DDX3X role characterisation in colorectal cancer: An oncogene or tumour suppressor?

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Bachelor's Degree in Biomedical Sciences (2022-2023)

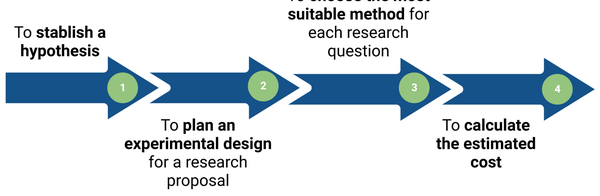
1. Research proposal elaboration

This final degree thesis has consisted of the **design of a research proposal** on a relevant topic in the current biomedical research field.

Methodology

- Revision of reviews and original articles found in PubMed
- Searches in web pages of providers of kits, reagents and consumables for reaearch. ThermoFisher SCIENTIFIC, SIGMA-ALDRICH, addgene

Aims



Keywords

Colorectal cancer, DDX3X, dual-role protein, β-catenin, Snail, targeted therapy.

2. Introduction

The prognosis of **colorectal cancer (CRC)** is currently unsatisfactory, with high rates of relapse and subsequent metastatic spread. Thus, new combinatorial targeted therapies are needed to accomplish **long-term control of CRC**.

DDX3X is a **dual role protein** that has oncogenic and tumour suppressor described roles in CRC by enhancing β-catenin stability and inhibiting Snail, respectively.

Snail/E-cadherin and **Wnt/β-catenin** pathways are interconnected and involved in the initiation of **epithelial to mesenchymal transition (EMT)** in CRC, a process that has been associated with increased rate of cancer recurrence and decreased survival of CRC patients.

Therefore, DDX3X emerges as a potential target for the treatment of CRC. However, the context in which DDX3X expresses each role needs to be clarified to determine which patients could **benefit from a DDX3X inhibitor therapy**.

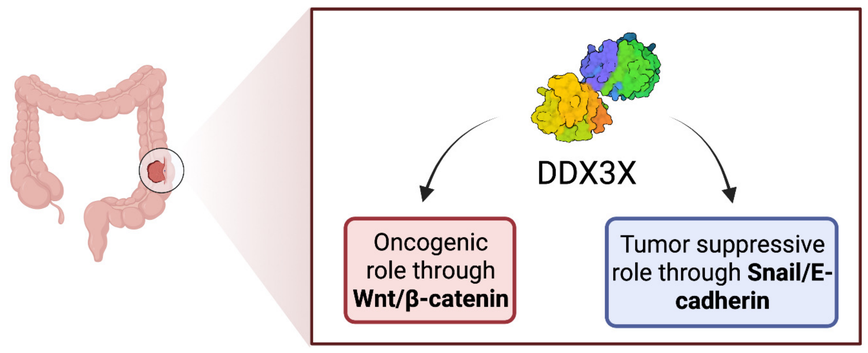


Figure 1. *DEAD-Box RNA helicase-3 X-linked (DDX3X) as a dual role protein in CRC.*

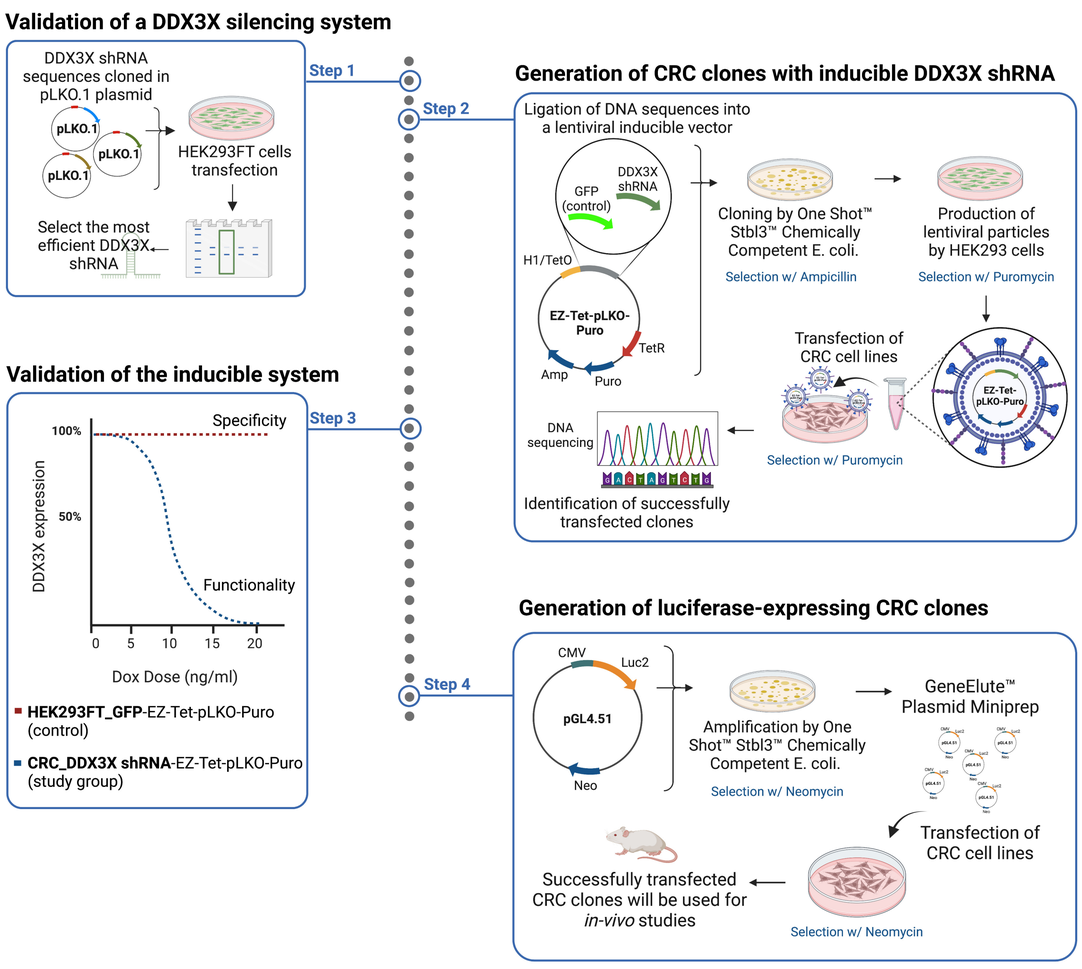
3. Aims & Hypothesis

Given that DDX3X oncogenic role has only been described in Adenomatous Polyposis Coli (APC)-wild-type CRC cells, and 70% of sporadic CRCs emerge from APC inactivating mutations, the aim of this work is to **investigate the role of DDX3X in CRCs harbouring APC mutations** in Wnt/β-catenin signalling pathway.

It is hypothesized that in CRCs with this genetic background DDX3X can express its tumour suppressor role through the repression of Snail, thus excluding these patients from the treatment with a DDX3X inhibitor.

4. Methods. Generation of CRC clones with inducible expression of a DDX3X shRNA

A lentiviral vector containing an inducible shRNA will be prepared to *knock-down* DDX3X expression in HCT116 cell line (control) and DLD-1, SW480, and Colo205 cell lines (which harbour APC-mutations).



5. Workflow

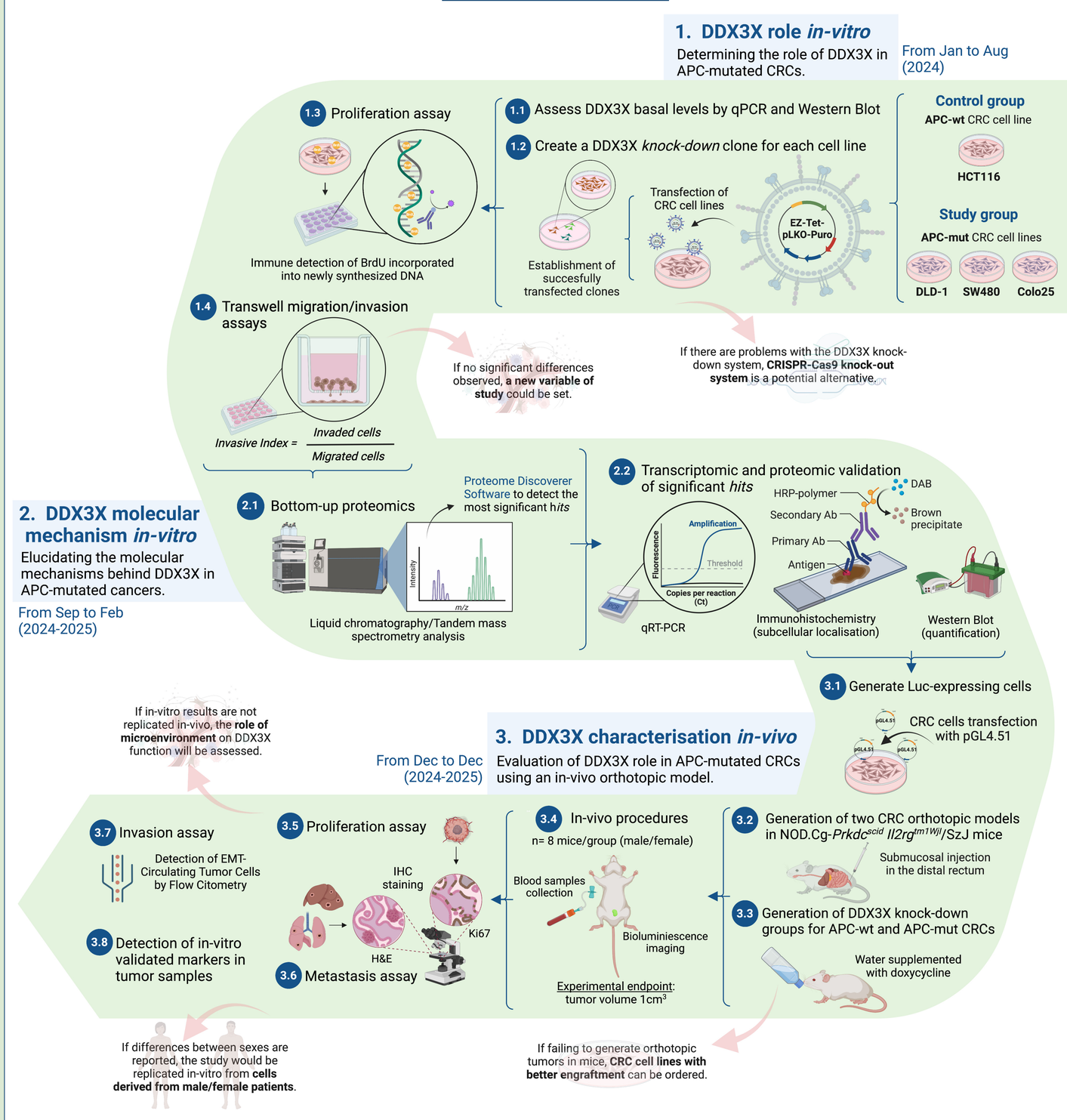


Figure 2. *Worflow schematic representation including the timings and proposed contingency plans in some critical steps.*

6. Expected results

- It is expected to find out if the **mutational status of APC** can help to **distinguish which patients can benefit from a treatment with a DDX3X inhibitor** in combination with other targeted therapies.
- If DDX3X acts as a tumour suppressor through Snail inhibition in CRCs with APC loss, as hypothesised, in 70% of sporadic CRCs DDX3X expression might be beneficial.

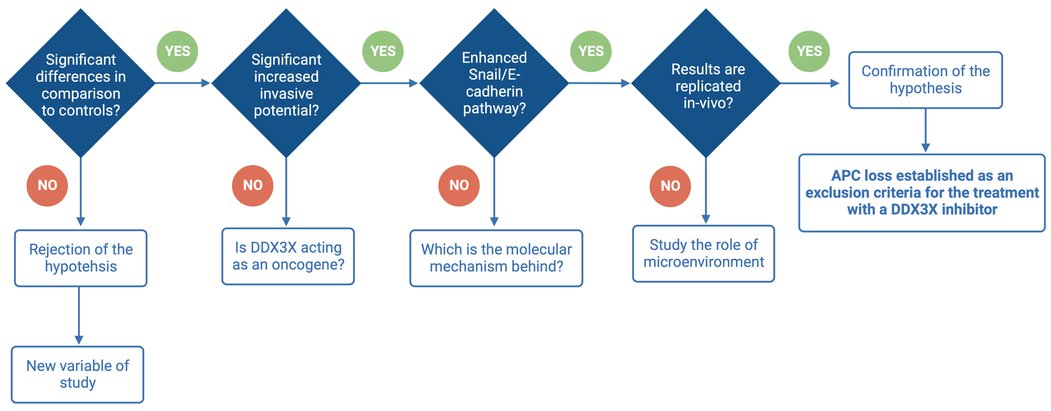
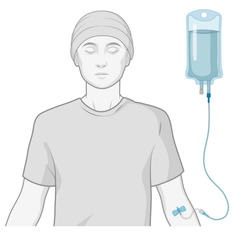


Figure 3. *Flow chart of the possible results in DDX3X knock-down group of APC-mutated cell lines (study group).*

7. Relevance of the study

Translational application → Establishing inclusion/exclusion criteria for the treatment with a DDX3X inhibitor will allow the election of the proper combinatorial therapies for CRC patients (personalized treatment).



8. Diffusion plan

- Publication in **Oncology Journals** with high impact factor.

- Presentation of results in national and international **congresses**.

WORLD CONGRESS ON Gastrointestinal Cancer ESMO

9. Financial expression of the project

The estimated cost of this two-year project is **169.881,22 €**.

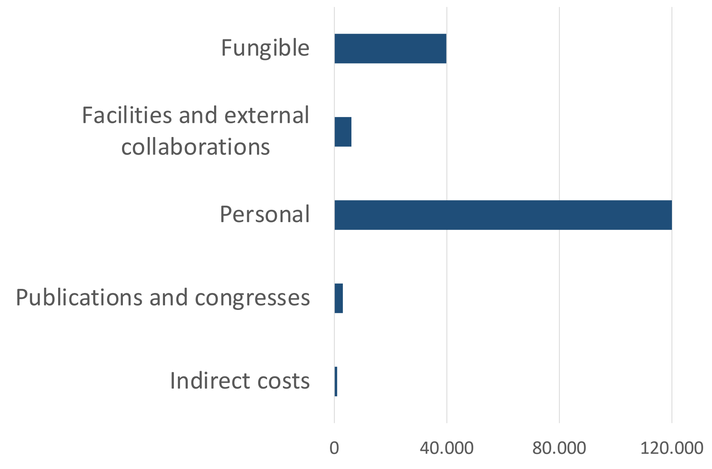


Figure 4. *Graphic representation of the cost of the different items included in the budget.*