Newsletter
May 2020

European Network for Innovative Diagnosis and Treatment of Chronic Neutropenias

What is EuNet-INNOCHRON

EuNet-INNOCHRON is an ambitious COST (European Cooperation in Science & Technology) action which is aiming to promote the research in the field of Chronic Neutropenias (CNP). Our multidisciplinary network involves enthusiastic clinicians and scientists with specialist interest in Congenital and Acquired Neutropenia from 31 different countries.

The main aims of the Action are:

(a) To promote science, training and education on advanced laboratory techniques for the accurate diagnosis and treatment of patients with different types of CNP, early recognition of MDS/AML evolution and appropriate intervention;

(b) To create working groups which will also collaborate with existing neutropenia networks for a multidisciplinary and holistic approach in CNP patients and a better characterization and understanding of this haematological disorder. This will lead to development of individualized and precision medicine therapeutic approaches for subtypes of patients.

(c) To organize, interconnect and implement the CNP patient Registries and Biobanks at the European level under the ethical standards of the European Legal Framework, taking also into account the regulations of the participating countries for patient recruitment and monitoring of clinical, genetic and other laboratory data, disease progression and treatment experience.

EuNet-INNOCHRON

Objectives

The main objectives of the EuNet-INNOCHRON Action are as follows:

(a) Development of common diagnostic algorithms and treatment guidelines for patients with different types of CNPs aligned with the concepts of precision medicine.

(b) Harmonization of the laboratory investigation of different types of CNPs by exchanging tools, reagents, protocols and experience through inter-laboratory collaborations.

(c) Development of training modules, accessible for Early Career Investigators (ECI) and other researchers as well, compiling existing knowledge, advanced methods and techniques.

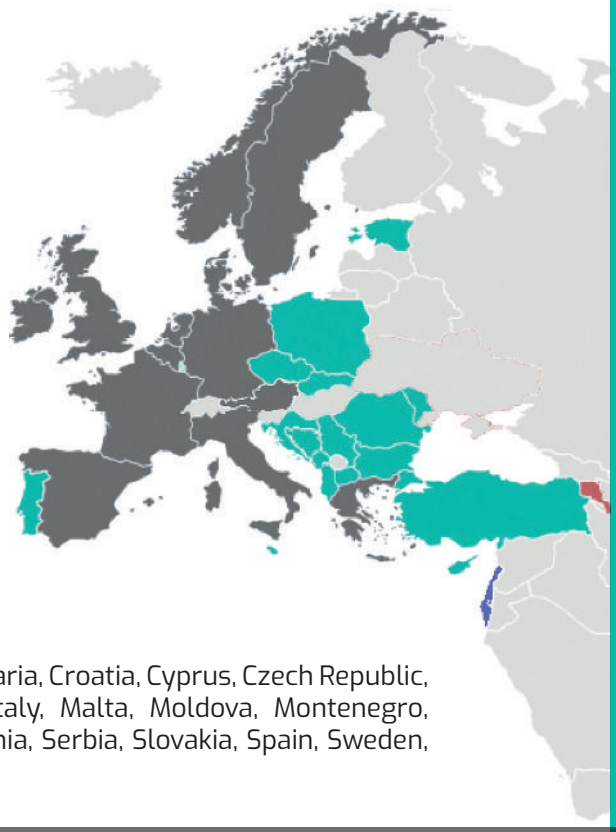
(d) Organizing and expansion of CNP patient Registries and Biobanks

(e) Development of entrepreneurial innovation and increase competitiveness of European research and industry though the active implication of SMEs involved in areas related to the EuNetINNOCHRON.

Five groups of clinicians and scientists will work in parallel but also in close collaboration in order to complete this Action. The kick-off meeting took place in Brussels on 19 November 2019, denoting the official start of the Action. EuNet-INNOCHRON is open to any clinician or researcher with special interest on neutropenias from COST Members/Countries participating in the Action. The working groups and their topics are as follows:

- WORKING GROUP (WG)-1:
  Congenital Neutropenias
- WORKING GROUP (WG)-2:
  Acquired Neutropenias
- WORKING GROUP (WG)-3:
  Mechanisms of Leukaemic Evolution
- WORKING GROUP (WG)-4:
  Investigation of Targets for Novel Therapies
- WORKING GROUP (WG)-5:
  CNP Patient Registries and Biobanking

31 COST Members
01 COST Int. Partner (UoW, USA)
01 Participating Organization (EHA)
01 NNC (Armenia)
48 Months



Albania, Armenia, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Ireland, Israel, Italy, Malta, Moldova, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Turkey, United Kingdom, USA

Kick-off meeting, 1st Management committee meeting (19 November 2019)

This very important meeting was held in Brussels with the invaluable coordination of the hosting team of our Action's COST officers . The Main Proposer, Prof. Helen Papadaki presented the Aims of the Action and focused on the Tasks and Deliverables of the WGs. The participants had a very interactive discussion regarding what needs to be done in each of the WG and how this would best communicated to the scientific community. Finally, decisions were made about the financial aspects and budget distribution. And so, ... our Action officially started!

2nd Management Committee meeting and 1st Working Groups meeting (16 March 2020)

Who ever said that the covid-19 pandemic could stop our enthusiasm for the Action ? The 2-days' meeting originally planed for Clare College, University of Cambridge UK, finally transformed to a successful e-meeting where more than 70 individual colleagues participated. Of course, nothing could have been organized without the dedication of the Local Organizers Prof. A. Warren and his colleague M. Dawes.

Highlights of the online 2nd Management Committee meeting and 1st Working Groups meeting

Updates from the Action Chair, Prof H. Papadaki:

a) There was an update of the current participating members of the Action with Croatia, Israel, Montenegro, Bosnia and Herzegovina having joined the Action since the MC1 meeting in November 2019 with a total number of 30 members by March 2020. Also, University of Washington, Seattle was mentioned as a COST International Partner and the EHA as a participating Organization of the Action.

> But who knows... the invitation is still open and our Action is willing to welcome more participating members!

b) The update regarding the Implementation of COST policies on i) Inclusiveness and Excellence (Inclusiveness Target Countries; ITC), ii) Promotion of gender balance and ECIs was well received. The Action Chair informed the participants, that more than half of the COST participating members are ITCs, which implies a small success on that field. Also, it was mentioned that 60% of our MC members and MC substitute members are women which is encouraging considering the gender imbalance in the Science fields. However, after reviewing the percentage of senior vs young investigators it was mutually agreed that much have to be done in encouraging more ECIs and younger investigators to actively participate in the Action.

2) Short Term Scientific Missions (STSM)
The survey among the Action's participants conducted by Prof. O. Karanfilski , as the STSM Coordinator, highlighted different fields of interest in offering and receiving training in the context of EuNet- INNOCHRON. It was apparent that clinical/laboratory training, CRISPR, NGS, anti-neutrophil Antibodies and iPSCs were the most requested fields for training.

"What is your field of expertise or interest? Any offer or request for training will be taken into account! Don't hesitate to participate!"

Guidelines Session

F. Cerisoli from the Guideline (GL) Committee of the EHA illustrated the options and support that the EHA offers for Guidelines and there is a great opportunity for a possible joint venture between our COST Action EuNet-INOCHRON and the EHA GL Committee Guidelines on diagnosis and treatment of Neutropenia.

J. Palmblad presented a diagnostic algorithm published in Expert Rev Hematol. 2016 on the management of Neutropenia in adults which underlines the elements that mainly differentiate adult and pediatric age, whereas F. Fioredda presented the process of updating the "Diagnosis and Treatment of Neutropenia" from the Italian Guidelines.
This session ended with all the participants agreeing on the need of the European Neutropenia Guidelines and were in favour of prioritizing the joint project with the EHA during the EuNet-INNOCHRON COST Action. Who could not agree on the importance of this task?

Highlights of the MC and WG sessions

Working Group 1 'Congenital Neutropenias' session

Prof. K. Welte presented the up to date knowledge regarding congenital neutropenia as a multigene-disorder with high genotype-phenotype heterogeneity.

Prof. A. Warren presented interesting data regarding a new eIF6 overexpression mouse model and he discussed its role in drug screening and in understanding the role of Shwachman-Diamond syndrome (SBDS) protein in the biology of this disease.

Dr. A. Skakic & S. Pavlovic presented data from a novel human kidney cell model lacking SLC37A4 expression as a tool to study the pathogenesis of Glycogen Storage Disease type Ib (GSD 1b) and to identify novel therapeutics.

Dr. V. Bezzerri discussed the hypothesis that development of nonsense mutation suppression therapies could be a therapeutic option for BM failure syndromes.

Working Group 2 'Acquired Neutropenias' session

Prof. J. Palmblad presented the survey results about the diagnostic work up for neutropenic patients based on a questionnaire which was distributed to the participants.

Prof. P. Höglund shared his presentation regarding the challenges in anti-neutrophil antibody screening at the moment and gave a flavour of the new methods which are now being developed.

Prof. H. Papadaki in her presentation stressed the need to include myeloid NGS panel analysis and flow cytomentry in the diagnostic algorithm as this could be crucial in distinguishing benign and neutropenias preceding MDS.

Dr K. Stamatopoulos with a great experience in this field discussed about the oligoclonal expansions of cytotoxic T cells and their role in the development of non-antibody mediated neutropenias.

Working Group 3 'Mechanisms of Leukaemic Evolution' session

Dr P. Olofsen presented new unpublished findings regarding the role of elevated oxidative stress in hematopoietic progenitors of SCN patients and they explored the role of the promyelocyte leukemia (PML) protein in SCN. A collaboration with the Skokowa/Welte group, who has provided SCN/AML derived iPSC lines has been initiated.

Prof. I. Touw presented interesting data on the leukemic progression of SCN in a mouse model and the identification of a driver mutation in CXXC4.

Working Group 4 'Targets for Novel Therapies' session

Prof. J. Skokowa discussed the development of a novel in vitro model of CN, that helped to overcome the obstacles of limited numbers of available primary bone marrow HSC of pediatric patients with CN and a lack of experimental animal models, which would help for further research in this field.

Prof. J. Cichy gave a presentation about the potential of inhibitors of neutrophil elastase for treatment of ELANE-associated Congenital Neutropenia.

Dr B. Bajoghli discussed about the use of zebrafish as a model system to study congenital neutropenia, as there is no reliable animal model so far to study JAGN1 and HAX1-associated CN.

Prof. A. J. Warren presented a hypothesis that a small molecule that reduces the affinity of eIF6 for the ribosome would provide a potential therapeutic approach for patients with SDS.

Working Group 5 'CNP Patients Registries and Biobanking'

Dr C. Zeidler presented data from the Severe Chronic Neutropenia International Registry (SCNIR) - European Branch and she gave an overview about the genetic subtypes and the Partner Countries.

Dr K. Stamatopoulos introduced basic concepts about biobanking and he presented the BBMRI-ERIC infrastructure with special emphasis on data registration. He also mentioned that the current experience from BBMRI-ERIC Institute of Applied Biosciences at CERTH can be adapted to meet EuNet-INNOCHRON's needs.

ACTION PLANS

Long-term planning

One Training School will be organized per year and at least four STSMs per year. The Training School of the next Grant Period was agreed to be on autoimmune neutropenias with a particular focus on the technology. The specific dates in November 2020 and place will be announced soon, after the end of the covid-19 pandemic.

Are you thinking of visiting a Lab within the Network and getting training on a specific technique? Get prepared! Four STSM will be advertised soon.

Young EuNet-INNOCHRON Group

The Young EuNet-INNOCHRON Group is almost ready for further actions !! If you are a young investigator and you want to develop further yourself within the Action or you wish to express us your ideas how the Network can promote further the young generation, please contact the Chair of the Young EuNet-INNOCHRON Group, Dr Maksim Klimiankou (maksim.klimiankou@med.uni-tuebingen.de).

Time flies..

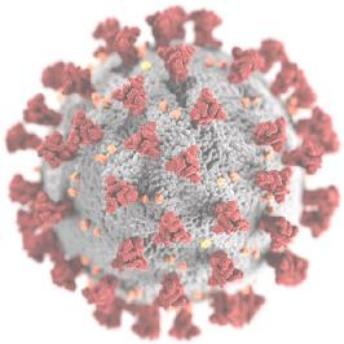
Our next Management Committee Meeting co-located with the 2nd Working Groups Meeting (WG2) and Early Carreer Investigators Workshop (MC3/WG2/ECI Workshop) will be held in Tuebingen, Germany on a date around late February-early March 2021 that will be announced considering the current covid-19 pandemic.

EuNet-INNOCHRON and the covid-19 pandemic

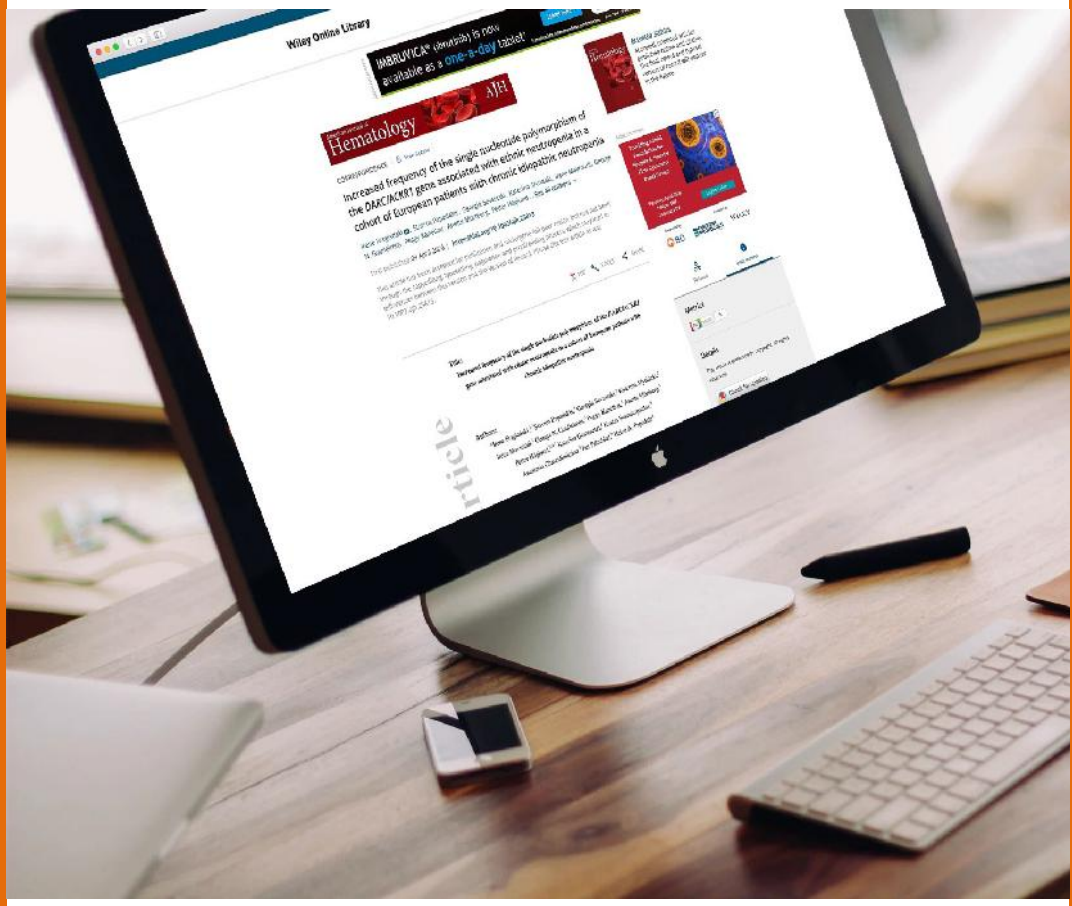
There is currently limited experience on CNP patients and covid-19 infection. The EuNet-INNOCHRON participants will collect data from patients with different types of CNP who have been infected so far from covid-19. A questionnaire for children and adult patients is being prepared in collaboration with the EHA-SWG on Granulocytes and Constitutional Marrow Failure Syndromes. The questionnaire will be distributed among EuNet-INNOCHRON participants.

A forum has also been prepared in our website to facilitate continuous discussions and sharing of experience among the EuNet-INNOCHRON participants.

We are expecting our Young EuNet-INNOCHRON members to be very active in these online discussions!



Our website and social media provide updates and general information regarding the EuNet-INNOCHRON aims, activities, meetings, publications, future plans and information about existing and new members.



Publications

The first paper that acknowledges COST CA18233 EuNet-INNOCHRON Action has been published in American Journal of Hematology with the title "Increased frequency of the single nucleotide polymorphism of the DARC/ACKR1 gene associated with ethnic neutropenia in a cohort of European patients with chronic idiopathic neutropenia." Am J Hematol. 2020 Apr 3.
URL: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.25813

It is a collaboration between the Greek and Swedish Groups showing increased frequency of the DARC/ACKR1 polymorphism associated with ethnic neutropenia - known to be rare/absent in Europe - among patients with chronic idiopathic neutropenia in Greece.

In this context, we have posted on our website (https://eunet-innochron.eu/images/Research_Protocol_on_ENP_associated_SNP.pdf) the protocols used and further scientific questions to be further investigated and we encourage you to estimate the frequency of the SNP among patients with unexplained neutropenia. Your thoughts and results are welcome!

who is who

Prof Helen Papadaki
Action's Chair

"We believe that this wide network of researchers with special interest on chronic neutropenias will give unique opportunities for interactions among experts and younginvestigators from different parts of the world and will provide answers in many so far unanswered issues. Such a huge concerted action focused on neutropenias has never been put in place before and we are very enthusiastic about the new collaborations and initiatives."

Dr Carlo DUFOUR
Action's Vice Chair

"This is a unique opportunity to share and to improve knowledge on neutropenia throughout the Continent. We expect that this action will give imnpulse to research in the field and would definitely improve the care of the patients."

Prof Antonio ALMEIDA
Science Communication Manager

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Prof Jan PALMBLAD
Chair of the Editorial Committee

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