Liver Cell Death and Regeneration: Understanding the Mystery of the Liver

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Your Liver

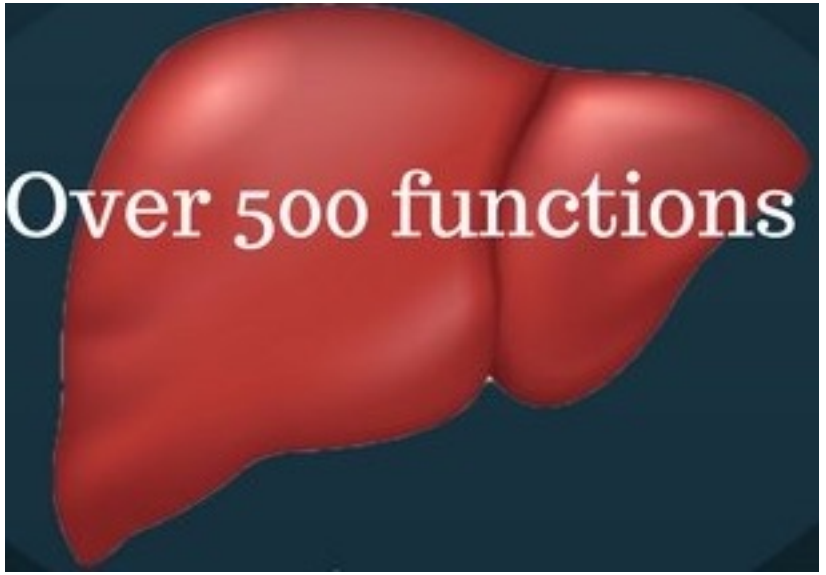
- Largest internal organ
- Located in the upper right side of your abdomen behind the rib cage
- Holds 13% of body's blood supply
- Only organ that can regenerate

What Does Your Liver Do?

Removes potentially toxic by-products of certain medications

Breaks down nutrients from food to produce energy

Helps your body fight infection by removing bacteria from the blood



Processes glucose

Regulates blood clotting

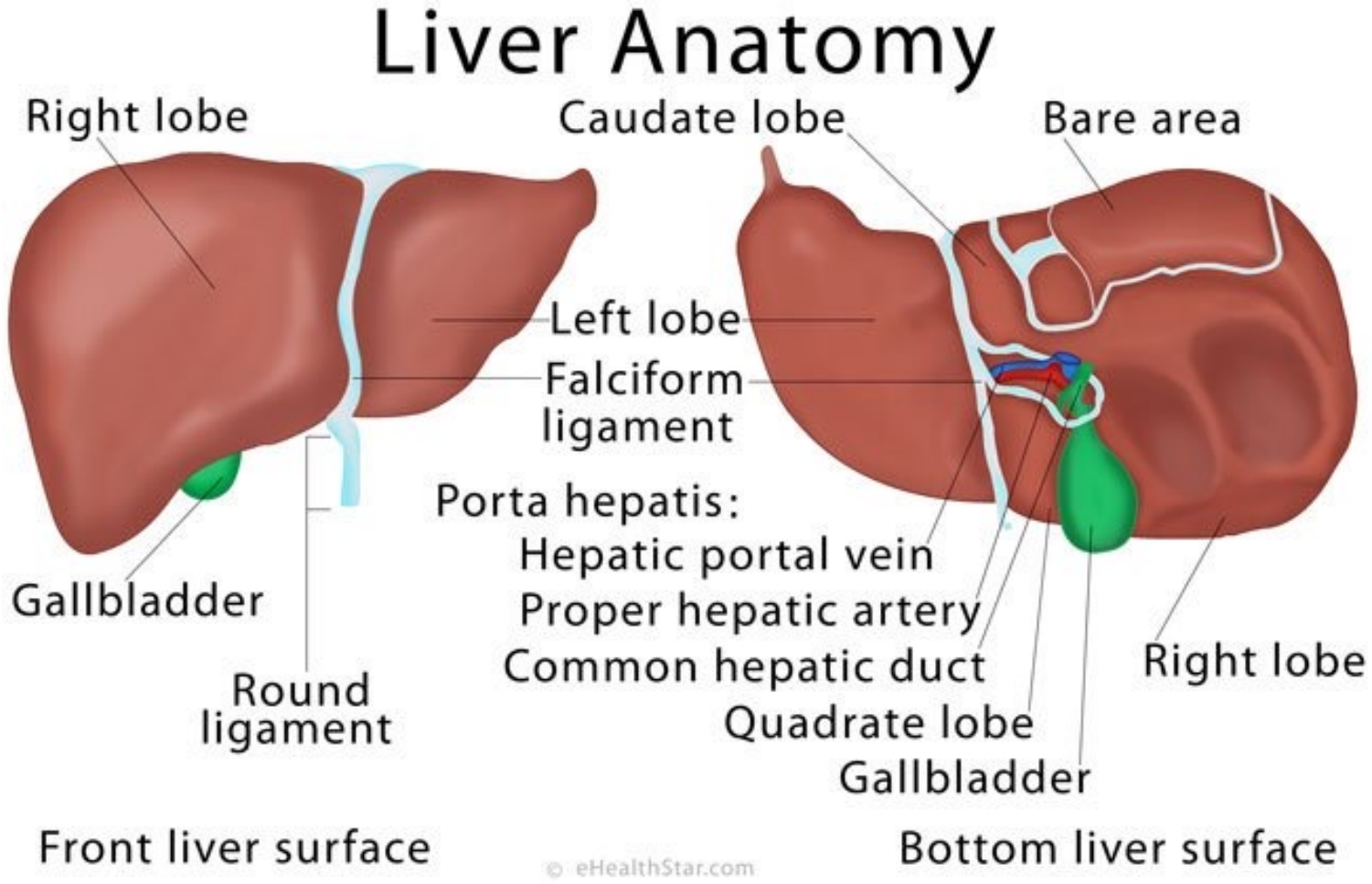
Produces albumin

Produces bile which is a fluid that helps you digest food

Prevents shortages of nutrients by storing vitamins, minerals and sugar

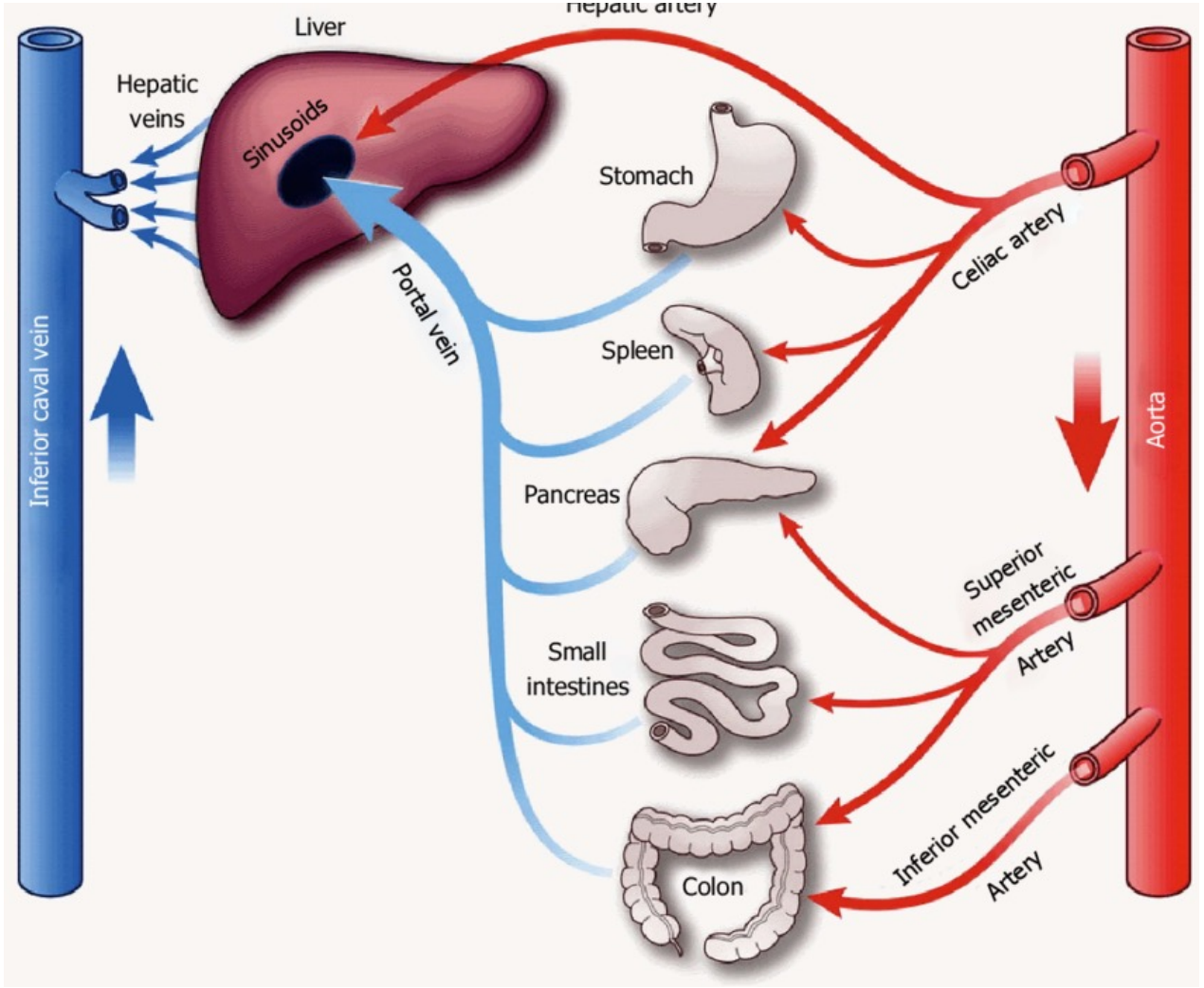
Normal Liver Anatomy

- Weighs up to 3.5 lbs in healthy individuals
- 4 lobes (unequal sizes):
  - Right (largest)
  - Left
  - Caudate
  - Quadrate

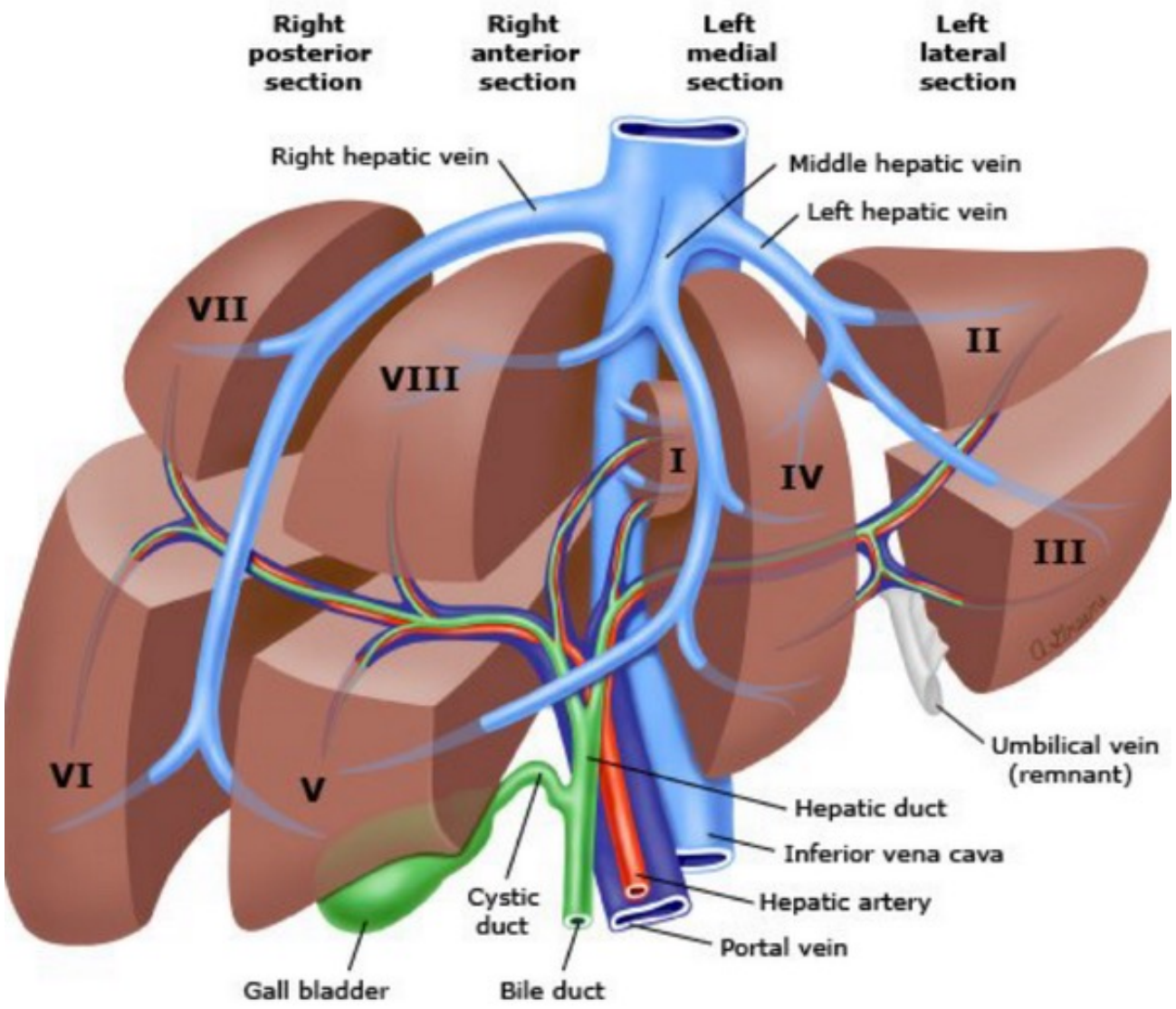


Dual Blood Supply to the Liver

- Hepatic Artery
  - 25% blood
  - Oxygen rich
- Portal Vein
  - 75% blood
  - Nutrient rich

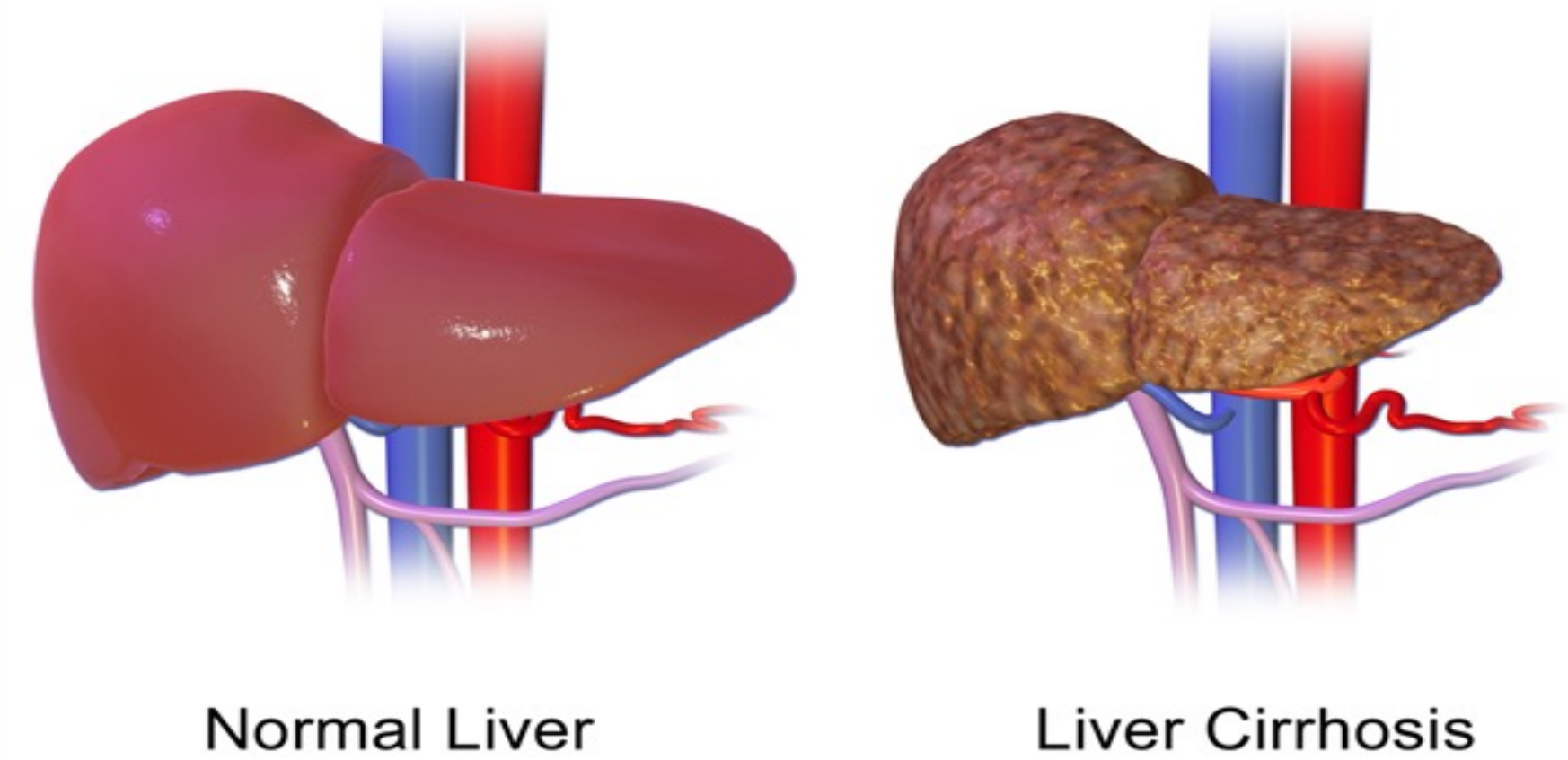


Liver Segments and Hilum



- Vascular supply is important as that is how surgeons decide resection of liver segments
  - I = Caudate
  - II-IV = Left lobe
  - V-VIII = Right lobe
- Portal vein, hepatic artery, and common bile duct enter through hilum
  - Branches of these 3 then travel within “portal tracts”

Healthy Liver vs Cirrhotic Liver



Normal Liver

Liver Cirrhosis

Grading Liver Injury Via Biopsy

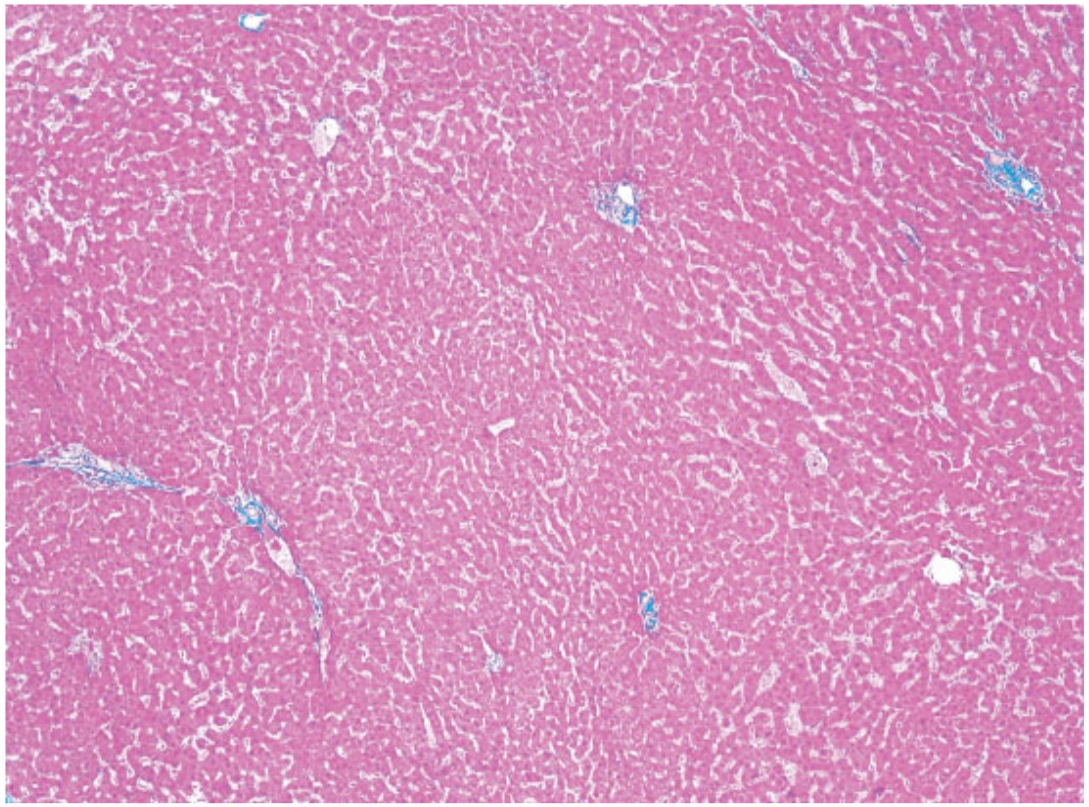
Metavir Score System

Metavir score system	Fibrosis stage
F0	No fibrosis can be detected
F1	Fibrosis exists with expansion of portal zones
F2	Fibrosis exists with expansion of most portal zones, and occasional bridging
F3	Fibrosis exists with expansion of most portal zones, marked bridging, and occasional modules
F4	Presence of cirrhosis

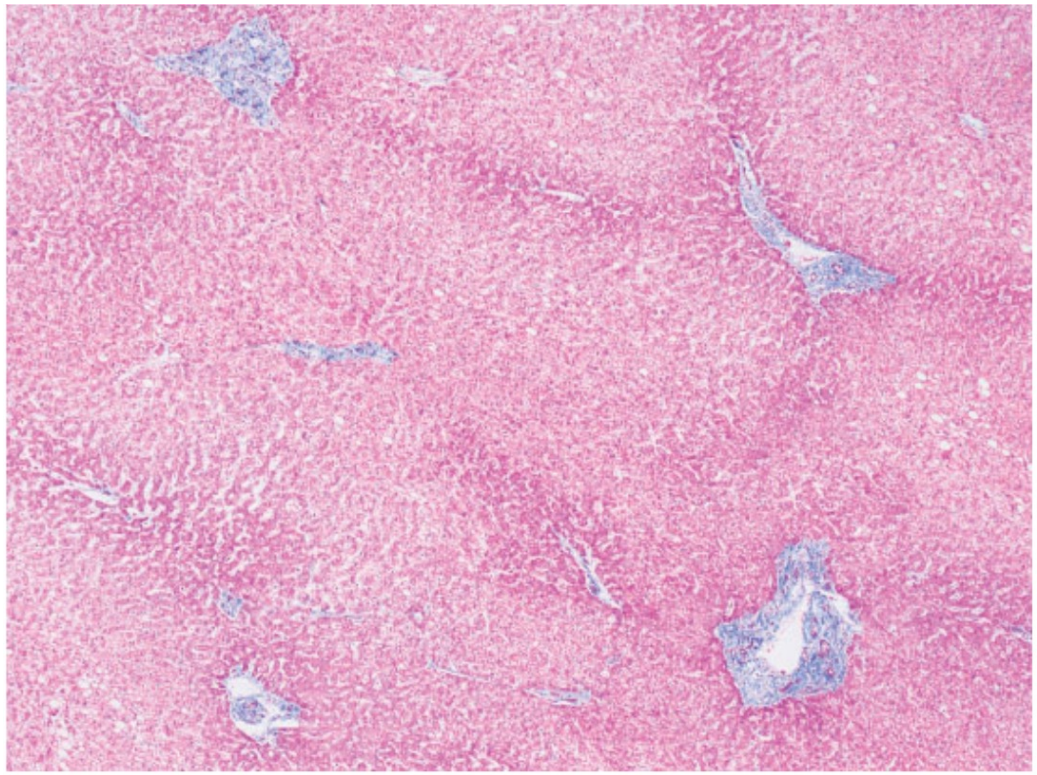
The Metavir score system and fibrosis stage

Assessing Fibrosis: Trichome Staining (Blue=Fibrosis)

Stage 0 = No Fibrosis

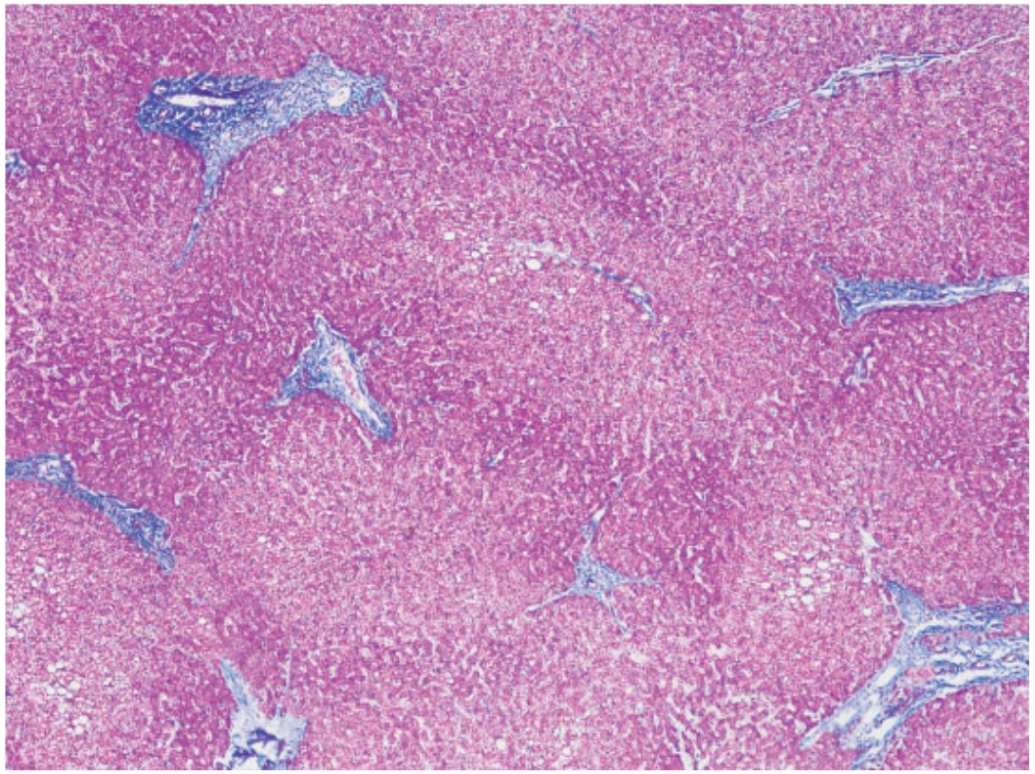


Stage 1 – Portal Fibrosis

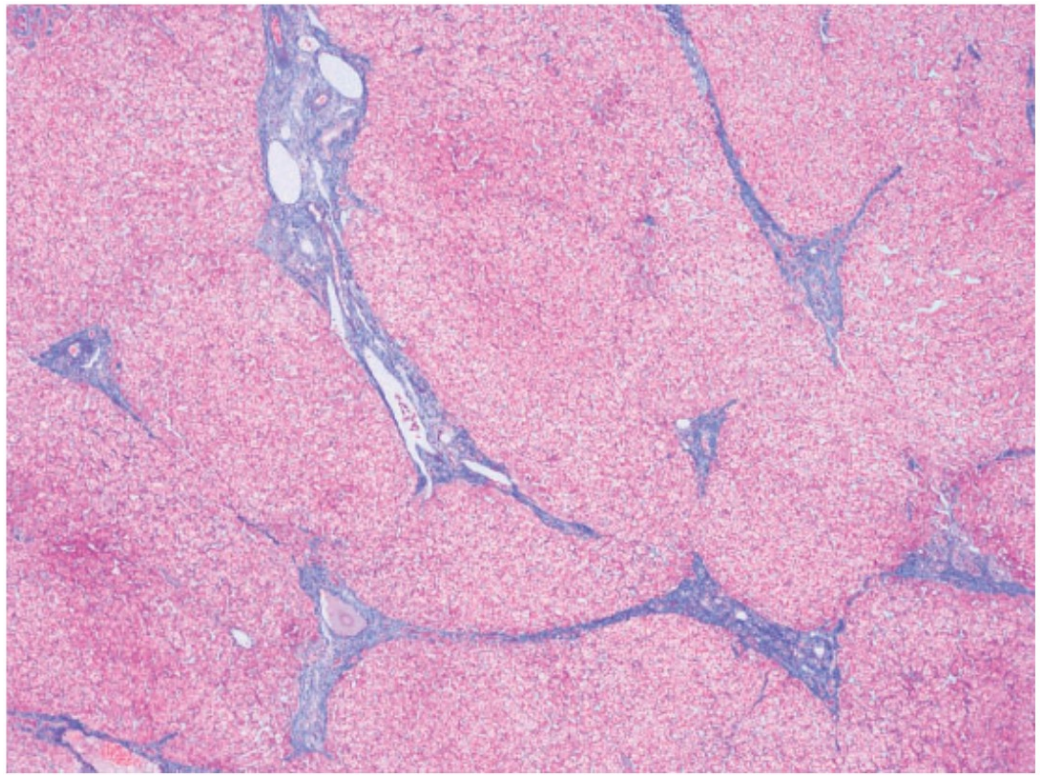


Assessing Fibrosis: Trichome Staining (Blue=Fibrosis)

Stage 2 = Periportal Fibrosis

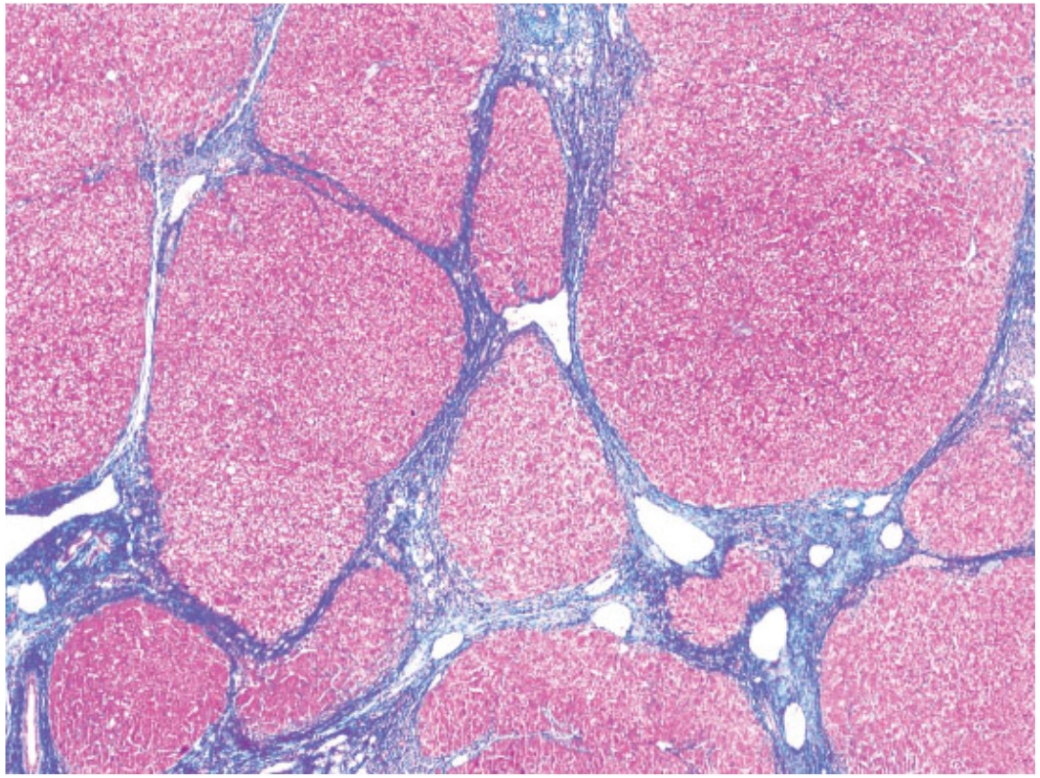


Stage 3 – Bridging Fibrosis



Cirrhosis

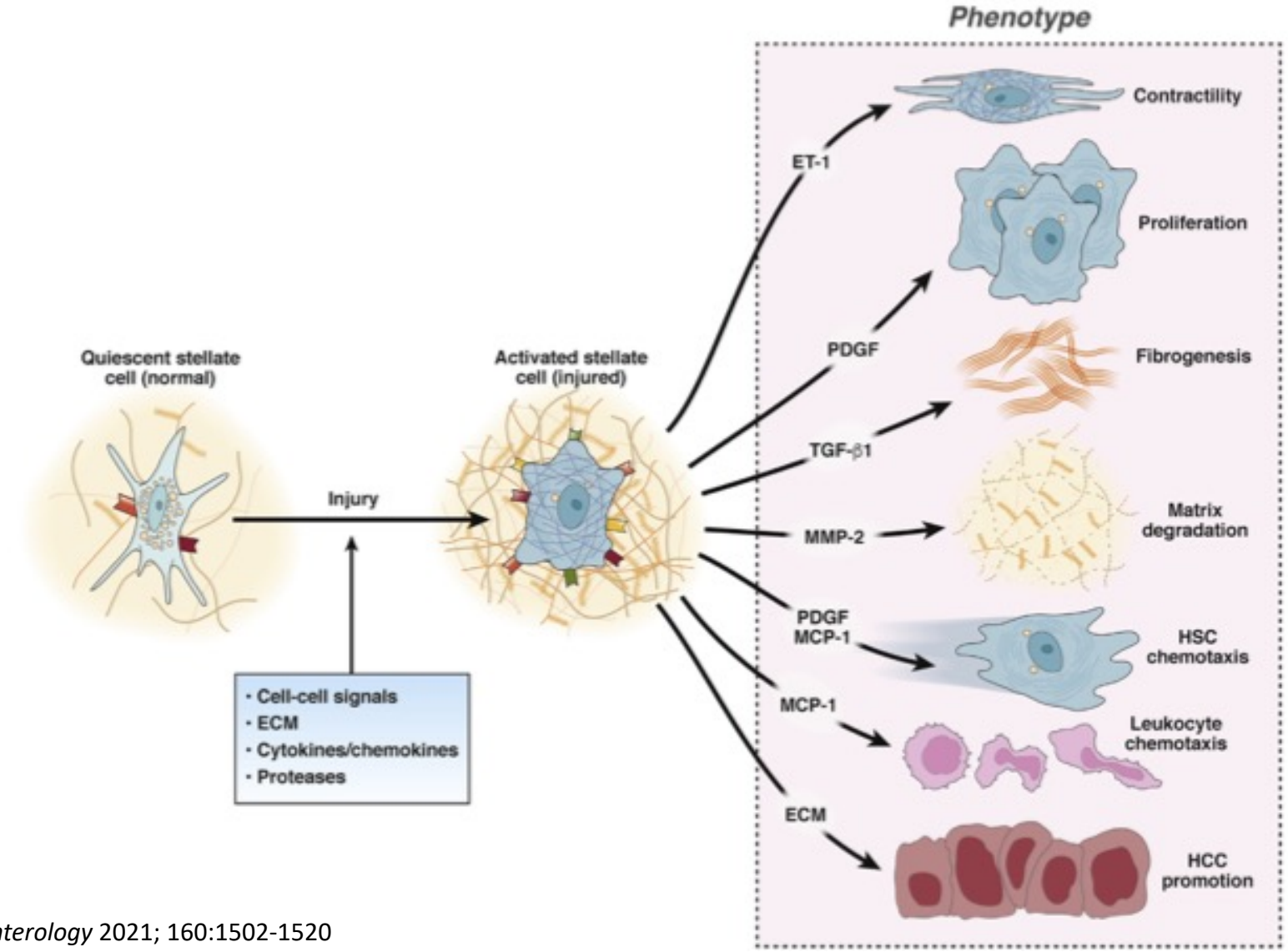
Stage 4 = Cirrhosis



- Definition: Increase in diffuse connective tissue, resulting in changes in morphology and function.
- Not defined by etiology of liver disease but rather describes the end result of many chronic liver diseases.

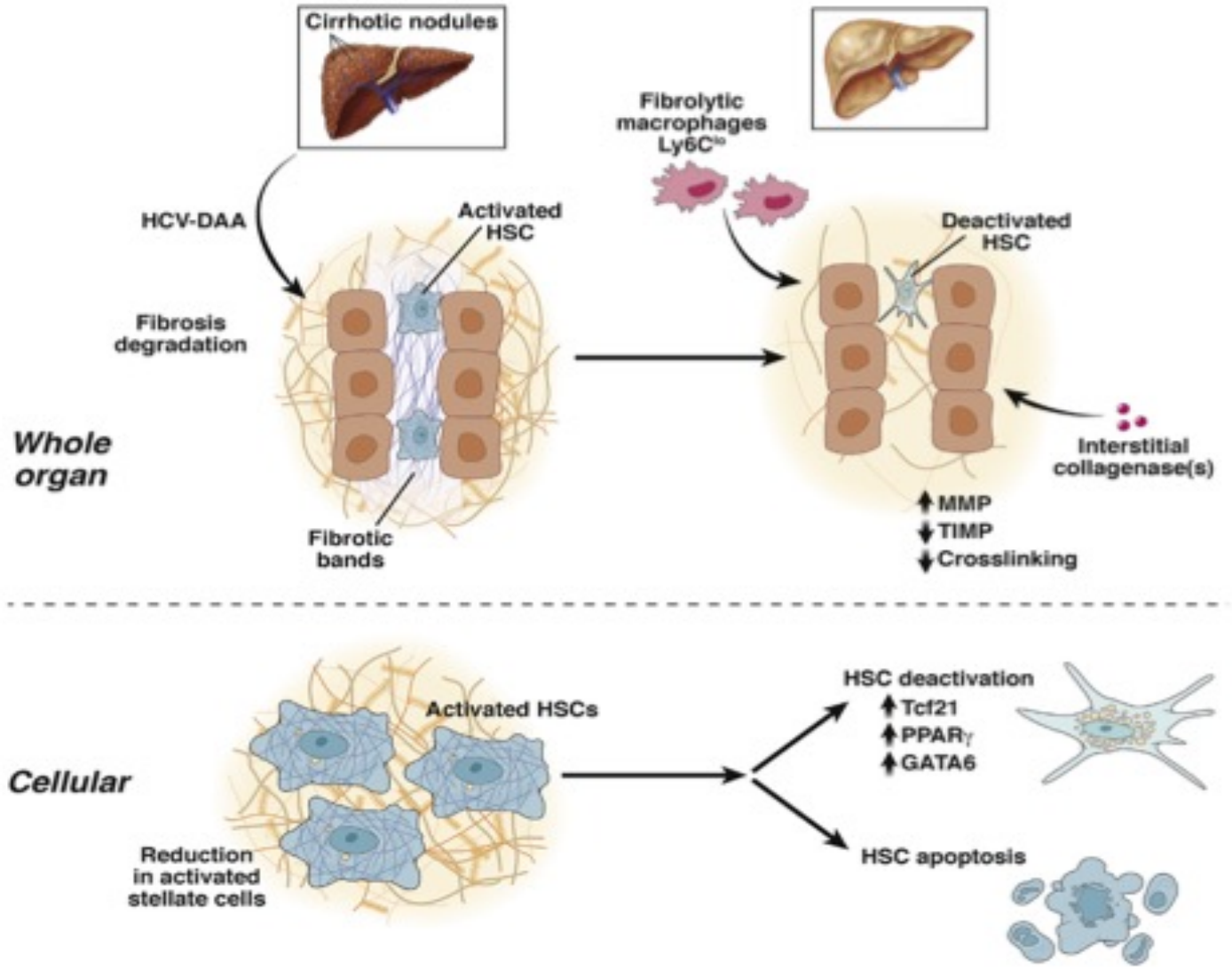
Fibrogenic Response

Hepatic Stellate Cells (HSCs): Key Source of Fibrogenesis



Rockey DC and SL Friedman, *Gastroenterology* 2021; 160:1502-1520

Mechanism of Fibrosis Regression



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Fibrosis Regression

Factors Linked to Fibrosis Regression

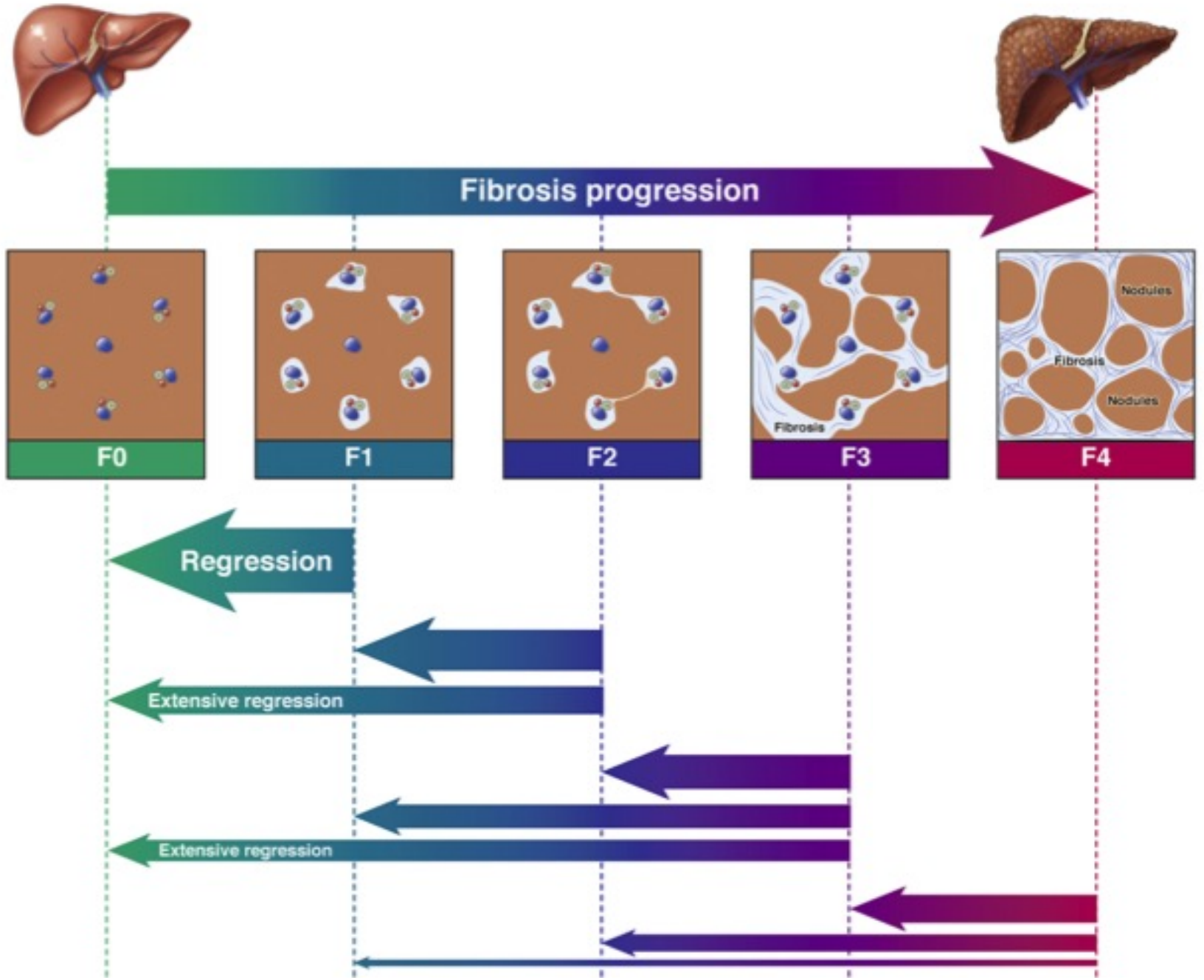
- Elimination of the underlying disease
  - Control viral replication in HBV and HDV chronic infection
  - Curative therapy with direct-acting antivirals in HCV
  - Control excess iron in hemochromatosis
  - Remove ingestion of alcohol in alcoholic liver disease
  - Immunosuppressive treatment for autoimmune liver disease
  - Weight loss and bariatric surgery in NASH

Fibrosis Reversal in Cirrhosis After HCV SVR

Study	Therapy	N	Follow-up	Outcome assessed using	Key finding(s)
Poynard et al, 2002[b]	IFN based	153	12 mo	Liver histology	75 patients had a reduction in Metavir fibrosis stage (23 to stage 3; 26 to stage 2; 23 to stage 1; 3 to stage 0); the mean fibrosis score decreased from 4–1.9 overall
Rout et al, 2019[d]	DAA	95	12 mo	TE	The percentage of patients with cirrhosis (25.5%) at baseline declined to (18.1%) at 1 year of follow-up
Kawagishi et al, 2020	DAA	23	12 mo	TE	9 patients had regression, including 4 to stage 0–2
Prakash et al, 2020	DAA	90	24 mo	FIB-4	39% had reduction in FIB-4 to <2.67 (predefined cirrhosis threshold)

[b]Fibrosis was assessed at end of treatment; not at SVR
[d]Excluded patients with decompensation

Rockey DC and SL Friedman, *Gastroenterology* 2021; 160:1502-1520



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Challenges

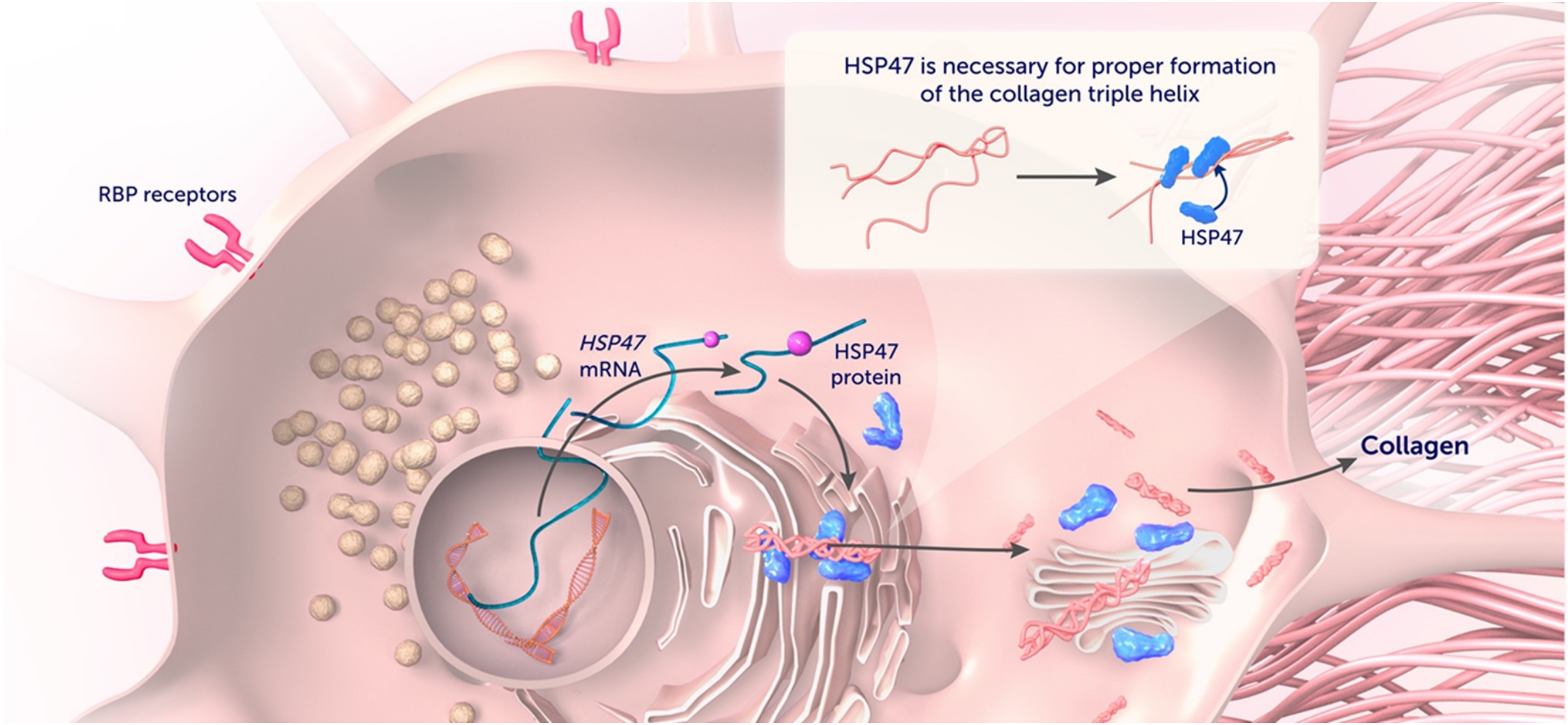
- Fibrosis regression requires serial liver biopsies which rarely happens in clinical practice.
- Development of validated non-invasive markers of fibrosis regression necessary.
- Some data in HCV patients cured with DAA therapies but data limited to 2-3 year follow up.
  - Is this maintained long term?
- Is ≥2 stage improvement possible?
- Is there a point of no return?
  - Likely when there is severe architectural distortion, vascular collapse and portal hypertension.

Rockey DC and SL Friedman, *Gastroenterology* 2021; 160:1502-1520

BMS-986263 (siRNA targeting HSP47 mRNA): Promising Anti-fibrotic?

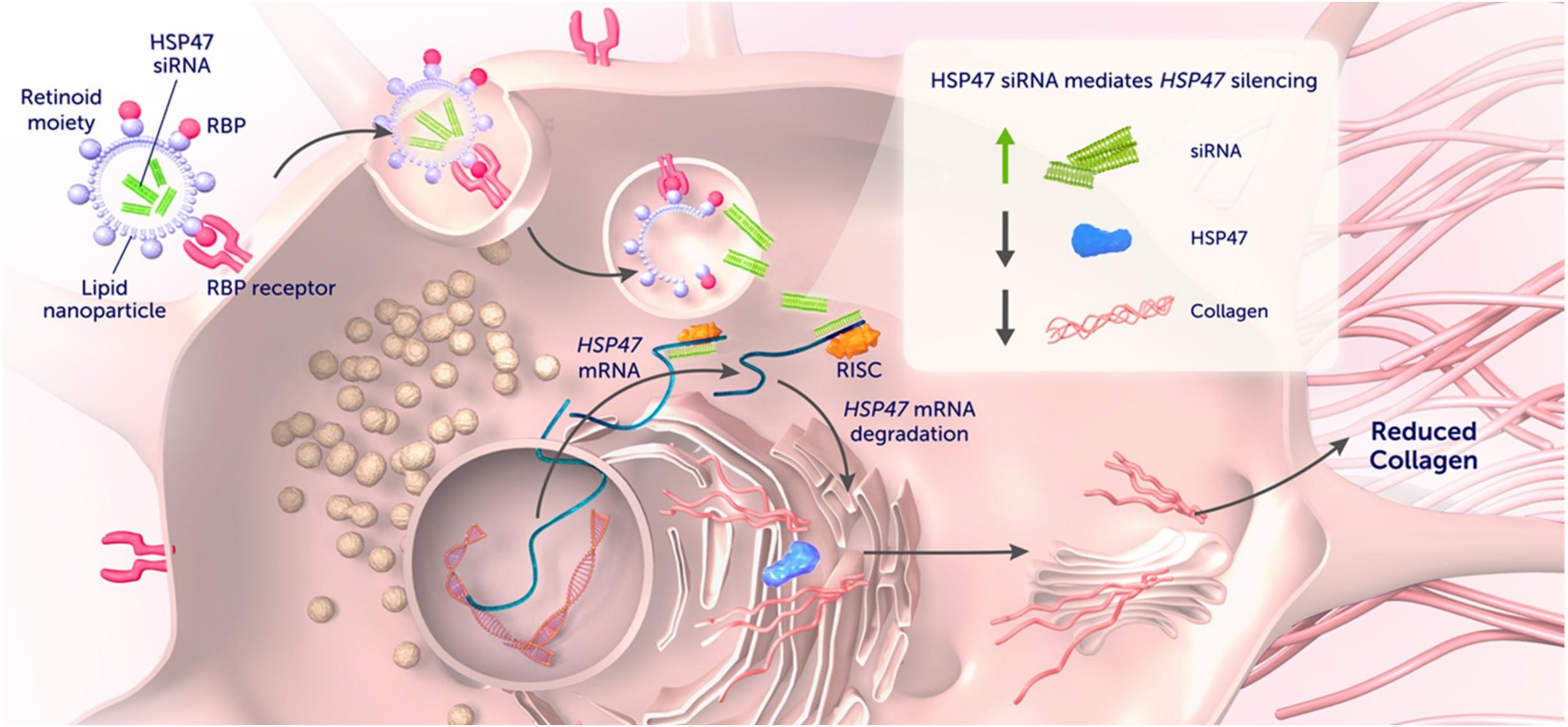
Lawitz, EJ et al., *Hepatology*. 2022 Apr;75(4): 912-923. doi: 10.1002/hep.32181.

HSP47 Function in Hepatic Stellate Cells



HSP47, heat shock protein 47; RBP, retinol-binding protein.

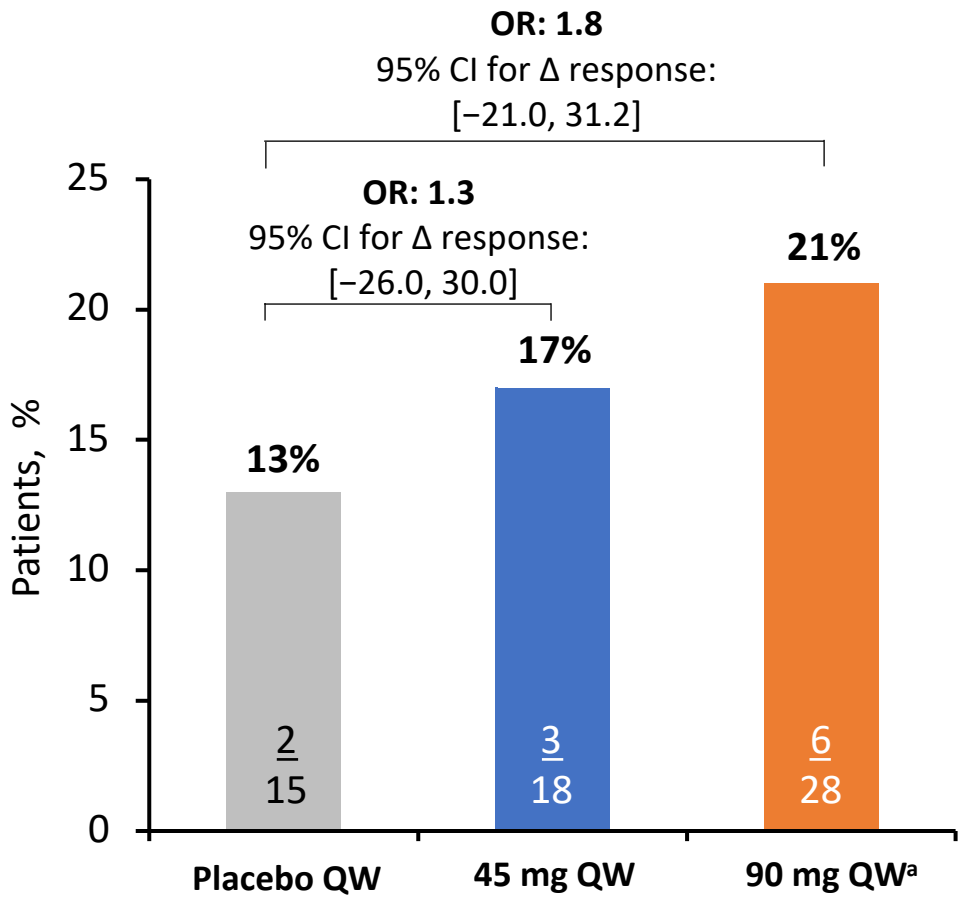
BMS-986263-Mediated Silencing of *HSP47*



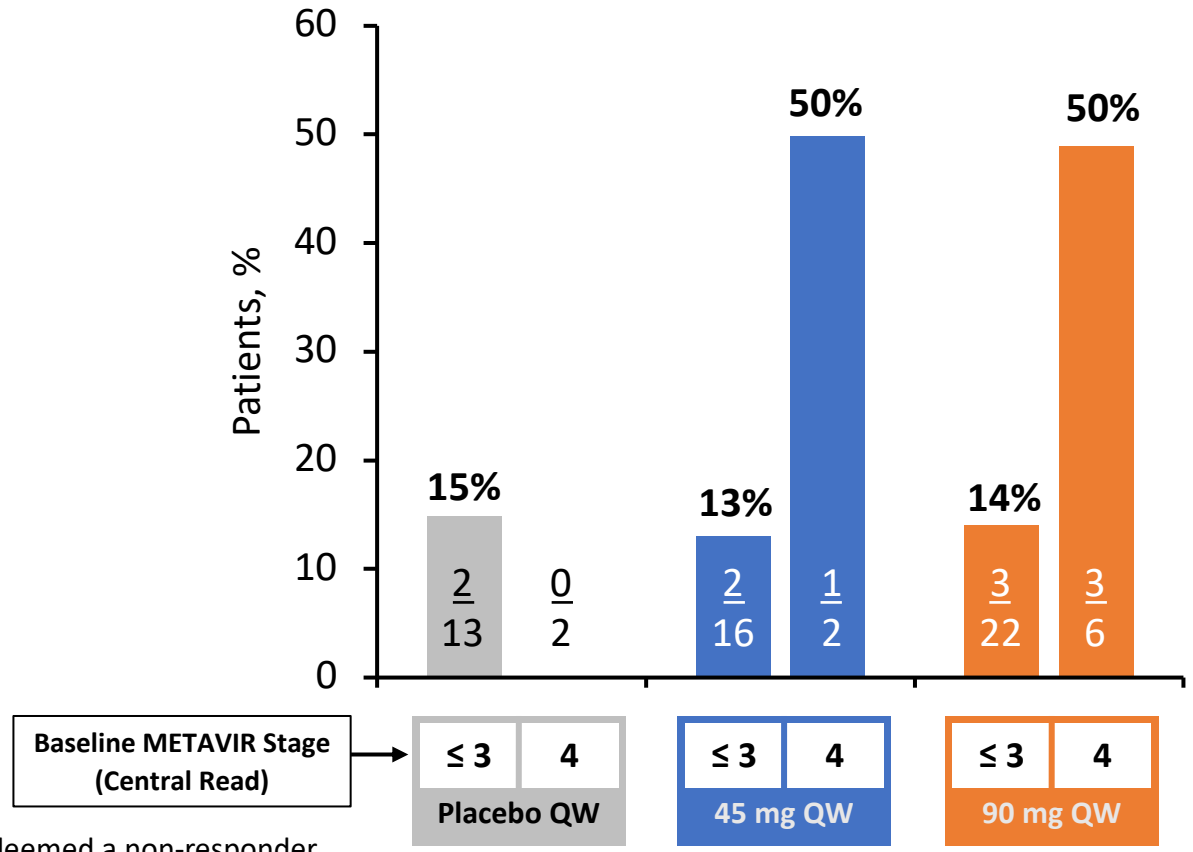
HSP47, heat shock protein 47; RBP, retinol-binding protein, RISC, RNA-induced silencing complex.

≥1 Stage Improvement in METAVIR at Week 12

≥ 1 METAVIR Stage Improvement, All Patients (Primary Endpoint)



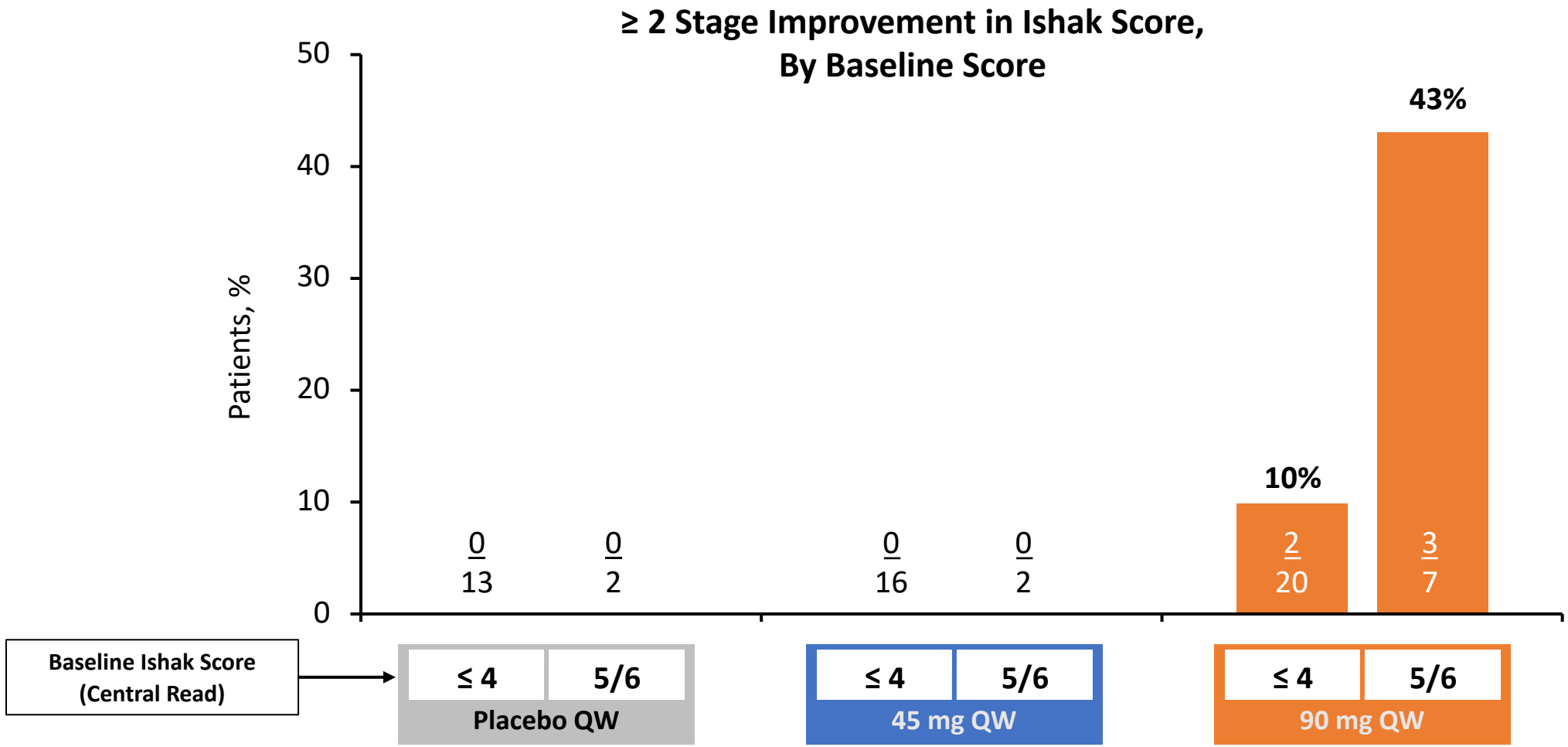
≥ 1 METAVIR Stage Improvement, By Baseline Stage



[a] 1 patient in BMS-986263 90 mg group (F2) had an inadequate Week 12 biopsy and was deemed a non-responder.

Lawitz, E et al., Presented at AASLD conference, November 2019

≥2 Stage Improvement in Ishak Score at Week 12

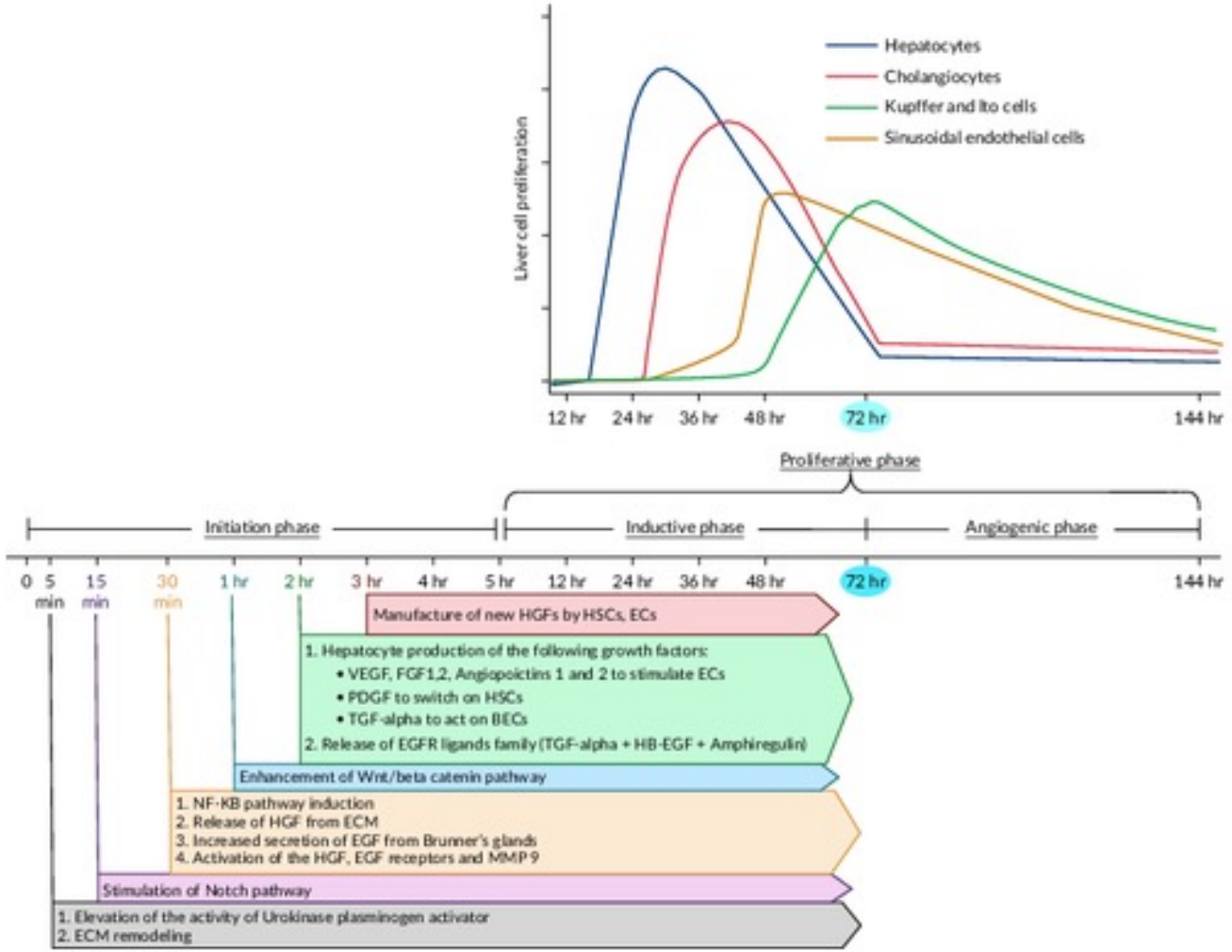


[a] 1 patient in BMS-986263 90 mg group (F2) had an inadequate Week 12 biopsy and was deemed a non-responder.

Lawitz, E et al., Presented at AASLD conference, November 2019

Liver Regeneration

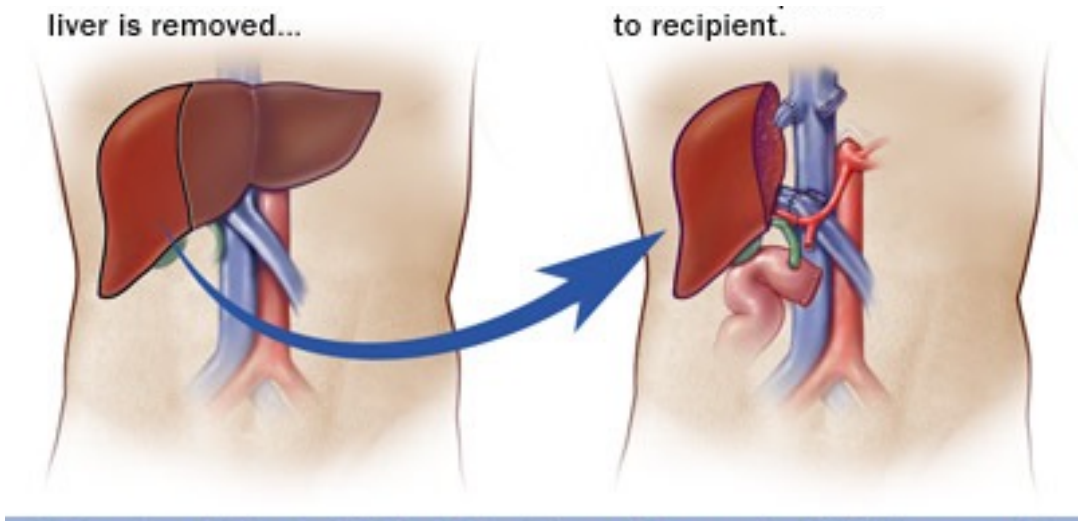
Temporal Sequence of Liver Regeneration After Partial Hepatectomy

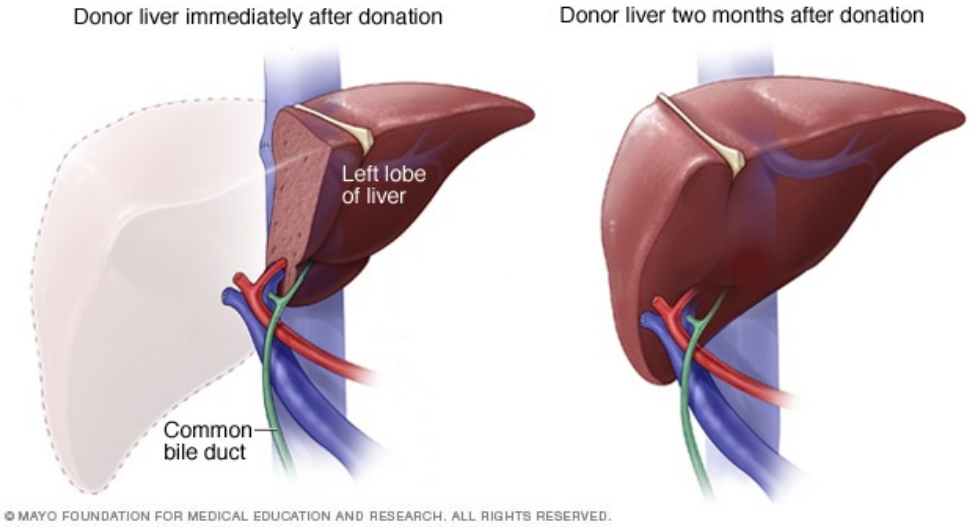


Rmilah AA et al., *WIREs Mechanisms of Disease*, Vol 8(3), 2019.

Is Liver Regeneration Possible?

- Yes!
- The liver has the greatest regenerative capacity of any organ in the body.
- Living Donor Liver Transplant (LDLT)





Summary

- The liver is the second most complex organ in the body after the brain.
- Fibrosis regression is possible in many when underlying disease is managed/cured.
- Questionable whether cirrhosis can be reversed.
- Regeneration: Living Donor Liver Transplant (LDLT)