Genetic and functional aspects of DNA oxidative damage repair and their potential use in the prognosis and therapy of patients with multiple sclerosis

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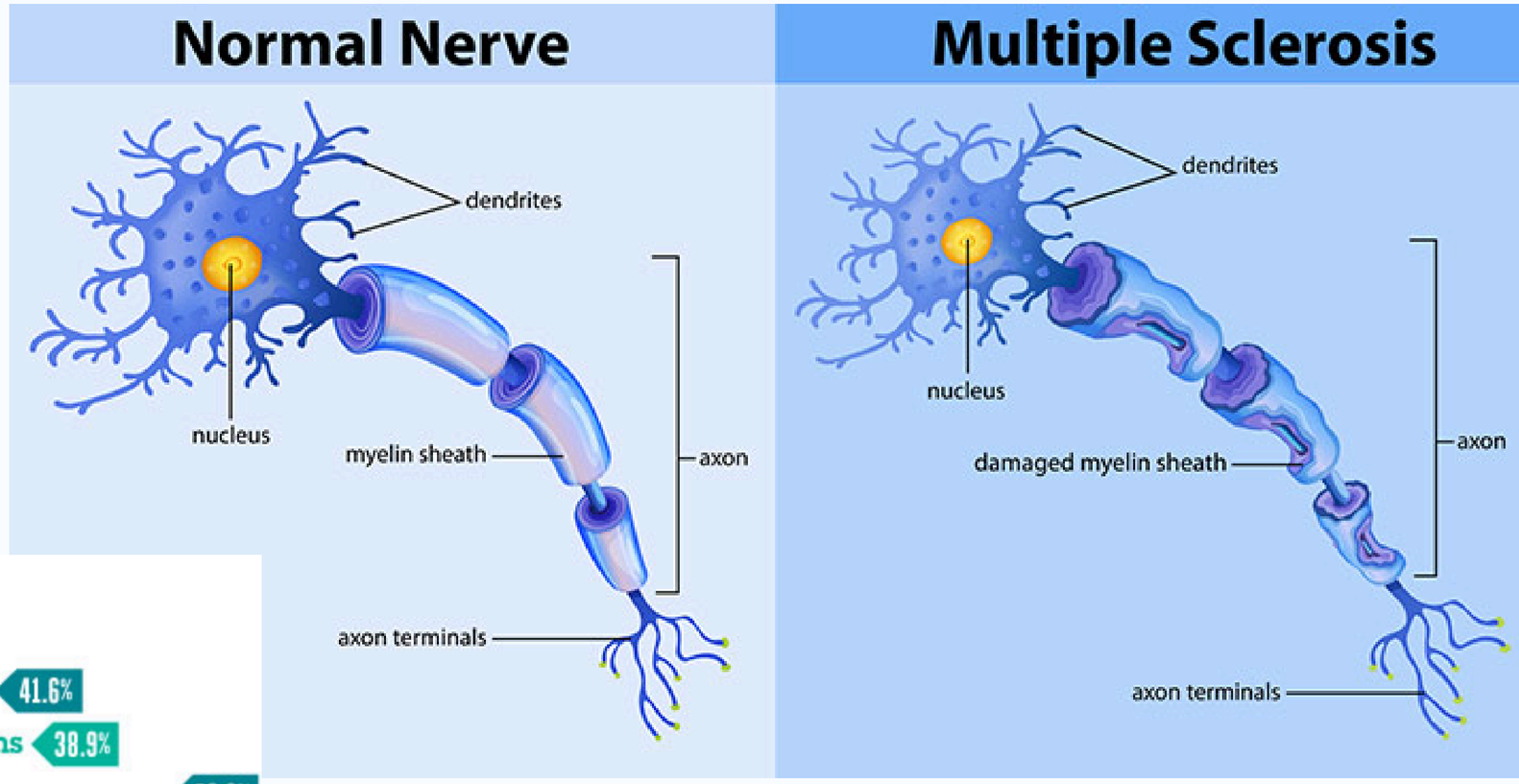
Neuroimmunology

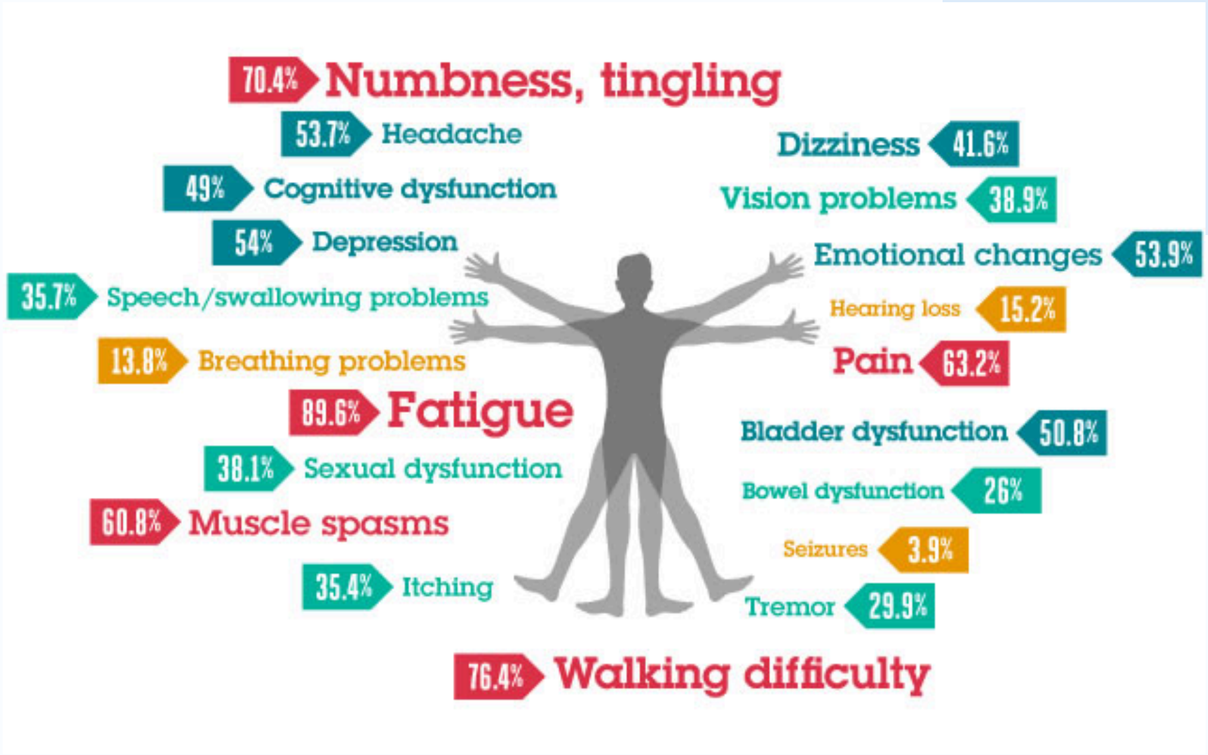
Multiple sclerosis

Neuromyelitis optica - Devic's disease (NMOSD)

Myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD)

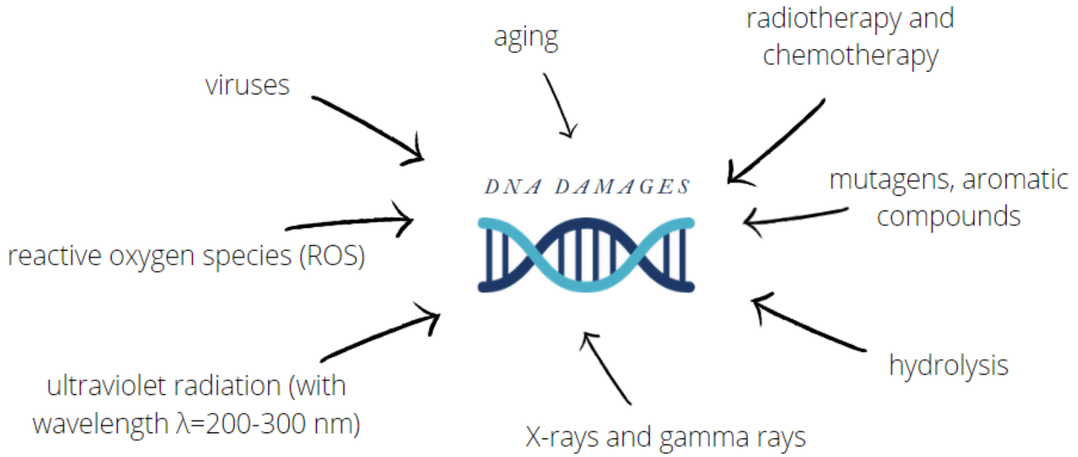
Multiple sclerosis





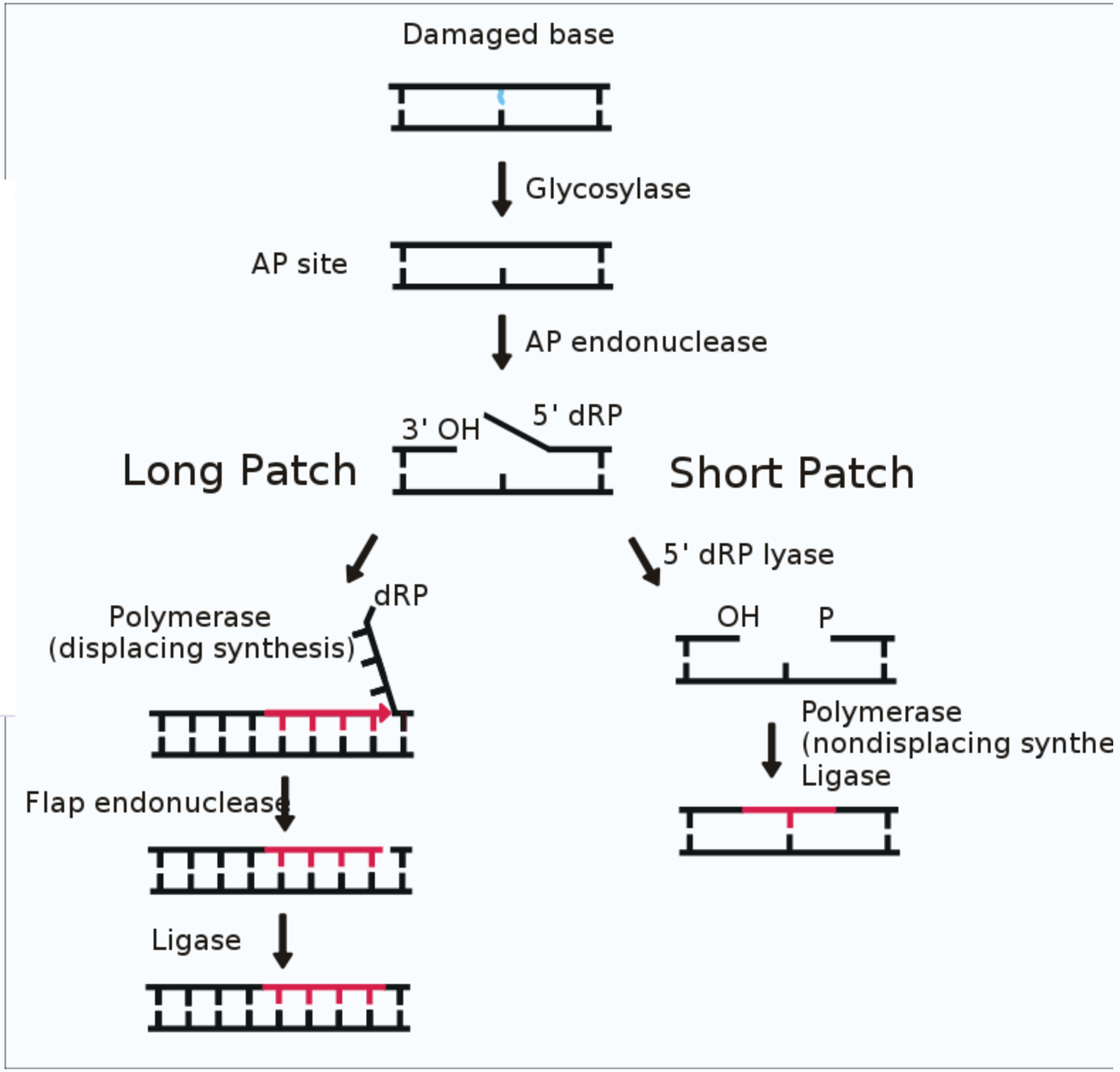
Epidemiology:
50 000 of people in Poland

Base excision repair

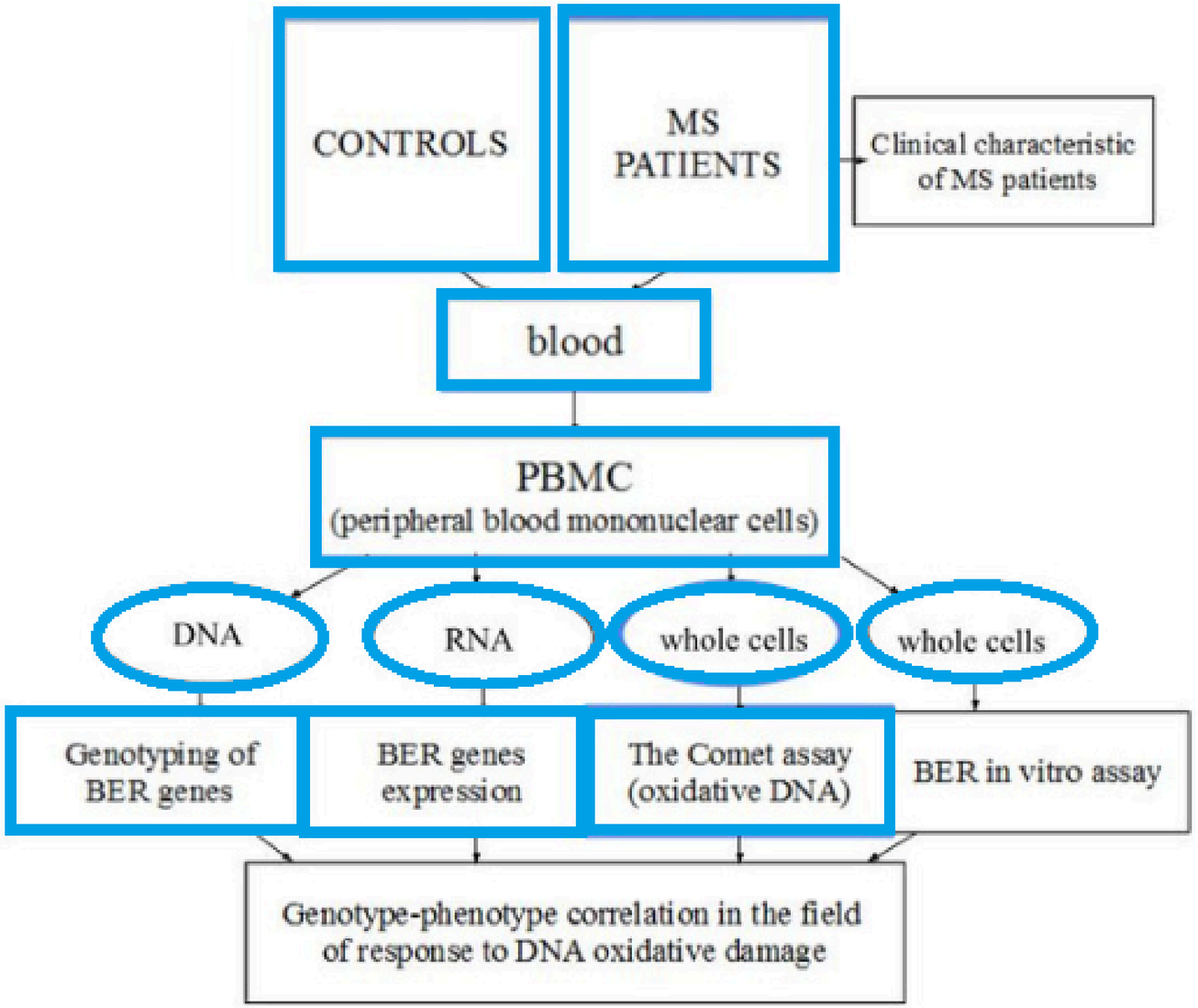


OXIDATION

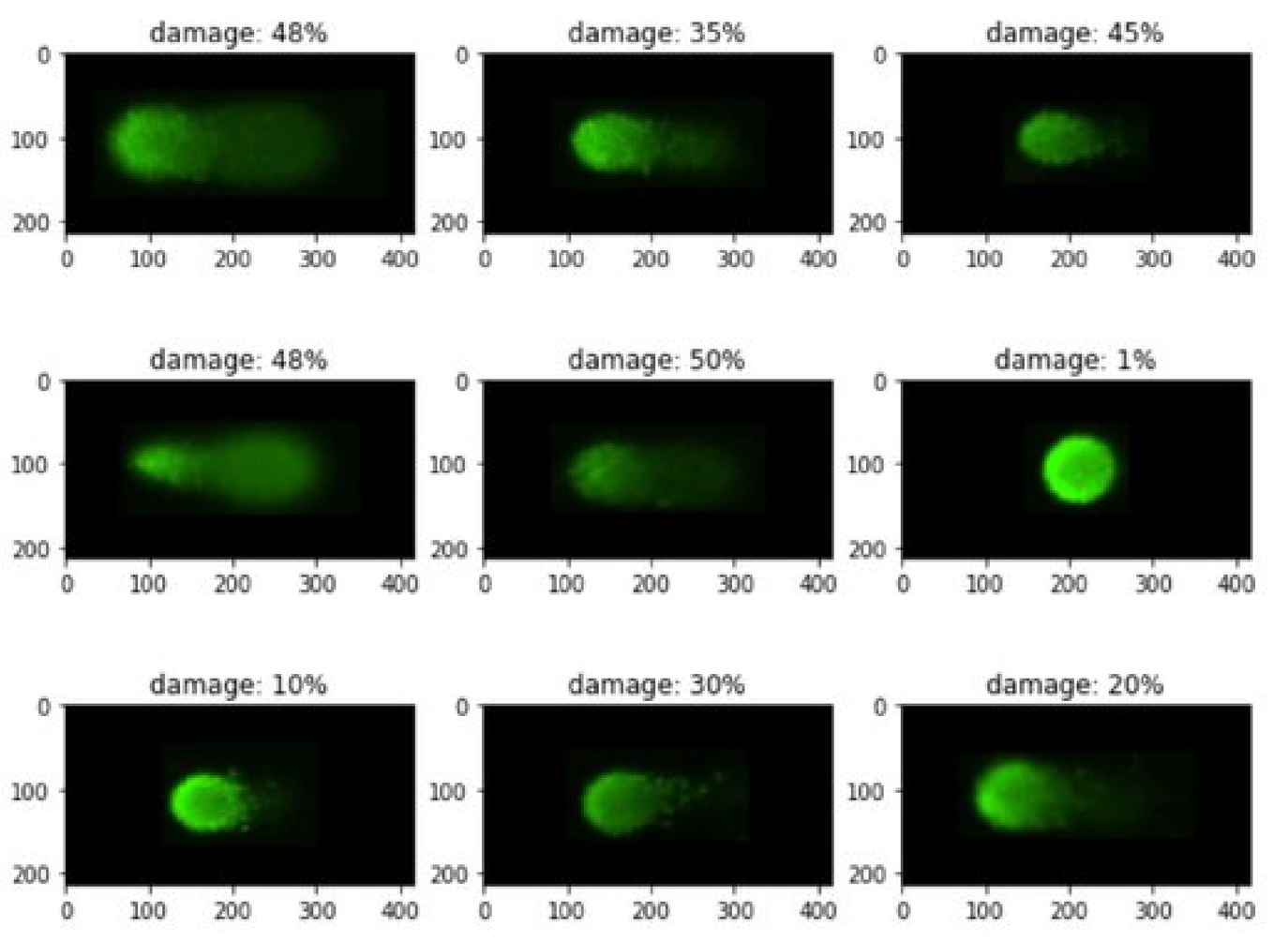
guanine oxidation to 8-oxoguanine, DNA strand breaks

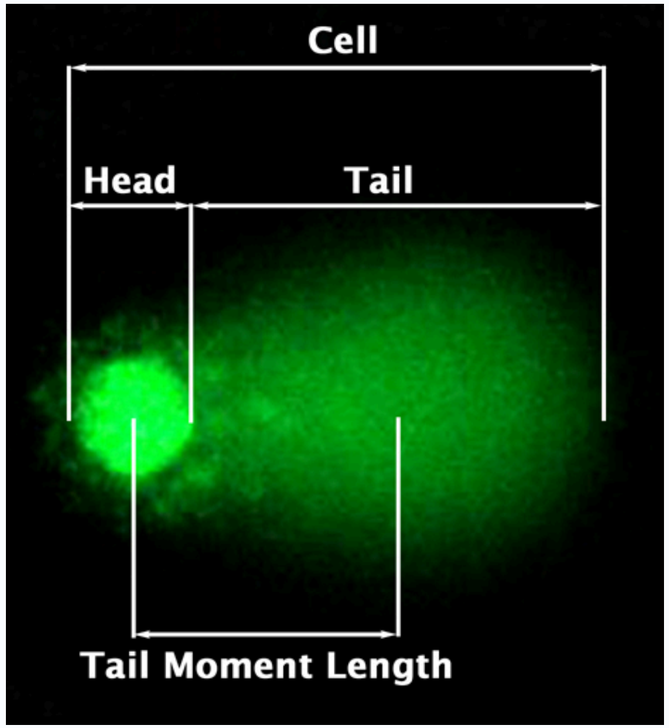


My project


CONTROLS
MS PATIENTS
Clinical characteristic of MS patients
blood
PBMC
(peripheral blood mononuclear cells)
DNA
RNA
whole cells
whole cells
Genotyping of BER genes
BER genes expression
The Comet assay (oxidative DNA)
BER in vitro assay
Genotype-phenotype correlation in the field of response to DNA oxidative damage

The comet assay - assessment of oxidative DNA damages in PBMCs





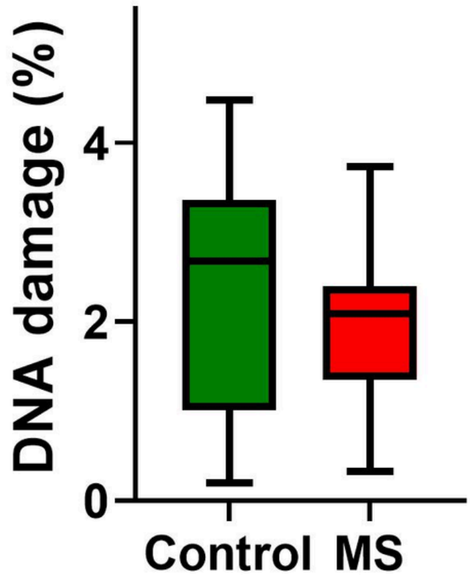


Fig_1 - Endogenous DNA damage in peripheral blood mononuclear cells (PBMCs) isolated from Multiple sclerosis (SM) and healthy subjects. DNA damage was measured as the percentage of DNA in the tail in the alkaline version of the comet assay. The value of cells scored for each individual was 100. Differences between groups were analyzed using the Mann–Whitney rank sum test Analysis.

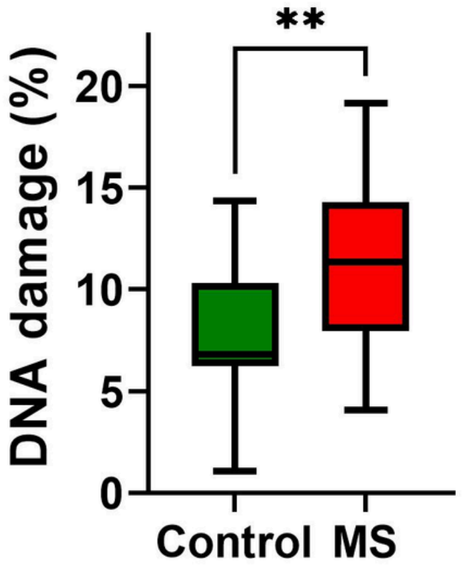


Fig_2 - Peripheral blood mononuclear cells (PBMCs) isolated from Multiple sclerosis (SM) patients were more sensitive to tert-butyl hydroperoxide (7 μ M) than PBMCs isolated from healthy subjects. DNA damage was measured as the percentage of DNA in the tail in the alkaline version of the comet assay. The value of cells scored for each individual was 100. Differences between groups were analyzed using the Mann–Whitney rank sum test Analysis, ** means $p < 0.01$

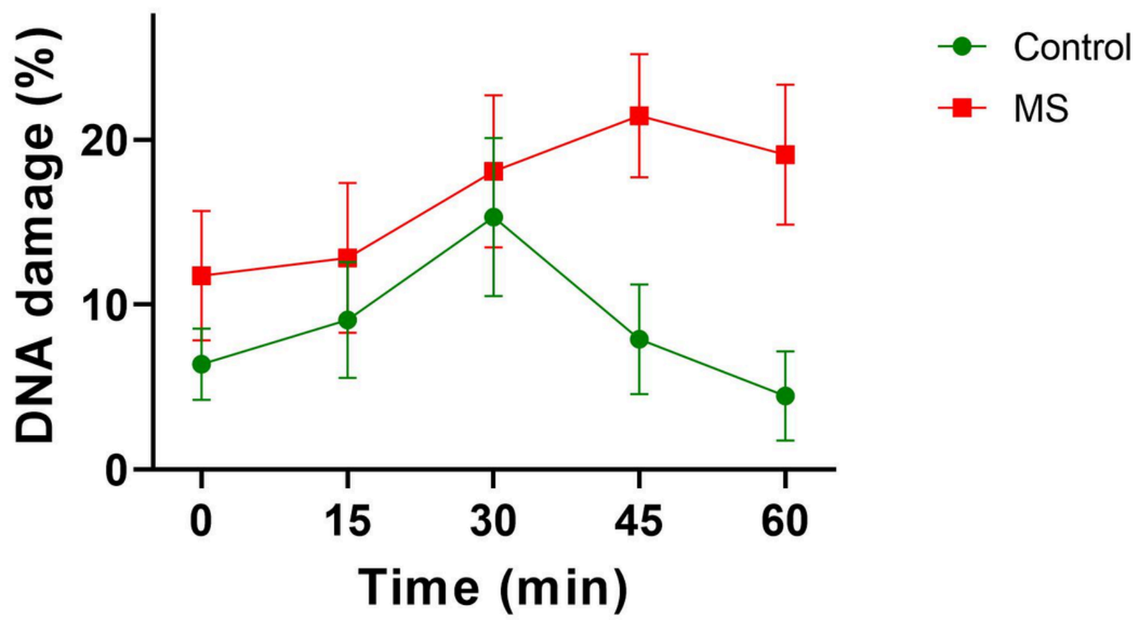
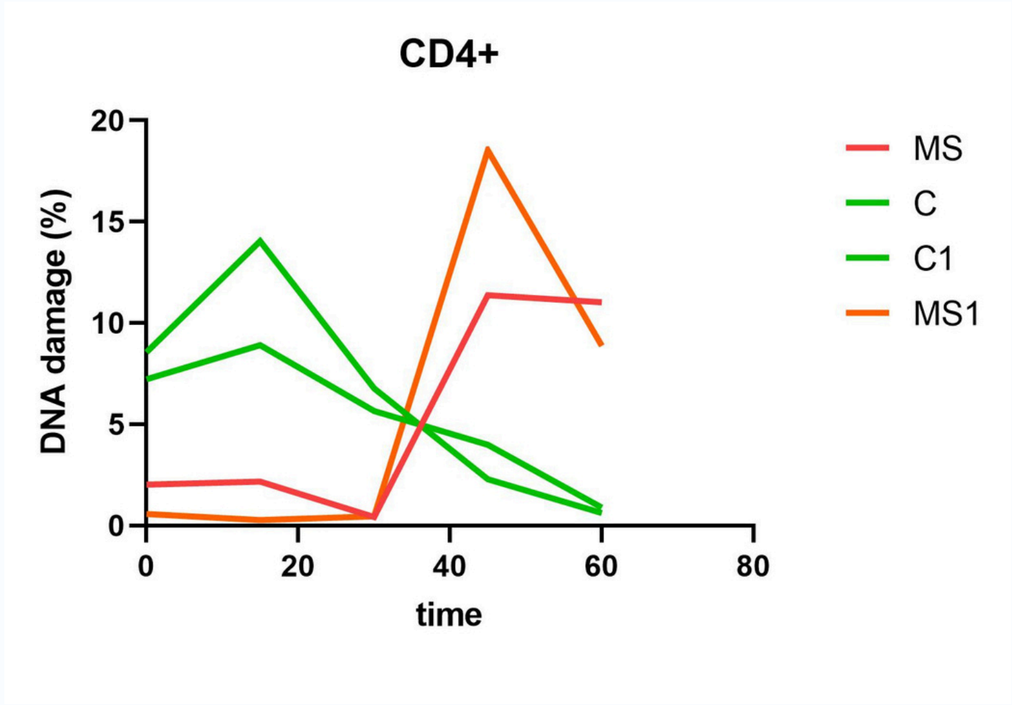
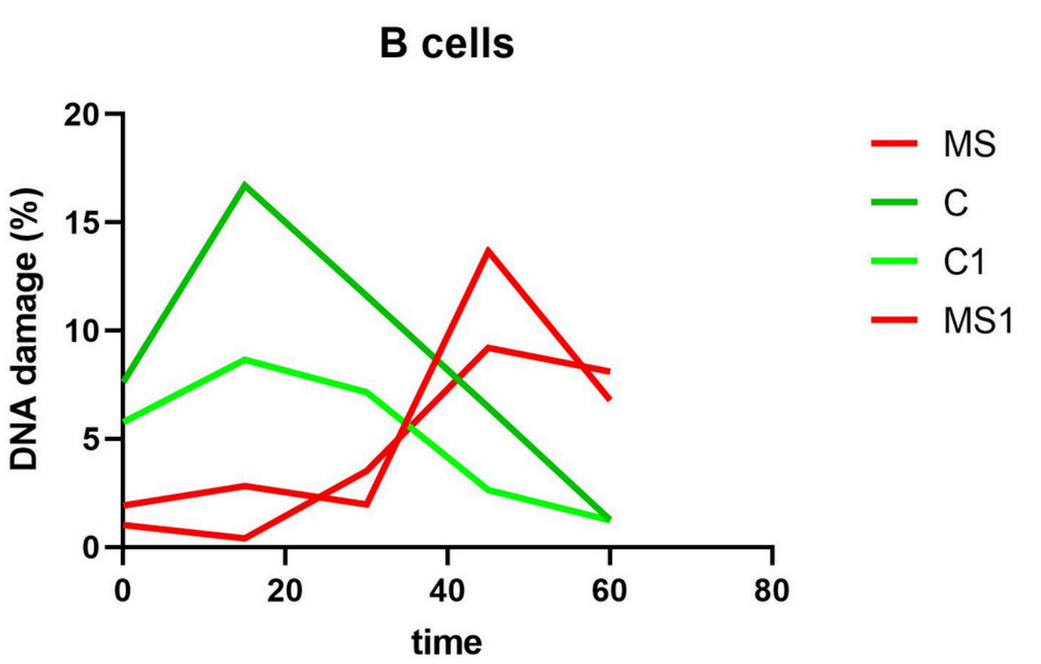
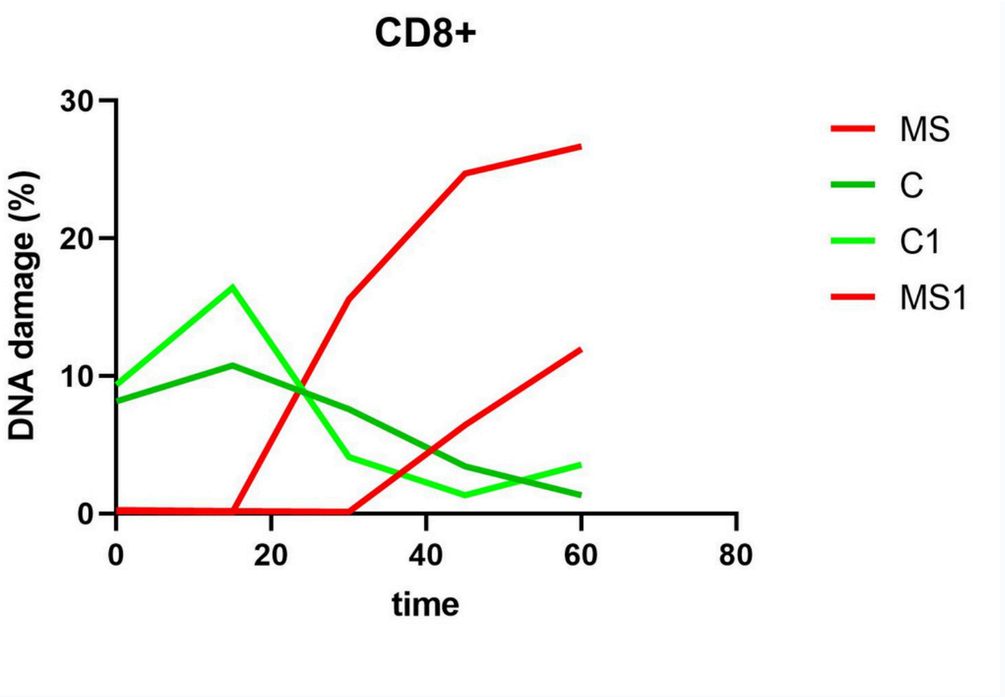


Fig_3 - Peripheral blood mononuclear cells (PBMCs) isolated from Multiple sclerosis (SM) patients (red line) have less efficient DNA repair than PBMCs isolated from healthy subjects (green line). Repair of DNA lesions evoked by tert-butyl hydroperoxide in the PBMC is presented. PBMCs were allowed to recover their DNA for 60 min after incubation with tert-butyl hydroperoxide. DNA damage was measured as the percentage of DNA in the tail in the alkaline version of the comet assay. The value of cells scored for each individual was 100.

Repair efficiency in magnetically isolated PBMCs







NMOSD biomarkers of relapse Luminex data - longitudinal spaghetti plots

Complement Proteins	Chemokines	Cytokines
C2	CCL1/I-309/TCA-3	IFN-alpha
C9	CCL11/Eotaxin	IFN-beta
C5a	CCL13/MCP-4	IFN-gamma
	CCL14	IL-1 beta/IL-1F2
	CCL17/TARC	IL-10
	CCL2/JE/MCP-1	IL-12/IL-23 p40
	CCL22/MDC	IL-13
	CCL24/Eotaxin-2/MPIF-2	IL-15
	CCL25/TECK	IL-17/IL-17a
	CCL3/MIP-1alpha	IL-18/IL-1F4
	CCL4/MIP-1beta	IL-1ra/IL-1F3
	CCL7/MCP-3/MARC	IL-2
	CCL8/MCP-2	IL-23
	CX3CL1/Fractaline	IL-4
	CXCL1/GRO alpha/KC/CINC-1	IL-6

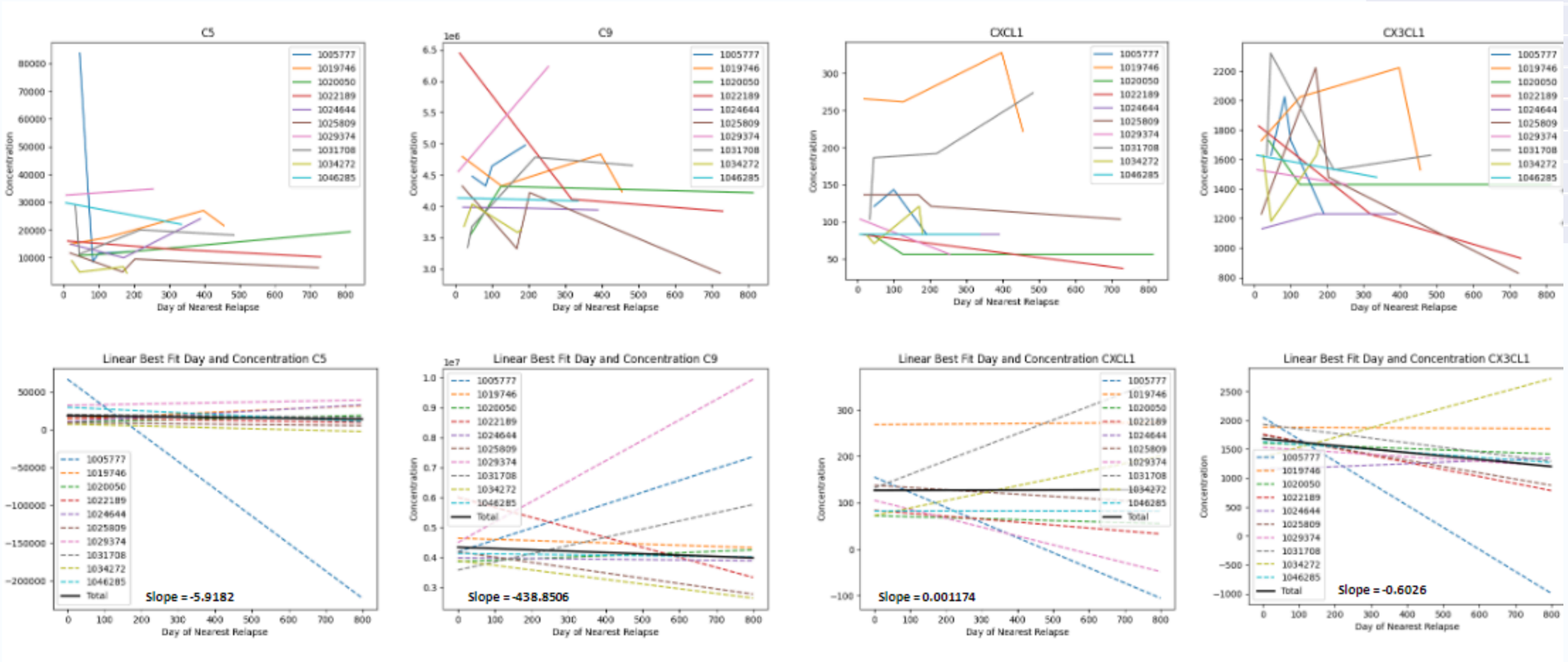


Fig. 4 Spaghetti plots - cytokines tested in Luminex assay. Preeliminary data.

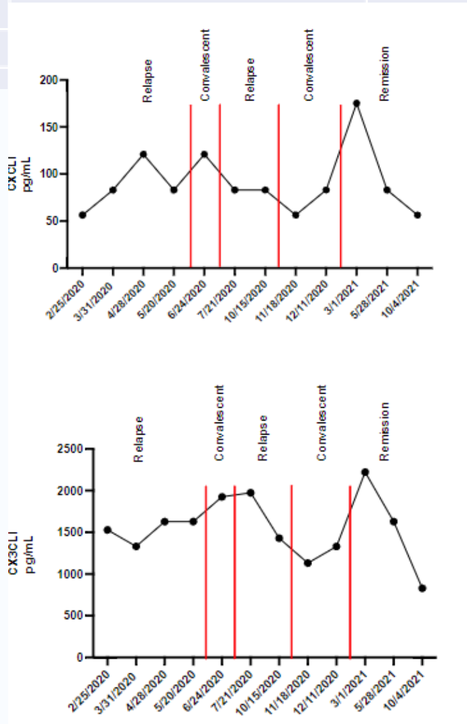


Fig. 5 Cytokines level tested in Luminex assay - longitudinal study. Preeliminary data.

Achievements

Conferences:

Oral presentations:

- American Academy of Neurology Annual Meeting 2024 12-18.04.2024

Filipek, B., Yandamuri, S., Obaid, A., Thurman, J., Makhani, N., Nowak, R., Guo, Y., Lucchinetti, C., Flanagan, E., Longbrake, E., & O'Connor, K. (2024). Phenotypes of B cells producing autoantibodies in MOGAD patients (N1.002). Neurology, 102(17_supplement_1). https://doi.org/10.1212/wnl.0000000000208259

Posters:

- American Academy of Neurology Annual Meeting 2024 12-18.04.2024

Filipek, B., & Poplawski, T. (2024). Elevated level of DNA damage and impaired repair of DNA oxidative damage in multiple sclerosis patients (P7-6.010). Neurology, 102(17_supplement_1). https://doi.org/10.1212/wnl.0000000000208336

- The Americas Committee for Treatment and Research in Multiple Sclerosis Forum - ACTRIMS 2024 29-02.03.2024

P049. Novel Biomarkers in Neuromyelitis Optica

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1Department of Pharmaceutical Microbiology and Biochemistry, Medical University of Lodz, Lodz, POLAND, 2Department of Neurology and Immunobiology, Yale University, New Haven, CT, 3Department of Medicine, David Geffen School of Medicine at University of California Loss Angeles (UCLA), Los Angeles, CA.

P329. Distinct Post-Cytotoxic NK Cells Arise in Autoantibody-Mediated Neurologic Diseases

S. S. Yandamuri1, **B. Filipek2**, N. Lele3, I. Cohen3, J. L. Bennett4, R. J. Nowak3, E. S. Sotirchos5, E. E. Longbrake3, E. M. Mace6, K. C. O'Connor3;
1Neurology and Immunobiology, Yale University, New Haven, CT, 2Department of Pharmaceutical Microbiology and Biochemistry, Medical University of Lodz, Lodz, POLAND, 3Yale University, New Haven, CT, 4University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, 5Neurology, Johns Hopkins University, Baltimore, MD, 6Columbia University, New York, NY.

The abstracts mentioned above are in the publishing process in Multiple Sclerosis Journal.

actrims FORUM 2024

Submitted abstracts to ECTRIMS 2024:

Impaired DNA damage of oxidative DNA lesions in CD4+ and CD8+ T but not B Cells Isolated from Patients with Multiple Sclerosis

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1Department of Pharmaceutical Microbiology and Biochemistry, Medical University of Lodz, Lodz, POLAND

Assessment of the correlation between clinical features and the level of oxidative DNA lesions in multiple sclerosis patients

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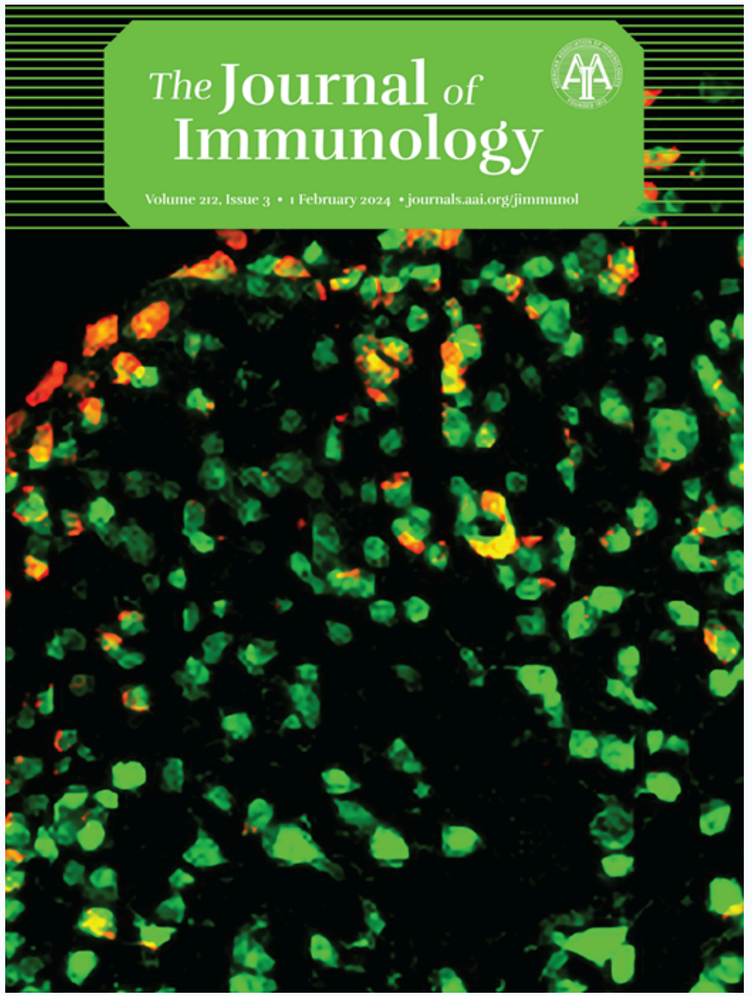
1Department of Pharmaceutical Microbiology and Biochemistry, Medical University of Lodz, Lodz, POLAND

Publications:

Yandamuri, S.S., **Filipek, B**., Lele, N., Cohen, I., Bennett, J. L., Nowak, R. J., Sotirchos, E. S., Longbrake, E. E., Mace, E. M., & O'Connor, K. C. (2024). A noncanonical CD56dimCD16dim/− NK cell subset indicative of prior cytotoxic activity is elevated in patients with autoantibody-mediated neurologic diseases. The Journal of Immunology, 212(5), 785–800. https://doi.org/10.4049/jimmunol.2300015



Stipends:

Scholarships of the National Agency for Academic Exchange under "STER - Internationalisation of Doctoral Schools" Programme at the Medical University of Lodz 2023/2024 academic year

Scholarships:

6-months international internship in the Department of Neurology, Yale School of Medicine, under the programme: “Internationalisation Empowerment of Doctoral School at Medical University of Lodz” (InterEmpowereD) Nawa Ster 01.05.2023-31.10.2023.

POLISH NATIONAL AGENCY FOR ACADEMIC EXCHANGE

Thank you!

Beata Filipek,MD

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