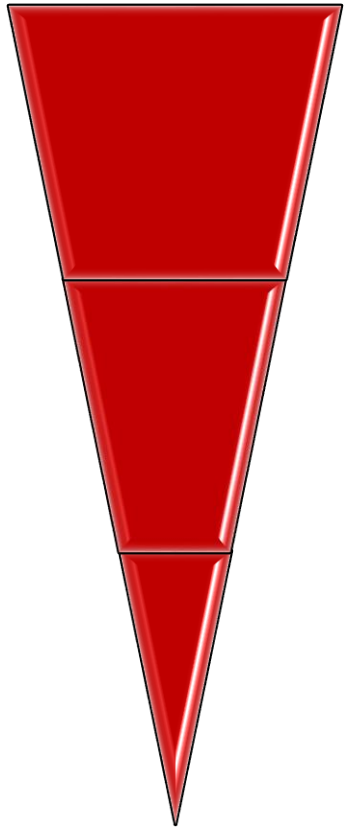
HIGH-RISK NEUROBLASTOMA SURVIVORS SHOW SIGNS OF IMMUNOSENESCENCE EARLY AFTER THERAPY AND RETAIN INCREASED MYELOID CELL ACTIVATION STATUS

Jan Frič

Marcela Hortová-Kohoutková
Kamila Bendíčková
Petra Lázničková
Ivana Andrejčinová
Ondřej Vymazal
Veronika Bosáková
Miriam Slezáková

Tomáš Kepák
Zdeňka Křenová

From aging to immunosenescence



Aging

- Cellular senescence, stem cell exhaustion, genomic instability
- Inflammaging, epigenetic and metabolic remodelling

Cellular senescence

- Intrinsic (oxidative damage, telomere attrition)
- Extrinsic origin (UV, γ-irradiation, chemotherapeutic drugs)
- Telomere attrition, $p16^{INK4a}$ expression, SASP

Immunosenescence

- Cell subset redistribution, replicative senescence
- Compromised functionality, pro-inflammatory cytokines

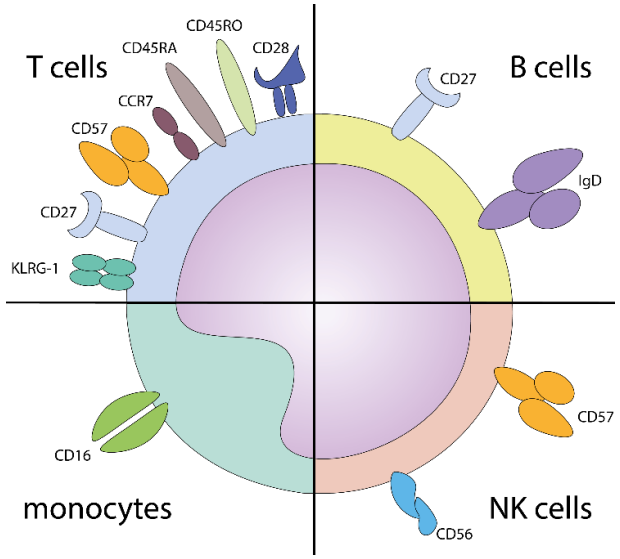
López-Otín, 2013, Cell
Leonardi, 2018, Immunity and Ageing
Herranz, Gil, 2018, J Clin Invest
Franceschi, 2017, Trends Endocrinol Metabol
Jose SS et al.2017, Front Immunol

Lázničková P, 2021, Front in Aging
Hortová-Kohoutková M, Lázničková P, Frič J, 2021, Bioessays
Jose SS,...Buřilová P,..., 2018, Front Genet

Hallmarks of immunosenescence

Immune cell surface markers

- Cell subset redistribution
- Replicative senescence
- Mostly studies in T cells



Immune cell functionality

- Impaired chemotaxis, antigen presentation, phagocytosis
- $p16^{INK4a}$ expression, telomere attrition, immunometabolic changes

Inflammaging/Chronic low-grade inflammation

- pro-inflammatory cytokines
- TNF-α, IL-6, CRP

Leonardi, 2018, Immunity and Ageing
Franceschi, 2017, Trends Endocrinol Metabol

BioEssays

PROBLEMS & PARADIGMS | Open Access

How immune-cell fate and function are determined by metabolic pathway choice

The bioenergetics underlying the immune response

Marcela Hortová-Kohoutková, Petra Lázničková, Jan Frič

First published: 16 November 2020 | https://doi.org/10.1002/bies.202000067 | Citations: 1

ORIGINAL RESEARCH article

Front. Genet., 29 August 2018 | https://doi.org/10.3389/fgene.2018.00345

The Telomerase Complex Directly Controls Hematopoietic Stem Cell Differentiation and Senescence in an Induced Pluripotent Stem Cell Model of Telomeropathy

Shyam Sushama Jose, Federico Tidu, Petra Burilova, Tomas Kepak, Kamila Bendickova and Jan Fric

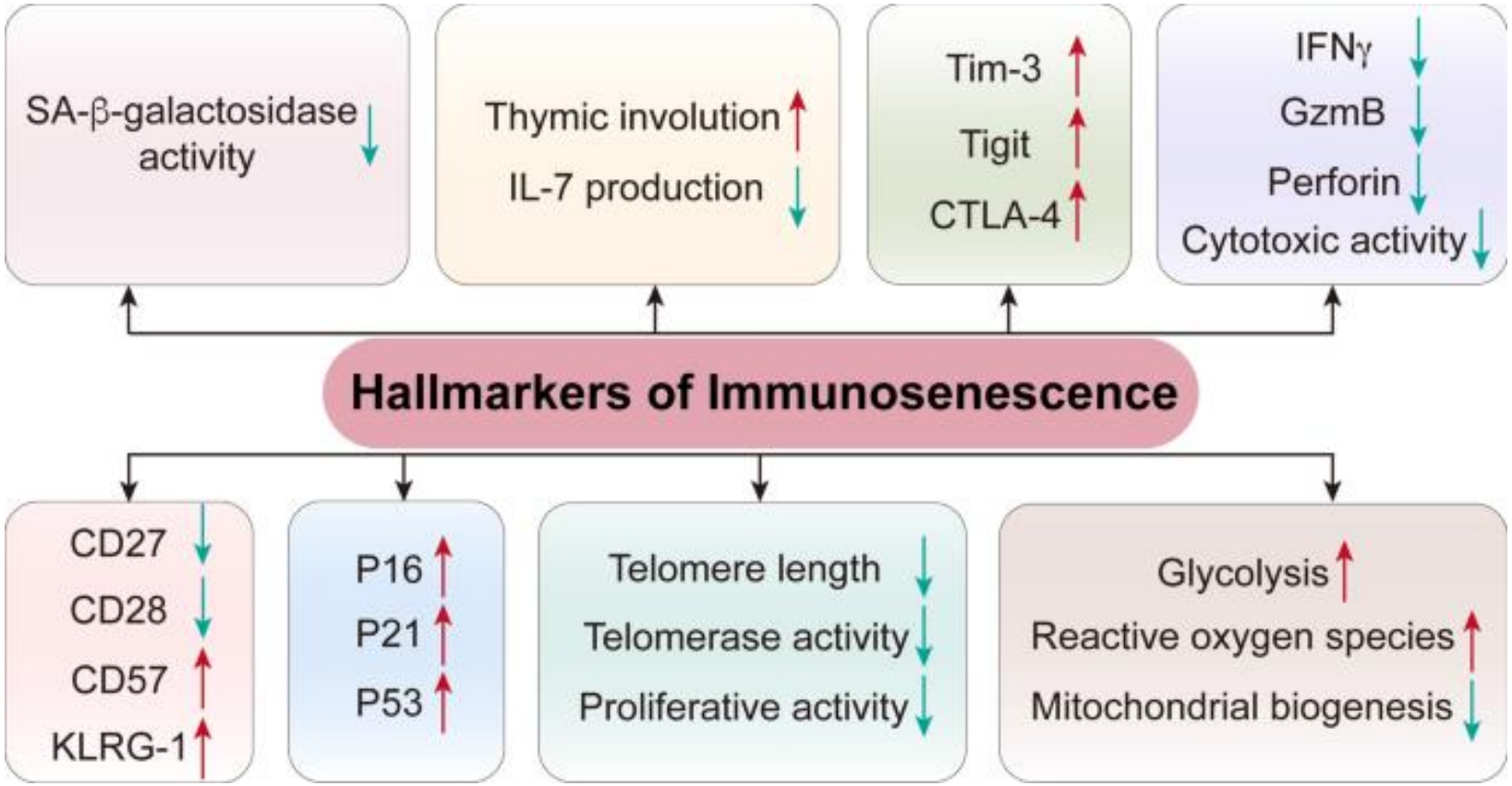
MINI REVIEW article

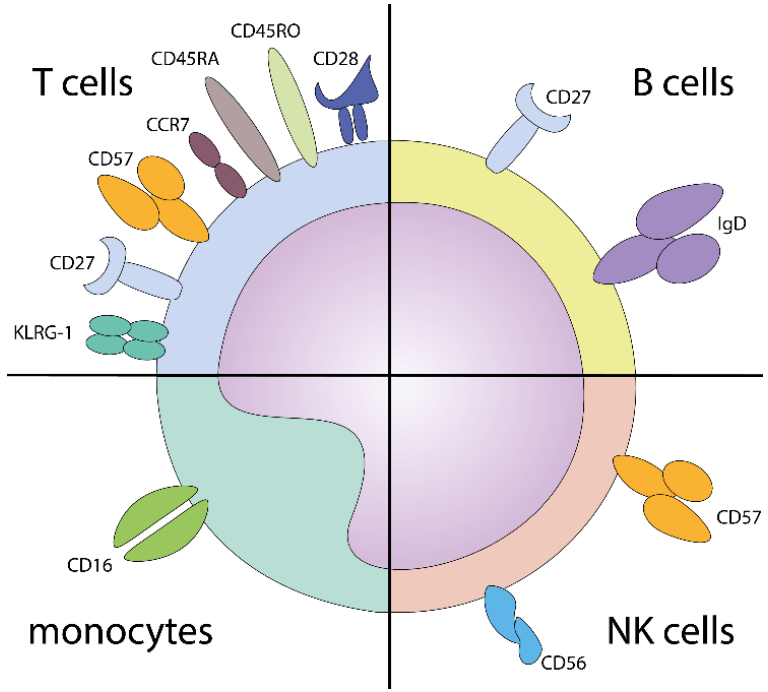
Front. Immunol., 04 September 2017 | https://doi.org/10.3389/fimmu.2017.01078

Chronic Inflammation in Immune Aging: Role of Pattern Recognition Receptor Crosstalk with the Telomere Complex?

Shyam Sushama Jose, Kamila Bendickova, Tomas Kepak, Zdenka Krenova and Jan Fric

Immunosenescence – aging of the immune system

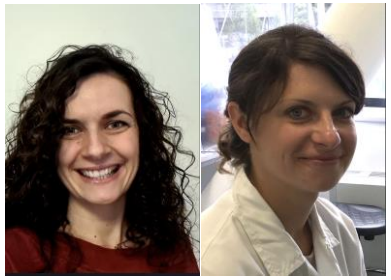




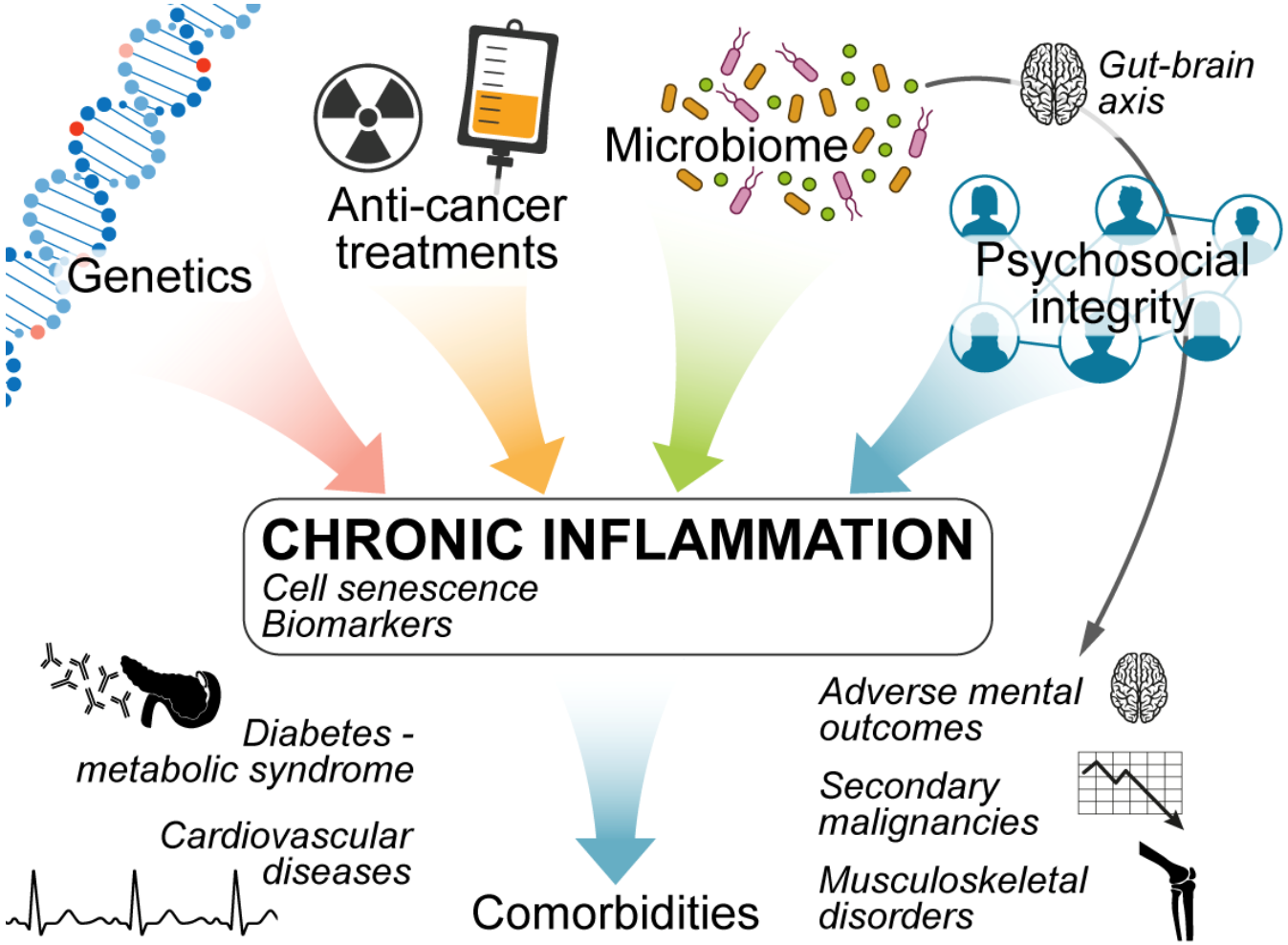
Lázničková P, Bendíčková K, Kepák T and Frič J (2021) Immunosenescence in Childhood Cancer Survivors and in Elderly: A Comparison and Implication for Risk Stratification. *Front. Aging* 2:708788. doi: 10.3389/fragi.2021.708788

Lian, J., Yue, Y., Yu, W. *et al.* Immunosenescence: a key player in cancer development. *J Hematol Oncol* **13,** 151 (2020). https://doi.org/10.1186/s13045-020-00986-z

Immunosenescence – aging of the immune system



Do children cancer survivors CCS develop signs of accelerated immunosenescence?



AZV 2017 – 2020

ENOCH 2019-2023

MAGNET 2017-2022

CCS Cohorts

Children's Medical Center, University Hospital Brno
Zdenka Křenová & Tomáš Kepák, Jaroslav Štěrba

Elderly cohorts with comorbidities

Cardiovascular Magnetic Resonance (CMR): Roman Panovský

Lenka Rossmeislová

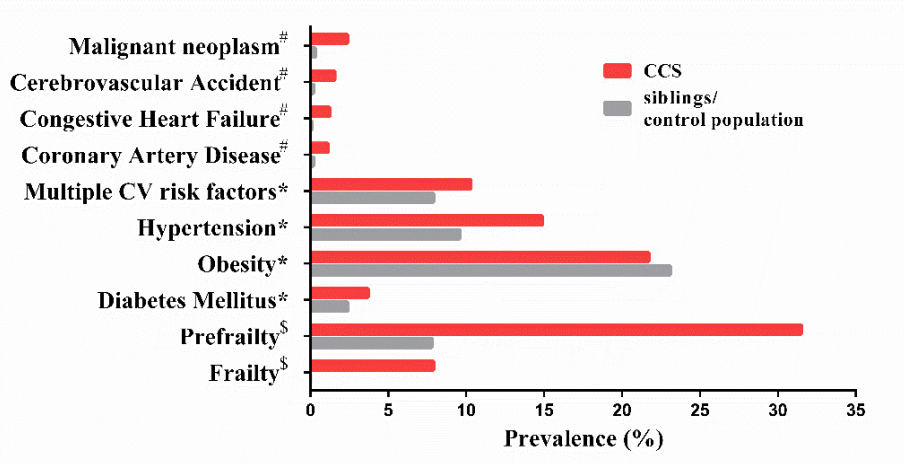
Dementia (DTM):
Kateřina Sheardová, Rafal Marciniak

Late adverse effects of therapy endanger CCS

Myocardial infarction
Cardiomyopathy
Hearing loss
Life-threatening infection
Atherosclerotic heart disease
Frailty
Late adverse effects
Renal dysfunction
Hepatic dysfunction
Adverse psychosocial effects
Neurocognitive deficits
Pulmonary fibrosis

Late effects in childhood cancer survivors

- 75% - 1 or more late effects
- 50% - 3 or more late effects



PLOS MEDICINE

OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors

Sofie de Fine Licht, Kathrine Rugbjerg, Thorgerdur Gudmundsdottir, Trine G. Bonnesen, Peter Haubjerg Asdahl, Anna Sällfors Holmqvist, Laura Madanat-Harjuoja, Laufey Tryggvadottir, Finn Wesenberg, Henrik Hasle, Jeanette F. Winther, Jørgen H. Olsen, on behalf of the ALiCCS study group

Published: May 9, 2017 • https://doi.org/10.1371/journal.pmed.1002296

Original Contribution | Clinician's Corner

June 27, 2007

Medical Assessment of Adverse Health Outcomes in Long-term Survivors of Childhood Cancer

Maud M. Geenen, MD; Mathilde C. Cardous-Ubbink, MSc; Leontien C. M. Kremer, MD, PhD; et al

Author Affiliations | Article Information

JAMA. 2007;297(24):2705-2715. doi:10.1001/jama.297.24.2705

VOLUME 36 · NUMBER 21 · JULY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Premature Physiologic Aging as a Paradigm for Understanding Increased Risk of Adverse Health Across the Lifespan of Survivors of Childhood Cancer

Kirsten K. Ness, James L. Kirkland, Maria Monica Gramatges, Zhaoming Wang, Mondira Kundu, Kelly McCastlain, Xiujie Li-Harms, Jinghui Zhang, Tamar Tchkonia, Saskia Martine Francesca Pluijm, and Gregory T. Armstrong

Ness K K. J, 2013, Clin Oncol; Franceschi, 2018, Front Med; Lázničková, 2021, Front Aging

Childhood cancer and evidence of immunosenescence-related phenotype

- Incidence of childhood cancer types in the Czech Republic between 1994 and 2016.

Immunosenescence in survivors of non-hematological solid tumors?

REVIEW article
Front. Aging, 19 July 2021 | https://doi.org/10.3389/fragi.2021.708788

Immunosenescence in Childhood Cancer Survivors and in Elderly: A Comparison and Implication for Risk Stratification

Petra Lázničková[1,2], Kamila Bendíčková[1], Tomáš Kepák[1,3] and Jan Frič[1,4]*

- Immunosenescence studied in hematological malignancies

Cell type	Immune cell phenotype	CCS
T cells ($CD3^+$)	**$CD4^+CD38^+$ HLA-DR^+**	ALL, AML[112]
	$CD4^+$ central memory	ALL, Hodgkin lymphoma, Non-Hodgkin lymphoma[113]
	$CD4^+CD28^-$	ALL, AML[112]
	$CD8^+CD38^+$ HLA-DR^+	ALL, AML[112]
	$CD8^+$ central memory	ALL, Hodgkin lymphoma, Non-Hodgkin lymphoma[113]
	$CD8^+CD28^-$	Not found
Monocytes	**$CD14^+CD16^+$**	ALL[119]

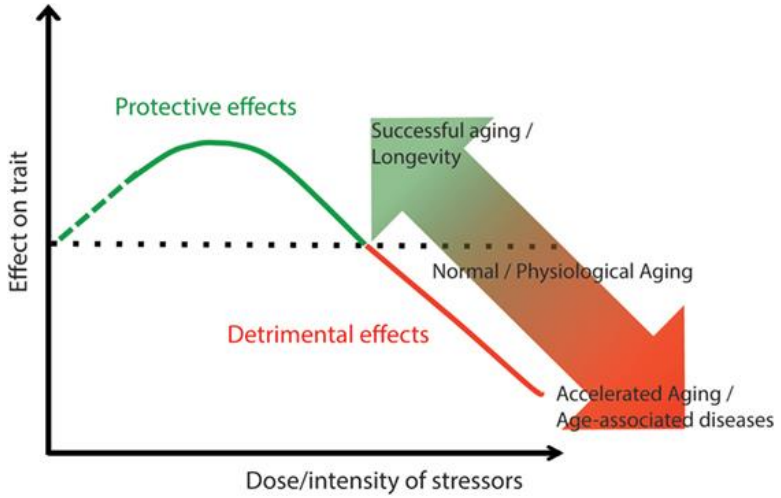
Potential induction of immunosenescence in high-risk neuroblastoma survivors

Neuroblastoma

- The most frequent extra-cranial solid tumor in early childhood
- Age of diagnosis 50% < 2yo
  75% < 5yo
- Poor prognosis for high-risk neuroblastoma patients, frequent relapses

HR NB treatment:

- Chemotherapy
- Stem cell harvesting
- Surgery
- HSC transplantation
- Radiotherapy



Ness K K. J, 2013, Clin Oncol; Franceschi, 2018, Front Med

Does high-risk neuroblastoma treatment induce innate immunity and T cell subsets alterations related to immunosenescence?

European Journal of Immunology
Basic·Clinical·Translational

Letter to the editor | Open Access

Childhood survivors of high-risk neuroblastoma show signs of immune recovery and not immunosenescence

Petra Lázničková, Tomáš Kepák, Marcela Hortová – Kohoutková, Luděk Horváth, Kateřina Sheardová, Rafal Marciniak, Carmine Vacca, Michaela Šiklová, Teresa Zelante, ... See all authors

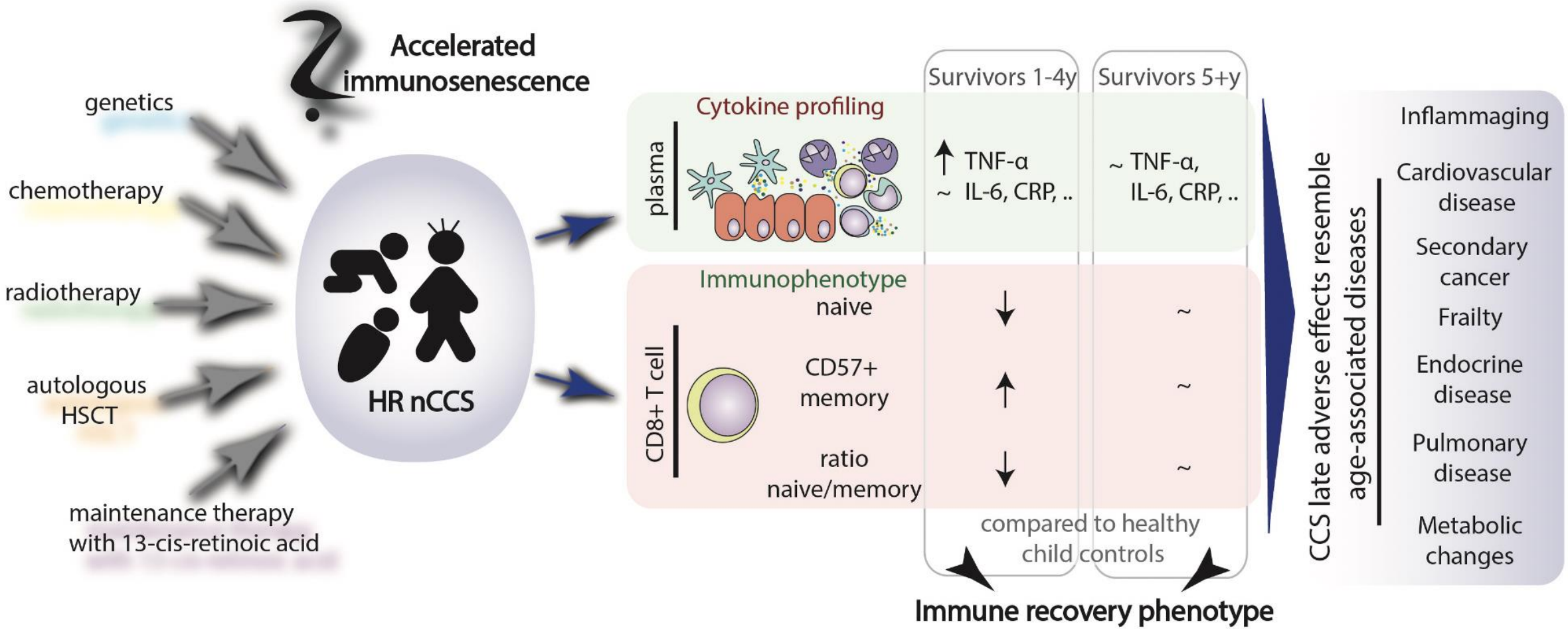
First published: 03 August 2020 | https://doi.org/10.1002/eji.202048541 | Citations: 2

Demographic characterization table - Survivors 1-4y are younger than Survivors 5+y

High-risk neuroblastoma survivors	Survivors 1-4y	Survivors 5+y	p value	
Number of participants (n)	14	22	–	
Sex (male/female), n (%)	9 (64)/5 (36)	13 (59)/9 (41)	>0,9999	
Age at study recruitment, median (min-max)	5 (2-8)	12 (5-27)	<0,0001	
Age at diagnosis - median (min-max)	2 (0-7)	2 (0-12)	0.824	
Years after transplantation, median (min-max)	2 (0-3)	8 (2-18)	<0,0001	
Years since diagnosis, median (min-max)	3 (1-4)	8 (5-20)	<0,0001	
Autologous HSCT, n (%)	14 (100)	22 (100)	>0,9999	
Chemotherapy, n (%)	14 (100)	22 (100)	>0,9999	
Radiotherapy, n (%)	13 (93)	22 (100)	>0,9999	
Relapse, n (%)	2 (14)	2 (9)	0.6092	
Death, n (%)	1 (7)	0 (0)	0.3611	
Refractory disease, n (%)	2 (14)	3 (14)	>0,9999	
Child controls			**p value (Survivors 1-4y)**	**p value (Survivors 5+y)**
Number of participants (n)	19		–	–
Sex (male/female), n (%)	6 (32)/13 (68)		0.8382	0.4971
Age at study recruitment, median (min-max)	14 (1-23)		0.2613	>0,9999
Elderly – Mild Cognitive Impairment (MCI)			**p value (Survivors 1-4y)**	**p value (Survivors 5+y)**
Number of participants (n)	23		–	–
Sex (male/female), n (%)	8 (35)/15 (65)		>0,9999	0.6613
Age at study recruitment, median (min-max)	74 (57-71)		<0,0001	<0,0001
MMSE mean, SD (min-max)	27.26, 1.63 (24-29)		–	–

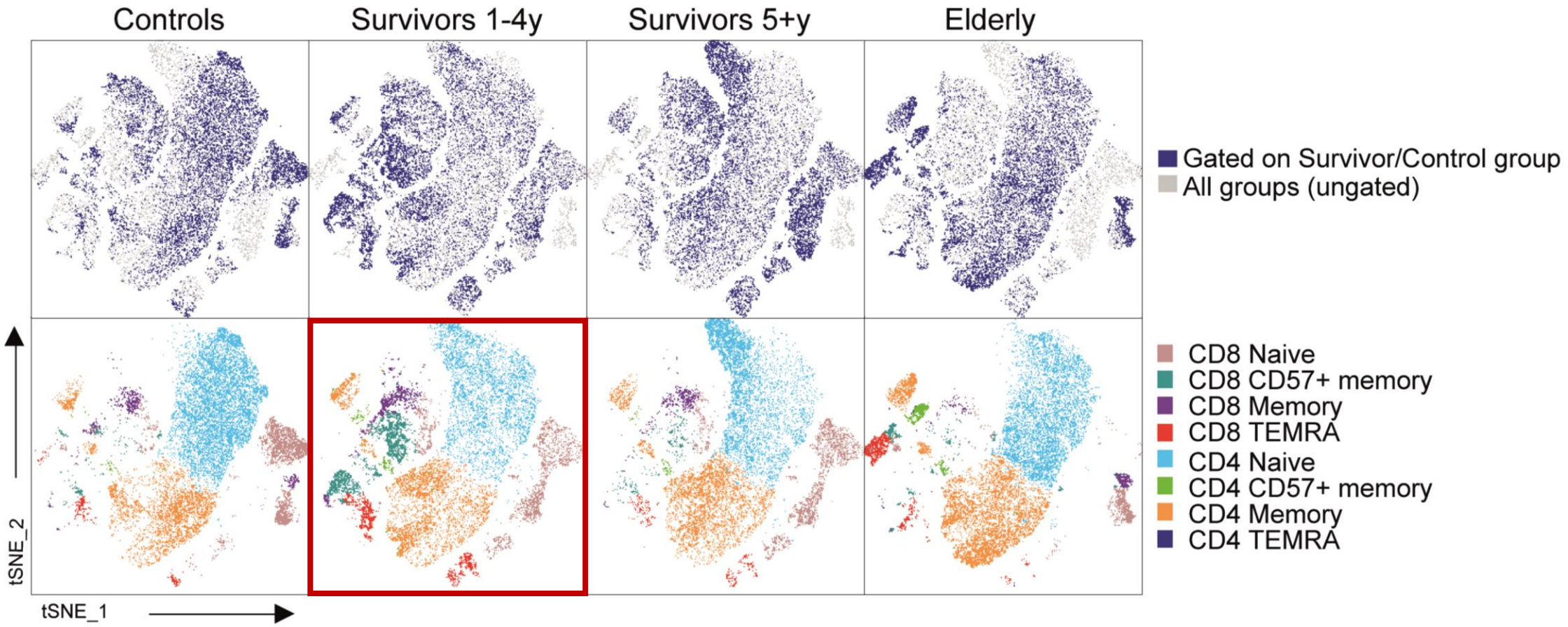
Lázničková P, Kepák T**, Hortová-Kohoutková M, Horváth L**, Sheardová K, Marciniak R, Vacca C, Šiklová M, Zelante T, Rossmeislová L, Křenová Z, Štěrba J, **Bendíčková K, Frič J:** Childhood survivors of high-risk neuroblastoma show signs of immune recovery and not immunosenescence. Eur J Immunol. (2020) Aug 3. (IF 5.179) doi: 10.1002/eji.202048541. PMID: 32744364

CCS 1 and 5+ years after successful therapy of high-risk neuroblastoma show transient changes of T cells with signs of immunosenescence



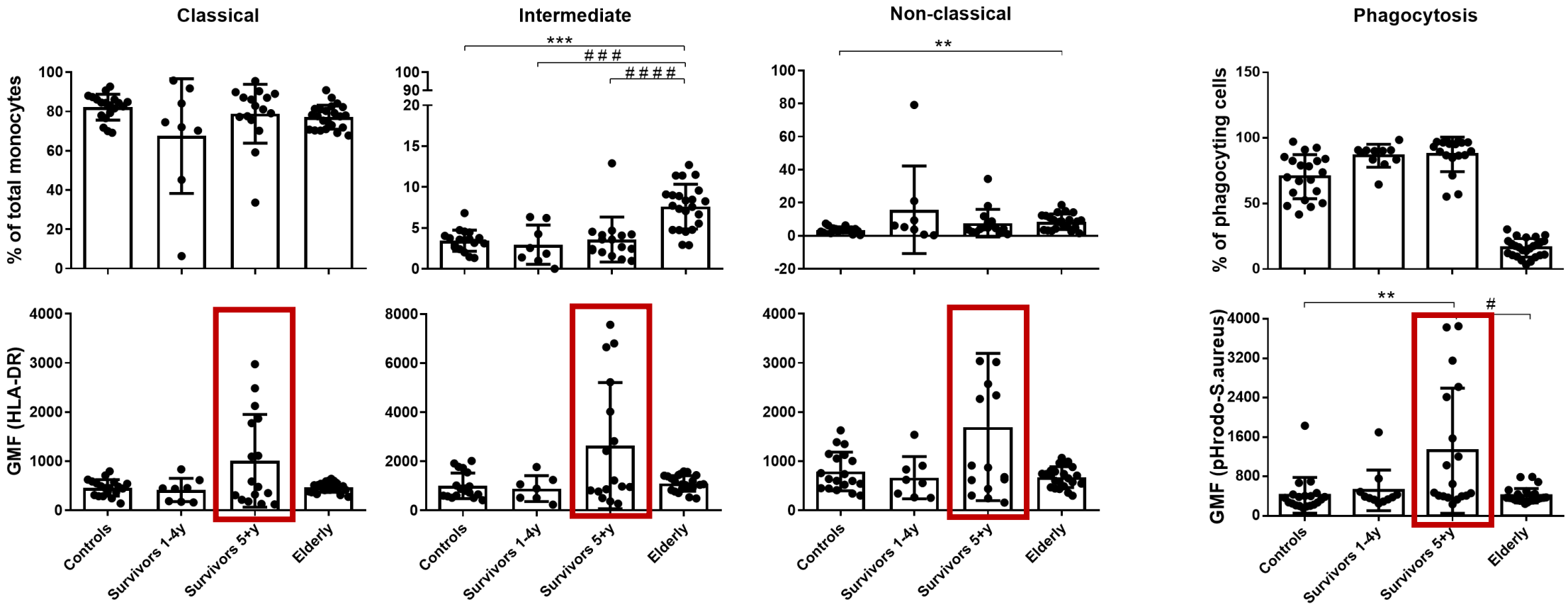
Lázničková P, Kepák T**, Hortová-Kohoutková M, Horváth L**, Sheardová K, Marciniak R, Vacca C, Šiklová M, Zelante T, Rossmeislová L, Křenová Z, Štěrba J, **Bendíčková K, Frič J:** Childhood survivors of high-risk neuroblastoma show signs of immune recovery and not immunosenescence. Eur J Immunol. (2020) Aug 3. (IF 5.179) doi: 10.1002/eji.202048541. PMID: 32744364

CCS 1 a 5^{+} years after successful therapy of high risk neuroblastoma show transient changes of T cells with signs of immunosenescence



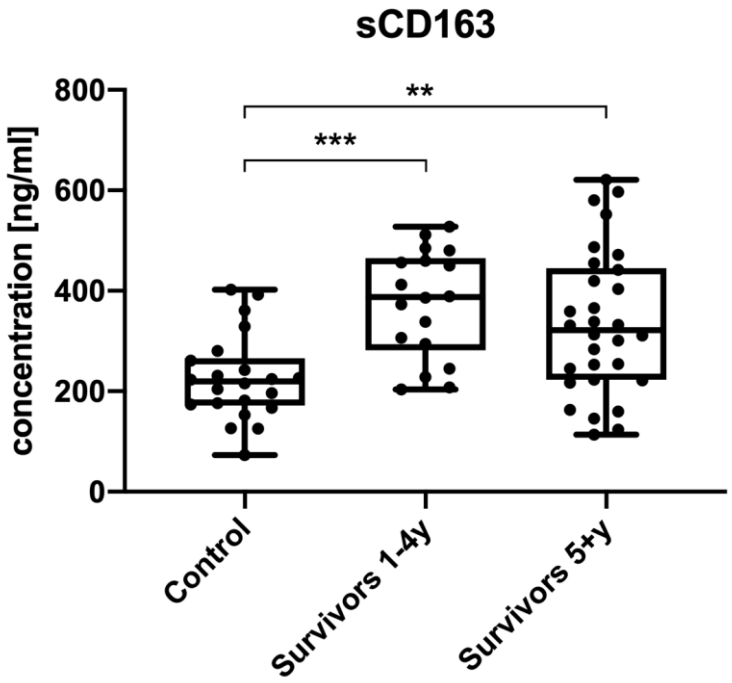
Lázničková P, Kepák T**, Hortová-Kohoutková M, Horváth L**, Sheardová K, Marciniak R, Vacca C, Šiklová M, Zelante T, Rossmeislová L, Křenová Z, Štěrba J, **Bendíčková K, Frič J:** Childhood survivors of high-risk neuroblastoma show signs of immune recovery and not immunosenescence. Eur J Immunol. (2020) Aug 3. (IF 5.179) doi: 10.1002/eji.202048541. PMID: 32744364

CCS 5+ years after successful therapy of high-risk neuroblastoma show long-term changes of myeloid cells



Lázničková P, Bendíčková K, Frič J, unpublished

CCS 1 a 5+ years after successful therapy of high risk neuroblastoma show long-term changes of myeloid cells



European Journal of Haematology

Original Article

Monocyte/macrophage-derived soluble CD163: a novel biomarker in multiple myeloma

Morten N. Andersen, Niels Abildgaard, Maciej B. Maniecki, Holger J. Møller, Niels F. Andersen

First published: 24 February 2014 | https://doi.org/10.1111/ejh.12296 | Citations: 37

frontiers in Oncology

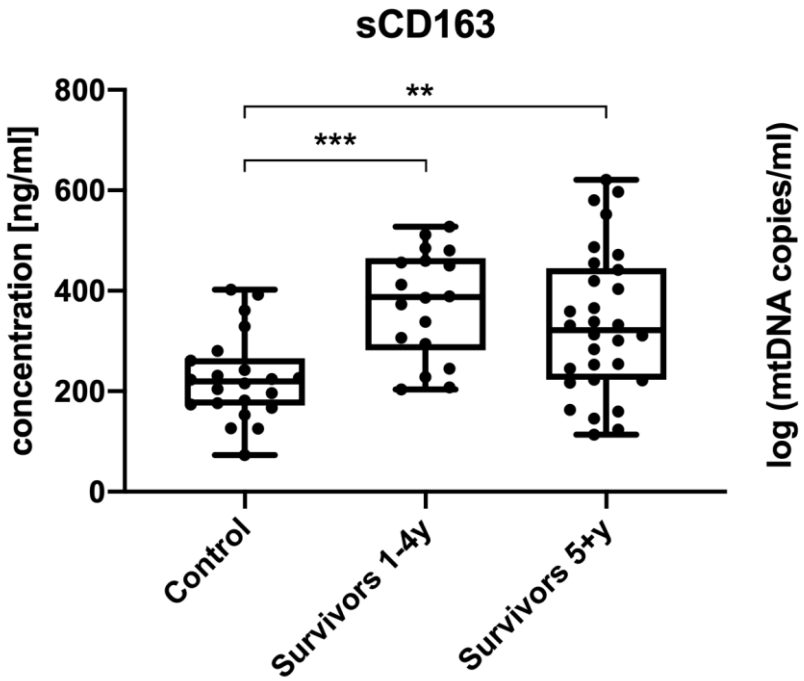
Front Oncol. 2020; 10: 585297. PMCID: PMC7683770
Published online 2020 Nov 10. doi: 10.3389/fonc.2020.585297 PMID: 33240816

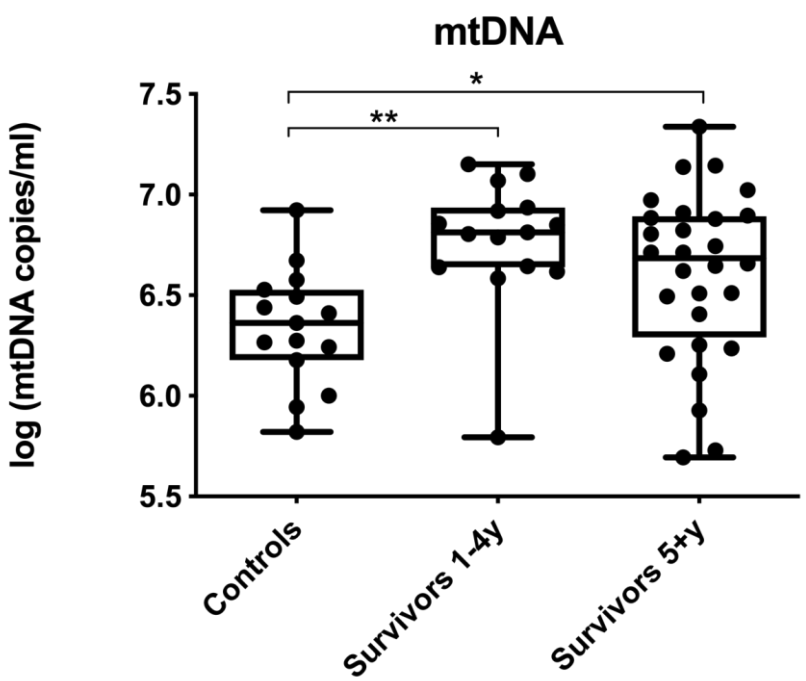
Is sCD163 a Clinical Significant Prognostic Value in Cancers? A Systematic Review and Meta-Analysis

Shushu Qian, [1,†] Hong Zhang, [1,†] Huibo Dai, [1] Bangyun Ma, [1] Fang Tian, [2] PengJun Jiang, [1] Haoran Gao, [1] Xiaocao Sha, [1] and Xuemei Sun [1,*]

Lázničková P, Bendíčková K, Frič J, unpublished

CCS 1 a 5+ years after successful therapy of high risk neuroblastoma show long-term changes of myeloid cells





Aging Cell Open Access ANATOMICAL SOCIETY

ORIGINAL PAPER | Open Access

Cell-free DNA as a biomarker of aging

Yee Voan Teo, Miriam Capri, Cristina Morsiani, Grazia Pizza, Ana Maria Caetano Faria, Claudio Franceschi, Nicola Neretti

First published: 20 December 2018 | https://doi.org/10.1111/acel.12890 | Citations: 34

European Journal of Immunology Basic · Clinical · Translational

Regular Article | Free Access

Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging"

Marcello Pinti, Elisa Cevenini, Milena Nasi, Sara De Biasi, Stefano Salvioli, Daniela Monti, Stefania Benatti, Lara Gibellini, Rodolfo Cotichini, Maria Antonietta Stazi, Tommaso Trenti ... See all authors

First published: 27 January 2014 | https://doi.org/10.1002/eji.201343921 | Citations: 189

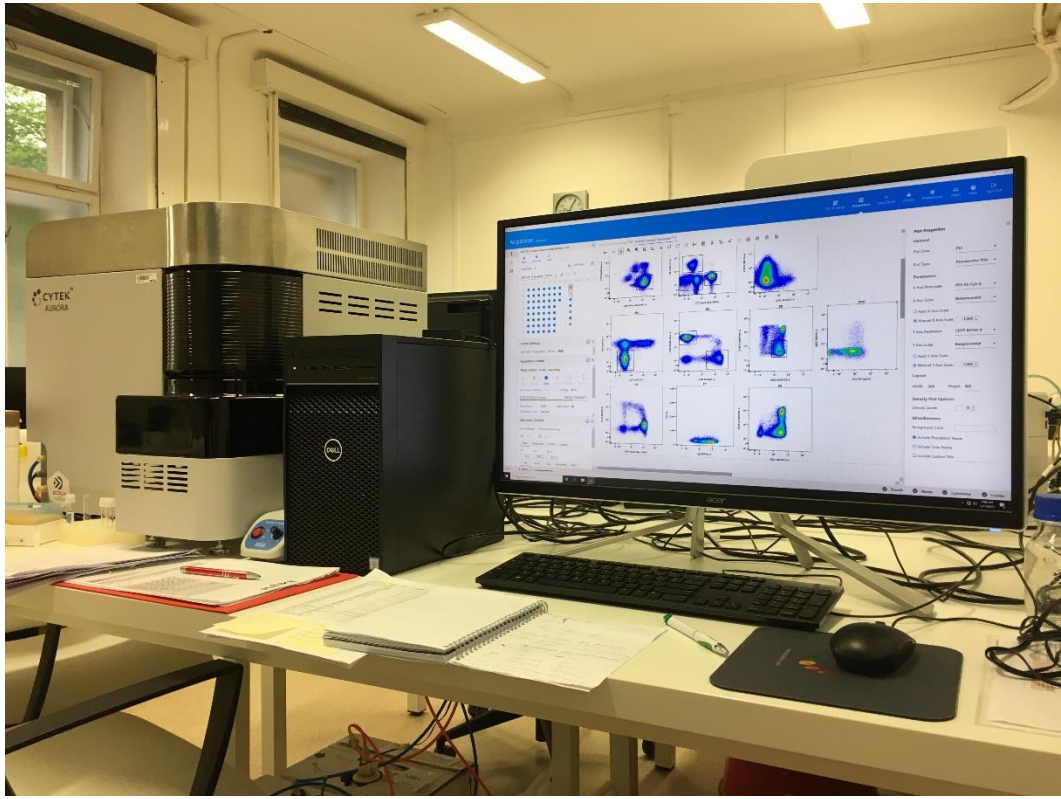
Lázničková P, Bendíčková K, Frič J, unpublished

Deep immunophenotyping of neuroblastoma patients and survivors - ongoing analysis

Spectral flow cytometer – Cytek Aurora

- 32 markers at once

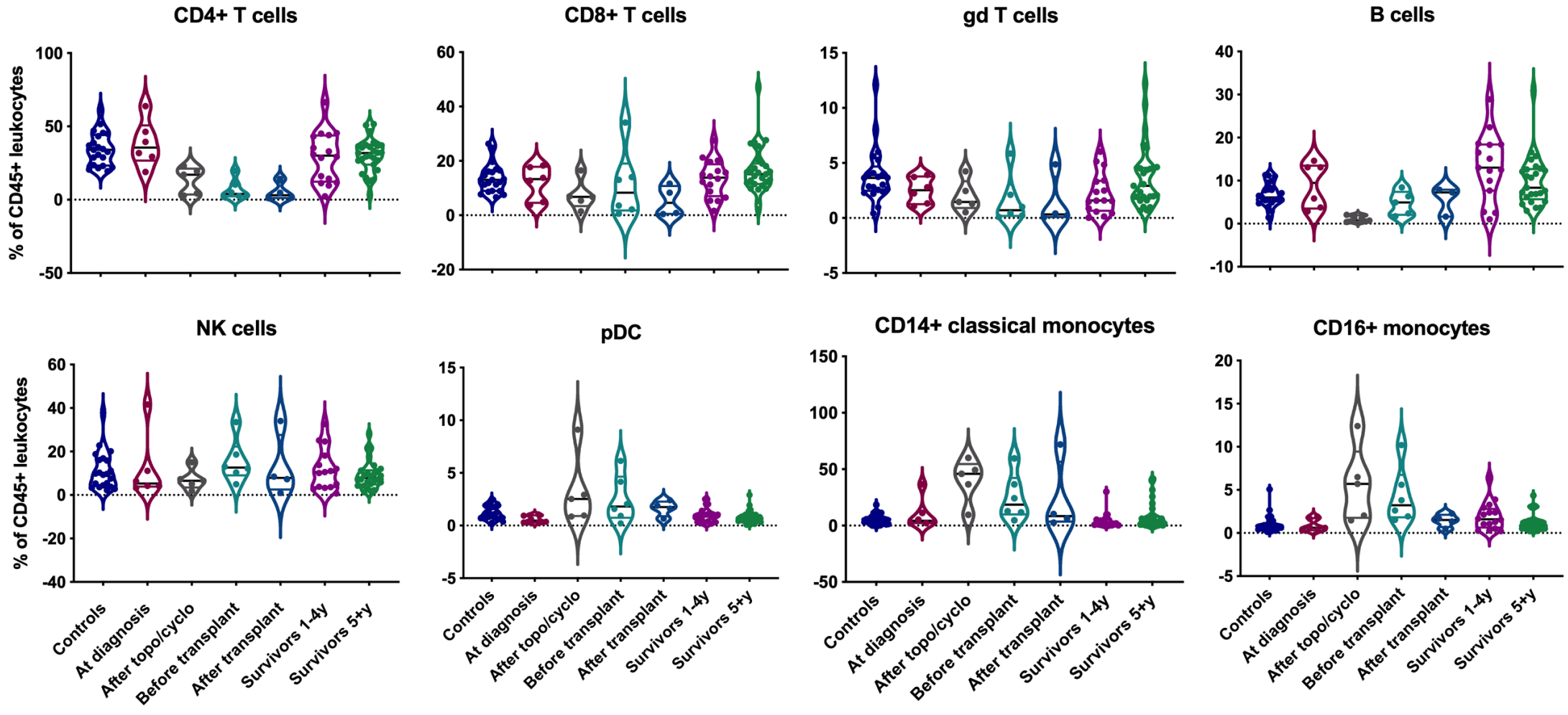
- T cells, B cells, Monocytes, NK cells, DCs
- activation, maturation, aging/exhaustion markers



Jan Musil, PhD, Dpt of Immunomonitoring
Tereza Feglarová, PhD, Dpt of Modern Immunotherapy

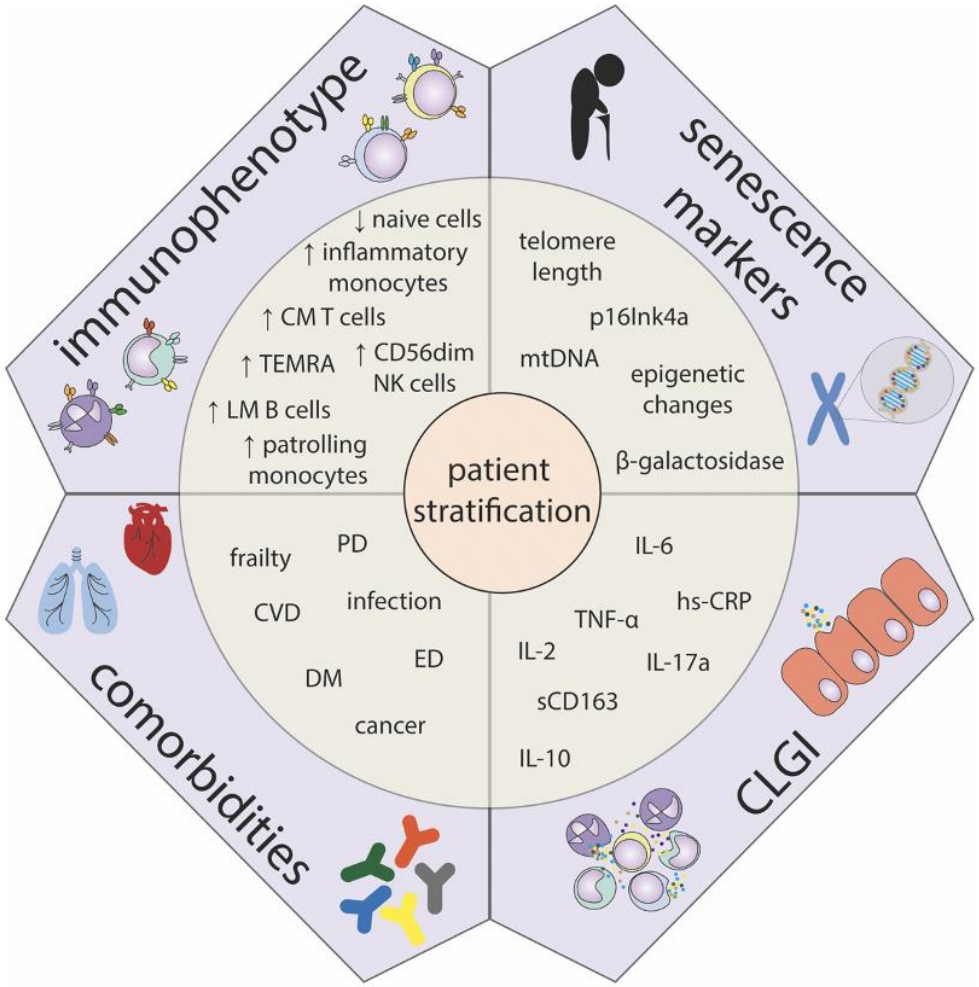
Lázničková P, Bendíčková K, Frič J, unpublished

Major peripheral blood mononuclear cell lineages during HR NB treatment - ongoing analysis



Lázničková P, Bendíčková K, Frič J, unpublished

Research of immunosenecence in cohorts with chronic inflammation and comorbidities



Jose SS, Tidu F, Burilova P, Kepak T, Bendickova K, Fric J.: The Telomerase Complex Directly Controls Hematopoietic Stem Cell Differentiation and Senescence in an Induced Pluripotent Stem Cell Model of Telomeropathy.: Front Genet. 2018 Aug 29;9:345. doi: 10.3389/fgene.2018.00345.

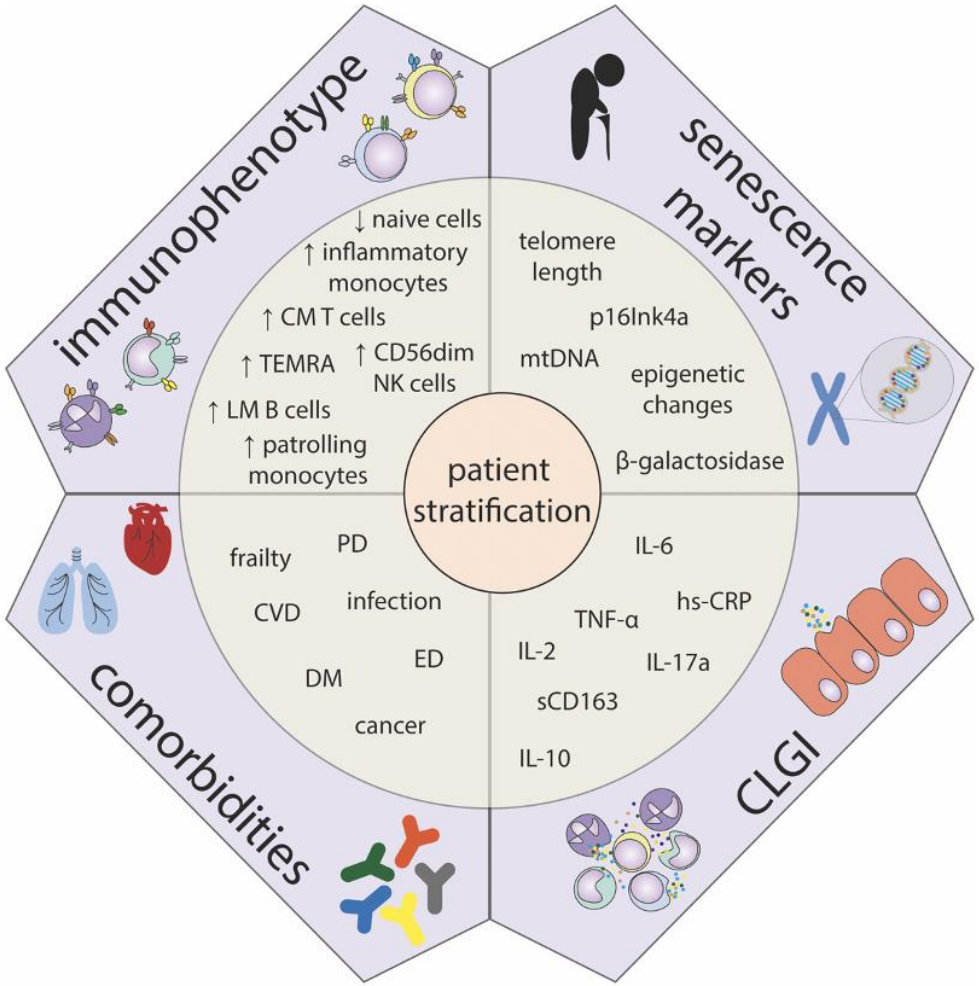
Jose SS, Bendickova K, Fric J.: High-Throughput Screening of Senescence Markers in Hematopoietic Stem Cells Derived from Induced Pluripotent Stem Cells. Methods Mol Biol. 2018;1771:121-130. doi: 10.1007/978-1-4939-7792-5_10.

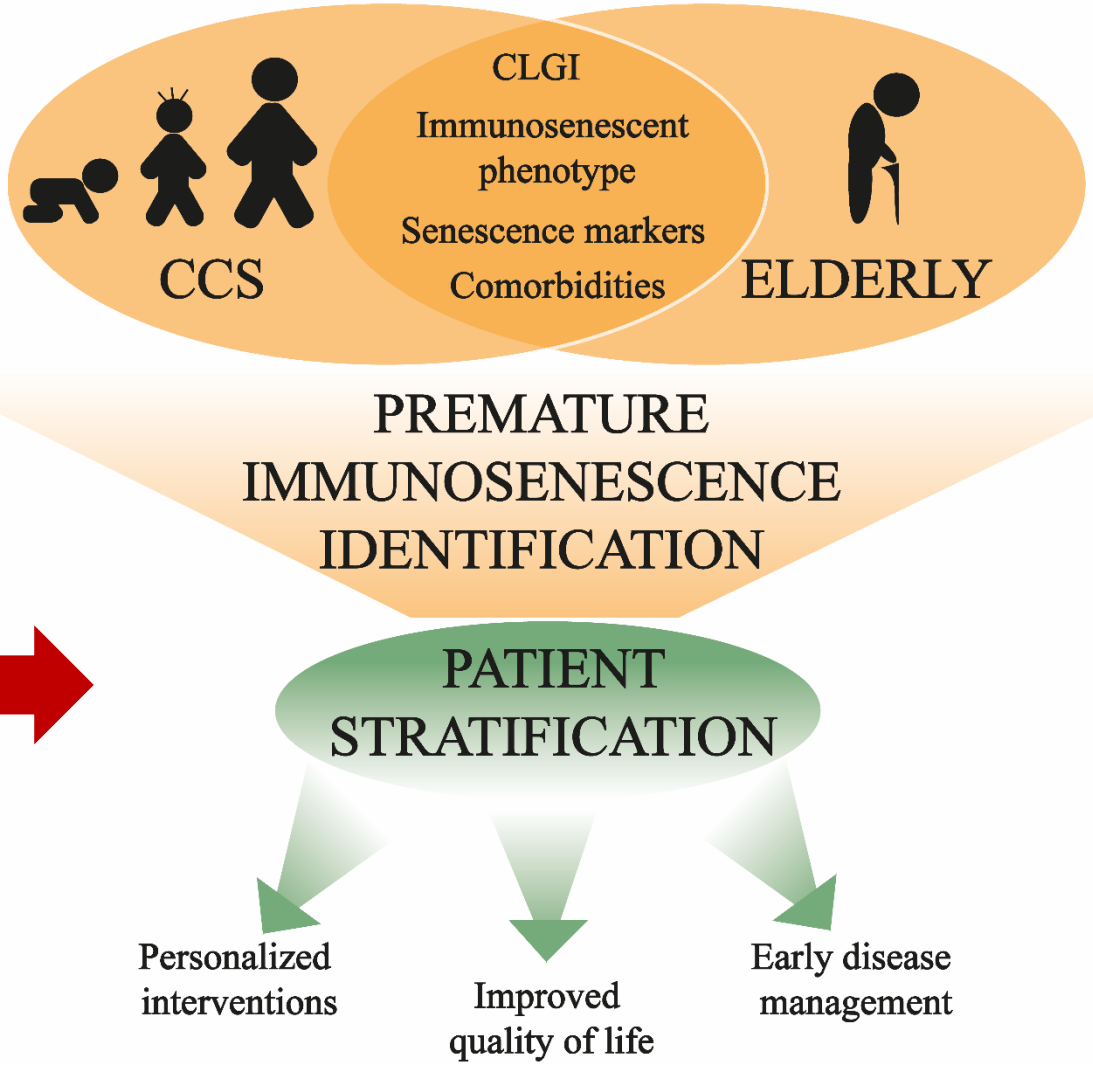
Jose SS, Bendickova K, Kepak T, Krenova Z and Fric J Chronic Inflammation in Immune Aging: Role of Pattern Recognition Receptor Crosstalk with the Telomere Complex? Front. Immunol., 2017

Lázničková P, Kepák T**, Hortová-Kohoutková M, Horváth L**, Sheardová K, Marciniak R, Vacca C, Šiklová M, Zelante T, Rossmeislová L, Křenová Z, Štěrba J, **Bendíčková K, Frič J:** Childhood survivors of high-risk neuroblastoma show signs of immune recovery and not immunosenescence. Eur J Immunol. (2020) Aug 3. (IF 5.179) doi: 10.1002/eji.202048541. PMID: 32744364

Marciniak R, Šumec R, Vyhnálek M, **Bendíčková K, Lázničková P**, Forte G, Jeleník A, Římalová V, **Frič J,** Hort J, Sheardová K.: The Effect of Mindfulness-Based Stress Reduction (MBSR) on Depression, Cognition, and Immunity in Mild Cognitive Impairment: A Pilot Feasibility Study. Clin Interv Aging. (2020) Aug 12;15:1365-1381. (IF 3.023) doi: 10.2147/CIA.S249196. PMID: 32848377

Long-term goals of immunosenescence research - stratification of survivors with increased risk of comorbidities development





Marcela Hortová-Kohoutková
Kamila Bendíčková
Petra Lázničková
Ivana Andrejčinová
Ondřej Vymazal
Veronika Bosáková
Miriam Slezáková

Statistics department
Michael Šitina

DTM-Dementia
Kateřina Sheardová
Rafal Marciniak

Giancarlo Forte

Department of Modern Immunotherapy
Tereza Feglarová
Lucie Sládková
Eva Mašínová
Marek Jedlička
Tereza Fiedlerová

Children Hospital, Brno
Tomáš Kepák (+POTR)
Zdeňka Křenová
Petr Šťourač

Lenka Rossmeislová

University of Perugia
Teresa Zelante
Giuseppe Paolicelli
Luigina Romani

Latvian Institute of Organic Synthesis
Marina Marecka-Kuka

Singapore Immunology Network, A*Star
Anis Larbi

Tereza Kubasová
Ivan Rychlík

Interreg Österreich-Tschechische Republik
Europäischer Fonds für regionale Entwicklung
European Commission
MARIE CURIE ACTIONS

@FricLab
jan.fric@fnusa.cz