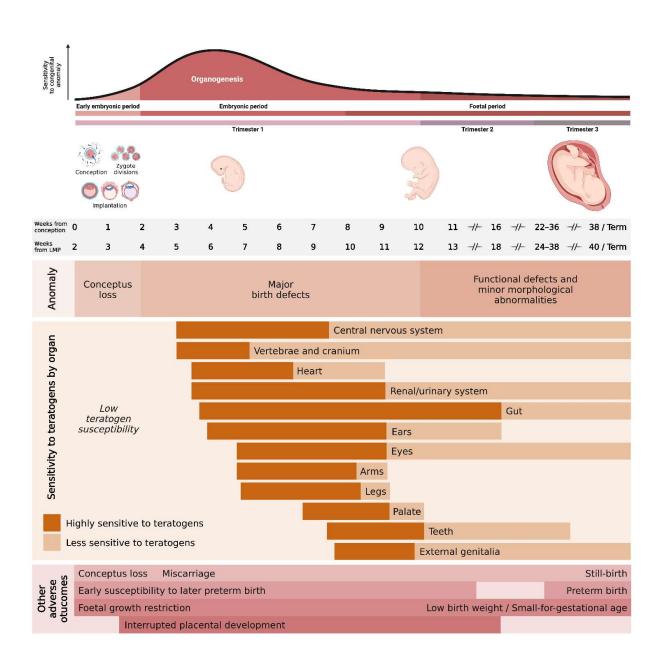
Yearly Report 2022 PharmaTox





Report editors: Hedvig Nordeng, N. Christine Øien

Contact: <u>h.m.e.nordeng@farmasi.uio.no</u>

www.mn.uio.no/farmasi/english/research/groups/pharmatox/

Cover illustration: Emilie W Olstad using BioRender

Photo credit: See the PharmaTox website for details



PharmaTox at a glance

The PharmaTox Strategic Research Initiative was established January 1, 2015, with the aim to determine the impact of specific medications on neurodevelopment and propose molecular and cellular mechanisms involved. The second phase, PharmaTox 2.0, was started in 2019.

We aim to challenge the current understanding of how pharmaceuticals act on the nervous system and generate novel insights on molecular mechanisms of drug neurotoxicity, including pharmacoepigenetic effects.

Moreover, we wish to be a driver of scientific renewal at the Faculty of Mathematics and Natural Sciences, dedicated to research, technical training, and education. The cultural renewal lies in a strong focus on interdisciplinary teamwork, career development, creation of an inspiring learning environment, and focus on generic competencies, and international leadership. The research projects within PharmaTox involve specialists in neurotoxicology, pharmacology, teratology, statistics, bioinformatics, epigenetics, and epidemiology.

Key numbers 2022

We unite more than 40 researchers at the MN faculty, have 10 external partners, and multiple national and international collaborators.

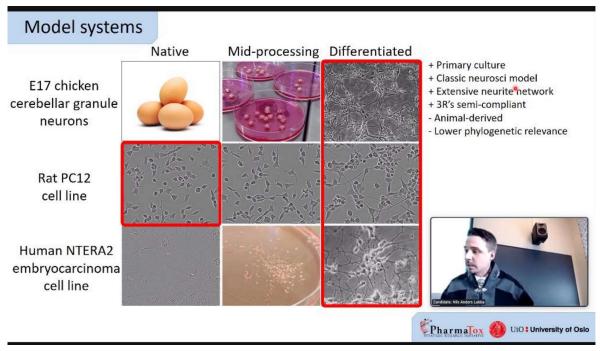
- 2 PhD defences
- 7 scientific publications
- 6 posters/oral presentations/external lectures
- 5 media coverages, 4 multimedia events
- 2 visits from international guest researchers
- 2 research grants awarded (a total of 650 000 NOK)

2021: 1 PhD defence, 17 scientific publications, 17 posters/oral presentations/external lectures, 13 media coverages, 6 multimedia events, 2 visits from international guest researchers, 3 research grants awarded.

2020: 2 PhD defences, 31 international publications, 9 national scientific publications/guidelines, 22 posters, 16 international presentations, 15 national presentations/external lectures, 36 media coverages.

PhD defence: Nils-Anders Labba

PharmaTox PhD student **Nils-Anders Labba** has successfully defended his doctoral thesis «In vitro models and methods for assessment of developmental neurotoxicity and neuroprotection». Congratulations!



The disputation took place digitally. Photo: private



Photo: Hemispherian AS

On February 4, 2022, PharmaTox PhD student **Nils-Anders Labba** from the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, defended his doctoral thesis "*In vitro* models and methods for assessment of developmental neurotoxicity and neuroprotection". His trial lecture was entitled "Epigenetics and its role in neuronal differentiation."

Labba's supervisors were **Professor Ragnhild Elisabeth Heimtun Paulsen**, Section for Pharmacology and Pharmaceutical Biosciences,

Department of Pharmacy, University of Oslo, and **Associate Professor Ragnhild Eskeland**, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo.

PhD defence – Gerd Marie Eskerud Harris

PharmaTox PhD student **Gerd Marie Eskerud Harris** has defended her doctoral thesis "Migraine pharmacotherapy during pregnancy: Utilization patterns and associations with child neurodevelopment". Congratulations!



Photo: Private

On September 10th, 2022, PharmaTox PhD student **Gerd Marie Eskerud Harris** from the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, defended her doctoral thesis "Migraine pharmacotherapy during pregnancy: Utilization patterns and associations with child neurodevelopment." Her trial lecture was entitled "Causal inference based on observational data: when can we trust our results?".

Harris' supervisors include Professor **Hedvig Nordeng**, Section for Pharmaceutics and Social Pharmacy, Department of Pharmacy, University of Oslo, **Assistant Professor Mollie Wood**, Department of Epidemiology, Gillings School of Public Health, University of North Carolina at Chapel Hill, USA.



Real word – artificial worlds: Improving causal inference in perinatal pharmacoepidemiology using machine learning approaches on real-world and artificial data

The UiO:LifeScience-funded convergence environment UiO:RealArt, led by PharmaTox professor Hedvig Nordeng in collaboration with a multidisciplinary team of researchers, launched in 2022.

UiO:RealArt held its constitutional leadership meeting in January 2022. The project has completed three milestones in 2022:

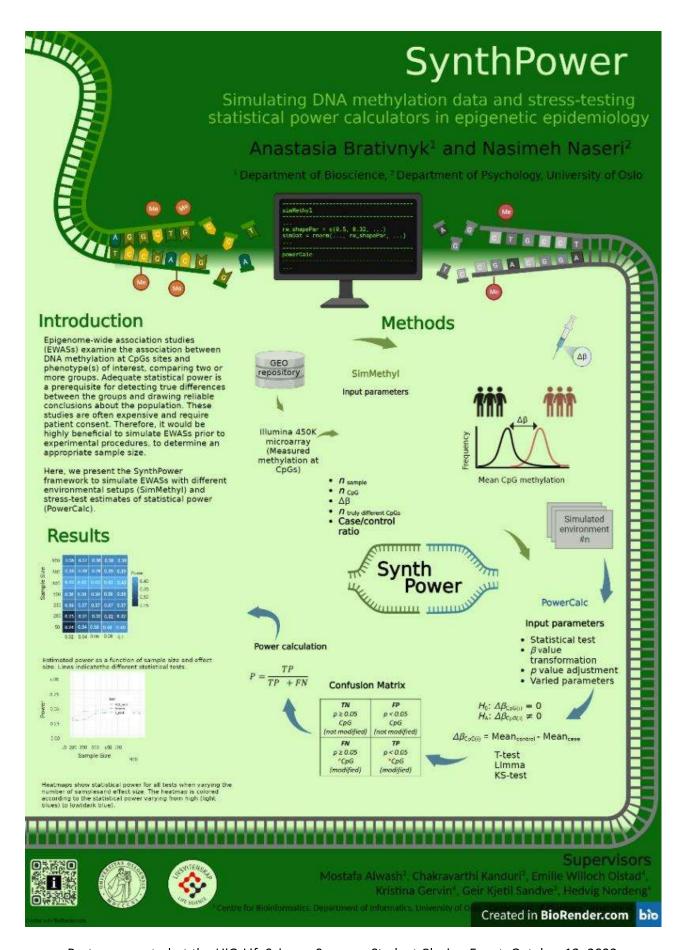
- Obtain REK and SIKT (formerly NSD) approval for the protocol "Epigenetic effects of medications during pregnancy and the risk of neurodevelopmental disorders in childhood: Improving causal inference."
- First postdoc hire: Milena Pavlovic, IFI.
- First PhD student hire: Akhila Reddy, FAI.

In addition, the convergence environment hosted and supervised four UiO:LifeScience-funded summer students. This resulted in the following two posters:

- Prenatal exposure to psychotropics and analgesics. Students: Leite MA, Fawad F. Supervisors: Torkildsen JK, **Nordeng HME**.
- SynthPower Simulating DNA methylation data and stress-testing statistical power calculators in epigenetic epidemiology. Students: Brativnyk A, Naseri N. Supervisors: Alwash M, Kanduri C, Olstad EW, Gervin K, Sandve GK, Nordeng HME.

All four students participated in the UiO:LifeScience closing event on October 13, 2022. Out of the six projects chosen to give oral presentations, one project was supervised by UiO:RealArt. In addition to giving a high-quality, oral presentation, Nasimeh Naseri and Anastasia Brativnyk was awarded the jury award for best academic poster for "SynthPower – Simulating DNA methylation data and stress-testing statistical power calculators in epigenetic epidemiology."

The convergence environment will increase its activity level in 2023. In addition to filling its remaining two positions, UiO:RealArt will launch a journal club and quarterly skill swap sessions. Please visit the UiO:RealArt home page for updates on their activities. www.uio.no/english/research/strategic-research-areas/life-science/research/convergence-environments/uiorealart/news/



Prenatal exposure to psychotropics and analgesics

Impact on cognition, language and educational outcomes in children and adolescents - a systematic literature review

Mila Apostolova Leite, Fatima Fawad, Janne von Koss Torkildsen¹, Hedvig Nordeng²

¹ Department of Special Needs Education, UiC ² Department of Pharmacy, UiO



Methods that are used to measure language and education are heterogeneous. Thus, there is a need for a systematic review of assessments that have been used to measure language skills and educational performance in the pharmaco-epidemiological literature. These measures need to be valid and reliable for the results to be comparable, and for the author to be able to draw conclusions based on these methods.

METHODS

Databases used for this systematic review were Pubmed, Embase, PsycInfo and Medline.

Participants were Children (individuals under the age of 18), prenatally exposed to analgesic, psychotropic or anticpileptic medication.

Outcome was language, educational, or cognitive outcomes that had been assessed either by diagnoses, or by standardized psychometric instruments.

RESEARCH QUESTIONS

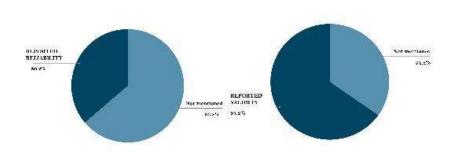
- 1. Give an overview of measures used for language, cognition and educational outcomes in studies of prenatal exposure to analgesics/psychotropics in pregnancy.
- To what degree are reliability and validity of outcome measures reported in these studies?

Reliability and Validity

The eligible studies were assessed for whether the author commented on the reliability or validity of the outcome measures used in the study.

Reliability is a measure of consistency of scores for the same patient, over repeated measurements.

Validity is the extent to which an instrument truly measures the construct(s) it is intended to measure.



RESULTS

The literature search yielded in total 7,984 references. After removal of 2,452 duplicates, 5,532 references were left for title and abstract screening. Of these, 232 were assessed in full text.

69 eligible studies were included for the review.

CONCLUSION

Out of all 69 studies included, 45 reported on the validity of the outcome measure, while only 25 reported on the reliability. Considering the variety of outcome measures used across the studies, authors should be transparent regarding the validity and reliability of these measures.









Poster presented at the UiO:LifeScience Summer Student Closing Event, October 13, 2022.

SynthPwr: Simulating DNA methylation data and stresstesting statistical power calculators in epigenetic epidemiology

Mostafa Alwash is a PharmaTox-funded postdoc with Geir Kjetil Ferkingstad Sandve. His work on power calculators is an integral part of PharmaTox and UiO:RealArt and builds on the work of the UiO:LifeScience summer students.



A cornerstone in performing reproducible science is to have sufficiently powered studies. That is, both the original and replication study should be able to detect any true differences between the test groups. Within the field of epigenome-wide association studies (EWAS), several "power calculators" have been introduced to supervise the selection of appropriate sample sizes to address the research question at hand. However, evidence of clinical test-retest studies failing and literature reviews on EWAS power indicating

that it is not fully assessed, bring into question the validity of the methodology underlying power calculators and their capacity to accurately estimate sufficiently realistic power to serve as useful heuristics for planning expensive real-world studies.

One of the most robust calculators, pwrEWAS is a central blueprint for the methodology adopted in this project for stress testing epigenetic power calculators. This project termed SynthPwr seeks to first replicate the results of a state-of-the-art tool for producing EWAS power and second, design varied environmental (*i.e.*, parametric) simulation setups to study the influence of variables on overall power. These experiments on environmental scenarios help to make the practical boundaries of power calculators clear, by providing grounded results that promote replicability and avoid the risk of under and overpowering studies. Future work seeks to evaluate the impact of data processing procedures (*e.g.*, normalization) on power calculators to more accurately bring practice in line with theory.

Awarded research grants

- 1. **UiO:Life Science summer students grants 2022** | 12 students on 9 selected projects, out of 40 funded projects | 600,000 NOK
 - a. **1 summer student:** Create an accuracy-measuring algorithm for the Mobili medication dispenser system. *Supervisors:* Granås AG, Mulac A, Bjørn T.
 - b. **1 summer student:** Developing a software for simulation of multi-omic molecular datasets with known causal mechanisms. *Supervisors: Kanduri C, Gervin K, Olstad EW, Sandve GK, Nordeng HME* (UiO:RealArt).
 - c. **2 summer students:** How do we measure language and educational outcomes in studies on medication safety in pregnancy? **Supervisors:** Torkildsen JvK, **Nordeng HME** (UiO:RealArt).
 - d. **1 summer student:** Using simulation to stress-test statistical power calculators in epigenetic epidemiology. *Supervisors: Alwash M, Gervin K, Olstad EW, Sandve GK, Nordeng HME (UiO:RealArt)*.
 - e. **2 summer students:** Towards personalized treatment for depression and anxiety: an assessment of prescription-diagnosis trajectories. *Supervisors: Trinh NTH, Lupattelli A, Nordeng HME*.
 - f. 1 summer student: Early prediction of difficult-to-treat depression/anxiety in pregnant women using medical and pharmacy dispensation data. Supervisors: Trinh NTH, Lupattelli A, Nordeng HME.
 - g. **1 summer student:** Birth experiences among women during the COVID-19 pandemic- a multinational European study write your first scientific publication this summer! *Supervisor: Nordeng HME*.
 - h. **2 summer students:** Association between antidepressant exposure during pregnancy and placental weight/birth weight ratio. *Supervisors: Lupattelli A*.
 - i. 1 summer student: Perceived effectiveness of partner support in discontinuers, continuers and initiators of antidepressants in preconception, pregnancy and after childbirth: results from the HEALTHx2 study. Supervisors: Tauqueer F, Lupattelli A.
- UiOLifeScience event support | Genetics/epigenetics and their applications in pharmacoepidemiology | Nhung Trinh/Sina Rostami/Emilie Willoch Olstad/Angela Lupattelli | 50,000 NOK

Guest researchers

Vivian Ugochinyere Ukah, McGill University, Montreal, Canada, March – June, 2022.
 Epidemiological analysis of Norwegian health registry data on treatment of cardiovascular disease during the COVID-10 pandemic. Main supervisor: Nordeng HME. Funded through the iAPOGEE INTPART program. INTPART iAPOGEE

Thomas Boissiere-O'Neill, University of Bordeaux, France. February 14–July 6, 2022.
 Antibiotics and miscarriage. Main supervisor: Nordeng HME. Co-supervisor: Hurley E.
 Funded through the iAPOGEE INTPART program. INTPART iAPOGEE

Scientific publications

- Samara A, Spildrejorde M, Sharma A, Falck M, Leithaug M, Modafferi S, Bjørnstad PM, Gervin K, Lyle R, Eskeland R. A multi-omics approach to visualize early neuronal differentiation in 4D. iScience 2022 Oct 4;25(11):105279. doi: 10.1016/j.isci.2022.105279. eCollection 2022 Nov 18.
- Harris GM, Wood M, Ystrom E, Nordeng H. Association of Maternal Use of Triptans
 During Pregnancy With Risk of Attention-Deficit/Hyperactivity Disorder in Offspring.

 JAMA Netw Open. 2022 Jun 1;5(6):e2215333.
- 3. **Labba NA**, Wæhler HA, Houdaifi N, Zosen D, Haugen F, **Paulsen RE**, Hadera MG, **Eskeland R**. Paracetamol perturbs neuronal arborization and disrupts the cytoskeletal proteins SPTBN1 and TUBB3 in both humans and chicken in vitro models. Toxicol Appl Pharmacol. 2022 Aug 15;449:116130. doi: 10.1016/j.taap.2022.116130. Epub 2022 Jun 15.
- 4. **Olstad EW, Nordeng HME, Sandve GK, Lyle R, Gervin K.** Low reliability of DNA methylation across Illumina Infinium platforms in cord blood: implications for replication studies and meta-analyses of prenatal exposures. Clinical Epigenetics 2022 Jun 28; 14.(1): 80. doi: 10.1186/s13148-022-01299-3.
- 5. **Trønnes JN**, **Lupattelli A**, **Ystrøm E**, **Nordeng H**. Analysis of Prenatal Exposure to Opioid Analgesics and Scholastic Skills in Children in Fifth Grade in Norway. JAMA Network Open Jul 1 2022; 5(7): 1-14. doi: 10.1001/jamanetworkopen.2022.22425.
- 6. Spildrejorde M, Samara A, Sharma A, Leithaug M, Falck M, Modafferi S, Sundaram AYM, Acharya G, Nordeng H, Eskeland R, Gervin K, Lyle R. Multi-omics analysis of paracetamol exposure identifies dysregulated genes involved in neurotoxicity and neuronal differentiation of human embryonic stem cells. Genome Biology (submitted). Also published on bioRxiv. https://www.biorxiv.org/content/10.1101/2022.12.08.519620v1
- Samara A, Falck M, Spildrejorde M, Leithaug M, Acharya G, Lyle, R, Eskeland R. Robust neuronal differentiation of human embryonic stem cells for neurotoxicology. (2022). STAR Protocols 2022; 3: 101533. 10.1016/j.xpro.2022.101533.

Conference presentations

1. **Trinh NTH**, Houghtaling J, Bernal FLM, **Hurley E**, Gesquiere E, Halvorsen L, **Nordeng HME**. Norwegian registries onto OMOP Common Data Model: mapping challenges and opportunities for pregnancy studies. OHDSI Europe symposium collaborator showcase, Rotterdam, June 2022 (oral presentation and poster).

- 2. **Olstad EW**, **Nordeng H**, Lyle R, **Gervin K**. DNA methylation in umbilical cord blood Associations with prenatal (es)citalopram exposure and neurodevelopmental outcomes. Epigenomics of common diseases, Hinxton, England, November 16–18, 2022 (poster).
- 3. **Lupattelli A.** The long-term metabolic safety of antidepressants in pregnancy on the offspring. Marce society international meeting, London, September 2022 (workshop).
- 4. Abellan A, Burn E, **Trinh NTH**, Fernández-Bertolín S, Hurley E, Morales DR, **Nordeng HME**, Duarte-Salles T. Pregnancy extension table in the OMOP CDM. OHDSI Europe symposium collaborator showcase, Rotterdam, June 2022 (poster).

External lectures

- (Epi)genetics in Pharmacoepidemiology Workshop. Oslo, Norway, September 26-27,
 2022. Lupattelli A, Olstad EW, Trinh N, Rostami S. Supported by UiO:Life Sciences and iAPOGEE. (Epi)genetics in Pharmacoepidemiology Workshop
- H. Nordeng. Pregnancy Studies Using Real-world Data from Asia and Europe: Norwegian Mother, Father and Child Cohort Study (MoBa) with focus on neurodevelopmental outcomes. ERC STG project DrugsInPregnancy. ISPE's 14th Asian Conference on Pharmacoepidemiology, National Cheng Kung University, Tainan, Taiwan, 21—23 October 2022.

Media coverages

- 1. Liten risiko ved bruk av migrenemedisin under svangerskapet | Titan | Harris GME
- 2. <u>Medisin mot akutte migreneanfall fører ikkje til åtferdsvanskar når barnet veks til</u> | forskning.no| **Harris GME**
- 3. <u>Triptans in Pregnancy and ADHD in Kids: New Reassuring Data</u> | Medscape Neurology | **Nordeng HME** (interviewee)
- 4. <u>Prenatal triptan exposure does not increase ADHD risk in offspring</u> | Healio Women's Health & OB/GYN | **Harris GME** (interviewee)
- Sjekk hvilke forskere som publiserte mest i 2021 | khrono.no | Nordeng HME

Multimedia

- PharmaTox-video med Hedvig Nordeng og Harald Eia | PharmaTox, PharmaSafe, UiO |
 Nordeng HME (interviewee)
- PharmaTox-video med Eivind Ystrøm og Harald Eia | PharmaTox, PharmaSafe, UiO |
 Gervin K (interviewee)
- 3. PharmaTox, PharmaSafe, UiO **Ystrøm E** (interviewee)
- PharmaTox-video med Geir Kjetil Sandve og Harald Eia | PharmaTox, PharmaSafe, UiO | Sandve GK (interviewee)

PharmaTox members

Name	Position	Institute	Role (funding)
Hedvig Nordeng	Professor	FAI	PharmaTox head
Ragnhild Eskeland	Ass. professor	IMB	PharmaTox leader group
Ragnhild Paulsen	Professor	FAI	PharmaTox leader group
Geir Kjetil Sandve	Professor	IFI	PharmaTox leader group
Sven Ove Samuelsen	Professor	MI	PharmaTox leader group
Robert Lyle	Professor	FAI	PharmaTox leader group
Eivind Ystrøm	Professor	FAI	PharmaTox member – ERC STG
Mollie Wood	Guest researcher	FAI	Former PharmaTox post doc
Mostafa Alwash	Post doc	IFI	Funded by PharmaTox 2.0
Emilie Willoch Olstad	PhD	FAI	Funded by PharmaTox 2.0
Kristina Gervin	Post doc	FAI	Funded by PharmaTox and ERC STG
Nils Anders Labba	PhD	FAI	Funded by PharmaTox – Innovation
Mari Spildrejorde	PhD	OUS	PharmaTox member – FRIMEDBIO
Athina Samara	Researcher	KI/IBV	PharmaTox member
Angela Lupattelli	Ass. professor	FAI	PharmaTox member – NFR-YRT
Nhung Trinh	Post doc	FAI	PharmaTox member – NFR YRT
Lene Maria Sundbakk	PhD	FAI	PharmaTox member – MN (KD)
Johanne Naper	PhD	FAI	PharmaTox member - ERC STG
Gerd Marie Eskerud	PhD	FAI	PharmaTox member – Ekstrastiftelsen (NKS)
Jannike Mørch Andersen	Assoc. prof.	FAI	PharmaTox member
Mona Gaarder	Technician	FAI	PharmaTox member
Cecilie Morland	Assoc. Prof.	FAI	PharmaTox member
Jannike Mørch Andersen	Assoc. Prof.	FAI	PharmaTox member
Alena Hadzic	PhD	FAI	PharmaTox member
Linda Thøring Øverberg	PhD	FAI	PharmaTox member
Marvin Lambertus	PhD	FAI	PharmaTox member
Samuel Geiseler	Post doc	FAI	PharmaTox member
Eivind Hovig	Professor	IFI	PharmaTox member
Naima Azouzi	Post doc	IMB	PharmaTox member
Hallvard Wæhler	PhD	IMB	PharmaTox master student
Josephine Sena Lumor	Master in pharmacy	FAI	PharmaTox master student
Kate Lapane Division of Epidemiology of Chronic Diseases and Vulnerable Populations, University of Massachusetts (UMass), USA	Prof.	USA	PharmaTox QLS partner
Lavinia Schuler-Faccini Genetics Dpt., Biosciences Institute, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil	Professor	Brazil	PharmaTox QLS partner
Ksenia Zagorodnikova North-Western State Medical University n.a.Mechnikov (NWSMU), St Petersburg	Dr.med	Russia	PharmaTox QLS partner

Christina Chambers Center for Better Beginnings, School of Medicine, University of California, San Diego	Professor	USA	PharmaTox QLS partner
Gabriel Balaban	Post doc	IFI	Alumnus
Emil Aas Stoltenberg	PhD	MI	Alumnus
Martin Falck	PhD	IBV	Funded by PharmaTox- Alumnus
Mussi Ghezu Hadera	Post doc	FAI	Alumnus
Magnus Leithaug	Lab researcher	OUS	PharmaTox member – Alumnus
Sarah Hjort Andersen	PhD	FAI	Alumna
Ignacio Cuervo	PhD	IBV	Alumnus
Beata Nadratowska-Wesolowska	Researcher	IMB	Alumna
Christian Page	Post doc	MI/FHI	PhamaTox member - Alumnus
Guro C. Mustorp	Master in Biosciences	IMB	Alumna
Ankush Sharma	Post doc	IBV/IFI	Alumnus
Niloufar Mozaffari	Master in pharmacy	FAI	PharmaTox master student, guest researcher - Alumna

News

Below are a selection of news item from our website. Please visit our website to get our latest updates and news: https://www.mn.uio.no/farmasi/english/research/groups/pharmatox/.



Published Nov. 9, 2022 9:00 AM

<u>PharmaTox's leader Prof. Hedvig Nordeng is third most published female</u>
<u>scientist in Norway</u>

Please join us in congratulating Prof. Nordeng on her publication record for 2021.

Published Aug. 31, 2022 7:20 PM

Workshop on (epi)genetics in pharmacoepidemiology!

Are you interested in how genetic and epigenetic data can be used to gain new insights in epidemiology?





Published Aug. 31, 2022 7:10 PM

Many great summer student projects!

We had a great group of UiO:Life Science students working with us this summer! They had backgrounds from biosciences, health economy, psychology, neuroscience, public health and informatics.

Published July 14, 2022 10:46 AM

PharmaTox researchers at EEPE summer course in Florence!

PharmaTox-affiliated postdoc Nhung Trinh and PhD student Emilie Willoch Olstad attended the one-week summer course "Genetic and Epigenetic Epidemiology" in Florence, Italy, organised by the European Educational Programme in Epidemiology (EEPE). The course covered both fundamental knowledge and emerging methodologies within the field, presented by lecturers at the forefront of genetic and epigenetic epidemiological research.





Published June 26, 2022 2:23 PM

New paper from PharmaTox researchers!

PharmaTox researchers have published a new paper in *Toxicology* and *Applied Pharmacology*: "Paracetamol perturbs neuronal arborization and disrupts the cytoskeletal proteins SPTBN1 and TUBB3 in both human and chicken in vitro models". Read it here.

Published Mar. 30, 2022 8:49 AM

PharmaTox-video med Kristina Gervin og Harald Eia

Da Kristina Gervin starter på det hun kaller en litt barnslig forklaring av epigenetikk, ber Harald Eia om den ikkebarnslige forklaringen. Han angrer seg umiddelbart.





Published Mar. 28, 2022 7:26 PM
We congratulate Eivind Ystrøm with the ERC Consolidator grant!

The PharmaTox associated professor Eivind Ystrøm has been awarded the ERC Consolidator grant. Congratulations!

Published Jan. 11, 2022 2:27 PM Yearly report 2021

The PharmaTox yearly report of 2021 is now available! Download it here.







UiO: University of Oslo









