Année de publication : 2017

A Gordon Robertson, Juliann Shih, Christina Yau, Ewan A Gibb, Junna Oba, Karen L Mungall, Julian M Hess, Vladislav Uzunangelov, Vonn Walter, Ludmila Danilova, Tara M Lichtenberg, Melanie Kucherlapati, Patrick K Kimes, Ming Tang, Alexander Penson, Ozgun Babur, Rehan Akbani, Christopher A Bristow, Katherine A Hoadley, Lisa Iype, Matthew T Chang, , Andrew D Cherniack, Christopher Benz, Gordon B Mills, Roel G W Verhaak, Klaus G Griewank, Ina Felau, Jean C Zenklusen, Jeffrey E Gershenwald, Lynn Schoenfield, Alexander J Lazar, Mohamed H Abdel-Rahman, Sergio Roman-Roman, Marc-Henri Stern, Colleen M Cebulla, Michelle D Williams, Martine J Jager, Sarah E Coupland, Bita Esmaeli, Cyriac Kandoth, Scott E Woodman (2017 Aug 16)

Integrative Analysis Identifies Four Molecular and Clinical Subsets in Uveal Melanoma.

Cancer cell : 204-220.e15 : DOI : S1535-6108(17)30295-7

Résumé

Comprehensive multiplatform analysis of 80 uveal melanomas (UM) identifies four molecularly distinct, clinically relevant subtypes: two associated with poor-prognosis monosomy 3 (M3) and two with better-prognosis disomy 3 (D3). We show that BAP1 loss follows M3 occurrence and correlates with a global DNA methylation state that is distinct from D3-UM. Poor-prognosis M3-UM divide into subsets with divergent genomic aberrations, transcriptional features, and clinical outcomes. We report change-of-function SRSF2 mutations. Within D3-UM, EIF1AX- and SRSF2/SF3B1-mutant tumors have distinct somatic copy number alterations and DNA methylation profiles, providing insight into the biology of these low- versus intermediate-risk clinical mutation subtypes.

E I Andersson, S Pützer, B Yadav, O Dufva, S Khan, L He, L Sellner, A Schrader, G Crispatzu, M Oleś, H Zhang, S Adnan-Awad, S Lagström, D Bellanger, J P Mpindi, S Eldfors, T Pemovska, P Pietarinen, A Lauhio, K Tomska, C Cuesta-Mateos, E Faber, S Koschmieder, T H Brümmendorf, S Kytölä, E-R Savolainen, T Siitonen, P Ellonen, O Kallioniemi, K Wennerberg, W Ding, M-H Stern, W Huber, S Anders, J Tang, T Aittokallio, T Zenz, M Herling, S Mustjoki (2017 Aug 15)

Discovery of novel drug sensitivities in T-PLL by high-throughput ex vivo drug testing and mutation profiling.

Leukemia : DOI : 10.1038/leu.2017.252

Résumé

T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive neoplasm of mature T-cells with an urgent need for rationally designed therapies to address its notoriously chemo-refractory behavior. The median survival of T-PLL patients is <2 years and clinical trials are difficult to execute. Here we systematically explored the diversity of drug responses in T-PLL patient samples using an ex vivo drug sensitivity and resistance testing platform and

correlated the findings with somatic mutations and gene expression profiles. Intriguingly, all T-PLL samples were sensitive to the cyclin-dependent kinase inhibitor SNS-032, which overcame stromal-cell-mediated protection and elicited robust p53-activation and apoptosis. Across all patients, the most effective classes of compounds were histone deacetylase, phosphoinositide-3 kinase/AKT/mammalian target of rapamycin, heat-shock protein 90 and BH3-family protein inhibitors as well as p53 activators, indicating previously unexplored, novel targeted approaches for treating T-PLL. Although Janus-activated kinase-signal transducer and activator of transcription factor (JAK-STAT) pathway mutations were common in T-PLL (71% of patients), JAK-STAT inhibitor responses were not directly linked to those or other T-PLL-specific lesions. Overall, we found that genetic markers do not readily translate into novel effective therapeutic vulnerabilities. In conclusion, novel classes of compounds with high efficacy in T-PLL were discovered with the comprehensive ex vivo drug screening platform warranting further studies of synergisms and clinical testing.Leukemia advance online publication, 1 September 2017; doi:10.1038/leu.2017.252.

V Soumelis (2017 Aug 15)

Molecular and cellular discoveries in inflammatory dermatoses.

Journal of the European Academy of Dermatology and Venereology : JEADV : 3-7 : DOI : 10.1111/jdv.14373

Résumé

It was no earlier than 1986 that T helper (Th)1 and Th2 cells were described for the first time, opening the field of lymphocyte diversity and the investigation of the physiopathology of inflammatory diseases such as atopic dermatitis and psoriasis. Since that time, much research has been carried out showing a very complex communication network leading to inflammatory responses. Nowadays, understanding the cellular and molecular components of the inflammatory network and of the different crosstalks not only for groups of diseases but also for the individual patient is mandatory for developing and personalizing treatments. The aim of the present proceeding was to provide an update concerning some of the most recent molecular and cellular discoveries in inflammatory skin diseases and especially of AD.

Claire Beauvineau, Corinne Guetta, Marie-Paule Teulade-Fichou, Florence Mahuteau-Betzer (2017 Aug 14)

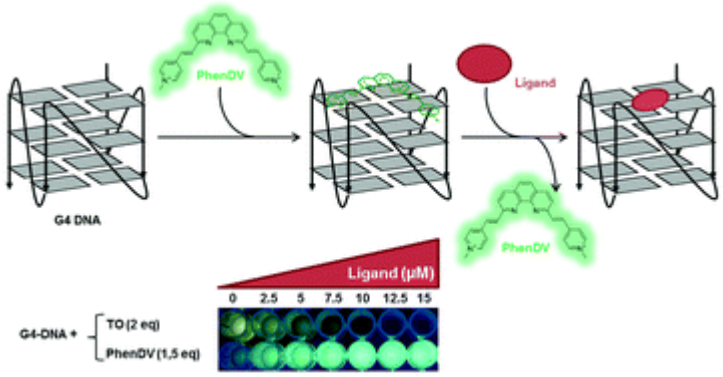
PhenDV, a turn-off fluorescent quadruplex DNA probe for improving the sensitivity of drug screening assays

Organic & Biomolecular Chemistry : 15 : 7117-7121 : DOI : 10.1039/c7ob01705g

Résumé

We report a new turn-off fluorescent probe, PhenDV, for the identification of high affinity quadruplex (G4) DNA ligands. This push–pull fluorophore displays a high fluorescence quantum yield in water (ΦF = 0.21) and is a selective and strong quadruplex DNA binder. We describe its use as a fluorescent indicator for the G4 Fluorescent Intercalator Displacement

(FID) assay as its fluorescence is strongly quenched when bound to G4 DNA and fully restored when displaced by ligand. This probe improves the sensitivity of the G4-FID assay, as the read out relies on increased fluorescence instead of quenching observed with classical on/off probes



Friederike Ufer, Pablo Vargas, Jan Broder Engler, Joseph Tintelnot, Benjamin Schattling, Hana Winkler, Simone Bauer, Nina Kursawe, Anne Willing, Oliver Keminer, Ora Ohana, Gabriela Salinas-Riester, Ole Pless, Dietmar Kuhl, Manuel A Friese (2017 Aug 8)

Arc/Arg3.1 governs inflammatory dendritic cell migration from the skin and thereby controls T cell activation.

Science immunology : eaaf8665 : DOI : 10.1126/sciimmunol.aaf8665

Résumé

Skin-migratory dendritic cells (migDCs) are pivotal antigen-presenting cells that continuously transport antigens to draining lymph nodes and regulate immune responses. However, identification of migDCs is complicated by the lack of distinguishing markers, and it remains unclear which molecules determine their migratory capacity during inflammation. We show that, in the skin, the neuronal plasticity molecule activity-regulated cytoskeleton-associated protein/activity-regulated gene 3.1 (Arc/Arg3.1) was strictly confined to migDCs. Mechanistically, Arc/Arg3.1 was required for accelerated DC migration during inflammation because it regulated actin dynamics through nonmuscle myosin II. Accordingly, Arc/Arg3.1-dependent DC migration was critical for mounting T cell responses in experimental autoimmune encephalomyelitis and allergic contact dermatitis. Thus, Arc/Arg3.1 was restricted to migDCs in the skin and drove fast DC migration by exclusively coordinating cytoskeletal changes in response to inflammatory challenges. These findings commend Arc/Arg3.1 as a universal switch in migDCs that may be exploited to selectively modify immune responses.

Richard Belvindrah, Kathiresan Natarajan, Preety Shabajee, Elodie Bruel-Jungerman, Jennifer Bernard, Marie Goutierre, Imane Moutkine, Xavier H Jaglin, Mythili Savariradjane, Theano

Irinopoulou, Jean-Christophe Poncer, Carsten Janke, Fiona Francis (2017 Aug 7)
Mutation of the α-tubulin Tuba1a leads to straighter microtubules and perturbs neuronal migration.
The Journal of cell biology : 2443-2461 : DOI : 10.1083/jcb.201607074

Résumé

Brain development involves extensive migration of neurons. Microtubules (MTs) are key cellular effectors of neuronal displacement that are assembled from α/β-tubulin heterodimers. Mutation of the α-tubulin isotype TUBA1A is associated with cortical malformations in humans. In this study, we provide detailed in vivo and in vitro analyses of Tuba1a mutants. In mice carrying a Tuba1a missense mutation (S140G), neurons accumulate, and glial cells are dispersed along the rostral migratory stream in postnatal and adult brains. Live imaging of Tuba1a-mutant neurons revealed slowed migration and increased neuronal branching, which correlated with directionality alterations and perturbed nucleus-centrosome (N-C) coupling. Tuba1a mutation led to increased straightness of newly polymerized MTs, and structural modeling data suggest a conformational change in the α/β-tubulin heterodimer. We show that Tuba8, another α-tubulin isotype previously associated with cortical malformations, has altered function compared with Tuba1a. Our work shows that Tuba1a plays an essential, noncompensated role in neuronal saltatory migration in vivo and highlights the importance of MT flexibility in N-C coupling and neuronal-branching regulation during neuronal migration.

G Beinse, F Berger, P Cottu, M-E Dujaric, I Kriegel, M-N Guilhaume, V Diéras, L Cabel, J-Y Pierga, F-C Bidard (2017 Aug 6)
Circulating tumor cell count and thrombosis in metastatic breast cancer.
Journal of thrombosis and haemostasis : JTH : 1981-1988 : DOI : 10.1111/jth.13792

Résumé

Essentials Tumor cells circulating in blood (CTC) may favor thrombotic events in cancer patients. We assessed the impact of CTC on the risk of thrombosis in metastatic breast cancer. Baseline CTC detection was the only independent factor associated with the risk of thrombosis. CTC detection under therapy may be the hidden link between tumor progression & thrombosis.

Vicente J Planelles-Herrero, James J Hartman, Julien Robert-Paganin, Fady I Malik, Anne Houdusse (2017 Aug 5)
Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil.
Nature communications : 190 : DOI : 10.1038/s41467-017-00176-5

Résumé

Omecamtiv mecarbil is a selective, small-molecule activator of cardiac myosin that is being developed as a potential treatment for heart failure with reduced ejection fraction. Here we determine the crystal structure of cardiac myosin in the pre-powerstroke state, the most relevant state suggested by kinetic studies, both with (2.45 Å) and without (3.10 Å) omecamtiv mecarbil bound. Omecamtiv mecarbil does not change the motor mechanism nor does it influence myosin structure. Instead, omecamtiv mecarbil binds to an allosteric site that stabilizes the lever arm in a primed position resulting in accumulation of cardiac myosin in the primed state prior to onset of cardiac contraction, thus increasing the number of heads that can bind to the actin filament and undergo a powerstroke once the cardiac cycle starts. The mechanism of action of omecamtiv mecarbil also provides insights into uncovering how force is generated by molecular motors.Omecamtiv mecarbil (OM) is a cardiac myosin activator that is currently in clinical trials for heart failure treatment. Here, the authors give insights into its mode of action and present the crystal structure of OM bound to bovine cardiac myosin, which shows that OM stabilizes the pre-powerstroke state of myosin.

Jiyeon Choi, Mai Xu, Matthew M Makowski, Tongwu Zhang, Matthew H Law, Michael A Kovacs, Anton Granzhan, Wendy J Kim, Hemang Parikh, Michael Gartside, Jeffrey M Trent, Marie-Paule Teulade-Fichou, Mark M Iles, Julia A Newton-Bishop, D Timothy Bishop, Stuart MacGregor, Nicholas K Hayward, Michiel Vermeulen, Kevin M Brown (2017 Aug 1)
A common intronic variant of PARP1 confers melanoma risk and mediates melanocyte growth via regulation of MITF.
Nature genetics : 49 : 1326-1335 : DOI : 10.1038/ng.3927

Résumé

Previous genome-wide association studies have identified a melanoma-associated locus at 1q42.1 that encompasses a ~100-kb region spanning the PARP1 gene. Expression quantitative trait locus (eQTL) analysis in multiple cell types of the melanocytic lineage consistently demonstrated that the 1q42.1 melanoma risk allele (rs3219090[G]) is correlated with higher PARP1 levels. In silico fine-mapping and functional validation identified a common intronic indel, rs144361550 (-/GGGCCC; r(2) = 0.947 with rs3219090), as displaying allele-specific transcriptional activity. A proteomic screen identified RECQL as binding to rs144361550 in an allele-preferential manner. In human primary melanocytes, PARP1 promoted cell proliferation and rescued BRAF(V600E)-induced senescence phenotypes in a PARylation-independent manner. PARP1 also transformed TERT-immortalized melanocytes expressing BRAF(V600E). PARP1-mediated senescence rescue was accompanied by transcriptional activation of the melanocyte-lineage survival oncogene MITF, highlighting a new role for PARP1 in melanomagenesis.

Marion Salou, Katarzyna Franciszkiewicz, Olivier Lantz (2017 Jul 28)
MAIT cells in infectious diseases.

Current opinion in immunology : 7-14 : DOI : S0952-7915(17)30054-7

Résumé

In humans, MAIT cells represent the most abundant T cell subset reacting against bacteria. Their frequency in the blood is decreased in a large variety of infectious diseases of either bacterial or viral origin. MAIT cells accumulate at the site of bacterial infection and are protective in experimental infection models. Recent epidemiological evidence supports an implication of MAIT cells in protecting against tuberculosis. MAIT cells can be activated either through direct recognition of microbial ligands or by inflammatory cytokines such as IL-12 and IL-18. MAIT cells secrete IFN-γ, IL-17 and/or other effector molecules according to the context of triggering. MAIT cells can kill bacterially infected epithelial cells in vitro. Herein, we summarize and discuss the data suggesting a role for MAIT cells in infectious diseases.

Verga D., Hamon F., Nicoleau C., Guetta C., Wu T.-D., Guerquin-Kern J.-L., Marco S. & Teulade-Fichou M.-P. (2017 Jul 27)

Chemical Imaging by NanoSIMS Provides High- Resolution Localization of the G-Quadruplex Interactive Drug (Br)-PhenDC3 on Human Chromosomes

Journal of Molecular Biology and Molecular Imaging : 4 : 1029

Résumé

Determining the distribution of biologically active compounds within cells is a major issue to understand their mechanism of action and to optimize their properties. Over the past decade DNA secondary structures called G-quadruplexes (G4) have been identified as key modulators of genomic functions. This very active research field has led to the development of G4-targeted molecular probes that are used to track quadruplex forming domains in cells, which is achieved, in most cases, by conventional fluorescence microcopy. However, the intrinsic low resolution of fluorescence microcopy as well as the necessity to tag the drugs with fluorophores represent strong limitations. Here we present the use of secondary ion mass spectroscopy imaging (nanoSIMS) for mapping within metaphase human chromosomes the distribution of a bromobisquinolinium phenanthroline derivative (Br- PhenDC3) used as G-quadruplex probe. In addition a statistical approach to increase the accuracy and the spatial resolution of the nanoSIMS imaging was implemented as a plug in for the image analysis software ImageJ. The results demonstrate the presence of Br-PhenDC3both at terminal and interstitial regions of chromosomes and constitute a demonstration of the effectiveness of nanoSIMS imaging as an alternative method for accurate genome-wide mapping of DNA interactive drugs.

Immaculada Martínez-Rovira, Josep Puxeu-Vaqué, Yolanda Prezado (2017 Jul 25)

Dose evaluation of Grid Therapy using a 6 MV flattening filter-free (FFF) photon beam: A Monte Carlo study.

Medical physics : 5378-5383 : DOI : 10.1002/mp.12485

Résumé

Spatially fractionated radiotherapy is a strategy to overcome the main limitation of radiotherapy, i.e., the restrained normal tissue tolerances. A well-known example is Grid Therapy, which is currently performed at some hospitals using megavoltage photon beams delivered by Linacs. Grid Therapy has been successfully used in the management of bulky abdominal tumors with low toxicity. The aim of this work was to evaluate whether an improvement in therapeutic index in Grid Therapy can be obtained by implementing it in a flattening filter-free (FFF) Linac. The rationale behind is that the removal of the flattening filter shifts the beam energy spectrum towards lower energies and increase the photon fluence. Lower energies result in a reduction of lateral scattering and thus, to higher peak-to-valley dose ratios (PVDR) in normal tissues. In addition, the gain in fluence might allow using smaller beams leading a more efficient exploitation of dose-volume effects, and consequently, a better normal tissue sparing.

Boris Guirao, Yohanns Bellaïche (2017 Jul 22)
Biomechanics of cell rearrangements in Drosophila.
Current opinion in cell biology : 113-124 : DOI : S0955-0674(17)30049-2

Résumé

To acquire their adequate size and shape, living tissues grow and substantially deform as they develop. To do so, the cells making up the tissue can grow and deform as well, but they can also divide, intercalate and die. Among those cell behaviors, cell intercalation, also named cell rearrangement, is a major contributor to the morphogenesis of many cohesive tissues since it enables tissues to drastically deform as they develop while keeping their cohesiveness and avoiding extreme deformation of their cells. Here we review the mechanical principles and biological regulations at play during cell rearrangements in Drosophila tissues by first describing them in other cellular materials and by categorizing them. We then briefly discuss their quantifications and their interplay with other cell processes.

Marie-Paule Teulade-Fichou, Joël Lefebvre, Corinne Guetta, Florent Poyer, Florence Mahuteau-Betzer (2017 Jul 13)
Copper-alkyne complexation is responsible for the Nucleolar Localisation of Quadruplex Nucleic Acid Drugs Labelled by Click Chemistry.
Angewandte Chemie (International ed. in English) : 56 : 11365-11369 : DOI : 10.1002/anie.201703783

Résumé

G-quadruplex(es) (G4) are non-canonical nucleic acid structures found in guanine-rich sequences. They can be targeted with small molecules (G4-ligands) acting as reporters, for tracking both in vitro and in cells. We explored the cellular localisation of PhenDC3, one of

the most powerful G4 ligands, by synthesising two clickable azide and alkyne derivatives (PhenDC3-alk, PhenDC3-az) and labelling them in situ with the corresponding Cy5 click partners. A careful comparison of the results obtained for the copper-based CuAAC and copper-free SPAAC methodologies in fixed cells implicated Cu(I) /alkyne intermediates in the non-specific localisation of ligands (and fluorophores) to the nucleoli. By contrast, SPAAC yielded similar nucleoplasmic labelling patterns in fixed and live cells. Our findings demonstrate the need for great care when using CuAAC to localise drugs in cells, and show that SPAAC gives results that are more consistent between fixed and live cells.

Zeina Bash-Imam, Gabriel Thérizols, Anne Vincent, Florian Lafôrets, Micaela Polay Espinoza, Nathalie Pion, Françoise Macari, Julie Pannequin, Alexandre David, Jean-Christophe Saurin, Hichem C Mertani, Julien Textoris, Didier Auboeuf, Frédéric Catez, Nicole Dalla Venezia, Martin Dutertre, Virginie Marcel, Jean-Jacques Diaz (2017 Jul 11)

Translational reprogramming of colorectal cancer cells induced by 5-fluorouracil through a miRNA-dependent mechanism.

Oncotarget : 46219-46233 : DOI : 10.18632/oncotarget.17597

Résumé

5-Fluorouracil (5-FU) is a widely used chemotherapeutic drug in colorectal cancer. Previous studies showed that 5-FU modulates RNA metabolism and mRNA expression. In addition, it has been reported that 5-FU incorporates into the RNAs constituting the translational machinery and that 5-FU affects the amount of some mRNAs associated with ribosomes. However, the impact of 5-FU on translational regulation remains unclear. Using translatome profiling, we report that a clinically relevant dose of 5-FU induces a translational reprogramming in colorectal cancer cell lines. Comparison of mRNA distribution between polysomal and non-polysomal fractions in response to 5-FU treatment using microarray quantification identified 313 genes whose translation was selectively regulated. These regulations were mostly stimulatory (91%). Among these genes, we showed that 5-FU increases the mRNA translation of HIVEP2, which encodes a transcription factor whose translation in normal condition is known to be inhibited by mir-155. In response to 5-FU, the expression of mir-155 decreases thus stimulating the translation of HIVEP2 mRNA. Interestingly, the 5-FU-induced increase in specific mRNA translation was associated with reduction of global protein synthesis. Altogether, these findings indicate that 5-FU promotes a translational reprogramming leading to the increased translation of a subset of mRNAs that involves at least for some of them, miRNA-dependent mechanisms. This study supports a still poorly evaluated role of translational control in drug response.