

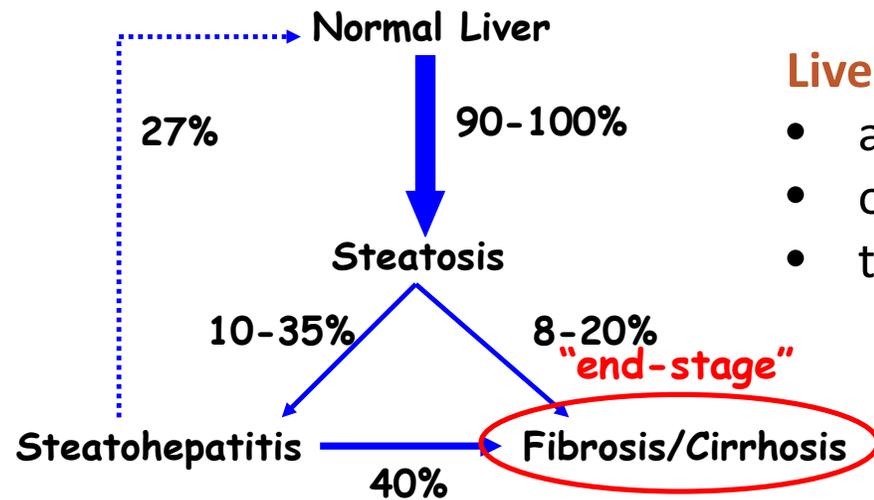
How Alcohol-Induced Changes to Liver ECM Influence Seeding of Liver Metastases

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GRADUATE RESEARCH FELLOW

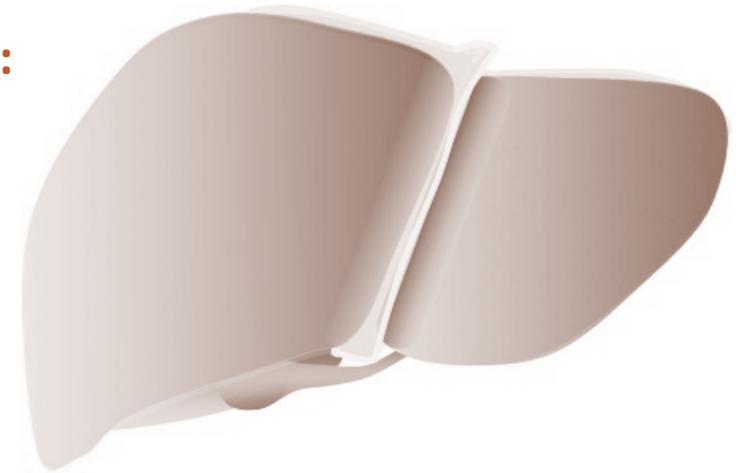
UNIVERSITY OF LOUISVILLE

Hepatic ECM Homeostasis and Liver Disease



Liver disease may be caused by:

- alcohol (ASH)
- obesity (NASH)
- toxic chemicals (TASH)



Fibrosis

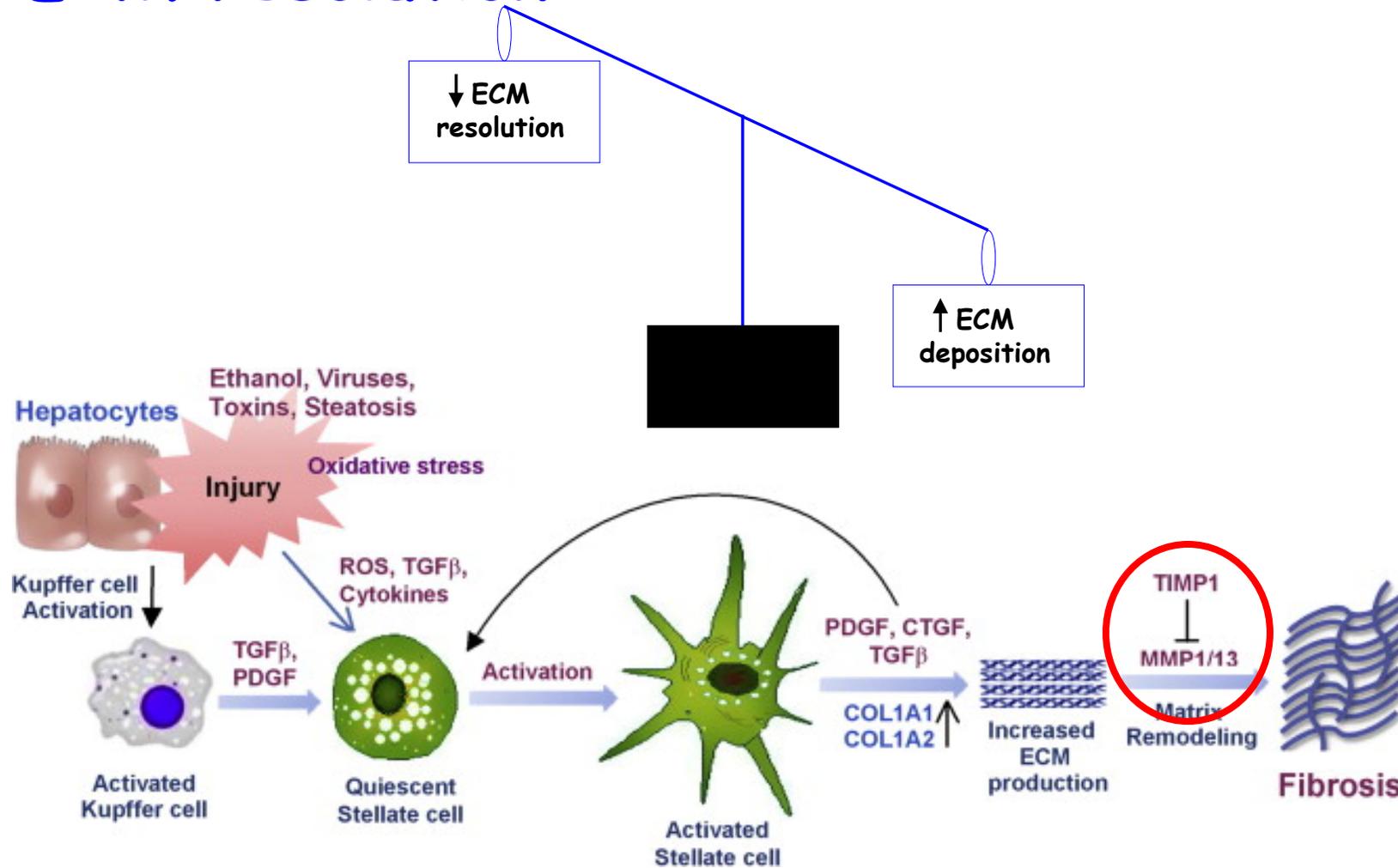
- dramatic remodeling and scarring of liver
- mediated by imbalance between injury and repair
- potentially reversible

Earlier stages

- hepatic ECM responds dynamically to stress
- impact is poorly understood
- may be a more effective target

Increased ECM deposition

Decreased ECM resolution

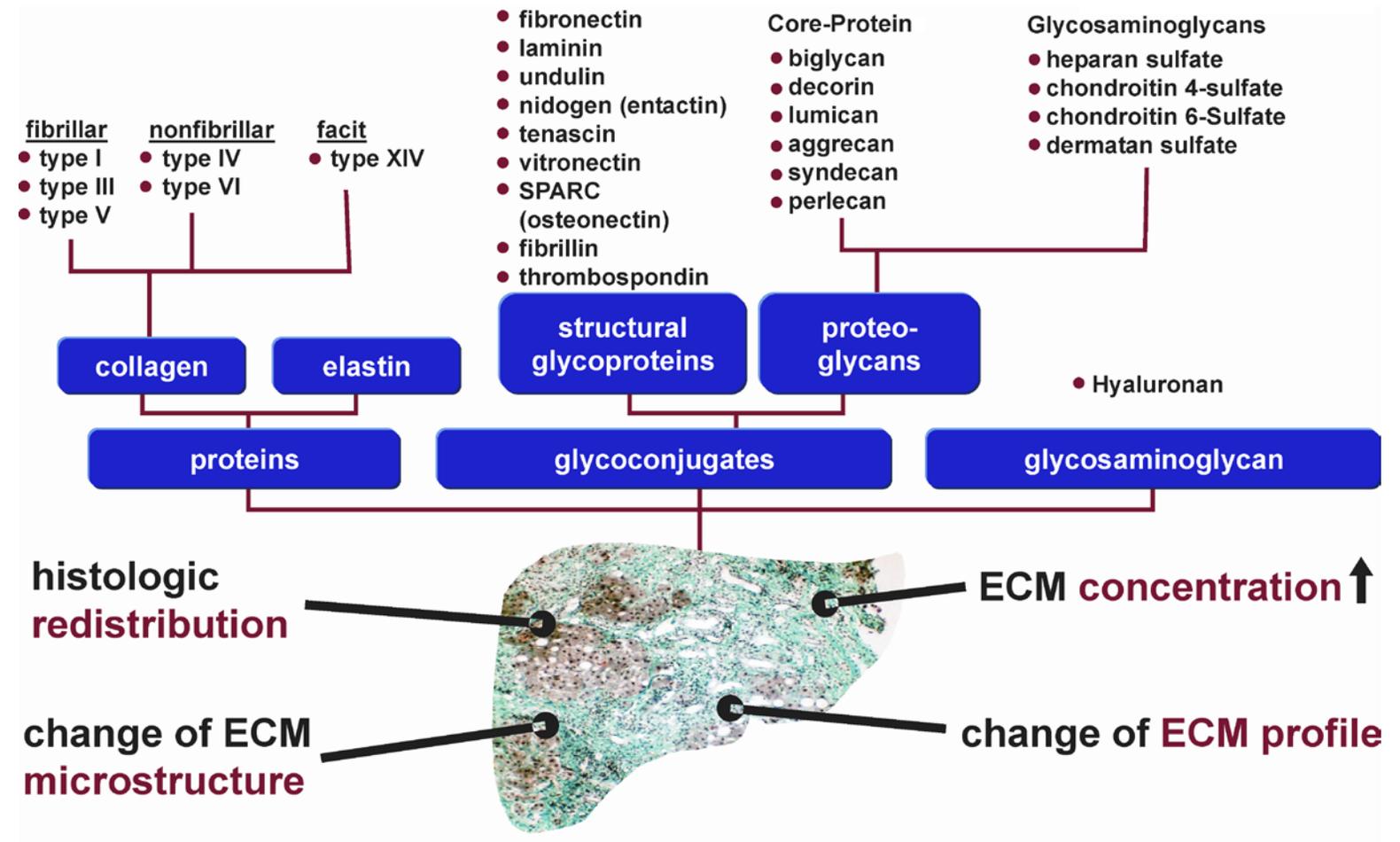


Mormone et al. *Chem Biol Interact* 193:225-31
Ramachandran and Iredale *QJM* 105:813-817

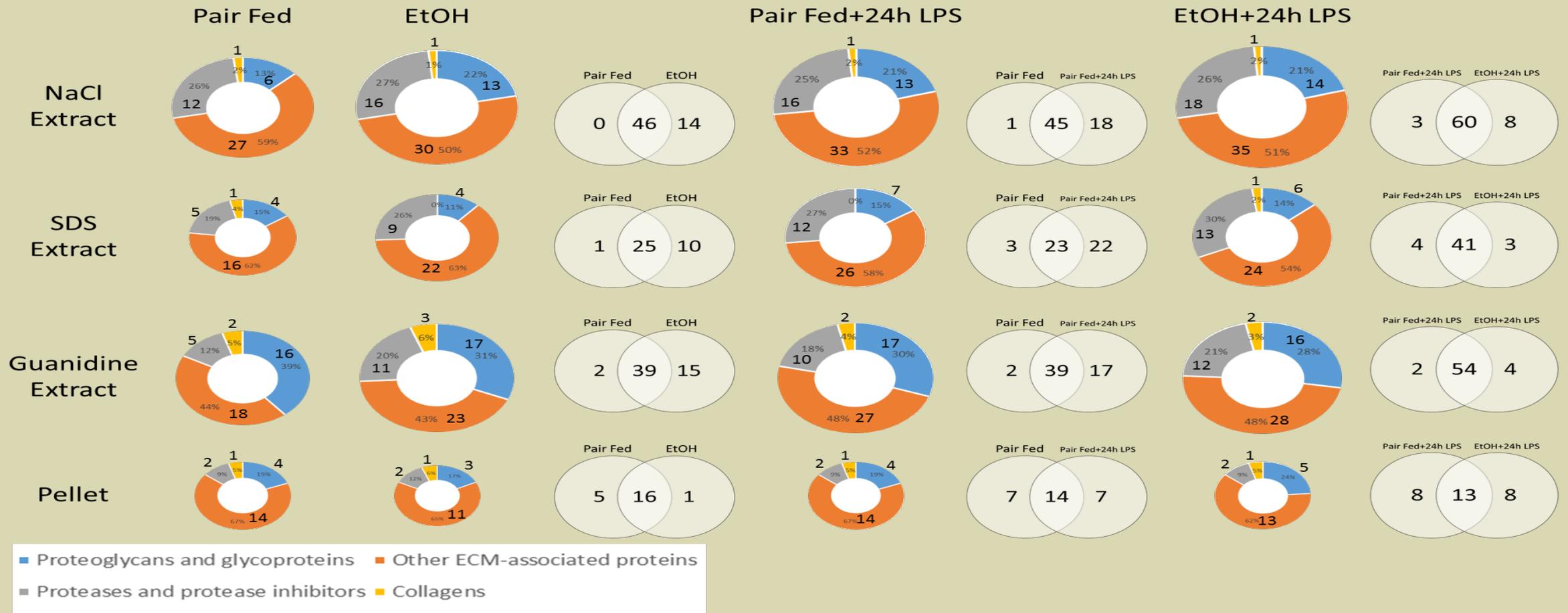


ECM in fibrosis; more than collagen

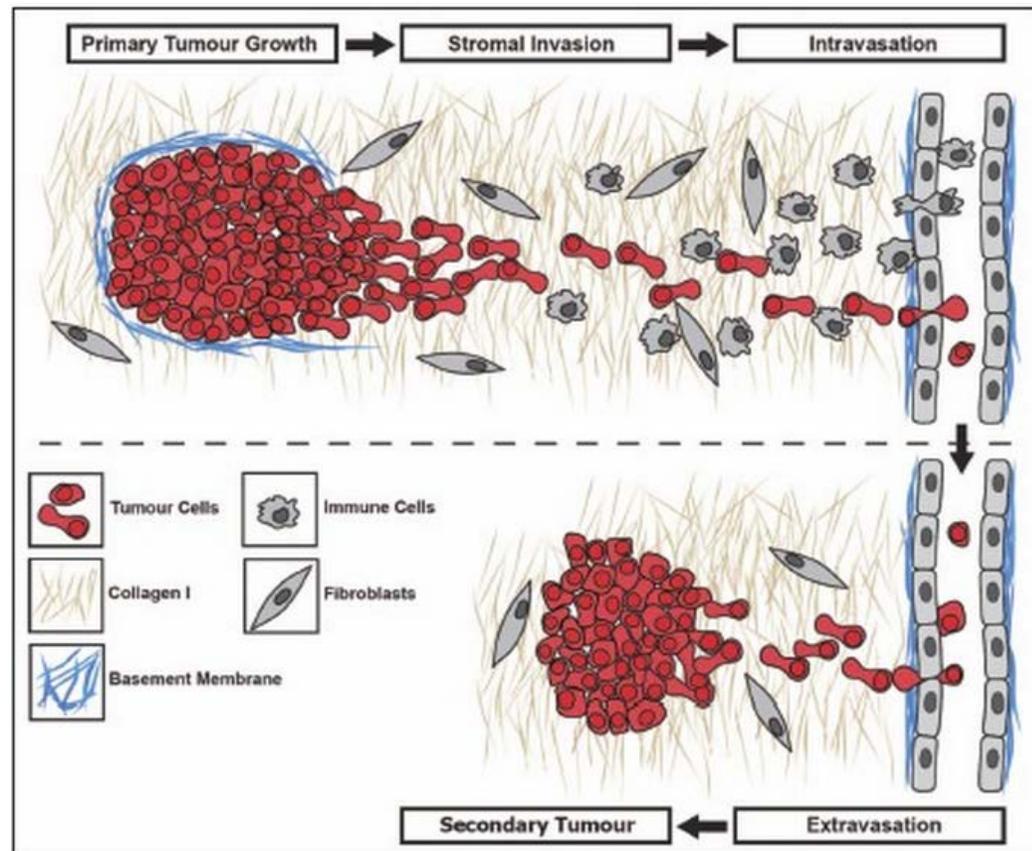
Other matrices contribute to hepatic fibrosis and are upregulated in disease models -e.g., fibronectin, elastin, laminin, and hyalurin



Hepatic ECM Responds Dynamically to Stress



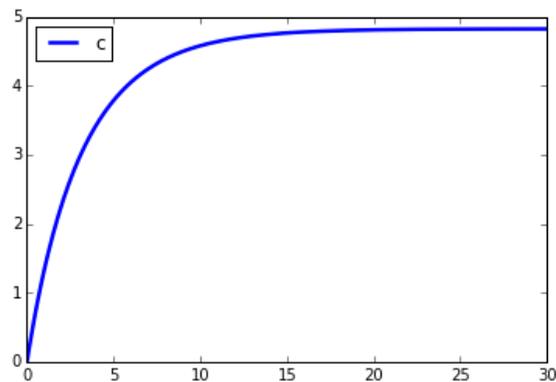
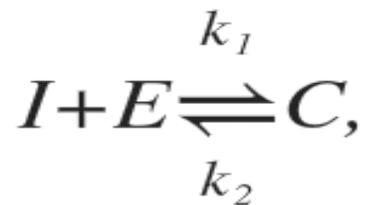
ECM & Integrin Interactions in Cancer



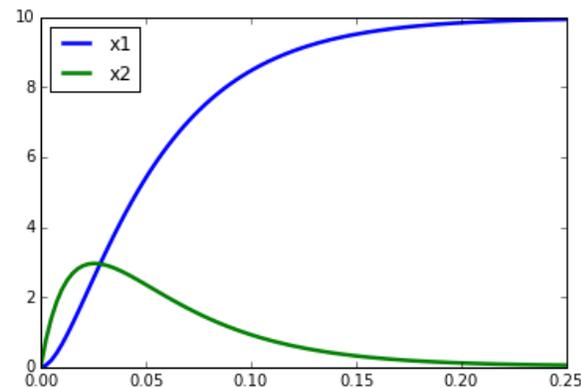
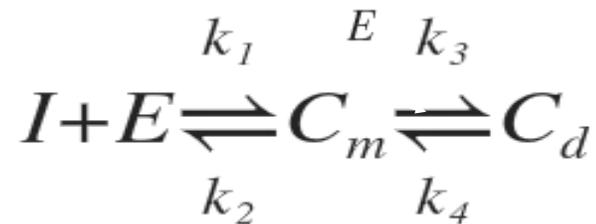
- ❖ 3D architecture of ECM for primary and metastatic lesions has critical influence on tumor cells and their sensitivity to therapeutics
- ❖ ECM modulates changes in adhesion, invasion, proliferation, and migration
- ❖ ECM phenotype in tissues can vary with tumor progression
- ❖ Tumor angiogenesis is important in metastatic cascade for intravasation

Integrin Binding Model

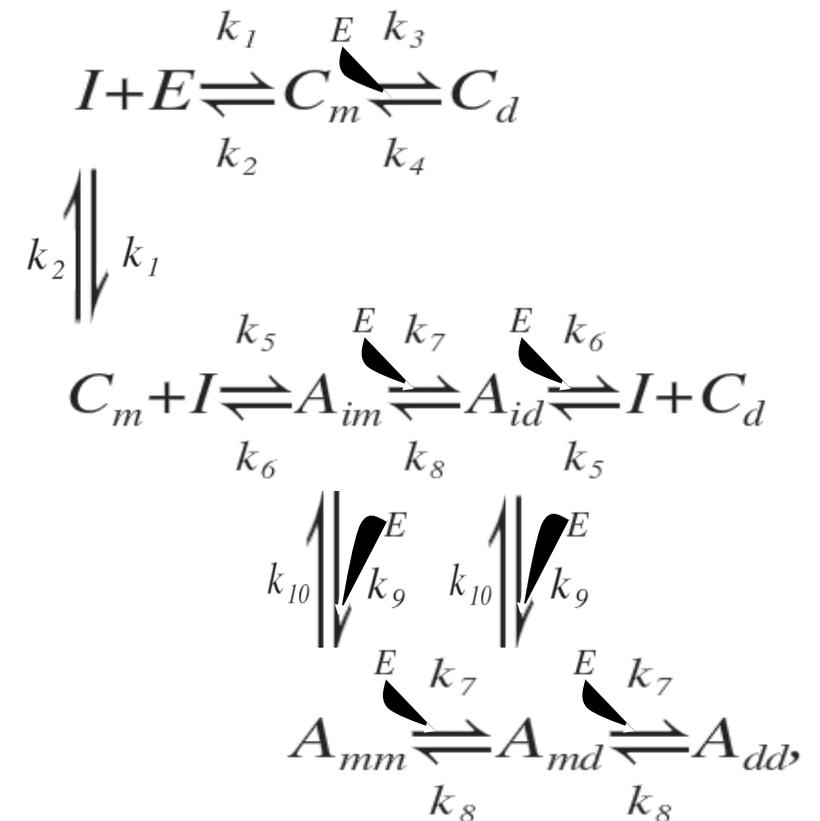
Bimolecular model



Divalent Model

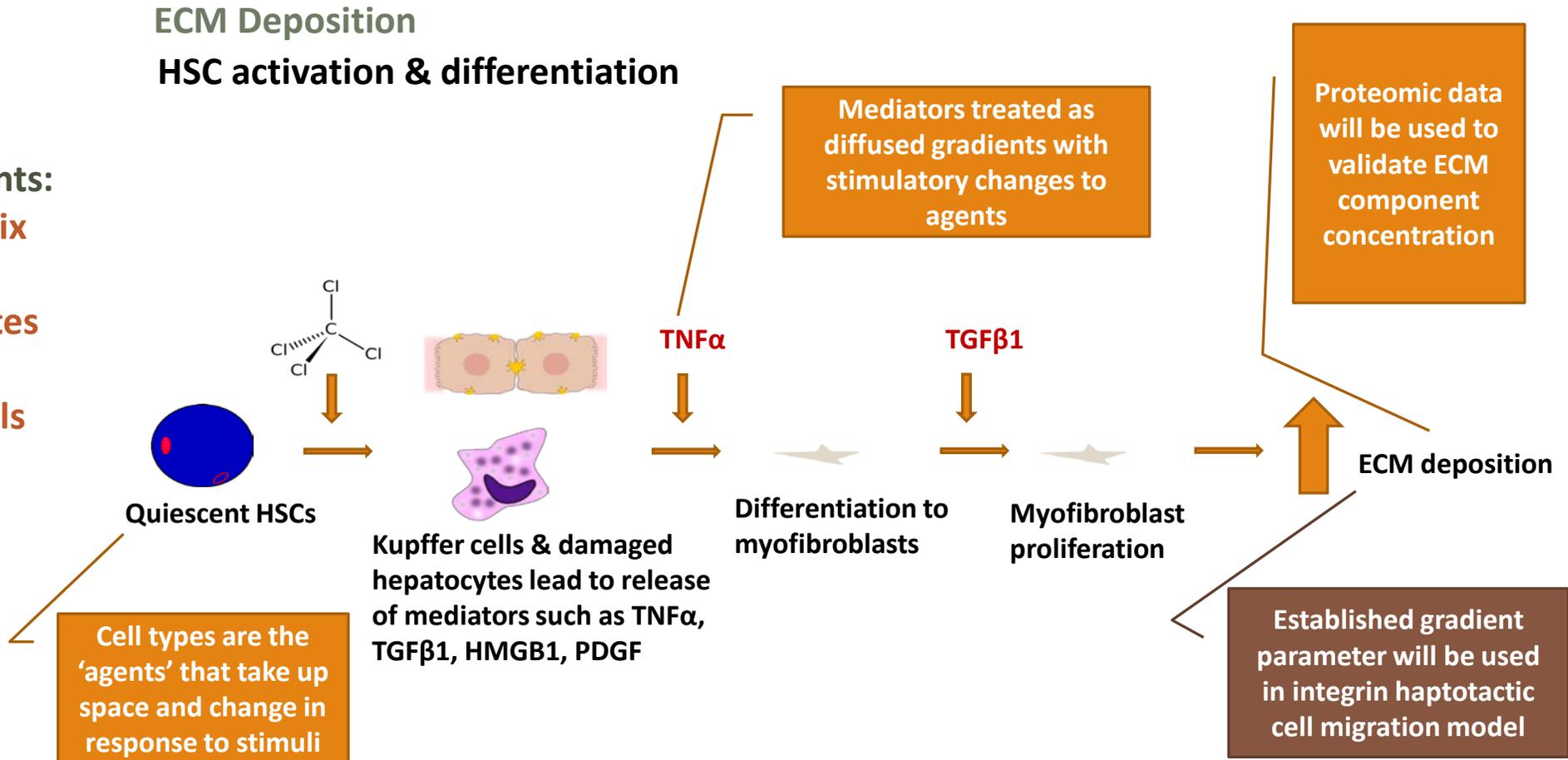


Receptor Aggregation



Agent-Based Model

Components:
ECM Matrix
Sinusoid
Hepatocytes
HSCs
Tumor Cells



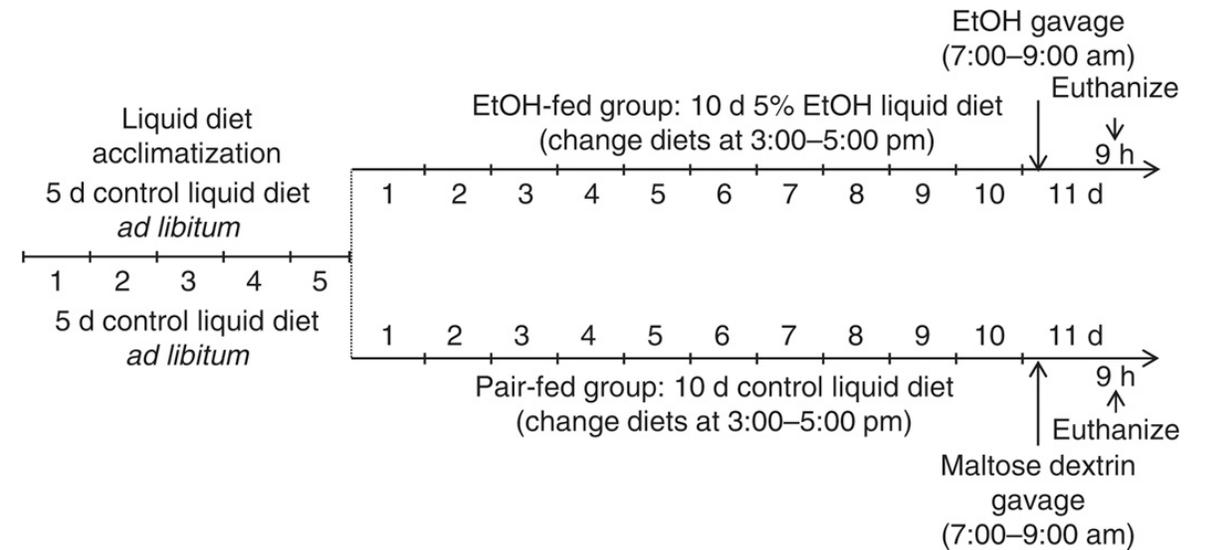
Mouse Model



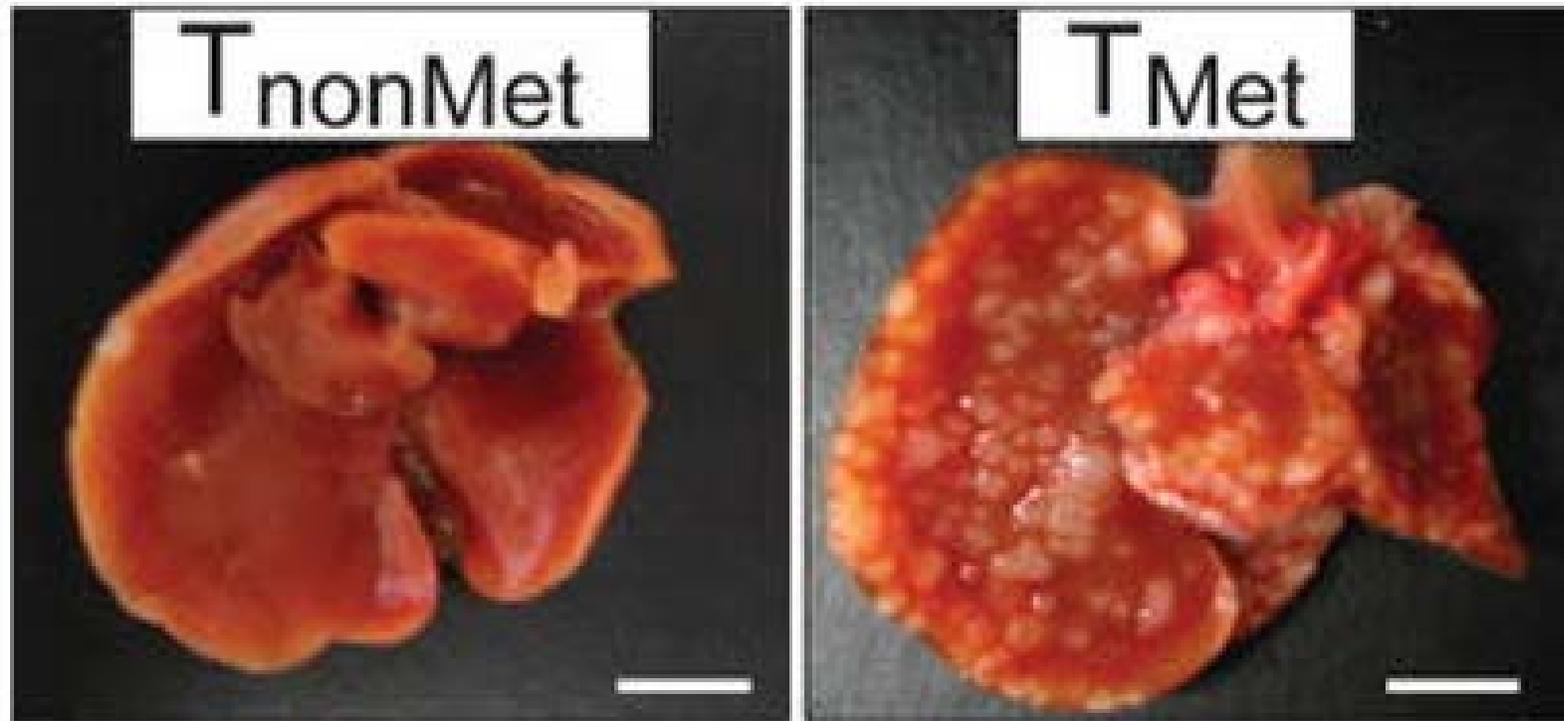
- B6 129 background
- Alcohol feeding followed by allograft transplantation of metastatic or non-metastatic cell lines

Lieber DeCarli diet-induced ASH

- NIAAA acute-on-chronic model
- 6 wk chronic alcohol-fed model

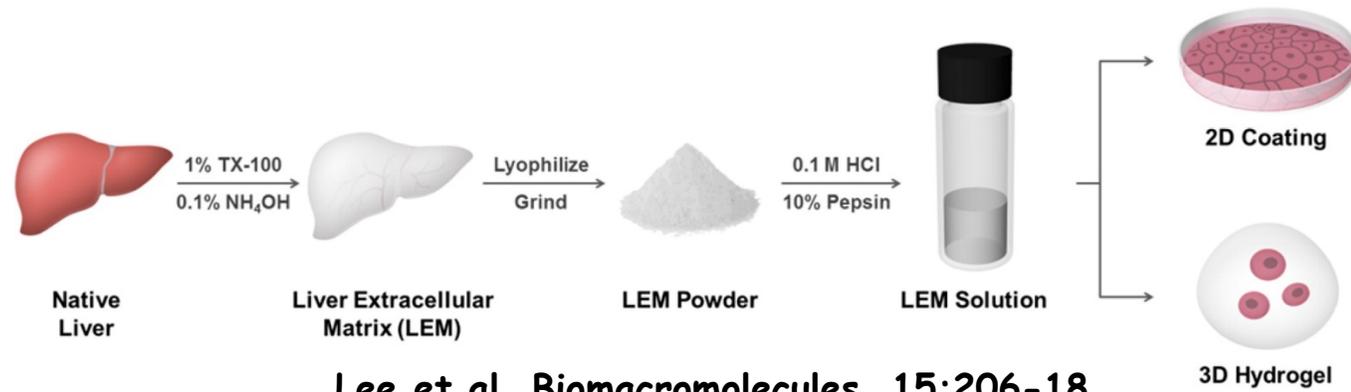


Metastatic Model



**T_{nonMet} & T_{met} :
Equivalent
proliferation rates in
culture;
 T_{Met} has higher
potential for liver
tumor nodule
formation than
 T_{nonMet}**

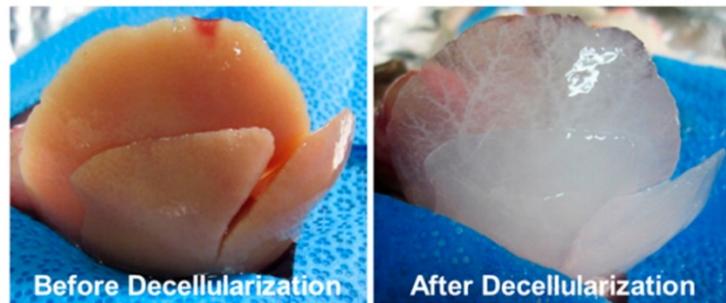
In Vitro ECM Model



Lee et al. *Biomacromolecules*. 15:206-18

3D Hydrogel Model:
Decellularized livers from metastatic models will be utilized to test metastatic cell migration in response to various stimuli

- Functionalize with integrin binding motifs (RGD peptides)
- Other chemotactic factors



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