UiT The Arctic University of Norway

Jobbnorge ID: 273496
Deadline: 2/28/2025
Website: https://uit.no/startsida
Scope: Fulltime
Duration: Fixed Term

16 PhD Fellow positions in Hub Molecules of Metabolism and Signalling - Key regulators of Life

About the project

In the context of the European Horizon funded Marie Skłodowska-Curie Actions - doctoral network HubMOL - Hub Molecules of Metabolism and Signalling - Key regulators of Life, we have 16 PhD positions available at 10 different research institutions and 4 companies across Europe.

HubMOL brings together internationally leading academic and industrial expertise in epigenetics, mathematical modelling and high-resolution stable isotope labelling based analysis of the dynamics of metabolic cofactors and post translational modifications (PTMs) and will use advanced in vitro and animal models for translational studies to develop knowledge based nutritional intervention strategies for hub molecules. The hub molecules of life that include ATP (adenosine triphosphate), NAD (nicotinamide adenine dinucleotide), CoA (coenzyme A), FAD (flavine adenine dinucleotide) and SAM (S-adenosylmethionine), comprise a set of cofactors that are crucial for all cellular functions. More information can be found at the project website: https://uit.no/research/hubmol

HubMOL has 16 subprojects and applicants have to specify the subproject they apply to and can mention additional 2 subprojects of interest. Motivation for the selection should be provided. Applicants that do not specify the subproject or provide the motivation for their choice will not be considered.

The positions are for a period of three years and are available with earliest start in the second half of 2025 and latest start end of 2025.

Subproject 1

Subproject 1 with employment at the Department of Biomedicine, University of Bergen, Norway https://www.uib.no/en/biomedisin:

Dynamics and interdependence of cellular NAD, CoA, SAM, FAD and ATP pools

Metabolic conversions and signaling functions of different hub molecules are interconnected. Previous work has also demonstrated that the level of one hub molecule can be limited by the deficiency of another one owing to its cofactor role. However, while these interdependencies are critical for cell homeostasis, they have not been systematically studied.

Objectives: (1) Establish analytical procedures to determine concentrations and turnover rates of NAD, CoA, FAD, SAM and ATP and their biosynthetic intermediates (2) Set up suitable cell model systems with modulated HubMOL concentrations and turnovers (3) Establish interdependencies of hub molecule dynamics and exploit them to re-adjust imbalances.

Subproject specific requirements

- Profound knowledge of cellular metabolism
- Documented practical experience with cell biology or LC-MS analytics

Supervisor: Mathias Ziegler (group webpage: https://www.uib.no/en/rg/nad-group)

Subproject 2

Subproject 2 with employment at The Arctic University of Norway in Tromsø, Norway https://uit.no/enhet/amb:

Establish mathematical models resembling subcellular NAD, FAD, SAM, ATP and CoA dynamics and their linkage. This subproject will include:

- The collection of biochemical knowledge and kinetic parameters of enzymes and transporters involved in the metabolism of these hub molecules using AI assisted literature search
- The compilation of a searchable database with the collected information
- Analysis of stable isotope labelling data and development of a mathematical model integrating newly derived data and literature based prior knowledge

Subproject specific requirements:

- Documented experience with LC-MS analytics or profound knowledge of cellular metabolism
- Programming skills, preferentially in Python are advantageous

Admission to the PhD programme is a prerequisite for employment, requirements are found at: PhD at UiT The Arctic University of Norway | UiT

Supervisor: Ines Heiland https://uit.no/research/bsysbio

Subproject 3

Subproject 3 with employment at the University Medical Center in Groningen, https://bscs.umcg.nl/en/, Netherlands:

This subproject will focus on coenzyme A biosynthetic pathways in cell and animal models and explore supplementation strategies in genetic deficiencies and their effect on other hub molecules with a focus on NAD. While most inborn errors in CoA biosynthesis lead to neurodegenerative diseases, some mutations lead to dilated cardiomyopathies. The organ specific effects of CoA deficiencies are little understood and will be investigated in the project.

Subproject specific requirements:

- Interest in fundamental research and in (coenzyme A) metabolism in health and disease.
- Clinical translation.

Supervisor: Ody Sibon, https://bscs.umcg.nl/en/people/sibon-ody-c-m/

Subproject 4

Subproject 4 with employment at Simula https://www.simula.no **,** Norway, Department of Computational Physiology:

This subproject aims to study the role of hub molecules in cellular processes and explore their potential for treating metabolic diseases. Coenzyme A (CoA) is a hub molecule involved in many biochemical reactions and metabolism. Deficiency in CoA biosynthesis has been shown to increase the risk of life-threatening heart rhythm disorder. The goal of this project is to use computational modeling to understand the mechanisms underlying CoA disorder and arrhythmogenesis. To achieve this goal, the candidate will:

- Develop a detailed model of cardiomyocyte electrophysiology, including energetics and CoA synthesis.
- Investigate the link between CoA biosynthesis and its effect on the cardiac action potential.
- Conduct 3D simulations in patient-specific heart geometries to study how changes contribute to arrhythmia generation.

Subproject specific requirements:

- We are looking for interested candidates who have a background in computational modeling and biological systems.

Supervisor: Hermenegild Arevalo (hermenegild@simula.no).

Subproject 5

Subproject 5 with employment at MS-Omics https://www.msomics.com/ in Denmark:

Modelling of microbial influence on NAD metabolisms combining LC-MS/MS methods for NAD and CoA metabolites, global metabolic profiling and metagenomic sequencing. The gut microbiome's potential influence on NAD and CoA metabolism involves the microbial breakdown of dietary compounds, which serve as NAD and CoA precursors, and the presence of bacterial enzymes that impact NAD and CoA biosynthesis and utilization. Additionally, gut-derived factors such as SCFAs, inflammation, and immune interactions may further modulate NAD and CoA metabolism by affecting nutrient absorption and cellular responses. The availability of mice intestinal samples from different sections of the gut allows a precise measurement of where and how metabolites are modified or absorbed.

Objectives: (1) Measure NAD metabolites, global metabolome and the metagenome in samples from mice (2) Elucidate gut-microbiome-NAD and CoA metabolism by identification of specific taxa and metabolic pathways responsible for NAD and CoA precursors synthesis and breakdown (3) Apply integrative multi-omics analysis for modelling the NAD metabolites, metabolic pathways in the gut microbiota.

Subproject specific requirements:

- The candidate can be either a strong analytical scientist with a high interest in programming and modelling.
- Or the candidate could be a bioinformatician with LC-MS/MS and laboratory experience.

Supervisor: Morten Danielsen https://www.msomics.com/

Subproject 6

Subproject 6 with employment at Josep Carreras Leukaemia Research Institute (IJC) in Spain: http://www.carrerasresearch.org/en

Background: Cancers have an altered metabolism. This altered metabolism can be leveraged for the identification of cancer-specific vulnerabilities. The proof-of-concept has been made for NAD metabolism with synthesis inhibitors showing efficacy in some preclinical cancer models.

Objectives: (1) Analysing the expression of and the dependency on NAD-generating and metabolizing enzymes in cancer samples and cell lines, with a particular focus on enzymes located in the nucleus. (2) Determine genetic and pharmacologic perturbations of nuclear NAD levels in cultured cancer cells. (3) Determine the impact of these perturbations on gene expression and chromatin structure.

Subproject specific requirements:

- Technical expertise in cell culture methods, generation of genetically modified cell lines, molecular biology and biochemistry.
- Some knowledge of Spanish is helpful.

Supervisor: Marcus Buschbeck http://www.carrerasresearch.org/en/directory/marcus-buschbeck-109

Subproject 7

Subproject 7 with employment at Eisbach Bio Munich, Germany https://www.eisbach.bio/:

Synergy between HPF1-mediated serine ADP-ribosylation of chromatin and ALC1 chromatin remodeller function in the DNA damage mediated and NAD-dependent activation of the nuclear enzymes PARP1/2. Background: The conversion of the metabolite NAD into poly-(ADP-ribose) (PAR) during DNA damage is crucial in cancer. PARP1/2 inhibitors are clinically useful but have toxicity and resistance issues. HPF1 completely alters PARylation's target amino acid in the DNA damage response, yet its potential as a cancer target remains underexplored.

Objectives: (1) Dissect the functions and biological roles of ALC1 and HPF1 in PARP1/2-mediated DNA damage responses; (2) Determine the role of HPF1 in the NAD-dependent and poly-(ADP-ribose)-mediated recruitment of ALC1 chromatin remodeller to DNA damage sites; (3) Establish the mechanism of PARP inhibitor sensitization mediated by ALC1 and HPF1 in isolation and together.

Supervisor: Andreas Ladurner (andreas@eisbach.bio)

Subproject 8

Subproject 8 with employment at The University of Innsbruck, Austria www.uibk.ac.at/de/:

In this subproject we qabnt to develop mass spectrometry-based proteo-metabo-flux approaches to study the dynamic interplay between the availability and turnover of hub molecules (acetyl-CoA, SAM) and PTMs, including PTM crosstalk (histone acetylation & methylation).

Subproject specific requirements:

- Knowledge of chromatography (UPLC, HPLC, HILIC, IC, RP) and mass spectrometry (ideally high resolution orbitrap mass spectrometry)
- sample preparation for metabolite and/or protein analysis including protein/histone modifications,
- programming skills (R, Python) and experience in cell culture are required.
- Knowledge in the field of molecular biology and biochemical methods (western blot, electrophoresis, isolation of organelles, mitochondrial respiration) is desirable.

Supervisor: Marcel Kwiatkowski https://www.uibk.ac.at/biochemistry/people/kwiatkowski/marcel-kwiatkowski.html

Subproject 9

Subproject 9 with employment at The Arctic University of Norway in Tromsø, Norway https://uit.no/enhet/amb:

Develop mathematical models linking the dynamics of S-Adenosyl Methionine (SAM) and Acetyl-CoA metabolism to protein acetylation and methylation. This subproject will include:

- Develop data analysis and modelling-based approaches to correct stable isotope-based protein modification dynamics for cofactor biosynthesis dynamics
- Build and extend both small scale dynamic and genome scale metabolic models to reflect substrate requirements through protein modifications and consequently potential limitations for PTMs.

Subproject specific requirements:

- Documented experience with LC-MS analytics or profound knowledge of cellular metabolism
- Programming skills, preferentially in Python are advantageous but are not required, but it is expected that the candidates develops the required programming skills within the course of the project as a large part of the project is programming based

Admission to the PhD programme is a prerequisite for employment, requirements are found at: PhD at UiT The Arctic University of Norway | UiT

Supervisor: Ines Heiland https://uit.no/research/bsysbio

Subproject 10

Subproject 10 with employment at the National Research Council Naples Italy www.cnr.it/en **:**

CtBP1/BARS, a sensor of the NADH/AcylCoA - Consequences on cell functions Background: BARS, a member of the C-terminal-binding protein (CtBP) family, is a dual function protein acting as transcription regulator in the nucleus in its dimeric/tetrameric NADH-bound form, and as membrane-fission protein (in its AcylCoA-bound monomeric form) in intracellular traffic steps such as formation of post-Golgi tubular/pleiomorphic carriers, macropinosomes, COPI-dependent transport vesicles and partitioning of the Golgi complex during mitosis. BARS also plays a role as a metabolic/redox sensor that is activated by NADH-binding. Increase in NADH level inhibits the monomeric fission-competent form of BARS and, thus, intracellular membrane transport. This mechanism supports cellular energy homeostasis by reducing energy consumption.

Objectives: (1) In vitro studies to evaluate NAD-NADH-AcylCoA binding constants related to BARS structural transition (chromatography and cryoTEM studies). (2) Modulate the cellular concentrations of the BARS-ligands: verify/validate structural transition in intact cells 3) use appropriate cell systems, as developed in our lab, to analyze the interplay between NAD and AcylCoA metabolism and BARS functions 4) verify the activity of small molecules (already available from a virtual screening campaign) to modulate BARS activity in pathological conditions (methods available in the lab)

Subproject specific requirements: Previous experiences in the field of cell biology of trafficking, protein-protein interaction studies, biochemistry of small molecules, and in the field of imaging (fluorescence, correlative, electronic microscopy) will be considered positively for the evaluation.

Supervisor: Daniela Corda (daniela.corda@cnr.it)

Subproject 11

Subproject 11 with employment at the Research Center One Health Ruhr (RCOHR) Essen, Germany (https://www.uaruhr.de/researchallianceruhr/onehealthruhr.html.en)

The protein kinase mTOR is a central controller of metabolism and ageing. mTOR is dysregulated in most cancers as well as in metabolic, neurodegenerative and congenital disorders, and is therefore of major biomedical interest as a drug target and biomarker. mTOR is at the center of a complex signaling and metabolic network, and exists in two structurally and functionally distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2. In response to growth factors, nutrients, energy and stress, mTORC1 enhances anabolic processes such as translation, and represses catabolic processes such as autophagy. In this project we have identified posttranslational modifications of mTORC1 regulatory proteins as well as several enzymes that are of interest in this context. However, the cellular impact of these modifications and the signaling and metabolic networks governing them are poorly understood. The HubMOL-funded DC will investigate how these enzymes and protein modifications link the mTOR kinase network to metabolism and identify the role of connected hub molecules. This goal will be achieved by combining biochemistry and cell biology techniques with state-of-the-art proteomics and metabolomics.

Subproject specific requirements:

- The candidate should have theoretical and practical knowledge in cell culture techniques, biochemistry techniques (e.g. immune detections, fractionations, enzyme assays) and microscopy.
- Previous experience in the field of mass spectrometry-based proteomics and/or metabolomics is a plus.

Supervisor: Kathrin Thedieck https://metabolic-signaling.eu/prof-dr-kathrin-thedieck/

Subproject 12

Subproject 12 with employment at the University of Copenhagen, Denmark www.cbmr.ku.dk/research/**:**

The subprojects aims to understand the role of the NAD+ generating and consuming pathways for maintaining tissue function and adaptability in response to metabolic stress. We employ innovative preclinical models to manipulate NAD-related metabolites cell type-specifically and determine functional implications. We have developed several novel and unique experimental models and techniques related to in vivo animal research.

We have preliminary data from quantitative mass spectrometric analysis of skeletal muscle that show key proteins in the insulin signaling cascade are ADP-ribosylated. Since ADP ribosylation (ADPr) is mediated by NAD+-consuming ADP-ribosyltransferases, this indicates a yet unrecognized interplay between insulin signaling and cellular NAD+ metabolism. Our hypothesis is that ADPr plays an essential role to regulate insulin sensitivity in skeletal muscle, and our over-arching aim is to determine the role of this posttranslational modification (PTM) for maintaining cellular glucose homeostasis and insulin action. Your tasks would be to define and compare insulin-induced ADP ribosylomes of insulin sensitive and resistant skeletal muscle, and to identify key modifications that are important for insulin signaling to mediate glucose disposal. We strive to understand the molecular basis for ADPr in skeletal muscle insulin resistance, and we are looking for candidates who are motivated to integrate data available from high-resolution mass spectrometry-based proteomics analyses with approaches in in vivo physiology and molecular biology.

Subproject specific requirements:

- A curious mindset with a strong interest in skeletal muscle metabolism, in vivo physiology, and bioinformatics.
- Basic knowledge about LC-MS/MS-based proteomics, sample preparation and MS data processing is an advantage.

Supervisor: Jonas Thue Treebak
Email: jttreebak@sund.ku.dk, direct phone: +45 2480 5398, https://cbmr.ku.dk/research/research-groups/treebakgroup/?pure=en/persons/5073

Subproject 13

Subproject 13 with employment at Leipzig University, Germany https://www.uni-leipzig.de/personenprofil/mitarbeiter/dr-antje-garten**:**

Background: Obesity is one of the most prevalent non-communicable diseases and knowledge on both pathogenesis and treatment is incomplete. Hub molecules modulate adipocyte function via their impact on energy metabolism and signalling pathways, by acetylating, phosphorylating and methylating signalling molecules. Nutritional supplementation with hub molecules/precursors could be used to positively influence adipose tissue function and counteract metabolic disturbances. No systematic/comprehensive study of combining hub molecules has been performed on human adipocyte models and human adipose tissue. So far, studies reporting on circulatory hub molecule or precursor levels in healthy or obese children are also lacking.

Objectives: We will determine the impact of supplementation with combinations of hub molecules on (1) adipocyte, (2) check if effects differ between healthy and diseased human adipocyte/adipose tissue models, (3) determine corresponding changes in gene expression (4) measure hub molecule precursors in serum of a large cohort of healthy and obese children and adolescents (LIFE Child study) and determine associations with glucose and fatty acid serum levels, inflammatory status, weight status and liver function.

Subproject specific requirements:

- Strong interest in wet lab research.
- The candidate should be a team player.
- Ideally, they should have some interest in energy metabolism and not be afraid of data science as well as have some previous experience with or the drive to learn R for statistical analyses and data visualization.

Supervisor: Antje Garten https://www.uni-leipzig.de/personenprofil/mitarbeiter/dr-antje-garten

Subproject 14

Subproject 14 with employment at MIMETAS, Leiden Netherlands https://www.mimetas.com/en/home/**:**

Liver on-a-chip models for liver metabolic dysregulation research Background: Imbalances in metabolic networks are increasingly recognized as potential targets in various liver diseases, including NAFLD and NASH, offering novel avenues for therapeutic interventions. Utilizing liver-on-a-chip models to investigate metabolic dysregulation in the liver offer a unique platform to simulate liver metabolism and study its dysregulation, providing critical insights for targeted treatments and drug development.

Objectives: (1) Develop 3D human (disease specific) models to mimic liver architecture and the NAFLD and NASH environment. (2) Develop liver-on-a-chip model-based readouts for hub molecules suitable for high-throughput screening; (3) Validate the model with tool compounds including nutraceuticals on 3D liver disease models.

Subproject specific requirements: Experienced in high quality tissue culture, (confocal) microscopy and image analysis software; experience with (live) cell-based assays and molecular analysis techniques (incl qPCR, ELISA, IF); A passion to support new therapy discovery and development, and have an affinity to work in an international, fast-growing high-tech environment at the edge of industry and academia

Supervisor: Dorota Kurek (d.kurek@mimetas.com)

Subproject 15

Subproject 15 with employment at the University Medical Center in Groningen Netherlands https://www.rug.nl/:

This subproject will focus on the role of coenzyme A in energy metabolism, particularly in inherited disorders of fatty-acid oxidation and CoA biosynthesis. The relationship between the primary enzyme deficiencies and the disease symptoms is often incompletely understood. The complexity of the metabolic pathways and their high connectivity require a systems biology approach. In this project we will explore the effect of the nutritional status on CoA and fatty-acid dynamics using stable-isotope labelling, mass spectrometry and computational modelling.

Subproject specific requirements:

- Interest at the interface of fundamental biomedical science, computational modelling, and clinical translation.

Supervisor: Barbara Bakker https://www.rug.nl/staff/b.m.bakker/

Subproject 16

Subproject 16 with employment at Nestle Research, Switzerland, www.nestlehealthscience.com **:**

Interplay of metabolic fluxes between dietary NAD+ precursors Background: Nestlé Research has performed a range of pre-clinical and clinical studies with NAD precursors including a comparative clinical metabolomics study of the NAD metabolome in blood cells of healthy adults, and demonstrated health efficacy of different dietary NAD precursors that are tissue-specific and involve complex metabolic cross-talks. In our research program on the nutritional management of sarcopenia, we have demonstrated that NAD levels are low in skeletal muscle of sarcopenic patients and that trigonelline (a novel NAD precursor) associates with muscle health in humans7.

Objectives: (1) Characterize cell type specific uptake and changes of the NAD metabolome in liver, kidney, muscle, and blood cells treated with different dietary NAD precursors (NR, NMN, NAM, trigonelline, tryptophane) (2) Characterization of NAD precursor metabolic fluxes in cells using isotope tracing (HILIC-HRMS). (3) Modelling of metabolic fluxes in the NAD metabolome using cellular data and pre-existing clinical data, and prediction of synergies between NAD precursors and interaction with physiopathology. (4) Validation of combinations of NAD precursors on age-related health benefits using existing lifespan and healthspan assays in C. elegans.

Supervisor: Jerome Feige and Stefan Christen (jerome.feige@rd.nestle.com, stefan.christen@rd.nestle.com)

Qualifications and subproject requirements

- A masters degree in biochemistry, cell biology, biomedicine, analytical chemistry (subprojects 1,2,5,8,9,15) or bioinformatics with good understanding of biochemistry (subprojects 2,5,9)
- Proven prior knowledge in hub molecule relevant topics
- A high level of motivation and interest for topics of HubMOL
- High-level of collaborative and communicative skills.
- Relevant expertise in cell metabolism and fields related to the HubMOL projects
- Excellent level of English speaking and writing skills (required).

Application

- Cover letter explaining your motivation and which position in HubMOL you are applying for
- CV
- Diploma for bachelor's and master's degree
- Transcript of grades/academic record for all degrees
- Explanation of the grading system for foreign education (Diploma Supplement if available)
- Documentation of English proficiency
- References with contact information
- Master’s thesis, and any other academic works

Qualification with a master’s degree is required before commencement in the position. If you are near completion of your master’s degree, you may still apply and submit a draft version of the thesis and a statement from your supervisor or institution indicating when the degree will be obtained. You must still submit your transcript of grades for the master’s degree with your application.

All documentation to be considered must be in English. Diplomas and transcripts must also be submitted in the original language, if not in English. If English proficiency is not documented in the application, it must be documented before starting in the position. We only accept applications and documentation sent via Jobbnorge within the application deadline.

Assessment
The applicants will be assessed by an expert committee. The committee's mandate is to undertake an assessment of the applicants' qualifications based on the written material presented by the applicants, and the detailed description draw up for the positions.

The applicants who are assessed as best qualified will be called to an interview. There will be a two-stage interview process. The interview should among other things, aim to clarify the applicant’s motivation and personal suitability for the position.

Mobility rule
Researchers can be of any nationality, but they are required to undertake physical, transnational mobility (i.e., move from one country to another) when taking up their appointment.

Additionally, researchers shall not have resided or carried out their main activity in the country of their host organization for more than 12 months in the 3 years immediately prior to the reference date.

Researchers who are refugees in an EU Member State or a Horizon Europe Associated Country according to the Geneva Convention are exempted from the mobility rules above if they fulfil the other eligibility conditions.

Doctoral Candidates (DCs) rule

Applicants must be doctoral candidates, i.e. not already in possession of a doctoral degree at the date of the recruitment.

Researchers who have successfully defended their doctoral thesis but who have not yet formally been awarded the doctoral degree will not be considered eligible. See Article 6.2.A (b) (i) of the HE unit model grant agreement.

Applicants must meet the admission requirements of the doctorate degree program of the hiring institutions for each position.

Additional information

Place of service:
- Different locations
- Hansine Hansens veg 18 9019 Tromsø (Tromsø - Romsa Municipality)