

Funding Programme *FET-Open Challenging Current Thinking*
01.01.2019 - 31.12.2024

FAU - UKER - SWANSEA - LNMU - CNIC - REDOXIS AB/PRONOXIS - GRCC



Germany - United Kingdom - Ukraine - Spain - Sweden - France **Jan 1 – Dec 31, 2023**

NeutroCure Newsletter 2023

Welcome to our fourth NeutroCure Newsletter.

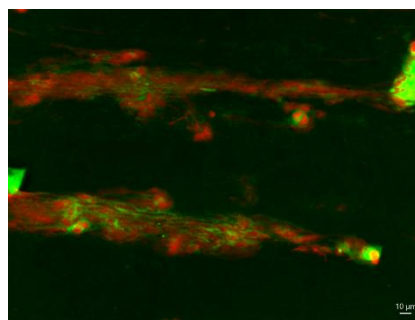
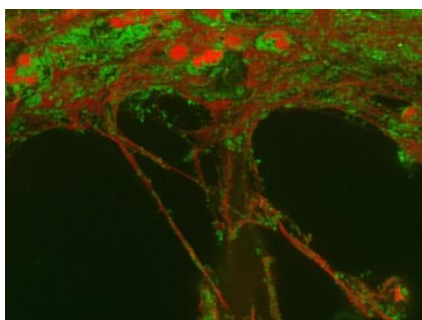
SUMMARY

Our goal is to develop novel drugs based on amplification of reactive oxygen species (ROS) for enabling an effective immune system. An over-active immune system may lead to chronic inflammation, pain and loss of function. Our hypothesis is that resolution of inflammation is dependent on the timely production of ROS by the first inflammatory cell on the scene, the neutrophil, to maximise clearance of pro-inflammatory debris.

We have adopted two distinctive ROS-amplifier compound classes which act via different mechanisms. One class is targeting the fMLP receptor and the second class adopts a radical chemistry amplification of aminoferrocene. The details of specific modifications to the core structures will form the basis of future patent filings to protect the intellectual property developed within the project and to provide a commercially protected portfolio. During 2023, we have been focussed on developing the short-list of lead compounds.

Furthermore, the scale-up programme has been highly successful, after optimising syntheses to yield 500mg/month, and compounds are being made available to the consortium for in vivo studies.

We continue to develop methods for visualising neutrophils. The collaborations within the consortium have enabled the co-localisation for the first time, between drug candidates and neutrophils NETs being formed within tumours. Figures 1-3 from Rostyslav Bilyy's lab below illustrate the release of NETs.



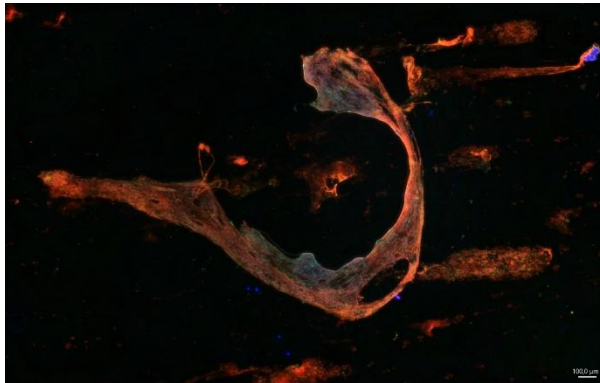
NETs isolated from human eye were stained with PI (red), and neutrophil binding probe (green, patent pending) - labeled with SQ215 (<https://doi.org/10.1021/acsabm.3c00997>). Imaging Keyence BX-Z 800 at 100x 1.45 NA with optical sectioning.

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NETs isolated from human eye were stained with PI (red), Ly6C-FITC (blue), and Neutrophil binding probe (green, patent pending) - labeled with SQ215 (<https://doi.org/10.1021/acsabm.3c00997>). Imaging Keyence BX-Z 800 at 40x 0.9 NA.

NEWS FROM RESEARCH TEAMS

Congratulations to Rostyslav Billy who was appointed to the Institute of Cellular Biology and Pathology "Nicolae Simionescu" in Bucharest Romania in October 2023.

Andres Hidalgo was invited a plenary speaker to the Cell Symposia in China during June 2023 among many other symposia, listed below.

Cell
Symposia



Myeloid cells: From development to function and dysfunction

in partnership with Shanghai Institute of Immunology
Shanghai Jiao Tong University School of Medicine
June 28–30, 2023 — Shanghai, China

[HOME](#) [PROGRAM](#) [LOCATION](#) [EXHIBITION & SPONSORSHIP](#) [DEADLINES](#) [HELP & FAQs](#) [CONTACT](#)

Speaker

Andrés Hidalgo, Yale, USA

Data noise and immune behaviours. Gordon Research Conference on Directed Cell Migration, Galveston (US). January 2023. Invited speaker.

Understanding neutrophils. 25th anniversary, ZMBE Munster (Germany). May 2023. Keynote speaker.

Multidimensional inflammation within vessels. Gordon Research Conference on Atherosclerosis. Castelldefels, Spain. June 2023. Invited speaker.

Neutrophils in cancer. Cancer Research UK Marshall Symposium. West Sussex, UK, July 2023. (Zoom talk).

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He also gave a presentation at the Vascular Biology & Therapeutics Program & Cardiovascular Research Center 2023 Retreat on November 16, 2023.

Malin Hultquist and Redoxis have been actively engaging in conference attendance, including BIO international (Boston, USA) 05-10.06.23, BioEurope2023 and NLS in November 2023, providing many opportunities to engage with industry leaders, share the latest news.



Martin Herrmann (UKER) presented NeutoCure findings at KCH-Retreat Mannheim, 30.06.2023.

Markus Hoffmann (UKSH) was invited to present at the following conferences:

20th International Fasting Congress of the ÄGHE. Berlin, Germany, 24./25.6.2023.

15th International Conference on Complement Therapeutics. Kolymvari, Greece, 27.-30.5.2023.

3rd Resolution Days. Besancon, France, 26.-29.4.2023.

European Phagocyte Workshop. Budapest, Hungary, 29.3.-1.4.2023.

International Symposium in Honour of Prof. Günter Steiner. Vienna, Austria, 22.2.2023.

Meeting of The Arbeitskreis Dermatologische Forschung. Innsbruck, Austria, 23.2.-26.2.2023.

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Rostyslav Bilyy (LNMU) presented at

18th RECOOP Bridges in Life Sciences Annual Conference, Bucharest, Hungary,
19.04.2023 – 22.04.2023.

7th International Conference on Cancer Immunotherapy & Immunomonitoring (CITIM),
Vilnius, Lithuania, 23.04.2023 – 28.04. 2023.

Andriy Mokhir (FAU) presented at

Redox Biology Congress 2023, Vienna, Austria, 06-09.06.23.

We are delighted to announce that Khushboo Borah-Slater (second from left), an alumna of the NeutroCure programme, was awarded a prize fellowship for her research from the L'Oreal-UNESCO Women in Science programme. She attended the UK Prime Minister's residence to receive her award.



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PUBLIC ENGAGEMENT

For public engagement on NeutroCure goals, the following events were organized and delivered by consortium members:

1. A. Mokhir: A lecture for students of Department of Chemistry and Pharmacy advertising NeutroCure research topics (recruiting the students for BSc and MSc theses projects): June-July 2023.
2. R. Bilyy, a lecture “Potential of NeutroCure to treat neutrophil-related disorders”, at Western Ukrainian Specialized Children’s Medical Centre, specialized on treatment of ROS-deficient CGD-related conditions in patients of Western Ukraine, Lviv, Ukraine, Feb 16 2023.
3. R. Bilyy, a lecture “NEUTROCURE: ROS-on-demand production for modulation of neutrophil functions and antitumor activity”, at plenary session of 7th International Conference on Cancer Immunotherapy & Immunomonitoring (CITIM) – 23.04.2023 – 28.04. 2023, Vilnius, Lithuania.

CONSORTIUM MEETINGS

In 2023, we increased the frequency of meetings to enable rapid dissemination of new findings between group members.

We held formal consortium meetings on zoom on the last Thursday in every month to share knowledge between partners and increase opportunities for early career researchers to present their findings.

The typical agenda has been as follows, and is scheduled to enable participants to join from across the world according to their schedules:

Agenda

16:00 - 17:30 (German time): Short progress reports of research groups (10 min + discussion)

17:30 - 18:00: Discussion of organizational issues.

PUBLICATIONS 2023

Cyanine-and Rhodamine-Derived Alkynes for the Selective Targeting of Cancerous Mitochondria through Radical Thiol-Yne Coupling in Live Cells

J Köckenberger, I Klemm, C Sauer, A Arkhypov, V Reshetnikov, A Mokhir, et al
Chemistry–A European Journal, e202301340

Neutrophil Extracellular Traps Drive Dacryolithiasis

L Zlatař, T Timm, G Lochnit, R Bilyy, T Bäuerle, M Munoz-Becerra, et al
Cells 12 (14), 1857

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Neutrophil Aggregates and Elastin Degradation Compromise Lung Architecture in Fatal COVID-19
T Narasaraju, I Neeli, S Criswell, A Krishnappa, W Meng, V Silva, G Bila, et al

Pre-conditioning of gingival epithelial cells with sub-apoptotic concentrations of curcumin prevents pro-inflammatory cytokine release
MM Grant, AE Scott, JB Matthews, HR Griffiths, ILC Chapple
Journal of Periodontal Research 58 (3), 634-645

FPR2 shapes an immune-excluded pancreatic tumor microenvironment and drives T-cell exhaustion in a sex-dependent manner
F He, AHM Tay, A Calandigary, E Malki, S Suzuki, T Liu, Q Wang, et al
Cancer Research 83 (10), 1628-1645

Adipose tissue macrophages as potential targets for obesity and metabolic diseases
X Li, Y Ren, K Chang, W Wu, HR Griffiths, S Lu, D Gao
Frontiers in Immunology 14, 1153915

Moonlighting chromatin: when DNA escapes nuclear control
J Singh, M Boettcher, M Dölling, A Heuer, B Hohberger, M Leppkes, et al
Cell Death & Differentiation 30 (4), 861-875

TNF- α -Mediated Endothelial Cell Apoptosis Is Rescued by Hydrogen Sulfide
L Diaz Sanchez, L Sanchez-Aranguren, K Wang, CM Spickett, HR Griffiths, et al
Antioxidants 12 (3), 734

Breaking the gingival barrier in periodontitis
L Vitkov, J Singh, C Schauer, B Minnich, J Krunic, H Oberthaler, et al
International Journal of Molecular Sciences 24 (5), 4544

Transcriptional Insights of Oxidative Stress and Extracellular Traps in Lung Tissues of Fatal COVID-19 Cases
A Hosseini, D Stojkov, T Fettelet, R Bilyy, S Yousefi, HU Simon
International journal of molecular sciences 24 (3), 2646

Blood transcriptome responses in patients correlate with severity of COVID-19 disease
Y Wang, K Schughart, TM Pelaia, T Chew, K Kim, T Karvunidis, et al
Frontiers in immunology 13, 1043219

Transient receptor potential melastatin 2 regulates neutrophil extracellular traps formation and delays resolution of neutrophil-driven sterile inflammation.
Cao, Xue; Li, Yanhong; Luo, Yubin; Chu, Tianshu; Yang, Hang; Wen, Ji; Liu, Yi; Zhao, Yi; Herrmann, Martin;
Journal of Inflammation 20, 1, 1-9 2023.

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Oral neutrophils-the good, the bad, and the ugly.

Vitkov, Ljubomir; Herrmann, Martin; Knopf, Jasmin;
Frontiers in Immunology 14, 1225210 2023.

Suppression of neutrophils by sodium exacerbates oxidative stress and arthritis. Zlatar, Leticija; Mahajan, Aparna; Muñoz-Becerra, Marco; Weidner, Daniela; Bila, Galyna; Bilyy, Rostyslav; Titze, Jens; Hoffmann, Markus H; Schett, Georg; Herrmann, Martin;
Frontiers in Immunology 14, 2023.

Neutrophil Extracellular Traps Drive Dacryolithiasis.

Zlatar, Leticija; Timm, Thomas; Lochnit, Günter; Bilyy, Rostyslav; Bäuerle, Tobias; Munoz-Becerra, Marco; Schett, Georg; Knopf, Jasmin; Heichel, Jens; Ali, Mohammad Javed;
Cells 12, 14, 1857 2023.

3D-Shaped Binders of Unfolded Proteins Inducing Cancer Cell-Specific Endoplasmic Reticulum Stress In Vitro and In Vivo.

Klemt, I.; Varzatskii, O.; Selin, R.; Vakarov, S.; Kovalska, V.; Bila, G.; Bilyy, R.; Voloshin, Y.; Cuartero, I.C.; Hidalgo, A.; ... , Mokhir, A.
Journal of the American Chemical Society 2023, 145, 22252–22264, doi:10.1021/jacs.3c08827.

Stunning of neutrophils accounts for the anti-inflammatory effect of clodronate liposomes.

Culemann S, Knab K, Euler M, Wegner A, Garibagaoglu H, Ackermann J, Fischer K, Kienhoefer D, Crainiciuc G, Hahn J, Grüneboom A, Nimmerjahn F, Uderhardt S, Hidalgo A, Schett G, Hoffmann MH, Krönke G.
J Exp Med 2023, 220(6):e20220525.

Reset of Inflammatory Priming of Joint Tissue and Reduction of the Severity of Arthritis Flares by Bromodomain Inhibition. Friščić J, Reinwald C, Böttcher M, Houtman M, Walker KI, Kirchner P, Wirth B, Weidner D, Krüger R, Trajkovic V, Ekici AB, Klein K, Mougiakakos D, Ospelt C, Schett G, Hoffmann MH.

Arthritis & Rheumatology 2023. 75(4): 517-32. doi: 10.1002/art.42378.

Neutrophils as drivers of vascular injury in sickle cell disease.

Torres LS and Hidalgo A.
Immunological Reviews 314(1): 302-312, 2023.

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TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease.

Zekavat SM, Matesanz N, Viana-Huete V, Jorshery SD, Zurriaga MA, Uddin M, Trinder M, Paruchuri K, Zorita V, Ferrer-Perez A, Amoros-Perez M, Kunderfranco P, Carriero R, Greco CM, Aroca-Crevillen A, Hidalgo A, Damrauer SM, Ballantyne CM, Niroula A, Gibson CJ, Pirruccello J, Griffin G, Ebert BL, Libby P, Fuster V, Zhao H, Ghassemi M, Natarajan P, Bick AG, Fuster JJ and Klarin D.

Nature Cardiovascular Research 2: 144-158, 2023.

Strategies of neutrophil diversification.

Palomino-Segura M, Sicilia J, Ballesteros I, Hidalgo A.

Nature Immunology 24(4): 575-584, 2023.

The circadian neutrophil, inside-out.

Ovadia S, Özcan A and Hidalgo A.

Journal of Leukocyte Biology 113(6): 555-566, 2023.

Airway allergy causes alveolar macrophage death, profound alveolar disorganization and surfactant dysfunction.

Feo-Lucas L, Godio C, Minguito de la Escalera M, Alvarez-Ladron N, Villarubia LH, Vega-Perez A, Gonzalez-Cintado L, Dominguez-Andres J, Garcia-Fojeda B, Montero-Fernandez C, Casals C, Autillo C, Perez-Gil J, Crainiciuc G, Hidalgo A, Lopez-Bravo M and Ardavin C. Frontiers Immunology 14: 1125984, 2023.

COMMUNICATIONS

Google Scholar is used to gather Neutrocure publications together in a searchable format. It identifies the teams of scholars who are citing our work. Our specific link is <https://scholar.google.com/citations?hl=en&user=16tXi1gAAAAJ>. The figure below shows the increase in recognition and citations of papers published by consortium members since 2018, and the exponential increase in those citations since the NeutroCure project was funded by the EU.

Safe ROS amplifiers as drugs

European Consortium

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scholar.google.com/citations?hl=en&user=16tXl1gAAAAJ

Scholar



NeuroCure

NeuroCure Consortium

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ROS NETs neutrophil extracellular traps

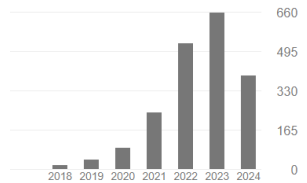
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TITLE	CITED BY	YEAR
Co-option of neutrophil fates by tissue environments I Ballesteros, A Rubio-Ponce, M Genua, E Lusito, I Kwok, ... Cell 183 (5), 1282-1297. e18	287	2020
Patients with COVID-19: in the dark-NETs of neutrophils M Ackermann, HJ Anders, R Bilyy, GL Bowlin, C Daniel, R De Lorenzo, ... Cell Death & Differentiation 28 (11), 3125-3139	244	2021
Programmed 'disarming' of the neutrophil proteome reduces the magnitude of inflammation JM Adrover, A Aroca-Crevillén, G Crainiciuc, F Ostos, Y Rojas-Vega, ... Nature immunology 21 (2), 135-144	223	2020
Neutrophil phenotypes and functions in cancer: A consensus statement DF Quail, B Amulic, M Aziz, BJ Barnes, E Eruslanov, ZG Fridlender, ... Journal of Experimental Medicine 219 (6), e20220011	154	2022
Lysosome-targeting amplifiers of reactive oxygen species as anticancer prodrugs S Daum, MSV Reshetnikov, M Sisa, T Dumych, MD Lootsik, R Bilyy, E Bila, ... Angewandte Chemie International Edition 56 (49), 15545-15549	138	2017
Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue M Rosina, V Ceci, R Turchi, L Chuan, N Borcherdig, F Sciarretta, ... Cell metabolism 34 (4), 533-548. e12	109	2022

Cited by

	All	Since 2019
Citations	1982	1964
h-index	19	19
i10-index	27	27



Co-authors

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