IOWA STATE UNIVERSITY

Materials Science & Engineering

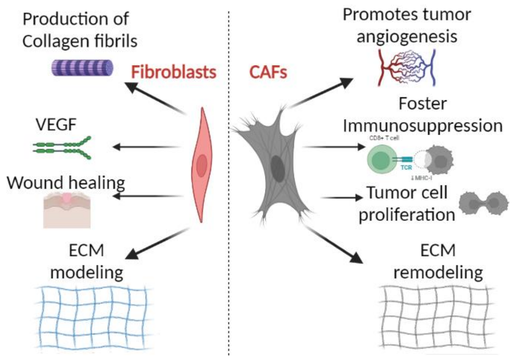
Tanzeel Ur Rehman[1], Dr. Kaitlin M. Bratlie[1,2]

1) Department of Materials Science & Engineering; 2) Department of Chemical & Biological Engineering, Iowa State University, Ames, Iowa 50011

Targeting cancer-associated fibroblasts within a tumor microenvironment via liposomes with arginine-based surface modifiers

Background

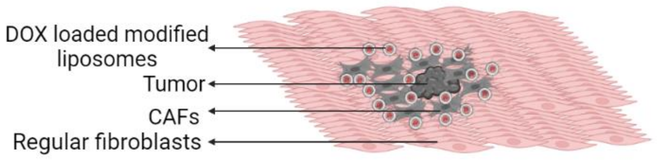
- Fibroblasts and myofibroblasts are activated repair cells that produce and organize extracellular matrix (ECM) and rebuild/recover tissue integrity after injury
- However, in a cancer microenvironment, myofibroblasts can act as cancer-associated fibroblasts (CAFs), enhancing tumor progression and metastasis
- Therefore, there is an urgent need to synthesize a drug delivery vehicle (liposomes) that actively target CAFs, while being more toxic towards CAFs compared to regular fibroblasts



Functions of fibroblasts (left) vs CAFs (right)

Goal

Synthesize DOPE:DOPC liposomes & modify their surface such that the liposomes attack only the CAFs in the tumor microenvironment (TME)

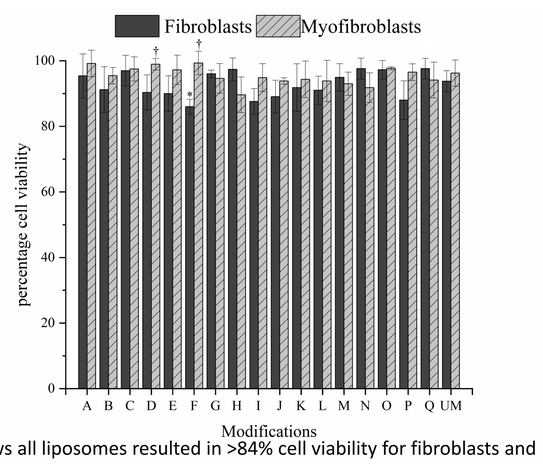


DOX loaded modified liposomes targeting only the CAFs in TME

Results

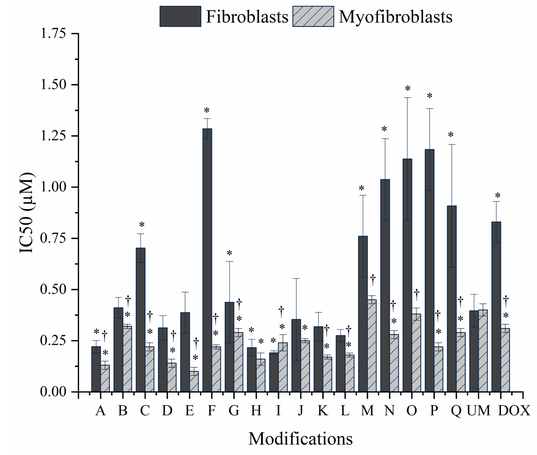
Data are expressed as the means ± standard deviation. (*) indicates $p < 0.05$ for values compared to their respective UM liposome values using pairwise comparison, while (†) indicates $p < 0.05$ for myofibroblast compared to fibroblast for the same modification. UM = unmodified liposomes.

(a)



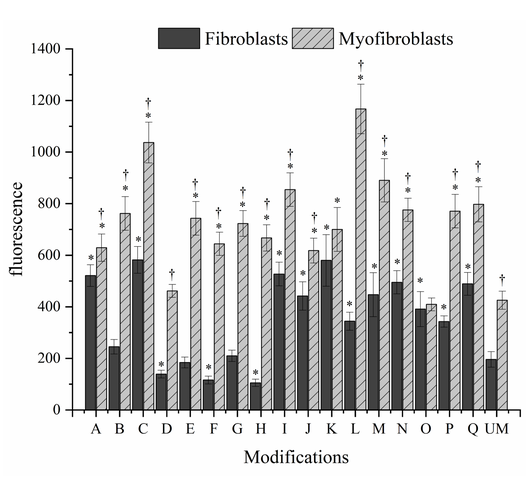
(a) Shows all liposomes resulted in >84% cell viability for fibroblasts and myofibroblasts

(b)



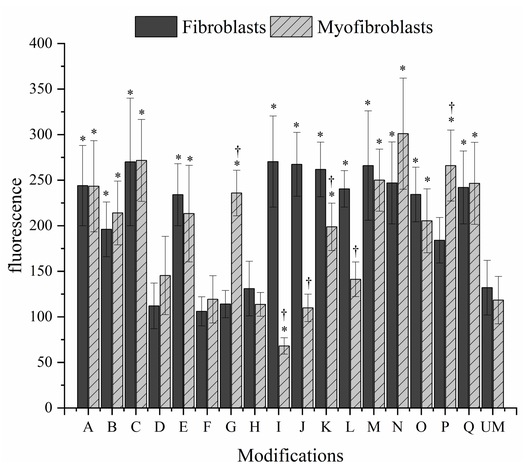
(b) Shows all modified liposomes (except I) resulted in lower IC_{50} values for myofibroblasts compared to fibroblasts

(c)



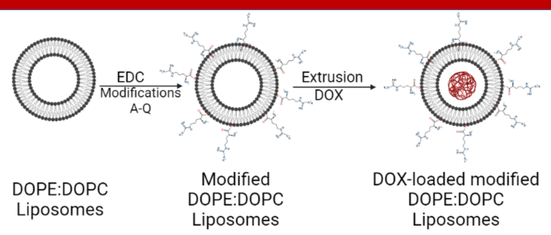
(c) Demonstrates all modified liposomes showed a higher internalization in myofibroblasts compared to fibroblasts at 37 °C

(d)

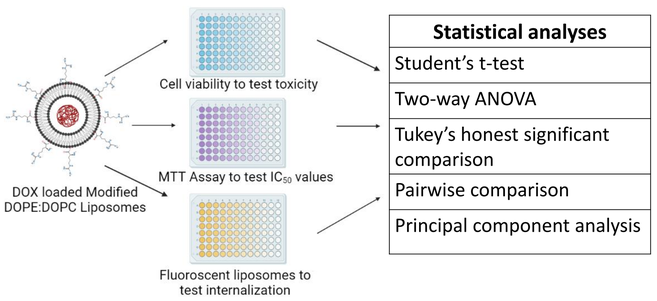


(d) No trend was seen in the internalization of cells when the modification do not play an active role at 4 °C

Materials & Methods

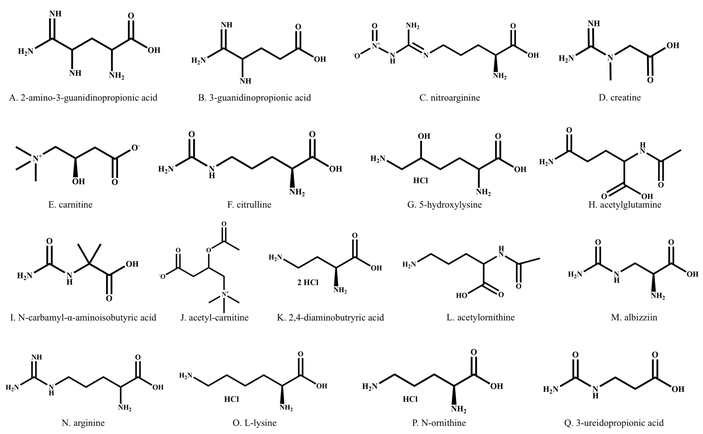


Schematic representing synthesis, modification, and DOX loading of DOPE:DOPC liposomes



Statistical analyses
Student's t-test
Two-way ANOVA
Tukey's honest significant comparison
Pairwise comparison
Principal component analysis

Modified liposomes subjected to different assays



17 different modification used for this study, labeled A-Q

Conclusion and Significance

- DOPE:DOPC liposomes were modified using 17 different arginine-like surface modifiers to enhance the liposomes' targetability to myofibroblasts (CAFs) in TME
- Different trends between internalization of liposomal FC and IC50 values were observed; a more positive correlation was seen between internalization and IC50 values for myofibroblasts
- For myofibroblasts, 15 out of 17 modifications showed significantly lower IC50 values compared to fibroblasts with a significant increase in cell internalization, improving targeted delivery to myofibroblasts in a tumor microenvironment
- This work attests to the significance of investigating the interactions of modified and unmodified liposomes with fibroblasts and myofibroblasts. The finding of this study advocate that liposomes modified with arginine derivations are promising and efficient nanoparticle drug delivery vehicles for myofibroblasts in a tumor microenvironment.