Targeted Starch Nanoparticles for Cancer Therapy

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WATERLOO ENGINEERING

Ontario Centres of Excellence

ECOSYNTHETIX® SUSTAINABLE POLYMERS FOR PLANET EARTH™

Objective

To optimize the design parameters of a starch nanoparticle based targeted drug delivery platform for cancer therapy

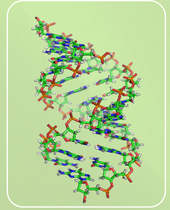
Introduction

Cancer will affect 40% of Canadians at some point in their lifetime (www.cancer.ca). Standard chemotherapy treatment of cancer uses anti-mitotic drugs such as docetaxel or doxorubicin which kill cells when they are dividing. This focuses the treatment effects to rapidly-dividing cancer cells; however other cells such as those in hair follicles and the gastrointestinal tract also replicate frequently and are thus attacked by a systemically-dosed drug. Often the administration of chemotherapy is stopped or never started because the risk of taking chemotherapy is considered greater than the potential benefit. Thus there is a need to reduce the dose of chemotherapy drugs without reducing the therapeutic benefit.

In partnership with EcoSynthetix Inc., we have modified their starch nanoparticles into a new targeted drug delivery vehicle we call an "Aptamer Bioconjugate Drug Delivery Device". These nanoparticles use a single-stranded DNA aptamer, code-named AS1411, as an active targeting system for many different cancer types. They also help reduce the dose of the drug while maintaining its therapeutic effect.

Carrier (EcoSphere® Starch Nanoparticles)

- Bio-based - no toxicity, biodegradable
- Cross-linked mesh allows encapsulation of drug and controlled release
- Uniform small particle size evades clearance and increases cell uptake



Targeting Molecule (DNA Aptamer AS 1411)

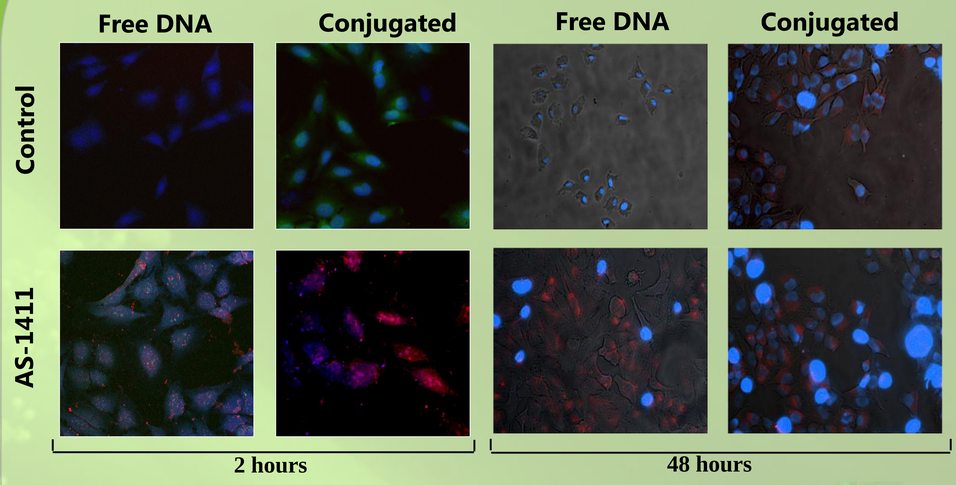
- Binds to Nucleolin receptor, a target in many different cancer types
- Poor *in vivo* lifetime if un-conjugated, while conjugated very stable

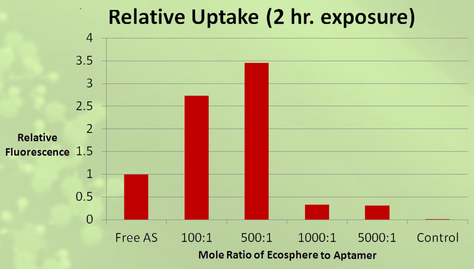
Anti-Cancer Drug (Doxorubicin/Adriamycin)

Currently used in practice - effective at killing cancer cells

Results

Device Uptake (HeLa)

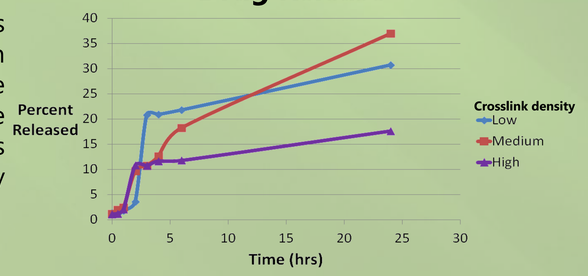




The relative uptake plot indicates that the ratio of 500 glucose units to 1 aptamer unit is the optimal ratio to maximize targeting efficiency while minimizing wasted aptamer – this meets our secondary requirement.

Drug Release

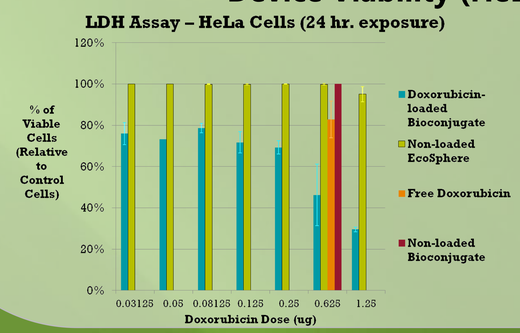
The drug release studies indicate that the medium crosslinked nanoparticle shows the optimal release characteristics and meets one of our tertiary requirements.



Device Properties

	Unmodified EcoSphere	Carboxylated EcoSphere	Aptamer Bioconjugate
Size (nm)	169 ± 15.2	141.2 ± 11.2	156.2 ± 32.4
Zeta Potential (mV)	4 ± 2.3	-25 ± 0.8	-31 ± 1.2

Device Viability (HeLa)



The LDH assay studies the dose vs. response behaviour of our device and shows that it is more effective with a higher dose – this meets our secondary customer requirement.

Fabrication

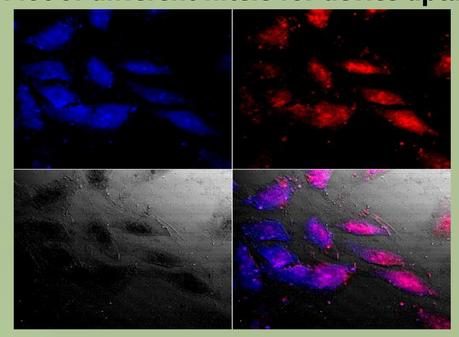
2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO) oxidizes the starch nanoparticles to create carboxyl groups (-COOH) by the process known as TEMPO-mediated carboxylation. NaBr is needed to stabilize this reaction. Hypochlorite (NaClO) initiates the reaction by keeping the pH at 10.2-10.5. HCl lowers pH and reprotonates carboxyl groups.

1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydro chloride (EDC) and N-hydroxysuccinimide (NHS) are used to form carboxyl-amino covalent linkages. We use this mechanism to link the carboxylated starch nanoparticle to the 3'-amine-modified ssDNA aptamer.

Conclusions

- Our device met **all** primary (device uptake) and secondary (viability, relative uptake) customer requirements
- Some tertiary requirements were met (pH dependence and varying crosslink density)
- The design is patent pending

Plot of different filters for device uptake



Acknowledgements

- Professor Juewen Liu and students of Liu Lab
- University of Waterloo Fourth Year Design Fund
- David Donkor
- EcoSynthetix Inc.
- Ontario Centres of Excellence - Connections

References

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