Tailoring glioblastoma treatment based on longitudinal analysis of post-surgical tumor microenvironment

Type de document	Article de revue
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Auteur	Franck Debarbieux
Auteur	Hervé Luche
Auteur	Dominique Figarella-Branger
Auteur	Marie-Anne Estève
Auteur	Emeline Tabouret
Auteur	Aurélie Tchoghandjian
Résumé	Glioblastoma (GBM), an incurable primary brain tumor, typically requires surgical intervention followed by chemoradiation; however, recurrences remain fatal. Our previous work demonstrated that a nanomedicine hydrogel (GemC12-LNC) delays recurrence when administered post-surgery. However, tumor debulking also triggers time-dependent immune reactions that promote recurrence at the resection cavity borders. We hypothesized that combining the hydrogel with an immunomodulatory drug could enhance therapeutic outcomes. A thorough characterization of the post-surgical microenvironment (SMe) is crucial to guide combinatorial approaches., In this study, we performed cellular resolution imaging, flow cytometry and spatial hyperplexed immunofluorescence imaging to characterize the SMe in a syngeneic mouse model of tumor resection. Owing to our dynamic approach, we observed transient opening of the blood–brain barrier (BBB) during the first week after surgery. BBB permeability post-surgery was also confirmed in GBM patients. In our murine model, we also observed changes in immune cell morphology and spatial location post-surgery over time in resected animals as well as the accumulation of reactive microglia and anti-inflammatory macrophages in recurrences compared to unresected tumors since the first steps of recurrence growth. Therefore we investigated whether starting a systemic treatment with the SMAC mimetic small molecule (GDC-0152) directly after surgery would be beneficial for enhancing microglial anti-tumoral activity and decreasing the number of anti-inflammatory macrophages

	around the GemC12-LNC hydrogel-loaded tumor cavity. The immunomodulatory effects of this drug combination was firstly shown in patient-derived tumoroids. Its efficacy was confirmed in vivo by survival analysis and correlated with reversal of the immune profile as well as delayed tumor recurrence., This comprehensive study identified critical time frames and immune cellular targets within the SMe, aiding in the rational design of combination therapies to delay recurrence onset. Our findings suggest that post-surgical systemic injection of GDC-0152 in combination with GemC12-LNC local treatment is a promising and innovative approach for managing GBM recurrence, with potential for future translation to human patient.
Date	2024-11-28
Catalogue de bibl.	PubMed Central
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11603899/
Consulté le	10/12/2024 11:48:16
Extra	PMID: 39605004 PMCID: PMC11603899
Volume	43
Pages	311
Publication	Journal of Experimental & Clinical Cancer Research : CR
DOI	10.1186/s13046-024-03231-4
Abrév. de revue	J Exp Clin Cancer Res
ISSN	0392-9078
Date d'ajout	10/12/2024 11:48:17
Modifié le	10/12/2024 11:48:17

- **Pièces jointes**
  - PubMed Central Full Text PDF
  - PubMed Central Link

Self-demixing of mRNA copies buffers mRNA:mRNA and mRNA:regulator stoichiometries

Type de document	Article de revue
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Auteur	Szilvia Ecsedi
Auteur	Mokrane Khier
Auteur	Zhou Yi
Auteur	Alia Bahri
Auteur	Amira Ouertani
Auteur	Florian Valero
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Auteur	Sami Rouquet
Auteur	Stéphane Robert
Auteur	Agnès Loubat
Auteur	Danielle Adekunle
Auteur	Arnaud Hubstenberger
Résumé	Cellular homeostasis requires the robust control of biomolecule concentrations, but how do millions of mRNAs coordinate their stoichiometries in the face of dynamic translational changes? Here, we identified a two-tiered mechanism controlling mRNA:mRNA and mRNA:protein stoichiometries where mRNAs super-assemble into condensates with buffering capacity and sorting selectivity through phase-transition mechanisms. Using C. elegans oogenesis arrest as a model, we investigated the transcriptome cytosolic reorganization through the sequencing of RNA super-assemblies coupled with single mRNA imaging. Tightly repressed mRNAs self-assembled into same-sequence nanoclusters that further co-assembled into multiphase condensates. mRNA self-sorting was concentration dependent, providing a self-buffering mechanism that is selective to sequence identity and controls mRNA:mRNA stoichiometries. The cooperative sharing of limiting translation repressors between clustered mRNAs prevented the disruption of mRNA:repressor stoichiometries in the cytosol. Robust control of mRNA:mRNA and mRNA:protein stoichiometries emerges from mRNA self-demixing and cooperative super-assembly into multiphase multiscale condensates with dynamic storage capacity.
Date	2023-09-07
Langue	eng
Titre abrégé	Self-demixing of mRNA copies buffers mRNA
Catalogue de bibl.	PubMed
Extra	PMID: 37703874
Pages	S0092-8674(23)00907-8
Publication	Cell
DOI	10.1016/j.cell.2023.08.018
Abrév. de revue	Cell
ISSN	1097-4172
Date d'ajout	14/09/2023 14:35:05
Modifié le	14/09/2023 14:35:05

- **Marqueurs :**
  - sorting
  - buffering
  - homeostasis
  - mRNA nanoclusters
  - mRNA translation

- multiscale condensates
- oocyte
- phase separations and transitions
- quiescence
- RNA condensates
- RNA stoichiometry
- transcriptomics

Pièces jointes

- Cardona et al. - 2023 - Self-demixing of mRNA copies buffers mRNAmRNA and.pdf
- PubMed entry

- # Region-specific microRNA alterations in marmosets carrying SLC6A4 polymorphisms are associated with anxiety-like behavior

Type de document	Article de revue
Auteur	Natalia Popa
Auteur	Dipankar Bachar
Auteur	Angela C. Roberts
Auteur	Andrea M. Santangelo
Auteur	Eduardo Gascon
Résumé	Background Psychiatric diseases such as depression and anxiety are multifactorial conditions, highly prevalent in western societies. Human studies have identified a number of high-risk genetic variants for these diseases. Among them, polymorphisms in the promoter region of the serotonin transporter gene (SLC6A4) have attracted much attention. However, due to the paucity of experimental models, molecular alterations induced by these genetic variants and how they correlate to behavioral deficits have not been examined. In this regard, marmosets have emerged as a powerful model in translational neuroscience to investigate molecular underpinnings of complex behaviors. Methods Here, we took advantage of naturally occurring genetic polymorphisms in marmoset SLC6A4 gene that have been linked to anxiety-like behaviors. Using FACS-sorting, we profiled microRNA contents in different brain regions of genotyped and behaviorally-phenotyped marmosets. Findings We revealed that marmosets bearing different SLC6A4 variants exhibit distinct microRNAs signatures in a region of the prefrontal cortex whose activity has been consistently altered in patients with depression/anxiety. We also identified Deleted in Colorectal Cancer (DCC), a gene previously linked to these diseases, as a downstream target of the differently expressed microRNAs. Significantly, we showed that levels of both microRNAs and DCC in this region were highly correlated to anxiety-like behaviors. Interpretation Our findings establish links between genetic variants,

	molecular modifications in specific cortical regions and complex behavioral responses, providing new insights into gene-behavior relationships underlying human psychopathology. Funding This work was supported by France National Agency, NRJ Foundation, Celphedia and Fondation de France as well as the Wellcome Trust.
Date	2022-7-26
Catalogue de bibl.	PubMed Central
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9334339/
Consulté le	12/09/2022 16:44:45
Extra	PMID: 35905539 PMCID: PMC9334339
Volume	82
Pages	104159
Publication	eBioMedicine
DOI	10.1016/j.ebiom.2022.104159
Abrév. de revue	eBioMedicine
ISSN	2352-3964
Date d'ajout	12/09/2022 16:44:45
Modifié le	12/09/2022 16:44:45

- **Pièces jointes**
  - PubMed Central Full Text PDF
  - PubMed Central Link

- # Stem cell regionalization during olfactory bulb neurogenesis depends on regulatory interactions between Vax1 and Pax6

Type de document	Article de revue
Auteur	Nathalie Coré
Auteur	Andrea Erni
Auteur	Hanne M Hoffmann
Auteur	Pamela L Mellon
Auteur	Andrew J Saurin
Auteur	Christophe Beclin
Auteur	Harold Cremer
Résumé	Different subtypes of interneurons, destined for the olfactory bulb, are continuously generated by neural stem cells located in the ventricular and subventricular zones along the lateral forebrain ventricles of mice. Neuronal identity in the olfactory bulb depends on the existence of defined microdomains of pre-determined neural stem cells along the

	ventricle walls. The molecular mechanisms underlying positional identity of these neural stem cells are poorly understood. Here, we show that the transcription factor Vax1 controls the production of two specific neuronal subtypes. First, it is directly necessary to generate Calbindin expressing interneurons from ventro-lateral progenitors. Second, it represses the generation of dopaminergic neurons by dorsolateral progenitors through inhibition of Pax6 expression. We present data indicating that this repression occurs, at least in part, via activation of microRNA miR-7.
Date	2021-06-28 08:39:12
Catalogue de bibl.	PubMed Central
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7440913/
Consulté le	28/06/2021 10:39:12
Extra	PMID: 32762844 PMCID: PMC7440913
Volume	9
Pages	e58215
Publication	eLife
DOI	10.7554/eLife.58215
Abrév. de revue	eLife
ISSN	2050-084X
Date d'ajout	13/12/2021 10:37:44
Modifié le	13/12/2021 10:37:44

- **Pièces jointes**
  - PubMed Central Link
  - Texte intégral

- # Systemic Administration of G-CSF Accelerates Bone Regeneration and Modulates Mobilization of Progenitor Cells in a Rat Model of Distraction Osteogenesis

Type de document	Article de revue
Auteur	Flavy Roseren
Auteur	Martine Pithioux
Auteur	Stéphane Robert
Auteur	Laure Balasse
Auteur	Benjamin Guillet
Auteur	Edouard Lamy
Auteur	Sandrine Roffino

Résumé	Granulocyte colony-stimulating factor (G-CSF) was shown to promote bone regeneration and mobilization of vascular and osteogenic progenitor cells. In this study, we investigated the effects of a systemic low dose of G-CSF on both bone consolidation and mobilization of hematopoietic stem/progenitor cells (HSPCs), endothelial progenitor cells (EPCs) and mesenchymal stromal cells (MSCs) in a rat model of distraction osteogenesis (DO). Neovascularization and mineralization were longitudinally monitored using positron emission tomography and planar scintigraphy. Histological analysis was performed and the number of circulating HSPCs, EPCs and MSCs was studied by flow cytometry. Contrary to control group, in the early phase of consolidation, a bony bridge with lower osteoclast activity and a trend of an increase in osteoblast activity were observed in the distracted callus in the G-CSF group, whereas, at the late phase of consolidation, a significantly lower neovascularization was observed. While no difference was observed in the number of circulating EPCs between control and G-CSF groups, the number of MSCs was significantly lower at the end of the latency phase and that of HSPCs was significantly higher 4 days after the bone lengthening. Our results indicate that G-CSF accelerates bone regeneration and modulates mobilization of progenitor cells during DO.
Date	2021-03-28
Langue	eng
Catalogue de bibl.	PubMed
Extra	Number: 7 PMID: 33800710 PMCID: PMC8037338
Volume	22
Publication	International Journal of Molecular Sciences
DOI	10.3390/ijms22073505
Numéro	7
Abrév. de revue	Int J Mol Sci
ISSN	1422-0067
Date d'ajout	13/12/2021 10:37:36
Modifié le	13/12/2021 10:37:36

- **Marqueurs :**
  - bone formation
  - endothelial progenitor cells
  - G-CSF
  - hematopoietic stem/progenitor cells
  - mesenchymal stromal cells
  - neovascularization

Pièces jointes

- PubMed entry

- Texte intégral

CeO2 Nanomaterials from Diesel Engine Exhaust Induce DNA Damage and Oxidative Stress in Human and Rat Sperm In Vitro

Type de document	Article de revue
Auteur	Martina Cotena
Auteur	Mélanie Auffan
Auteur	Stéphane Robert
Auteur	Virginie Tassistro
Auteur	Noémie Resseguier
Auteur	Jérôme Rose
Auteur	Jeanne Perrin
Résumé	Cerium dioxide nanomaterials (CeO2 NMs) are widely used in nano-based diesel additives to decrease the emission of toxic compounds, but they have been shown to increase the emission of ultrafine particles as well as the amount of released Ce. The Organization for Economic Cooperation and Development included CeO2 NMs in the priority list of nanomaterials that require urgent evaluation, and the potential hazard of aged CeO2 NM exposure remains unexplored. Herein, human and rat sperm cells were exposed in vitro to a CeO2 NM-based diesel additive (called EnviroxTM), burned at 850 °C to mimic its release after combustion in a diesel engine. We demonstrated significant DNA damage after in vitro exposure to the lowest tested concentration (1 µg·L−1) using the alkaline comet assay (ACA). We also showed a significant increase in oxidative stress in human sperm after in vitro exposure to 1 µg·L−1 aged CeO2 NMs evaluated by the H2DCF-DA probe. Electron microscopy showed no internalization of aged CeO2 NMs in human sperm but an affinity for the head plasma membrane. The results obtained in this study provide some insight on the complex cellular mechanisms by which aged CeO2 NMs could exert in vitro biological effects on human spermatozoa and generate ROS.
Date	2020/12
Langue	en
Catalogue de bibl.	www.mdpi.com
URL	https://www.mdpi.com/2079-4991/10/12/2327
Consulté le	25/11/2020 11:11:38
Autorisations	http://creativecommons.org/licenses/by/3.0/
Extra	Number: 12 Publisher: Multidisciplinary Digital Publishing Institute
Volume	10
Pages	2327

Publication	Nanomaterials
DOI	10.3390/nano10122327
Numéro	12
Date d'ajout	13/12/2021 10:37:00
Modifié le	13/12/2021 10:37:00

- **Marqueurs :**
  - ageing
  - combustion
  - DNA damage
  - nanoparticles
  - NMs life cycle
  - Oxidative stress
  - reproductive toxicity

Pièces jointes

  - Full Text PDF
  - Snapshot

- # Evaluation of PIG-A-mutated granulocytes and ex-vivo binucleated micronucleated lymphocytes frequencies after breast cancer radiotherapy in humans

Type de document	Article de revue
Auteur	Rémi M. Bonetto
Auteur	Pierre Castel
Auteur	Stéphane P. Robert
Auteur	Virginie M. Tassistro
Auteur	Magalie Claeys-Bruno
Auteur	Michelle Sergent
Auteur	Camille A. Delecourt
Auteur	Didier Cowen
Auteur	Xavier Carcopino
Auteur	Thierry G. Orsière
Résumé	Although the PIG-A gene mutation frequency (MF) is considered a good proxy to evaluate the somatic MF in animals, evidence remains scarce in humans. In this study, a granulocyte PIG-A-mutant assay was evaluated in patients undergoing radiation therapy (RT) for breast cancer. Breast cancer patients undergoing adjuvant RT were prospectively enrolled. RT involved the whole breast, with (WBNRT) or without (WBRT) nodal area irradiation. Blood samples were obtained from participants before (T0) RT, and T1, T2, and T3 samples

were collected 3 weeks after the initiation of RT, at the end of RT, and at least 10 weeks after RT discontinuation, respectively. The MF was assessed using a flow cytometry protocol identifying PIG-A-mutant granulocytes. Cytokinesis-blocked micronucleated lymphocyte (CBML) frequencies were also evaluated. Thirty patients were included, and five of them had received chemotherapy prior to RT. The mean (±SD) PIG-A MFs were 7.7 (±12.1) per million at T0, 5.2 (±8.6) at T1, 6.4 (±8.0) at T2 and 3.8 (±36.0) at T3. No statistically significant increases were observed between the PIG-A MF at T0 and the MFs at other times. RT significantly increased the CBML frequencies: 7.9 ‰ (±3.1‰) versus 33.6‰ (±17.2‰) ($p < .0001$). By multivariate analysis, the CBML frequency was correlated with age at RT initiation ($p = .043$) and irradiation volume at RT discontinuation ($p = .0001$) but not with chemotherapy. RT for breast cancer therapy failed to induce an increase in the PIG-A MF. The PIG-A assay in humans needs further evaluation, in various genotoxic exposures and including various circulating human cells.

Date	Nov 09, 2020
Langue	eng
Catalogue de bibl.	PubMed
Extra	PMID: 33169419
Publication	Environmental and Molecular Mutagenesis
DOI	10.1002/em.22413
Abrév. de revue	Environ Mol Mutagen
ISSN	1098-2280
Date d'ajout	13/12/2021 10:36:59
Modifié le	13/12/2021 10:36:59

- **Marqueurs :**
  - granulocyte
  - human
  - micronucleus assay
  - mutation
  - PIG-A gene
  - radiotherapy

Pièces jointes

  - Bonetto et al. - 2020 - Evaluation of PIG-A-mutated granulocytes and ex-vi.pdf
  - PubMed entry

- # Long Non-coding RNA T-UCstem1 Controls Progenitor Proliferation and Neurogenesis in the

Postnatal Mouse Olfactory Bulb through Interaction with miR-9

Type de document	Article de revue
Auteur	Emilia Pascale
Auteur	Christophe Beclin
Auteur	Alessandro Fiorenzano
Auteur	Gennaro Andolfi
Auteur	Andrea Erni
Auteur	Sandro De Falco
Auteur	Gabriella Minchiotti
Auteur	Harold Cremer
Auteur	Annalisa Fico
Résumé	Neural stem cell populations generate a wide spectrum of neuronal and glial cell types in a highly ordered fashion. MicroRNAs are essential regulators of this process. T-UCstem1 is a long non-coding RNA containing an ultraconserved element, and in vitro analyses in pluripotent stem cells provided evidence that it regulates the balance between proliferation and differentiation. Here we investigate the in vivo function of T-UCstem1. We show that T-UCstem1 is expressed in the forebrain neurogenic lineage that generates interneurons for the postnatal olfactory bulb. Gain of function in neural stem cells increased progenitor proliferation at the expense of neuron production, whereas knockdown had the opposite effect. This regulatory function is mediated by its interaction with miR-9-3p and miR-9-5p. Based thereon, we propose a mechanistic model for the role of T-UCstem1 in the dynamic regulation of neural progenitor proliferation during neurogenesis., • T-UCstem1 is expressed in the SVZ-RMS-OB neurogenic system • T-UCstem1 controls proliferation of neuronal progenitors in the subventricular zone • T-UCstem1 regulates neuron addition to the olfactory bulb • T-UCstem1 acts through miR-9-3p and miR-9-5p , In this study, Fico, Beclin, and colleagues show that the long non-coding RNA T-UCstem1 is expressed in the forebrain neurogenic lineage generating interneurons for the postnatal olfactory bulb. Increased T-UCstem1 levels in neural stem cells induced progenitor proliferation at the expense of neuron production, whereas its downregulation caused the opposite effect. This regulatory function is mediated by its interaction with miR-9.
Date	2020-9-24
Catalogue de bibl.	PubMed Central
URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7562942/
Consulté le	28/06/2021 10:42:21
Extra	Number: 4 PMID: 32976763 PMCID: PMC7562942

Volume	15
Pages	836-844
Publication	Stem Cell Reports
DOI	10.1016/j.stemcr.2020.08.009
Numéro	4
Abrév. de revue	Stem Cell Reports
ISSN	2213-6711
Date d'ajout	13/12/2021 10:37:45
Modifié le	13/12/2021 10:37:45

- **Pièces jointes**
  - PubMed Central Full Text PDF
  - PubMed Central Link

Prototyping Trastuzumab Docetaxel Immunoliposomes with a New FCM-Based Method to Quantify Optimal Antibody Density on Nanoparticles

Type de document	Article de revue
Auteur	A. Rodallec
Auteur	C. Franco
Auteur	S. Robert
Auteur	G. Sicard
Auteur	S. Giacometti
Auteur	B. Lacarelle
Auteur	F. Bouquet
Auteur	A. Savina
Auteur	R. Lacroix
Auteur	F. Dignat-George
Auteur	J. Ciccolini
Auteur	P. Poncelet
Auteur	R. Fanciullino
Résumé	Developing targeted nanoparticles is a rising strategy to improve drug delivery in oncology. Antibodies are the most commonly used targeting agents. However, determination of their optimal number at the surface remains a challenging issue, mainly due to the difficulties in measuring precisely surface coating levels when prototyping nanoparticles. We developed an original quantitative assay to measure the exact number of coated antibodies per nanoparticle. Using flow cytometry optimized for submicron particle analysis and beads covered with known amounts of human IgG-kappa mimicking various amounts of antibodies, this

	new method was tested as part of the prototyping of docetaxel liposomes coated with trastuzumab against Her2+ breast cancer. This quantification method allowed to discriminate various batches of immunoliposomes depending on their trastuzumab density on nanoparticle surface (i.e., 330 (Immunoliposome-1), 480 (Immunoliposome-2) and 690 (Immunoliposome-3), p = 0.004, One-way ANOVA). Here we showed that optimal number of grafted antibodies on nanoparticles should be finely tuned and highest density of targeting agent is not necessarily associated with highest efficacy. Overall, this new method should help to better prototype third generation nanoparticles.
Date	Mar 05, 2020
Langue	eng
Catalogue de bibl.	PubMed
Extra	Number: 1
Volume	10
Pages	4147
Publication	Scientific Reports
DOI	10.1038/s41598-020-60856-z
Numéro	1
Abrév. de revue	Sci Rep
ISSN	2045-2322
Date d'ajout	13/12/2021 10:36:14
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- **Pièces jointes**
  - PubMed entry
  - Texte intégral

- # miR-9 Does Not Regulate Lamin A Expression in Metastatic Cells from Lung Adenocarcinoma

Type de document	Article de revue
Auteur	Julien Guinde
Auteur	Audrey Benoit
Auteur	Diane Frankel
Auteur	Stéphane Robert
Auteur	Kevin Ostacolo
Auteur	Nicolas Lévy
Auteur	Philippe Astoul
Auteur	Patrice Roll
Auteur	Elise Kaspi

Résumé	In lung adenocarcinoma, low lamin A expression in pleural metastatic cells has been proposed as a pejorative factor. miR-9 physiologically inhibits the expression of lamin A in neural cells and seems to be a central actor in the carcinogenesis and the metastatic process in lung cancer. Thus, it could be a good candidate to explain the reduction of lamin A expression in lung adenocarcinoma cells. miR-9 expression was analyzed in 16 pleural effusions containing metastatic cells from lung adenocarcinoma and was significantly reduced in patients from the 'Low lamin A expression' group compared to patients from the 'High lamin A expression' group. Then, carcinoma cells selection by fluorescence-activated cell sorting (FACS) was performed according to epithelial membrane antigen (EMA) expression, reflecting lamin A expression. miR-9 was underexpressed in lamin A- carcinoma cells compared to lamin A+ carcinoma cells in patients from the 'Low lamin A expression' group, whereas there was no difference of miR-9 expression between lamin A+ and lamin A- carcinoma cells in patients from the 'High lamin A expression' group. These results suggest that miR-9 does not regulate lamin A expression in metastatic cells from lung adenocarcinoma. On the contrary, miR-9 expression was shown to be reduced in lamin A-negative carcinoma cells.
Date	2020-02-26
Langue	eng
Catalogue de bibl.	PubMed
Extra	PMID: 32111074 PMCID: PMC7084260
Volume	21
Pages	E1599
Publication	International Journal of Molecular Sciences
DOI	10.3390/ijms21051599
Numéro	5
Abrév. de revue	Int J Mol Sci
ISSN	1422-0067
Date d'ajout	24/01/2022 13:56:54
Modifié le	24/01/2022 13:56:54

- **Marqueurs :**
  - Humans
  - MicroRNAs
  - Cell Line, Tumor
  - Gene Expression Regulation, Neoplastic
  - Adenocarcinoma of Lung
  - Carcinogenesis
  - lamin A
  - Lamin Type A
  - lung adenocarcinoma
  - Lung Neoplasms

- microRNA-9
- Mucin-1
- Pleural Effusion
- pleural effusions

Pièces jointes

- PubMed entry
- Texte intégral

- # A squalamine derivative, NV669, as a novel PTP1B inhibitor: in vitro and in vivo effects on pancreatic and hepatic tumor growth

Type de document	Article de revue
Auteur	Sylvie Carmona
Auteur	Jean-Michel Brunel
Auteur	Rénaté Bonier
Auteur	Véronique Sbarra
Auteur	Stéphane Robert
Auteur	Patrick Borentain
Auteur	Dominique Lombardo
Auteur	Eric Mas
Auteur	René Gerolami
Résumé	NV669 is an aminosterol derived from squalamine found to possess strong anticancer effects. The aim of this study was to investigate NV669's beneficial effects on human pancreatic and hepatic cancer models and to decipher the cellular and molecular mechanisms involved in tumor growth decrease upon treatment with NV669. Pancreatic (BxPC3, MiaPaCa-2) and hepatic (HepG2, Huh7) cancer cells were treated with NV669, and the effects recorded on proliferation, cell cycle and death. Results showed that NV669 inhibited the viability of cancer cells, induced cell cycle arrest and subsequently promoted apoptosis. This was accompanied by a decrease in the expression of cyclin B1 and phosphorylated Cdk1 and by a cleavage of pro-apoptotic caspase-8 and PARP-1. Taken together, our studies showed that NV669 inhibits the proliferation of pancreatic and hepatic cancer cells through the regulation of G2/M phase transition via the cyclin B1-Cdk1 complex. In vitro NV669 inhibits PTP1B activity and FAK expression. NV669 impacts on the expression of adhesion molecules CDH-1, -2 and -3 in BxPC3 and Huh7 lines that form cell monolayers. Consecutively NV669 induces cell detachment. This suggests that NV669 by inhibiting PTP1B induces cell detachment and apoptosis. Subsequently, our in vivo results showed that NV669 inhibited the growth of pancreatic and hepatic tumor xenografts with a significant cell cycle arrest in pre-mitotic phase and an increase of

	tumor cell apoptosis. Therefore, NV669 may serve as an alternative anticancer agent, used alone or in association with other medications, for the treatment of pancreatic adenocarcinoma and hepatocellular carcinoma.
Date	Nov 19, 2019
Langue	eng
Titre abrégé	A squalamine derivative, NV669, as a novel PTP1B inhibitor
Catalogue de bibl.	PubMed
Extra	Number: 62
Volume	10
Pages	6651-6667
Publication	Oncotarget
DOI	10.18632/oncotarget.27286
Numéro	62
Abrév. de revue	Oncotarget
ISSN	1949-2553
Date d'ajout	13/12/2021 10:36:15
Modifié le	13/12/2021 10:36:15

- **Marqueurs :**
  - cancer
  - aminosterol
  - liver
  - pancreas
  - PTP1B

Pièces jointes

  - PubMed entry
  - Texte intégral

- # Deciphering the Crosstalk Between Myeloid-Derived Suppressor Cells and Regulatory T Cells in Pancreatic Ductal Adenocarcinoma

Type de document	Article de revue
Auteur	Carole Siret
Auteur	Aurélie Collignon
Auteur	Françoise Silvy
Auteur	Stéphane Robert
Auteur	Thierry Cheyrol
Auteur	Perrine André

Auteur	Véronique Rigot
Auteur	Juan Iovanna
Auteur	Serge van de Pavert
Auteur	Dominique Lombardo
Auteur	Eric Mas
Auteur	Anna Martirosyan
Résumé	Pancreatic ductal adenocarcinoma (PDAC) is a fatal disease with rising incidence and a remarkable resistance to current therapies. The reasons for this therapeutic failure include the tumor's extensive infiltration by immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). By using light sheet fluorescent microscopy, we identified here direct interactions between these major immunoregulatory cells in PDAC. The in vivo depletion of MDSCs led to a significant reduction in Tregs in the pancreatic tumors. Through videomicroscopy and ex vivo functional assays we have shown that (i) MDSCs are able to induce Treg cells in a cell-cell dependent manner; (ii) Treg cells affect the survival and/or the proliferation of MDSCs. Furthermore, we have observed contacts between MDSCs and Treg cells at different stages of human cancer. Overall our findings suggest that interactions between MDSCs and Treg cells contribute to PDAC immunosuppressive environment.
Date	2019
Langue	eng
Catalogue de bibl.	PubMed
Volume	10
Pages	3070
Publication	Frontiers in Immunology
DOI	10.3389/fimmu.2019.03070
Abrév. de revue	Front Immunol
ISSN	1664-3224
Date d'ajout	13/12/2021 10:36:15
Modifié le	13/12/2021 10:36:15

- **Marqueurs :**
  - pancreatic cancer
  - immune cell interactions
  - immunosuppression
  - MDSC
  - Tregs

Pièces jointes

- PubMed entry
- Texte intégral

- # Les P-bodies: Des gouttelettes microscopiques pour stocker les messagers de protéines régulatrices

Type de document	Article de revue
Auteur	Maïté Courel
Auteur	Marianne Bénard
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Date	04/2018
Langue	fr
Titre abrégé	Les P-bodies
Catalogue de bibl.	DOI.org (Crossref)
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Volume	34
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Publication	médecine/sciences
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- **Pièces jointes**
  - Courel et al. - 2018 - Les iP-bodiesi Des gouttelettes microscopiqu.pdf
- # Dendritic cell-based vaccination: powerful resources of immature dendritic cells against pancreatic adenocarcinoma

Type de document	Article de revue
Auteur	Aurélie Collignon
Auteur	Françoise Silvy
Auteur	Stéphane Robert
Auteur	Malika Trad

Auteur Sébastien Germain
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Auteur Richard Tomasini
Auteur Bernard Bonnotte
Auteur Dominique Lombardo
Auteur Eric Mas
Auteur Evelyne Beraud

Résumé Pancreatic adenocarcinoma (PAC) has a poor prognosis. One treatment approach, investigated here, is to reinforce antitumor immunity. Dendritic cells (DCs) are essential for the development and regulation of adaptive host immune responses against tumors. A major role for DCs may be as innate tumoricidal effector cells. We explored the efficacy of vaccination with immature (i)DCs, after selecting optimal conditions for generating immunostimulatory iDCs. We used two models, C57BL/6Jrj mice with ectopic tumors induced by the PAC cell line, Panc02, and genetically engineered (KIC) mice developing PAC. Therapeutic iDC-vaccination resulted in a significant reduction in tumor growth in C57BL/6Jrj mice and prolonged survival in KIC mice. Prophylactic iDC-vaccination prevented subcutaneous tumor development. These protective effects were long-lasting in Panc02-induced tumor development, but not in melanoma. iDC-vaccination impacted the immune status of the hosts by greatly increasing the percentage of CD8+ T-cells, and natural killer (NK)1.1+ cells, that express granzyme B associated with Lamp-1 and IFN-γ. Efficacy of iDC-vaccination was CD8+ T-cell-dependent but NK1.1+ cell-independent. We demonstrated the ability of DCs to produce peroxynitrites and to kill tumor cells; this killing activity involved peroxynitrites. Altogether, these findings make killer DCs the pivotal actors in the beneficial clinical outcome that accompanies antitumor immune responses. We asked whether efficacy can be improved by combining DC-vaccination with the FOLFIRINOX regimen. Combined treatment significantly increased the lifespan of KIC mice with PAC. Prolonged treatment with FOLFIRINOX clearly augmented this beneficial effect. Combining iDC-vaccination with FOLFIRINOX may therefore represent a promising therapeutic option for patients with PAC.

Date 2018
Langue eng
Titre abrégé Dendritic cell-based vaccination
Catalogue de bibl. PubMed
Extra Number: 12
Volume 7
Pages e1504727

Publication	Oncoimmunology
DOI	10.1080/2162402X.2018.1504727
Numéro	12
Abrév. de revue	Oncoimmunology
ISSN	2162-4011
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- **Marqueurs :**
  - pancreatic cancer
  - animal models
  - Active immunotherapy
  - cancer vaccines
  - DC-based tumor immunotherapy
  - FOLFIRINOX

Pièces jointes

  - PubMed entry

- # [The PIG-A gene as a new biomarker of mutagenesis: proof of concept and technical specifications]

Type de document	Article de revue
Auteur	Pierre Castel
Auteur	Xavier Carcopino
Auteur	Stéphane Robert
Auteur	Rémi Bonetto
Auteur	Didier Cowen
Auteur	Thierry Orsiere
Résumé	Gene mutations are not directly detected by current genotoxicity assays and most of them need a cell culture step. The whole blood PIG-A assay consists in the detection of the mutation frequency within the PIG-A sentinel gene by identification of glycosyl-phosphatidyl-inositol (GPI-) deficient cells. PIG-A mutated/GPI-deficient cells can be detected by flow cytometry as they no longer express surface fluorescence for GPI-linked markers. The last researches have focused on cell enrichment techniques leading to increased throughput and sensitivity. The results of this new and promising biomarker of mutagenesis, performed in humans or rodents, are now available within 2 hours after blood collection.
Date	Apr 2017
Langue	fre

Titre abrégé	[The PIG-A gene as a new biomarker of mutagenesis
Catalogue de bibl.	PubMed
Extra	Number: 4
Volume	33
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Publication	Medecine Sciences: M/S
DOI	10.1051/medsci/20173304014
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- **Marqueurs :**
  - Humans
  - Animals
  - Biomarkers
  - Membrane Proteins
  - Mutation
  - DNA Damage
  - DNA Mutational Analysis
  - Mutagenesis
  - Mutagenicity Tests
  - Mutation Rate

Pièces jointes

  - PubMed entry
  - Texte intégral

- # Acetylsalicylic acid differentially limits the activation and expression of cell death markers in human platelets exposed to Staphylococcus aureus strains

Type de document	Article de revue
Auteur	Adrien Chabert
Auteur	Pauline Damien
Auteur	Paul O. Verhoeven
Auteur	Florence Grattard
Auteur	Philippe Berthelot
Auteur	Fabrice Zeni
Auteur	Laurence Panicot-Dubois

Auteur	Stéphane Robert
Auteur	Françoise Dignat-George
Auteur	Marie-Ange Eyraud
Auteur	Bruno Pozzetto
Auteur	Bernard Payrastre
Auteur	Fabrice Cognasse
Auteur	Olivier Garraud
Auteur	Hind Hamzeh-Cognasse
Résumé	Beyond their hemostatic functions, platelets alter their inflammatory response according to the bacterial stimulus. Staphylococcus aureus is associated with exacerbated inflammation and thrombocytopenia, which is associated with poor prognosis during sepsis. Acetylsalicylic acid and statins prevent platelet aggregation and decrease the mortality rate during sepsis. Therefore, we assessed whether these two molecules could reduce in vitro platelet activation and the inflammatory response to S. aureus. Platelets were exposed to clinical strains of S. aureus in the presence or absence of acetylsalicylic acid or fluvastatin. Platelet activation, aggregation, and release of soluble sCD62P, sCD40 Ligand, RANTES and GROα were assessed. Platelet cell death was evaluated by analyzing the mitochondrial membrane potential, phosphatidylserine exposure, platelet microparticle release and caspase-3 activation. All S. aureus strains induced platelet activation but not aggregation and decreased the platelet count, the expression of cell death markers and the release of RANTES and GROα. Acetylsalicylic acid but not fluvastatin limited platelet activation and inflammatory factor release and restored the platelet count by protecting platelets from Staphylococcus-induced expression of cell death markers. This study demonstrates that acetylsalicylic acid limits S. aureus-induced effects on platelets by reducing cell death, revealing new strategies to reduce the platelet contribution to bacteremia-associated inflammation.
Date	07 17, 2017
Langue	eng
Catalogue de bibl.	PubMed
Extra	Number: 1
Volume	7
Pages	5610
Publication	Scientific Reports
DOI	10.1038/s41598-017-06024-2
Numéro	1
Abrév. de revue	Sci Rep
ISSN	2045-2322
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- **Marqueurs :**
  - Blood Platelets
  - Humans
  - Biomarkers
  - Platelet Activation
  - Platelet Aggregation
  - Cell Death
  - Aspirin
  - Bacterial Adhesion
  - Platelet Aggregation Inhibitors
  - Staphylococcal Infections
  - Staphylococcus aureus

Pièces jointes

  - PubMed entry
  - Texte intégral

- # High-Throughput Isolation of Giant Viruses in Liquid Medium Using Automated Flow Cytometry and Fluorescence Staining

Type de document	Article de revue
Auteur	Jacques Y. B. Khalil
Auteur	Stephane Robert
Auteur	Dorine G. Reteno
Auteur	Julien Andreani
Auteur	Didier Raoult
Auteur	Bernard La Scola
Résumé	The isolation of giant viruses using amoeba co-culture is tedious and fastidious. Recently, the procedure was successfully associated with a method that detects amoebal lysis on agar plates. However, the procedure remains time-consuming and is limited to protozoa growing on agar. We present here advances for the isolation of giant viruses. A high-throughput automated method based on flow cytometry and fluorescent staining was used to detect the presence of giant viruses in liquid medium. Development was carried out with the Acanthamoeba polyphaga strain widely used in past and current co-culture experiments. The proof of concept was validated with virus suspensions: artificially contaminated samples but also environmental samples from which viruses were previously isolated. After validating the technique, and fortuitously isolating a new Mimivirus, we automated the technique on 96-well plates and tested it on clinical and environmental samples using other protozoa. This allowed us to detect more than 10 strains of previously known species of giant viruses and seven new strains of a new virus lineage. This automated high-throughput method demonstrated significant time saving, and higher

	sensitivity than older techniques. It thus creates the means to isolate giant viruses at high speed.
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Langue	eng
Catalogue de bibl.	PubMed
Volume	7
Pages	26
Publication	Frontiers in Microbiology
DOI	10.3389/fmicb.2016.00026
Abrév. de revue	Front Microbiol
ISSN	1664-302X
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- **Marqueurs :**
  - Flow Cytometry
  - automated system
  - fluorescence staining
  - gating strategy
  - giant viruses
  - high-throughput
  - protozoa

Pièces jointes

  - PubMed entry
  - Texte intégral

- # A pancreatic tumor-specific biomarker characterized in humans and mice as an immunogenic onco-glycoprotein is efficient in dendritic cell vaccination

Type de document	Article de revue
Auteur	Aurélie Collignon
Auteur	Adriana Teodora Perles-Barbacaru
Auteur	Stéphane Robert
Auteur	Françoise Silvy
Auteur	Emmanuelle Martinez
Auteur	Isabelle Crenon
Auteur	Sébastien Germain
Auteur	Stéphane Garcia
Auteur	Angèle Viola

Auteur	Dominique Lombardo
Auteur	Eric Mas
Auteur	Evelyne Béraud
Résumé	Oncofetal fucose-rich glycovariants of the pathological bile salt-dependent lipase (pBSDL) appear during human pancreatic oncogenesis and are detected by themonoclonal antibody J28 (mAbJ28). We aimed to identify murine counterparts onpancreatic ductal adenocarcinoma (PDAC) cells and tissue and investigate the potential of dendritic cells (DC) loaded with this unique pancreatic tumor antigen to promote immunotherapy in preclinical trials. Pathological BSDLs purified from pancreatic juices of patients with PDAC were cleaved to generate glycosylated C-terminal moieties (C-ter) containing mAbJ28-reactive glycoepitopes. Immunoreactivity of the murine PDAC line Panc02 and tumor tissue to mAbJ28 was detected by immunohistochemistry and flow cytometry. C-ter-J28+ immunization promoted Th1-dominated immune responses. In vitro C-ter-J28+-loaded DCskewed CD3+ T-cells toward Th1 polarization. C-ter-J28+-DC-vaccinations selectively enhanced cell immunoreactivity to Panc02, as demonstrated by CD4+- and CD8+-T-cell activation, increased percentages of CD4+- and CD8+-T-cells and NK1.1+ cells expressing granzyme B, and T-cell cytotoxicity. Prophylactic and therapeutic C-ter-J28+-DC-vaccinations reduced ectopic Panc02-tumor growth, provided long-lasting protection from Panc02-tumor development in 100% of micebut not from melanoma, and attenuated progression of orthotopic tumors as revealed by MRI. Thusmurine DC loaded with pancreatic tumor-specific glycoepitope C-ter-J28+ induce efficient anticancer adaptive immunity and represent a potential adjuvant therapy for patients afflicted with PDAC.
Date	Sep 15, 2015
Langue	eng
Catalogue de bibl.	PubMed
Extra	Number: 27
Volume	6
Pages	23462-23479
Publication	Oncotarget
DOI	10.18632/oncotarget.4359
Numéro	27
Abrév. de revue	Oncotarget
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- **Marqueurs :**
  - Humans

- Flow Cytometry
- Animals
- biomarker
- Mice
- Cell Line, Tumor
- Biomarkers, Tumor
- Gene Expression Profiling
- pancreatic cancer
- Pancreatic Neoplasms
- Mice, Inbred C57BL
- Glycoproteins
- Active immunotherapy
- cancer vaccines
- Antibodies, Monoclonal
- Antigens, Neoplasm
- Carcinoma, Pancreatic Ductal
- CD3 Complex
- Dendritic Cells
- Epitopes
- Gene Expression Regulation, Neoplastic
- Glycosylation
- Granzymes
- HEK293 Cells
- Immunohistochemistry
- Immunotherapy
- Lymphocyte Activation
- Melanoma, Experimental
- Mice, Nude
- Neoplasm Transplantation
- Protein Structure, Tertiary
- T-Lymphocytes, Cytotoxic
- tumor-associated antigen

Pièces jointes

- PubMed entry
- Texte intégral