The successful case of starting a company with drug targets

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Science

Seminal paper revealing for the 1st time an unexpected survival mechanism of a subset of cancer cells (alternative lengthening of telomeres – ALT – pathway). **We have shown that inhibiting the enzymatic activity of the FANCM induces selective death of ALT cancer cells.**

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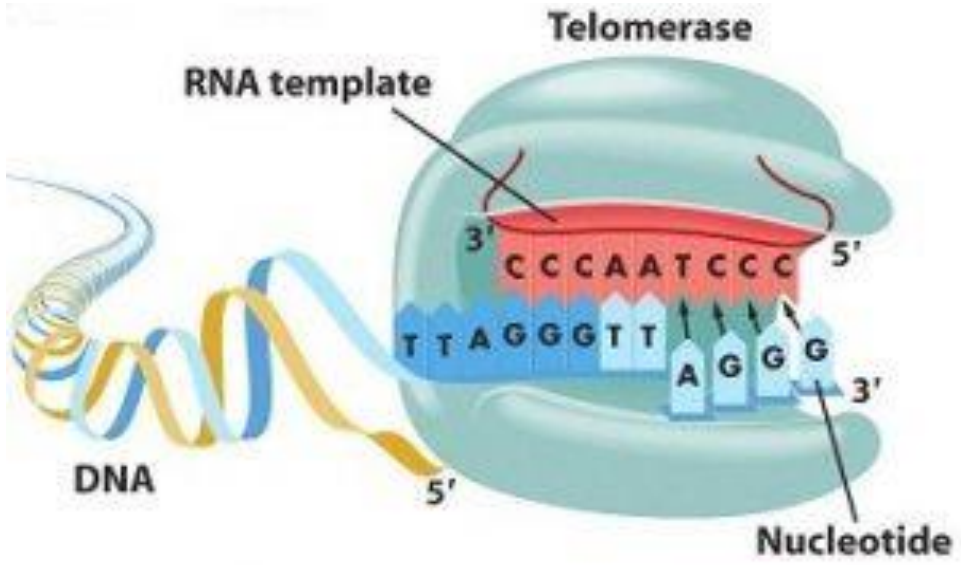
FANCM limits ALT activity by restricting telomeric replication stress induced by deregulated BLM and R-loops

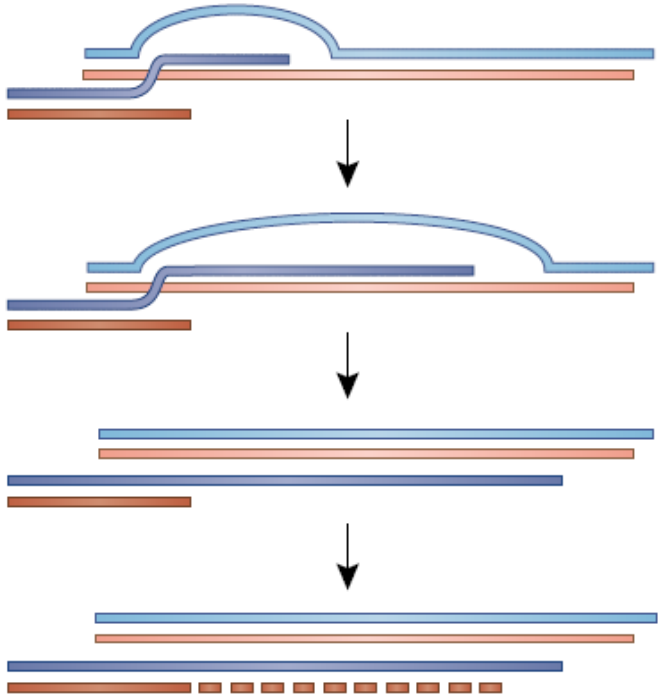
Bruno Silva, Richard Pentz, Ana Margarida Figueira, Rajika Arora, Yong Woo Lee, Charlotte Hodson, Harry Wischnewski, Andrew J. Deans & Claus M. Azzalin ✉

Telomeres are maintained by one of two mechanisms

(i) Telomerase



(ii) Alternative Lengthening of Telomeres (ALT)



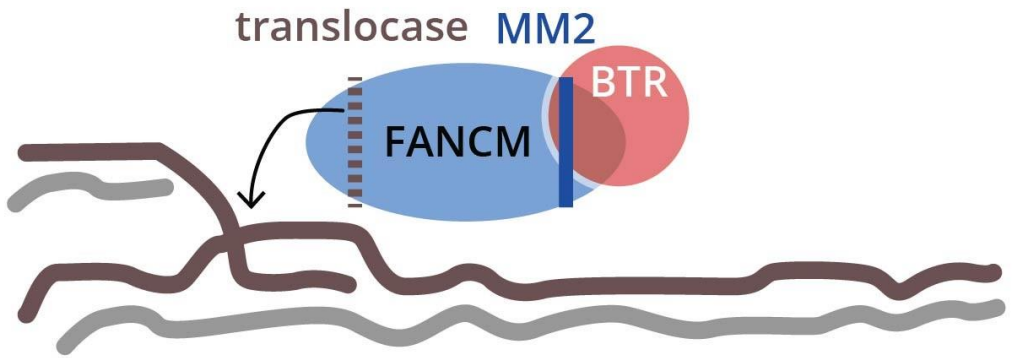
FANCM

- FANCM is a member of the Fanconi anaemia (FA) core complex of proteins

- Members of this group of proteins are involved in the cellular response to DNA damage

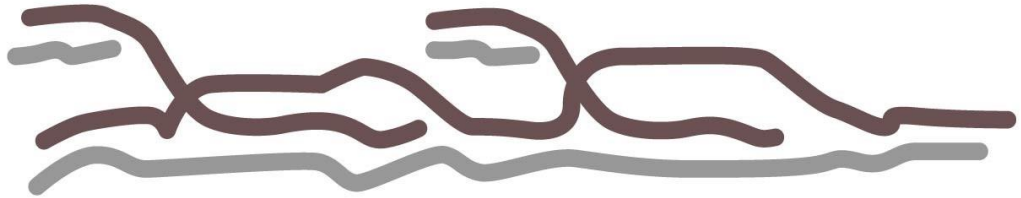
FANCM is essential for ALT cell viability

FANCM-proficient ALT cell



Alleviated telomeric replication stress
Regulated ALT (telomere elongation)
Cell proliferation

FANCM-deficient ALT cell



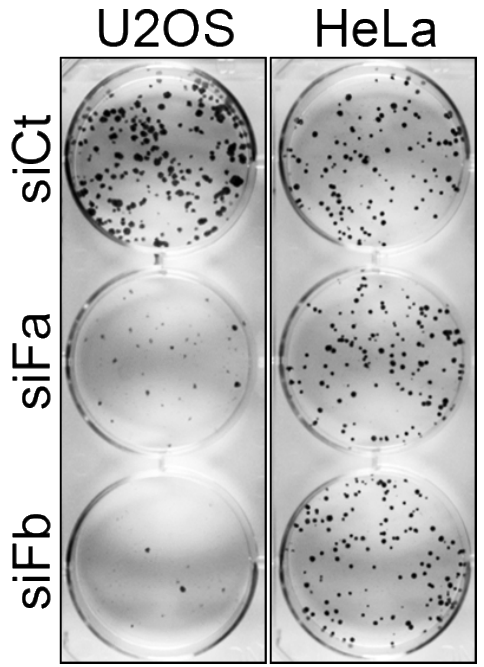
Excessive telomeric replication stress
Excessive ALT (telomere dysfunction)
Cell death

Initial data – siRNA depletion of FANCM

- ALT osteosarcoma U2OS cells and telomerase-positive cervical carcinoma HeLa cells were **depleted for FANCM** using two independent siRNAs (siFa and siFb)

- Cells were transfected only once with siRNAs and seeded for colony forming assays.

<u>ALT cells stop proliferating while non-ALT cells were unaffected</u>



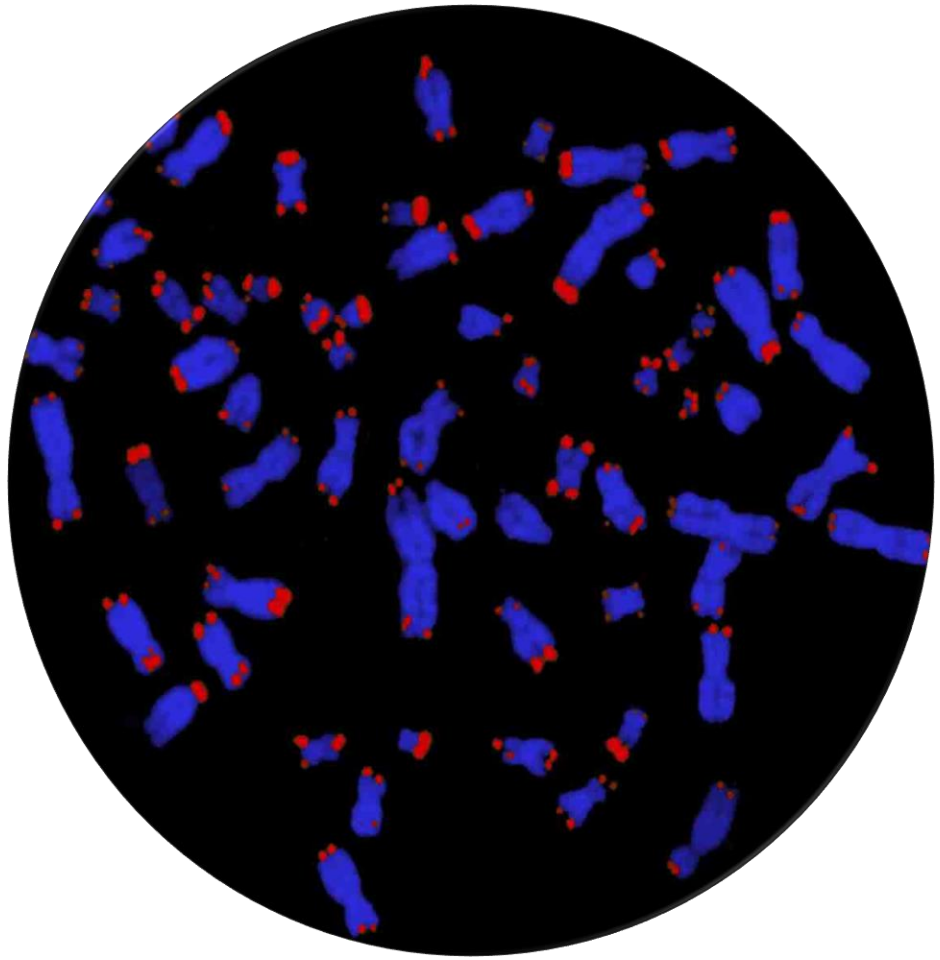
i. primary normal cells are also insensitive to FANCM depletion.

ii. CRISPR/Cas9 KO cells can be generated in telomerase-positive and in primary cells but not in ALT cells.

iii. complementation experiments using FANCM mutants deficient for ATPase activity revealed the essentiality of the helicase domain for telomere maintenance and ALT cell survival.

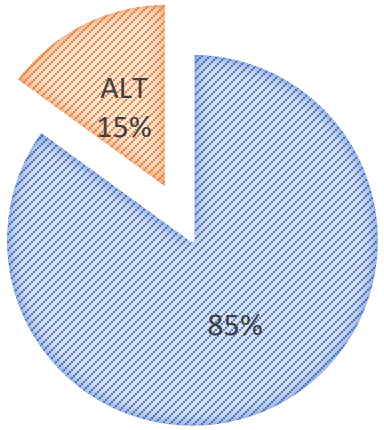
ALT cancers

- ALT is activated in approximately **10 -15%** of all cancers
- Prevalent in **bone** and **soft tissue sarcomas**, **pancreatic** cancers and **brain** cancers (where it is activated in approximately 40% of cases)
- **ALT cancers** are typically aggressive and hard-to-treat, with **poor prognosis**
- Improved treatment strategies for these types of cancers are important
- **There are currently no known drugs** that specifically target ALT-positive cancers



ALT Cancers – Unmet medical need

10 - 15%
Human cancers



1 million deaths
ALT-positive cancers/year

Very aggressive and chemotherapy resistant cancers

Osteosarcoma

Soft Tissue Sarcoma

Gastric carcinoma

Neuroblastoma

Astrocytoma

Glioblastoma

Non-specific treatment

High prevalence in paediatric cancers

From invention disclosure to seed funding

- **Apr 2019**: invention disclosed to the TTO
- **May 2019**: provisional patent application in the UK (same day of publication in Nature); opportunity identified to join forces with the Children's Medical Research Institute (CMRI) in Australia (paper disclosing another strategy to target FANCM published the same day)
- **Jun – Aug 2019**: industry's interest based on paper publication only (first indicator of potential)
- **Sep 2019**: IIA with CMRI to combine both targets in a single start-up company
- **Sep 2019 – Dec 2019**: fundraising efforts, med chem expertise and initial contacts with CROs for development plan (a lot of interest generated from VCs at Bio-EU)
- **Jan 2020 – Apr 2020**: due diligence with select qualified investors; drug discovery expert hired to manage contacts with CROs and finalise development plan for investment
- **Apr 2020 – Jun 2020**: PCT application with the two targets; negotiation of licence agreement and SHA with Biogeneration Ventures (BGV)
- **26th of June 2020**: Incorporation of Tessellate Bio n.V. with €2M seed round

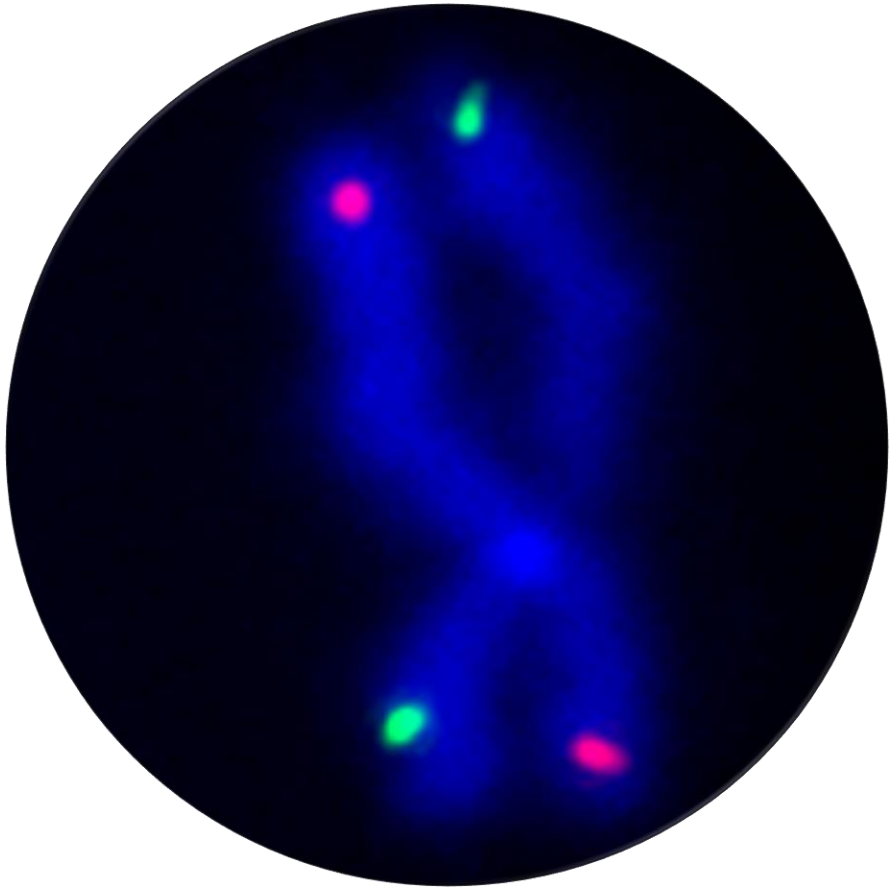
Overview of company at seed stage

- Tessellate Bio brings together the expertise and intellectual property of **two leading ALT cancer biology labs:**
  - Instituto de Medicina Molecular Joao Lobo Antunes (Portugal)
  - Children's Medical Research Institute (Australia)
- Harnessing the potential of increasing telomeric replication stress to **selectively kill ALT cancer cells** with **two druggable targets**
- **Shareholders**: Claus Azzalin and Hilda Pickett (scientific founders), iMM, CMRI and BGV
- **Initial team**: Interim CEO (appointed by BGV), COO, drug discovery consultant (working virtually)
- **Licence agreement** included equity considerations, milestone payments, corporate and sublicensing income, royalties (reach-through clauses to future molecules to be developed)

Inhibition of ALT cancer cell growth by targeting FANCM

- **Option 1**: Target the ATPase (helicase) activity of FANCM

- **Option 2**: Protein:protein targeting of the FANCM:BTR interface between the MM2 domain of FANCM and the RMI subcomplex of BTR (the crystal structure of this interaction has been solved, and this interaction has been the subject of a high-throughput small molecule screen (Voter AF et al., 2016))



Current status of the company

- **€20M** in seed funding + **€15M** w/ convertible loan and ongoing fundraising of **€60M** Series A round
- Forbion as a new shareholder
- Ambitious plan to become a **leader in synthetic lethality** with multiple programs in the pipeline (2 initial targets + external targets licensed in / discovered internally)
- Company with more than **30 collaborators**, including seasoned executive team (CEO, CSO, COO and CBO) and other key leadership positions (Head of Discovery Biology, Head of Bioinformatics, Head of Diagnostics, Head of Chemistry, etc.)
- **Physical labs** opened in Stevenage UK
- **Key next milestones** (ALT): development candidate (Q2/2025); First-in-Man (Q2/2026); Phase 1b PoC (Q4/2027)

Main learnings

- **Not all** novel drug targets are attractive to industry / investors
- **Novel drug targets** can be an attractive investment opportunity if **disease-modifying therapeutic options** are enabled and are properly **validated according to industry standards**
- It is also important that novel targets are based on **world-class science** (unique discovery capacities and scientific leadership) and are within **hot scientific / therapeutic areas** (e.g.: DDR and synthetic lethality in oncology)
- A business case with novel drug targets is more attractive if **more than one target** within the same unexploited therapeutic space can be included in the "package" (PIs with international scientific leadership can identify potential external targets to consider)
- Industry is very keen on investing / licensing in novel drug targets, but this may block scientific publications for some time
- If the targets are a good case for starting up a company, **investors' selection is critical**
- The business case and development plan needs to involve **experienced drug discovery / med chem experts**
- Licensing arrangements need to contemplate **reach-through clauses for molecules** that show the desired activity

Thank you!

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