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ABSTRACTS COLLECTION

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Presenting author names **are underlined** in the contributor lists.

## P01

## CANCER GENETICS

### P01.001.A Hypoxia-mimetic agent DFO inhibits cancer cell proliferation and induces DNA damage

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**Background/Objectives:** Hypoxia is common in solid tumour microenvironments and has been associated with radiotherapy resistance and poor clinical outcomes. Replicating hypoxic conditions in vitro requires incubation at 1% $O_2$, 5% $CO_2$ and 94% $N_2$. This nitrogen-induced hypoxia is costly and time-consuming since it needs 24 hours to establish hypoxia. An alternative technique to replicate hypoxic conditions is the use of mimetics like deferoxamine (DFO). This molecule is an iron chelating agent that facilitates the accumulation of hypoxia-inducible factors and has been shown to induce apoptosis in breast tumor cell lines[1].

**Methods:** MCF7 (breast), VCAP (prostate), CAL33 (head and neck) and OVCAR-8 (ovarian) cancer cell lines were used to test the effect of DFO on proliferation using MTT and annexin-V/propidium iodide assays. DNA damage, specifically double strand break (DSB) formation, was tested by γH2AX foci quantification via immunofluorescence assays.

**Results:** DFO inhibited cell proliferation and apoptosis in a dose- and time-dependent manner. These effects were more marked than the one achieved through nitrogen-induced hypoxia. Additionally, DFO induces DNA damage through DSB formation.

**Conclusion:** Although DFO is usually used as a hypoxia-mimetic agent because it is cheaper and less time-consuming than nitrogen-induced hypoxia, our results show that it decreases cell proliferation and induces DNA damage through DSB formation. Therefore, its antitumoral effect should be further explored.

**Grants:** Study was financed by Gerencia Regional de Salud, JCyL (GRS2171/A/2020)

1. Lynn, J. V. et al. The Role of Deferoxamine in Irradiated Breast Reconstruction: A Study of Oncologic Safety. Plast. Reconstr. Surg. 143, 1666–1676 (2019).

**Conflict of Interest:** None declared

### P01.002.B Mapping of Splicing Regulatory Elements-rich intervals and identification of spliceogenic variants in ATM exon 7

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with disordered respiratory control, occurring soon after birth. Current techniques used to detect the expansion repeats are prone to PCR errors and false negative results; and short read NGS has low sensitivity to detect the expansion. Here we use Oxford Nanopore long-read technology and adaptive sampling to accurately detect the repeat expansion in *PHOX2B* in patients with CCHS.

**Methods:** Samples with known *PHOX2B* expansion repeats were sequenced on the PromethION 2 (P2) using R10.4.1 flow cells. DNA was sheared to between 14-20kb in length (Covaris g-tubes) and prepped using the ligation sequencing kit v14 (SQK-LSK114) from ONT. Adaptive sampling was used to target *PHOX2B*. The ONT EPI2ME package was used to generate VCF and variant annotation files. Once validated, samples were multiplexed to reduce cost and increase throughput using the Native barcoding kit v14 (SQK-NBD114.96).

**Results:** Expansion of the *PHOX2B* repeat was confirmed on control samples. A sample previously sequenced using short read technologies with a false negative result, was re-run in parallel with other test cases and controls, and the known expansion was detected.

**Conclusion:** Nanopore sequencing allows for better detection of expansion repeats that cannot be accurately detected by short read technologies.

**Conflict of Interest:** None declared

### P21.058.A PacBio Revio and ONT PromethION long-read sequencing in SV calling and variant phasing

**Giancarlo Tomio**[1], *Janine Meienberg*[1], *Timo Siegenthaler*[1], *Pamela Nicholson*[2], *Stefan Krebs*[3], *Gabor Matyas*[1,4]

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**Background/Objectives:** Short-read sequencing (SRS) is the most used technology in clinical sequencing, but it has limitations in areas of the genome harbouring complex structural variants (SVs) or repetitive/homologous sequence, and variant phasing information is often lost. Long-read sequencing (LRS) technologies do not suffer these challenges and have improved to the point of feasible use in clinical sequencing. Thus, we compared the latest Pacific Bioscience (PacBio) and Oxford Nanopore Technologies (ONT) LRS technologies in their ability to detect a known set of challenging variants.

**Methods:** Four DNA samples with SVs and single nucleotide variants previously detected by SRS (PCR-free WGS, PE150) were sequenced on a PacBio Revio as well as on an ONT PromethION and analysed with their respective standard pipelines. Several further SV callers were applied, and regions of interest were manually reviewed using Integrative Genomics Viewer.

**Results:** Our data revealed differences in the performance of the tested LRS approaches as well as in the performance of SV callers for challenging variants, including complex SVs and SVs with breakpoints in non-unique sequence regions. Nevertheless, both LRS approaches were able to detect breakpoints missed by SRS and to phase sequence variants according to their respective read lengths.

**Conclusion:** LRS can be the solution for breakpoint identification in repetitive regions and for characterisation of complex SVs not exceeding their read length. Improved SV callers are vital to take full advantage of LRS in clinical genetic testing. Current LRS technologies achieve SRS-like error rates at affordable prices and so enable an improved future for clinical sequencing.

**Conflict of Interest:** Giancarlo Tomio: None declared, Janine Meienberg: None declared, Timo Siegenthaler: None declared, Pamela Nicholson: None declared, Stefan Krebs: None declared, Gabor Matyas PacBio and ONT provided reagents free of charge

### P21.059.B Thymidylate synthase disruption to limit cell proliferation in cell therapies

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**Background/Objectives:** Many diseases or genetic conditions could be envisioned to be treated with cell transplantations with or without gene therapy. However, the use of additional or genetically modified, such as CRISPRed cells carries a risk of malignant cell proliferation.

**Methods:** Here, we describe a novel metabolic safety system to control cell proliferation without added genetic elements. For this, we inactivated a key enzyme for nucleotide metabolism, *TYMS*, in several cell types, thus obtaining cells that proliferate only when supplemented with exogenous thymidine but fail to replicate in its absence.

**Results:** We show that under thymidine supplementation, *TYMS*$^{-/-}$ cell lines and pluripotent stem cells proliferate normally, produce teratomas and differentiate into potentially therapeutic cell types such as pancreatic beta cells. After differentiation, the postmitotic cells do not require thymidine to function, as seen by prolonged in vivo production of human insulin in implanted mice. Hence, this method allows robust cell culture and manufacture while mitigating the risk of uncontrolled growth of transplanted cells.

**Conclusion:** We describe engineering fully functional human cells, which can be cultured and manufactured robustly under supplementation of thymidine. This allows the genetic manipulation and production of therapeutic cells. However, since the cell proliferation can be controlled, the recipients of the cells are safe from possible oncogenic modifications.

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**Conflict of Interest:** None declared

### P21.060.C Streamlined implementation of nanopore sequencing in clinical routine diagnostics within the lonGER consortium

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