Année de publication : 2021

Pavel Mozgunov, Xavier Paoletti, Thomas Jaki (2021 Jan 7)
A benchmark for dose-finding studies with unknown ordering.
Biostatistics (Oxford, England) : DOI : kxaa054

Résumé

An important tool to evaluate the performance of a dose-finding design is the nonparametric optimal benchmark that provides an upper bound on the performance of a design under a given scenario. A fundamental assumption of the benchmark is that the investigator can arrange doses in a monotonically increasing toxicity order. While the benchmark can be still applied to combination studies in which not all dose combinations can be ordered, it does not account for the uncertainty in the ordering. In this article, we propose a generalization of the benchmark that accounts for this uncertainty and, as a result, provides a sharper upper bound on the performance. The benchmark assesses how probable the occurrence of each ordering is, given the complete information about each patient. The proposed approach can be applied to trials with an arbitrary number of endpoints with discrete or continuous distributions. We illustrate the utility of the benchmark using recently proposed dose-finding designs for Phase I combination trials with a binary toxicity endpoint and Phase I/II combination trials with binary toxicity and continuous efficacy.

Andrey Kleshnin, Léa Monet, Marina Plays, Hugo Vaysset, Claire Rougeulle, Stéphan Vagner (2021 Jan 6)
Amid darkness, light will prevail – a report on the 2020 annual SFC meeting on "Dark genome and Cancer"
Bulletin du cancer : DOI : S0007-4551(20)30510-5

Résumé

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Marsolier, Justine Prompsy, Pacôme Durand, Adeline Lyne, Anne-Marie Landragin, Camille Trouchet, Amandine Bento, Sabrina Tenreira Eisele, Almut Foulon, Sophie Baudre, Léa Grosselin, Kevin Bohec, Mylène Baulande, Sylvain Dahmani, Ahmed Sourd, Laura Letouzé, Eric Marangoni, Elisabetta Perié, Leïla Vallot, Céline (2021 Jan 4)
H3K27me3 is a determinant of chemotolerance in triple-negative breast cancer
bioRxivbioRxiv : DOI : 10.1101/2021.01.04.423386

Résumé

Triple-negative breast cancer is associated with the worst prognosis and the highest risk of recurrence among all breast cancer subtypes[1][1]. Residual disease, formed by cancer cells

persistent to chemotherapy, remains one of the major clinical challenges towards full cure[2][2],[3][3]. There is now consensus that non-genetic processes contribute to chemoresistance in various tumor types, notably through the initial emergence of a reversible chemotolerant state[4][4]–[6][5]. Understanding non-genetic tumor evolution stands now as a prerequisite for the design of relevant combinatorial approaches to delay recurrence. Here we show that the repressive histone mark H3K27me3 is a determinant of cell fate under chemotherapy exposure, monitoring epigenomes, transcriptomes and lineage with single-cell resolution. We identify a reservoir of persister basal cells with EMT markers and activated TGF-β pathway leading to multiple chemoresistance phenotypes. We demonstrate that, in unchallenged cells, H3K27 methylation is a lock to the expression program of persister cells. Promoters are primed with both H3K4me3 and H3K27me3, and removing H3K27me3 is sufficient for their transcriptional activation. Leveraging lineage barcoding, we show that depleting H3K27me3 alters tumor cell fate under chemotherapy insult – a wider variety of tumor cells tolerate chemotherapy. Our results highlight how chromatin landscapes shape the potential of unchallenged cancer cells to respond to therapeutic stress.

Federico Cocozza, Nathalie Névo, Ester Piovesana, Xavier Lahaye, Julian Buchrieser, Olivier Schwartz, Nicolas Manel, Mercedes Tkach, Clotilde Théry, Lorena Martin-Jaular (2021 Jan 4)

Extracellular vesicles containing ACE2 efficiently prevent infection by SARS-CoV-2 Spike protein-containing virus.

Journal of extracellular vesicles : e12050 : DOI : 10.1002/jev2.12050

Résumé

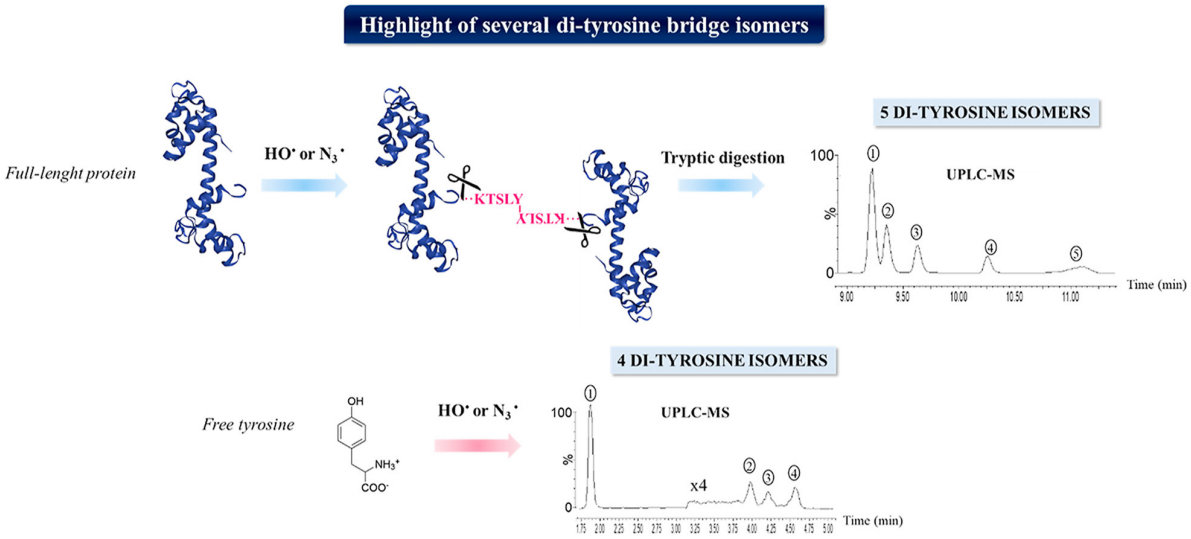
SARS-CoV-2 entry is mediated by binding of the spike protein (S) to the surface receptor ACE2 and subsequent priming by host TMPRSS2 allowing membrane fusion. Here, we produced extracellular vesicles (EVs) exposing ACE2 and demonstrate that ACE2-EVs are efficient decoys for SARS-CoV-2 S protein-containing lentivirus. Reduction of infectivity positively correlates with the level of ACE2, is much more efficient than with soluble ACE2 and further enhanced by the inclusion of TMPRSS2.

Anouchka Gatin, Isabelle Billault, Patricia Duchambon, Guillaume Van der Rest, Cécile Sicard-Roselli (2021 Jan 3)

Oxidative radicals ($HO^{\bullet}$ or $N_3^{\bullet}$) induce several di-tyrosine bridge isomers at the protein scale.

Free radical biology & medicine : 162 : 461-470 : DOI : 10.1016/j.freeradbiomed.2020.10.324

Résumé



Among protein oxidative damages, di-tyrosine bridges formation has been evidenced in many neuropathological diseases. Combining oxidative radical production by gamma radiolysis with very performant chromatographic separation coupled to mass spectrometry detection, we brought into light new insights of tyrosine dimerization. Hydroxyl and azide radical tyrosine oxidation leading to di-tyrosine bridges formation was studied for different biological compounds: a full-length protein (Δ25-centrin 2), a five amino acid peptide (KTSLY) and free tyrosine. We highlighted that both radicals generate high proportion of dimers even for low doses. Surprisingly, no less than five different di-tyrosine isomers were evidenced for the protein and the peptide. For tyrosine alone, at least four distinct dimers were evidenced. These results raise some questions about their respective role in vivo and hence their relative toxicity. Also, as di-tyrosine is often used as a biomarker, a better knowledge of the type of dimer detected in vivo is now required.

Yu Luo, Anton Granzhan, Daniela Verga, Jean-Louis Mergny (2020 Dec 28)

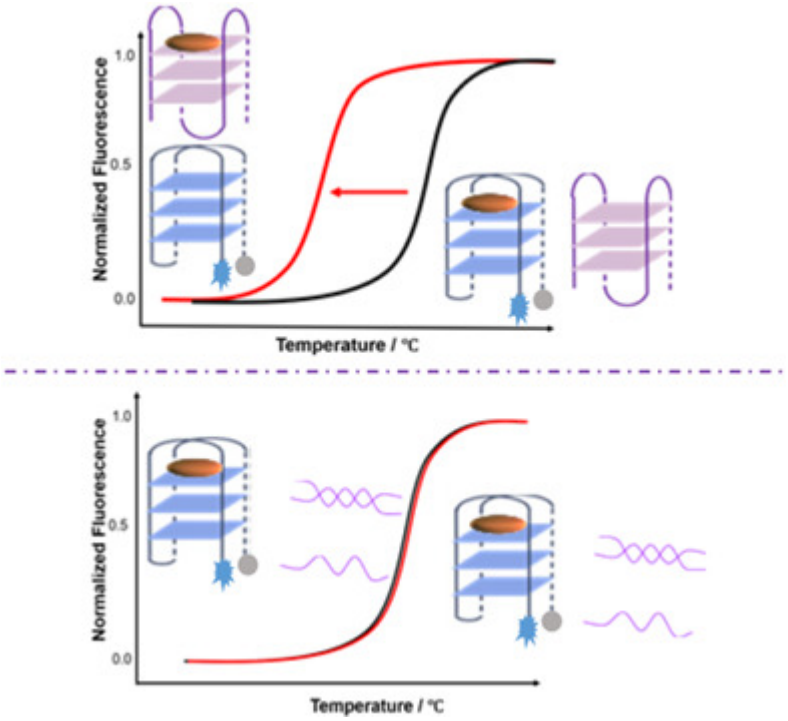
FRET-MC: A fluorescence melting competition assay for studying G4 structures in vitro.

Biopolymers : 112 : e23415 : DOI : 10.1002/bip.23415

Résumé

G-quadruplexes (G4) play crucial roles in biology, analytical chemistry and nanotechnology. The stability of G4 structures is impacted by the number of G-quartets, the length and positions of loops, flanking motifs, as well as additional structural elements such as bulges, capping base pairs, or triads. Algorithms such as G4Hunter or Quadparser may predict if a given sequence is G4-prone by calculating a quadruplex propensity score; however, experimental validation is still required. We previously demonstrated that this validation is not always straightforward, and that a combination of techniques is often required to unambiguously establish whether a sequence forms a G-quadruplex or not. In this article, we adapted the well-known FRET-melting assay to characterize G4 in batch, where the sequence

to be tested is added, as an unlabeled competitor, to a system composed of a dual-labeled probe (F21T) and a specific quadruplex ligand. PhenDC3 was preferred over TMPyP4 because of its better selectivity for G-quadruplexes. In this so-called FRET-MC (melting competition) assay, G4-forming competitors lead to a marked decrease of the ligand-induced stabilization effect (ΔT_m), while non-specific competitors (e.g., single- or double-stranded sequences) have little effect. Sixty-five known sequences with different typical secondary structures were used to validate the assay, which was subsequently employed to assess eight novel sequences that were not previously characterized.



Année de publication : 2020

Christine Lonjou, Séverine Eon-Marchais, Thérèse Truong, Marie-Gabrielle Dondon, Mojgan Karimi, Yue Jiao, Francesca Damiola, Laure Barjhoux, Dorothée Le Gal, Juana Beauvallet, Noura Mebirouk, Eve Cavaciuti, Jean Chiesa, Anne Floquet, Séverine Audebert-Bellanger, Sophie Giraud, Thierry Frebourg, Jean-Marc Limacher, Laurence Gladieff, Isabelle Mortemousque, Hélène Dreyfus, Sophie Lejeune-Dumoulin, Christine Lasset, Laurence Venat-Bouvet, Yves-Jean Bignon, Pascal Pujol, Christine M Maugard, Elisabeth Luporsi, Valérie Bonadona, Catherine Noguès, Pascaline Berthet, Capucine Delnatte, Paul Gesta, Alain Lortholary, Laurence Faivre, Bruno Buecher, Olivier Caron, Marion Gauthier-Villars, Isabelle Coupier, Sylvie Mazoyer, Luis-Cristobal Monraz, Maria Kondratova, Inna Kuperstein, Pascal Guénel, Emmanuel Barillot, Dominique Stoppa-Lyonnet, Nadine Andrieu, Fabienne Lesueur (2020 Dec 28)

Gene- and pathway-level analyses of iCOGS variants highlight novel signaling pathways underlying familial breast cancer susceptibility.
International journal of cancer : 1895-1909 : DOI : 10.1002/ijc.33457

Résumé

Single-nucleotide polymorphisms (SNPs) in over 180 loci have been associated with breast cancer (BC) through genome-wide association studies involving mostly unselected population-based case-control series. Some of them modify BC risk of women carrying a BRCA1 or BRCA2 (BRCA1/2) mutation and may also explain BC risk variability in BC-prone families with no BRCA1/2 mutation. Here, we assessed the contribution of SNPs of the iCOGS array in GENESIS consisting of BC cases with no BRCA1/2 mutation and a sister with BC, and population controls. Genotyping data were available for 1281 index cases, 731 sisters with BC, 457 unaffected sisters and 1272 controls. In addition to the standard SNP-level analysis using index cases and controls, we performed pedigree-based association tests to capture transmission information in the sibships. We also performed gene- and pathway-level analyses to maximize the power to detect associations with lower-frequency SNPs or those with modest effect sizes. While SNP-level analyses identified 18 loci, gene-level analyses identified 112 genes. Furthermore, 31 Kyoto Encyclopedia of Genes and Genomes and 7 Atlas of Cancer Signaling Network pathways were highlighted (false discovery rate of 5%). Using results from the « index case-control » analysis, we built pathway-derived polygenic risk scores (PRS) and assessed their performance in the population-based CECILE study and in a data set composed of GENESIS-affected sisters and CECILE controls. Although these PRS had poor predictive value in the general population, they performed better than a PRS built using our SNP-level findings, and we found that the joint effect of family history and PRS needs to be considered in risk prediction models.

Bchir Ahlem, Njima Manel, Ben Abdeljalil Nouha, Ben Hammouda Seiffeddine, Mighri Khalifa, Njim Leila, Zakhama Abdelfateh (2020 Dec 22)
High grade transformation of adenoid cystic carcinoma in the palate: Case report with review of literature.
International journal of surgery case reports : 162-166 : DOI : S2210-2612(20)31203-7

Résumé

Adenoid cystic carcinoma (ACC) is a rare tumor developed in minor salivary glands, the palate being the most common site.

Marion Salou, François Legoux, Olivier Lantz (2020 Dec 22)
MAIT cell development in mice and humans.
Molecular immunology : 31-36 : DOI : S0161-5890(20)30564-2

Résumé

MAIT cells arise in the thymus following rearrangement of a T cell receptor (TCR) reactive against microbial vitamin B2-derived metabolites presented by the MHC-Ib molecule, MR1. Mechanisms that are conserved in mammals ensure the frequent production of MR1-restricted TCRs and the intra-thymic differentiation of MR1-restricted thymocytes into effector cells. Upon thymic egress and migration into non-lymphoid tissues, additional signals modulate MAIT cell functions according to each local tissue environment. Here, we review the recent progress made towards a better understanding of the establishment of this major immune cell subset.

Johnathan Canton, Hanna Blees, Conor M Henry, Michael D Buck, Oliver Schulz, Neil C Rogers, Eleanor Childs, Santiago Zelenay, Hefin Rhys, Marie-Charlotte Domart, Lucy Collinson, Andres Alloatti, Cara J Ellison, Sebastian Amigorena, Venizelos Papayannopoulos, David C Thomas, Felix Randow, Caetano Reis E Sousa (2020 Dec 22)

The receptor DNGR-1 signals for phagosomal rupture to promote cross-presentation of dead-cell-associated antigens.

Nature immunology : 140-153 : DOI : 10.1038/s41590-020-00824-x

Résumé

Type 1 conventional dendritic (cDC1) cells are necessary for cross-presentation of many viral and tumor antigens to CD8 T cells. cDC1 cells can be identified in mice and humans by high expression of DNGR-1 (also known as CLEC9A), a receptor that binds dead-cell debris and facilitates XP of corpse-associated antigens. Here, we show that DNGR-1 is a dedicated XP receptor that signals upon ligand engagement to promote phagosomal rupture. This allows escape of phagosomal contents into the cytosol, where they access the endogenous major histocompatibility complex class I antigen processing pathway. The activity of DNGR-1 maps to its signaling domain, which activates SYK and NADPH oxidase to cause phagosomal damage even when spliced into a heterologous receptor and expressed in heterologous cells. Our data reveal the existence of innate immune receptors that couple ligand binding to endocytic vesicle damage to permit MHC class I antigen presentation of exogenous antigens and to regulate adaptive immunity.

Rienk Nieuwland, Juan M Falcón-Pérez, Clotilde Théry, Kenneth W Witwer (2020 Dec 21)

Rigor and standardization of extracellular vesicle research: Paving the road towards robustness.

Journal of extracellular vesicles : e12037 : DOI : 10.1002/jev2.12037

Résumé

Thomas Yvorra, Anke Steinmetz, Pascal Retailleau, Olivier Lantz, Frédéric Schmidt (2020 Dec 20)

Synthesis, biological evaluation and molecular modelling of new potent

clickable analogues of 5-OP-RU for their use as chemical probes for the study of MAIT cell biology.
European journal of medicinal chemistry : 113066 : DOI : S0223-5234(20)31038-2

Résumé

MAIT cells are preset αβ T lymphocytes that recognize a series of microbial antigens exclusively derived from the riboflavin biosynthesis pathway, which is present in most bacteria. The most active known antigen is unstable 5-(2-oxopropylideneamino)-6-(d-ribitylamino)uracil (5-OP-RU) which is stabilized when bound and presented to MAIT cells by MHC-related protein 1 (MR1). Here we describe the chemical synthesis and biological evaluation of new chemical probes for the study of MAIT cell biology. The two probes were ethinyl functionalized analogues of 5-OP-RU able to react through CuAAC also called « click chemistry ». The molecules up-regulated more MR1 than 5-OP-RU and they efficiently activated iVα19 Vβ8 TCR transgenic murine MAIT cells but not iVα19 TCRα transgenic MAIT cells indicating a surprisingly strong impact of the TRCβ chain. Moreover, the use of these molecules as chemical probes was validated in vitro by efficient and selective binding to MR1 revealed via fluorescence microscopy. This study was also complemented by molecular modelling investigation of the probes and the binary/ternary complexes they form with MR1 and the TCR. These new probes will be crucial to delineate the dynamics of 5-OP-RU at the cellular or whole organism level and to identify the cells presenting 5-OP-RU to MAIT cells in vivo.

J Barberet, C Binquet, M Guilleman, A Doukani, C Choux, C Bruno, A Bourredjem, C Chapusot, D Bourc'his, Y Duffourd, P Fauque (2020 Dec 15)
Do assisted reproductive technologies and in vitro embryo culture influence the epigenetic control of imprinted genes and transposable elements in children?
Human reproduction (Oxford, England) : 479-492 : DOI : 10.1093/humrep/deaa310

Résumé

Do assisted reproductive technologies (ART) and in vitro embryo culture influence the epigenetic control of imprinted genes (IGs) and transposable elements (TEs) in children?

Marine Verhulsel, Anthony Simon, Moencopi Bernheim-Dennery, Venkata Ram Gannavarapu, Lauriane Gérémie, Davide Ferraro, Denis Krndija, Laurence Talini, Jean-Louis Viovy, Danijela Matic Vignjevic, Stéphanie Descroix (2020 Dec 11)
Developing an advanced gut on chip model enabling the study of epithelial cell/fibroblast interactions.
Lab on a chip : 365-377 : DOI : 10.1039/d0lc00672f

Résumé

Organoids are widely used as a model system to study gut pathophysiology; however, they fail to fully reproduce the complex, multi-component structure of the intestinal wall. We present here a new gut on chip model that allows the co-culture of primary epithelial and stromal cells. The device has the topography and dimensions of the mouse gut and is based on a 3D collagen I scaffold. The scaffold is coated with a thin layer of laminin to mimic the basement membrane. To maintain the scaffold structure while preserving its cytocompatibility, the collagen scaffold was rigidified by threose-based post-polymerization treatment. This treatment being cytocompatible enabled the incorporation of primary intestinal fibroblasts inside the scaffold, reproducing the gut stromal compartment. We observed that mouse organoids, when deposited into crypts, opened up and epithelialized the scaffold, generating a polarized epithelial monolayer. Proper segregation of dividing and differentiated cells along the crypt-villus axis was achieved under these conditions. Finally, we show that the application of fluid shear stress allows the long-term culture of this intestinal epithelium. Our device represents a new biomimetic tool that captures key features of the gut complexity and could be used to study gut pathophysiology.

Valentin Partula, Mélanie Deschasaux-Tanguy, Stanislas Mondot, Agnès Victor-Bala, Nadia Bouchemal, Lucie Lecuyer, Christine Bobin-Dubigeon, Marion J Torres, Emmanuelle Kesse-Guyot, Bruno Charbit, Etienne Patin, Karen E Assmann, Paule Latino-Martel, Chantal Julia, Pilar Galan, Serge Hercberg, Lluis Quintana-Murci, Matthew L Albert, Darragh Duffy, Olivier Lantz, Philippe Savarin, Mohamed Nawfal Triba, Mathilde Touvier, (2020 Dec 10)

Associations between untargeted plasma metabolomic signatures and gut microbiota composition in the population of healthy adults.

The British journal of nutrition : 1-29 : DOI : 10.1017/S0007114520004870

Résumé

Host-microbial co-metabolism products are being increasingly recognized to play important roles in physiological processes. However, studies undertaking a comprehensive approach to consider host-microbial metabolic relationships remain scarce. Metabolomic analysis yielding detailed information regarding metabolites found in a given biological compartment holds promise for such an approach. This work aimed to explore the associations between host plasma metabolomic signatures and gut microbiota composition in healthy adults of the Milieu Intérieur study. For 846 subjects, gut microbiota composition was profiled through sequencing of the 16S rRNA gene in stools. Metabolomic signatures were generated through proton nuclear magnetic resonance analysis of plasma. The associations between metabolomic variables and α- and β-diversity indexes and relative taxa abundances were tested using multi-adjusted partial Spearman correlations, PERMANOVAs, and MaAsLins, respectively. A Multiple testing correction was applied (Benjamini-Hochberg, 10%-FDR). Microbial richness was negatively associated with lipid-related signals and positively associated with amino acids, choline, creatinine, glucose, and citrate ($-0.133 \leq$ Spearman's $\rho \leq 0.126$). Specific associations between metabolomic signals and abundances of taxa were detected (25 at the genus level and 19 at the species level): notably, numerous associations were observed for creatinine (positively associated with 11 species, and negatively associated with Faecalibacterium prausnitzii). This large-scale population-based study

highlights metabolites associated with gut microbial features and provides new insights into the understanding of complex host-gut microbiota metabolic relationships. In particular, our results support the implication of a « gut-kidney axis ». More studies providing a detailed exploration of these complex interactions, and their implications for host health are needed.