Année de publication : 2020

W González, M Dos Santos, C Guardiola, R Delorme, C Lamirault, M Juchaux, M Le Dudal, G Jouvion, Y Prezado (2020 Jan 10)

Minibeam radiation therapy at a conventional irradiator: Dose-calculation engine and first tumor-bearing animals irradiation.

Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics (AIFB) : 256-261 : DOI : S1120-1797(19)30537-X

Résumé

Minibeam radiation therapy (MBRT) is a novel therapeutic strategy, whose exploration was hindered due to its restriction to large synchrotrons. Our recent implementation of MBRT in a wide-spread small animal irradiator offers the possibility of performing systematic radiobiological studies. The aim of this research was to develop a set of dosimetric tools to reliably guide biological experiments in the irradiator.

Decaudin Didier, Frisch Dit Leitz Estelle, Nemati Fariba, Tarin Malcy, Naguez Adnan, Zerara Mohamed, Marande Benjamin, Vivet-Noguer Raquel, Halilovic Ensar, Fabre Claire, Jochemsen Aart, Roman-Roman Sergio, Alsafadi Samar. (2020 Jan 9)

Preclinical evaluation of drug combinations identifies co-inhibition of Bcl-2/XL/W and MDM2 as a potential therapy in uveal melanoma.

European Journal of CancerEuropean Journal of Cancer : DOI : 10.1016/j.ejca.2019.12.012

Résumé

Pol JG1,2,3,4,5, Caudana P6, Paillet J1,2,3,4,5,7, Piaggio E6,8, Kroemer G1,2,3,4,5,9,10,11. (2020 Jan 6)

Effects of interleukin-2 in immunostimulation and immunosuppression.

Journal of experimental medecine : 217(1) : DOI : 10.1084/jem.20191247

Résumé

M Dos Santos, R Delorme, R Salmon, Y Prezado (2020 Jan 5)

Minibeam radiation therapy: A micro- and nano-dosimetry Monte Carlo study.

Medical physics : 1379-1390 : DOI : 10.1002/mp.14009

Résumé

Minibeam radiation therapy (MBRT) is an innovative strategy based on a distinct dose

delivery method that is administered using a series of narrow (submillimetric) parallel beams. To shed light on the biological effects of MBRT irradiation, we explored the micro- and nanodosimetric characteristics of three promising MBRT modalities (photon, electron, and proton) using Monte Carlo (MC) calculations.

Manuel Rodrigues, Khadija Ait Rais, Flore Salviat, Nathalie Algret, Fatoumata Simaga, Raymond Barnhill, Sophie Gardrat, Vincent Servois, Pascale Mariani, Sophie Piperno-Neumann, Sergio Roman-Roman, Olivier Delattre, Nathalie Cassoux, Alexia Savignoni, Marc-Henri Stern, Gaëlle Pierron (2020 Jan 3)

Association of Partial Chromosome 3 Deletion in Uveal Melanomas With Metastasis-Free Survival.

JAMA ophthalmology : DOI : 10.1001/jamaophthalmol.2019.5403

Résumé

Studies on uveal melanomas (UMs) have demonstrated the prognostic value of 8q gain and monosomy 3, but the prognosis of UMs with partial deletion of chromosome 3 remains to be defined.

Yanzhang Luo, ShengQi Xiang, Peter Jan Hooikaas, Laura van Bezouwen, A S Jijumon, Carsten Janke, Friedrich Förster, Anna Akhmanova, Marc Baldus (2020 Jan 2)

Direct observation of dynamic protein interactions involving human microtubules using solid-state NMR spectroscopy.

Nature communications : 18 : DOI : 10.1038/s41467-019-13876-x

Résumé

Microtubules are important components of the eukaryotic cytoskeleton. Their structural organization is regulated by nucleotide binding and many microtubule-associated proteins (MAPs). While cryo-EM and X-ray crystallography have provided detailed views of interactions between MAPs with the microtubule lattice, little is known about how MAPs and their intrinsically disordered regions interact with the dynamic microtubule surface. NMR carries the potential to directly probe such interactions but so far has been precluded by the low tubulin yield. We present a protocol to produce [C, N]-labeled, functional microtubules (MTs) from human cells for solid-state NMR studies. This approach allowed us to demonstrate that MAPs can differently modulate the fast time-scale dynamics of C-terminal tubulin tails, suggesting distinct interaction modes. Our results pave the way for in-depth NMR studies of protein dynamics involved in MT assembly and their interactions with other cellular components.

Johannes Ommer, Joanna L Selfe, Marco Wachtel, Eleanor M O'Brien, Dominik Laubscher, Michaela Roemmele, Stephanie Kasper, Olivier Delattre, Didier Surdez, Gemma Petts, Anna

Kelsey, Janet Shipley, Beat W Schäfer (2020 Jan 1)
Aurora A Kinase Inhibition Destabilizes PAX3-FOXO1 and MYCN and Synergizes with Navitoclax to Induce Rhabdomyosarcoma Cell Death.
Cancer research : 832-842 : DOI : 10.1158/0008-5472.CAN-19-1479

Résumé

The clinically aggressive alveolar rhabdomyosarcoma (RMS) subtype is characterized by expression of the oncogenic fusion protein PAX3-FOXO1, which is critical for tumorigenesis and cell survival. Here, we studied the mechanism of cell death induced by loss of PAX3-FOXO1 expression and identified a novel pharmacologic combination therapy that interferes with PAX3-FOXO1 biology at different levels. Depletion of PAX3-FOXO1 in fusion-positive (FP)-RMS cells induced intrinsic apoptosis in a NOXA-dependent manner. This was pharmacologically mimicked by the BH3 mimetic navitoclax, identified as top compound in a screen from 208 targeted compounds. In a parallel approach, and to identify drugs that alter the stability of PAX3-FOXO1 protein, the same drug library was screened and fusion protein levels were directly measured as a read-out. This revealed that inhibition of Aurora kinase A most efficiently negatively affected PAX3-FOXO1 protein levels. Interestingly, this occurred through a novel specific phosphorylation event in and binding to the fusion protein. Aurora kinase A inhibition also destabilized MYCN, which is both a functionally important oncogene and transcriptional target of PAX3-FOXO1. Combined treatment with an Aurora kinase A inhibitor and navitoclax in FP-RMS cell lines and patient-derived xenografts synergistically induced cell death and significantly slowed tumor growth. These studies identify a novel functional interaction of Aurora kinase A with both PAX3-FOXO1 and its effector MYCN, and reveal new opportunities for targeted combination treatment of FP-RMS. SIGNIFICANCE: These findings show that Aurora kinase A and Bcl-2 family proteins are potential targets for FP-RMS.

Allard A, Bouzid M, Betz T, Simon C, Abou-Ghali M, Lemière J, Valentino F, Manzi J, Brochard-Wyart F, Guevorkian K, Plastino J, Lenz M, Campillo C*, Sykes C* (2020 Jan 1)
Actin modulates shape and mechanics of tubular membranes
bioRxiv : DOI : 10.1101/712505

Résumé

Davidson PM, Battistella A, Déjardin T, Betz T, Plastino J, Cadot B, Borghi N, Sykes C (2020 Jan 1)
Actin accumulates nesprin-2 at the front of the nucleus during confined cell migration
bioRxiv : DOI : 10.1101/713982

Résumé

Aurélie Teissandier, Nicolas Servant, Emmanuel Barillot, Deborah Bourc'his (2020 Jan 1)
Tools and best practices for retrotransposon analysis using high-throughput sequencing data.
Mobile DNA : 52 : DOI : 10.1186/s13100-019-0192-1

Résumé

Sequencing technologies give access to a precise picture of the molecular mechanisms acting upon genome regulation. One of the biggest technical challenges with sequencing data is to map millions of reads to a reference genome. This problem is exacerbated when dealing with repetitive sequences such as transposable elements that occupy half of the mammalian genome mass. Sequenced reads coming from these regions introduce ambiguities in the mapping step. Therefore, applying dedicated parameters and algorithms has to be taken into consideration when transposable elements regulation is investigated with sequencing datasets.

Année de publication : 2019

Stéphanie Lemaître, Florent Poyer, Paul Fréneaux, Sophie Leboucher, François Doz, Nathalie Cassoux, Carole D Thomas (2019 Dec 25)
Low retinal toxicity of intravitreal carboplatin associated with good retinal tumor control in transgenic murine retinoblastoma.
Clinical & experimental ophthalmology : DOI : 10.1111/ceo.13711

Résumé

Purpose

Retinoblastoma is a rare intraocular malignancy in children. Current treatments have many adverse effects. New therapeutic approaches like intravitreal injections of chemotherapies are currently being developed but their toxicities need to be evaluated on animal models. This study compares the efficacy and toxicity of intravitreal melphalan, topotecan and carboplatin, alone or in combination (sequential administration), in the LHBetaTag retinoblastoma mice.

Methods

Mice were divided into 9 groups: control, carboplatin 1.5 and 4µg, melphalan 0.1 and 1µg, topotecan 0.1 and 1µg, carboplatin 4µg/ topotecan 0.1µg and melphalan 1µg/ topotecan 0.1µg. The follow-up was performed using fundus imaging and optical coherence tomography combined with histopathological analysis. Absence of tumor and presence of calcified tumors were the criteria for therapeutic response assessment. Ocular complications were assessed after 4 weekly injections. Retinal toxicity was defined by the decrease of retinal thickness and of the number of retinal layers.

Results

Topotecan was inactive on retinal tumors. Melphalan (1µg) led to a complete tumor control in 91.7% of eyes. Carboplatin strongly decreased the tumor burden (85.7-93.8% of eyes without retinal tumor). The intravitreal injection itself led to ocular complications (25% of media opacities and 45.7% of retinal detachment). Only melphalan at 1µg showed a strong retinal toxicity. The two combinations showed a good efficacy in reducing the number of eyes with retinal tumors with a reduced retinal toxicity.

Conclusions

This preclinical study suggests that intravitreal injection of carboplatin has a low toxicity and could be evaluated in clinical practice to treat patients suffering from retinoblastoma.

Consuelo Guardiola, Ludovic De Marzi, Yolanda Prezado (2019 Dec 24)

Verification of a Monte Carlo dose calculation engine in proton minibeam radiotherapy in a passive scattering beamline for preclinical trials.

The British journal of radiology : 20190578 : DOI : 10.1259/bjr.20190578

Résumé

Proton minibeam radiation therapy (pMBRT) is a novel therapeutic strategy that combines the benefits of proton therapy with the remarkable normal tissue preservation observed with the use of submillimetric spatially fractionated beams. This promising technique has been implemented at the Institut Curie-Proton therapy centre (ICPO) using a first prototype of a multislit collimator. The purpose of this work was to develop a Monte Carlo-based dose calculation engine to reliably guide preclinical studies at ICPO.

Shensi Shen, Sara Faouzi, Amandine Bastide, Sylvain Martineau, Hélène Malka-Mahieu, Yu Fu, Xiaoxiao Sun, Christine Mateus, Emilie Routier, Severine Roy, Laurent Desaubry, Fabrice André, Alexander Eggermont, Alexandre David, Jean-Yves Scoazec, Stéphan Vagner, Caroline Robert (2019 Dec 18)

An epitranscriptomic mechanism underlies selective mRNA translation remodelling in melanoma persister cells.

Nature communications : 5713 : DOI : 10.1038/s41467-019-13360-6

Résumé

Cancer persister cells tolerate anticancer drugs and serve as the founders of acquired resistance and cancer relapse. Here we show that a subpopulation of BRAF mutant melanoma cells that tolerates exposure to BRAF and MEK inhibitors undergoes a reversible remodelling of mRNA translation that evolves in parallel with drug sensitivity. Although this process is associated with a global reduction in protein synthesis, a subset of mRNAs

undergoes an increased efficiency in translation. Inhibiting the eIF4A RNA helicase, a component of the eIF4F translation initiation complex, abrogates this selectively increased translation and is lethal to persister cells. Translation remodelling in persister cells coincides with an increased N6-methyladenosine modification in the 5′-untranslated region of some highly translated mRNAs. Combination of eIF4A inhibitor with BRAF and MEK inhibitors effectively inhibits the emergence of persister cells and may represent a new therapeutic strategy to prevent acquired drug resistance.

Mouawad L., Beswick V., Jamin N., Montigny C., Quiniou E., Barbot T. (2019 Dec 18)
Deciphering the mechanism of inhibition of SERCA1a by sarcolipin using molecular simulations
bioRxiv : DOI : 10.1101/2019.12.17.879825

Résumé

SERCA1a is an ATPase calcium pump that transports Ca^{2+} from the cytoplasm to the sarco/endoplasmic reticulum lumen. Sarcolipin (SLN), a transmembrane peptide, regulates the activity of SERCA1a by decreasing its Ca^{2+} transport rate, but its mechanism of action is still not well understood. To decipher this mechanism, we have performed normal modes analysis in the all-atom model, with the SERCA1a-SLN complex or the isolated SERCA1a embedded in an explicit membrane. The comparison of the results allowed us to provide an explanation for the action of SLN that is in good agreement with experimental observations. In our analyses, the presence of SLN locally perturbs the TM6 transmembrane helix and as a consequence modifies the position of D800, one of the key metal-chelating residues. Additionally, it reduces the flexibility of the gating residues, V304 and E309 in TM4, at the entrance of the Ca^{2+} binding sites, which would decrease the affinity for Ca^{2+}. Unexpectedly, SLN has also an effect on the ATP binding site more than 35 r A away, due to the straightening of TM5, a long helix considered as the spine of the protein. The straightening of TM5 modifies the structure of the P-N linker that sits above it, and which comprises the ^{351}DKTG^{354} conserved motif, resulting in an increase of the distance between ATP and the phosphorylation site. As a consequence, the turn-over rate could be affected. All this gives SERCA1a the propensity to go toward a Ca^{2+}-deprived E2-like state in the presence of SLN and toward a Ca^{2+} high-affinity E1-like state in the absence of SLN, although the SERCA1a-SLN complex was crystallized in an E1-like state. In addition to a general mechanism of inhibition of SERCA1a regulatory peptides, this study also provides an insight in the conformational transition between the E2 and E1 states.

Année de publication : 2020

Aviel Even, Giovanni Morelli, Loïc Broix, Chiara Scaramuzzino, Silvia Turchetto, Ivan Gladwyn-Ng, Romain Le Bail, Michal Shilian, Stephen Freeman, Maria M Magiera, A S Jijumon, Nathalie Krusy, Brigitte Malgrange, Bert Brone, Paula Dietrich, Ioannis Dragatsis, Carsten Janke, Frédéric Saudou, Miguel Weil, Laurent Nguyen (2019 Dec 18)

ATAT1-enriched vesicles promote microtubule acetylation via axonal transport.
Science advances : eaax2705 : DOI : 10.1126/sciadv.aax2705

Résumé

Microtubules are polymerized dimers of α- and β-tubulin that underlie a broad range of cellular activities. Acetylation of α-tubulin by the acetyltransferase ATAT1 modulates microtubule dynamics and functions in neurons. However, it remains unclear how this enzyme acetylates microtubules over long distances in axons. Here, we show that loss of ATAT1 impairs axonal transport in neurons in vivo, and cell-free motility assays confirm a requirement of α-tubulin acetylation for proper bidirectional vesicular transport. Moreover, we demonstrate that the main cellular pool of ATAT1 is transported at the cytosolic side of neuronal vesicles that are moving along axons. Together, our data suggest that axonal transport of ATAT1-enriched vesicles is the predominant driver of α-tubulin acetylation in axons.