Development of Targeted Therapeutics for Prostate Cancer

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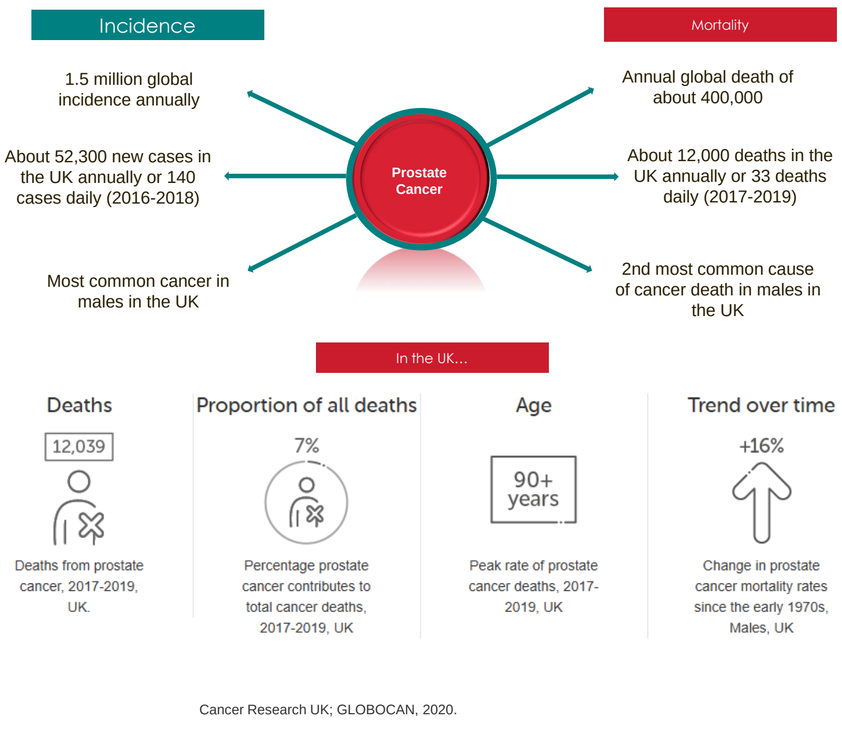
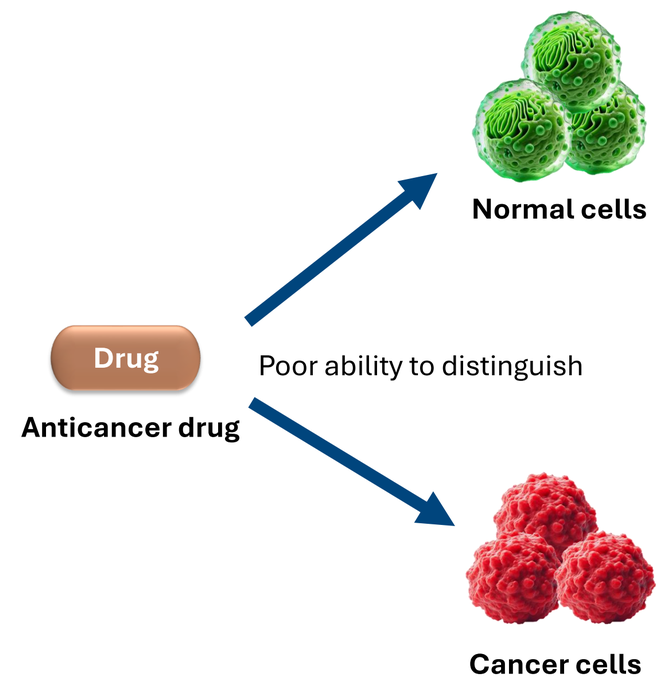
The Problem

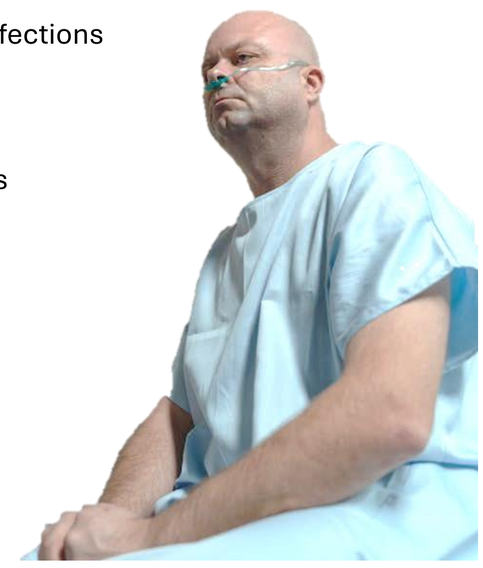


Cancer Research UK; GLOBOCAN, 2020.

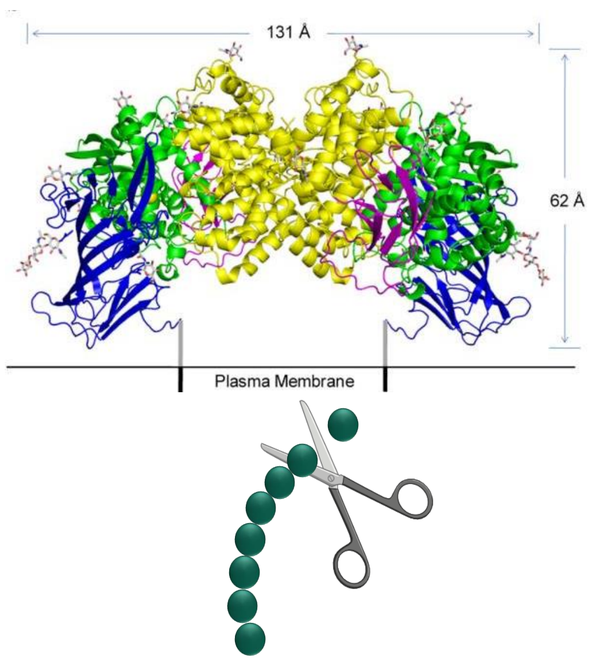


***Common toxicities**

- Loss of immunity and infections
- Hair loss
- Weakness and tiredness
- Sore skin
- Problems passing urine
- Loose or watery stool
- Erectile dysfunction
- Death

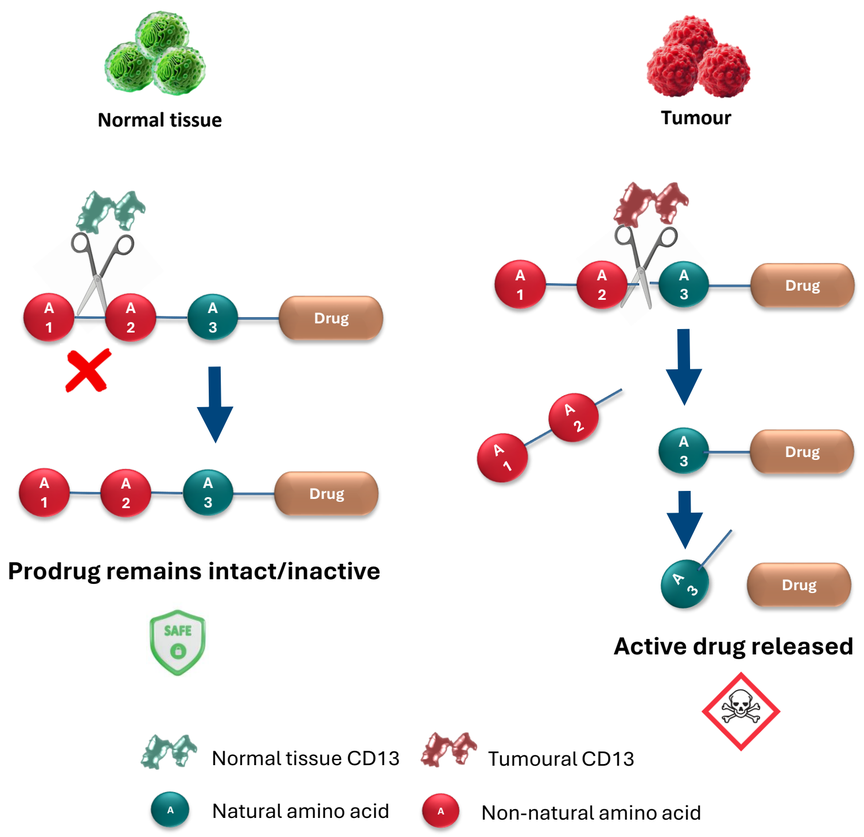


Our Approach

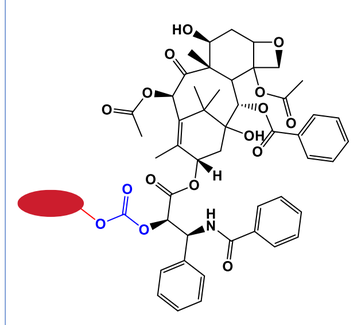


CD13 is an enzyme that has preference for cleaving neutral amino acids from the *N*-terminal of peptides and short proteins

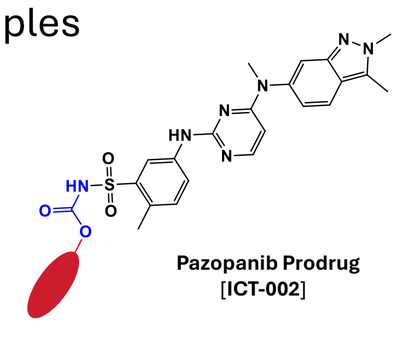
Barnieh *et al*. BBA, (2021)



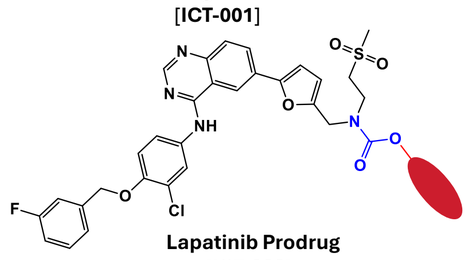
Examples



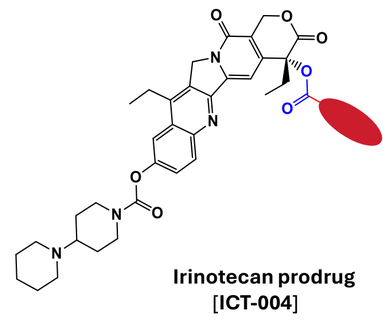
Paclitaxel Prodrug [ICT-001]



Pazopanib Prodrug [ICT-002]



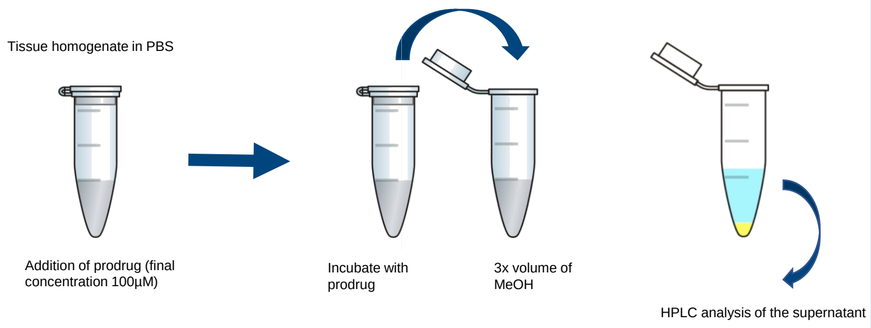
Lapatinib Prodrug [ICT-003]



Irinotecan prodrug [ICT-004]

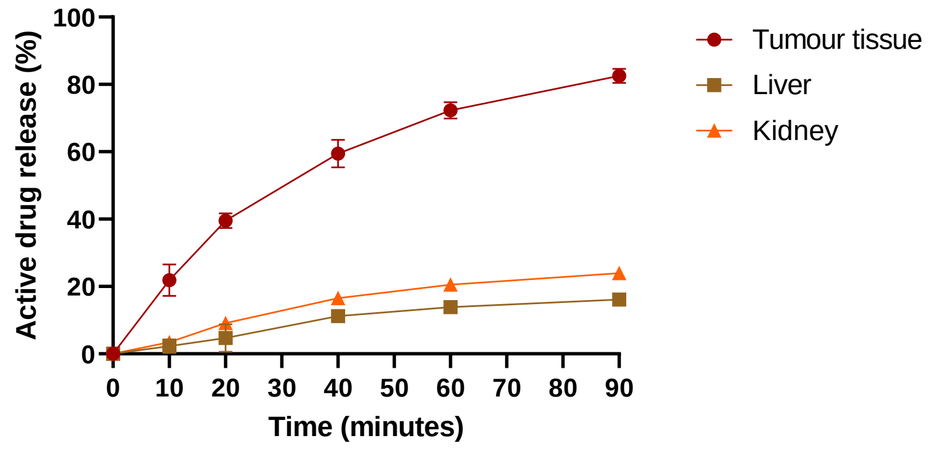
= (tumoral CD13 targeting peptide)

Our Findings



Future directions

1. Synthesis of more prodrugs to complete a mini-library
2. *Ex vivo* evaluation of the metabolism in tumour and normal tissue for determination of selectivity
3. MTT assay to evaluate effect of synthesised compounds on prostate cancer cells *vs* normal cells
4. Evaluation of drug activity in clinical prostate cancer tissues
5. *In vivo* testing of the lead PDC for determination of anticancer activity and PK profile



Release profile of active drug from its prodrug (DC). A faster release of the active drug is observed in the tumour xenograft, where half of the total active drug ($t_{1/2}$) was released within 30 minutes.

In the liver, the rate of release is observed to be much slower with a $t_{1/2}$ of 341 minutes, while in the kidney a $t_{1/2}$ of 229 minutes was observed. When compared to release in normal tissues, the prodrug showed a significant differential of 11.3 and 7.6 in liver and kidney respectively.

Summary and Conclusion

A small library of CD13-targeted prodrugs have been synthesised, purified, and characterised. The release profile of the active drug has been carried out, and shows that release of active drug proceeds 11-folds faster in tumour xenograft compared to what is observed in liver and kidney tissue xenografts

References

1. Ferlay J, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. 2024. [Last Accessed; October 4].

2. Barnieh F., Loadman P. & Falconer R. Is tumor-expressed aminopeptidase N (APN/CD13) structurally and functionally unique? BBA 1876, (2021).