LIVER STEATOSIS AND INSULIN RESISTANCE IN HEPATITIS C

from causes to consequences

Alfredo Alberti

Department of Histology,Microbiology and Medical Biotechnologies

Molecular Hepatology Unit

Venetian Institute of Molecular Medicine

University of Padova

ITALY

HEPATITIS C AS A METABOLIC DISEASE

HCV perturbs lipid metabolism

↓

Liver steatosis

HCV perturbs glucose homeostasis

↓

Insulin resistance

METABOLIC ABNORMALITIES AND HEPATITIS C

Which is the chicken ? ⟷ Which is the egg?

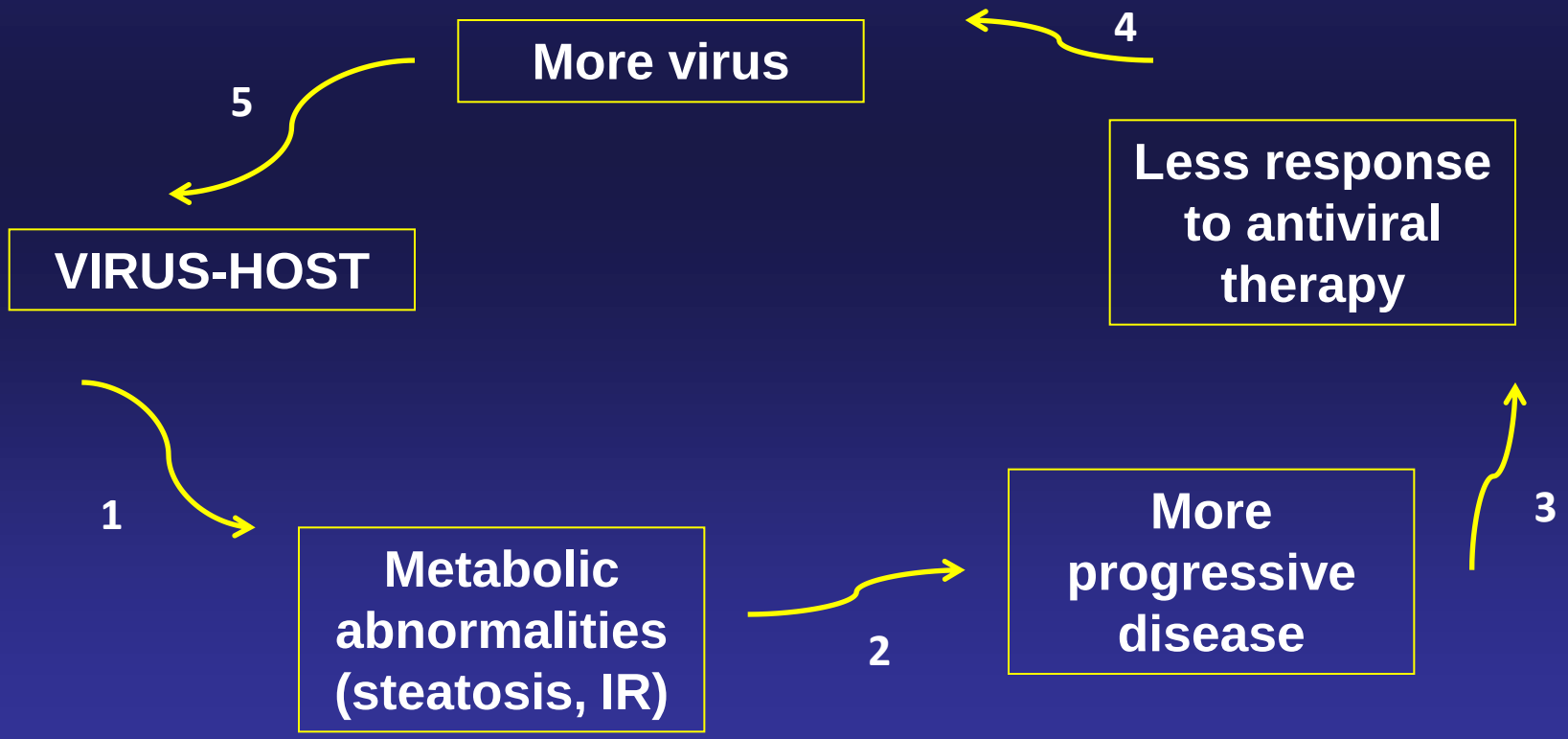
-VIRUS – INDUCED (viral steatosis-viral IR)

-HOST – INDUCED (Metabolic syndrome)

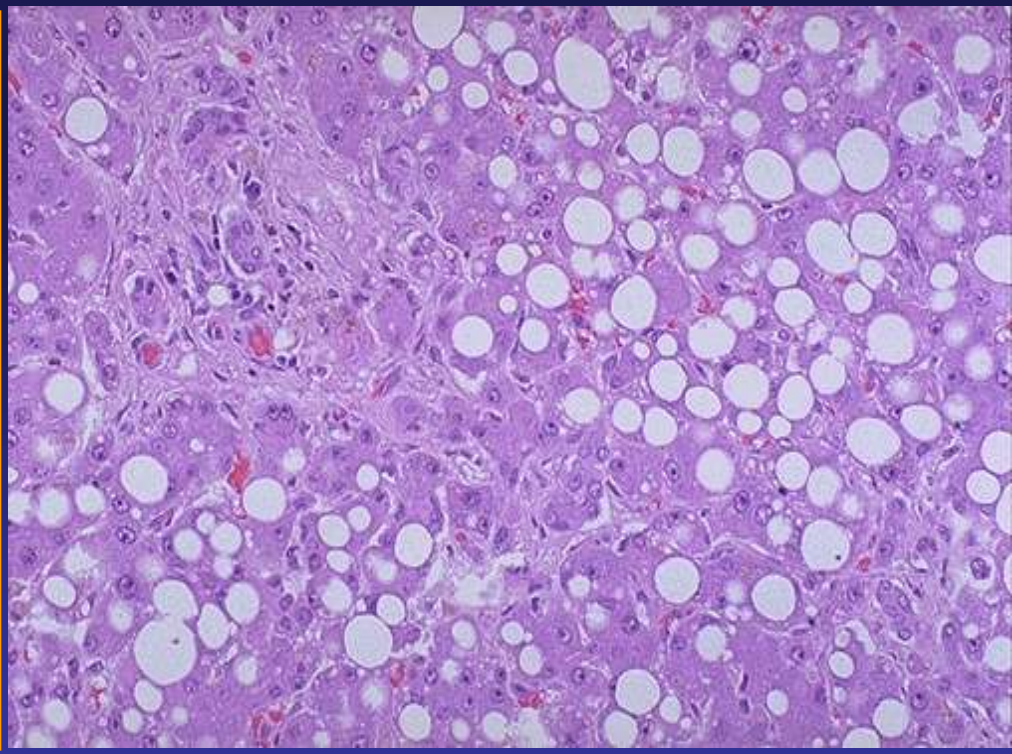
- MIXED – Triggered by HCV in a genetically and/or environmentally predisposed host

METABOLIC ABNORMALITIES AND HEPATITIS C

A VICIOUS CIRCLE OF GREAT CLINICAL IMPACT

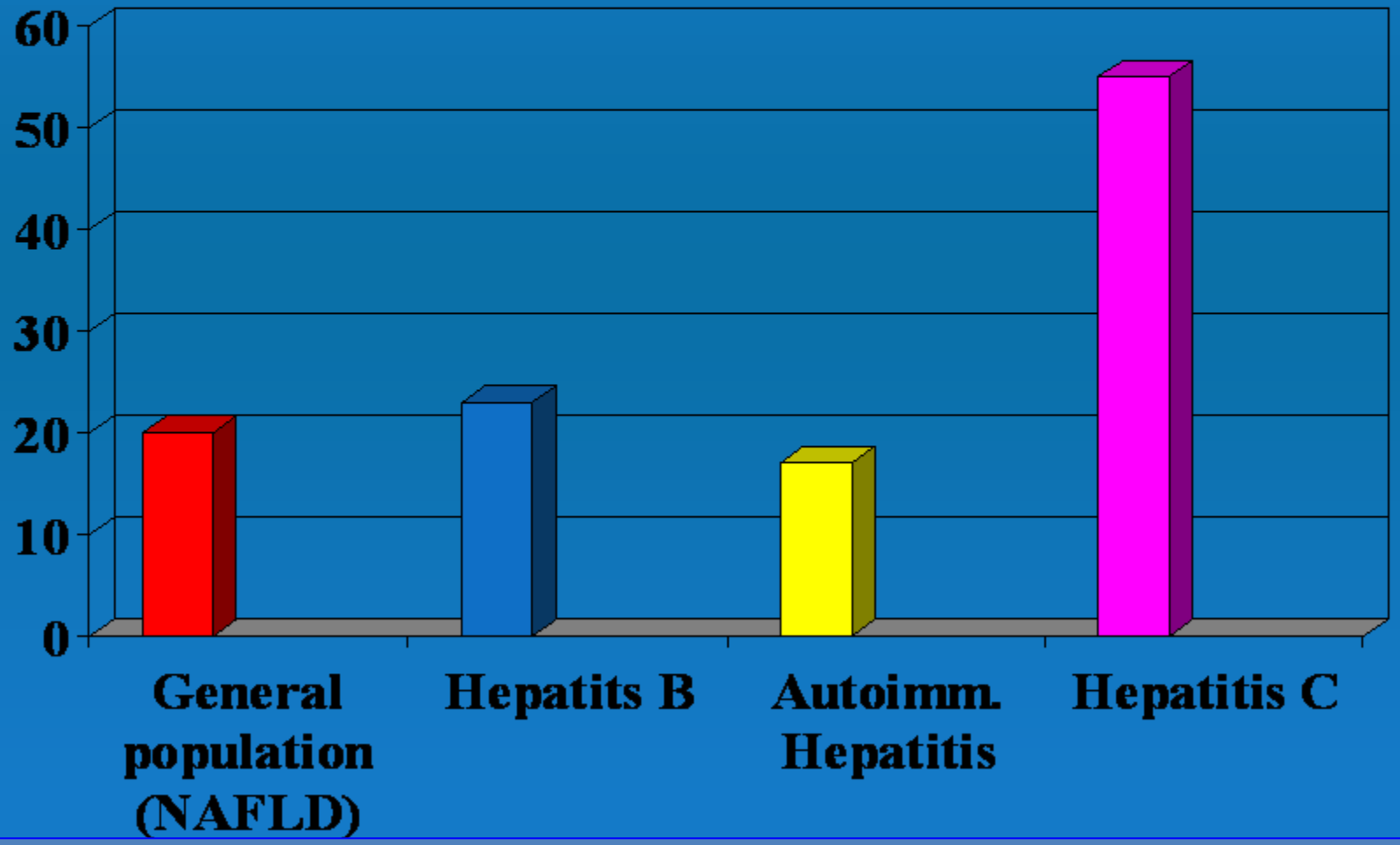


FATTY LIVER:
A FREQUENT FINDING IN HEPATITIS C



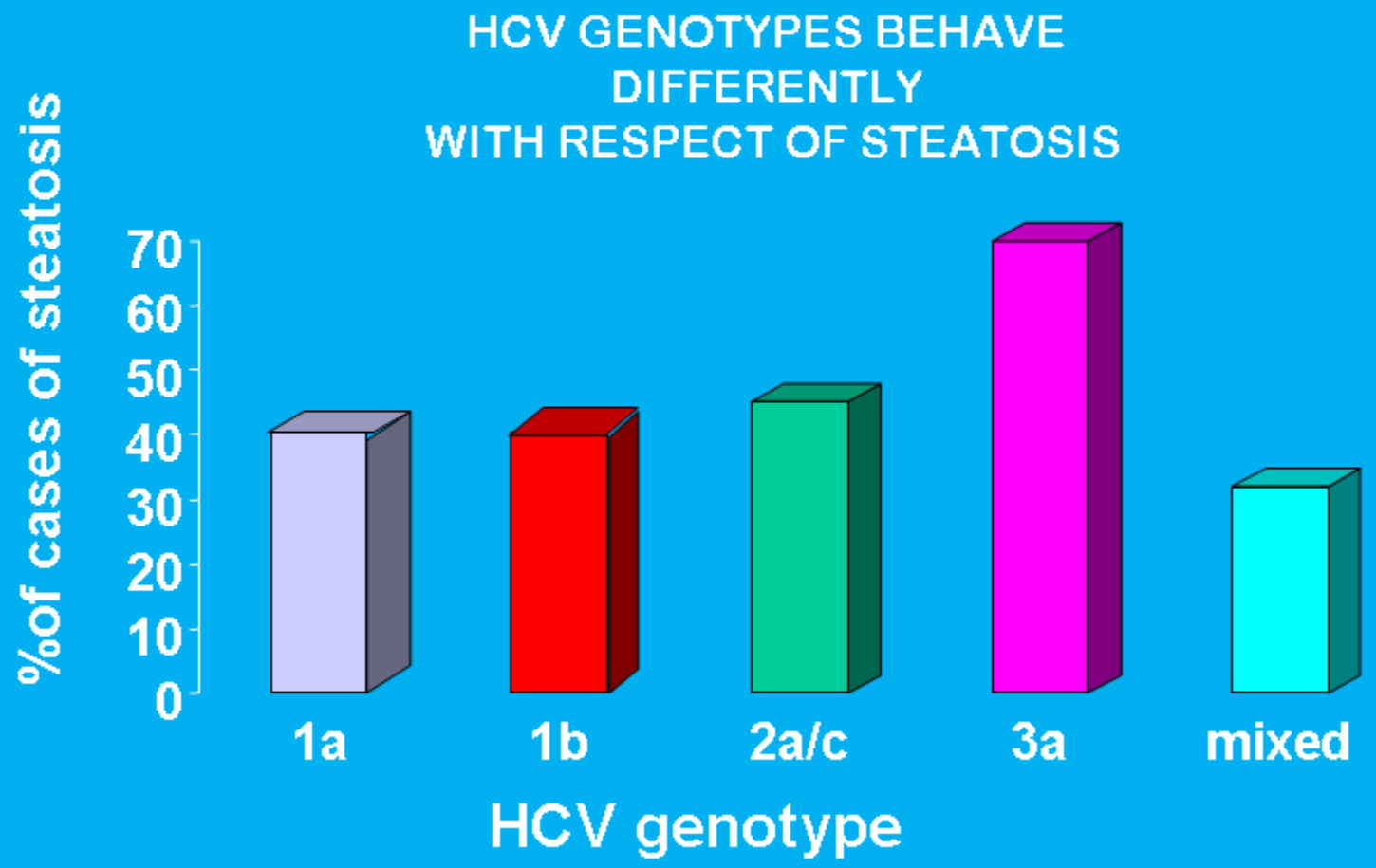
MEAN PREVALENCE OF STEATOSIS

(Lonardo A, Adinolfi LE et al. Gastroenterology 2004;126:586)



540 consecutive biopsy proven CHC

(Adinolfi LE et al. Hepatology 1999 and 2001 – Adinolfi 2009)



«viral» steatosis → Mainly HCV-3

→ No effect on response to IFN

→ Cleared by successful antiviral therapy

«host» steatosis → Mainly HCV-1 / 2

Associated with IR - MS

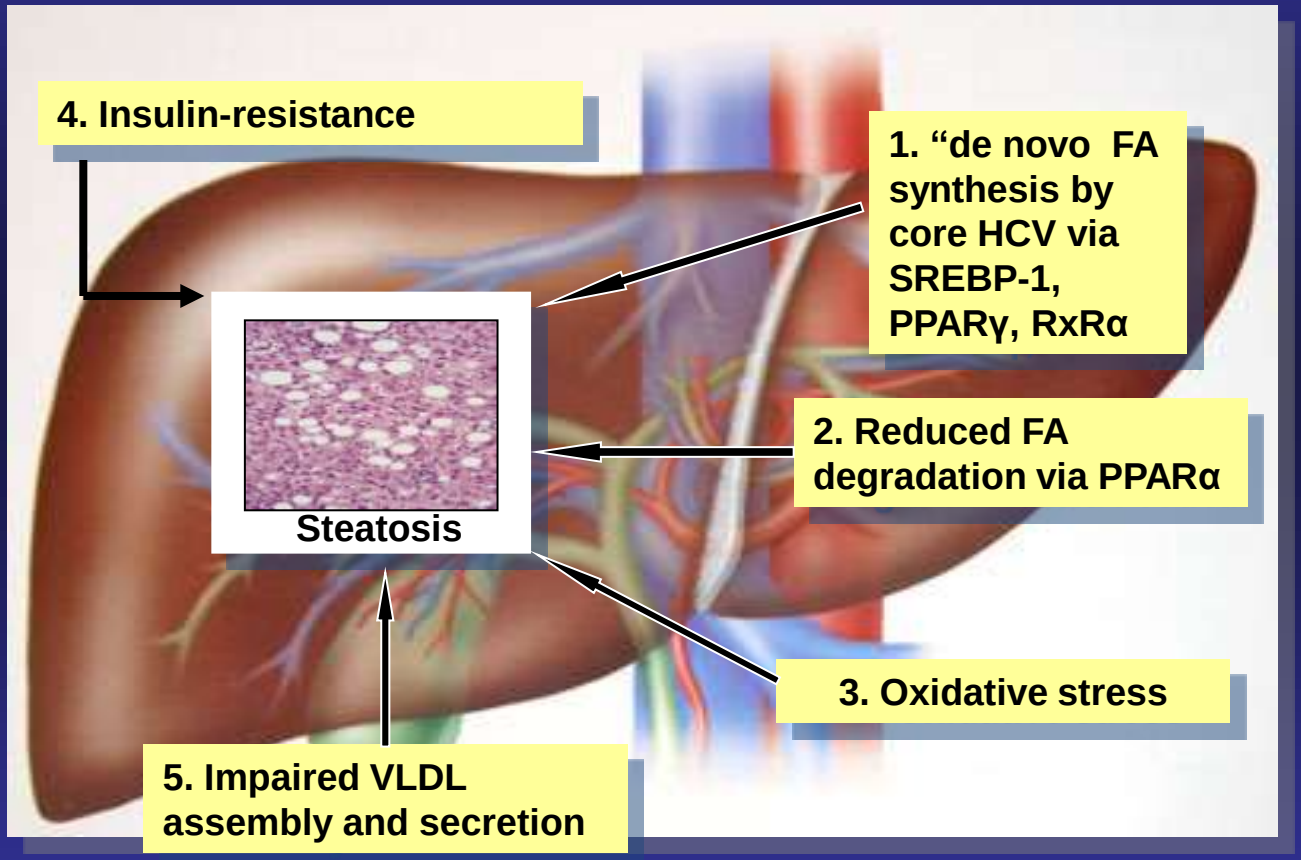
Reduced response to IFN

More progressive disease

Increased CV risk

MIXED FORMS ARE THE MOST FREQUENT PHENOTYPE

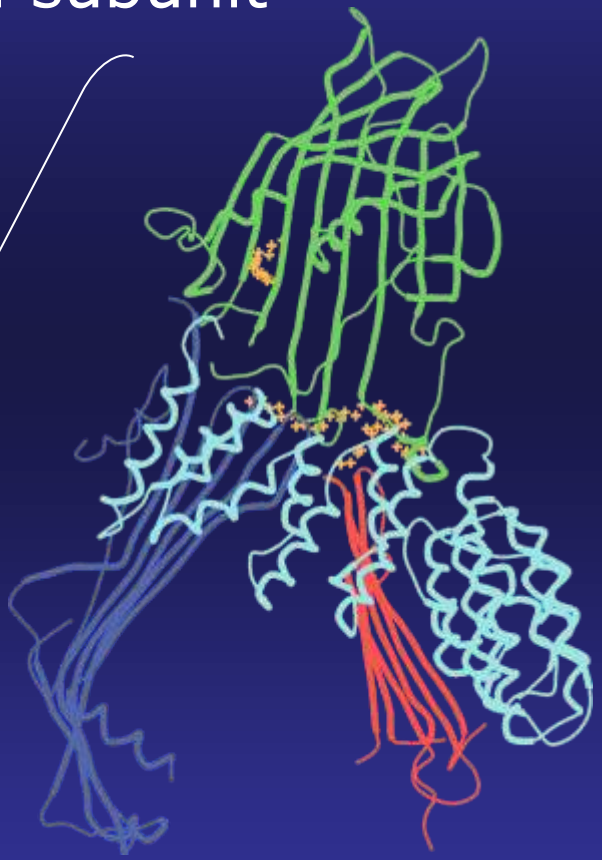
MECHANISMS OF VIRAL STEATOSIS IN HEPATITIS C



Microsomal Trygliceride Transfer Protein (MTP)

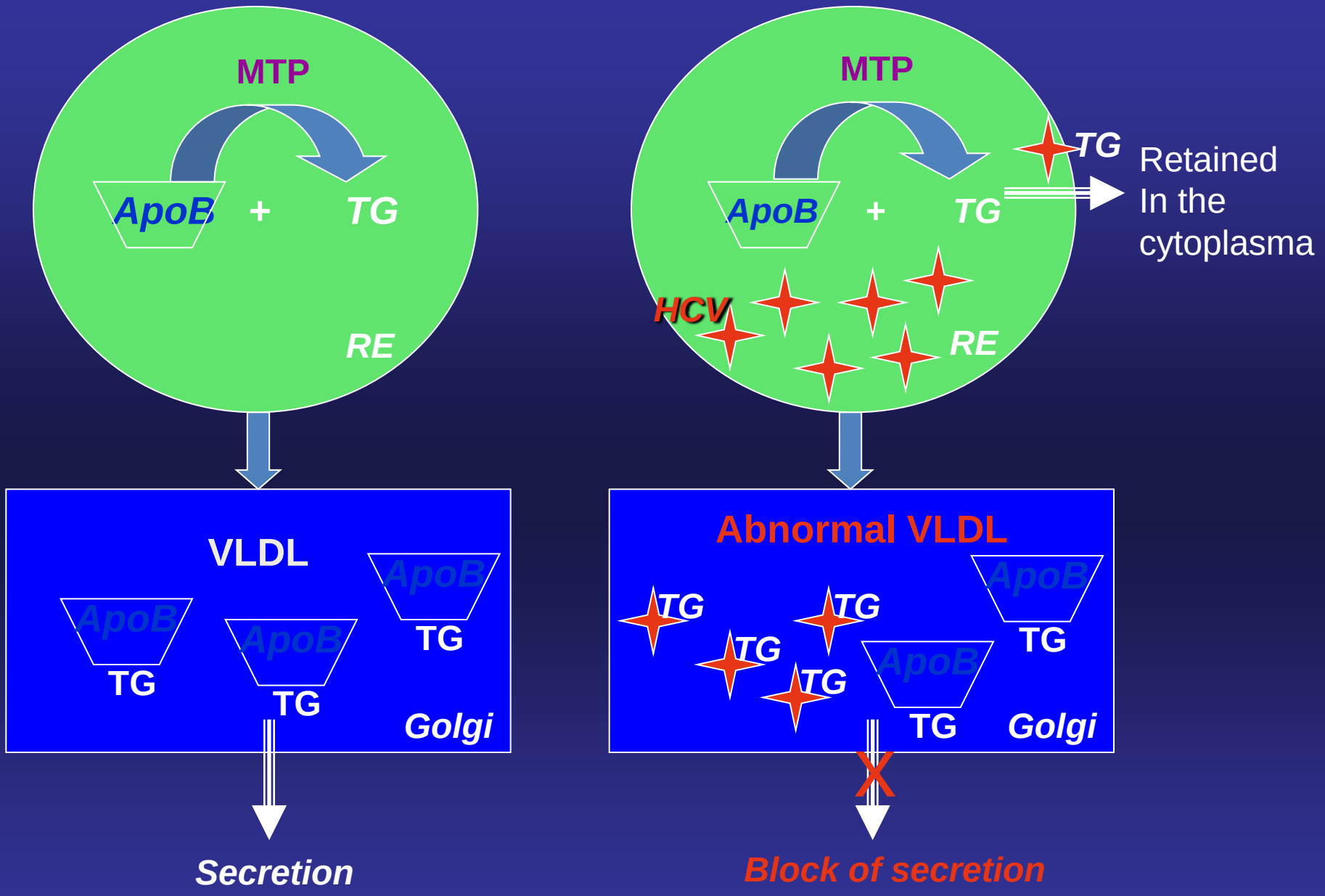
M subunit

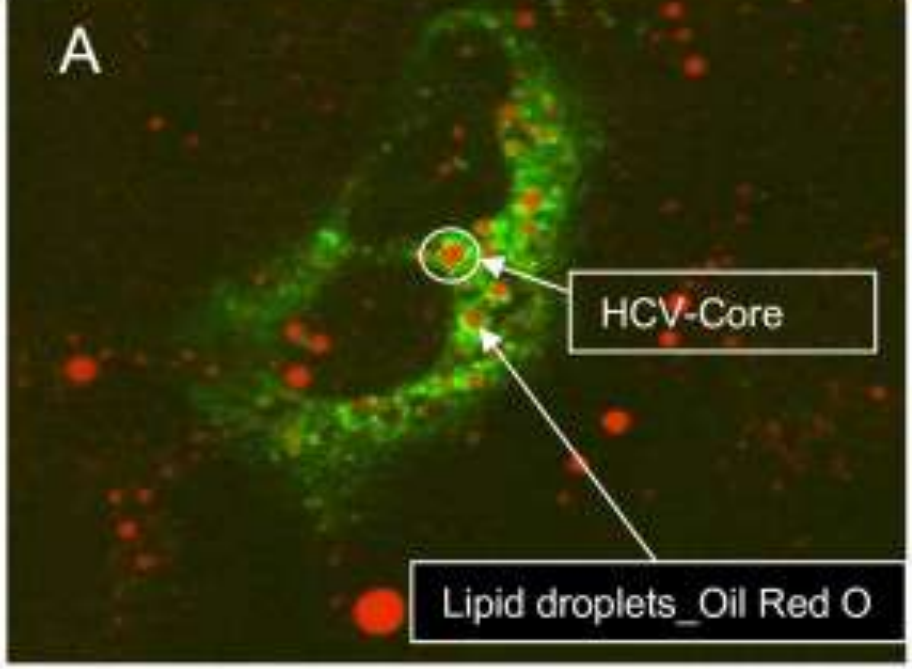
Membrane Association Domain

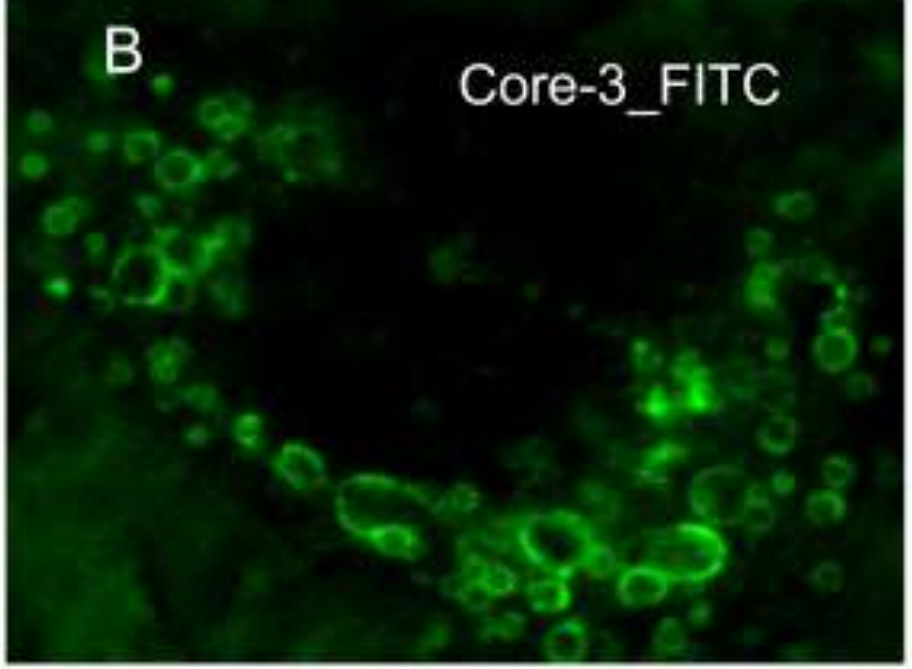


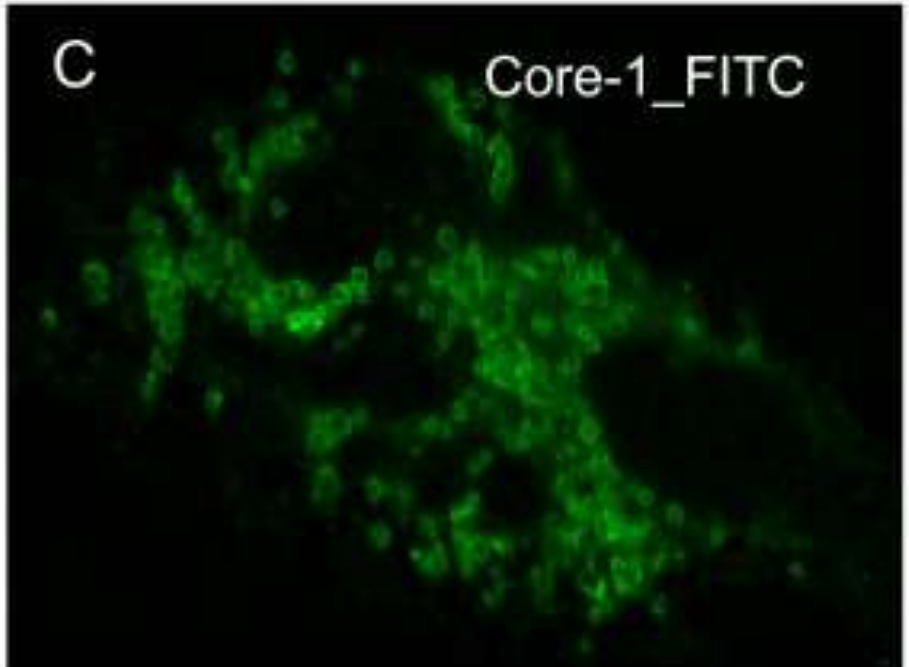
ApoB Binding Domain

Lipid Transfer Domain


MTP
ApoB
+
TG
RE
VLDL
ApoB
TG
ApoB
TG
ApoB
TG
Golgi
Secretion
MTP
TG
Retained
In the
cytoplasma
ApoB
+
TG
HCV
RE
Abnormal VLDL
TG
TG
TG
TG
ApoB
TG
ApoB
TG
Golgi
X
Block of secretion



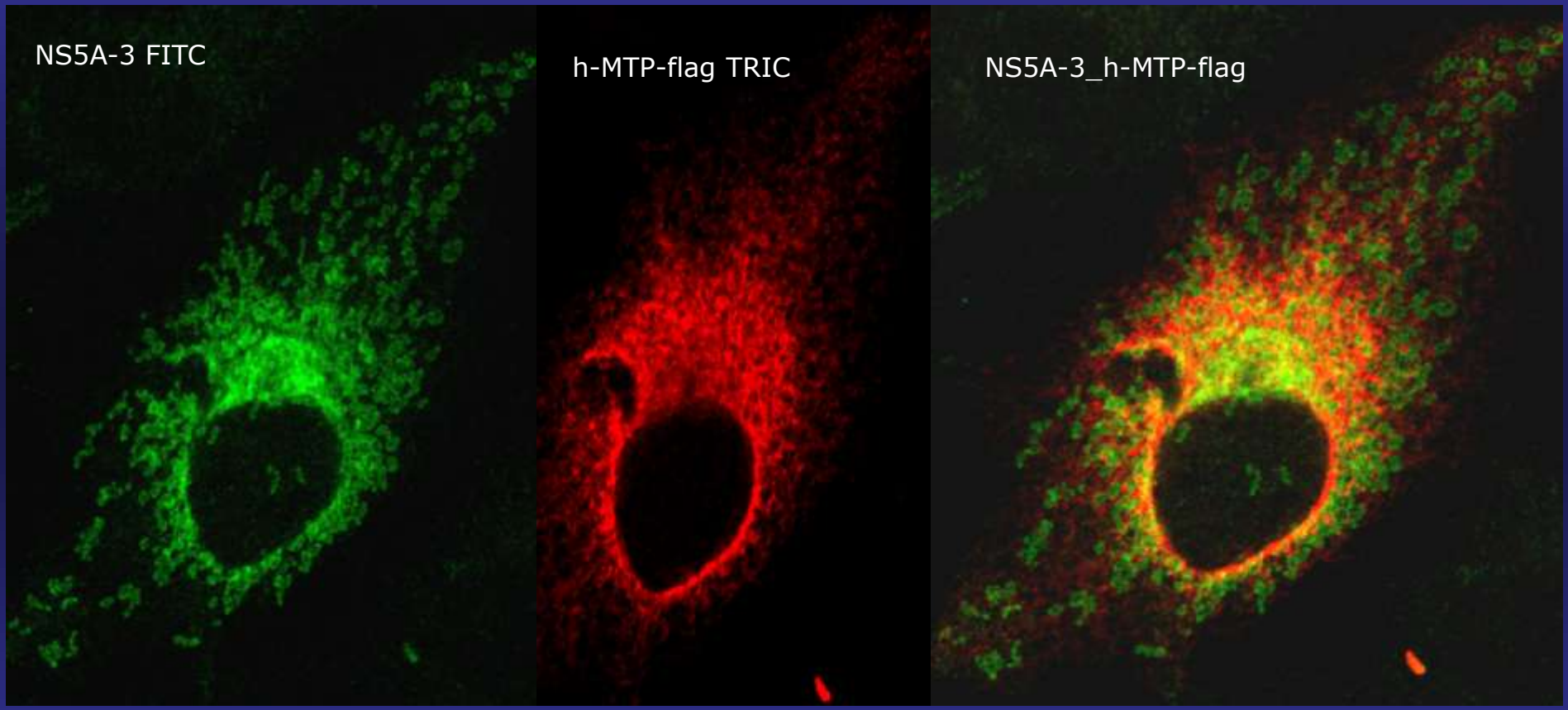




CORE PROTEIN OF HCV INDUCES LIPID DROPLETS IN LIVER CELLS

Mirandola et al 2010

NS5A HCV-3 colocalizes with MTP



Realdon et al 2011

GENETIC POLYMORPHISM OF MTP AND LIVER STEATOSIS IN HEPATITIS C

MTP(493)	% SEVERE STEATOSIS		
	HCV-1	HCV-2	HCV-3
TT	43%	39%	68%
GT	33%	30%	41%
GG	12%	10%	28%

Mirandola et al 2009

Mirandola et al. Nutrition & Metabolism 2010, 7:13
http://www.nutritionandmetabolism.com/content/7/1/13

Nutrition&Metabolism

REVIEW Open Access

Hepatic steatosis in hepatitis C is a storage disease due to HCV interaction with microsomal triglyceride transfer protein (MTP)

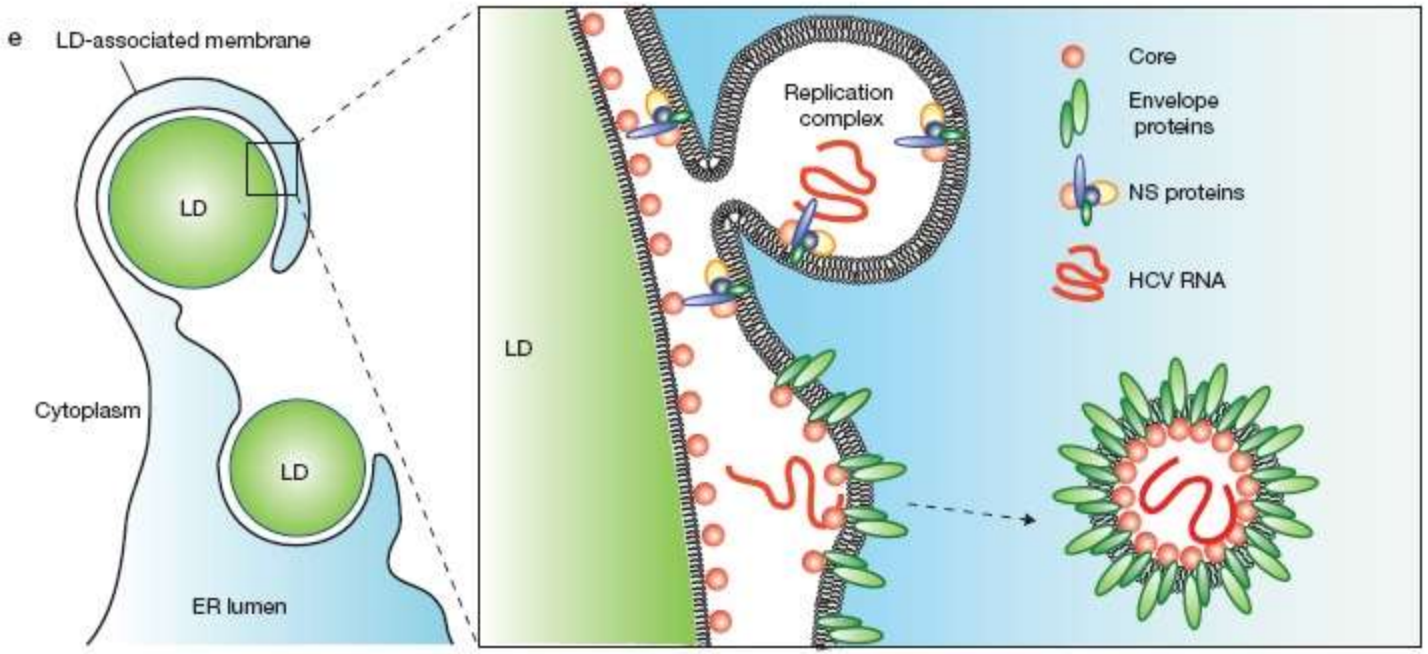
Silvia Mirandola[1], David Bowman[2], Mahmood M Hussain[2*], Alfredo Alberti[1*]

Patients with Viral steatosis have :

Liver accumulation of abnormal VLDL vescicles

Low plasma levels of { Cholesterol, Triglycerides, ApoB }

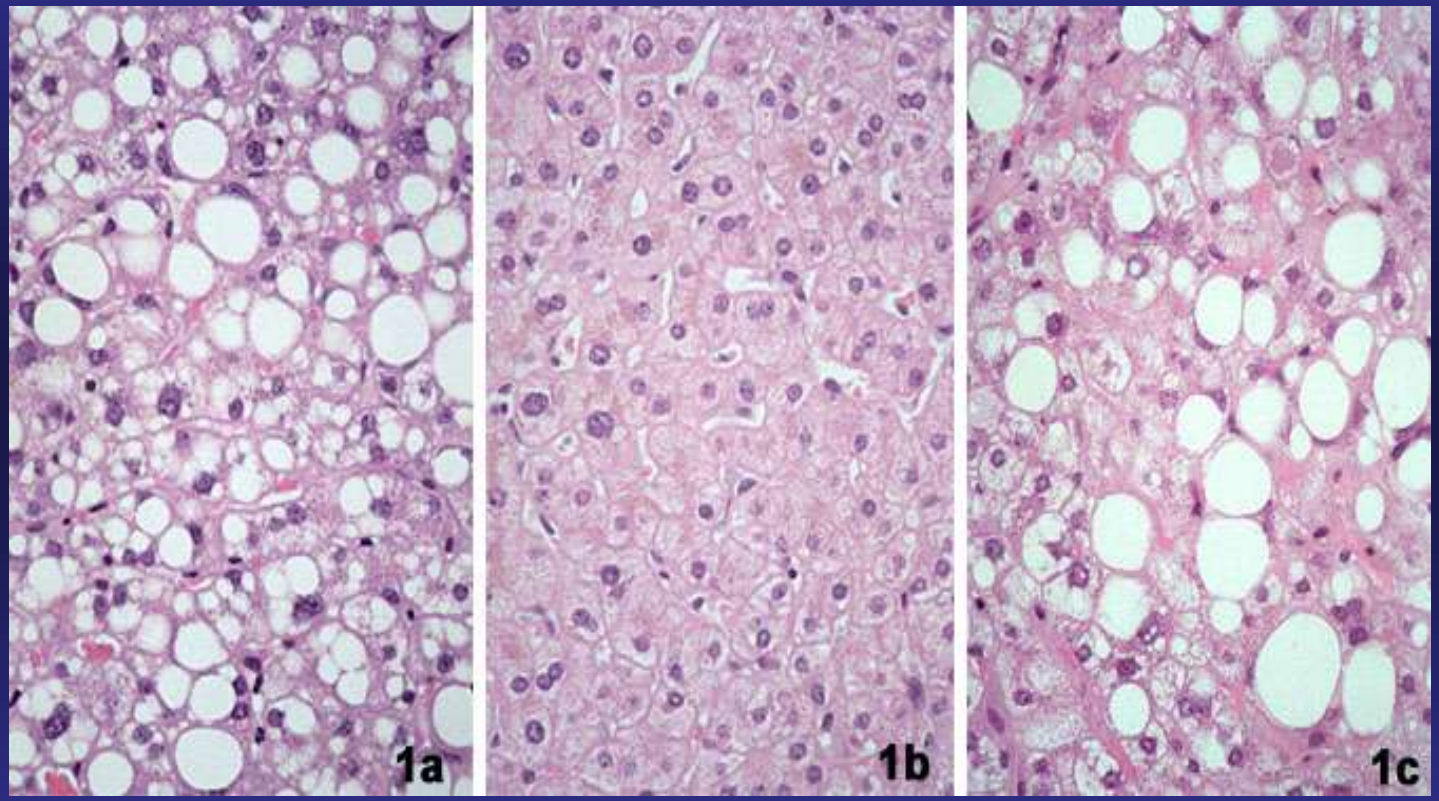
Lipid droplets are important organelles for hepatitis C virus production



A VIRUS THAT RIDES THE LIPOPROTEIN BUS !

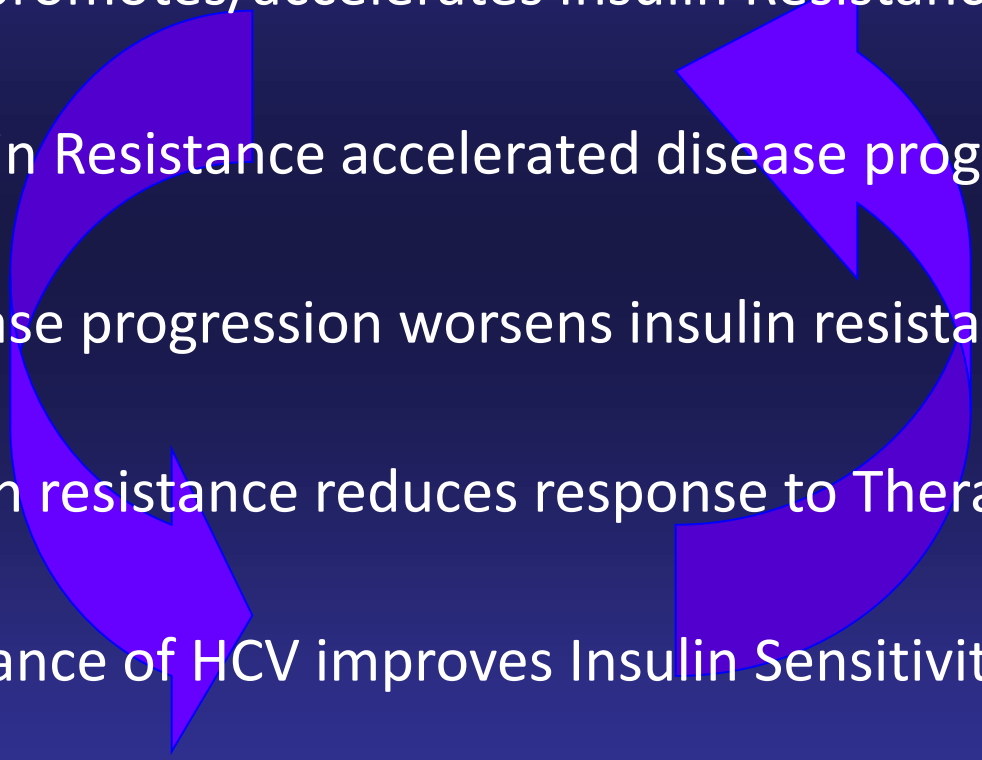
Miyanari et al, Nat Cell Biol, 2007; 9: 961

VIRAL STEATOSIS IN A PATIENT WITH HEPATITIS C AND EFFECT OF ANTIVIRAL THERAPY



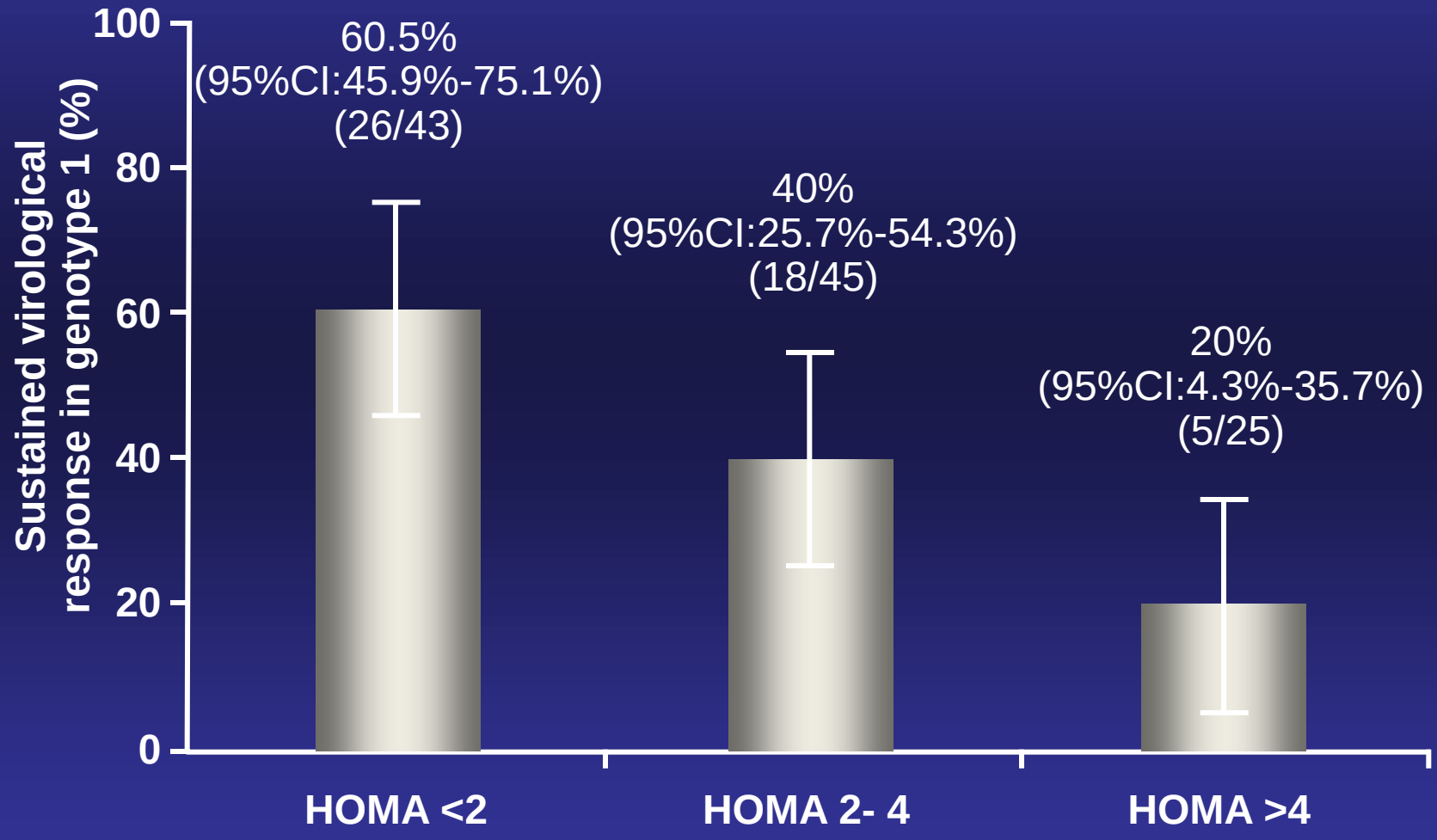
	Before IFN	After IFN	After reactivation
HCV-RNA	+++	neg	++++

INSULIN RESISTANCE AND HEPATITIS C
a Vicious Circle with Great Clinical Impact



- HCV promotes/accelerates Insulin Resistance
- Insulin Resistance accelerated disease progression
- Disease progression worsens insulin resistance
- Insulin resistance reduces response to Therapy
- Clearance of HCV improves Insulin Sensitivity

Insulin resistance impairs response: peginterferon alfa-2b (12KD) + ribavirin

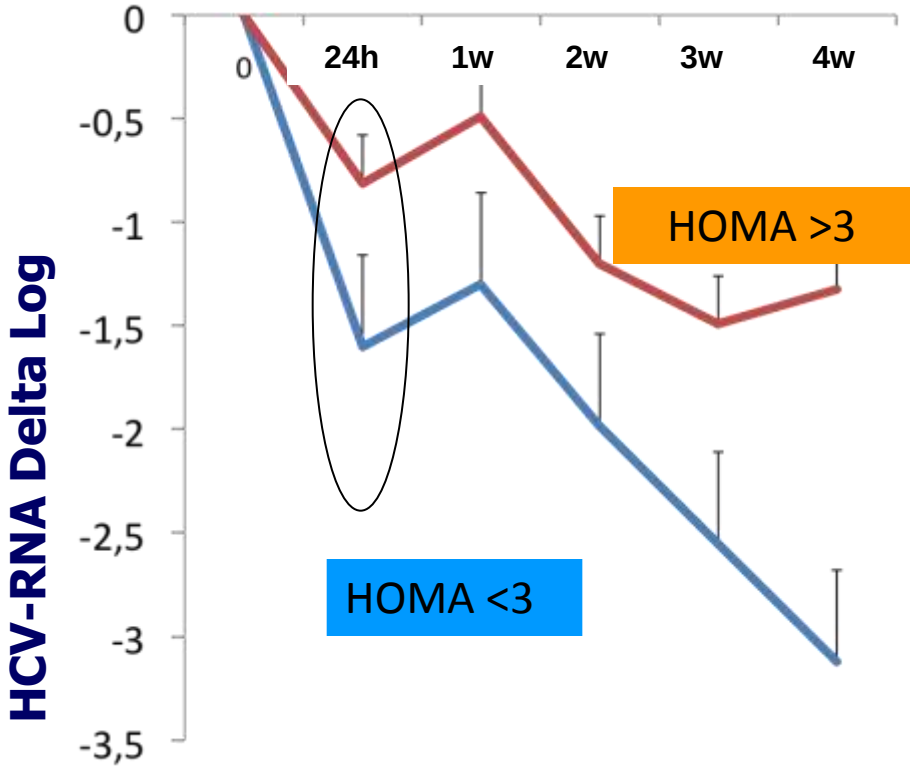


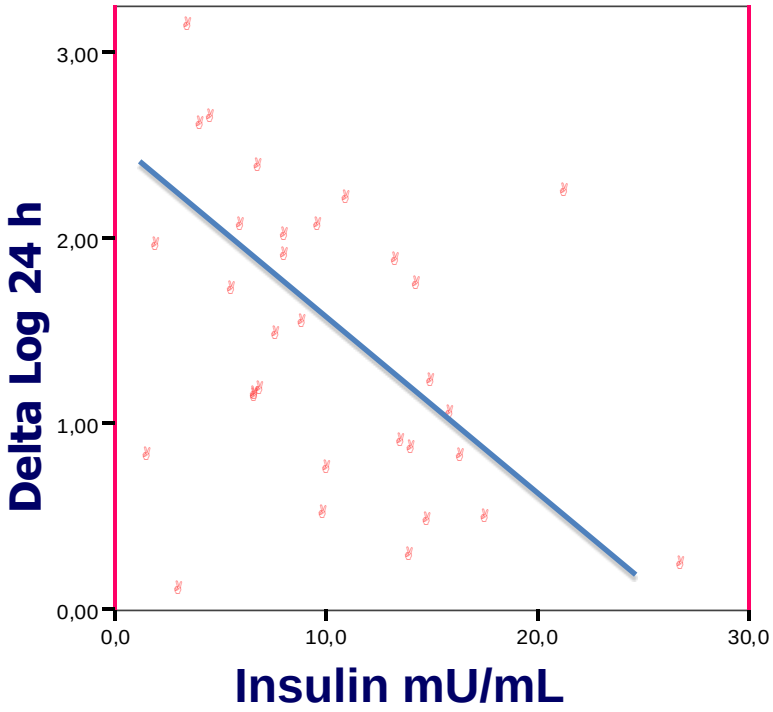
Romero-Gomez M *et al*. *Gastroenterology* 2005

MECHANISMS OF INSULIN RESISTANCE IN HEPATITIS C

- Direct effect of HCV in infected cells
  SOCS3 overexpression
- "Indirect" effect of chronic HCV infection
  upregulation of cytokines
  IL7
  IL18
  TNFalfa

VERY RAPID (24 hrs) RESPONSE TO IFN AND BASELINE IR AND INSULIN LEVELS





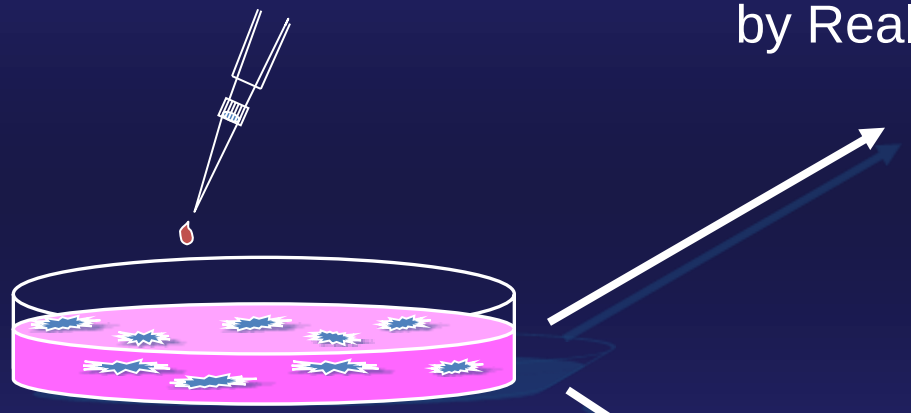
Bortoletto G, 2007

RECIPROCAL INTERFERENCE BETWEEN INSULIN AND INTERFERON-alpha SIGNALLING IN HEPATIC CELLS

Franceschini et al 2011

(INSULIN and IFN-alpha)

Gene Expression analysis
by Real Time PCR



Hepatoma cell line
(HepG2)

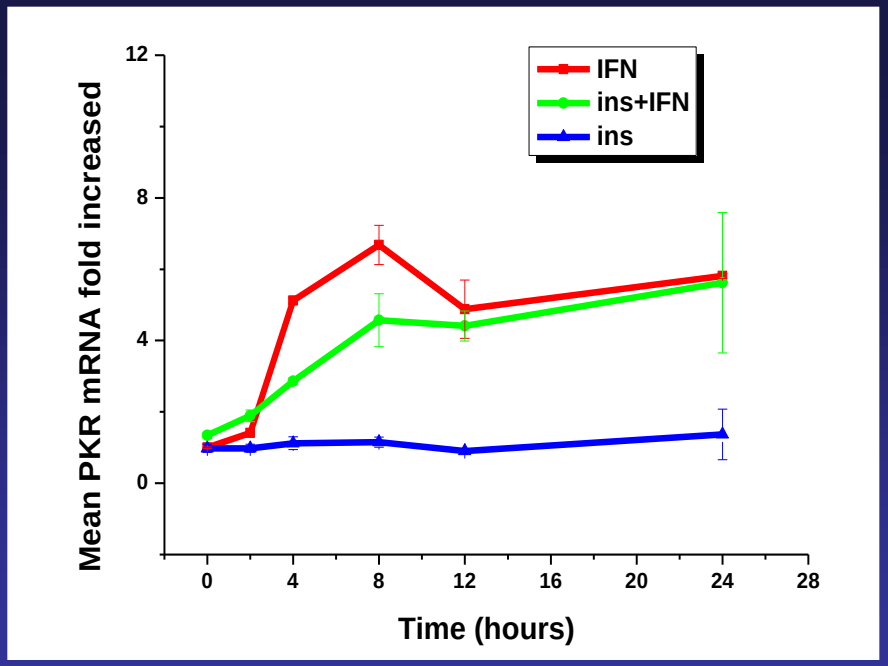
Protein expression analysis
by Western Blot

VIMM

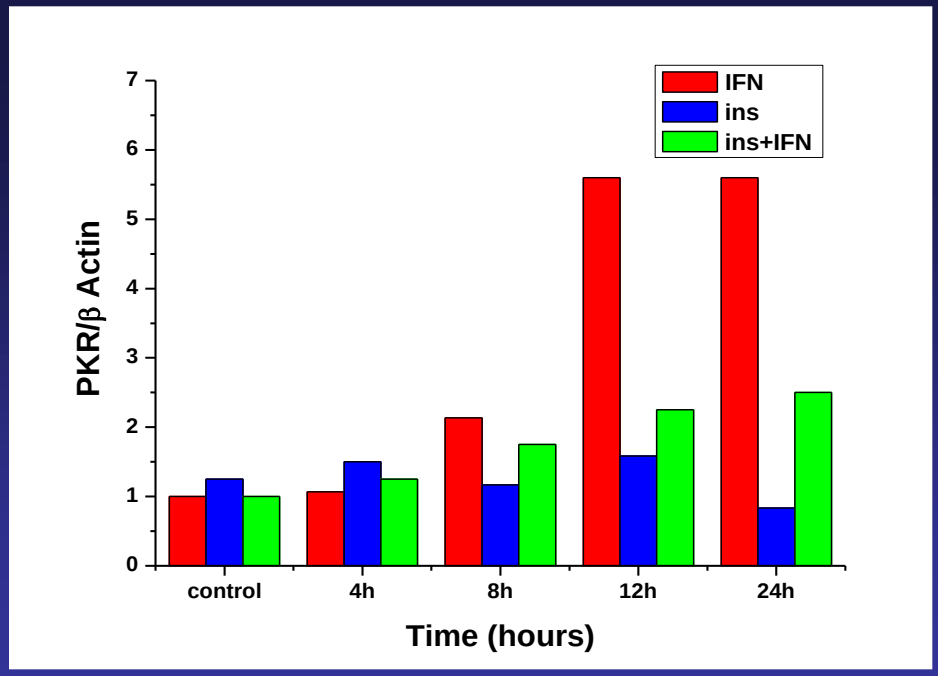
➢ INSULIN INHIBITS IFN-alpha SIGNALLING ON ISGs

• PKR

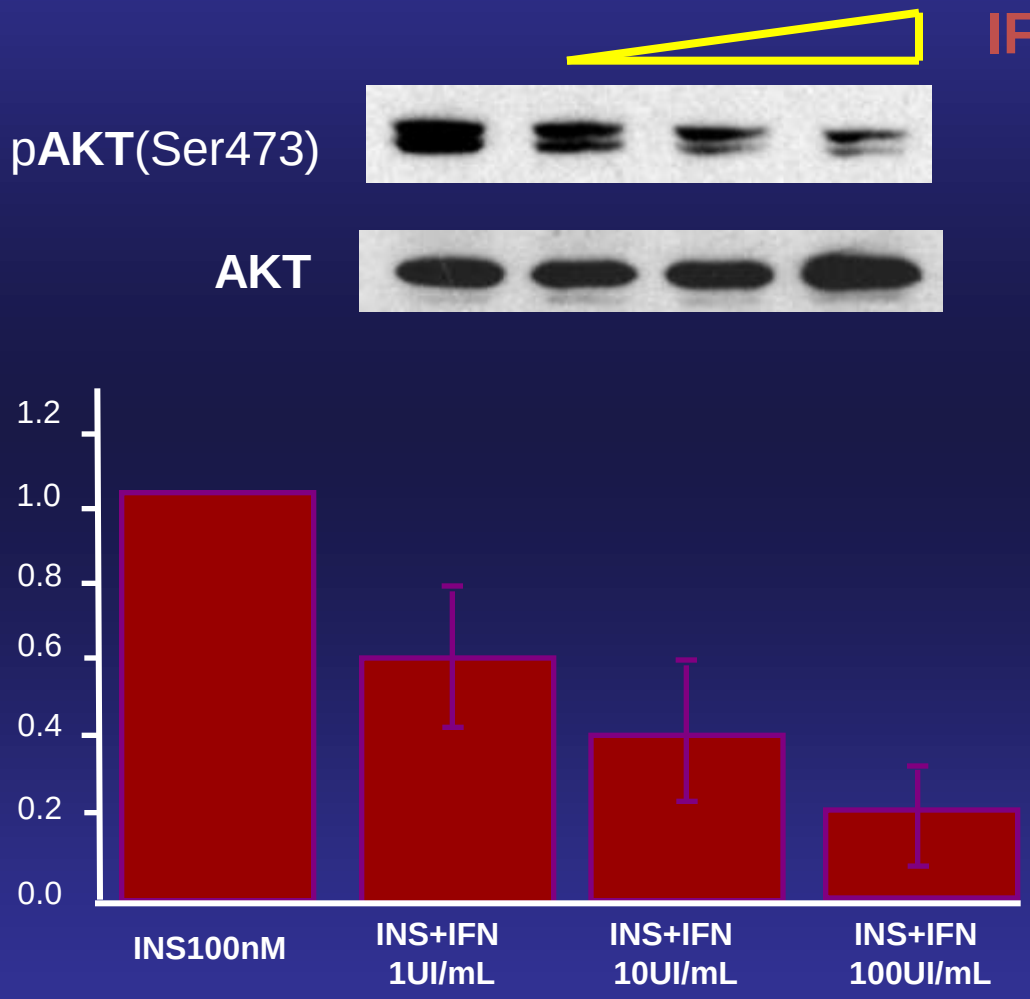
Gene expression



Protein expression



INTERFERON alpha INHIBITS AKT ACTIVATION BY INSULIN SIGNALLING



HOW TO MANAGE THESE METABOLIC DISARRANGEMENTS IN HEPATITIS C ?

To reduce fibrosis progression

To improve response to antiviral therapy

FIRST → Define the cause vs the consequence

SECOND → Treat the cause to correct the consequence

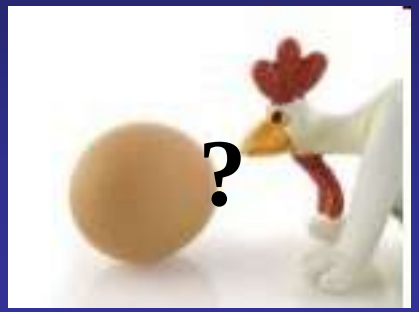
VIRUS - INDUCED

TREAT HCV

HOST - ASSOCIATED

TREAT HOST

MIXED



IMPROVING STEATOSIS AND INSULIN SENSIIVITY IN HCV

Diet and physical activity → useful in
- Obese
- Metabolic syndrome
- When succesful

Antiviral therapy → adequate
- Virus-induced IR
- Virus-induced steatosis
- With SVR

Insulin sensitizers → metformin, glitazones → Need further evolution

The Best Solution Still is

First International Course of Translational Hepatology, Florence, 2011