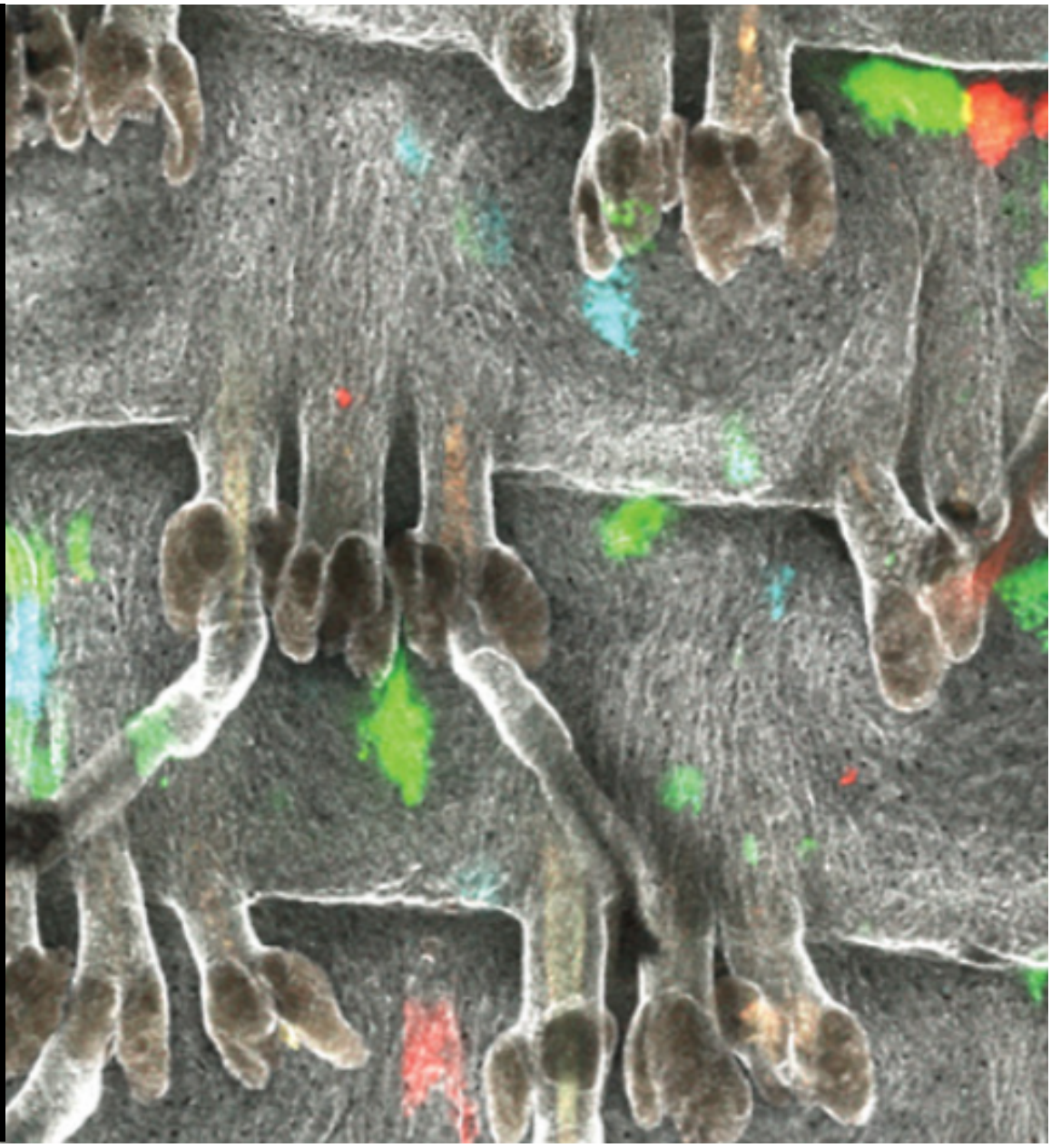
DANISH SINGLE-CELL NETWORK
NEWSLETTER

JULY-SEPTEMBER 2024

COVER IMAGE
Author: Rahul M. Sarate, Laboratory of Stem Cells and Cancer, Université Libre de Bruxelles, Belgium
Title: Mediated epidermal regeneration following basal cell ablation (2024)



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Immunotherapy drives mesenchymal tumor cell state shift and TME immune response in glioblastoma patients.

Hendriksen et al, (2024 Aug 5); Neuro Oncol. 2024 Aug 5;26(8):1453-1466. doi: 10.1093/neuonc/noae085

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Glioblastoma is an aggressive brain tumor with no curative treatment, and existing immunotherapies have shown limited effectiveness. This study investigates single-cell phenotypic and transcriptional dynamics during nivolumab treatment in glioblastoma patients. An integrative analysis of 76 tumor samples revealed a distinct aggressive phenotypic signature in both tumor cells and the tumor microenvironment post-nivolumab treatment. Treatment was linked to an increased transition to mesenchymal stem-like tumor cells, along with an uptick in tumor-associated macrophages (TAMs) and exhausted proliferative T cells. Further validation in a larger dataset (n = 298) identified a latent immune signature in 18% of primary glioblastoma samples, associated with mesenchymal states and immune responses. Importantly, patients with latent immune glioblastoma had shorter overall survival after immune checkpoint treatment. These findings suggest that a subset of glioblastoma patients may resist treatment due to a shift towards a more aggressive phenotype and may benefit from therapies targeting mesenchymal tumor cells.

B-cell characteristics define HCV reinfection outcome.

Underwood et al, (2024 Sep); J Hepatol. 2024 Sep;81(3):415-428. doi: 10.1016/j.jhep.2024.04.004

Copenhagen Hepatitis C Program (CO-HEP), Department of Infectious Diseases, Denmark.

This study investigates immune responses related to the rapid clearance of Hepatitis C virus (HCV) reinfection among individuals highly exposed to the virus. By analyzing broad neutralizing antibodies and E2-specific memory B cells in 15 individuals, the researchers found that broad nAb responses were linked to memory B cell recall but did not correlate with reinfection clearance. The study revealed strong evidence of antigen imprinting and a highly clonal B-cell receptor repertoire undergoing somatic hypermutation. Additionally, transcriptomic analysis indicated that cleared reinfections exhibited an activated profile in HCV-specific B cells that expanded rapidly upon reinfection. These findings suggest that the quality of memory B cell responses is crucial for protection against diverse HCV variants, offering insights for future vaccine development.

Resolution of Acinar Dedifferentiation Regulates Tissue Remodeling in Pancreatic Injury and Cancer Initiation.

Baldan et al, (2024 Sep); Gastroenterology. 2024 Sep;167(4):718-732.e18. doi: 10.1053/j.gastro.2024.04.031

Department of Pathology, Copenhagen University Hospital Rigshospitalet,; Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark.

Acinar-to-ductal metaplasia (ADM) plays a critical role in pancreatic ductal adenocarcinoma development, yet its induction and resolution are not well understood. This study identified Sox4 as a key up-regulated gene during ADM in both mouse and human models through comparative transcriptome analyses, validated by RNA in situ hybridization. Using a mouse model with acinar-specific Sox4 deletion and Kras mutation, the researchers demonstrated that Sox4 counteracts cellular dedifferentiation and maintains tissue homeostasis, while also being essential for the specification of mucin-producing and tuft-like cells. The study further revealed that Sox4 regulates stromal reactions non-cell-autonomously during disease progression and that its targets are activated upon KRAS inactivation, correlating with tumor regression. These findings highlight Sox4's role in restraining acinar dedifferentiation and suggest new strategies for promoting tissue homeostasis to prevent pancreatic ductal adenocarcinoma.

Intraocular pressure-related side-effects after endothelial keratoplasty.

Madsen et al, (2024 Sep); Acta Ophthalmol. 2024 Sep;102(6):674-682. doi: 10.1111/aos.16655

Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark.

This study aimed to evaluate circumpapillary retinal nerve fiber layer (RNFL) thickness and pupillary function following phacoemulsification with or without endothelial keratoplasty (EK) in patients with Fuchs' endothelial dystrophy and cataract. Results showed that RNFL thickness was significantly lower in the cataract extraction (CE) group compared to the EK group at 12 months post-surgery, but no negative impact on RNFL thickness was observed after EK. Pupillary function, including scotopic and photopic diameters, as well as pupillary constriction velocity, were similar between the CE and EK groups after 12 months, although patients treated with rebubbling exhibited a smaller scotopic pupil diameter. Overall, the findings suggest that EK does not adversely affect RNFL thickness compared to cataract surgery alone.

Benchmarking transcriptome deconvolution methods for estimating tissue- and cell-type-specific extracellular vesicle abundances.

Larsen et al, (2024 Sep); J Extracell Vesicles. 2024 Sep;13(9):e12511. doi: 10.1002/jev2.12511

Department of Molecular Medicine, University of Southern Denmark, Odense, Denmark.

This study addresses the challenge of determining tissue- and cell-type-specific abundances of extracellular vesicles (EVs) in body fluids by benchmarking 11 deconvolution methods on EV transcriptome data. Using data from four cell lines, in silico mixtures, and human plasma and urine samples, the authors identified methods that accurately estimated cell type-specific abundances of EVs. Four deconvolution methods showed consistent results across different urine EV cohorts, and three methods provided similar estimates for plasma EV abundance. The study emphasizes the significance of incorporating biological knowledge when developing tissue and cell type signatures for deconvolution. Ultimately, the algorithms DWLS and CIBERSORTx were found to produce highly accurate estimates of tissue- and cell-type-specific EV abundances in biological fluids.

Tipping-point transition from transient to persistent inflammation in pancreatic islets.

Holst-Hansen et al, (2024 Sep 12); NPJ Syst Biol Appl. 2024 Sep 12;10(1):102. doi: 10.1038/s41540-024-00427-4

Niels Bohr Institute, University of Copenhagen, Copenhagen, Denmark.

This study investigates the dual role of the pro-inflammatory cytokine IL-1β in pancreatic islets, showing that it can either enhance insulin secretion and β-cell proliferation or lead to β-cell death, depending on its concentration and exposure duration. Using a quantitative in silico model, the research identifies two key feedback mechanisms in the IL-1 regulatory network: a fast positive feedback that promotes IL-1 production and a slow negative feedback that mitigates its effects. The balance between these feedbacks determines whether islets exhibit transient or persistent IL-1 responses, with larger islets more susceptible to sustained inflammation. The findings suggest that this regulatory framework may apply to other pro-inflammatory cytokines and emphasize the importance of islet architecture in inflammatory responses. Further experimental validation is needed to verify these model predictions and enhance their clinical relevance.

Autologous micrografting improves regeneration of tissue-engineered urinary conduits in vivo.

Juul et al, (2024 Sep 25); Sci Rep. 2024 Sep 25;14(1):22028. doi: 10.1038/s41598-024-72876-0

Department of Health Technology, Technical University of Denmark, Kgs. Lyngby,; Department of Forensic Medicine, University of Copenhagen, Copenhagen, Denmark.

This study evaluates the feasibility and regenerative outcomes of using autologous micrografting for urogenital reconstructive surgery in minipigs, specifically focusing on collagen-based scaffolds reinforced with biodegradable mesh for bladder conduit implantation. Ten female minipigs received either micrografted scaffolds with autologous urothelial cells or acellular controls. After six weeks, assessments showed that the micrografted conduits exhibited significantly improved tissue regeneration, including better epithelialization, increased cell proliferation, reduced apoptosis, and enhanced vascularization compared to the acellular controls. The procedure was found to be technically feasible and safe, with no postoperative complications, suggesting that this innovative approach may advance urinary conduit reconstruction and warrants further clinical investigation.

Phenotypes, Genetics, and Estimated Prevalence of Focal Dermal Hypoplasia (Goltz Syndrome): A Single-Center Report.

Herlin et al, (2024 Sep 10); Pediatr Dermatol. 2024 Sep 10. doi: 10.1111/pde.15752

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Focal dermal hypoplasia (FDH), or Goltz syndrome, is a rare X-linked dominant disorder primarily affecting the skin, skeleton, and eyes, caused by pathogenic variants in the PORCN gene. This study characterized four genetically confirmed FDH patients (three females, one male) at Aarhus University Hospital, Denmark, highlighting characteristic dermatological features such as skin atrophy, fat herniations, and telangiectasias, along with limb malformations and eye abnormalities. Notably, one patient presented atypically with several malformations and only subtle skin changes, diagnosed through trio exome sequencing. The researchers identified four PORCN variants, three of which were novel, and estimated a point prevalence of 1.6 cases per million in Western Denmark and 1.2 cases per million nationwide. This study underscores the complexity of FDH and the need for multidisciplinary collaboration for effective diagnosis and care.

Single-cell multi-omics map of human fetal blood in Down syndrome.

Marderstein et al, (2024 Sep 25); Nature. 2024 Sep 25. doi: 10.1038/s41586-024-07946-4

Biotech Research & Innovation Centre (BRIC), University of Copenhagen, Denmark.

This study investigates dysregulated hematopoiesis in Down syndrome by integrating single-cell transcriptomics with chromatin accessibility and spatial transcriptomics from human fetal liver and bone marrow samples. Analyzing over 1.1 million cells from trisomic and disomic fetuses, the researchers found that gene expression differences were influenced by cell type and environment, revealing that hematopoietic stem cells (HSCs) in Down syndrome are "primed" for differentiation. They developed a Down syndrome-specific map linking non-coding elements to genes, uncovering that trisomy alters regulatory interactions, affecting enhancer activity and gene expression crucial for erythroid lineage differentiation. Additionally, they validated increased mitochondrial mass and oxidative stress associated with mutations in Down syndrome, highlighting significant regulatory changes that contribute to hematological abnormalities. This comprehensive multi-omic resource offers valuable insights into fetal hematopoiesis in Down syndrome.

Plug-and-play nucleic acid-mediated multimerization of biparatopic nanobodies for molecular imaging.

Teodori et al, (2024 Sep 10); Mol Ther Nucleic Acids. 2024 Aug 15;35(3):102305. doi:. 10.1016/j.omtn.2024.102305

Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C,; Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Gustav Wieds Vej; Department of Molecular Biology and Genetics, Universitetsbyen 81, 8000 Aarhus C, Denmark.

In cancer molecular imaging, the selection of high-specificity and high-affinity binders is crucial for effective imaging. Nanobodies have become promising alternatives to traditional antibodies due to their ease of production, rapid renal clearance, and better tissue penetration. This study introduces a Holliday junction-like nucleic acid-based scaffold to create homogeneous multivalent and multiparatopic displays of nanobodies, facilitating a plug-and-play assembly method for screening different configurations targeting the HER2 breast cancer biomarker. In vitro experiments showed enhanced binding avidity, particularly with a biparatopic construct, which demonstrated greater sensitivity than conventional antibodies. Additionally, the scaffold's adaptability for fluorescence and nuclear imaging in xenografted mice indicates its potential for future in vivo applications in cancer diagnostics and theranostics.

Long genetic and social isolation in Neanderthals before their extinction.

Slimak et al, (2024 Sep 11); Cell Genom. 2024 Sep 11;4(9):100593. doi: 10.1016/j.xgen.2024.100593

Lundbeck Foundation GeoGenetics Center, University of Copenhagen, Denmark.

The discovery of a late Neanderthal individual named "Thorin" from Grotte Mandrin in France has provided new insights into Neanderthal population structure and genetics. Fossils associated with Thorin, dating back approximately 50,000 to 42,000 years, include rare dentognathic specimens. Genetic analysis reveals that Thorin diverged around 105,000 years ago from other late Neanderthals and belonged to a small, isolated population with no evidence of genetic mixing with neighboring Neanderthal groups. This indicates a significant period of genetic isolation for Thorin's lineage and has implications for understanding the factors contributing to the Neanderthals' eventual disappearance.

Antibody density on bacteria regulates C1q recruitment by monoclonal IgG but not IgM.

Aymerich et al, (2024 Sep 4); Eur J Immunol. 2024 Sep 4:e2451228. doi: 10.1002/eji.202451228

Department of Biomedicine, Aarhus University, Aarhus, Denmark.

This study investigates how monoclonal antibodies trigger complement activation, which is essential for immune defense against pathogenic bacteria and could help combat antibiotic resistance. A novel bioassay was developed to quantify classical complement activation at the monoclonal antibody level, enabling the characterization of rare complement-activating antibacterial antibodies from post-immunization murine repertoires. The researchers found that individual IgM and IgG subclasses effectively activated the classical pathway, revealing different requirements for epitope density in C1q binding depending on the antibody isotype. Notably, the study concluded that antibody

density is crucial for C1q recruitment in IgG isotypes, while this was not the case for IgM, providing insights for antibody screening and vaccination strategies.

Differentiating leukemia subtypes based on metabolic signatures using hyperpolarized (13)C NMR.

Christensen et al, (2024 Sep 25); NMR Biomed. 2024 Sep 25:e5264. doi: 10.1002/nbm.5264

The MR Research Centre, Department of Clinical Medicine, Aarhus University, Denmark.

Leukemia encompasses various blood cancers that are challenging to differentiate due to their similar origins and genetic mutations, which can affect treatment responses. This study utilized hyperpolarized (13)C NMR spectroscopy to analyze the metabolic signatures of six leukemia cell lines: ML-1, CCRF-CEM, THP-1, MOLT-4, HL-60, and K562, using [1-(13)C]pyruvate and [1-(13)C]alanine for metabolite quantification. The results revealed distinct metabolic profiles among similar subtypes, including ML-1 and THP-1 (M4 and M5 AML), CCRF-CEM and MOLT-4 (T-ALL), and HL-60 and K562 (M1 and M2 AML). These findings highlight the potential of hyperpolarized (13)C NMR spectroscopy for differentiating leukemia subtypes and suggest that combining this technique with bioreactor setups could enhance leukemia management by enabling metabolic profiling from a single biopsy.

Platelet transfusions in adult ICU patients with thrombocytopenia: A sub-study of the PLOT-ICU inception cohort study.

Anthon et al, (2024 Sep); Acta Anaesthesiol Scand. 2024 Sep;68(8):1018-1030. doi: 10.1111/aas.14467.

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In a sub-study of the PLOT-ICU trial, which examined platelet transfusion practices in ICU patients with thrombocytopenia, data were collected from 504 patients across 43 hospitals in Europe and the U.S. About 20.8% of these patients received a total of 565 platelet transfusions, predominantly using pooled products (61.0%), followed by apheresis products (21.9%). The median volume for each transfusion was 253 mL, with fixed dosing being the most common practice (73.8%), while some centers used weight-based dosing. The median platelet count increment following a single prophylactic transfusion was 2 × 10^9/L, indicating limited effectiveness. Overall, significant variability was noted in transfusion practices regarding product types, volumes, and dosing strategies across different countries.

Late effects following HSCT for childhood ALL: A national single-center study using three different modalities of delivery of total body irradiation.

Uhlving et al, (2024 Sep); Pediatr Blood Cancer. 2024 Sep;71(9):e31163. doi: 10.1002/pbc.31163

Department of Radiation Oncology, Copenhagen University Hospital Rigshospitalet,; Department of Pediatrics and Adolescent Medicine, Copenhagen University Hospital, Denmark.

This study evaluated the impact of different total body irradiation (TBI) delivery techniques on acute and late toxicities in pediatric patients undergoing hematopoietic stem cell transplantation for acute lymphoblastic leukemia. Three TBI schedules were compared: 4 Gy daily fractions, 2 Gy fractions twice daily using 2D planning, and 2 Gy twice daily using 3D planning with intensity-modulated radiotherapy. While the 5-year event-free survival rates were comparable across groups, improvements were noted in cataract-free survival and a tendency towards fewer endocrinopathies with more fractionation. Acute toxicities, graft-versus-host disease incidences, and pulmonary function remained similar among the cohorts, indicating that TBI modality changes did not result in increased relapse rates. Further investigation into 3D-planning-IMRT technology is needed in larger studies.

The ABCF ATPase New1 resolves translation termination defects associated with specific tRNAArg and tRNALys isoacceptors in the P site.

Turnbull et al, (2024 Sep 1); Nucleic Acids Res. 2024 Sep 1:gkae748. doi: 10.1093/nar/gkae748

Department of Clinical Microbiology, Rigshospitalet, 2200 Copenhagen, Denmark.

This study investigates the role of the Saccharomyces cerevisiae ABCF ATPase New1 in translation termination and ribosome recycling. Using techniques like 5PSeq, single-particle cryo-electron microscopy, and readthrough reporter assays, the researchers found that the absence of New1 leads to ribosomal stalling at stop codons, particularly when preceded by lysine or arginine codons. The stalling is influenced not by the C-terminal amino acid but by the identity of the tRNA isoacceptor in the P-site. The findings indicate that specific tRNA isoacceptors can hinder translation termination efficiency and highlight that New1 is crucial for rescuing stalled ribosomes in these situations.

If you would like to announce anything single cell related, e.g. job announcement, event, your published paper, technology development etc., please contact us.

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