

Dynamic measurement of physiologic functions. *Any role in NASH diagnostics?*

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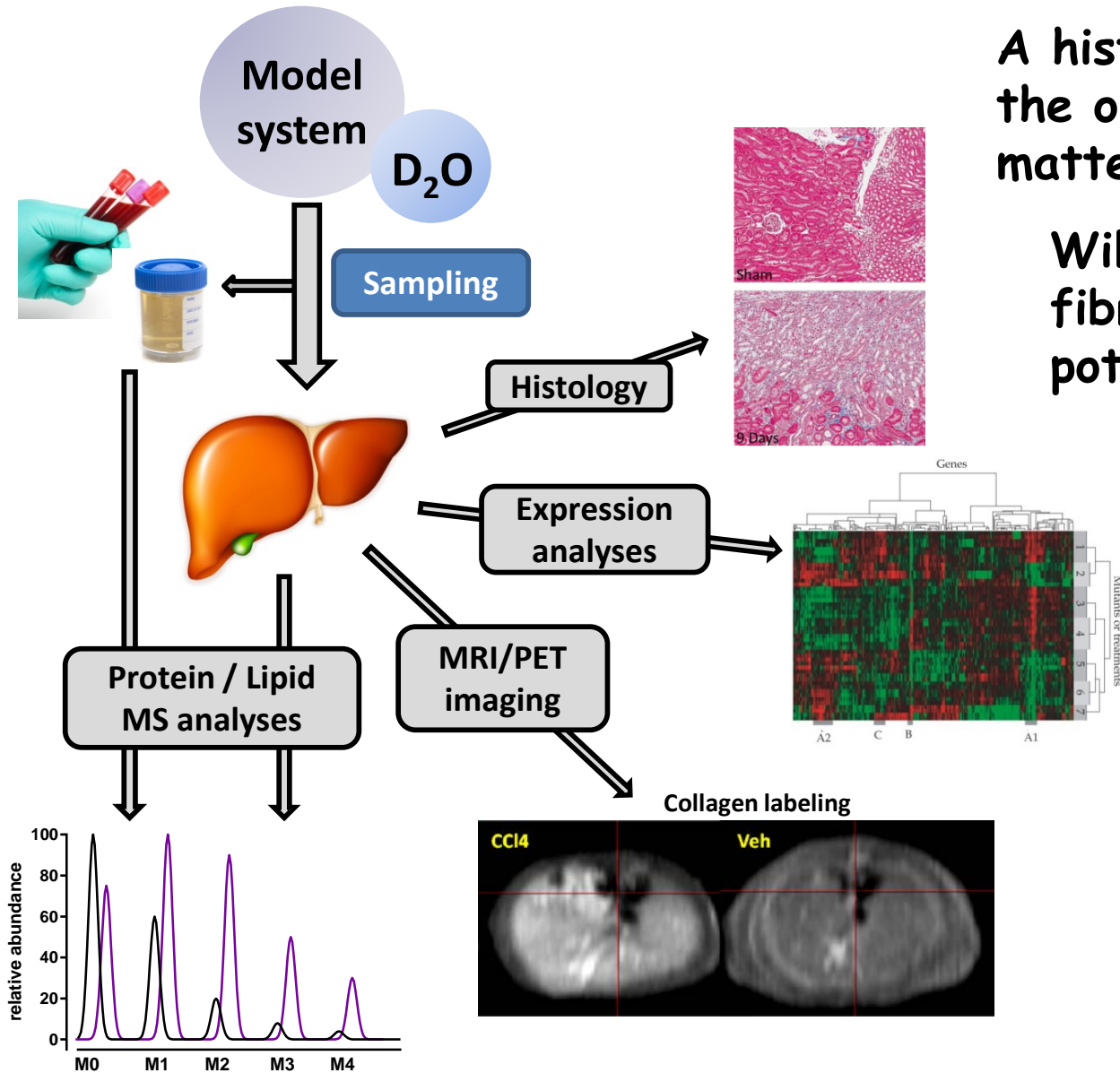
**CardioMetabolic Disease
Merck & Co
Kenilworth, NJ, USA**

**Human data generously shared by
Drs Arthur J McCullough and Takhar Kasumov
Cleveland Clinic Foundation**

**International Workshop on NASH Biomarkers
Washington DC, USA
April 29-30, 2016**

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Measures of ECM kinetics and metabolic impairments.



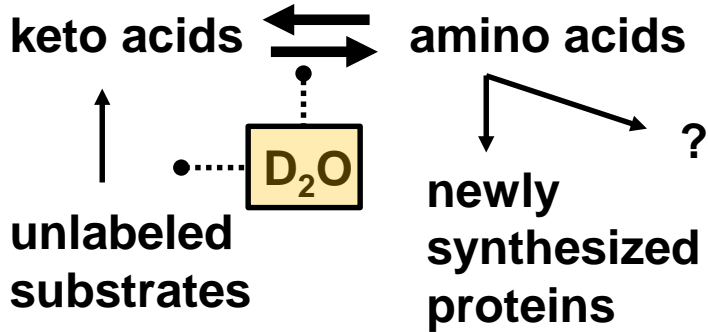
A histological readout is the only thing that really matters.

Will a marker of fibrogenesis (fibrogenic potential) be useful?

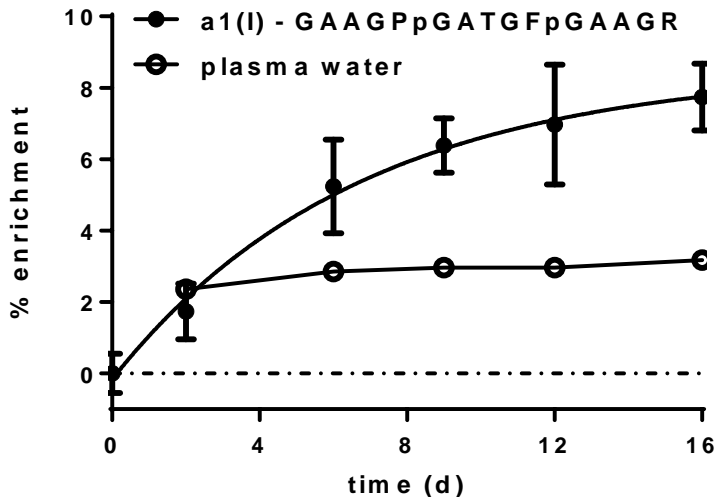
Using tracers to quantify protein flux.

1. How it works.

AJP Endo Metab 286: E665 (2004)

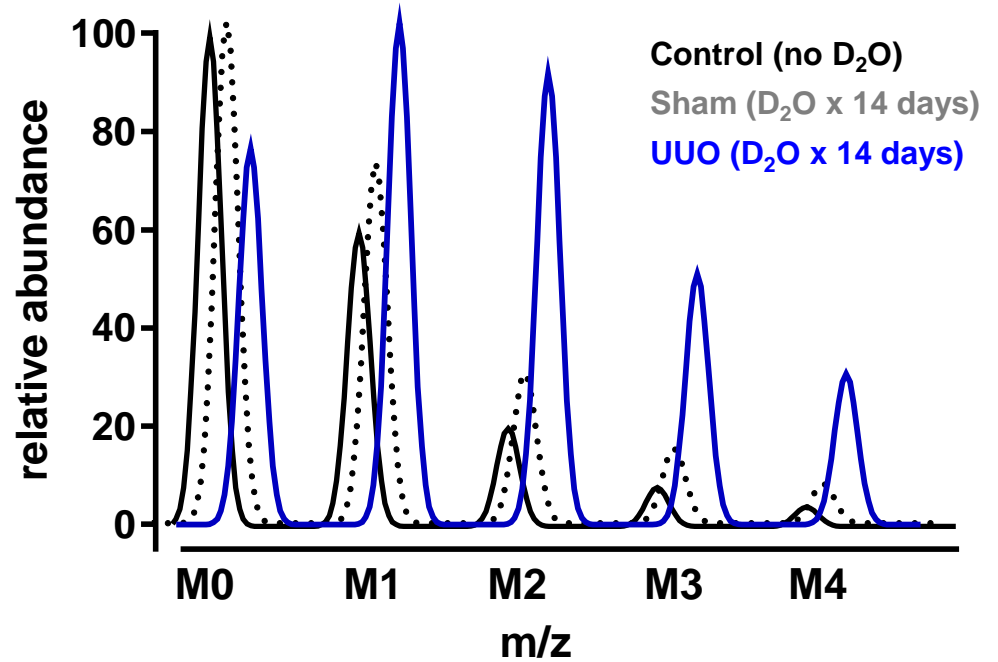


3. What the data might look like.



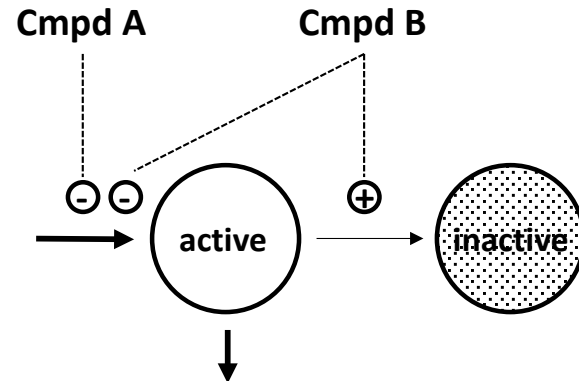
2. What we look for in the data.

Mol Cell Prot 12: 2653 (2009)

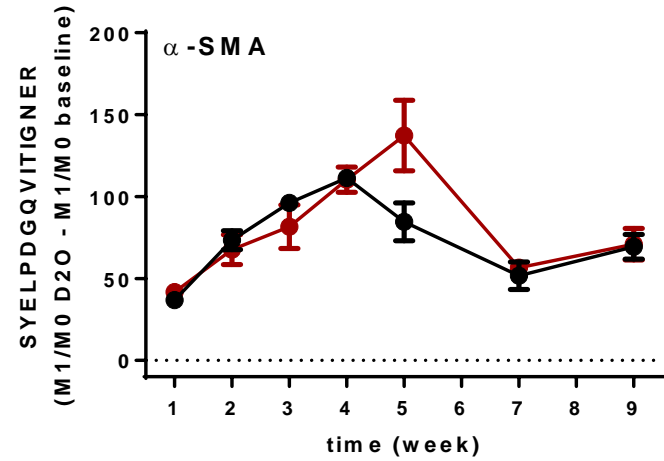
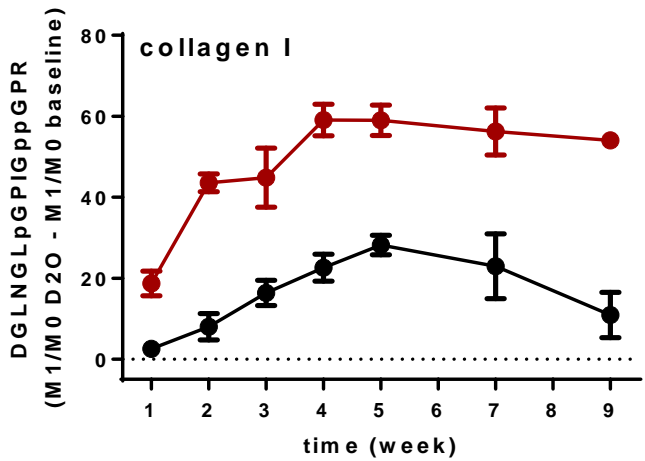
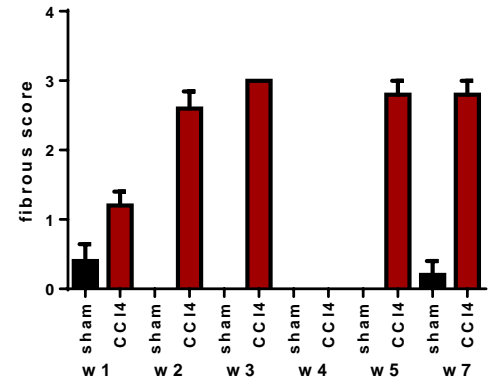
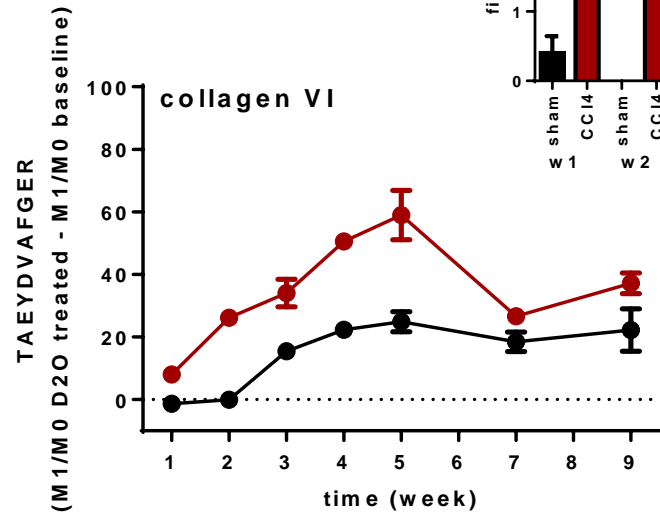
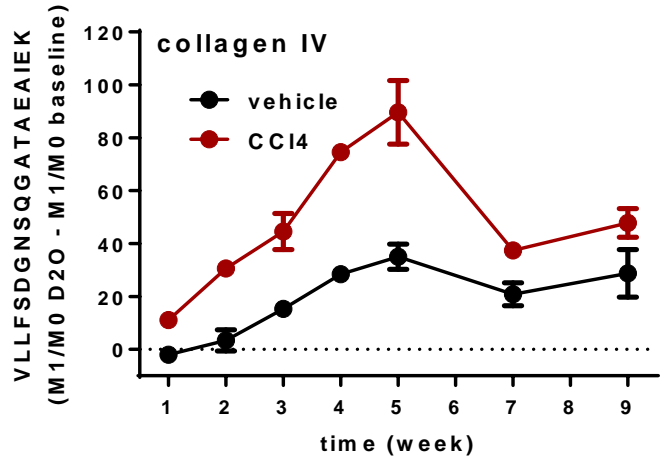


4. Potential issue(s) with modeling.

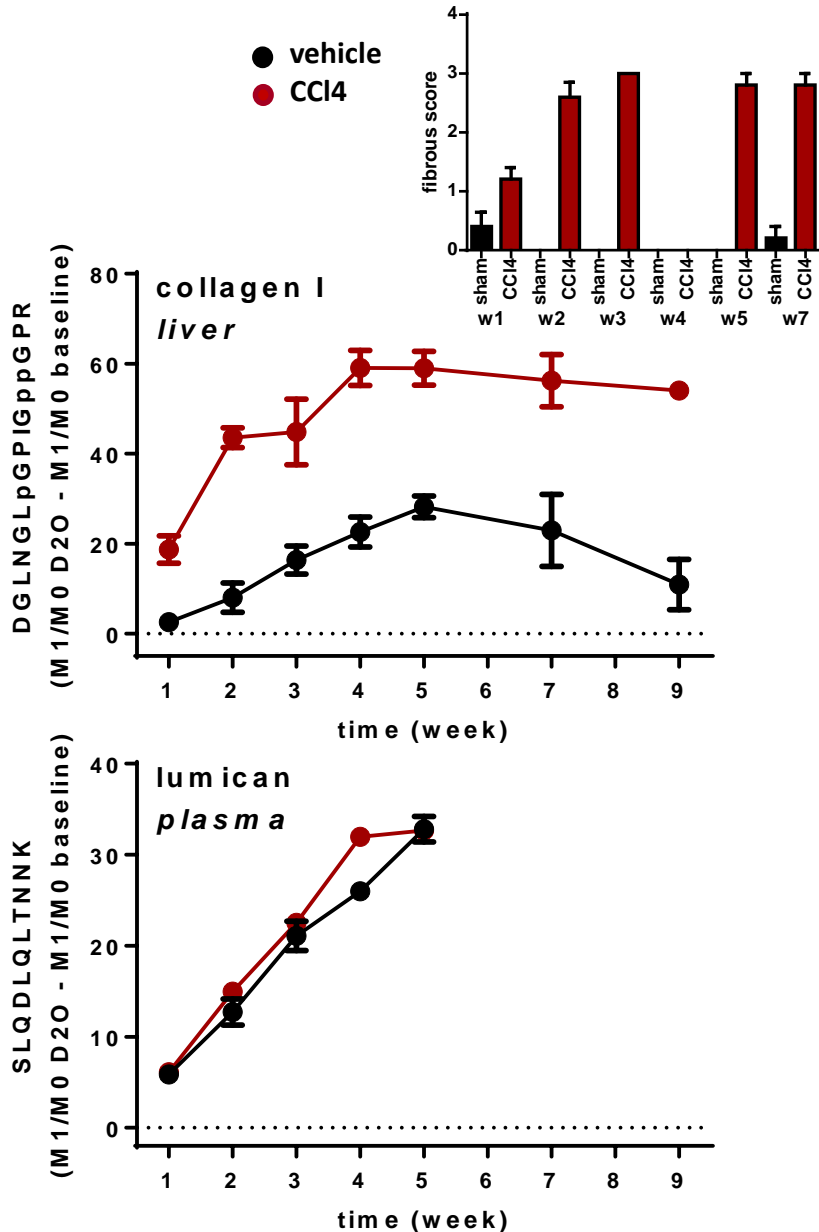
AJP Endo Metab. 309: E115 (2015)



Tissue-based measures of ECM kinetics in CCl₄-treated mice.



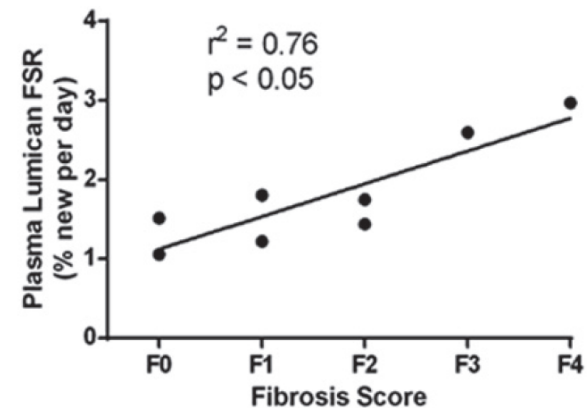
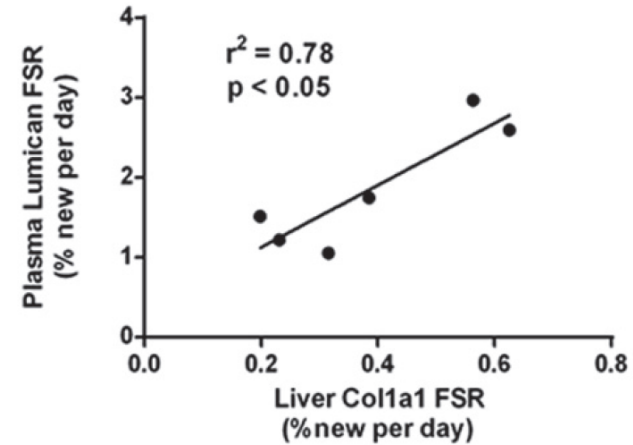
What about looking for soluble / kinetic markers in vivo?



Turnover Rates of Hepatic Collagen and Circulating Collagen-Associated Proteins in Humans with Chronic Liver Disease

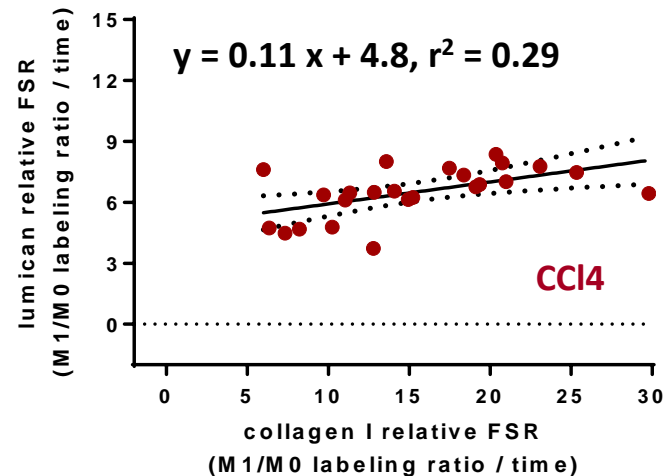
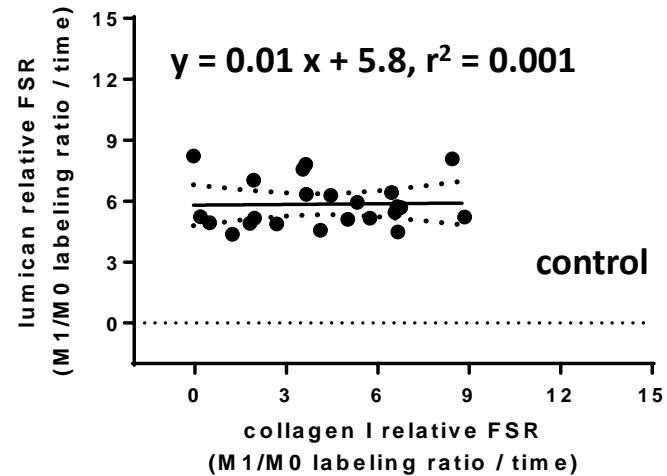
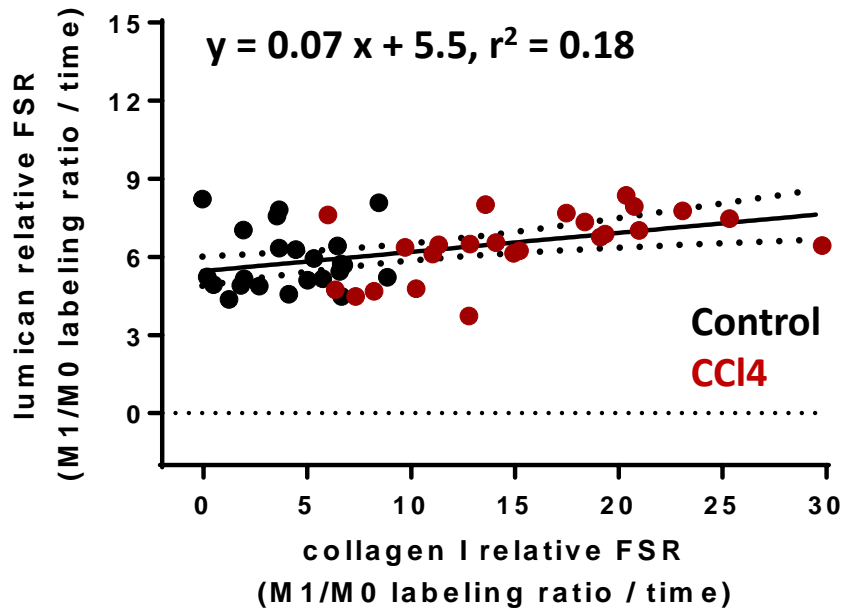
Martin L. Decaris¹*, Claire L. Emson¹*, Kelvin Li¹, Michelle Gatmaitan¹, Flora Luo¹, Jerome Cattin¹, Corelle Nakamura¹, William E. Holmes¹, Thomas E. Angel¹, Marion G. Peters³, Scott M. Turner¹*, Marc K. Hellerstein^{1,2}

In human HCV plasma lumican kinetics reflects liver collagen kinetics and fibrosis.
ML Decaris et al, PLoS One 2015



Evaluation of plasma lumican FSR in CCl₄ model.

Disconnect but ... humans vs rodents, viral vs chemical, modeling issues?



Could we look at proteins besides lumican?

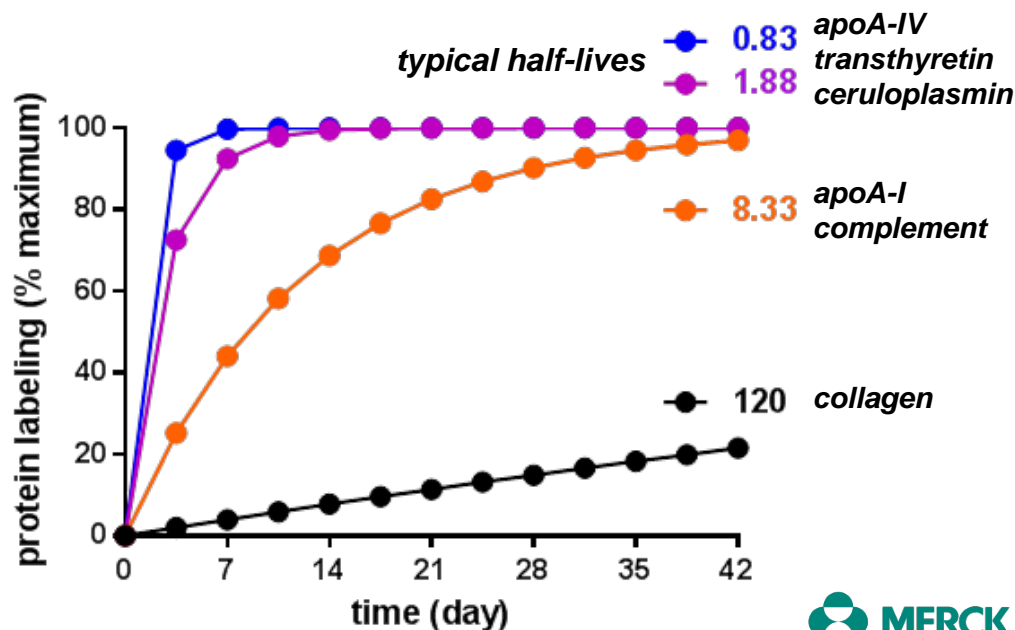
RESEARCH ARTICLE

Turnover Rates of Hepatic Collagen and Circulating Collagen-Associated Proteins in Humans with Chronic Liver Disease

Martin L. Decaris¹*, Claire L. Emson¹*, Kelvin Li¹, Michelle Gatmaitan¹, Flora Luo¹, Jerome Cattin¹, Corelle Nakamura¹, William E. Holmes¹, Thomas E. Angel¹, Marion G. Peters³, Scott M. Turner^{1*}, Marc K. Hellerstein^{1,2}

| Subject ID # | 003 | 004 | 005 | 007 | 008 | 009 | 010 | 011 |
|---|----------|----------|-----|-----|----------|---------|-----|-----|
| Diagnosis | HCV, HIV | HCV, HIV | AIH | HCV | HCV, HIV | HCV,OLT | HCV | HCV |
| Age at biopsy | 44 | 63 | 43 | 59 | 39 | 45 | 67 | 59 |
| Sex | M | M | M | M | M | M | F | M |
| D ₂ O Labeling Duration (days) | 33 | 22 | 20 | 56 | 47 | 22 | 29 | 21 |
| Liver biopsy* Fibrosis Score | 3 | 0 | 2 | 1 | 2 | 4 | 1 | 0 |
| Liver biopsy* Inflammation Score | 3 | 0 | 1 | 1 | 2 | 2 | 2 | 2 |
| Proteomic Tissue Analysis | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| Proteomic Plasma Analysis | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

“The primary objective of our study was to measure tissue collagen synthesis, a process that we presumed to be slow and in fact demonstrate here is slow (half-lives of 4 months to a year). As such, our study design was not optimized for the analysis of faster turnover proteins, including the majority of the more abundant plasma proteins,…”



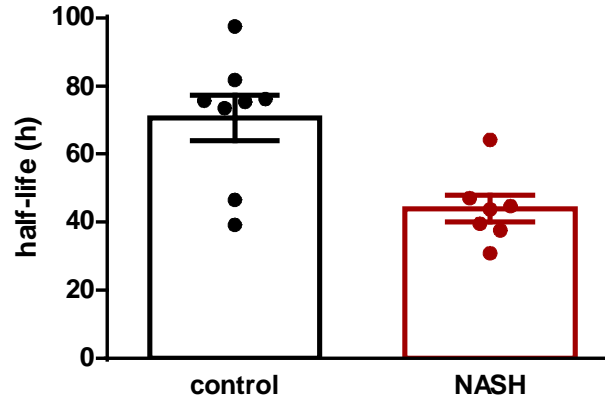
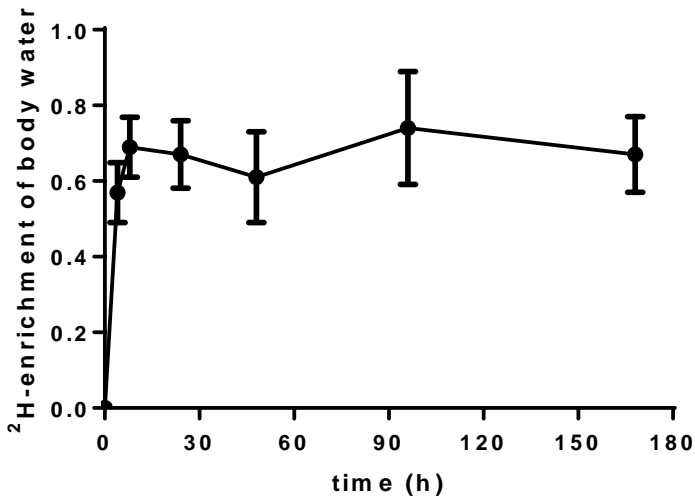
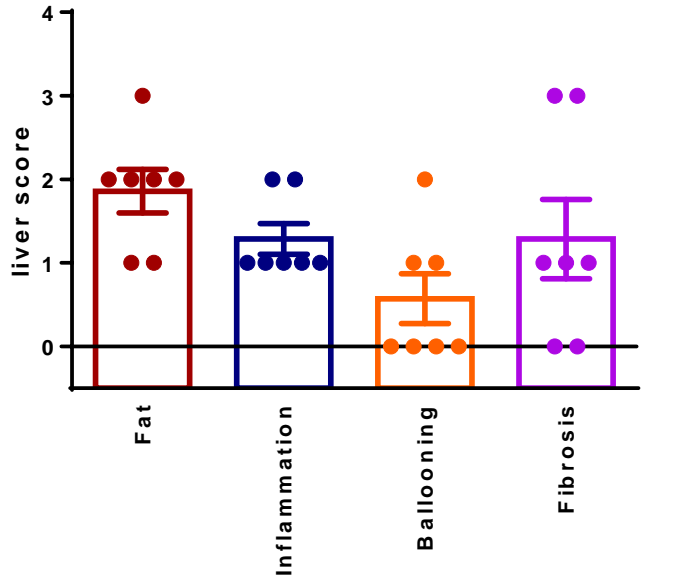
Integrative Proteomics, InTech Publishers, 2012.

Clinical translation.

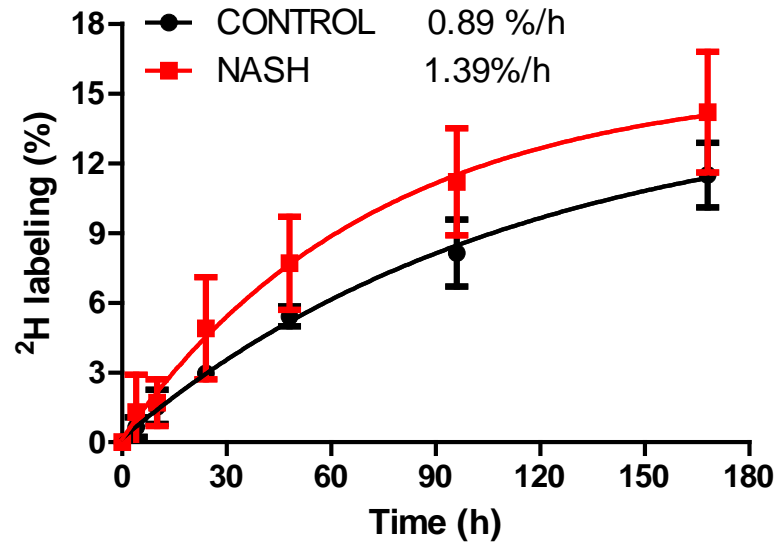
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The next data are not from Merck and do not reflect any ongoing collaboration. Data were generously donated because of a long standing interaction between Dr Previs and colleagues in Cleveland.

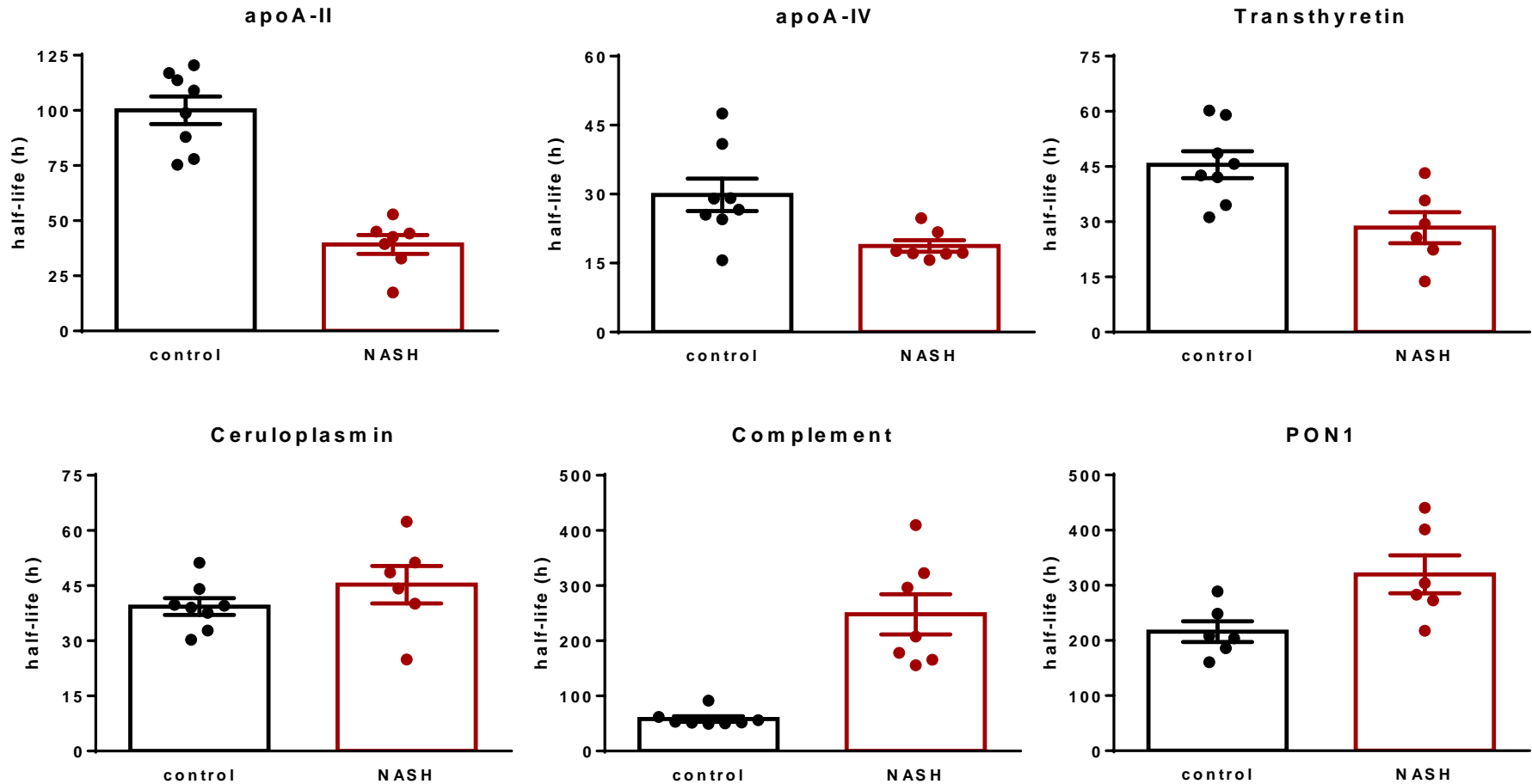
Clinical translation.



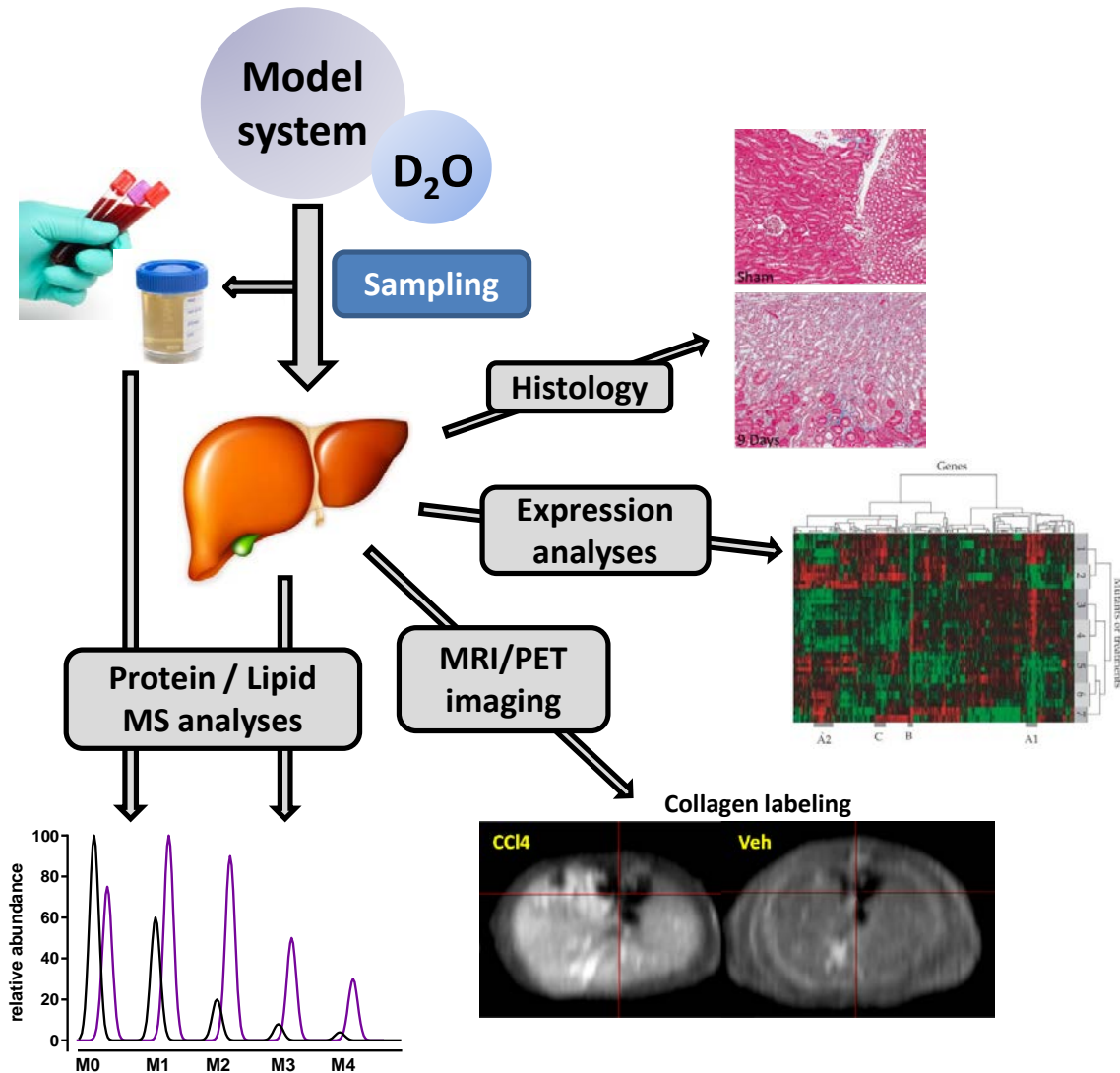
ApoA1 turnover



Clinical translation.



Summary and take home messages.



1. Merck is taking a comprehensive / collaborative approach to biomarker issues surrounding liver disease.

2. Stable tracers may yield novel insight regarding human biology.

Methods discussed herein allow translational studies, including studies in free-living subjects.

3. Colleagues from Cleveland Clinic have a novel set of samples and have started to examine some differences between control and NASH subjects.