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contre le cancer de l'enfant

UNIVERSITÉ
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HUG Hôpitaux Universitaires Genève

SIB Swiss Institute of Bioinformatics

Pharmacogenomics in pediatric hematopietic stem cell transplantation – integrative multiomics approach

Farmakogenomika pri presaditvi hematopietskih matičnih celic pri otrocih – pristop integrativne multiomike

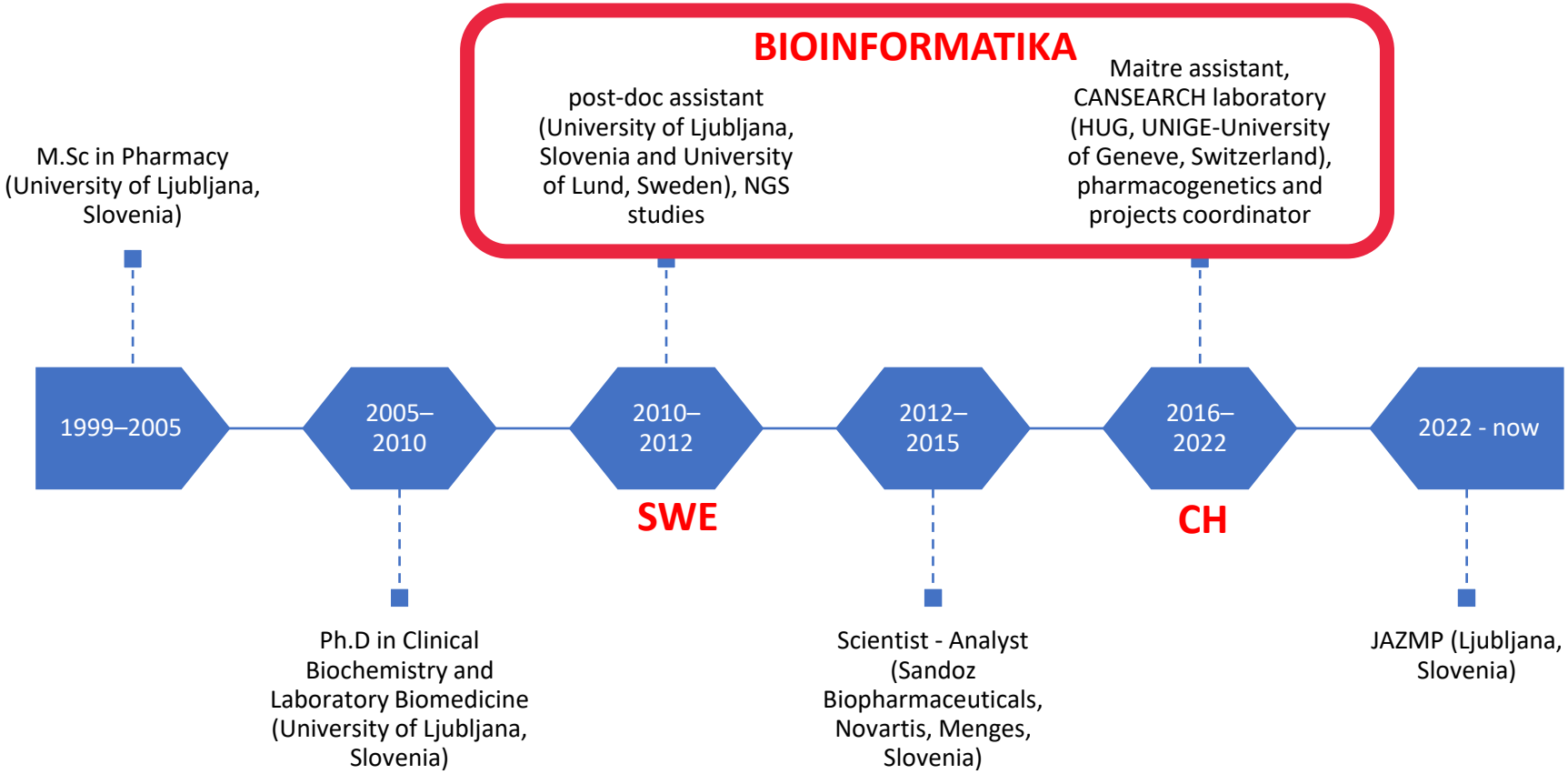
Simona Jurkovic Mlakar, PhD; Nicolas Waespe, MD; Isabelle Dupanloup, PhD; Mohamed Aziz Rezgui; Henrique Bittencourt, MD, PhD; Maja Krajinovic, MD, PhD; Claudia E. Kuehni, MD, MSc; Tiago Nava, MD, PhD; Marc Ansari, MD

VTIS Meeting, December 22nd, 2022

Simona Jurkovic Mlakar, PhD

CANSEARCH research platform for pediatric oncology and hematology, University of Geneva

Simona Jurkovic Mlakar PhD



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Univerza v Lundu, Švedska

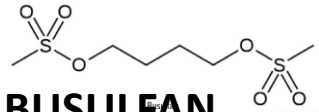
Univerza v Genevi, Švica

HSCT - presaditev hematopietskih matičnih celic

01
Izvedba **predhodnega zdravljenja za pridobitev krvnih zarodnih celic** iz kostnega mozga v krvni obtok

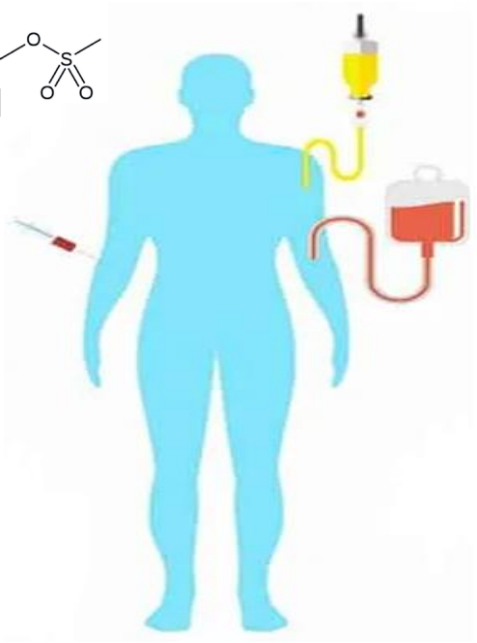
02
Zbiranje krvnih zarodnih celic iz krvnega obtoka in **zamrznitev krvnih zarodnih celic** v laboratoriju vse do uporabe

03
Uporaba **kemoterapije za uničenje ali delno uničenje lastnega imunskega sistema**



BUSULFAN

04
Vnos odmrznjenih zdravih krvnih matičnih celic z infuzijo v veno



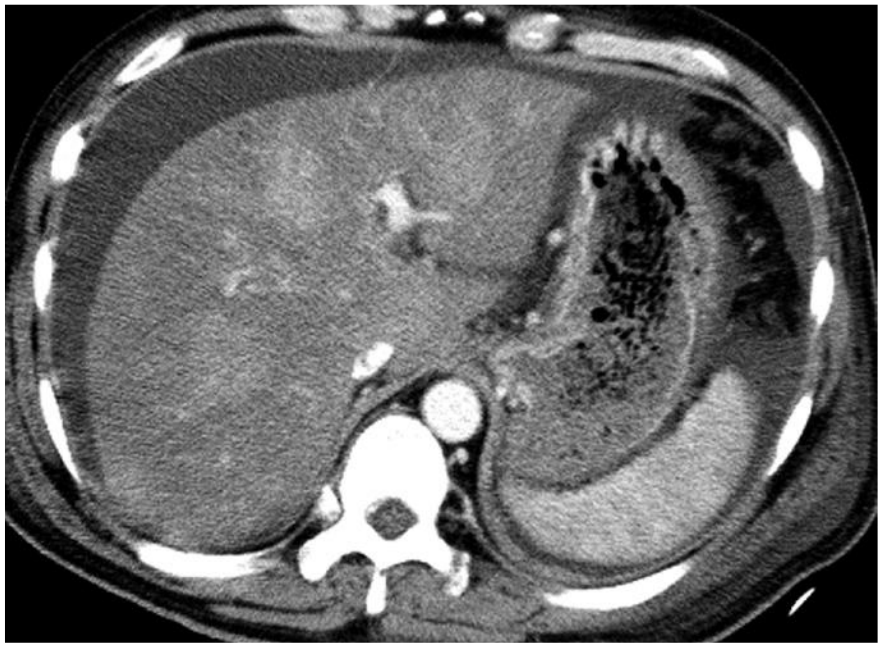
05
Zagotavljanje **podpornega zdravljenja** vsaj 4 tedne, ko se imunski sistem obnovi

Zapleti po HSCT:

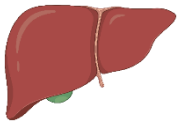
- **Sinusoidni obstruktivni sindrom (SOS)**
- Akutna reakcija presadka proti gostitelju (aGvHD)
- Relaps
- Pljučna toksičnost
- Hemoragični cistitis (HC)
- Zavrnitev presadka

Sinusoidni obstruktivni sindrom

- 10-60% otrok po HSCT[1]
- Simptomi:[2]
  - Hepatomegalija and abdominalna bolečina
  - Porast teže z ascitesom
  - Hiperbilirubinemija
  - Trombocitopenija
- Zdravljenje & profilaksa:
  - Defibrotid, podporna terapija



[1] Dalle J-H, Biology of Blood and Marrow Transplantation. 2016.
[2] Corbacioglu S, Biol. Blood Marrow Transplant. 2019. Image: Zhou H, Korean journal of radiology. 2014.



Rizični faktorji

- Klinični rizični faktorji[1]
  - Novorojenčki / mladostniki
  - Že obstoječa bolezen jeter, talasemija
  - Predhodno zdravljenje: gemtuzumab
  - Režim kondicioniranja z alkilatorji, zlasti busulfanom
- Nedosledne ugotovitve o možnih genetskih napovedovalcih
- Sistematični pregled literature[2]

[1] Dalle J-H, Biology of Blood and Marrow Transplantation. 2016.
[2] Waespe N, Strebel S, Jurkovic-Mlakar S et al., Journal of Personalized Medicine. 2021.

Sistematični pregled literature (Del 1)

Journal of *Personalized Medicine*

MDPI

Systematic Review

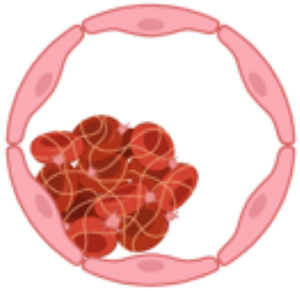
Genetic Predictors for Sinusoidal Obstruction Syndrome—A Systematic Review

Nicolas Waespe [1,2,3], Sven Strebel [1,2,4], Simona Jurkovic Mlakar [1], Maja Krajinovic [5,6,7], Claudia Elisabeth Kuehni [2,8], Tiago Nava [1,9] and Marc Ansari [1,9,*]

Waespe N, Strebel S, Jurkovic Mlakar S, et al. Journal of Personalized Medicine. 2021;11(5):347.

Sistematični pregled genetski rizičnih faktorjev (Del 1)

- 34 kandidatnih genov
  - **9 povezanih z SOS**
  - **2 gena validirana *(GSTA1, MTHFR)* v več kot eni študiji**
  - **2 gena identificirana *(LNPK, UGT2B10)* v WES analizi[2]**



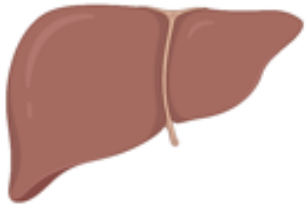
1. Koagulacija & endotelij

ABCB1, ACE, F2, F5, FGB, IL1B, ITGB3, ***LNPK,*** *P2RX7, SERPINE1, HADH, ZNF608*

2. Metabolize učinkovin

CYP2B6, *CYP2C19, CYP2C9,* ***GSTA1, GSTM1,*** *GSTO1, GSTO2,* ***GSTP1,*** *GSTT1, GSTZ1,* ***MTHFR, UGT2B10***

3. Drugi jetrni encimi



CPS1, CTH, *FMO3,* ***HFE, HPSE,*** *VDR, AMPH, AGPAT3, FAT3*

[1] Waespe N, Strebel S., Jurkovic Mlakar S et al.. Journal of Personalized Medicine. 2021.
[2] Ansari M, Biol Blood Marrow Transpl, 2020.

EWAS analiza podatkov (Del 2)

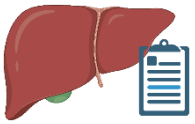
- **2 gena identificirana *(LNPK, UGT2B10)* v WES analizi[2]**

Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

Genetic Susceptibility to Hepatic Sinusoidal Obstruction Syndrome in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation

Marc Ansari[1,2], Kateryna Petrykey[3,4], Mohamed Aziz Rezgui[3], Veronica Del Vecchio[4], Jacques Cortyl[3], Reginald-Olivier Ralph[4], Tiago Nava[1,2,3], Patrick Beaulieu[3], Pascal St-Onge[3], Simona Jurkovic Mlakar[1,2], Patricia Huezo-Diaz Curtis[1,2], Chakradhara Rao S. Uppugunduri[1,2], Laurence Lesne[1,2], Yves Théoret[3,4,5], Yves Chalandon[6], Imke H. Bartelink[8], Jaap-Jan Boelens[7,9], Robbert G.M. Bredius[10], Jean-Hugues Dalle[11], Victor Lewis[12], Bill S. Kangarloo[8,2], Christina Peters[13], Daniel Sinnett[3,14], Henrique Bittencourt[3,4,5,14], Maja Krajinovic[3,4,5,14,*], on behalf of the Pediatric Disease Working Party of the European Society for Blood and Marrow Transplantation

Ansari M, Biol Blood Marrow Transpl, 2020.



Eksperimentalni rezultati - SOS (Del 3)

PLOS ONE

"A novel integrative multi-omics approach to unravel the genetic determinants of rare diseases with application in sinusoidal obstruction syndrome"
PLOS ONE, 2022, Accepted
Research article
Simona Jurkovic Mlakar, PhD; Nicolas Waespe, MD PhD; Isabelle Dupanloup, PhD; Mohamed Aziz Rezgui; Henrique Bittencourt, MD, PhD; Maja Krajinovic, MD, PhD; Claudia E. Kuehni, MD, MSc; Tiago Nava, MD, PhD; Marc Ansari, MD.

Jurkovic Mlakar S, Waespe N, et al. PLOS ONE. 2022; minor revisions before acceptance

Cilji

- Razviti nov analitski model, ki kombinira podatke iz:

  (i) kliničnega genomskega sekvenciranja,

  (ii) *in vitro* ekspresijske analize in

- Identificirati **kandidatne gene in genske variante za SOS.**

Utemeljitev

- Busulfan je pomemben sprožilec za SOS[1]
- Geni, ki so po izpostavljenosti busulfanu, deregulirani, so vpleteni v njegovo toksičnost[2]
- Linije limfoblastoidnih celic zdravih darovalcev so primerne za testiranje razlik v izražanju genov[3]

1. Corbacioglu S. Biol. Blood Marrow Transplant, 2019.
2. Hartford CM, Pharmacogenomics, 2007.
3. Wheeler HE, Pharmacogenomics, 2012.

Nov pristop

1. Razpoložljivi klinični podatki o 87 pediatričnih bolnikov, ki so bili podvrženi alogenski HSCT (predvsem BuCy kondicioniranje)[1]

   I. Podatki EWAS s SOS kot glavnim rezultatom (spremenjena merila v Seattlu)[2]

2. *In vitro* diferencialna genska ekspresija v šestih limfoblastoidnih celičnih linijah

   I. Sprememba izražanja genov po zdravljenju z busulfanom

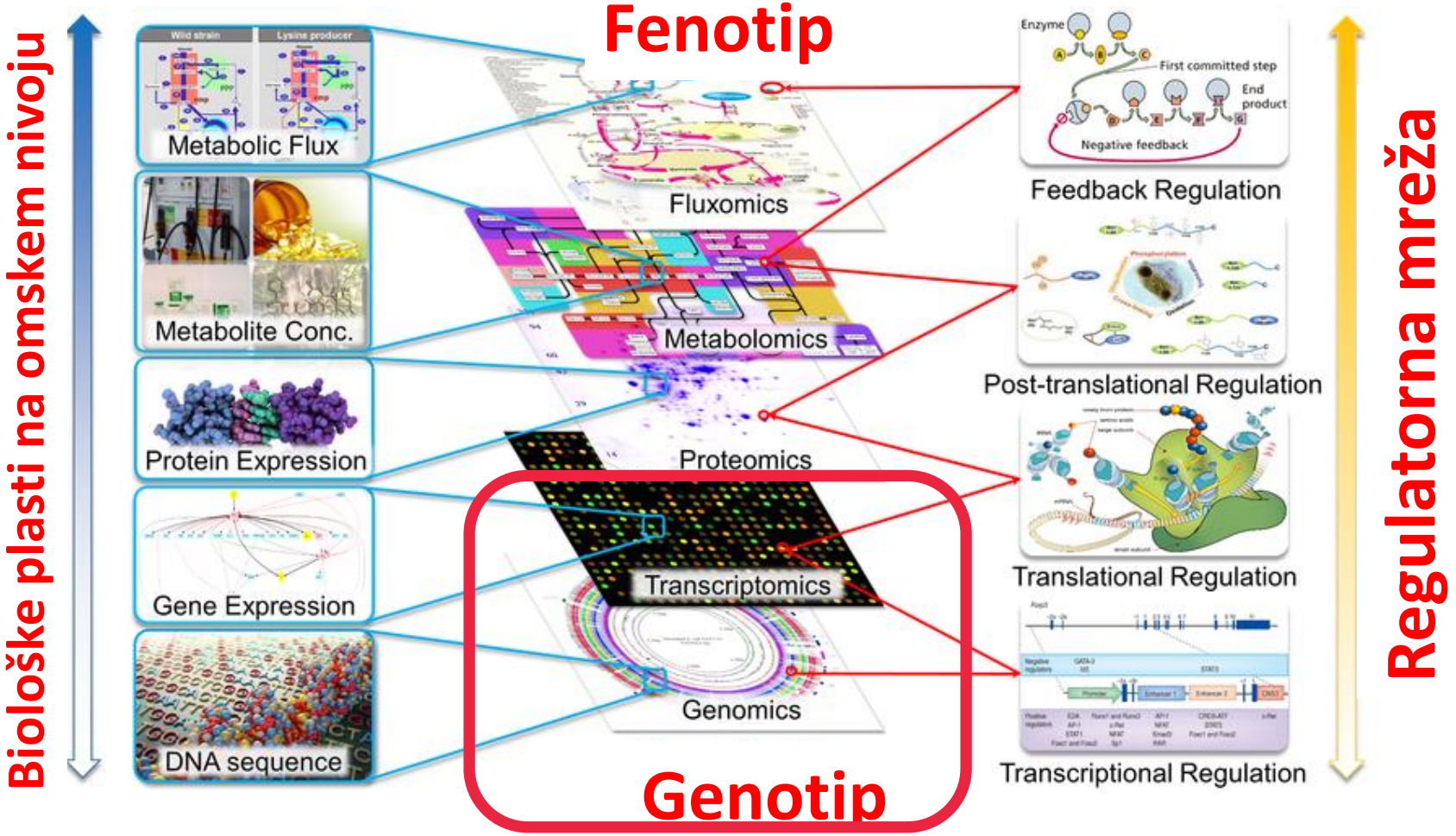
3. Povečanje moči za prepoznavanje genetskih determinant:

   I. integracija rezultatov iz večih neodvisnih eksperimentalnih poskusov za povečanje statistične moči

   II. celogenomska in hkratna večplastna analiza genetskih podatkov za večjo ločljivost podatkov

[1] Ansari M, Biol Blood Marrow Transpl, 2020.
[2] Coppell JA, Biology of Blood and Marrow Transplantation, 2010.

Multi-omika



Guo W, Feng X (2016). PLoS ONE 11(4): e0154188.

Potek dela (1)

Whole exome sequencing
12 patients with outcome (SOS), 75 controls

Data filtering to increase genetic homogeneity of sample

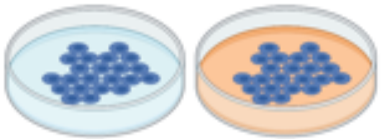
Association analysis at the polymorphism level

PLINK[1]

Compute association metrics at the gene level

VEGAS2[2]

Incorporation of *in vitro* expression data: combined test statistic



Identification of candidate genes and variants

Identification of biological functions or processes

[1] Purcell S. PLINK: tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007.
[2] Mishra A, VEGAS-2: Versatile Gene-based Association Study-2. Twin Res Hum Genet. 2015.

Potek dela (2)

Vključitev podatkov o genskem izražanju v LCL

RNA-seq

RNA extraction

Quality Control
FASTQC tool

C C C C C C
Untreated

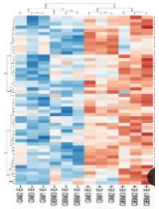
B B B B B B
Treated

Pre-processing

Alignment to reference genome
SAM tools
Conversion of SAM to BAM

Raw read counts for each sample
PCA analysis

Post-processing



Normalized read counts data

3093 deregulated genes
- 1708 upregulated in treated cells
- 1385 downregulated in treated cells

Differential Gene Expression (DEG)
edgeR, DeSeq2

Validation of Gene Expression (NANOSTRING or Real-Time PCR)

PLINK
(IC_{50}-SNPs,insdel)

In silico functional analysis: Ingenuity Pathway Analysis (GO, KEGG), GSEA

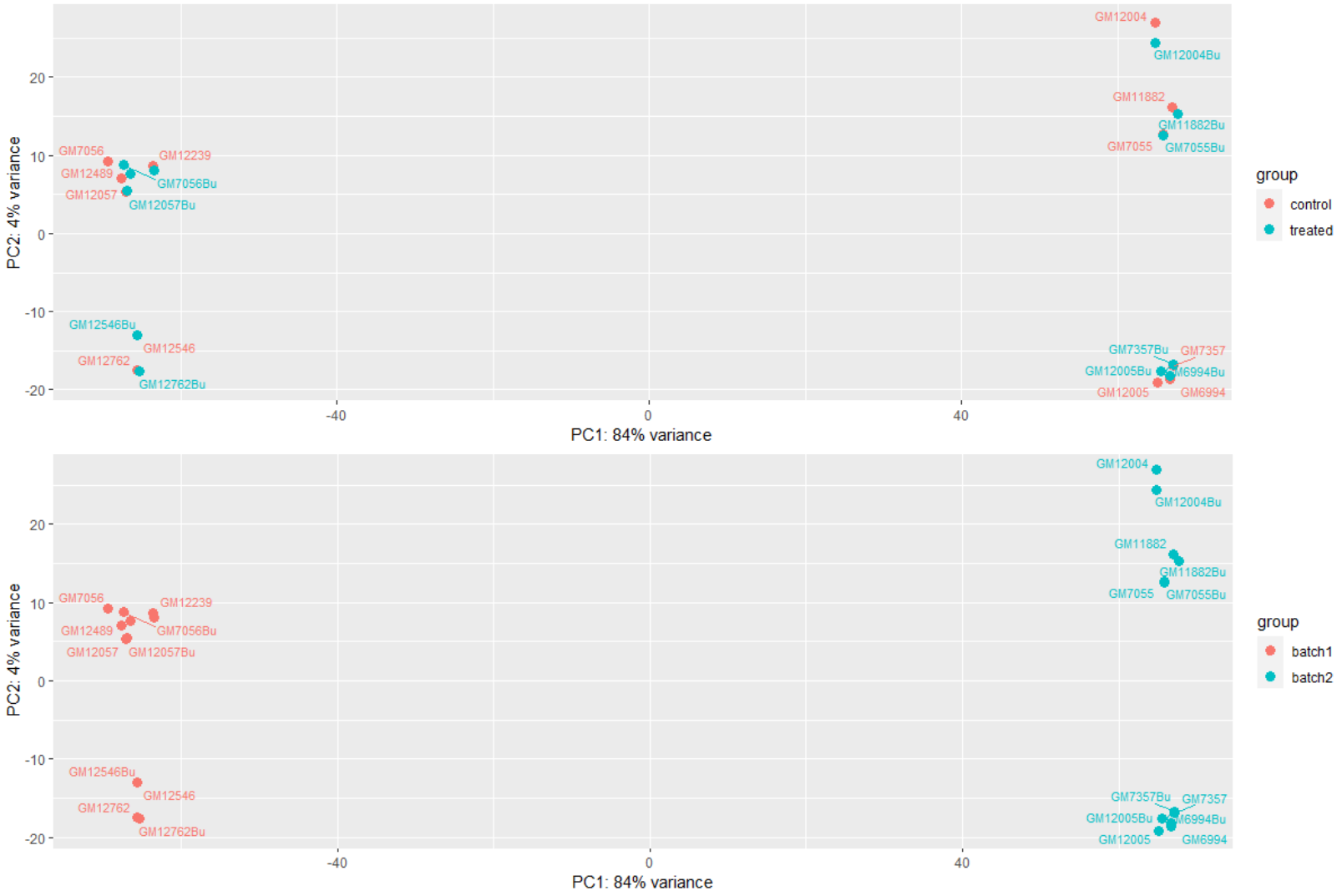
Protein expression
(Proteome Profiler Antibody Array or Western Blots)

Protein extraction

Functional exploration

Selection of genes for genetic association analysis

PCA analiza


GM12004
GM12004Bu
GM11882
GM11882Bu
GM7055
GM7055Bu
GM7056
GM12239
GM12489
GM7056Bu
GM12057
GM12057Bu
GM12546Bu
GM12546
GM12762
GM12762Bu
GM7357Bu
GM7357
GM12005Bu
GM6994Bu
GM12005
GM6994
PC2: 4% variance
PC1: 84% variance
group
control
treated
batch1
batch2

Selection of gene biomarkers and comparison between groups
- *2logFC>2,*
- *padjusted<0.05*

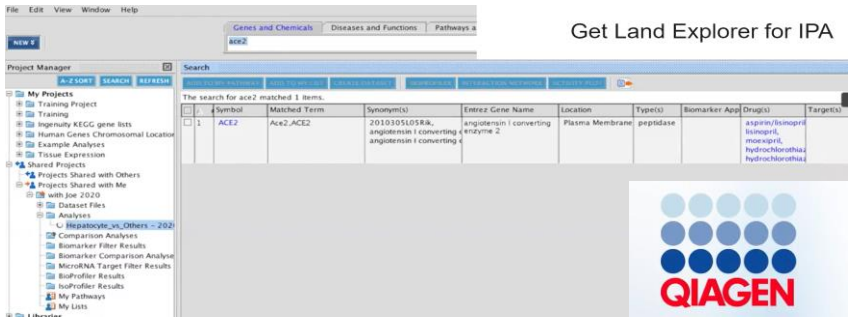
Top canonical pathways
Filter: Z-score above /1/
Fisher exact test: p-value<0.05

Output files

IPA→ GSEA

Examples (Bu-treatment):

Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score	Molecules
HMGB1 Signaling	3,67	0,0364	2	*CSF2,CXCL8,IFNG,LIF,SERPINE1,TNFSF15*
Neuroinflammation Signaling Pathway	2,33	0,02	2,236	*BDNF,CXCL8,GABBR2,GDNF,GRIN2C,IFNG*
Cardiac Hypertrophy Signaling (Enhanced)	1,88	0,0144	2,449	*CSF2,CXCL8,CXCR2,IFNG,LIF,PDE4C,TNFSF15*
Systemic Lupus Erythematosus In B Cell Signaling Pathway	1,85	0,0182	2,236	*CSF2,CXCL8,IFNG,LIF,TNFSF15*
Synaptogenesis Signaling Pathway	1,64	0,016	2,236	*BDNF,EPHA2,GRIN2C,LRP1,UNC13A*
Osteoarthritis Pathway	1,62	0,019	1	*COL2A1,CXCL8,CXCR2,LRP1*
cAMP-mediated signaling	1,52	0,0175	2	*CXCR2,GABBR2,HCAR3,PDE4C*
Hepatic Fibrosis Signaling Pathway	0,91	0,0109	2	*COL2A1,COL3A1,CXCL8,SERPINE1*



Selection of gene biomarkers and comparison between groups
- *2logFC>2,*
- *padjusted<0.05*

Output files

Top canonical pathways
Filter: Z-score above /1/
Fisher exact test: p-value<0.05

Upstream analysis
Top 10 upstream regulators (without compounds) and p<10-5, unbiased

Examples:

Upstream Regulator	Expr Log Ratio	Molecule Type	Predicted Activation State	Activation z-score	p-value of overlap	Target Molecules in Dataset	Mechanistic Network
TP53	-0,172	transcription regulator	Activated	3,142	4,25E-08	*ALDH1A3,AREG,BDNF,COL2A1,CO*	47 (17)
ULBP2	0,535	transmembrane receptor			0,00000482	*CCL1,CSF2,IFNG*	
CD33	0,362	other			0,00000768	*CSF2,CXCL8,IFNG*	26 (14)
NR3C2	0,015	ligand-dependent nuclear receptor		1,109	0,00000788	*COL3A1,CXCL8,CXCR2,PLIN4,RRAI*	26 (7)
Immunoglobulin		complex		0,549	0,0000124	*AREG,ATP4B,BDNF,CCL1,CSF2,CX*	36 (18)
NFKBIE	-0,12	transcription regulator			0,0000163	*CSF2,CXCL8,LIF*	41 (13)
SNAI1	0,04	transcription regulator		0,059	0,0000176	*AXL,COL2A1,CXCL8,GDF15,KRT17,*	46 (16)
ENTPD1	0,115	enzyme			0,0000224	*CXCL8,IFNG,SERPINE1*	37 (16)
CCL21		cytokine			0,0000385	*CSF2,CXCL8,IFNG*	46 (18)
IL10	-0,593	cytokine		-1,739	0,0000387	*CCL1,CEACAM1,CSF2,CXCL8,CXCL*	39 (17)

CD36 ***biased***

Output files

Selection of gene biomarkers and comparison between groups
- *2logFC>2,*
- *padjusted<0.05*

Top canonical pathways
Filter: Z-score above /1/
Fisher exact test: p-value<0.05

Upstream analysis
Top 10 upstream regulators (without compounds) and p<10-5, unbiased

Diseases BioFunctions
Top 10 categories and p<10-5,

Selection per CLINICAL OUTCOME: relapse, toxicity related outcomes

Examples:

Category	p-value	Molecules
Cancer	3.54E-11-2.84E-04	ADGRA2,ALDH1A3,A
Organismal Injury and Abnormalities	3.54E-11-3.03E-04	ADGRA2,ALDH1A3,A
Cellular Assembly and Organization	9.68E-11-2.63E-04	ADGRA2,AREG,AXL,
Cellular Function and Maintenance	9.68E-11-3E-04	ADGRA2,AREG,AXL,
Cardiovascular System Development and Function	1.56E-09-2.62E-04	ADGRA2,AREG,ATP4
Cell-To-Cell Signaling and Interaction	1.79E-09-2.82E-04	AREG,AXL,BDNF,CC
Organismal Development	1.88E-09-3E-04	ADGRA2,ALDH1A3,A
Gastrointestinal Disease	1.25E-08-2.61E-04	ADGRA2,ALDH1A3,A
Cellular Movement	1.4E-08-2.89E-04	ADGRA2,ALDH1A3,A

Selection of gene biomarkers and comparison between groups
- *2logFC>2,*
- *padjusted<0.05*

Output files

Top canonical pathways
Filter: Z-score above /1/
Fisher exact test: p-value<0.05

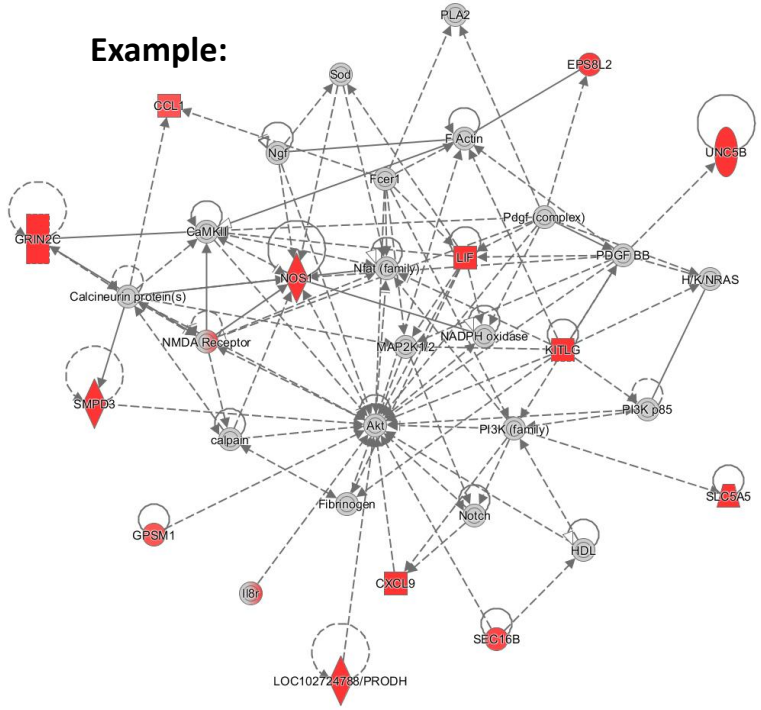
Upstream analysis
Top 10 upstream regulators (without compounds) and p<10-5, unbiased

Diseases BioFunctions
Top 10 categories and p<10-5,

Selection per CLINICAL OUTCOME: relapse, toxicity related outcomes

Networks
Top 3 networks

Example:



Klinični podatki bolnikov pri HSCT

HSCT (HSJ – Montréal):
45 bolnikov (52%): maligna bolezen
68 bolnikov (78%): mieloablativna HSCT
62 bolnikov (71%): BuCy

Outcomes		n (%)
Event free survival (events)	32	(37)
Death	17	(20)
Graft failure	14	(16)
Relapse	12	(14)
Sinusoidal obstruction syndrome	12	(14)
Total	**87**	**(100.0)**

- 292’064 SNP-ov
- 87 posameznikov (starost: 7.4 leta [0.1-23.5])
  - **12 posameznikov s SOS**, 75 kontrolnih vzorcev
  - 47 deklet, 40 fantov
  - Etnično poreklo:
    - Amerika (n=2)
    - Azija (n= 2)
    - Sub-Saharska Afrika (n= 12)
    - Južna Amerika (n= 1)
    - Severna Afrika (n= 7)
    - Evropejec s kitajskim poreklom (n= 1)
    - Evropa (n= 62)

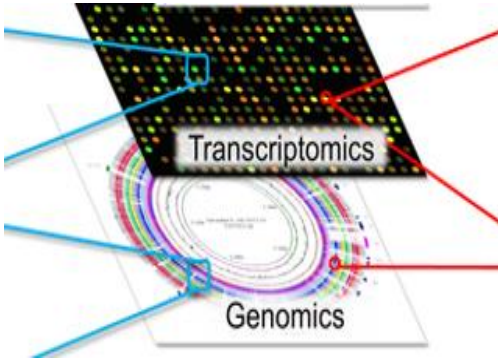
[1] Ansari M, Biol Blood Marrow Transpl, 2020.

Kontrola kakovosti (QC) podatkov o genotipih pred izvedbo GWAS –PLINK analiza

- Manjkajoči posamezniki/ manjkajoči SNP
  - 0 posameznikov
  - 21’138 SNP-ov
- Nedoslednosti v genetskem spolu posameznikov
  - 10 žensk
  - 1 moški
- Manjša frekvenca alelov (MAF) <0.05
  - 4’898 SNP-ov
- Odstopanja od Hardy–Weinberg-ovega ravnotežja (HWE)
  - 8’744 SNP-ov
- Stopnja heterozigotnosti
  - 1 posameznik (from Sub-Saharan Africa)
- sorodnost
  - 4 posamezniki
- Etnični odstopi
  - Azija (n= 2), Sub-Saharaska Afrika (n= 12), Južna Amerika (n= 1), Evropejec kitajskega izvora (n= 1)

→ KONČNO ŠTEVILO TESTIRANCEV: **57 posameznikov (11 SOS, 46 kontrol)**

ALTERNATIVNI PRISTOPI H KLASIČNEMU GWAS



- Klasični GWAS: vsak SNP se posamično testira glede povezave z zanimivimi fenotipi
- Popravek za večkratno testiranje (Bonferroni correction): da se izognemo lažnim pozitivnim rezultatom→ izguba statistične moči
- Ignoriranje korelacijske strukture med SNP, ki jih uvaja populacijska genetika (LD) in biološkimi odnosi (epistaza)
- Nov pristop, ki temelji na ***„machine/deep learning“*** → Zmanjšanje število kandidatnih SNP

1. VEGAS

2. Kombinirani test

Hôpitaux Universitaires Genève

A Versatile Gene-Based Test for Genome-wide Association Studies

Jimmy Z. Liu,[1,*] Allan F. Mcrae,[1] Dale R. Nyholt,[1] Sarah E. Medland,[1] Naomi R. Wray,[1] Kevin M. Brown,[2] AMFS Investigators,[3] Nicholas K. Hayward,[1] Grant W. Montgomery,[1] Peter M. Visscher,[1] Nicholas G. Martin,[1] and Stuart Macgregor[1,*]

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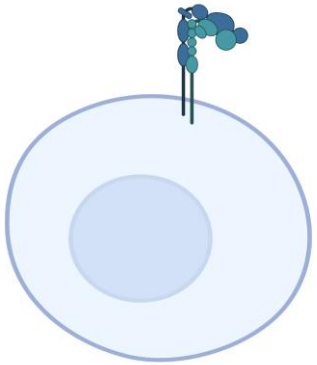
Analiza biološke poti

Identificiranih 35 genov

Integrin cell surface interactions, extracellular matrix organisation

ITGB8, HSPG2, ITGAM



Cellular senescence, apoptosis

CCND1, FAS, MDM2, TNFRSF10B, CALML6

Other genes

*DDR1, **HCAR3,** GPR137B, PTP4A1, PPL, AIM1, GBP5, PHYHIP, LACC1, UTRN, TRIM55, CLCF1, ANKRA2, POLH, DDX60, AFAP1L2, PGAP1, ZBTB7C, GNA15, MAP4K4 LINC01021, IL17RC, TMEM168, GAS7, TRPV3, SEMA6A, PADI4*

Zaključki

- Povečanje moči s kombinirano testno statistiko
- Identifikacija bioloških molekularnih poti, ki se zdijo obetavne za ponovitev (že znane predhodno: integrin/koagulacija ali presnova v jetrih)
- Identifikacija možnih novih mehanizmov (celično staranje, apoptoza)
- Možna prilagoditev analitske metode na druge bolezni

Omejitve & prednosti

\-

- Predpostavka: diferencialna ekspresija genov po izpostavljenosti busulfanu, povezana s kliničnim izidom
- Ni validacije

\+

- Kombinacija dveh neodvisnih testov v eno samo testno statistiko
- Predhodna izbira genov ni potrebna

HVALA.

Patients and families participating in the international study

Isabelle DUPANLOUP

Director: Prof Claudia Kuehni

Katharina FLANDERA
Ben SPYCHER
Christina SCHINDERA
Fabien BELLE
Luzius MADER
Tomas SLAMA
Fabienne LUZI
Maria OTTH
Shelagh REDMOND
Meltem ALTUN
Erika BRANTSCHEN
Anna GLENCK
Selma RIEDO
Cornelia STADTER

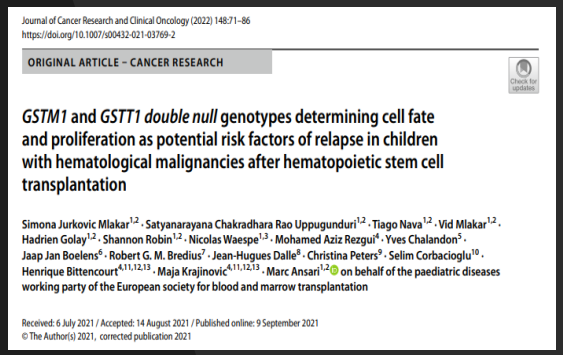
Frederic BALEYDIER
Fanette BERNARD
Mary BOUDAL-KHOSHBEEN
Marilyn BOVERO
Laurent CIMASONI
Armelle CIRELLI-LAMBALLE
Youssef DAALI
Violaine GUIGNON
Fabienne GUMY PAUSE
Hadrien GOLAY
Khalil Ben HASSINE

Director: Prof Marc ANSARI
Deputy director: Dr Tiago NAVA

Denis MARINO
Nelly HAFNER-BENICHOU
Veneranda MATTIELLO
Simona JURKOVIC MLAKAR
Vid MLAKAR
Fanny MUET
Shannon ROBIN
Yohann SARMIENTO
Rao UPPUGUNDURI
André von BÜREN

BITTENCOURT Henrique
KRAJINOVIC Maja
PETRYKEY Kateryna
REZGUI Aziz
THEORET Yves

Ostale objave-Švica



Journal of Cancer Research and Clinical Oncology (2022) 148:71–86
https://doi.org/10.1007/s00432-021-03769-2

ORIGINAL ARTICLE – CANCER RESEARCH

***GSTM1* and *GSTT1 double null* genotypes determining cell fate and proliferation as potential risk factors of relapse in children with hematological malignancies after hematopoietic stem cell transplantation**

Simona Jurkovic Mlakar[1,2] · Satyanarayana Chakradhara Rao Uppugunduri[1,2] · Tiago Nava[1,2] · Vid Mlakar[1,2] · Hadrien Golay[1,2] · Shannon Robin[1,2] · Nicolas Waespe[1,3] · Mohamed Aziz Rezgui[4] · Yves Chalandon[5] · Jaap Jan Boelens[6] · Robert G. M. Bredius[7] · Jean-Hugues Dalle[8] · Christina Peters[9] · Selim Corbacioglu[10] · Henrique Bittencourt[4,11,12,13] · Maja Krajinovic[4,11,12,13] · Marc Ansari[1,2] on behalf of the paediatric diseases working party of the European society for blood and marrow transplantation

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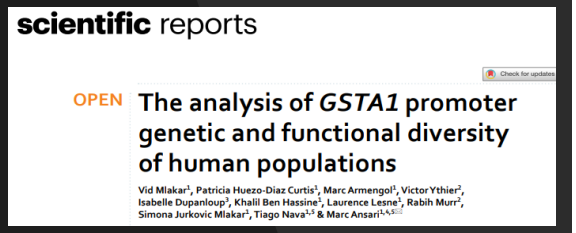


scientific reports

OPEN

The analysis of *GSTA1* promoter genetic and functional diversity of human populations

Vid Mlakar[1], Patricia Huezo-Diaz Curtis[1], Marc Armengol[1], Victor Ythier[2], Isabelle Dupanloup[3], Khalil Ben Hassine[1], Laurence Lesne[1], Rabih Murr[2], Simona Jurkovic Mlakar[1], Tiago Nava[1,2] & Marc Ansari[1,4,5]

Drug Metabolism Letters, 2021, *14*, 163-165

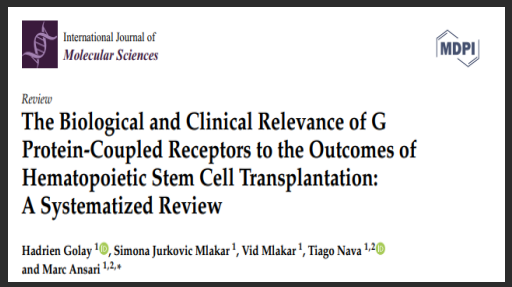
SHORT COMMUNICATION

BENTHAM SCIENCE

The Catalytic Activity of GSTM1 *In vitro* is Independent of MAPK8

Shannon Robin[1], Khalil Ben Hassine[1], Simona Jurkovic Mlakar[1], Vid Mlakar[1], Marc Ansari[1,2,*] and Chakradhara Rao S. Uppugunduri[1,*]

[1]*CANSEARCH Research Platform in Pediatric Oncology and Hematology, Department of Pediatrics, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland;* [2]*Division of Pediatric Oncology and Hematology, Department of Women, Child and Adolescent, University Geneva Hospitals, Geneva, Switzerland*



International Journal of *Molecular Sciences*

MDPI

Review

The Biological and Clinical Relevance of G Protein-Coupled Receptors to the Outcomes of Hematopoietic Stem Cell Transplantation: A Systematized Review

Hadrien Golay [1], Simona Jurkovic Mlakar [1], Vid Mlakar [1], Tiago Nava [1,2] and Marc Ansari [1,2,*]

nature › bone marrow transplantation › articles › article

Article | Published: 02 July 2021

Genetic susceptibility to acute graft versus host disease in pediatric patients undergoing HSCT

Marc Ansari, Kateryna Petrykey, Mohamed Aziz Rezgui, Veronica Del Vecchio, Jacques Cortyl, Milad Ameur, Tiago Nava, Patrick Beaulieu, Pascal St-Onge, Simona Jurkovic Mlakar, Chakradhara Rao S. Uppugunduri, Yves Théoret, Imke H. Bartelink, Jaap-Jan Boelens, Robbert G. M. Bredius, Jean-Hugues Dalle, Victor Lewis, Bill S. Kangarloo, Selim Corbacioglu, Daniel Sinnett, Henrique Bittencourt & Maja Krajinovic

Bone Marrow Transplantation **56**, 2697–2704 (2021) | Cite this article

489 Accesses | 2 Citations | 9 Altmetric | Metrics

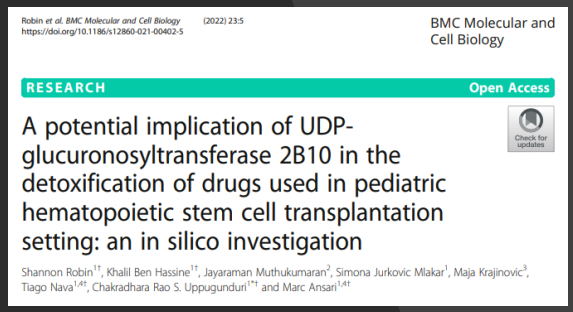
Mlakar *et al. Molecular Cancer* (2017) 16:114
DOI 10.1186/s12943-017-0686-8

Molecular Cancer

REVIEW Open Access

11q deletion in neuroblastoma: a review of biological and clinical implications

Vid Mlakar[1], Simona Jurkovic Mlakar[1], Gonzalo Lopez[3], John M. Maris[3,4], Marc Ansari[1,2] and Fabienne Gumy-Pause[1,2*]



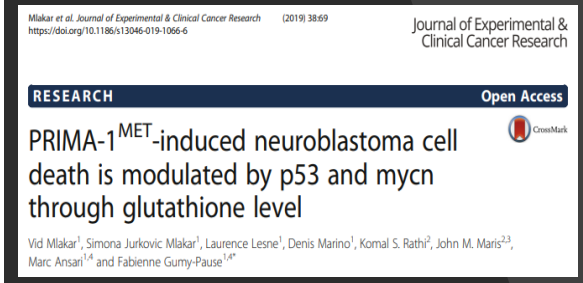
Robin *et al. BMC Molecular and Cell Biology* (2022) 23:5
https://doi.org/10.1186/s12860-021-00402-5

BMC Molecular and Cell Biology

RESEARCH Open Access

A potential implication of UDP-glucuronosyltransferase 2B10 in the detoxification of drugs used in pediatric hematopoietic stem cell transplantation setting: an in silico investigation

Shannon Robin[1†], Khalil Ben Hassine[1†], Jayaraman Muthukumaran[2], Simona Jurkovic Mlakar[1], Maja Krajinovic[3], Tiago Nava[1,4†], Chakradhara Rao S. Uppugunduri[1*†] and Marc Ansari[1,4†]



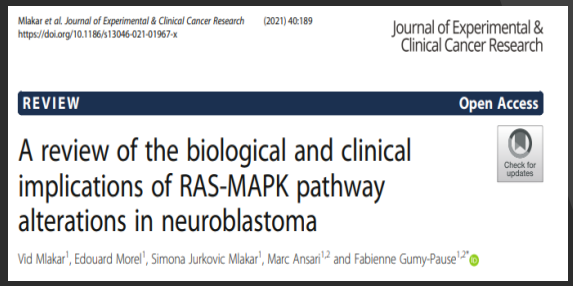
Mlakar *et al. Journal of Experimental & Clinical Cancer Research* (2019) 38:69
https://doi.org/10.1186/s13046-019-1066-6

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

PRIMA-1^{MET}-induced neuroblastoma cell death is modulated by p53 and mycn through glutathione level

Vid Mlakar[1], Simona Jurkovic Mlakar[1], Laurence Lesne[1], Denis Marino[1], Komal S. Rathi[2], John M. Maris[2,3], Marc Ansari[1,4] and Fabienne Gumy-Pause[1,4*]



Mlakar *et al. Journal of Experimental & Clinical Cancer Research* (2021) 40:189
https://doi.org/10.1186/s13046-021-01967-x

Journal of Experimental & Clinical Cancer Research

REVIEW Open Access

A review of the biological and clinical implications of RAS-MAPK pathway alterations in neuroblastoma

Vid Mlakar[1], Edouard Morel[1], Simona Jurkovic Mlakar[1], Marc Ansari[1,2] and Fabienne Gumy-Pause[1,2*]

Ostale objave -Švedska

Environment International 145 (2020) 106148

Contents lists available at ScienceDirect

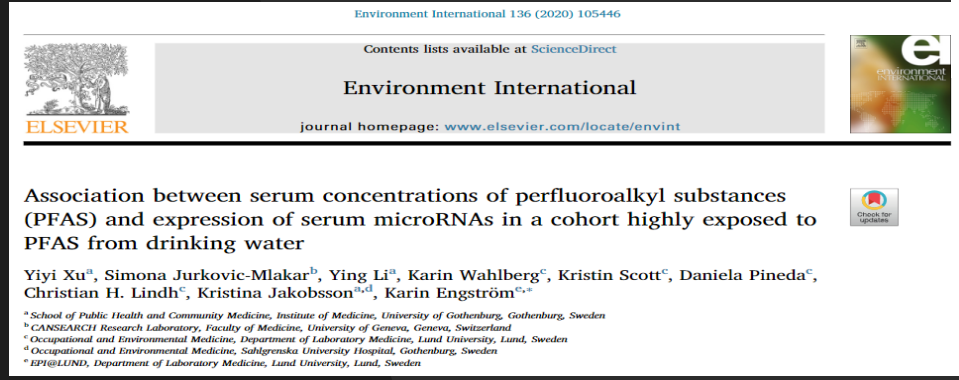
Environment International

journal homepage: www.elsevier.com/locate/envint

Associations between serum concentrations of perfluoroalkyl substances and DNA methylation in women exposed through drinking water: A pilot study in Ronneby, Sweden

Yiyi Xu [a], Simona Jurkovic-Mlakar [b], Christian H. Lindh [c], Kristin Scott [c], Tony Fletcher [d], Kristina Jakobsson [a,e], Karin Engström [f,*]

[a] School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[b] CANSEARCH Research Laboratory, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[c] Occupational and Environmental Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden
[d] London School of Hygiene and Tropical Medicine, London, United Kingdom
[e] Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[f] EPI@LUND, Department of Laboratory Medicine, Lund University, Lund, Sweden



Environment International 136 (2020) 105446

Contents lists available at ScienceDirect

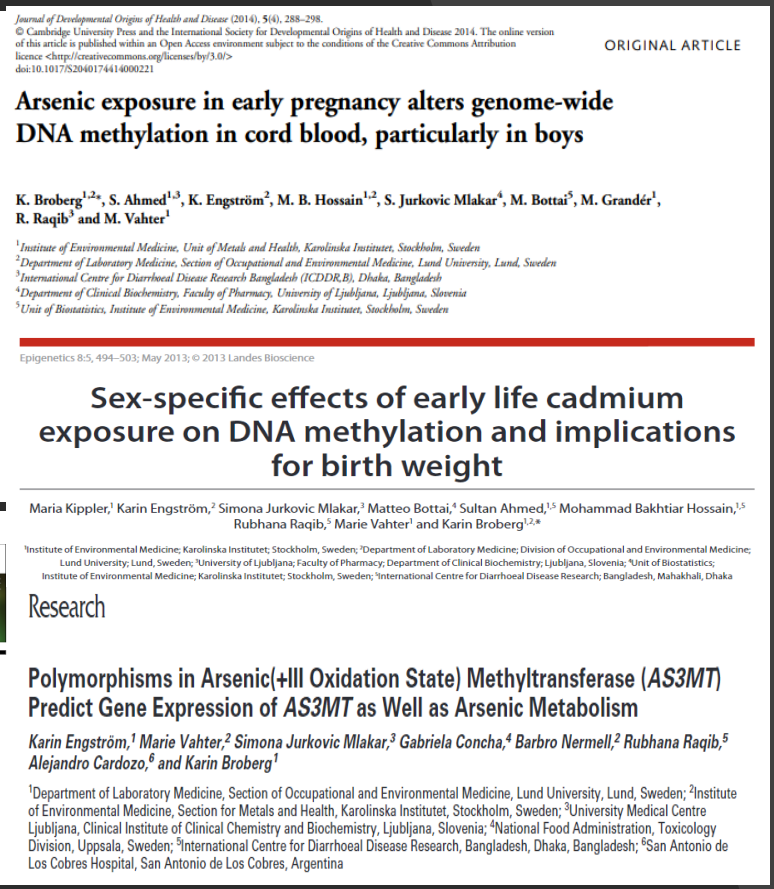
Environment International

journal homepage: www.elsevier.com/locate/envint

Association between serum concentrations of perfluoroalkyl substances (PFAS) and expression of serum microRNAs in a cohort highly exposed to PFAS from drinking water

Yiyi Xu[a], Simona Jurkovic-Mlakar[b], Ying Li[a], Karin Wahlberg[c], Kristin Scott[c], Daniela Pineda[c], Christian H. Lindh[c], Kristina Jakobsson[a,d], Karin Engström[c,*]

[a] School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[b] CANSEARCH Research Laboratory, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[c] Occupational and Environmental Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden
[d] Occupational and Environmental Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
[e] EPI@LUND, Department of Laboratory Medicine, Lund University, Lund, Sweden



Journal of Developmental Origins of Health and Disease (2014), 5(4), 288–298.

doi:10.1017/S2040174414000221

ORIGINAL ARTICLE

Arsenic exposure in early pregnancy alters genome-wide DNA methylation in cord blood, particularly in boys

K. Broberg[1,2*], S. Ahmed[1,3], K. Engström[2], M. B. Hossain[1,2], S. Jurkovic Mlakar[4], M. Bottai[5], M. Grandér[1], R. Raqib[3] and M. Vahter[1]

[1] Institute of Environmental Medicine, Unit of Metals and Health, Karolinska Institutet, Stockholm, Sweden
[2] Department of Laboratory Medicine, Section of Occupational and Environmental Medicine, Lund University, Lund, Sweden
[3] International Centre for Diarrhoeal Disease Research Bangladesh (ICDDR,B), Dhaka, Bangladesh
[4] Department of Clinical Biochemistry, Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia
[5] Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Epigenetics 8:5, 494–503; May 2013; © 2013 Landes Bioscience

Sex-specific effects of early life cadmium exposure on DNA methylation and implications for birth weight

Maria Kippler,[1] Karin Engström,[2] Simona Jurkovic Mlakar,[3] Matteo Bottai,[4] Sultan Ahmed,[1,5] Mohammad Bakhtiar Hossain,[1,5] Rubhana Raqib,[5] Marie Vahter[1] and Karin Broberg[1,2,*]

[1]Institute of Environmental Medicine; Karolinska Institutet; Stockholm, Sweden; [2]Department of Laboratory Medicine; Division of Occupational and Environmental Medicine; Lund University; Lund, Sweden; [3]University of Ljubljana; Faculty of Pharmacy; Department of Clinical Biochemistry; Ljubljana, Slovenia; [4]Unit of Biostatistics; Institute of Environmental Medicine; Karolinska Institutet; Stockholm, Sweden; [5]International Centre for Diarrhoeal Disease Research; Bangladesh, Mahakhali, Dhaka

Research

Polymorphisms in Arsenic(+III Oxidation State) Methyltransferase (*AS3MT*) Predict Gene Expression of *AS3MT* as Well as Arsenic Metabolism

Karin Engström,[1] Marie Vahter,[2] Simona Jurkovic Mlakar,[3] Gabriela Concha,[4] Barbro Nermell,[2] Rubhana Raqib,[5] Alejandro Cardozo,[6] and Karin Broberg[1]

[1]Department of Laboratory Medicine, Section of Occupational and Environmental Medicine, Lund University, Lund, Sweden; [2]Institute of Environmental Medicine, Section for Metals and Health, Karolinska Institutet, Stockholm, Sweden; [3]University Medical Centre Ljubljana, Clinical Institute of Clinical Chemistry and Biochemistry, Ljubljana, Slovenia; [4]National Food Administration, Toxicology Division, Uppsala, Sweden; [5]International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; [6]San Antonio de Los Cobres Hospital, San Antonio de Los Cobres, Argentina