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Drug Development in NASH Cirrhosis

Discovery On Target: Targeting NASH—Boston, MA

September 17, 2019

Boston, MA
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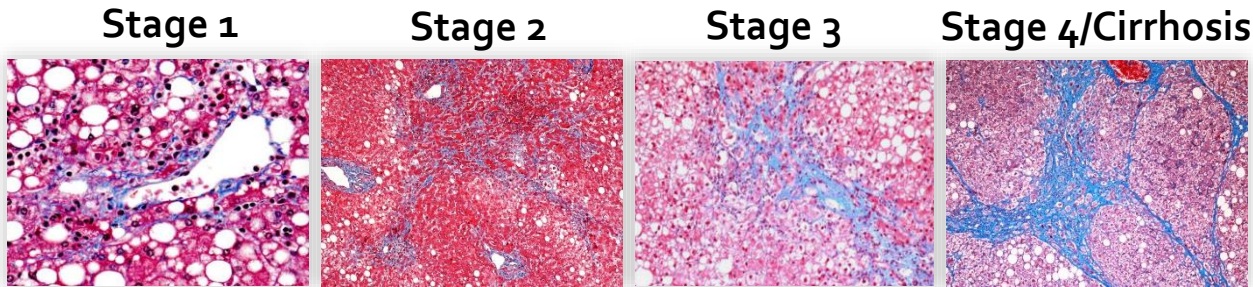
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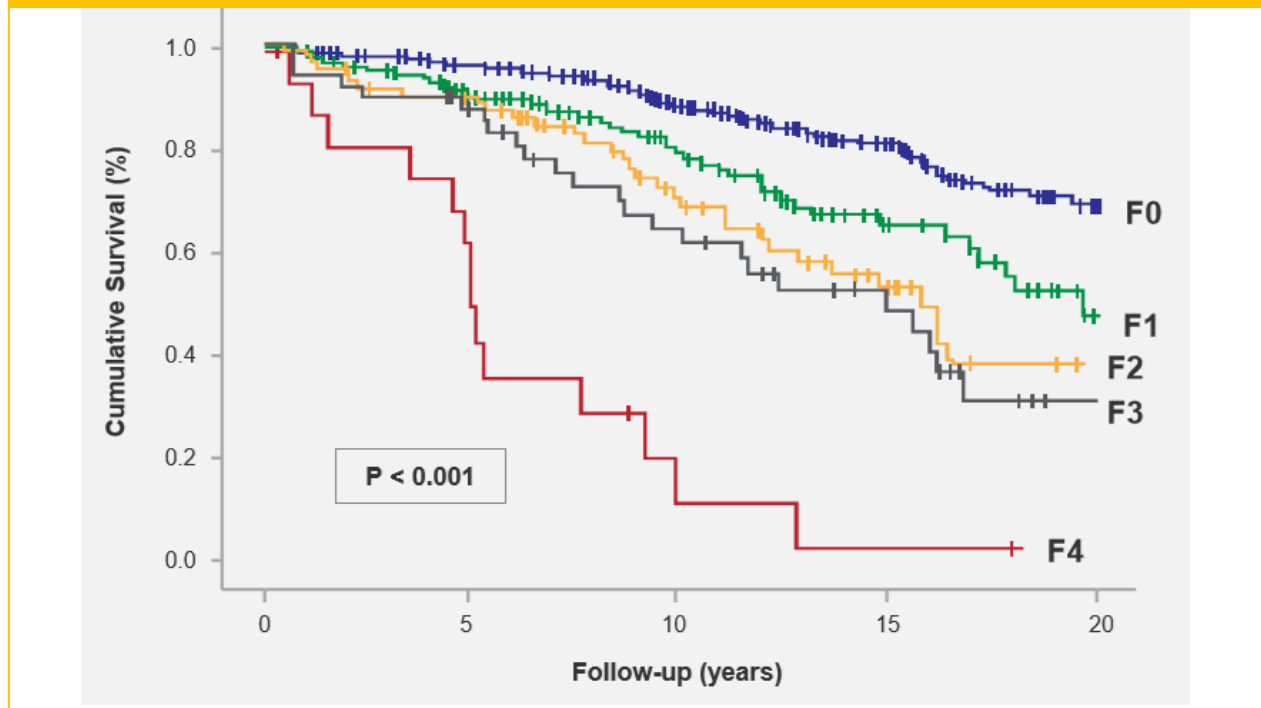
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NASH Fibrosis Stage Progression is Associated with Reduced Survival



Survival Free of Liver Transplantation Based on Fibrosis Stage¹



NASH and Fibrosis Stage

- Approximately one-third of patients with NASH will advance to Stage 3/4 fibrosis²
- An estimated 40% of NASH patients in the U.S. have a fibrosis stage of F2 or higher³
- NASH with advanced fibrosis carries the greatest risk of all-cause and liver-related mortality^{2,4,5}

¹ Graphic taken from ICPT presentation May 2018 which re-graphs data from Angulo, et al. *Gastroenterology* 2015;149:389-397

² Caldwell, et al. *Dig Dis* 2010;28:162-168

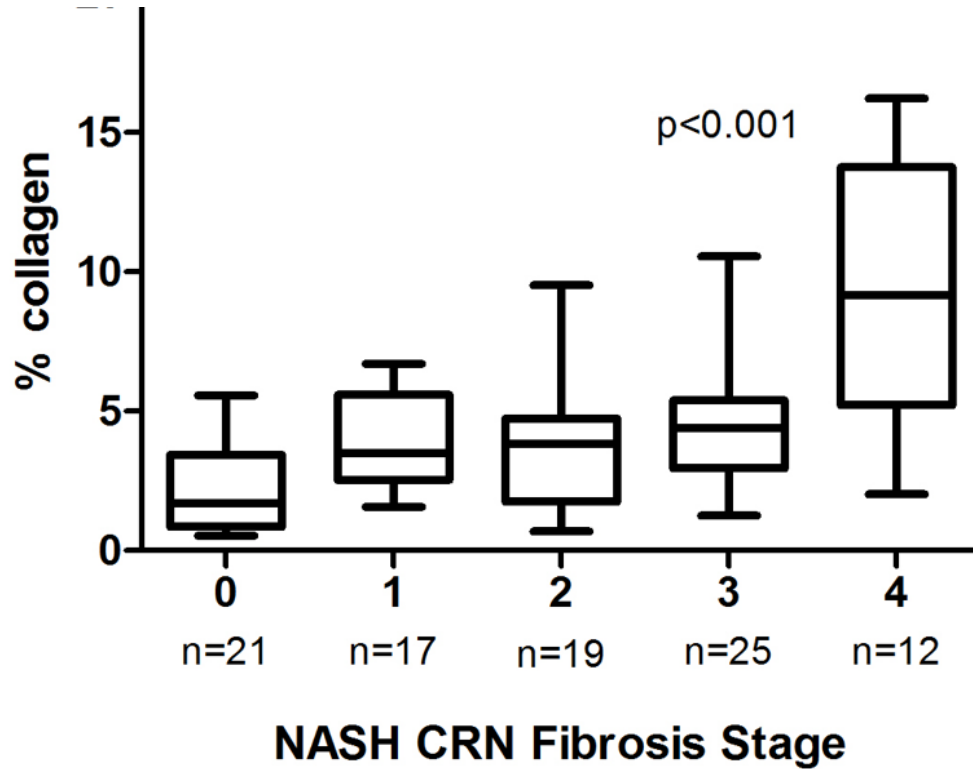
³ Estes, et al. *Hepatology* 2018;67:123-133

⁴ Dulai, et al. *Hepatology* 2017;65:1557-1565

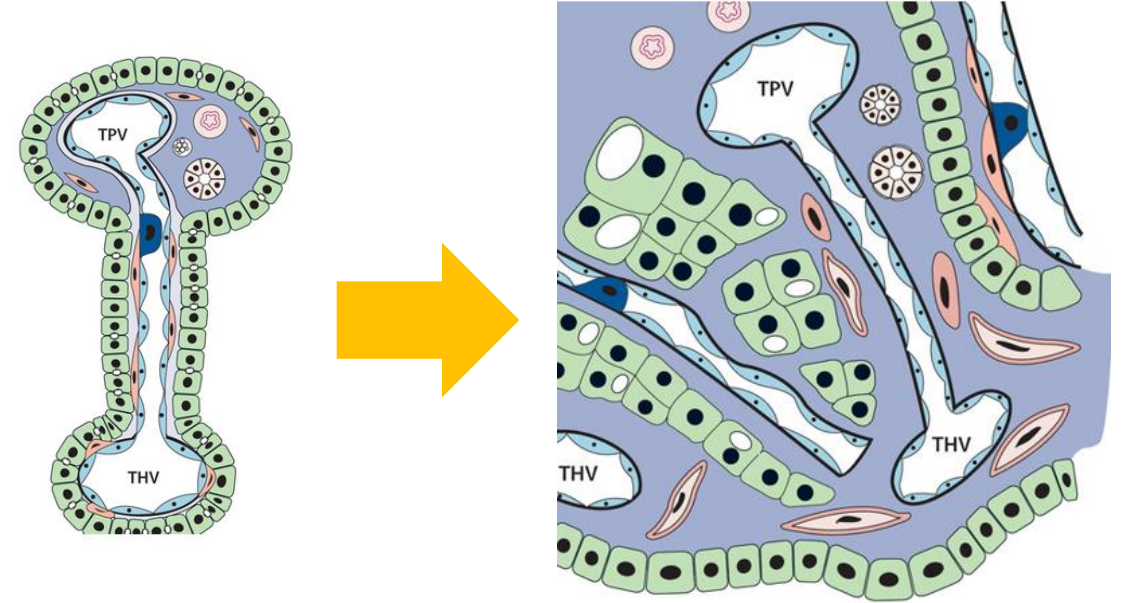
⁵ Hagstrom, et al. *J Hepatology* 2017;67:1265-1273

Fibrosis Continues to Accumulate in Cirrhosis and Distorts Liver Architecture

Amount of Fibrosis Covers Broad Range*



Distorted Architecture in Cirrhosis

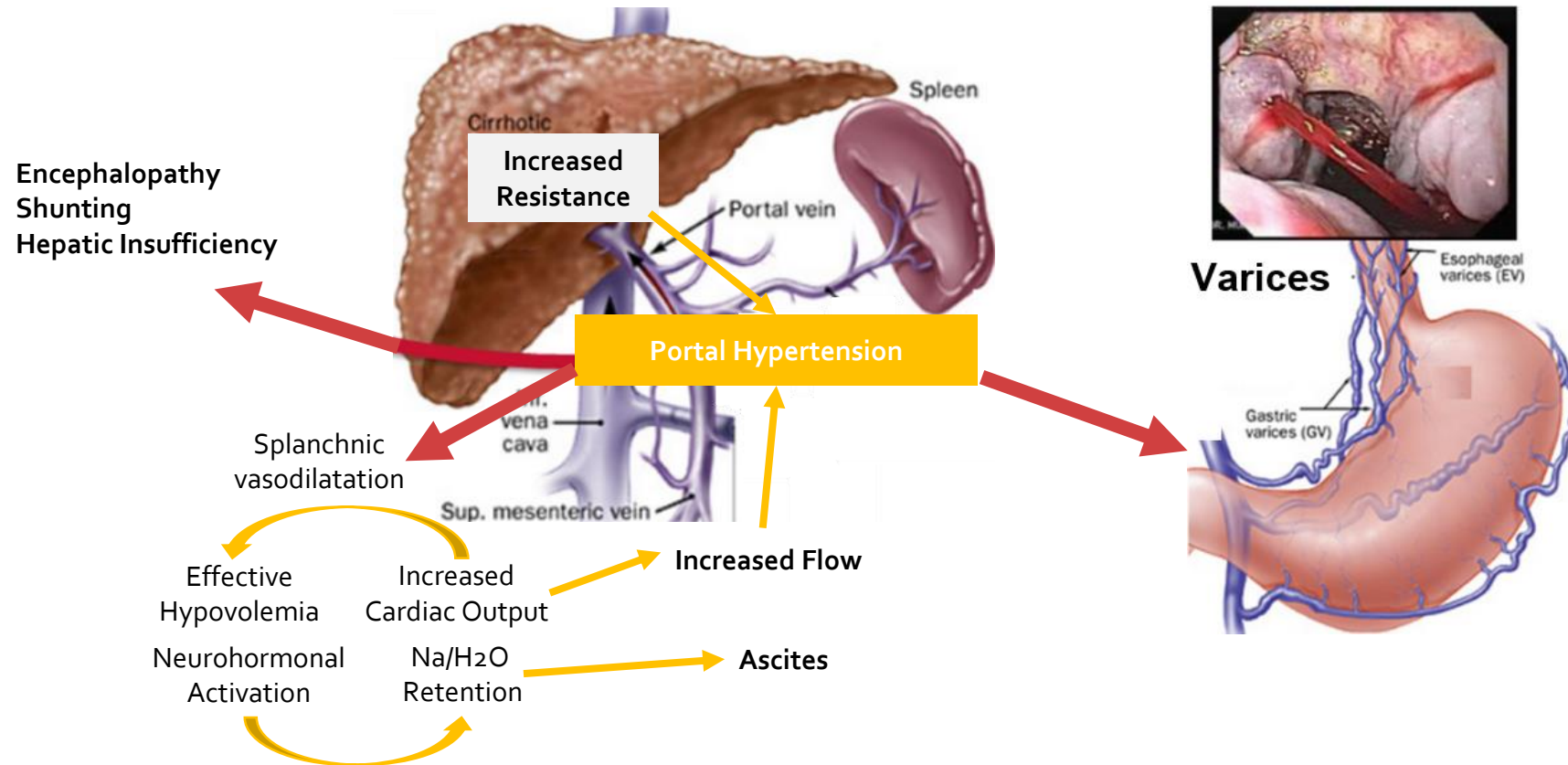


Cirrhosis causes portal hypertension by increasing resistance to blood flow

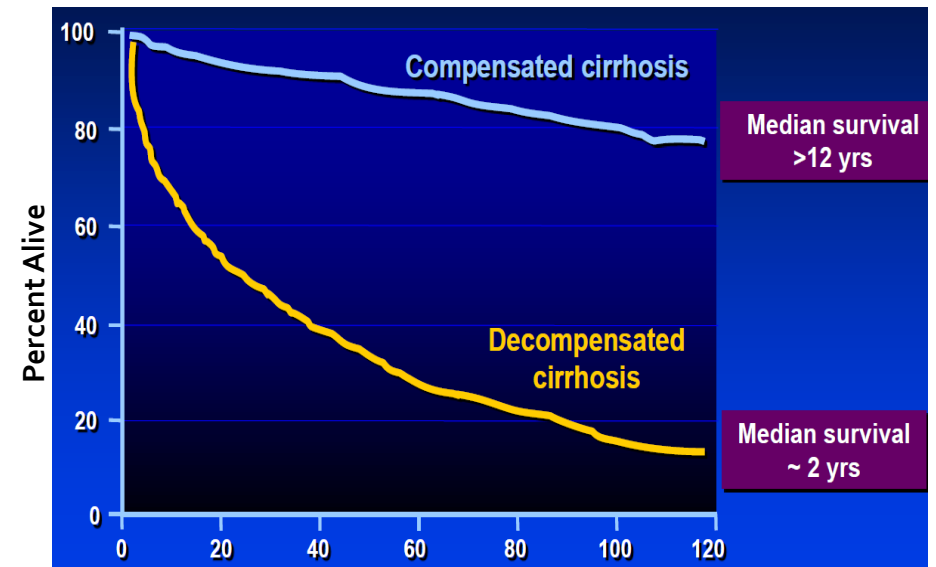
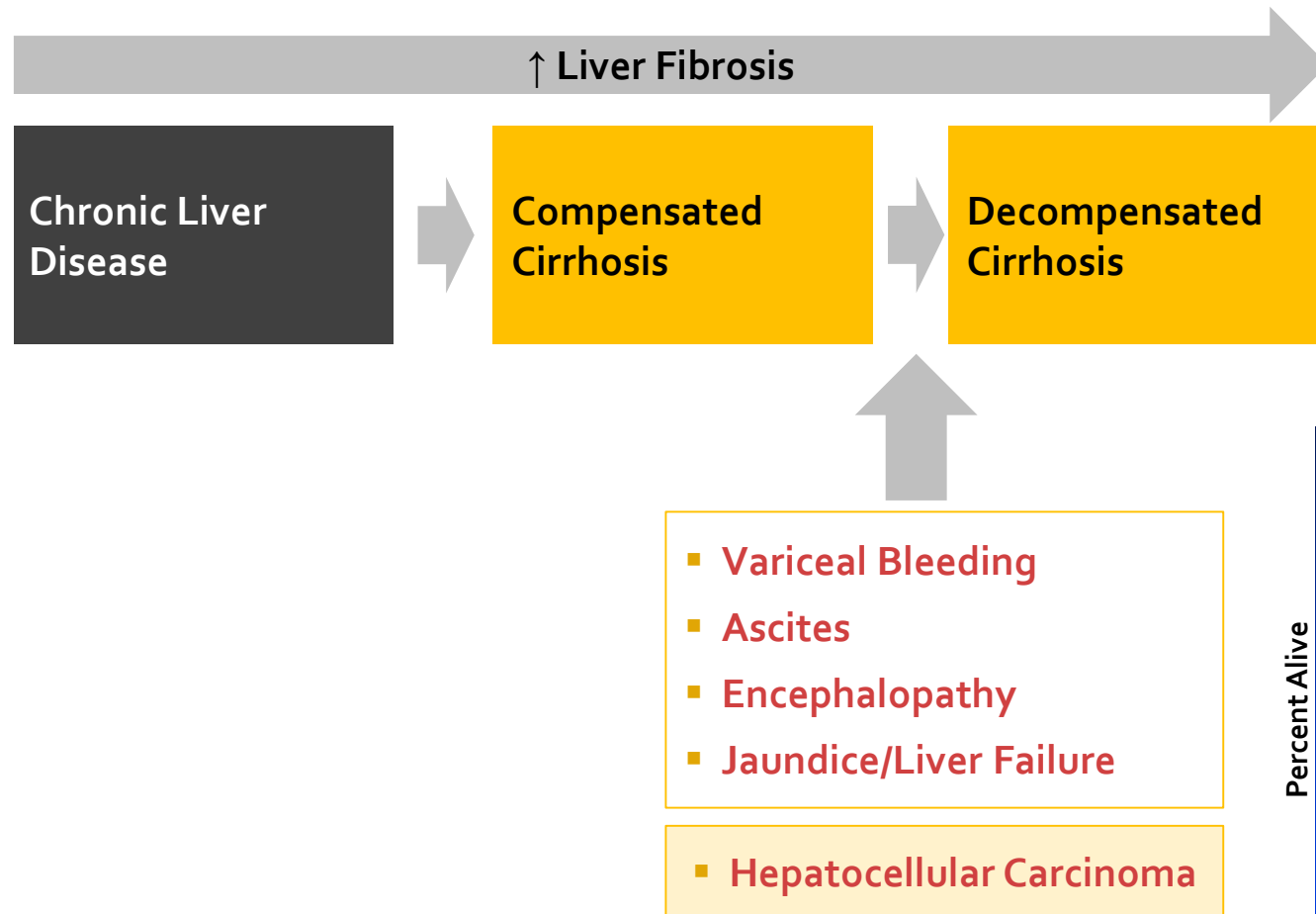
- Structural Components
- Non-structural Components

* Data from Goodman, Harrison, and Traber

Cirrhosis Complications Center Around Increased Portal Vein Blood Pressure

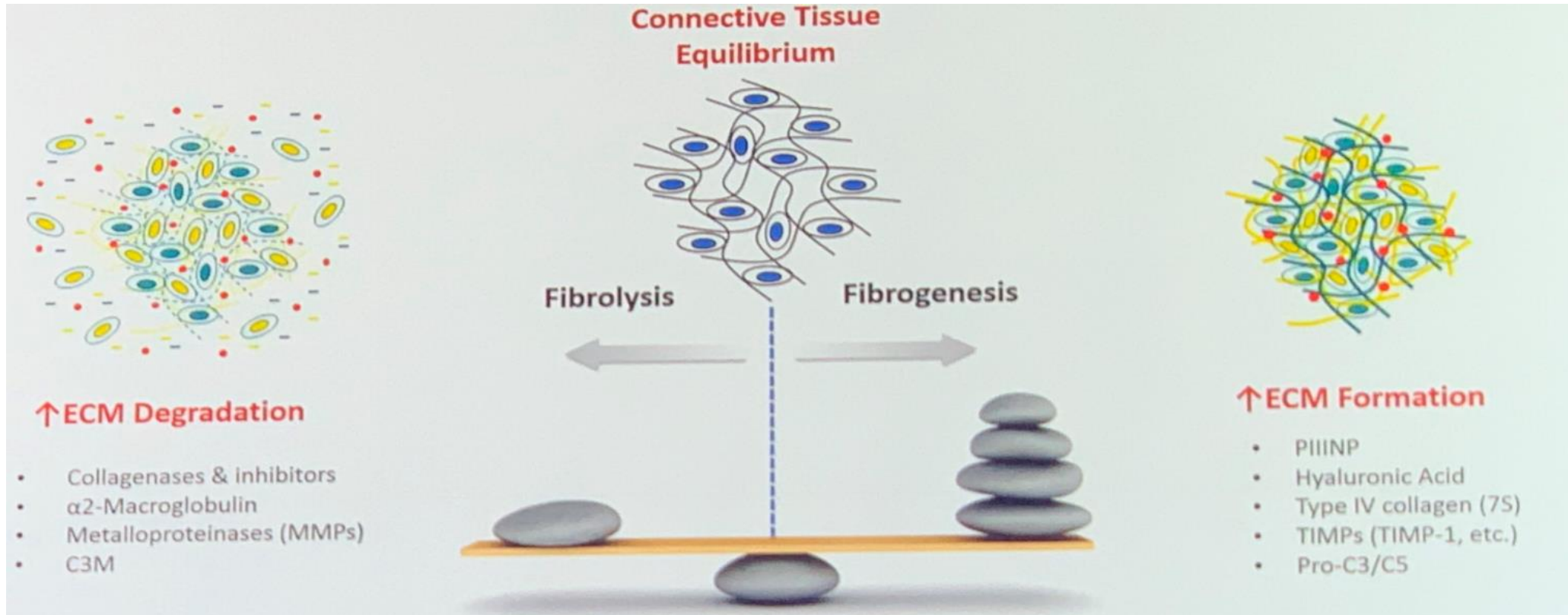


NASH Cirrhosis-Related Mortality Increases with Decompensation Events



D'Aminco et. Al., J Hepatol 2006;44:217 (Graphic borrowed from Dr. Guadalupe Garcia-Tso)

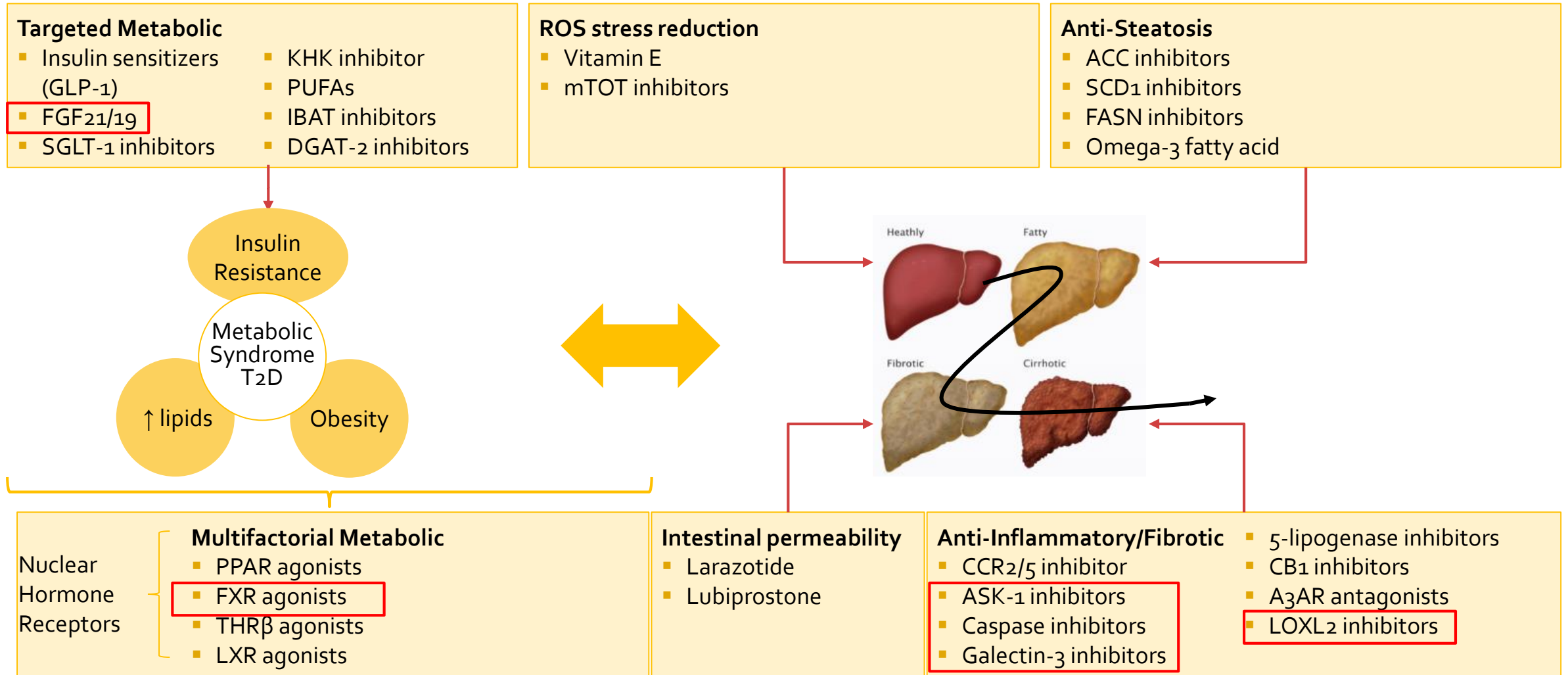
Equilibrium of Extracellular Matrix Turnover



- **Most drugs used in NASH cirrhosis trials are not specific nor potent, anti-fibrotic agents**
- **There are potential specific anti-fibrotics on the horizon, including oral integrin inhibitors**

Figure from ILC-2019 Presentation by Dr. Quentin Anstee

Categorization of NASH Development Assets (Those Used in Cirrhosis Highlighted)



Modified/Expanded from EASL2019 Phenex Presentation

Phase 3 and 2 Clinical Trials in NASH Cirrhosis Have Been Disappointing*

Drug (Company)	MOA	Phase	Study Description	Data	Status
Selonsertib (GILD)	ASK-1 inhibitor	3	STELLAR-4: Comp NASH cirrhosis EP: Fibrosis; composite outcomes	Failed primary	Also failed STELLAR3 (stage 3 NASH); ATLAS P2 combination trial ongoing
Obeticholic acid (ICPT)	FXR Agonist	3	REVERSE: Comp NASH cirrhosis EP: Fibrosis; composite outcomes	JUN 2021	Trial ongoing; In Aug 2019 increased patients from 540 to 900 and extended Rx 12 to 18 mo
Simtuzumab (GILD)	LOXL2 inhibitor	2	Comp NASH cirrhosis EP: Change in HVPG	Failed primary	Also failed in pre-cirrhotic NASH to improve fibrosis. Program discontinued
Belapectin (GALT)	Galectin-3 inhibitor	2	NASH-CX: Comp NASH cirrhosis EP: Change in HVPG	Failed primary	Post-hoc difference in HVPG without varices and reduced development of varices; no effect on fibrosis; P3 trial planned**
Emricasan (CNAT/Novartis)	Pan-caspase inhibitor	2 2	ENCORE-PH Change in HVPG ENCORE-LF Complications	Failed primary	Post-hoc analysis showed some effect in high HVPG sub-group; Currently not progressing
Pegbelfermin (BMS)	PEG-FGF21	2	Comp NASH cirrhosis EP: Fibrosis	JAN 2020	Completed trial enrollment

* Information on trial posted on clinicaltrials.gov or reported by company

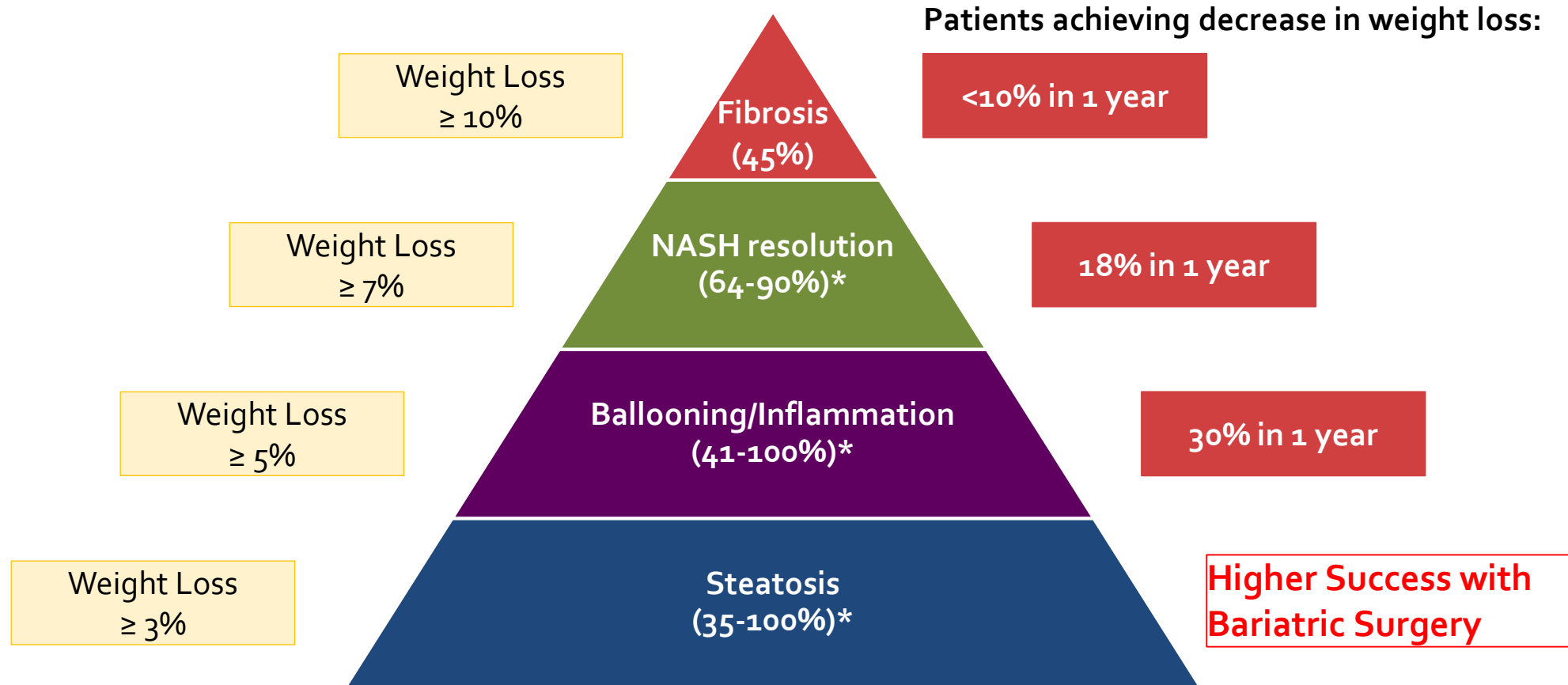
** Not posted on clinicaltrials.gov

Why Have NASH Cirrhosis Trials Failed?

- Mechanism of Action?
 - Most drugs tested have anti-fibrogenic/anti-inflammatory activity. None with demonstrable pro-fibrosis activity, although was a possible mechanism of simtuzumab.
- Adequacy of pre-clinical data?
 - Each of the drugs evaluated had effects on fibrosis in various rodent models of NASH and toxin-induced fibrosis. Indicates lack of good correlation of human results with animal models.
- Correct dosing in humans?
 - None of the drugs had adequate biomarkers of target engagement, particularly in determining pharmacodynamic activity in liver. Therefore, dose finding used indirect approaches, at best.
- Duration of therapy?
 - When the completed and ongoing trials were started, the conventional wisdom of opinion leaders that at least one year of therapy was required. Thus most of the trials included therapy for 1-2 years. Longer therapy may be required.
- Is there a need to combine anti-fibrotics with therapy to metabolic pathogenesis of NASH?

Foundation of Lifestyle Management for NASH: Weight Loss Pyramid

Weight loss benefits steatosis, ballooning/inflammation, NASH resolution, & fibrosis



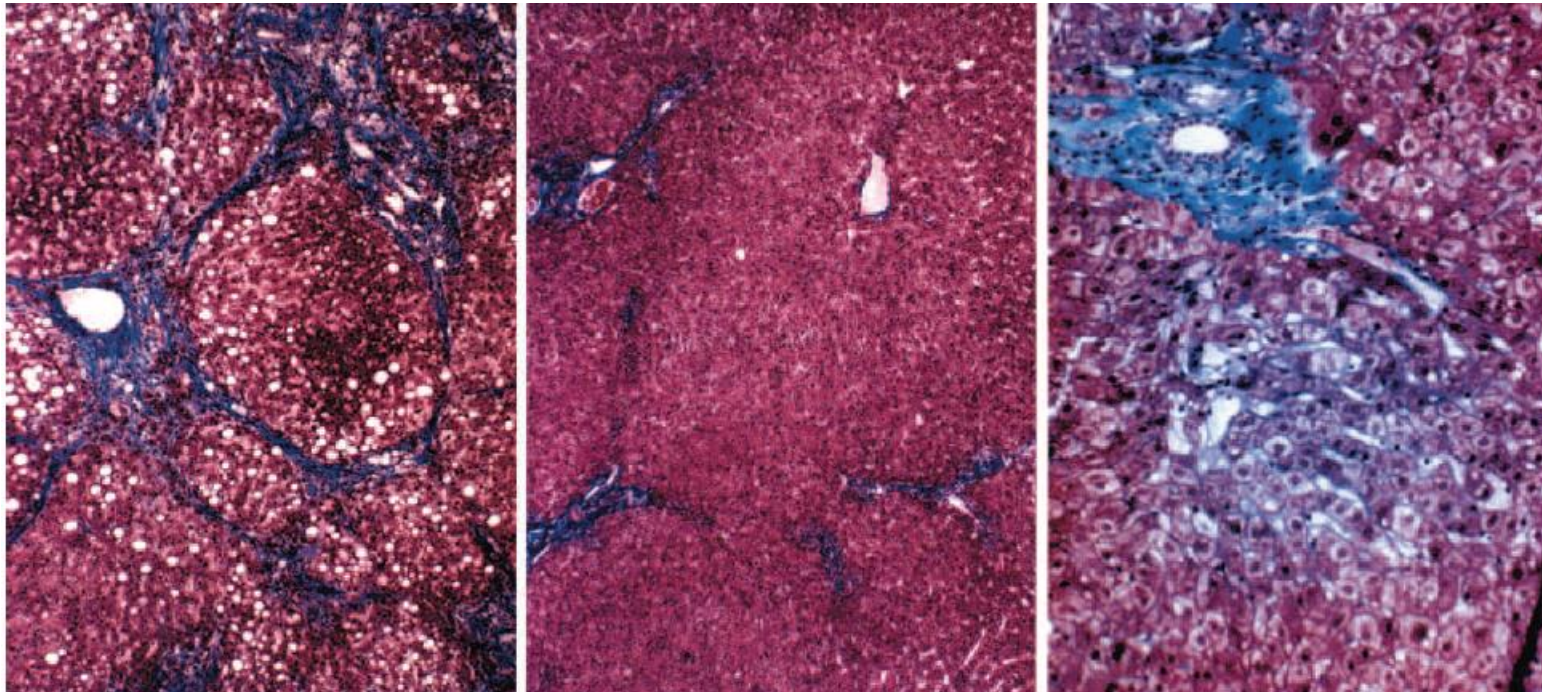
Adapted from Dr. Stephen Harrison's EASL2019 Presentation

Can Bariatric Surgery Reverse NASH Cirrhosis?

Month 0 (Surgery)
BMI 60
Wedge liver Biopsy
Ishak Stage 5 Fibrosis

Month 15
BMI 47
Wedge liver Biopsy
Ishak Stage 3 Fibrosis

Month 44
BMI 44
Needle liver biopsy
Ishak Stage 2 Fibrosis



Kral, et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. *Surgery* 2005;135:48-58

Approaches for Targeting Fibrosis in NASH Cirrhosis

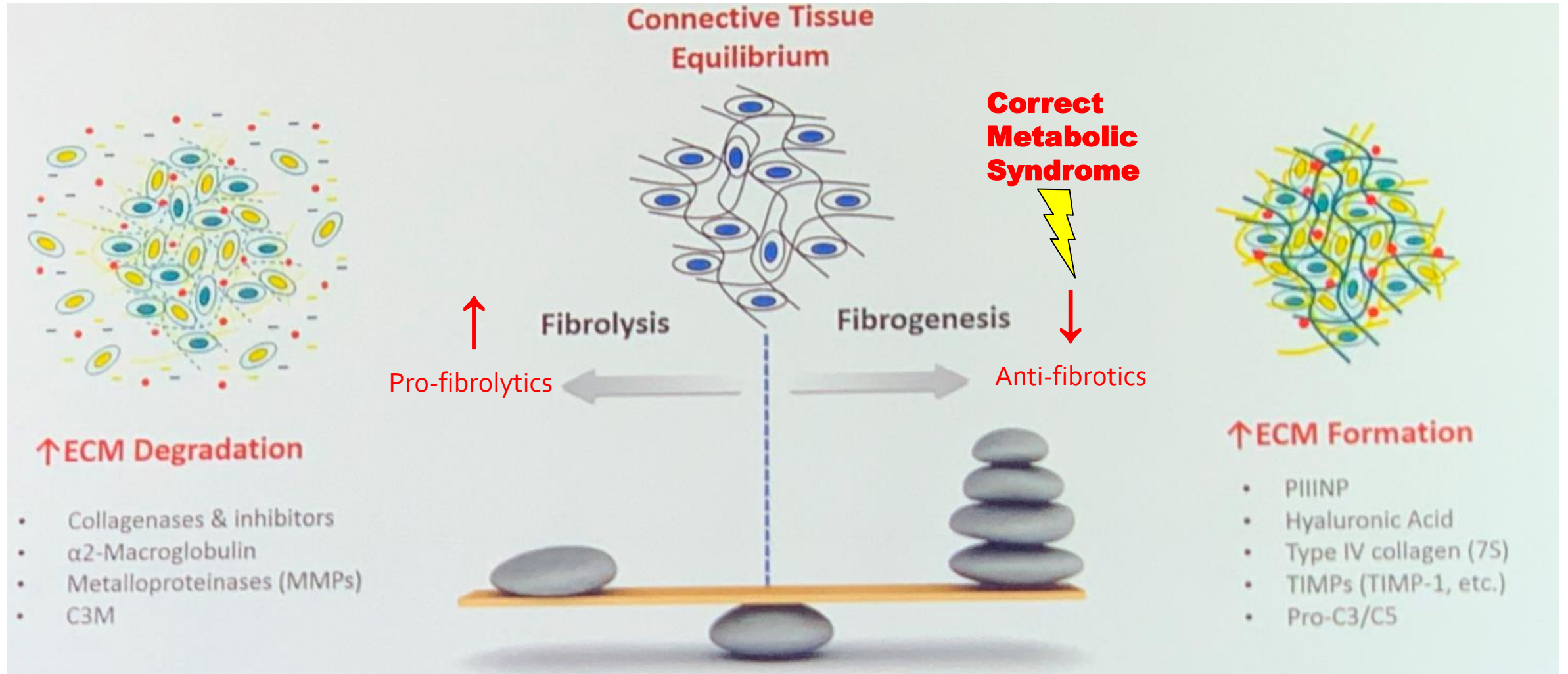
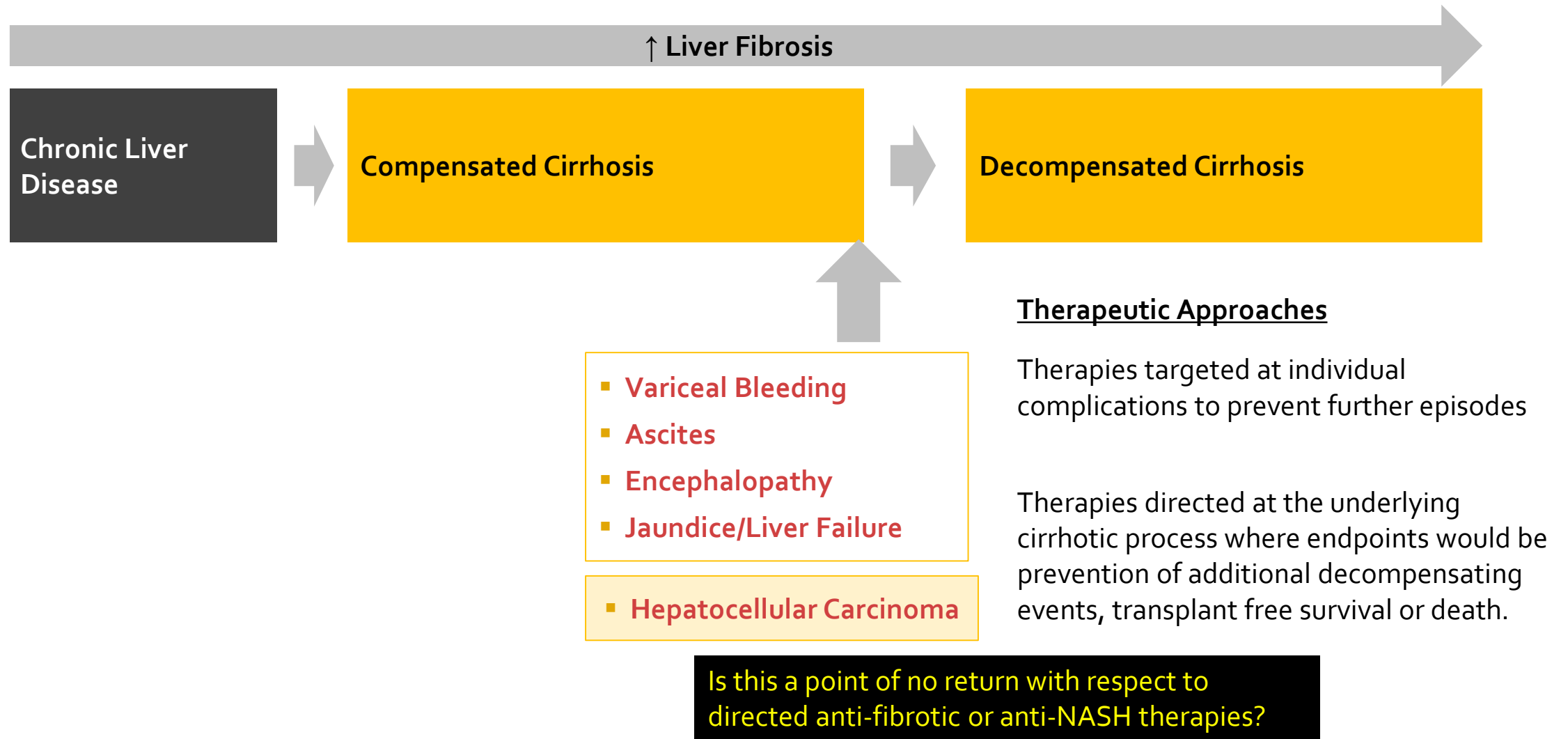


Figure from ILC-2019 Presentation by Dr. Quentin Anstee

Therapy of Decompensated NASH Cirrhosis



FDA Draft Guidance on Endpoints for Compensated NASH Cirrhosis*

Surrogates for Accelerated Approval	Traditional Approval
<p>FDA does not currently recognize any surrogate endpoints for accelerated approval under subpart H.</p> <p>Previously, the FDA did agree for phase 3 trials an endpoint of the proportion of patients who achieve ≥ 1 stage improvement in fibrosis without worsening of NASH</p> <p>“Histological improvements in fibrosis can be proposed and justified; however, at present the relationship between histological changes in cirrhosis and clinical outcomes has not been characterized, and further, reversal of cirrhosis (e.g., fibrosis stage F₄) may not be feasible. Because currently there is insufficient evidence to support the use of histological improvements as a surrogate endpoint that is reasonably likely to predict clinical benefit to support accelerated approval, in general, the FDA expects to evaluate drugs for the treatment of compensated NASH cirrhosis under the traditional approval pathway.”</p>	<p>Endpoint: Effect of the investigational drug relative to placebo on the composite endpoint of time from randomization to the first of any one of the following outcome events:</p> <ol style="list-style-type: none">1. Complication of ascites (bacterial peritonitis, diuretic-resistant ascites, hepato-pleural effusion, etc.)2. Variceal hemorrhage3. Hepatic encephalopathy4. Worsening in the MELD score to ≤ 15 (this assumes the MELD at enrollment is ≤ 12)5. Liver transplantation6. Death from any cause

*Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment, Guidance for Industry, U.S. FDA, June 2019
Timeframe for comments on the draft guidance closed in August 2019

Summary of Drug Development in NASH Cirrhosis

- The focus of drug development is on compensated NASH cirrhosis with the objective of preventing decompensation events and subsequent liver transplant or liver-related mortality.
- Results of clinical trials in NASH cirrhosis have been disappointing
- Phase 2 and 3 trials have been focused primarily on a reduction of at least one stage of fibrosis (reversal of cirrhosis), with several phase 2 trials focused on reduction of portal pressure measured by HVPG
- Recent FDA guidance has indicated there are no acceptable surrogate endpoints and the traditional approval pathway must be used which is based on a composite endpoint of clinical outcomes. Comment period for draft guidance has ended, but no timing for update.
- Clinical trials already underway will likely complete as designed, but newly initiated phase 3 trials will be governed by FDA guidance. Endpoints that deviate from the guidance, such as use of HVPG, progression to varices, or reversal of fibrosis, will require justification, agreement by the FDA, and subsequent listing on clinicaltrials.gov which will be public verification of a different endpoint from the guidance.
- Future investigation should focus on more specific and potent anti-fibrotics (e.g. anti-integrins), pro-fibrolytics, and combination with other drugs that affect the metabolic syndrome.

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Thank You!

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