

Hojící se rána jako nádorový archetyp

Karel Smetana, Jr., Lukáš Lačina, Michal, Kolář, Petr Malý,
Radek Šindelka

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Ústav molekulární genetiky, AVČR, Praha, Česká republika

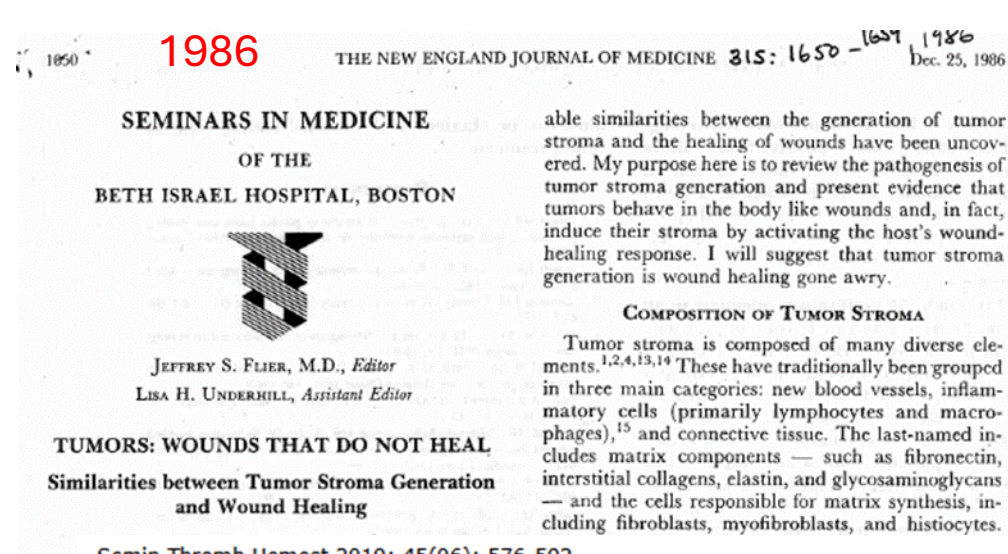
Biotechnologický ústav, AVČR, Praha, Česká republika

Ústav imunologie, Lékařská fakulta, Palackého Univerzita, Olomouc, Česká republika

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Tumor je rána, která se nehojí



Semin Thromb Hemost 2019; 45(06): 576-592
DOI: 10.1055/s-0039-1687908



Review Article

Thieme Medical Publishers 333 Seventh Avenue, New York, NY 10001, USA.

Tumors: Wounds That Do Not Heal—A Historical Perspective with a Focus on the Fundamental Roles of Increased Vascular Permeability and Clotting

Harold F. Dvorak

> [Author Affiliations](#)

Funding This work was supported by NIH grants P01 CA92644 and R01CA142262, by SDG, and by a contract from the National Foundation for Cancer Research.



NIH Public Access

Author Manuscript

Cancer Immunol Res. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Cancer Immunol Res. 2015 January ; 3(1): 1–11. doi:10.1158/2326-6066.CIR-14-0209.

Tumors: Wounds that do not heal--Redux

Harold F. Dvorak

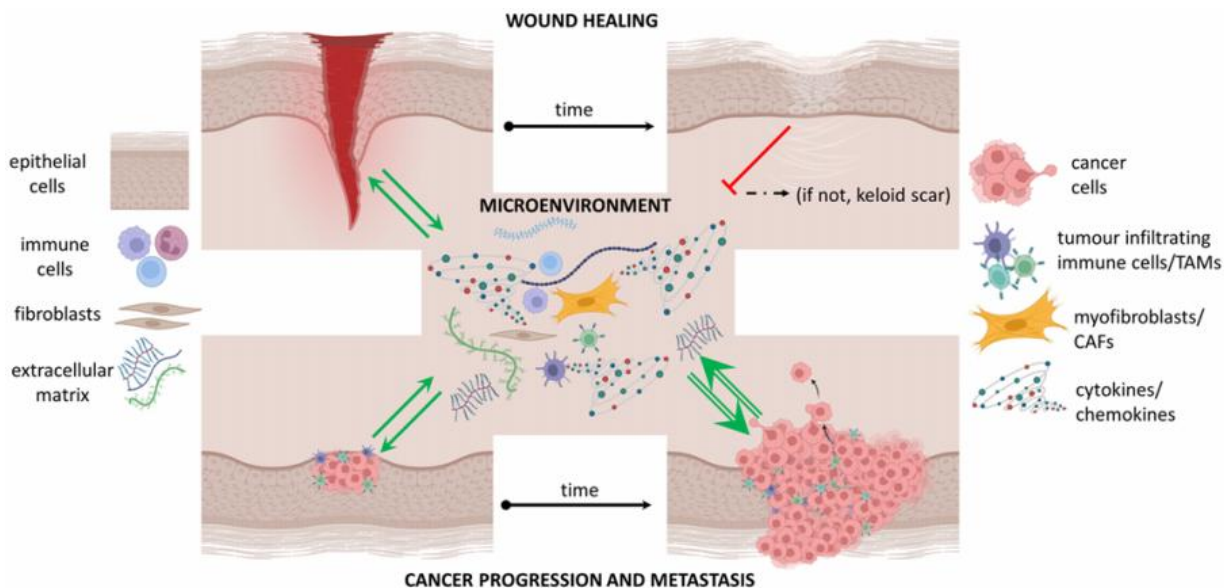




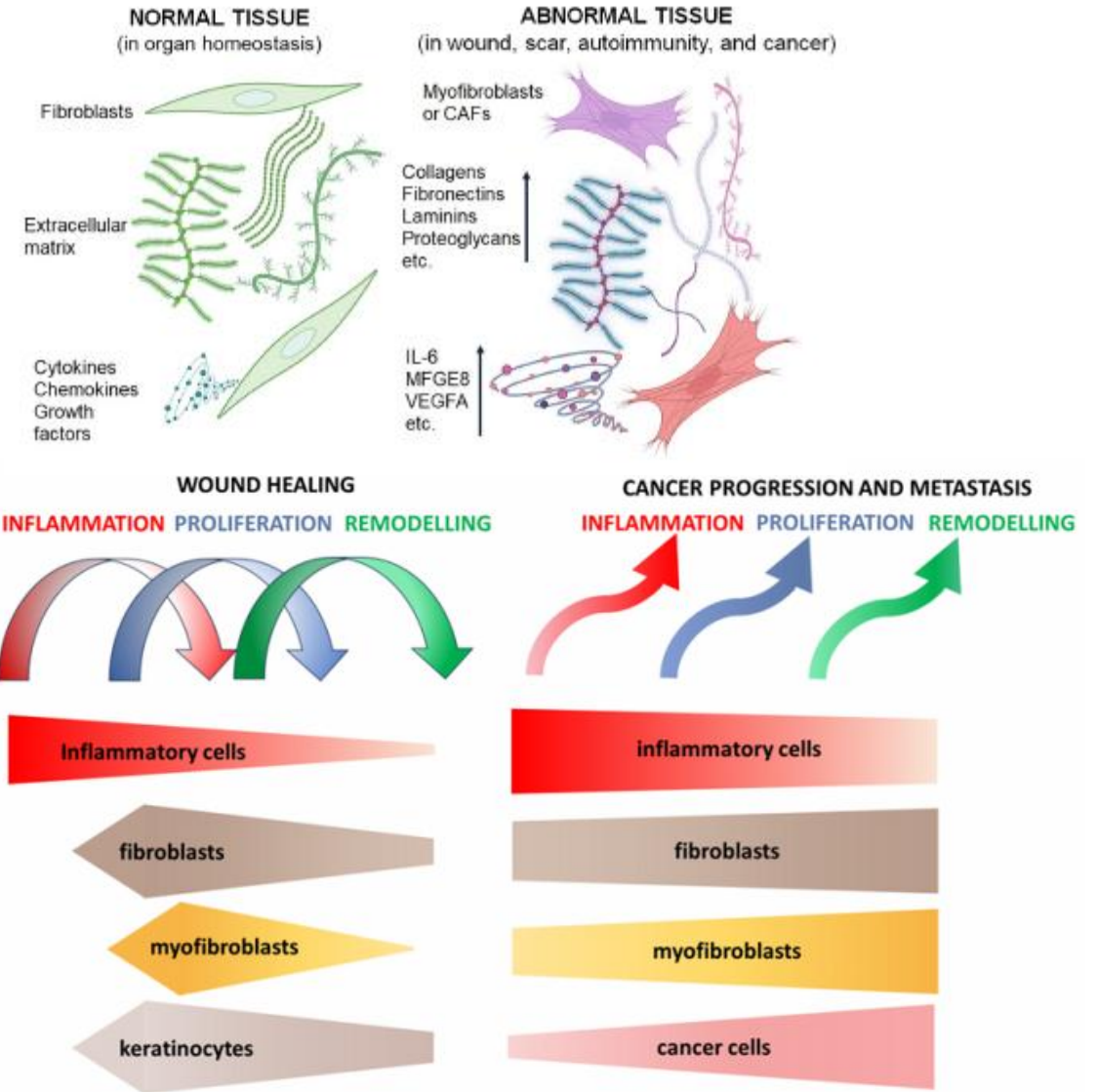
OPEN ACCESS

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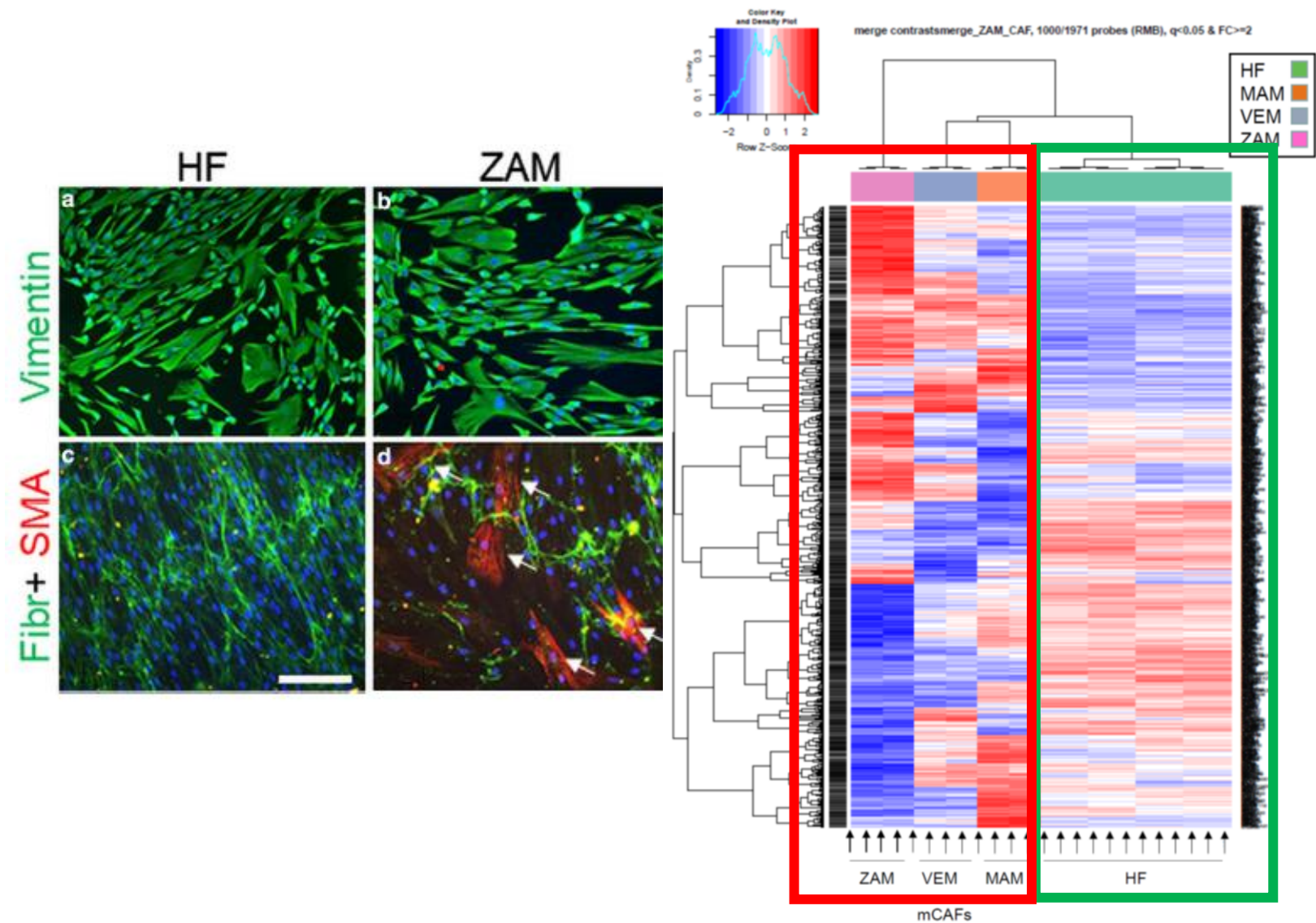
Wound healing: insights into autoimmunity, ageing, and cancer ecosystems through inflammation and IL-6 modulation

Lukáš Lacina^{1,2,3}, Michal Kolář⁴, Lucie Pfeiferová⁴, Peter Gal^{5,6,7,8*} and Karel Smetana Jr.^{1,2*}

Granulační tkáň u hojící se rány je podobná stromatu většiny karcinomů.



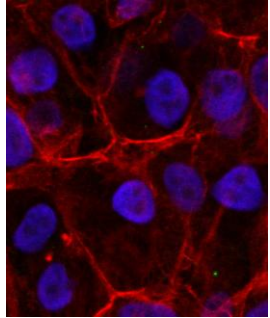
CAF představují důležitou složku nádorového ekosystému. Liší se od normálních fibroblastů aktivitou genů stimulující zánět.



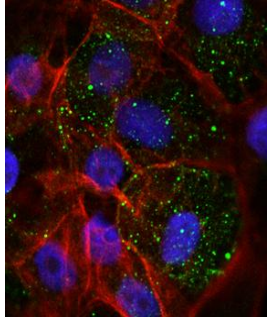
Symbol	Gene name	LFC	FDR	Kerat	Melanoma
IL8	interleukin 8 <i>CXCL8</i>	5.5	2.6e-06	+	+
ACAN	Aggrecan	4.27	3.6e-07	+	+
IL6	interleukin 6 (interferon, beta 2) <i>IL6</i>	3.87	7.5e-13	+	+
IL1B	Interleukin 1, beta <i>IL1B</i>	2.52	3.6e-08		
CXCL1	chemokine (C-C-C motif) ligand 1 (melanoma growth stimulating activity, alpha) <i>CXCL1</i>	2.49	0.0045	+	+
HBEGF	heparin-binding EGF-like growth factor	1.74	8.5e-06	+	
BDNF	brain-derived neurotrophic factor	1.46	5.3e-06		+
TGFB2	transforming growth factor, beta 2 <i>TGFB2</i>	1.25	0.00017		+
IGFBP7	insulin-like growth factor binding protein 7	1.23	0.00012	+	
GAP43	growth associated protein 43	1.21	2.3e-05	+	
CXCL16	chemokine (C-X-C motif) ligand 16 <i>CXCL16</i>	1.17	6.3e-05		+
BMP6	bone morphogenetic protein 6	1.11	0.0032		
KAZALD1	Kazal type serine peptidase inhibitor domain 1	1.03	0.016		
VEGFC	vascular endothelial growth factor C <i>VEGFC</i>	1.02	0.0066	+	+
CTGF	connective tissue growth factor	0.95	0.022		+
PDGFR	platelet-derived growth factor receptor-like	0.93	0.055		+
LEPRE1	leprecan-like 1	0.91	0.017		
IL17D	interleukin 17D <i>IL17D</i>	0.88	0.00021		+
VEGFA	vascular endothelial growth factor A <i>VEGFA</i>	0.82	0.029	+	+
BMP2	bone morphogenetic protein 2	0.73	0.028		+
LEPRE1	leucine proline-enriched proteoglycan (leprecan) 1	0.72	0.0011		

IL-6 je jedním z mediátorů zánětu. Asi pro nádor důležitý. Jeho hladina se zvyšuje při stárnutí.

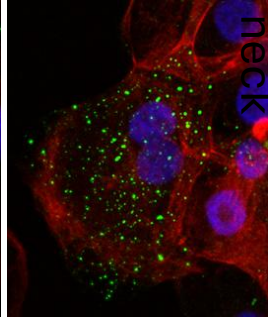
IL-4



IL-6



CXCL-8



Head and neck

Histol Histopathol (2019) 34: 125-136

<http://www.hh.um.es>

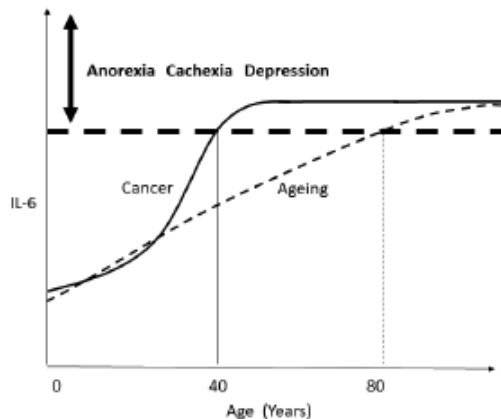
Histology and Histopathology
From Cell Biology to Tissue Engineering

Review

Interleukin-6: a molecule with complex biological impact in cancer

Lukáš Lacina^{1,2,3}, Jan Brábek⁴, Vladimír Král², Ondřej Kodet^{1,2,3} and Karel Smetana Jr^{1,2}

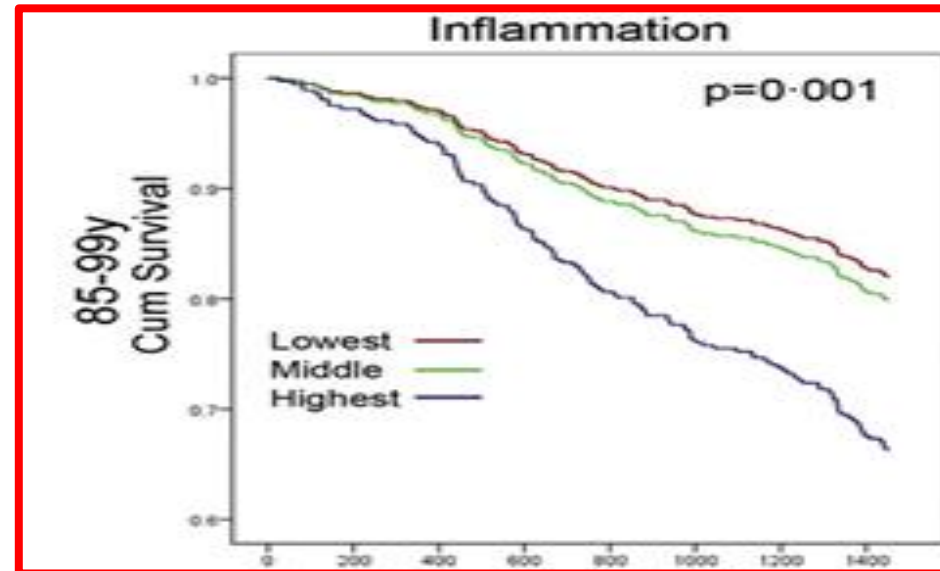
Cancer
Ovary
Prostate
Breast
Liver
Oral cavity, head and neck
Esophagus
Stomach
Colorectal
Pancreas
Larynx
Lung
Thyroid
Melanoma
Bone sarcoma

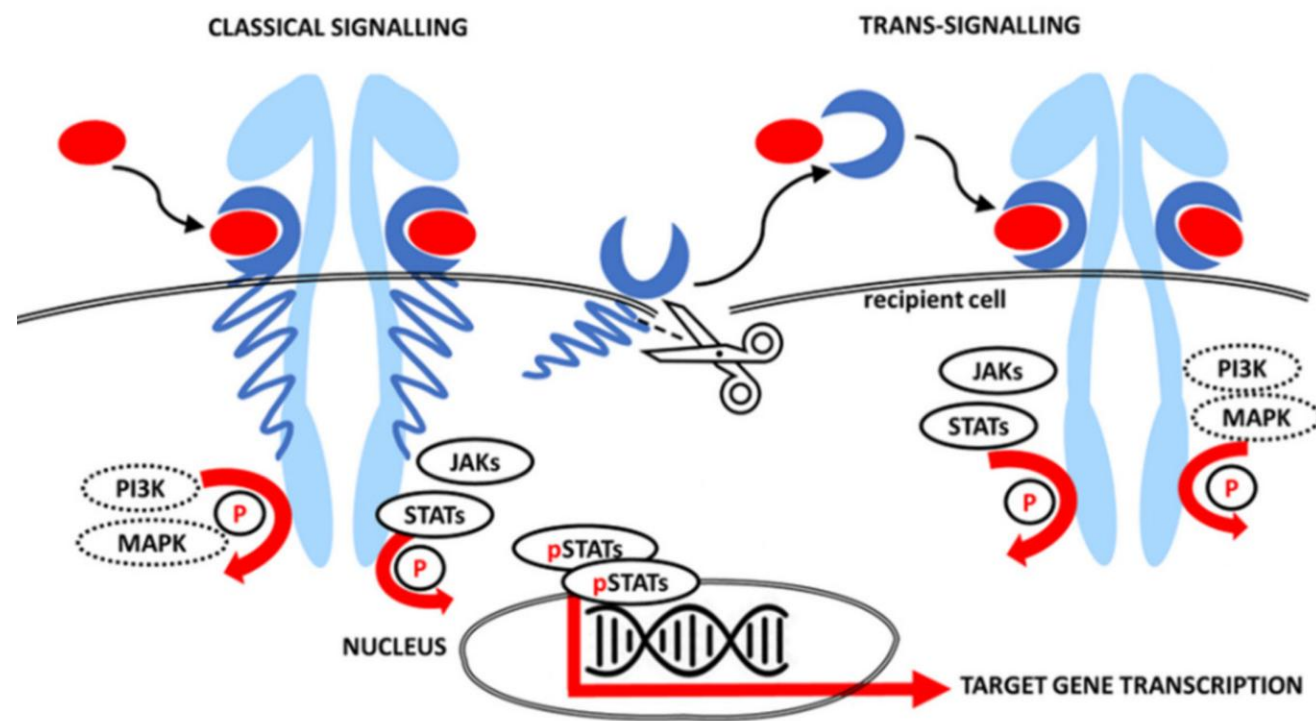


Research Article

Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians

Yasumichi Arai^{a,1}, Carmen M. Martin-Ruiz^{b,1}, Michiyo Takayama^c, Yukiko Abe^a, Toru Takebayashi^d, Shigeo Koyasu^{f,g}, Makoto Suematsu^{a,e}, Nobuyoshi Hirose^{a,*,2}, Thomas von Zglinicki^{b,*,2}





Receptor pro IL-6 (IL-6R) je komplikovaný. Podjednotka α je transmembránová nebo solubilní. Její kooperace s gp130 (β podjednotka, IL-6 ST) je nezbytná pro úspěšnou signalizaci. Ta se projeví fosforylací STAT3.

FDA + EMA schválili tocilizumab pro léčbu autoimunitních onemocnění a COVID-19. Představuje zlatý standard.



SELECT A CONDITION:

Moderate to Severe Rheumatoid Arthritis (RA)



Systemic Sclerosis with Early Interstitial Lung Disease (SSc-ILD)



Giant Cell Arteritis (GCA)



Polyarticular Juvenile Idiopathic Arthritis (PJIA)



Systemic Juvenile Idiopathic Arthritis (SJIA)



Coronavirus Disease 2019 (COVID-19)



RESEARCH

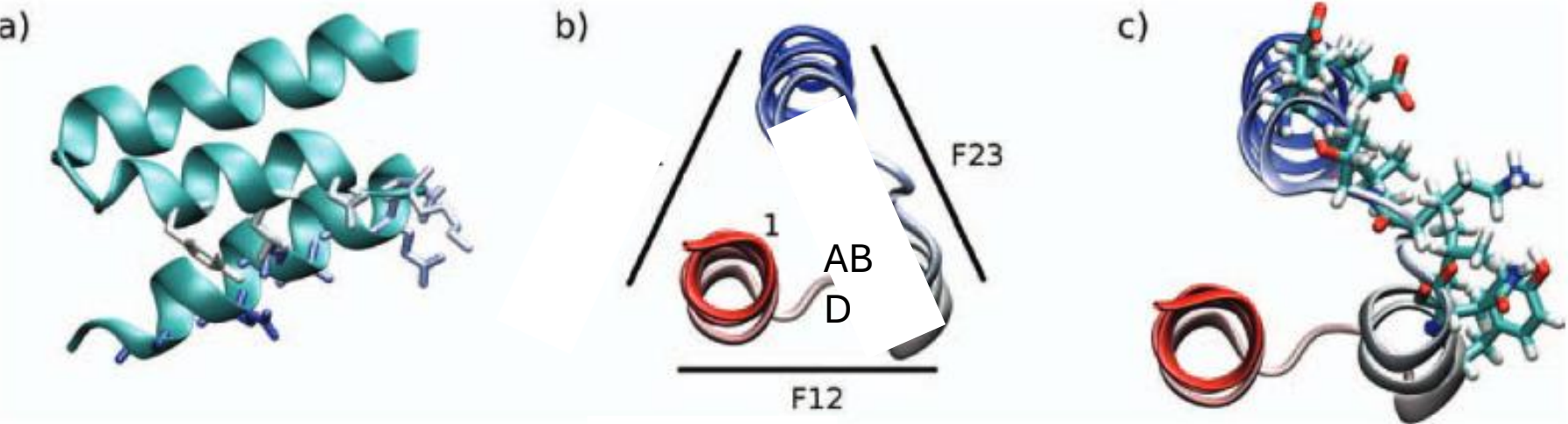
Open Access



Small protein blockers of human IL-6 receptor alpha inhibit proliferation and migration of cancer cells

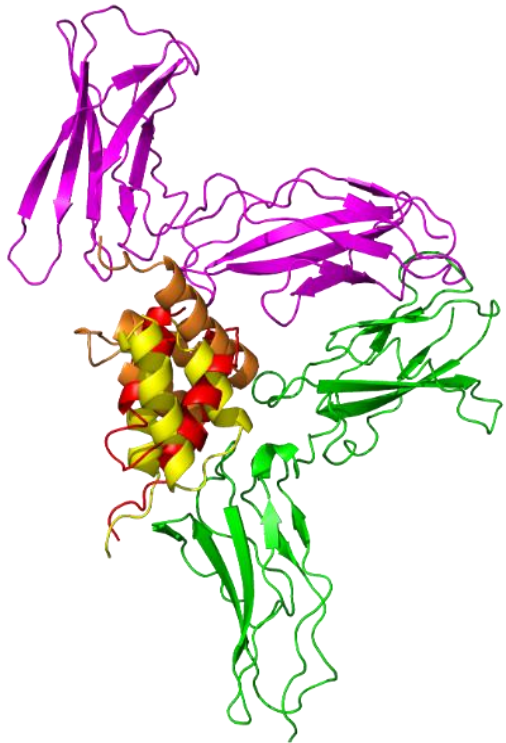
Yaroslava Groza¹, Lukáš Lacina^{2,3*}, Milan Kuchař¹, Leona Rašková Kafková⁴, Kateřina Zachová⁴, Olga Janoušková⁵, Radim Osička⁶, Jiří Černý⁷, Hana Petroková¹, Joanna Maria Mierzwicka¹, Natalya Panova¹, Petr Kosztu⁴, Kristýna Sloupenská⁴, Jan Malý⁵, Jozef Škarda⁸, Milan Raška⁴, Karel Smetana Jr.² and Petr Malý^{1*}

Albumin-vážící
doména (ABD)
streptokokového
G proteinu jako
základ pro vývoj
NEF inhibitorů α
řetězce IL-6R
(IL-6R α)

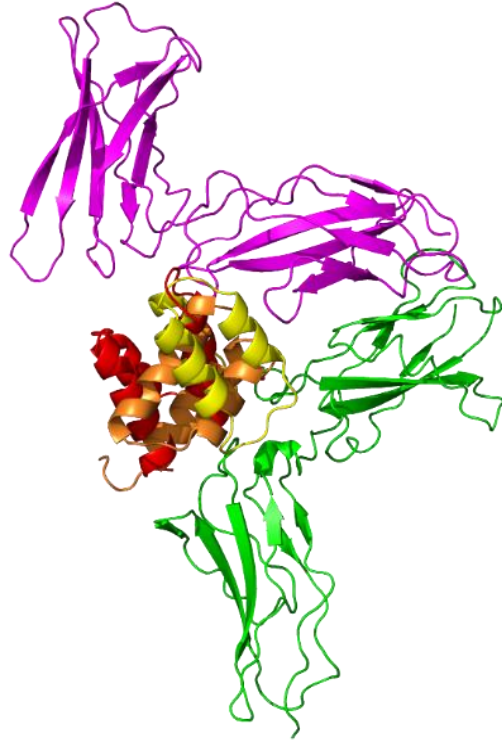


Randomizace 11 aminokyselin
ABD mezi helixem 2 a 3.
Kombinatorická knihovna
teoreticky obsahuje **10¹⁴**
variant.

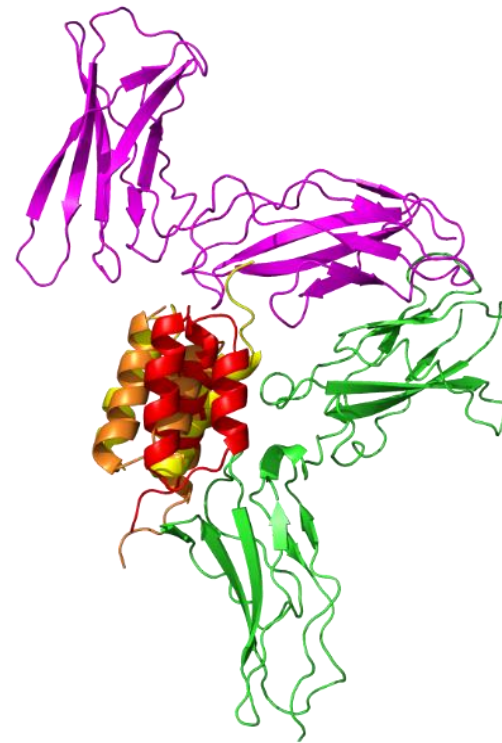
Predikce vazeb NEF variant s IL-6R α a IL-6R β komplexem



NEF108



NEF163



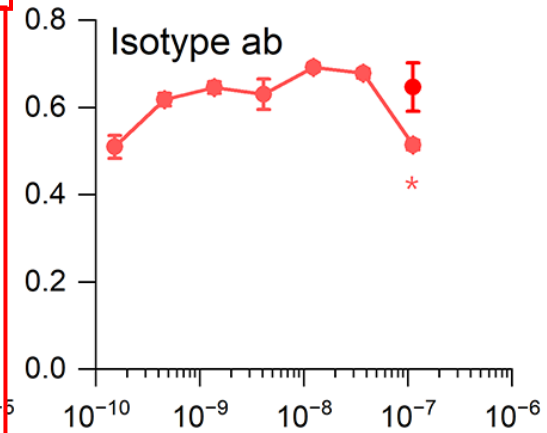
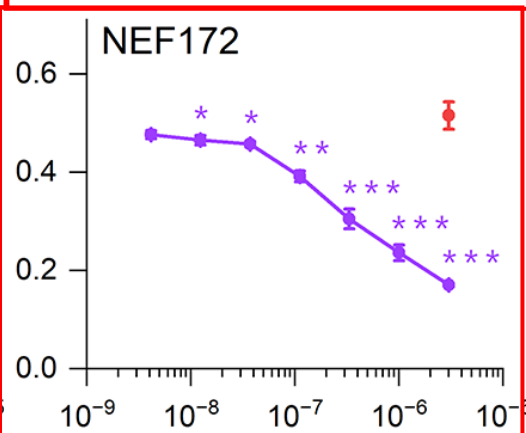
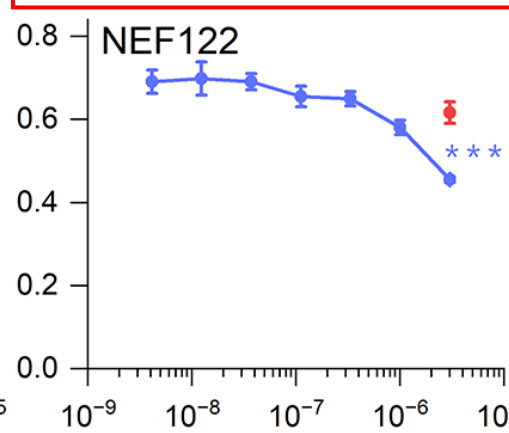
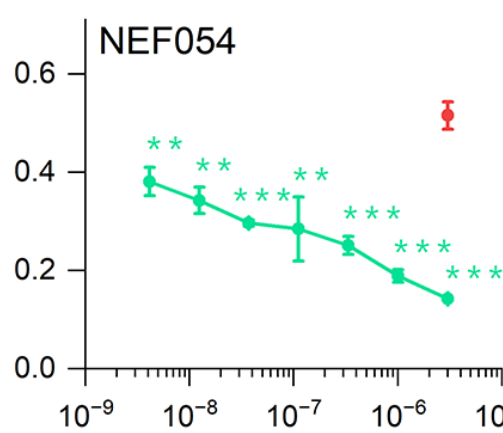
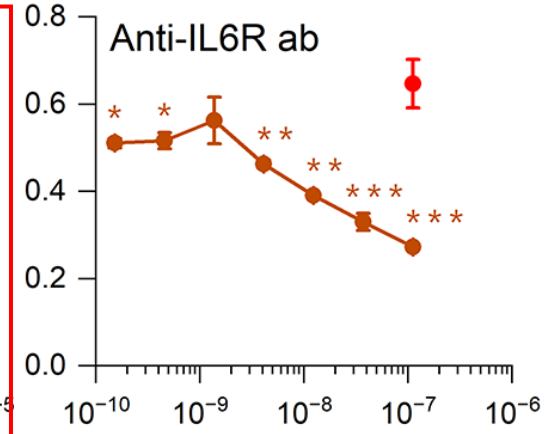
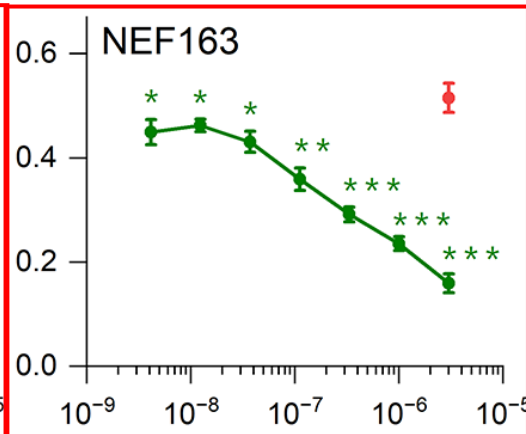
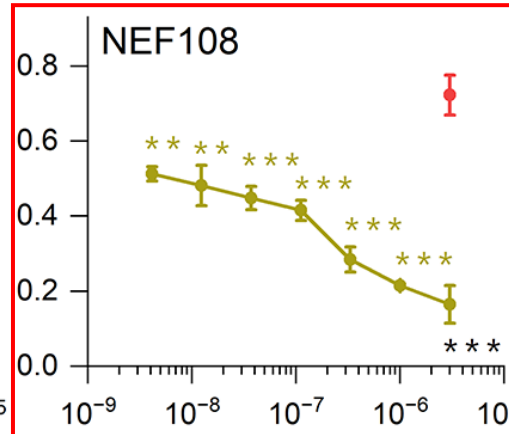
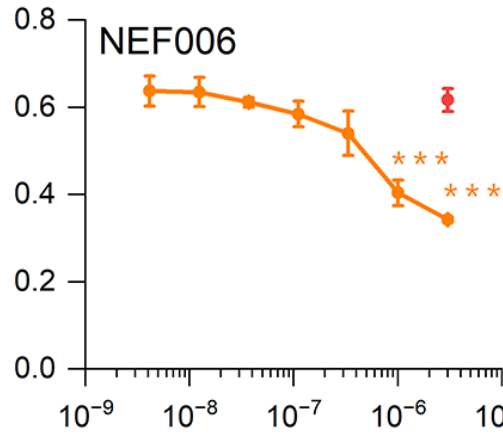
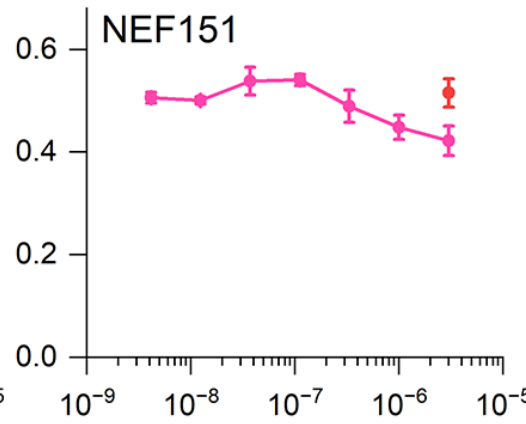
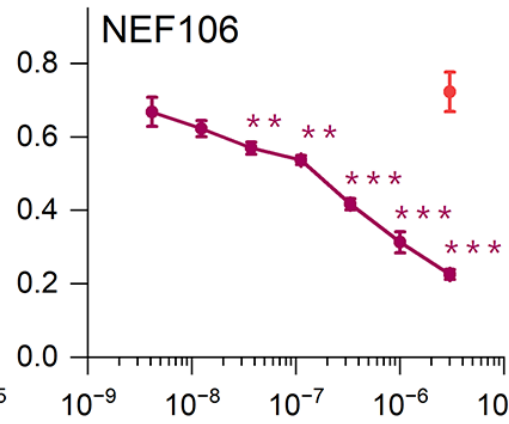
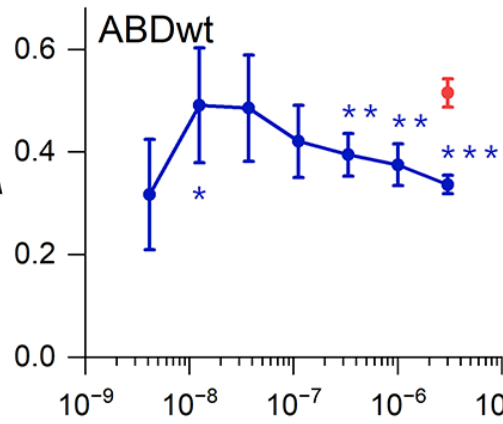
NEF172



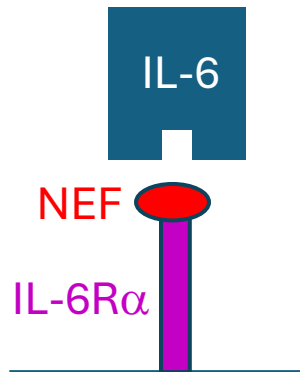
IL-6

Vazba IL-6 k
imobilizovanému
IL-6R α je inhibována
NEF.

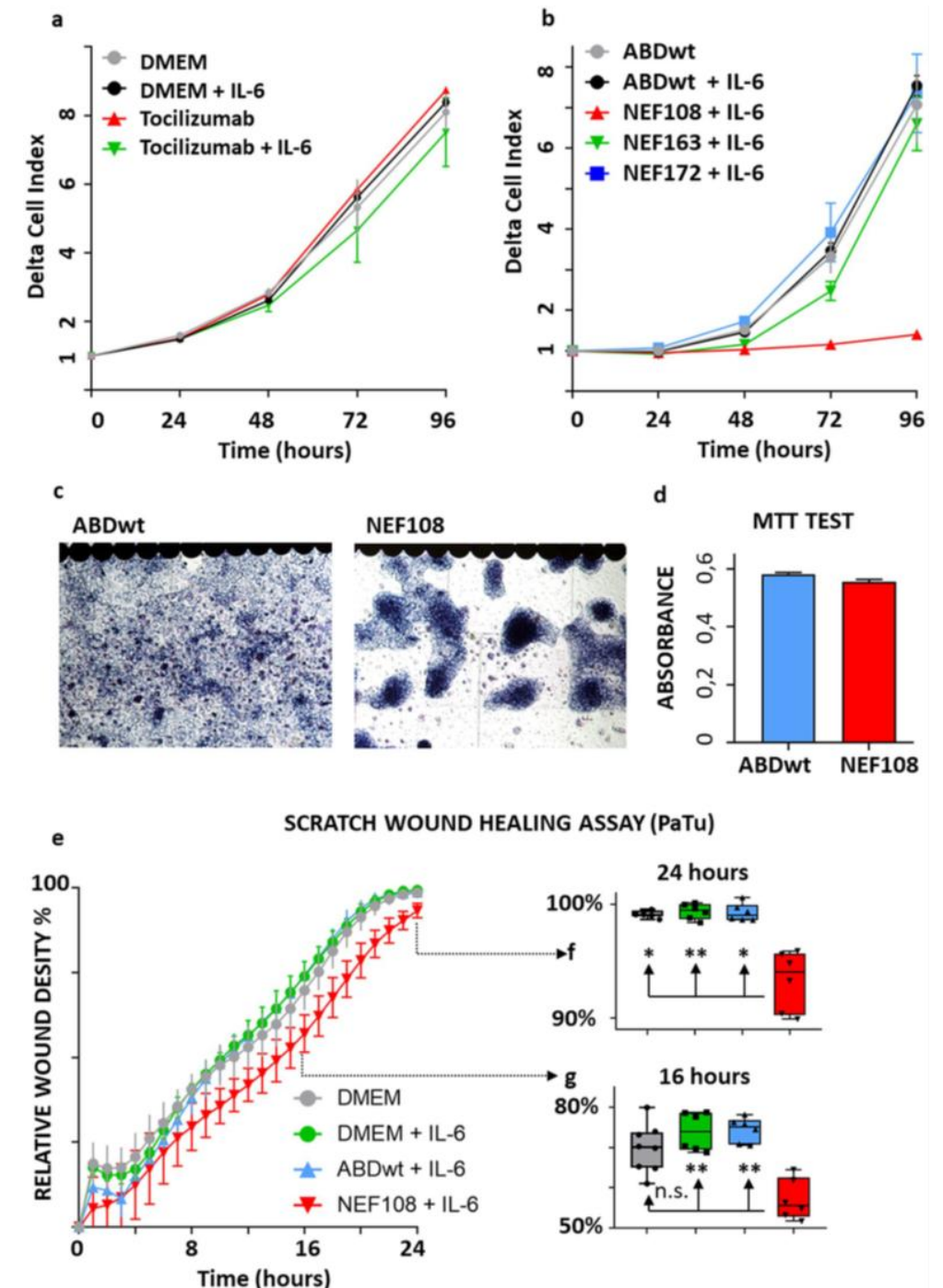
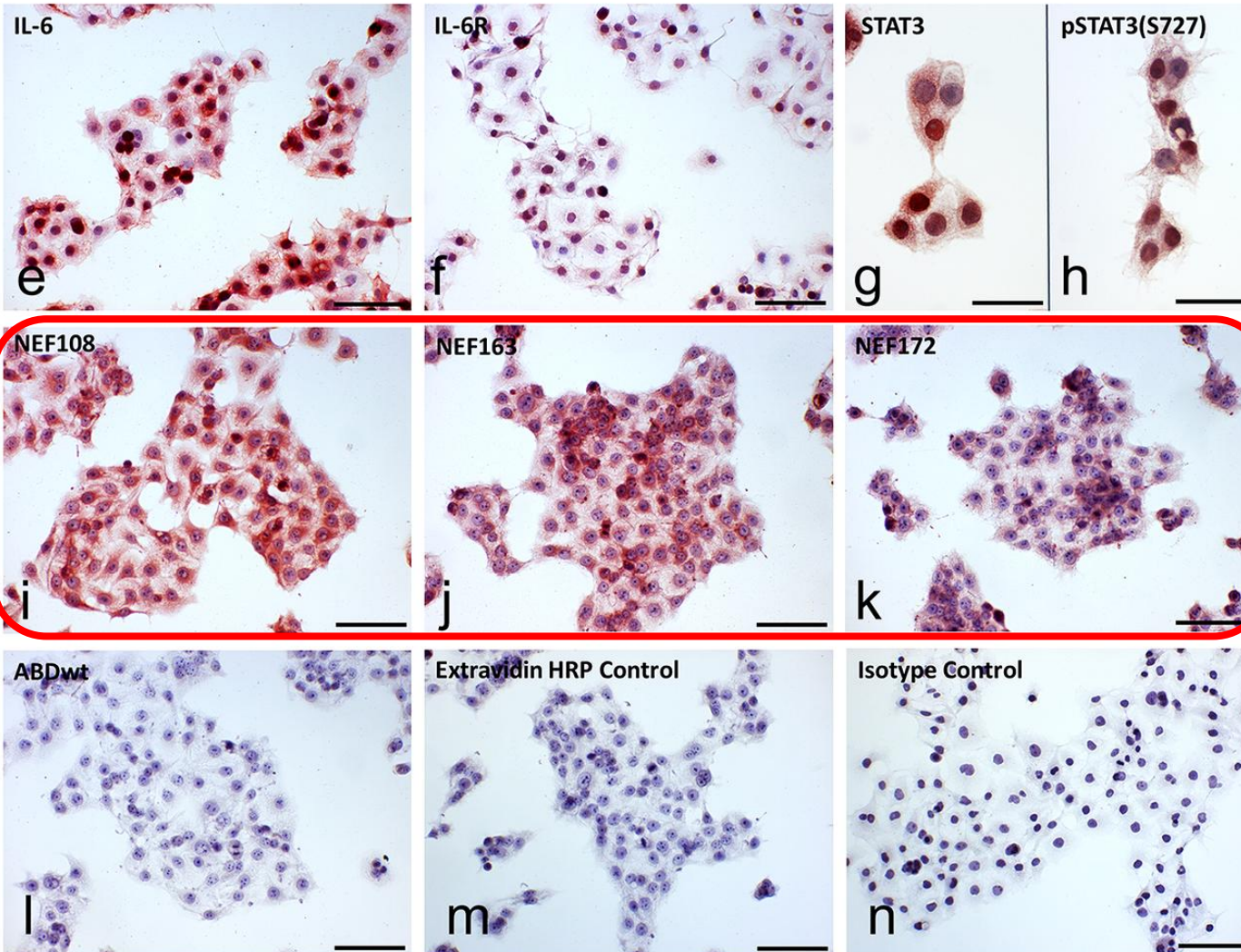
Absorbance (450 nm)



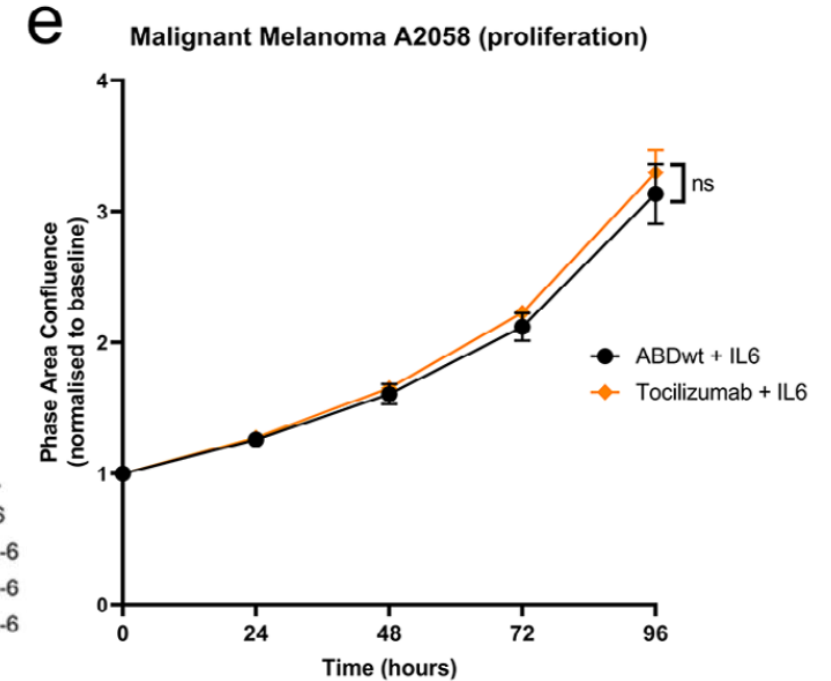
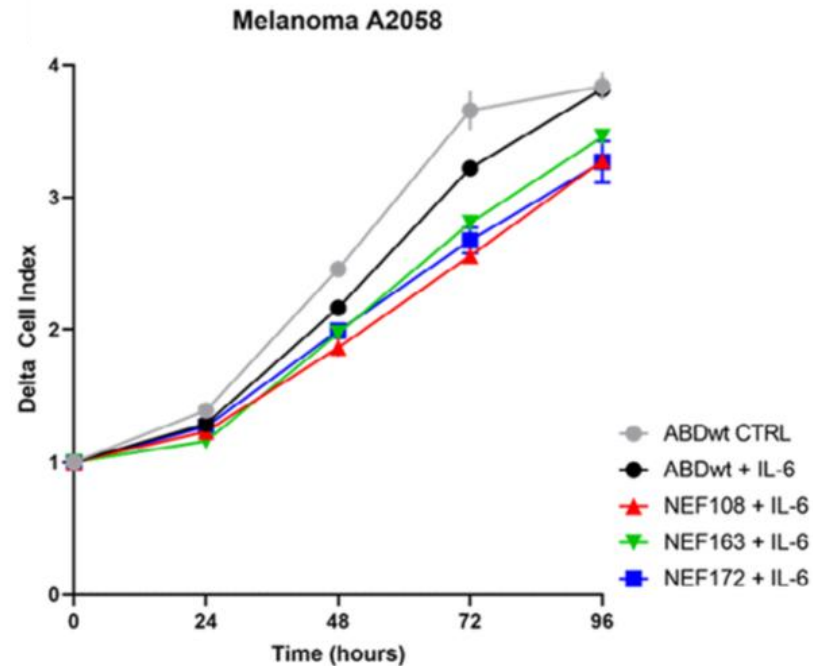
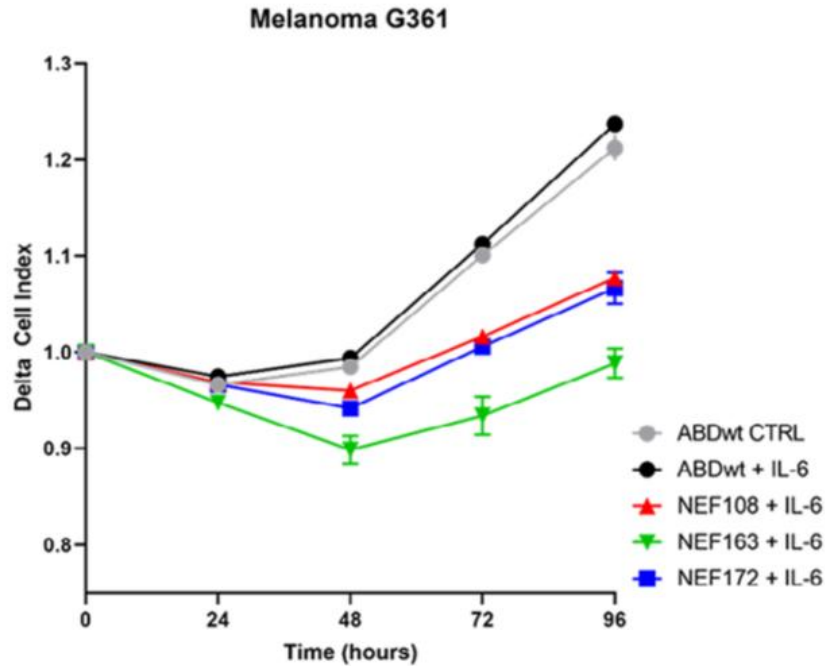
NEF variant concentration (M)



Vliv NEF inhibitorů na buňky PDAC - srovnání s tocilizumabem



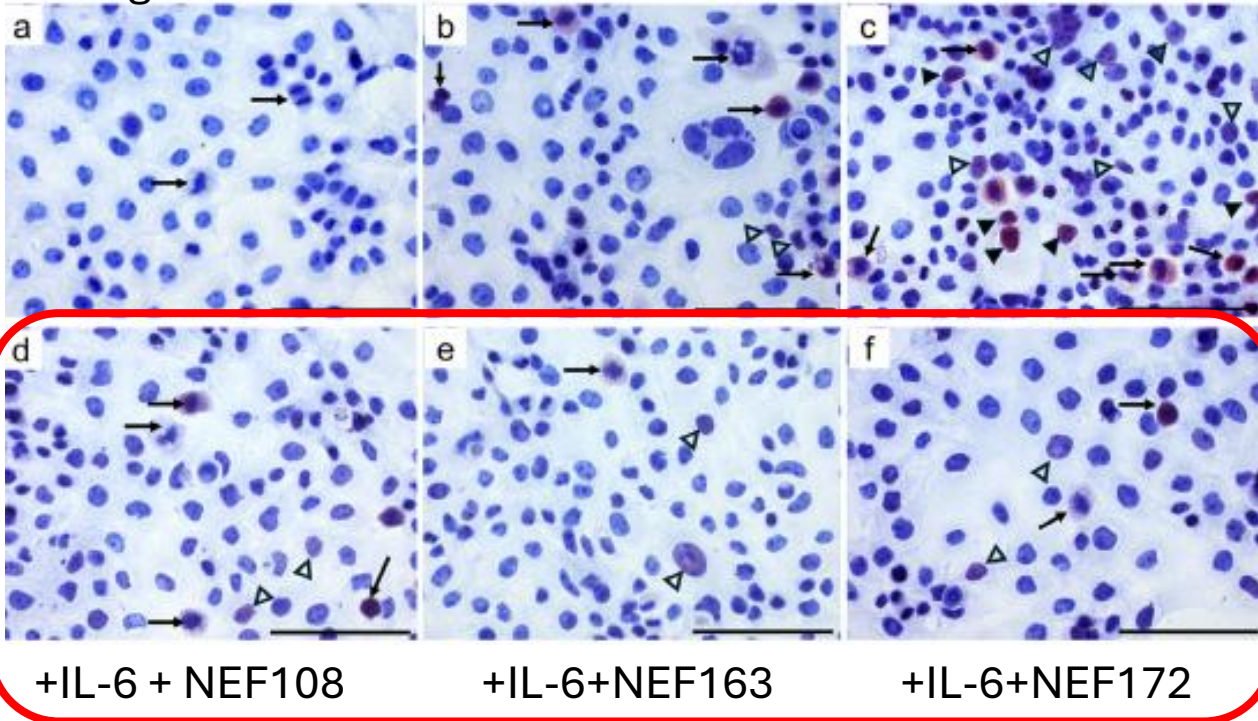
Vliv NEF inhibitorů na buňky melanomu -srovnání s tocilizumabem



Vliv NEF inhibitorů na expresi P-STAT3 u buněk PDAC po stimulaci IL-6

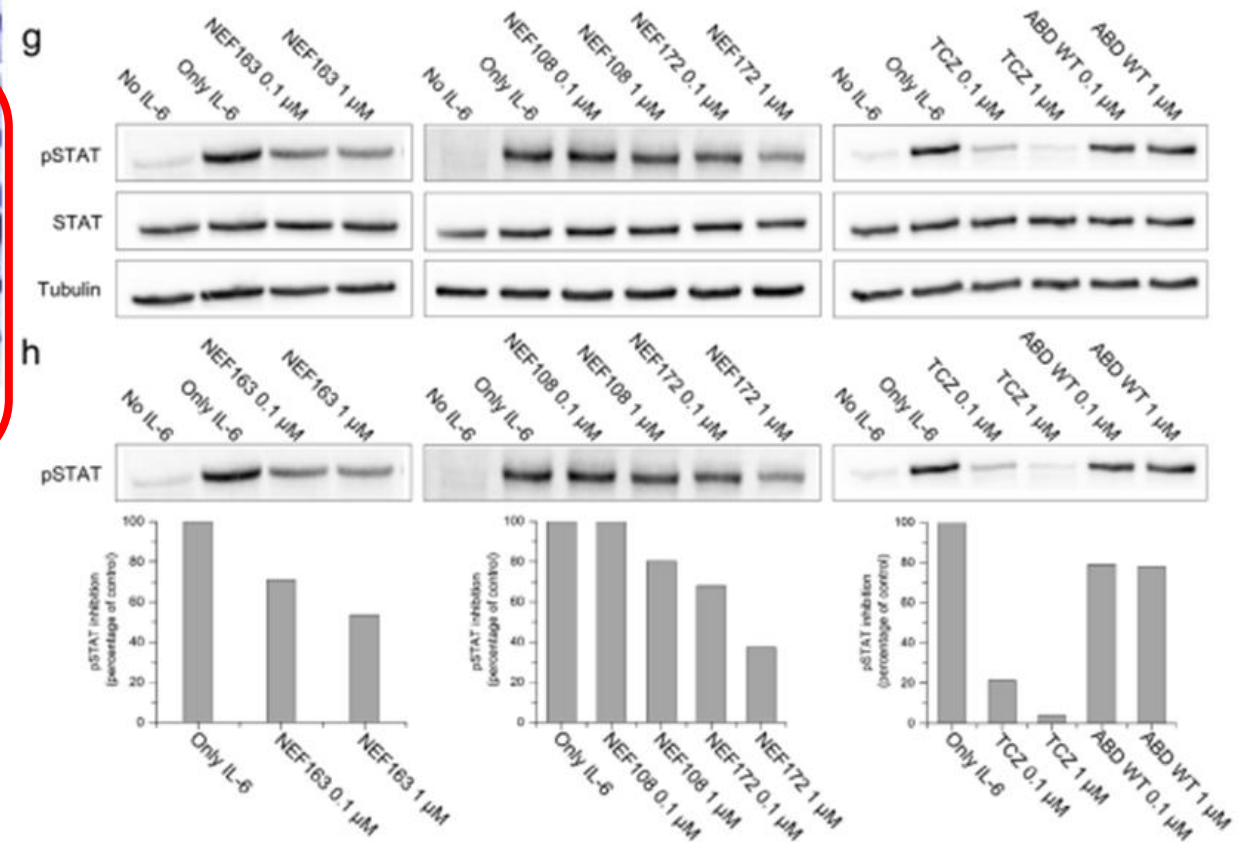
Negative control

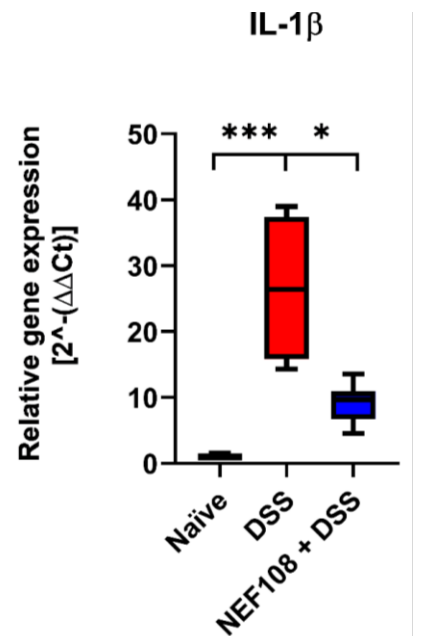
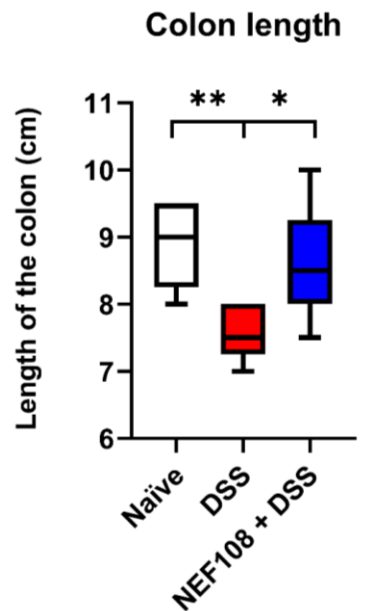
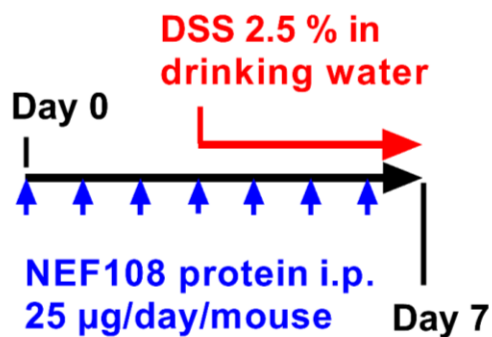
+IL-6



g

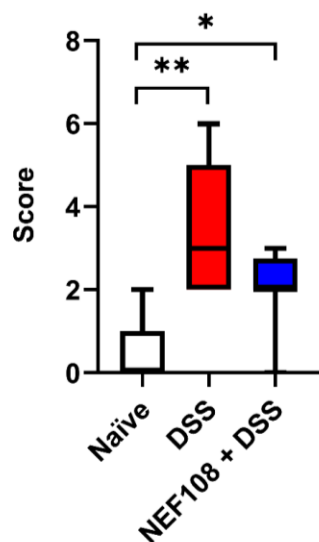
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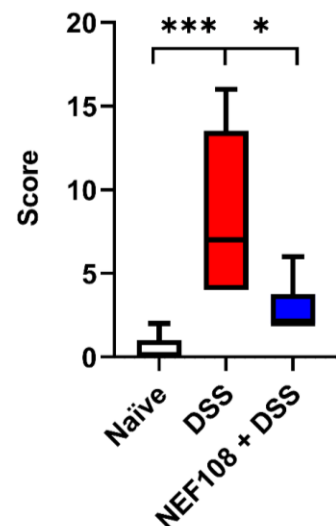


Protektivní účinek inhibitoru NEF108 v preventivním léčebném režimu testovaném na modelu DSS-indukované kolitidy.

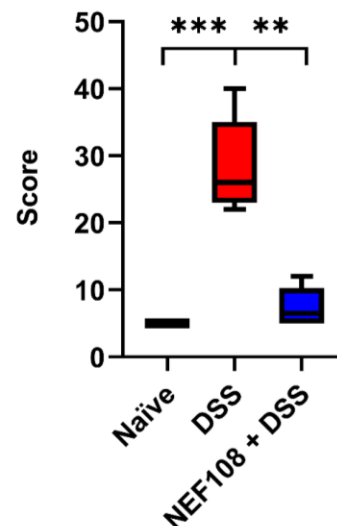
Inflammatory infiltration



Epithelial changes



Mucosal architecture



Pronádorový význam zánětu a IL-6 je klíčový

Inflammation and cancer: friend or foe?

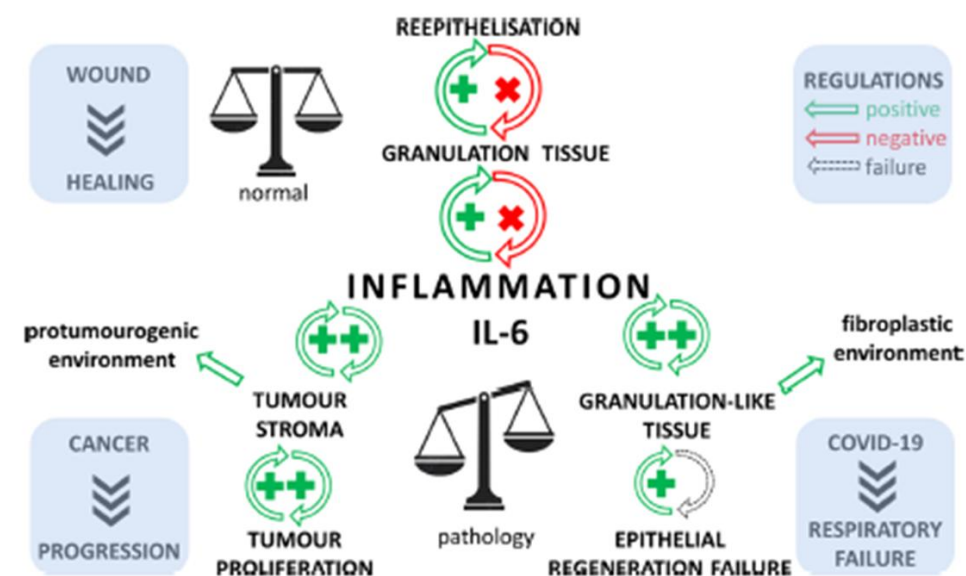
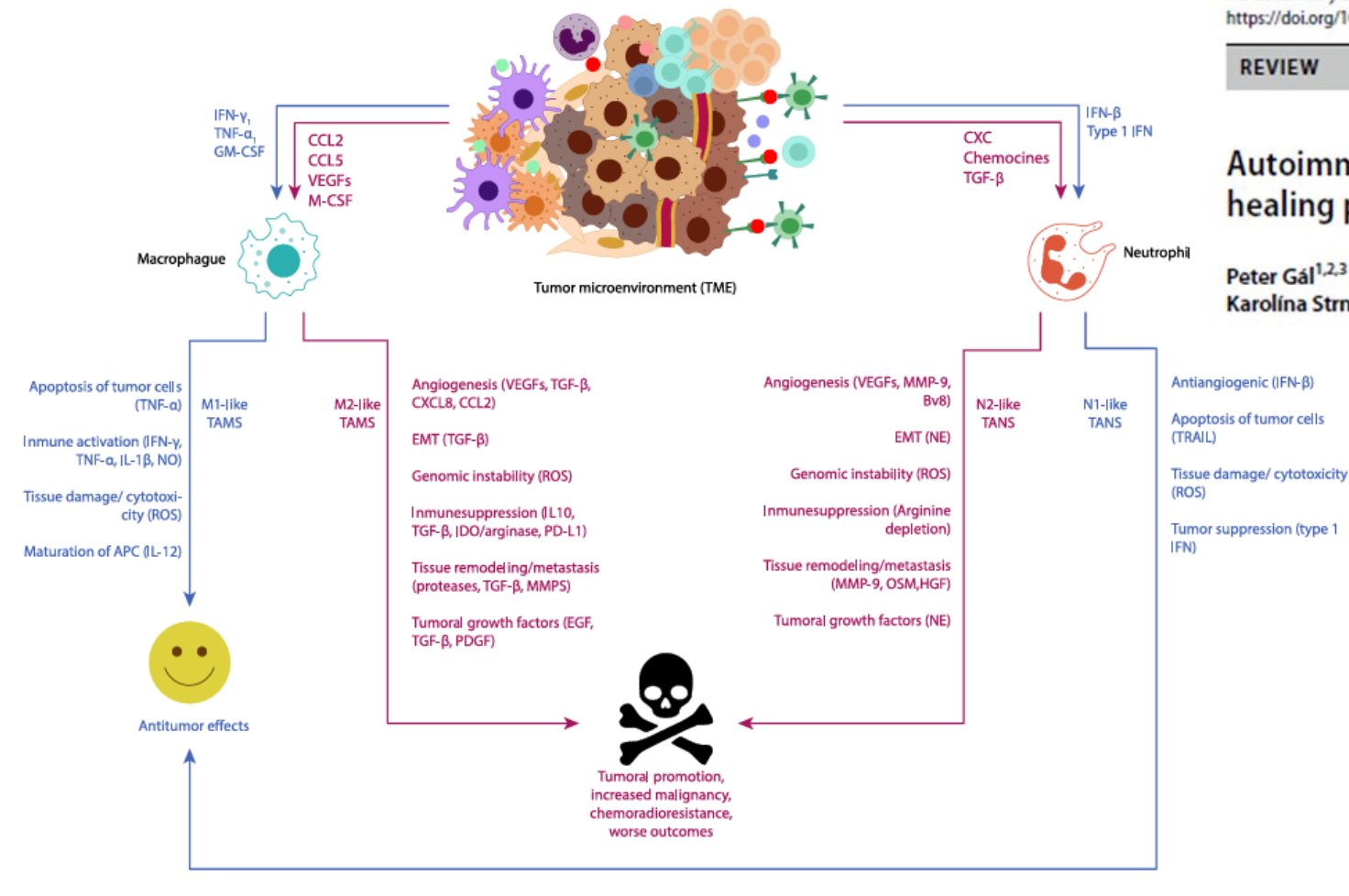
Andrés David Turizo-Smith^{1,2}, Samantha Córdoba-Hernandez²,
Lidy Vannessa Mejía-Guarnizo^{3,4},
Paula Stefany Monroy-Camacho⁴ and

Histochemistry and Cell Biology (2022) 158:415–434
<https://doi.org/10.1007/s00418-022-02140-x>

REVIEW

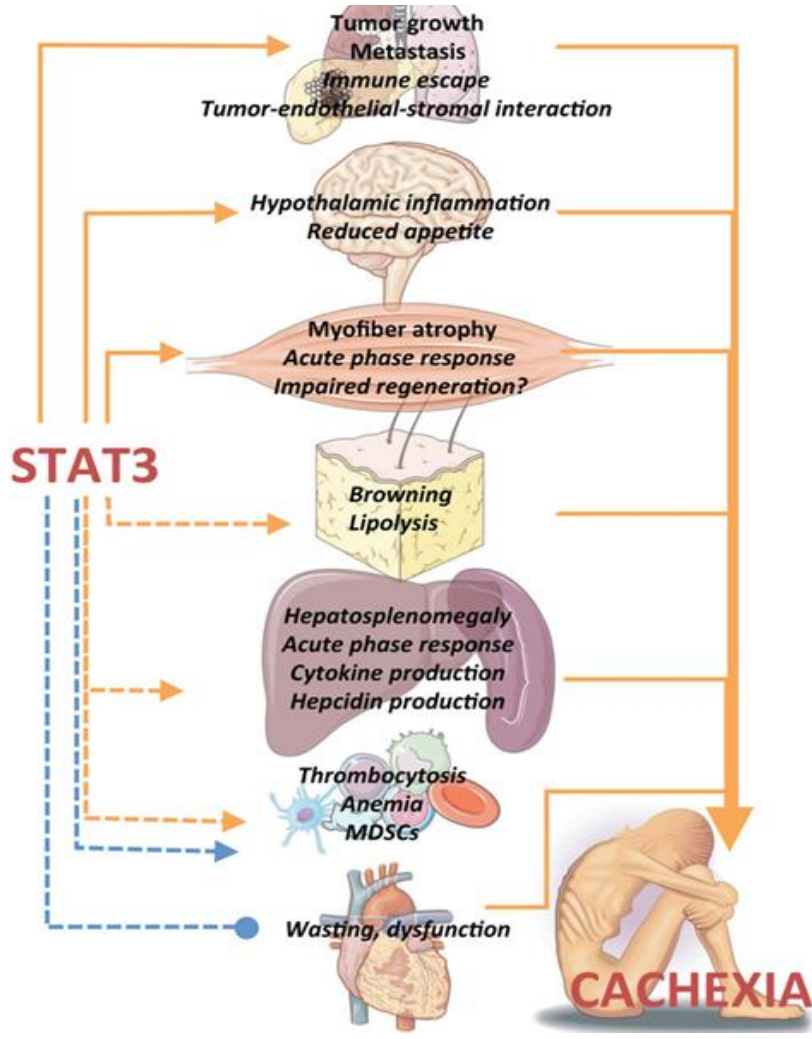
Autoimmunity, cancer and COVID-19 abnormally activate wound healing pathways: critical role of inflammation

Peter Gál^{1,2,3} · Jan Brábek^{4,5} · Michal Holub⁶ · Milan Jakubek^{7,8,9} · Aleksi Šedo¹⁰ · Lukáš Lacina^{8,11,12} · Karolína Strnadová^{8,11} · Petr Dubový¹³ · Helena Hornychová¹⁴ · Aleš Ryška¹⁴ · Karel Smetana Jr.^{8,11}



Review

STAT3 in the systemic inflammation of cancer cachexia

Teresa A. Zimmers^{a b c d}, Melissa L. Fishel^{c e f}, Andrea Bonetto^{a c d}


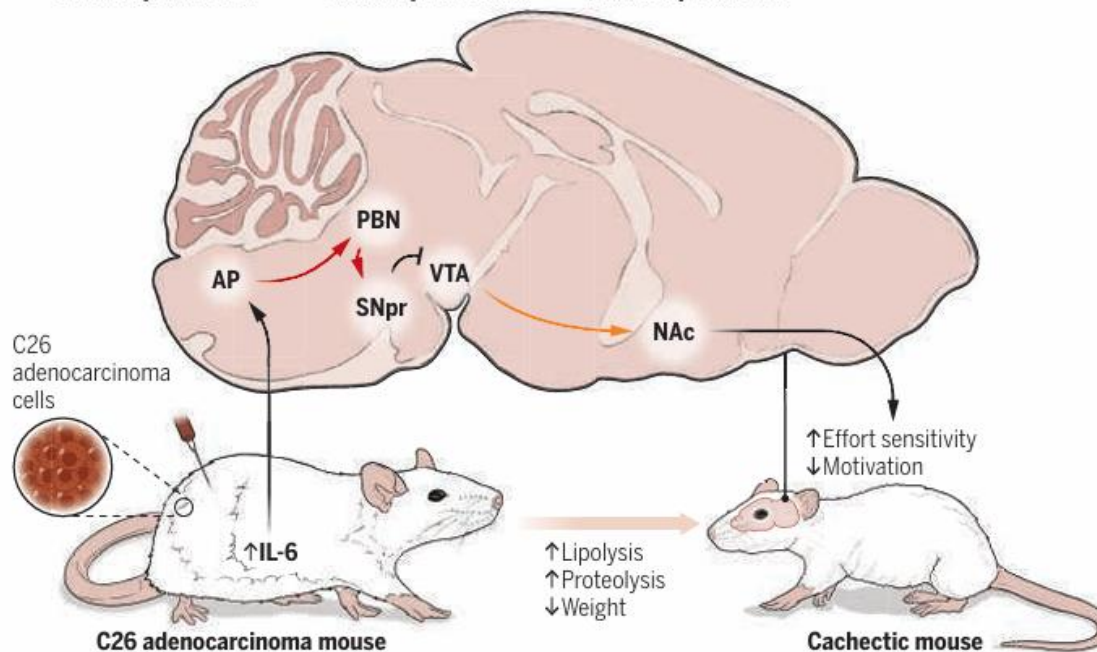
RESEARCH ARTICLE SUMMARY

NEUROSCIENCE

A neuroimmune circuit mediates cancer cachexia-associated apathy

Xiaoyue Aelita Zhu (朱晓悦)[†], Sarah Starosta[†], Miriam Ferrer[‡], Junxiao Hou (侯郡潇)[‡], Quentin Chevy, Federica Lucantonio, Rodrigo Muñoz-Castañeda, Fengrui Zhang (张峰瑞), Kaikai Zang (臧凯凯), Xiang Zhao (赵翔), Francesca R. Focchi, Mason Bergstrom, Aubrey A. Siebels, Thomas Upin, Michael Wulf, Sarah Evans, Alexxai V. Kravitz, Pavel Osten, Tobias Janowitz^{§*}, Marco Pignatelli^{§*}, Adam Kepecs^{§*}

→ Excitatory, increased → Excitatory, decreased —| Inhibitory, increased



IL-6 pomocí
aktivace
STAT3
odpovídá za
kachexii a
deprese v
terminální
fázi maligně
nemocných

Může nám to nějak pomoci v prevenci?

Ve tkáních seniorů je zánět podporující mikroprostředí.
Co kdybychom je redukovali.

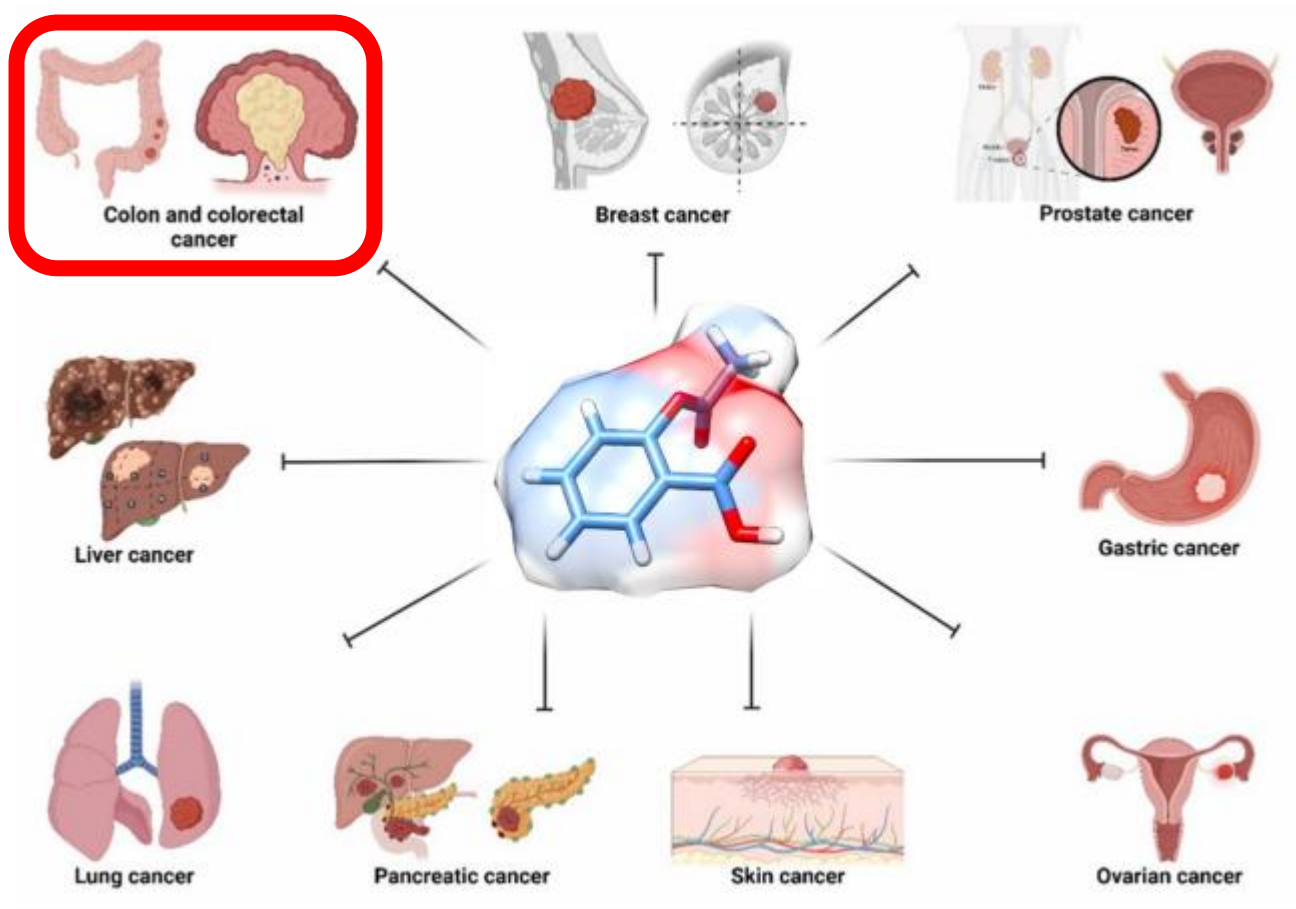
Nemohly by pomoci nesteroidní protizánětlivé léky?



REVIEW

Acetylsalicylic acid and cancer: updates on the new potential of a nature-inspired drug

Abdur Rauf¹ · Ahmed Olatunde² · Md. Rezaul Islam³ · Zubair Ahmad¹ · Nabia Hafeez⁴ · Hassan A. Hemeg⁵ · Muhammad Imran⁶ · Mohammad S. Mubarak⁷ · Giovanni Ribaudo⁸



Review article

Dual COX-2/15-LOX inhibitors: A new avenue in the prevention of cancer

Ali Aliabadi^a, Elham Khanniri^b, Mohammad Mahboubi-Rabbani^{a,*}, Maryam Bayanati^{b,*}



RSC Advances

REVIEW



Cite this: *RSC Adv.*, 2024, 14, 40031

Repurposing of Indomethacin and Naproxen as anticancer agents: progress from 2017 to present

Asmaa E. Kassab¹ and Ehab M. Gedawy²

Journal of Cachexia, Sarcopenia and Muscle 2023; 14: 2473–2497

Published online 26 September 2023 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/jcsm.13327

REVIEW

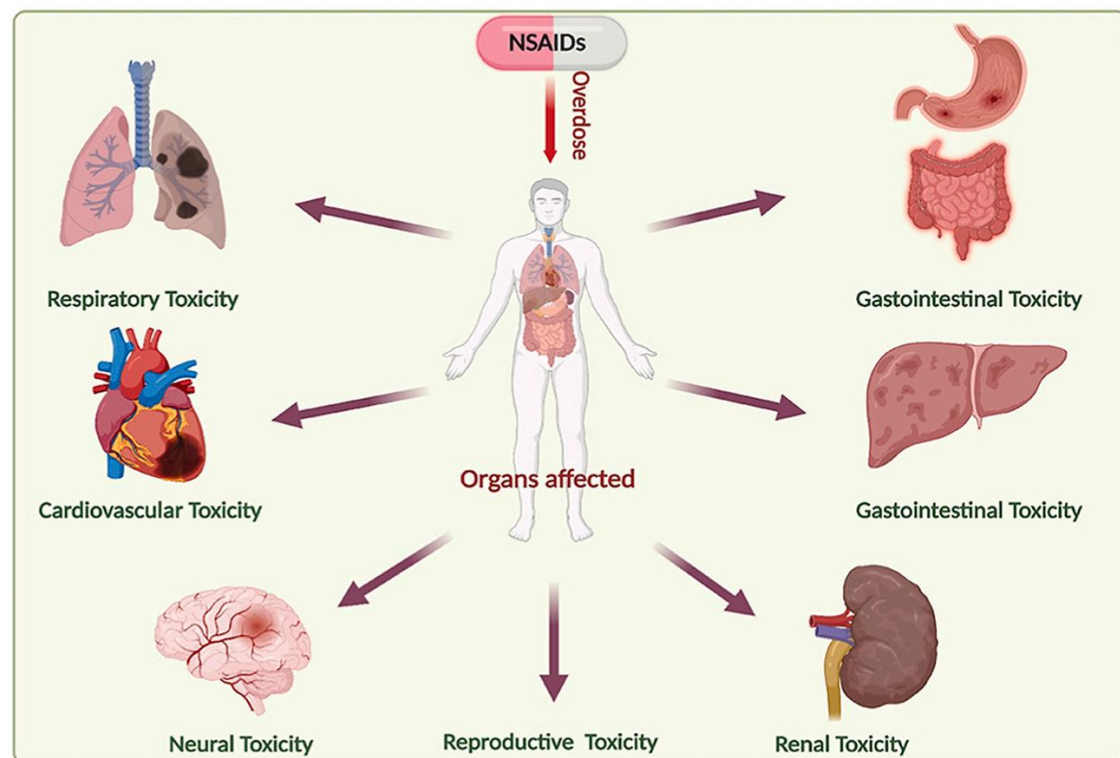
Non-steroidal anti-inflammatory drugs for treatment of cancer cachexia: A systematic review

Megan Bowers¹, Brittany Cucchiari^{2,3}, Joanne Reid⁴ & Adrian Slee^{2*}



Review

Non-steroidal anti-inflammatory drugs (NSAIDs): A current insight into its molecular mechanism eliciting organ toxicities

Nagesh Kishan Panchal, Evan Prince Sabina^{*}

Advanced Review

Challenges to develop novel anti-inflammatory and analgesic drugs

Bálint Botz,^{1,2†} Kata Bölcskei^{2,3†} and Zsuzsanna Helyes^{2,3,4*}

pharmaceutics



MDPI

Article

Therapeutic Liquid Formulations Based on Low Transition Temperature Mixtures for the Incorporation of Anti-Inflammatory Drugs

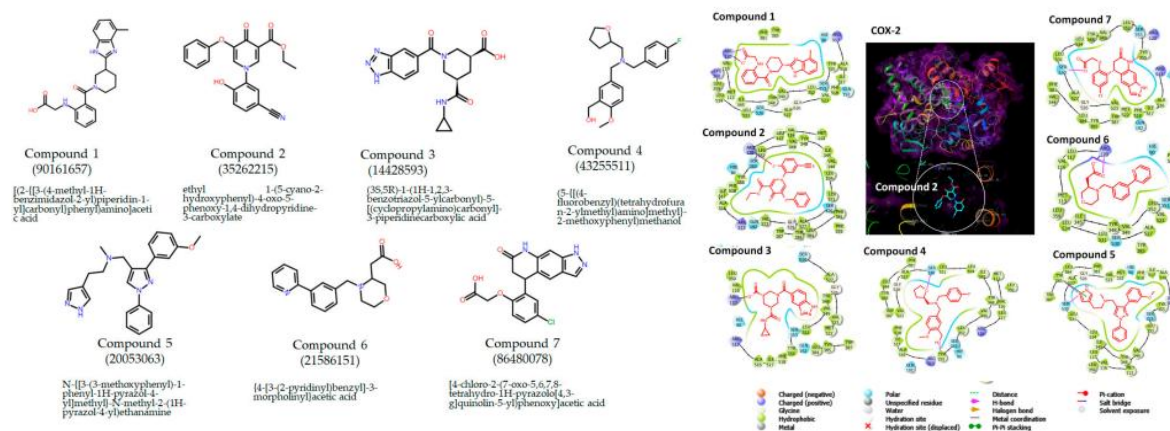
Ana Roda, Alexandre Paiva and Ana Rita C. Duarte^{*}

pharmaceutics

MDPI

Article

Drug Discovery of New Anti-Inflammatory Compounds by Targeting Cyclooxygenases

Shady Burayk^{1†}, Kentaro Oh-hashi² and Mahmoud Kandeel^{1,3,*†}

Závěry

- Nádorové mikroprostředí a hojící se poranění mají mnoho společného a příliš se neliší od autoimunitních onemocnění, fibróz a infekcí typu COVID-19.
- Zánět propojuje tyto patologické procesy. Buňky nádorového ekosystému využívají dráhy hojení poranění.
- Část z nich (iCAF) produkuje faktory podporující zánět včetně IL-6. Ten ovlivňuje biologické vlastnosti nádorových buněk (proliferace a migrace). Tyto faktory indukují kachexii a deperesi u pokročilých stavů nemoci.
- Inhibice IL-6R α pomocí NEF inhibitorů redukuje proliferaci a migraci nádorových buněk.
- Byla by možná chemoprevence u lidí se zvýšeným rizikem nádorů (např. seniorů) pomocí nesteroidních antirevmatik? Pozor na vedlejší účinky!!

Karlova univerzita

1. lékařská fakulta, Praha:

Anatomický ústav a BIOCEV: K.Strnadová, P.Szabo, M.Španko, H.Stýblová



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Ústav molekulární genetiky AVČR, Praha: M.Hradilová, Š.Kocourková, J.Novotný, L.Pfeiferová, H.Strnad, P.Svatoňová, J.Šáchová



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Financial support:

