Newsletter

European Network for Innovative Diagnosis and Treatment of Chronic Neutropenias

June 2021
What is EuNet-INNOCHRON

EuNet-INNOCHRON is a 4-year 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 33 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

Five groups of clinicians and scientists 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
  Chairs: Prof. Alan Warren, Prof. Karl Wette

- **WORKING GROUP (WG)-2:** Acquired Neutropenias
  Chairs: Prof. Petter Hoglund, Prof. Juergen Bux

- **WORKING GROUP (WG)-3:** Mechanisms of Leukaemic Evolution
  Chairs: Prof. Ivo Touw, Prof. Christina Mecucci

- **WORKING GROUP (WG)-4:** Investigation of Targets for Novel Therapies
  Chairs: Prof. Julia Skokova, Prof. Joanna Cichy

- **WORKING GROUP (WG)-5:** CNP Patient Registries and Biobanking
  Chairs: Dr. Jean Donadieu, Dr. Cornelia Zeidler, Dr. Kostas Stamatopoulos

- Action’s Chair: Prof. Helen Papadaki, University of Crete, Greece
  Vice-chair: Dr. Carlo Dufour, G.Gaslini Children’s Hospital, Italy

31 COST Members
01 COST Int.
  Partner (UoW, USA)
01 NNC (Armenia)
01 Companies
  (X4 Pharmaceuticals; EXUS, SB Bioanalytica)
01 Participating Organization (EHA)

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
3rd Management Committee (MC) meeting
(02 March 2021)

During the MC meeting, the extension of Grant Period 2 (GP2) for another 6 months, ending on 31st October 2021 was announced. Also, the Inclusiveness and Excellence COST policies were discussed with special focus on the gender balance and the involvement of more Young Investigators. In this context, the establishment of a Gender Equality Task Force was planned and an Early Career Investigators Workshop was scheduled for this year as an in-person meeting, to help young investigators in capacity building.

2nd Working Groups (WG) meeting
(03 March 2021)

Although our 2nd WG took place virtually again, it was a big success with more than 100 participants attending. Interesting presentations showcased the work that has been in progress within each WG and an update was made from the WG leaders/Vice-leaders, setting the grounds for the fulfillment of the Action’s Scientific Objectives.

2nd Working Groups (WG) meeting
(03 March 2021)

WG 1: Congenital Neutropenias

• "Role of BAALC in leukemogenesis in SCN patients."
  Prof. Julia Skokowa
• "Somatic genetic rescue of a germline ribosome assembly defect."
  Prof. Alan Warren

WG 2: Acquired Neutropenias

• "The clonal haemopoiesis and clonal evolution in CIN."
  Dr. Grigorios Tsaknakis - Prof. Helen Papadaki
• "The blood protein hCAP-18 in neutropenia: an 18-month experience of a new ELISA for clinical use."
  Prof. Petter Haglund

WG 3: Mechanisms of Leukaemic Evolution

• "Truncated CSF3 receptors induce pro-inflammatory responses in SCN."
  Dr. Patricia Olofsen
• "A new genetic subtype of SCN with an autosomal dominant inheritance."
  Prof. Ivo Touw
• "PML-controlled responses in SCN with ELANE-misfolding mutations."
  Dr. Patricia Olofsen

WG 4: Investigation of targets for novel therapies

• "Generation of a cellular model for investigating roles of elastase inhibitors in neutropenia."
  Prof. Joanna Cichy
• "Nicotinamide (vitamin B3) treatment improves response to G-CSF in CN and CyN patients."
  Prof. Julia Skokowa
• "SGTL2 inhibitor in Glycogen storage disease Ib and G6PC3."
  Dr. Jean Donadieu

WG 5: CNP Patients Registries and Biobanking

• "Classification of CNP."
  Dr. Jean Donadieu
• "Registry for CNP in Europe."
  Dr. Cornelio Zeidler
• "Biobanking."
  Dr. Kostas Stamatopoulos
Join us in the EuNet-INNOCHRON COVID-19 Registry

Questionnaire on the frequency and severity of SARS-CoV-2 infected patients with Chronic Neutropenia (CNP)

The EuNet-INNOCHRON in collaboration with EHA-SWG on Granulocytes and Constitutional Marrow Failure Syndromes has conducted an online survey on COVID-19 infection in patients with CNP to understand the impact of this pandemic on the entities. A user-friendly on-line platform has been developed (https://eunet-innochron.eu/patient-registry/) and the EuNet-INNOCHRON participants have the opportunity to register adult and paediatric CNP patients infected by COVID-19.

The platform is still open for new registrations, it is very easily accessible and its compilation takes just few minutes.

Data from the first seven registered patients (6 females, 1 male) have been collected so far. Five patients are under 18 years old and two are adults. None of them have comorbidities and only one had a history of previous recurrent bacterial infections. Positive PCR for COVID-19 was confirmed for six patients and one was diagnosed due to a positive antibody testing. Three had fever, cough was not mentioned by any of the patients and four of them had upper respiratory symptoms with rhinorrhoea. Sore throat, musculoskeletal pains and fatigue was mentioned by one of the adult patients. None of the patients had dyspnoea or gastrointestinal symptoms. X-ray was performed for four of the patients and it was unremarkable. None of the patients needed admission into hospital for specific treatment and none of the patients had symptoms for more than five days.

In conclusion, these preliminary data show that neutropenic patients with no comorbidities, don’t get severe COVID-19 disease.

The Stockholm, Sweden experience is rather similar to the above described cases. 154 CNP patients have been followed for 10 months (March 1 to December 31, 2020) for COVID-19 and seventeen out of them contracted COVID-19 (i.e. 11 %). None of the patients needed hospitalization and there were no fatalities. Compared to the Stockholm County population, this incidence rate was significantly higher (P=0.02) than the incidence in this general population, being 5.7%. Ethnic Neutropenia (ENP) and Familial Neutropenia (FNP) cases showed the highest rate of COVID-19. However, these data need to be strengthened by inclusion of more patients, if possible, from populations with higher (and lower) incidences of COVID-19.

Those who have similar materials are welcome to contact Jan Palmblad at Jan.Palmblad@ki.se

By Dr. Michail Spanoudakis, Warrington and Halton Hospitals NHS Foundation Trust, UK
Dr. Daniela Guardo, G.Gaslini Children’s Hospital, Italy
Prof. Jan Palmblad
Karolinska Institutet, Sweden

Why is Patient Data collected?
The EuNet-INNOCHRON COVID-19 Registry collects data for the better understanding of the frequency and severity of SARS-COV-2 infection in patients with CNP in order to improve patients’ care and treatment. The importance for “coupling information from registries” in order to obtain “new knowledge of great value” has been explicitly recognized in the European legislation (consideration 157 GDPR).

It is the responsibility of the participants to get the permission from their Institutions and we confirm that patients data are protected according to the GDPR. In view of a potential publication, we suggest that all participants who contribute will be included in the Authors.
The Part I of the Training School “Introduction to Autoimmune Neutropenias (AIN) and related clinical and lab problems” took place virtually in November 2, 2020. The Organisers Carlo Dufour, Francesca Fioredda and Helen Papadaki decided to have the Part II as a live event with hands-on experience in Genova, later in the year depending on the covid-19 pandemic.

The meeting covered all aspects of AIN in neonates, children and adults. A special session was focused on the techniques (immunofluorescence by microscope and flow cytometry, granulocyte agglutination, MAIGA) currently used for the identification of anti-neutrophil antibodies and novel technologies were also presented.

The SNP -46T>C rs2814778 in the DARK/ACKR1 is associated with the Duffy null phenotype of erythroid cells and with low neutrophil counts. The entity has been mostly described in individuals of African and Near and Middle East ancestry and is known as benign ethnic neutropenia but recently the term typical neutrophil count with Fy(a-b-) status was introduced (Merz LE & Achebe M, Blood 2021).

Recent data following a collaboration between the Swedish and the Greek partners of EuNet-INNOCHRON have shown that the DARC/ACKR1 SNP -46T>C rs2814778 and the resulting Fy(a-b-) status occur at a substantial frequency among European individuals with unexplained chronic neutropenia (CNP) (Fragiadaki I et al, AJH 2020). We have thus recommended that the genetic test for the rs2814778 SNP and/or the Duffy antigen red blood cell phenotype could be included in the diagnostic algorithm of European patients with unexplained CNP.

Join us in this open collaborative project to estimate the frequency of the DARK/ACKR1 SNP (rs2814778) among CNP patients in your country and share interesting cases within the consortium. Also, feel free to explore further within this entity, starting from open research questions we have highlighted https://eunet-innochron.eu/images/Research_Protocol_on_ENP-associated_SNPs.pdf .

We are looking forward to collaborating with you in this topic.

By Helen Papadaki, University of Crete, Greece
Chair of the EuNet-INNOCHRON
Training Course
Severe Congenital Neutropenia - A Clinical Approach

The EuNet-INNOCHRON held a virtual course on severe congenital neutropenia on March 24th-25th, 2021. The course covered various practical topics including the work-up of patients with neutropenia, the genetic approach to the diagnosis of the disease, the treatment and follow-up recommendations for these patients, insights into congenital neutropenia in adult, a summary of the Severe Chronic Neutropenia International Registry (SCNIR) data and an introduction to the molecular basis of the disease. In addition, an expert panel was held to discuss complex issues regarding treatment of patients with congenital neutropenia. Overall, five cases were presented by their treating physicians and discussed thoroughly.

The interest in the course exceeded the expectations, and over sixty physicians and researchers from ten countries participated. The recording of the talks is available online for those who were not able to join. A hands-on following training course is planned as well.

Organized by Dr Hannah Tamary and Dr Orna Steinberg-Shemer, Schneider Children’s Medical Center of Israel, Hematology/Oncology Division, Petach Tikva, Israel

Primary autoimmune neutropenia (AIN) is the most clinically relevant form of acquired neutropenia in children, typically characterized by onset in early infancy, mild to moderate phenotype and resolution within 3 years from diagnosis.

Join us in
THE STUDY ON CHILDHOOD AUTOIMMUNE NEUTROPENIA PRECEDING ACUTE LYMPHOBLASTIC LEUKEMIA

The aim of the study is to register children with primary AIN preceding acute lymphoblastic leukemia (ALL) and to identify risk factors for leukemic transformation. An online questionnaire was created, including demographic data, infections/vaccination/drugs prior to AIN, severity (with absolute neutrophil count) and duration of AIN, antineutrophil antibodies, infections/drugs during AIN, concomitant signs/symptoms/laboratory findings, period between onset of AIN and ALL, and ALL characteristics and outcome.

Providers from 12 institutions from 10 countries responded. Five cases were identified (4 boys and 1 girl), among whom 2 patients had positive antineutrophil antibodies. All patients had late onset of AIN (median age 6.2 years). Three patients had isolated neutropenia and two concomitant anemia. Three patients had symptoms (recurrent infections, fever, arthralgia). The period between onset of AIN and ALL ranged from 2 to 9 months. All children who developed ALL are in remission.

Future efforts should concentrate on the possible link of AIN and leukemic evolution.

By Prof. Jelena Roganovic
Clinical Hospital Centre Rijeka, Croatia
Guidelines on Diagnosis and Management of neutropenia is a joint venture of our COST Action EuNet-INNOCHRON together with the EHA GL Committee Guidelines which has been set up since the beginning of 2021. The great challenge is to put together the knowhow of a group of experts coming from different countries, backgrounds and fields of interest from the biological aspect to the clinical practice. Moreover, this is the first attempt to coordinate in one document the approach of diagnosis and treatment both in children and adults.

A number of key questions have been produced on specific topics and subgroups, created by mixing different expertise, are working on reviewing literature through a selection of papers with the highest quality of evidence. The Cochrane System will support the project regarding matters of treatment. After having summarized up the evidence and graded them according to the “Grade System rules”, a number of statements, which are the answers to the key questions, will be ready round mid-June 2021 and be further voted by the assembly during dedicated meetings providing the strength of consensus of the whole assembly.

The National Neutropenia Network provide newsletters with education, events, updates, and other information that is relevant to our constituents. We also provide information through our social media platforms and our website. If you need support for neutropenia, please visit our website to find stories about others with this condition and feel free to reach out to us for support. www.neutropenianet.org

By Mrs Kate Bottiger
Executive Director, National Neutropenia Network
Welcome to the family!

Get to know the EuNET-INNOCHRON Committee and let’s collaborate to make the difference! Exchange views with peers and senior researchers within EuNET-INNOCHRON. Find new collaborations, discuss and solve

Your ideas are welcome!

Young Investigators in EuNet-INNOCHRON are all researchers less than forty years old and Early Career Investigators (ECI) those who are within a time span of up to 8 years from the date they obtained their PhD/doctorate. EuNet-INNOCHRON wishes to promote training and education of the younger researchers and to give opportunities to ECIs to expand their ideas through a number of collaborative activities including exchanges between participating Institutions. The Action aims to maximally use the Networking Tools that COST offers such as Conference grants, Training Schools and Short Term Scientific Missions. We enthusiastically promote the idea to generate within EuNet-INNOCHRON the next generation of researchers and physician scientists with expertise in Neutropenia. Welcome Aboard!

Maksim Klimiankou, PhD
Chair of the Young EuNet-INNOCHRON
University Hospital Tübingen, Tübingen, Germany

“Study of rare disease conditions requires joint efforts of scientists from different countries and combination of clinical and bench research. Young EuNET-INNOCHRON initiative is a excellent ground for meeting of clinical and basic researchers and therefore greatly facilitates conduction of international projects on severe chronic neutropenia.”

Dr Valentino Bezzerri
Young EuNet-INNOCHRON Committee Member
Cystic Fibrosis Center, Azienda Ospedaliero Universitaria Ospedali Riuniti, Italy

“The Young EuNet-INNOCHRON initiative represents an excellent opportunity for the career development of young investigators, giving the chance to share personal experience with other international members and starting possible new collaborations. During the last year, several specific initiatives conducted by young scientists have taken place within the Young EuNet-INNOCHRON, including the Online Discussion Club and the facilities for the Exome Sequencing and the Screening of acquired AML/MDS associated genetic lesions in patients with severe neutropenia.”
The **YOUNG EuNet-INNOCHRON Group's Initiatives**

**Online Discussion Club (ODC)**

The ODC initiative has been organized by Dr. Valentino Bezzerri. It is a platform providing the possibility to young scientists to exchange opinions on their projects with other Young EuNet-INNOCHRON members, receive feedback from experts in the field, and find new contacts and collaborations.

The first ODC was conducted online on 6th May 2021 with a presentation entitled “Lab-on-chip for studying Shwachman-Diamond Syndrome” by Nora Selicato from the Cystic Fibrosis Center of Verona, Italy. It attracted more than 30 EuNet-INNOCHRON members. Special thanks to guest Moderator Dr. Alessandro Polini, Principal Investigator, CNR NANTOC - Istituto di Nanotecnologia del CNR, Lecce, Italy.

The 2nd ODC is scheduled for June 24, 2021. The presentation is focused on “MDSCs in CIN” by Dr. Nikoleta Bizymi, Haemopoiesis Research Laboratory, Heraklion, Crete, Greece and guest Moderator Prof. Panos Verginis, University of Crete, Greece.

The ODC is planned to be held every month by zoom, so stay tuned for more details.

**Exome sequencing of patients and families with genetically unclassified neutropenia**

The initiative has been proposed by Dr. Maksim Klimiankou, chair of the Young EuNet-INNOCHRON. The project offers collaboration for identification of novel gene mutations in patients with genetically unclassified neutropenia. Free of cost molecular genetic service for exome sequencing of patients and families with genetically unclassified neutropenia is provided. For candidate gene mutations, iPSC-based model of myeloid differentiation can be established and shared with project partners.

Thanks to collaboration with the Severe Congenital Neutropenia International Registry (SCNIR), more than 173 samples from patients with genetically unclassified neutropenia and their relatives have been collected.

**Sequencing and analysis of acquired AML/MDS associated genetic lesions in chronic neutropenia patients**

The project has also been initiated by Dr. Maksim Klimiankou and Prof. J. Skokowa, Division of Translational Oncology, University Hospital Tübingen, Germany. This initiative provides free of charge ultra-sensitive deep sequencing and analysis of acquired AML/MDS associated genetic lesions in CNP patients with high propensity to develop hematopoietic malignancy. The aim of this project is to characterize somatic mutation landscape which precedes leukemogenic transformation in CNP and develop pipeline for early detection of pre-leukemia clones in samples of CNP patients with high sensitivity and accuracy. The resulting guideline will facilitate conduction of screening program for early recognition of AML/MDS in CNP patients.

For more info you can contact

Dr. Valentino Bezzerri at valentino.bezzerri@ospedaliriuniti.marche.it
and Dr. Maksim Klimiankou at Maksim.Klimiankou@med.uni-tuebingen.de
I saw my first patient with cyclic neutropenia at the US National Institute of Health (NIH) in 1968. This young boy and his illness were fascinating, and my interests grew through a close relationship with his family. His father was the poet laureate for the US Library of Congress and wrote poetry about his son. My NIH studies broaden to investigations of congenital and acquired neutropenias and the regulation of hematopoiesis, under the mentorship of Dr Sheldon Wolff. I also studied cyclic neutropenia collies, and we investigated colony-stimulating factors in these interesting dogs. I love dogs and my children thought that I was becoming a veterinarian. After my NIH years, I continued to study neutropenia. I remember fondly going to Amgen when it was just a very small startup company to see if we might conduct a trial of G-CSF to treat cyclic neutropenia. It worked! Amgen gave me $500 toward the cost of a trip to Australia to report the results at a meeting to honor Ray Bradley, co-author with Don Metcalf on one of the original CSF reports. The Severe Chronic Neutropenia International Registry, which followed the original clinical trials, is the very best part of my career. I have enjoyed so much working with Karl Welte and my Registry colleagues. Through the Registry, we have helped so many patients with diagnosis and treatment of severe neutropenia. Our basic research activities have steadily advanced understanding and promise yet better therapies.

I am so grateful to all of the participants in the formation of the EuNet-INNOCHRON, especially Helen Papadaki. The outreach and influence of EuNet-INNOCHRON across Europe and beyond to every corner of the world will be enormous. I appreciate that so many leading physicians and researchers are participating and working together to advance our understanding of neutropenia. I look forward to when we can all be together again. I hope we will be very soon.

I am proud that the treatment with G-CSF, which we started 1987 in New York and 1988 in Europe saved the life of many children suffering from congenital neutropenias (CN). This was also the starting point of a previously unseen and incomparably successful cooperation of clinicians, scientists and Registries around the world, which led to a better understanding of this disorder of hematopoiesis and to the identification of causative gene mutations in the majority of CN patients. To deepen further the understanding of the pathomechanisms and treatment avenues at CN, EuNet-INNOCHRON was founded in 2019, an excellent network of dedicated clinicians and researchers from all over Europe who further will promote the understanding of the pathomechanisms of CN, the mechanisms of leukemia development, and the development of common diagnostic algorithms and treatment guidelines. I am very enthusiastic about this enterprise and happy to be part of it.

According to COST Inclusiveness and Excellence policy but also as part of its own commitment, EuNet-INNOCHRON promotes the gender equality within its multidisciplinary teams of scientists and clinicians, from the time of application and onwards, all over the time of the Action. Currently, 37 female Management Committee members/substitutes out of 70 participate in our Action, with a female and a male, Chair and vice-Chair, respectively. There are also 4 women among of 11 Working Group Leaders. I recently had the honor of leading the Gender Equality Task Force within the Action. We will collect and monitor sex/gender data and continue to support a gender equality perspective in all areas of our Action, from training to teaching and decision-making, follow-up specific European proposals/platforms/programmes of women scientists, and conduct activities and disseminate messages aimed at promoting gender equality at national and international levels.
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


Members Publications


The EHA2021 Virtual Congress will be a key moment to consolidate the knowledge and experience gained worldwide and bring together hematologists in a virtual environment.

**Discover EuNet-INNOCHRON COST Action during #EHA2021 Virtual Conference**

EuNet-INNOCHRON participates at the European Haematology Association Virtual Conference EHA2021 taking place 9th - 17th June, 2021.

During the dedicated session ‘EU Projects in Hematology’ on Wednesday 9th June, from 10.00-12.00 participants will have the opportunity to find out more about EuNet-INNOCHRON Action, its objectives, activities and participation opportunities for hematologists across the EU.

EuNet-INNOCHRON also participates as an exhibitor with its own virtual profile accessible through the congress platform https://ehaweb.org/congress/eha-congress-2021/eha2021-virtual-congress-platform/

The congress programme is available online https://ehaweb.org/congress/eha-congress-2021/program/program-at-a-glance/

To register https://ehaweb.org/congress/eha-congress-2021/registration/individual-registration/

EuNet-INNOCHRON has developed a close collaboration with EHA and appreciates the opportunity to communicate its work in the field of Chronic Neutropenias through the EHA2021 congress and platform.

We are excited to announce the 1st Call for Application for our first in-person meeting since the outbreak of the pandemic!

The 1st Early Career Investigators Meeting “Basic and Clinical Research on Chronic Neutropenias: A Bench-to-Bedside approach” will take place in Genova, Italy, 2-3 September 2021, with Dr Carlo Dufour and Dr Francesca Fioredda as our Hosts/Local Organizers.

Don't miss the opportunity to apply and attend the meeting with full reimbursement of the expenses by EuNet-INNOCHRON. You are also highly encouraged to submit an abstract of your recent research on Neutropenia.

Because a limited number of participants can attend, please see details on the application process. More information: https://eunet-innochron.eu/1st-early-career-investigators-workshop