

# Combination Development for Pre-Cirrhotic NASH

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**THE FORUM**

For Collaborative Research<sup>SM</sup>

# Disclosures

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- **Consultant/Advisor:**
  - Allergan, Allysta, Arrowhead, ARTham, Axcella, Blade, Boehringer Ingelheim, BMS, Coherus, Consynance, Cymabay, Durect, Enanta, Fortress, Gelesis, Gilead, HistoIndex, Intercept, Lipocine, Madrigal, Medimmune, Merck, Metacrine, Mundipharma, NGM, pH-Pharma, Prometheus, Siemens
- **Institutional research grants:**
  - Allergan, BMS, Cirus, Cymabay, Enanta, Galectin, Genfit, Gilead, Intercept, Madrigal, NGM, Prometheus

# Pathogenesis of NASH

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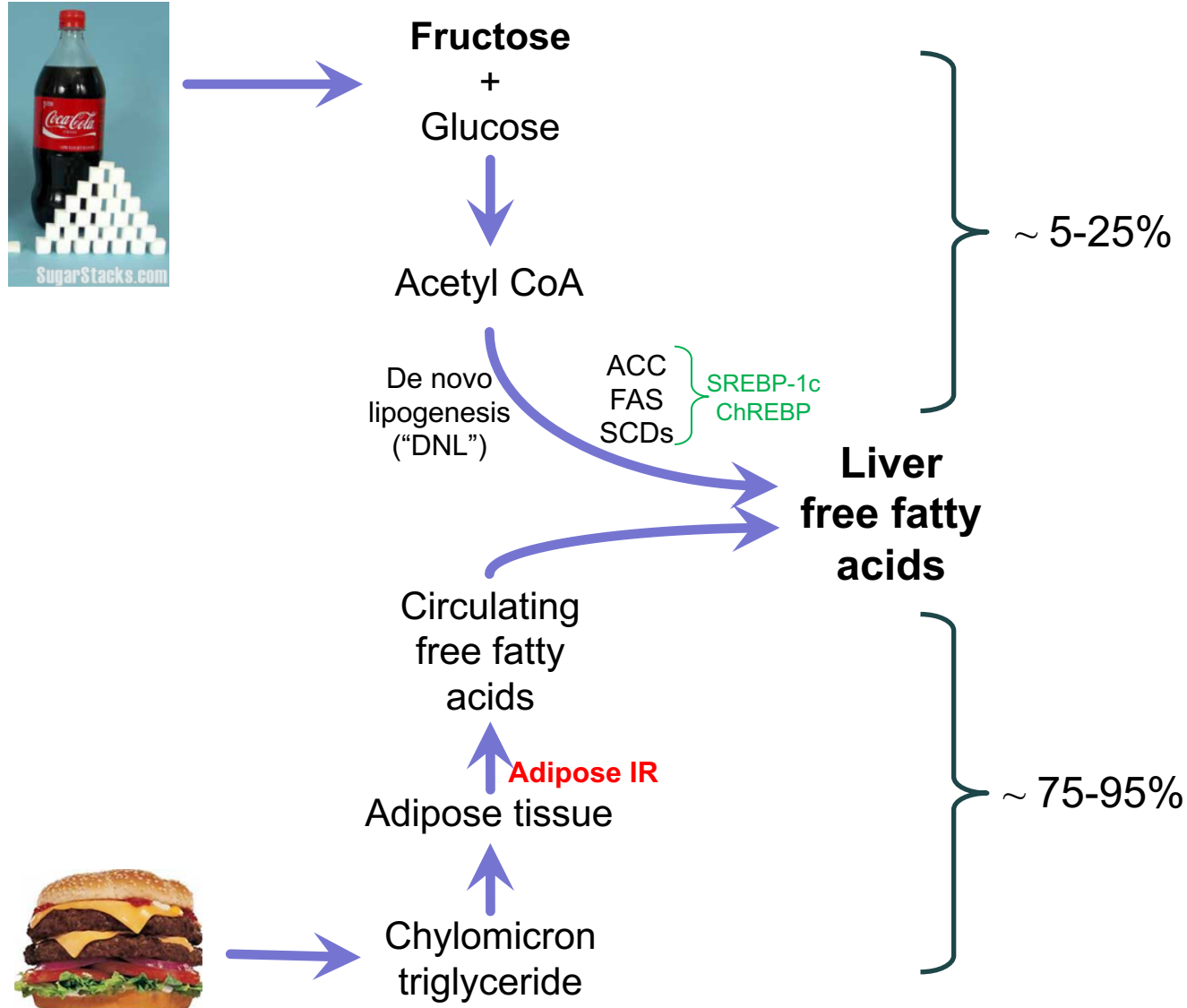
- “Substrate overload lipotoxic liver injury”
  - Free fatty acids promote the generation of toxic lipids
    - Neuschwander-Tetri BA. Hepatology 2010; 52:774-788.
    - Cusi K. Gastroenterology 2012;142:711-725.
    - Fuchs M, Sanyal AJ. J Hepatol 2012;56:291-293.
    - Machado and Diehl. Gastroenterology 2016;150:1769-1777.
    - Hirsova P et al (Gores). J Lipid Res 2016;57:1758-1770.
    - Mota M et al (Sanyal). Metabolism 2016;65:1049-61.
    - Marra F, Svegliati-Baroni G. J Hepatol 2018;68:280-295.
    - Musso G et al. Gastroenterology 2018;155:282-302.
- What happened to the “Two-hit hypothesis”?
  - (Hit 1: steatosis, Hit 2: oxidant stress, lipid peroxidation, injury)
  - Degree of steatosis does not correlate with NASH severity or outcomes
    - Angulo et al. Gastroenterology (2015) 149:389-397
  - Oxidant stress occurs but not yet shown to be necessary

# Substrate Overload Lipotoxic Liver Injury (NASH)

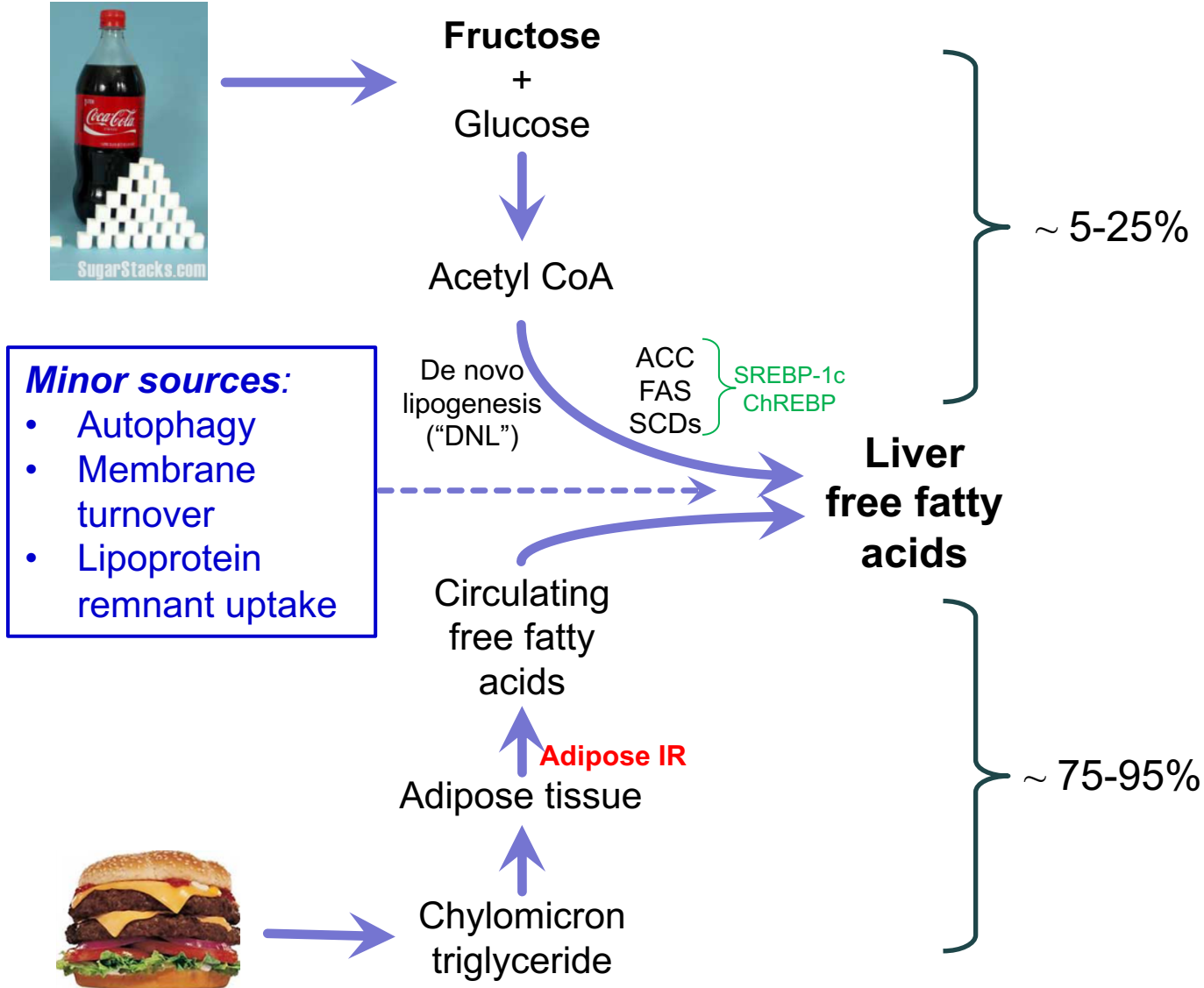
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**Liver  
free fatty  
acids**

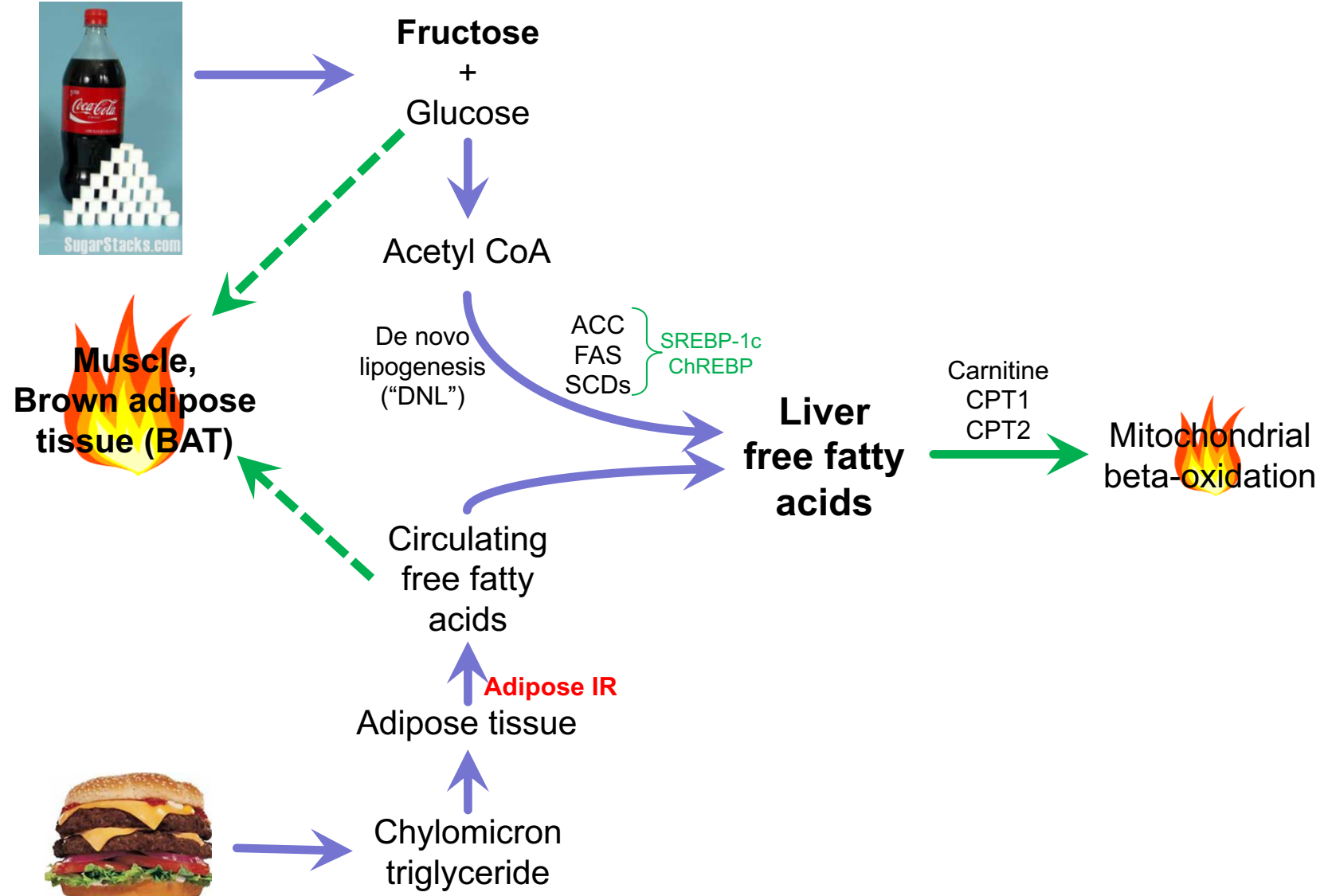
# Substrate Overload Lipotoxic Liver Injury (NASH)



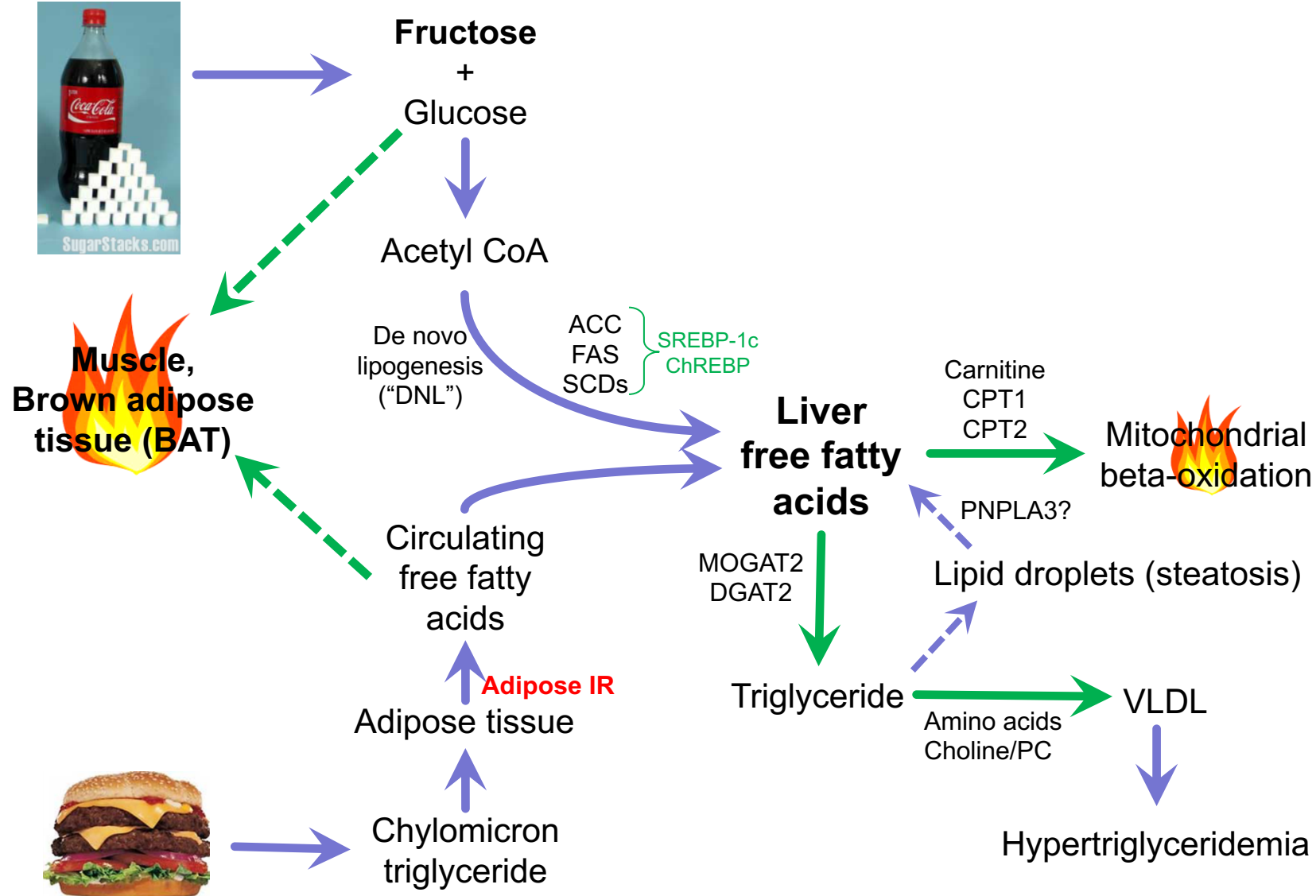
# Substrate Overload Lipotoxic Liver Injury (NASH)



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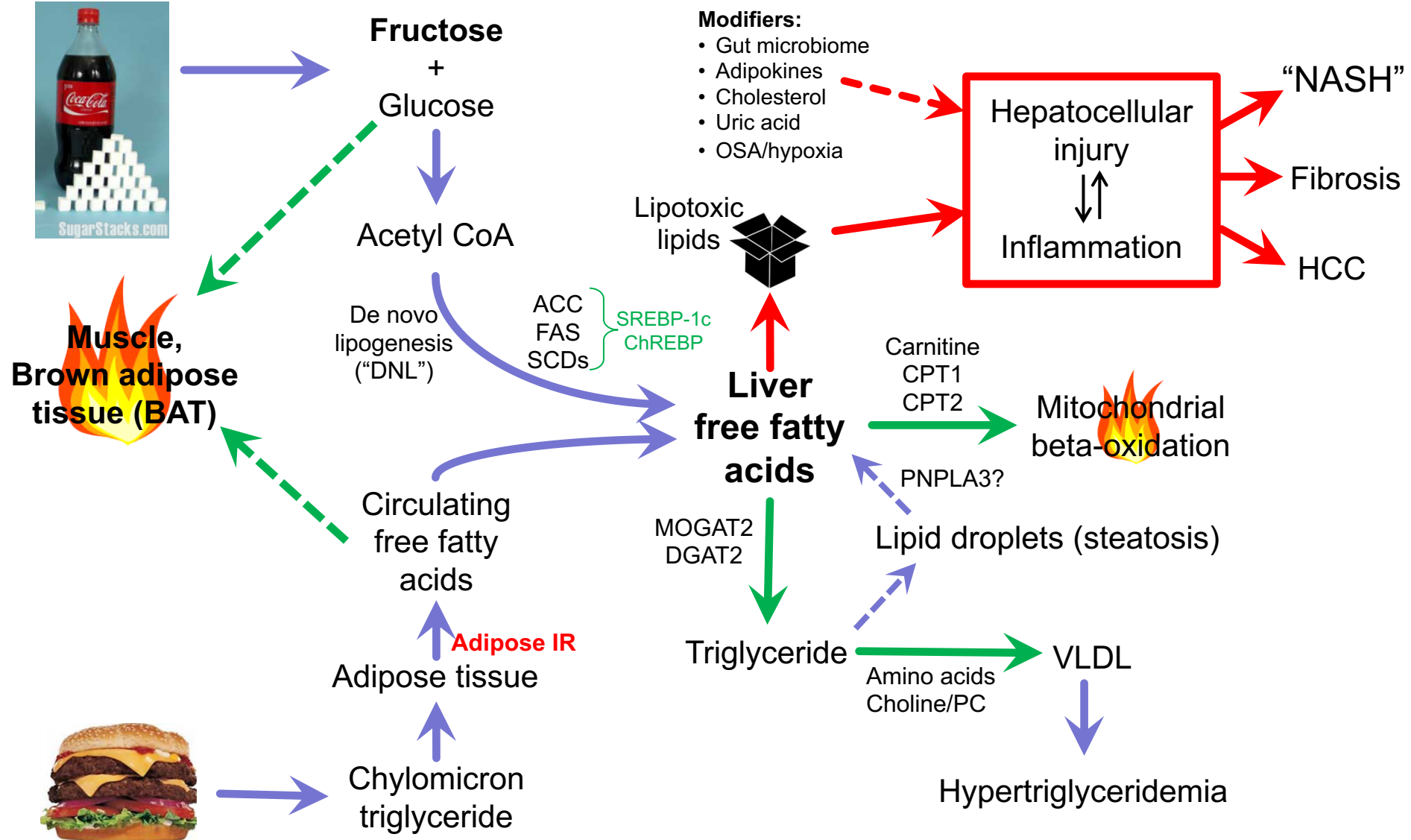


# Substrate Overload Lipotoxic Liver Injury (NASH)

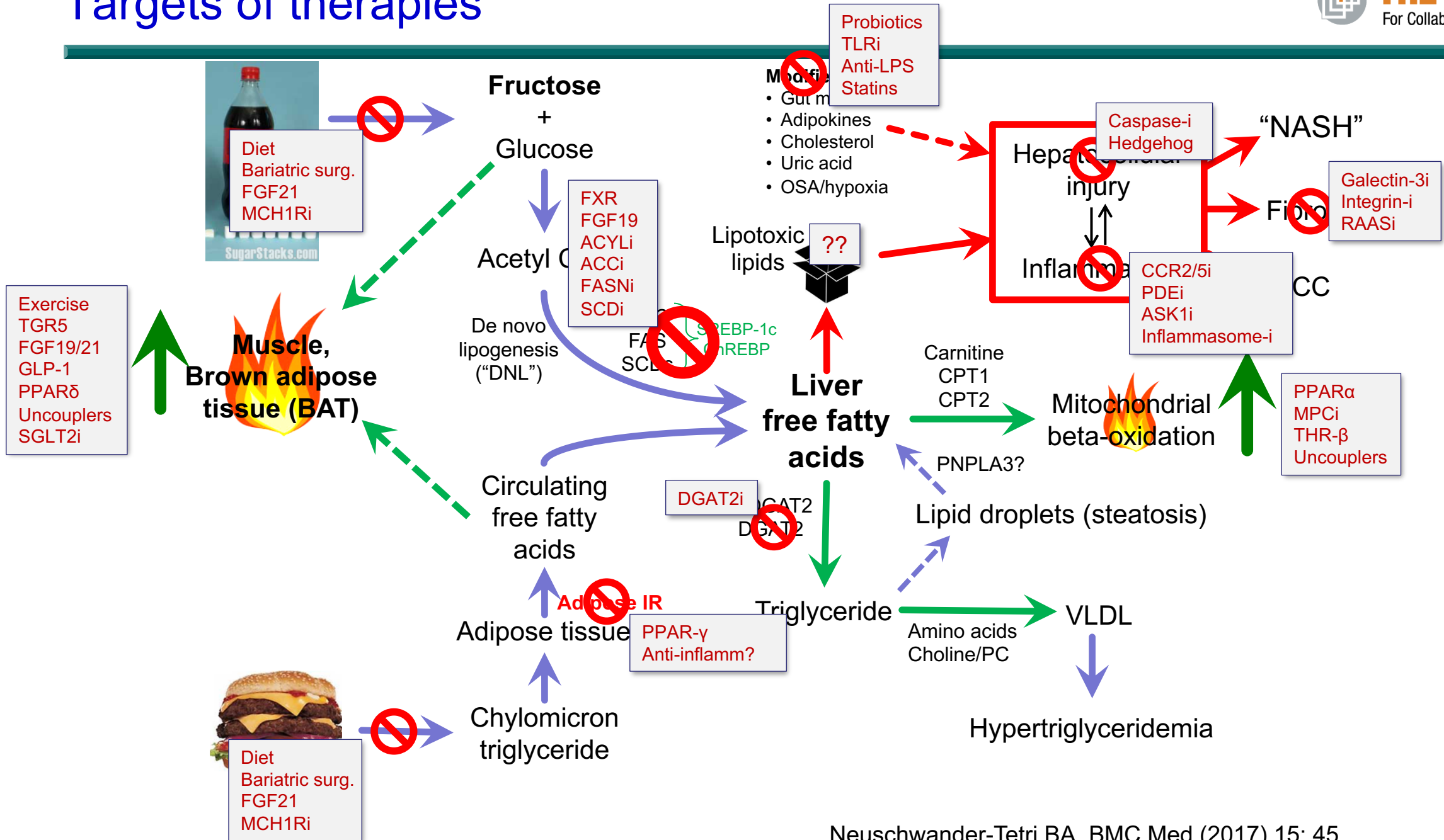




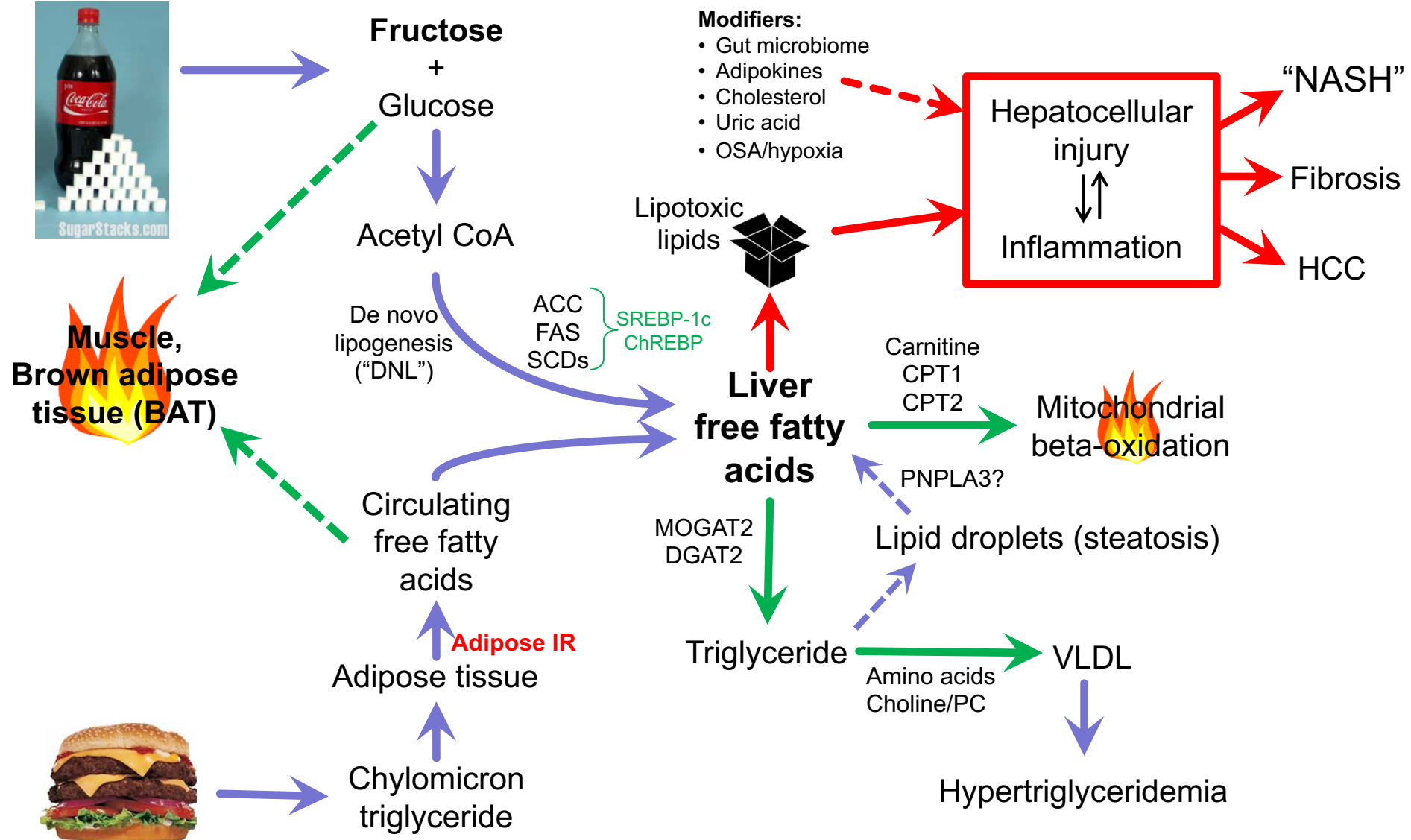
# Substrate Overload Lipotoxic Liver Injury (NASH)



# Targets of therapies



# Targets of combination therapies



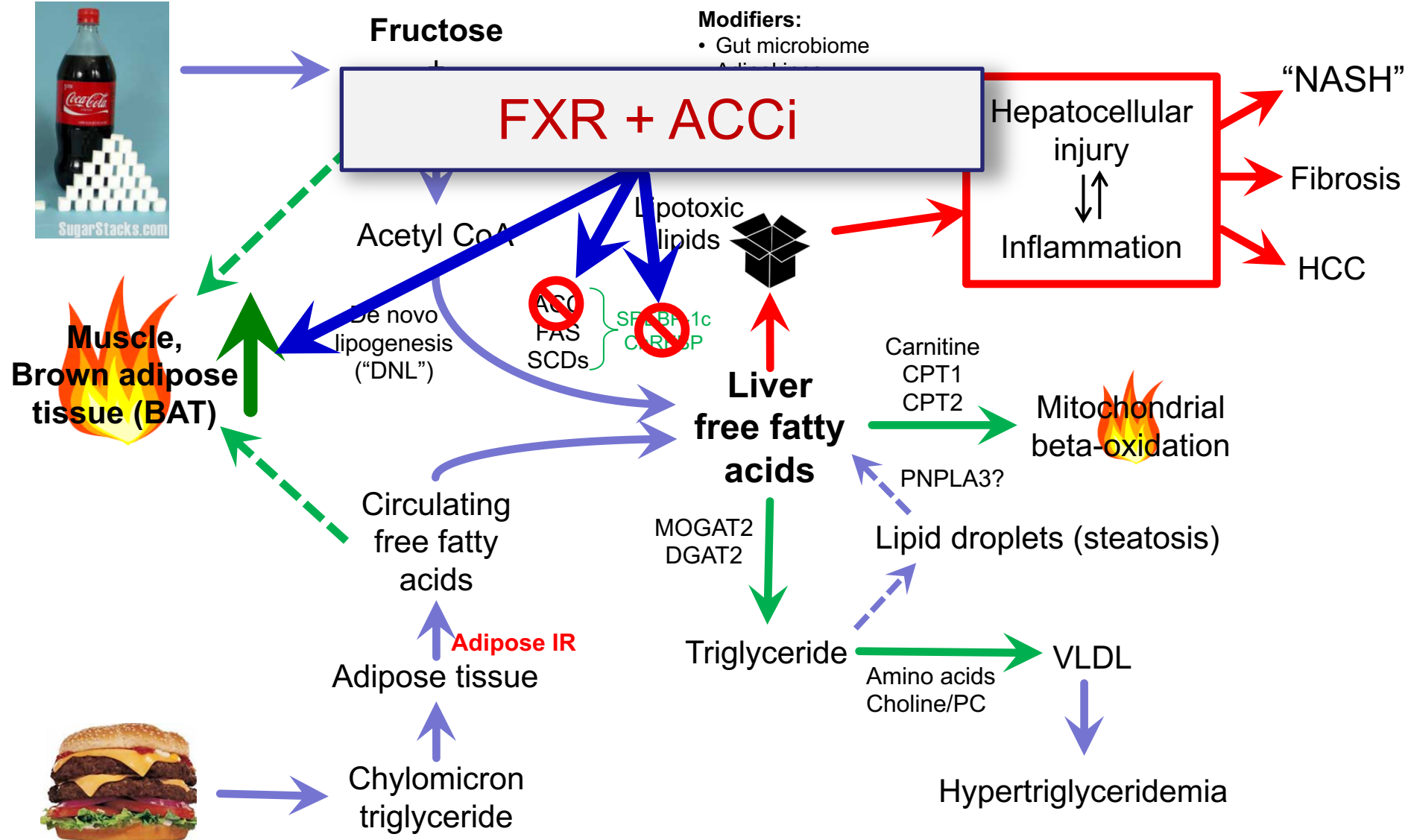
# Combination therapy trials—Industry (clinicaltrials.gov 9/5/19)

Drugs	Class	Sponsor(s)	Name	clinicaltrials.gov
FXR + CCR2/5i	tropifexor + CVC	Novartis, Allergan	TANDEM	NCT03517540
FXR + SGLT2i	tropifexor + licogliflozin	Novartis	ELIVATE	NCT04065841
FXR + ACCi + GLP1	cilafexor + firsocostat + semaglutide	Gilead, Novo Nordisk		NCT03987074
ACCi + DGAT2i	PF-05221304 PF-06865571	Pfizer, Novatis		NCT03776175
FXR + ACCi + ASK1i	cilafexor + firsocostat + selonsertib	Gilead	ATLAS	NCT03449446
FXR + ACCi + ASK1i + PPAR $\alpha$	cilafexor + firsocostat + selonsertib + fenofibrate	Gilead		NCT02781584

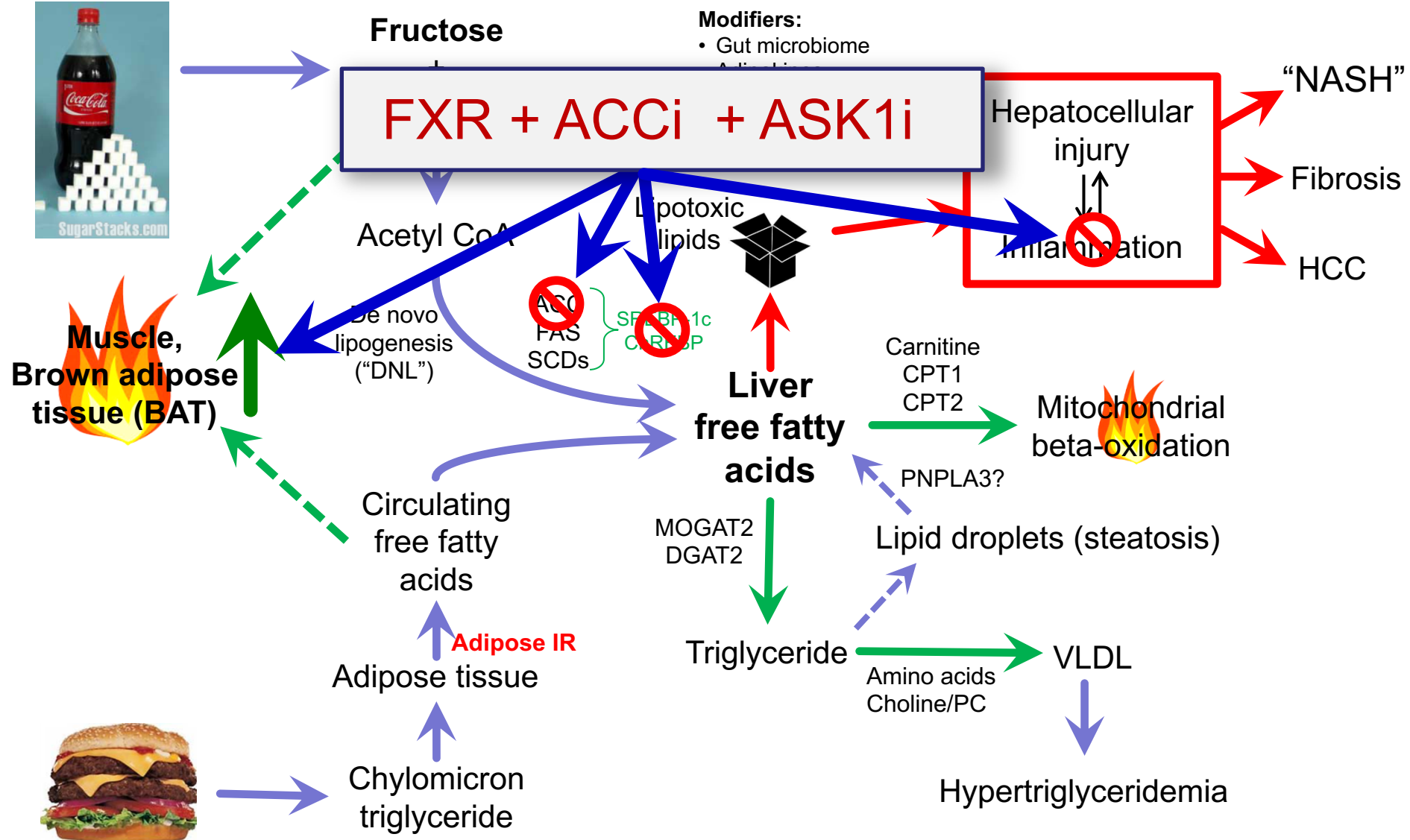
# Combination therapy trials—Academic (clinicaltrials.gov 9/5/19)

Drugs	Class	Sponsor(s)	Name	clinicaltrials.gov
Statin + carnitine	atorvastatin + L-carnitine	Academic	NALCAT	NCT01617772
GLP1 + PPAR- $\gamma$	alogliptin + pioglitazone	Academic		NCT03950505
SGLT1 + PPAR- $\gamma$	empagliflozin + pioglitazone	Academic		
PPAR $\alpha/\gamma$ + PPAR- $\gamma$	saroglitazar + pioglitazone	Academic	GLAZED	NCT02265276

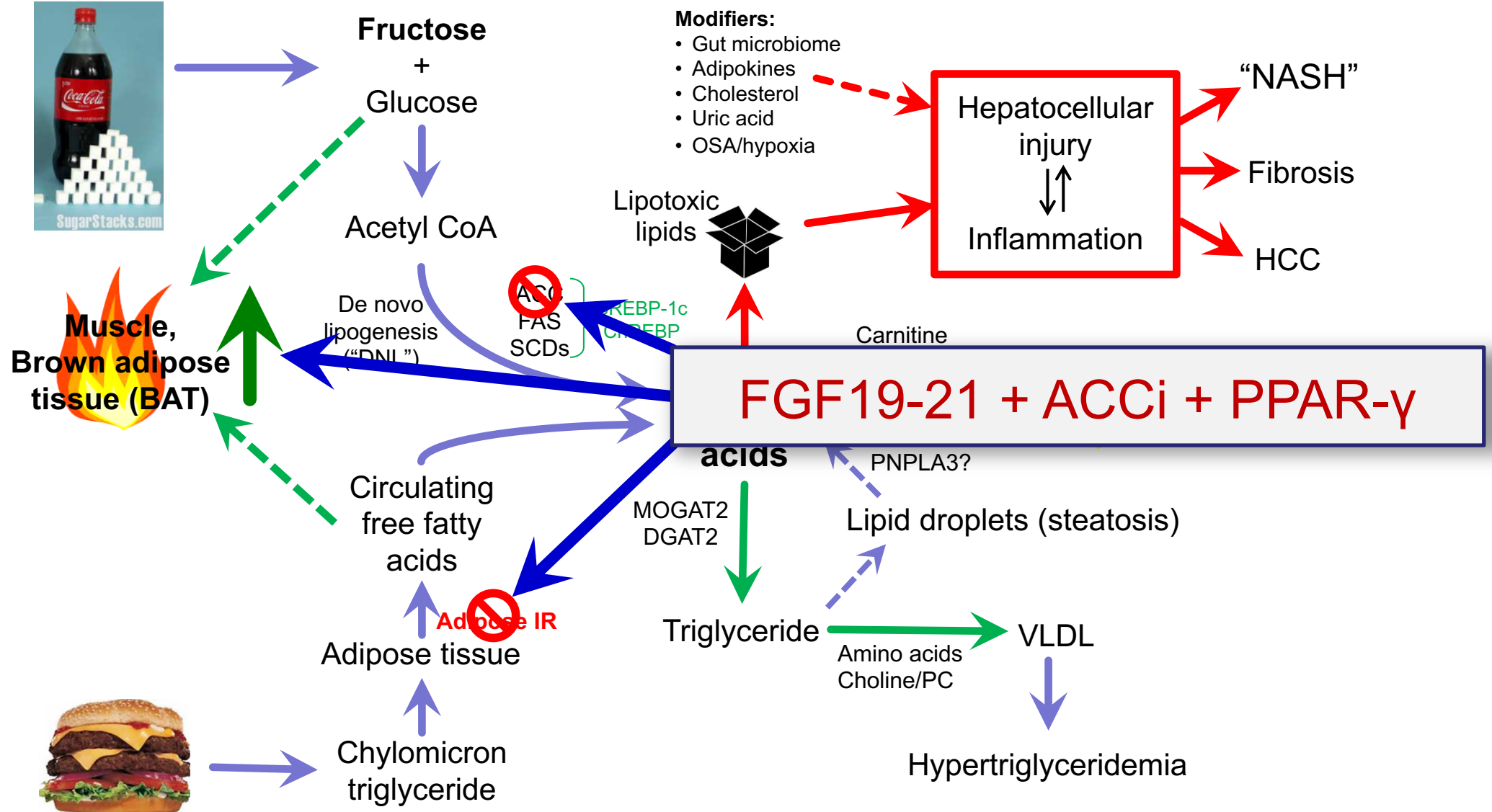
# Targets of combination therapies



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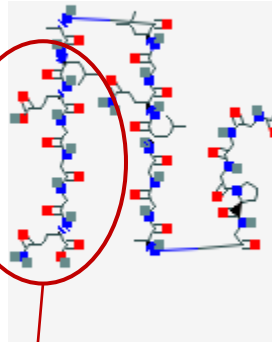
# Targets of combination therapies--Hypothetical





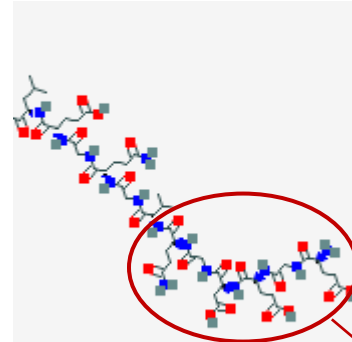
# Combination peptide hormones

Peptide 1



**Target 1**  
(eg, GLP-1 receptor)

Peptide 2



**Target 2**  
(eg, glucagon receptor)



# Combination peptide hormones

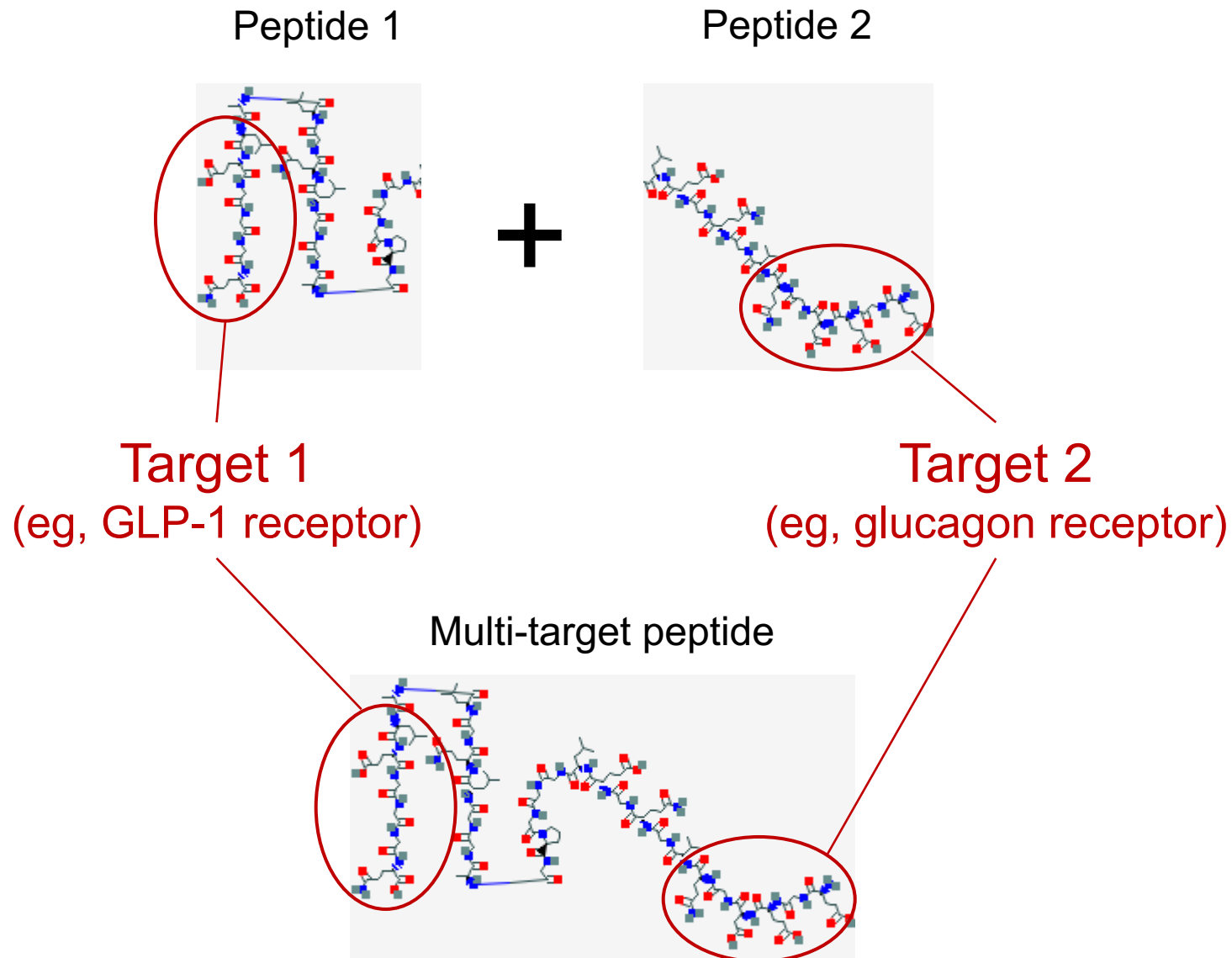
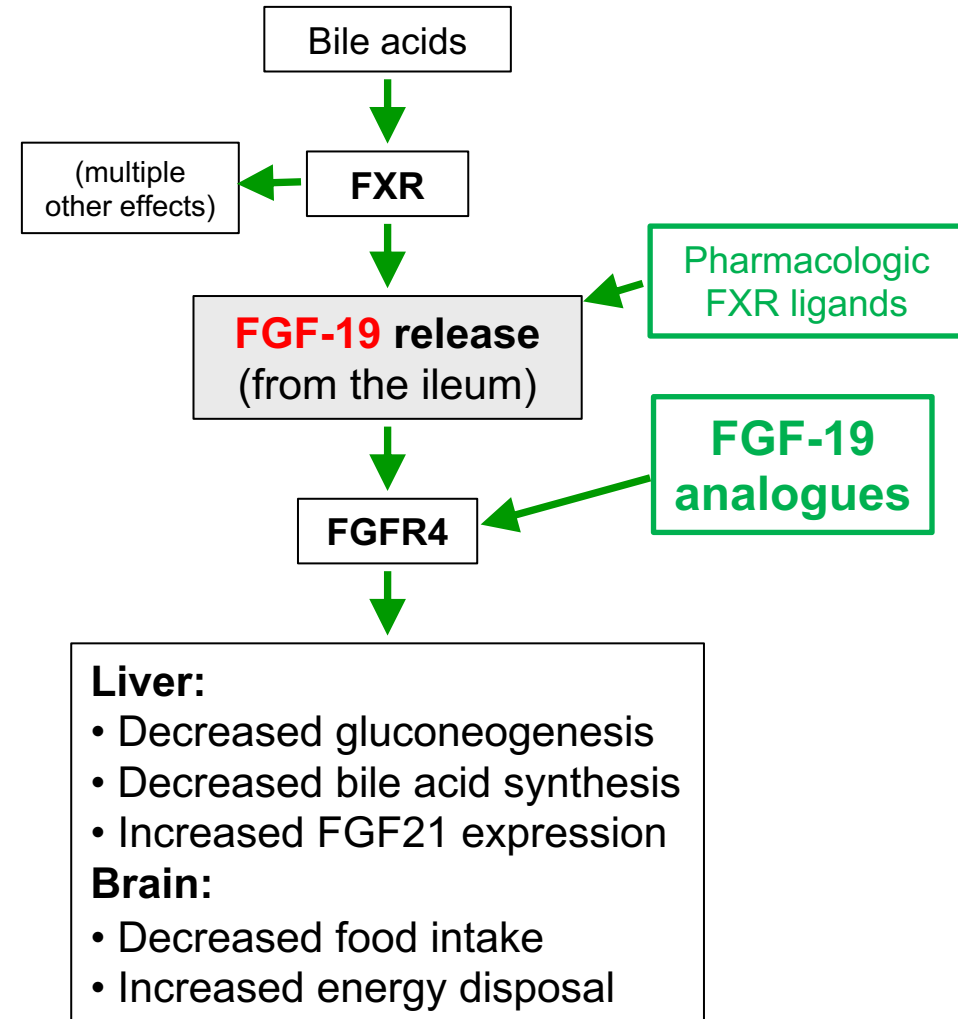
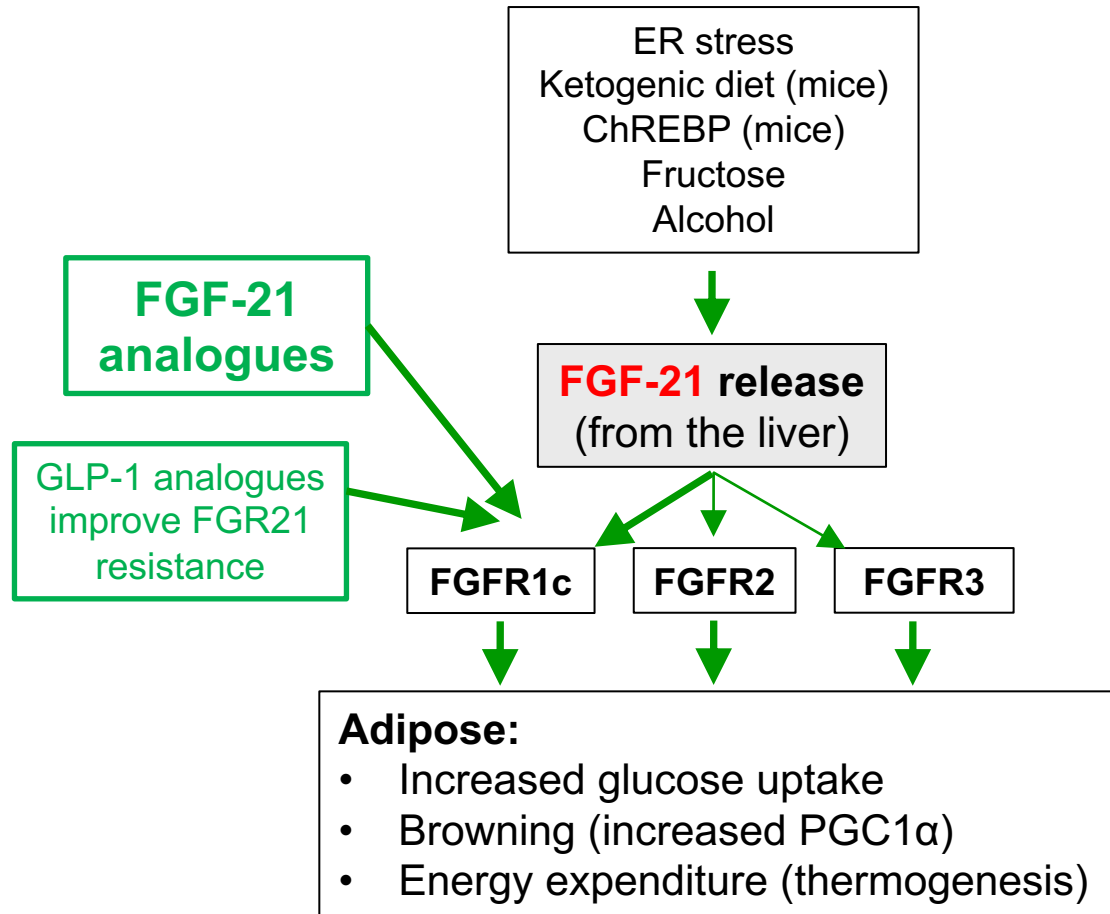


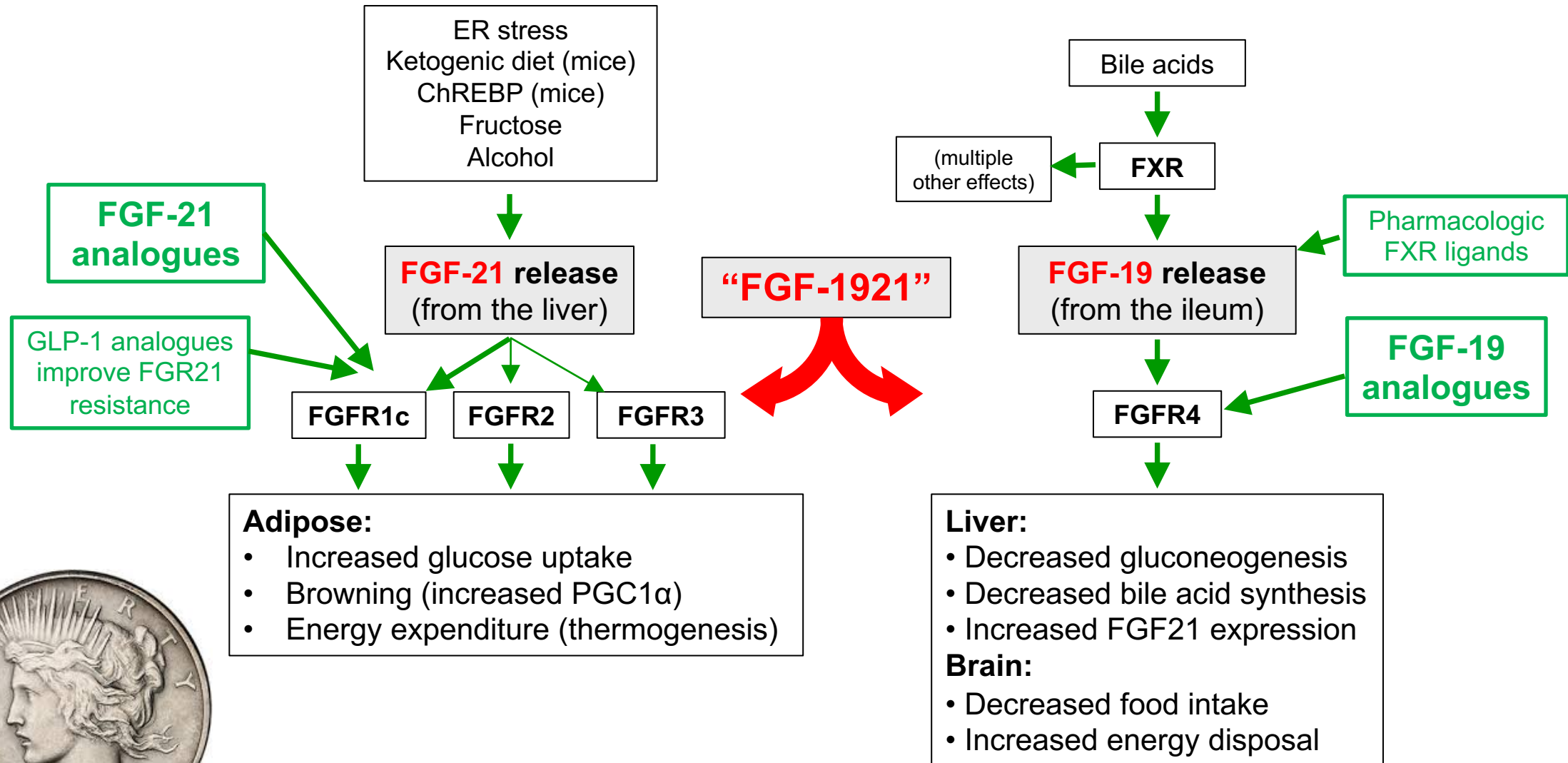
Table 1. Potential Next Generation GLP1-Based Polyagonists<sup>a</sup>

peptide	GLP-1R	GIPR	GCGR	ref and/or ClinicalTrials.gov identifier	phase of clinical development
TAK-094	✓	✓	•	83	Phase 1 planned
NNC0090-2746	✓	✓	•	58, NCT02205528	discontinued
RO6807952	✓	✓	•	NCT01358929	discontinued
LY3298176	✓	✓	•	NCT02759107	Phase 2
oxyntomodulin	✓	•	✓	51	N/A
G49	✓	•	✓	84	N/A
MEDI0382	✓	•	✓	85, NCT02394314	Phase 2
SAR425899	✓	•	✓	NCT02411825	Phase 2
MK-8521	✓	•	✓	NCT01982630	Phase 2, stopped
BI 456906	✓	•	✓	NCT03175211	Phase 1
LY3305677	✓	•	✓	NCT02972645	Phase 1
NNC9204-1177	✓	•	✓	NCT02941042	Phase 1
MOD-6031	✓	•	✓	NCT02692781	Phase 1, stopped
JNJ-64565111	✓	•	✓	NCT03235219	Phase 2
OPK-88003	✓	•	✓	NCT03406377	Phase 2
NNC9204-0530 <sup>b</sup>	•	•	✓	NCT02870231	Phase 1
HM15211	✓	✓	✓	NCT03374241	Phase 1
NNC9204-1706	✓	✓	✓	NCT03095807	Phase 1

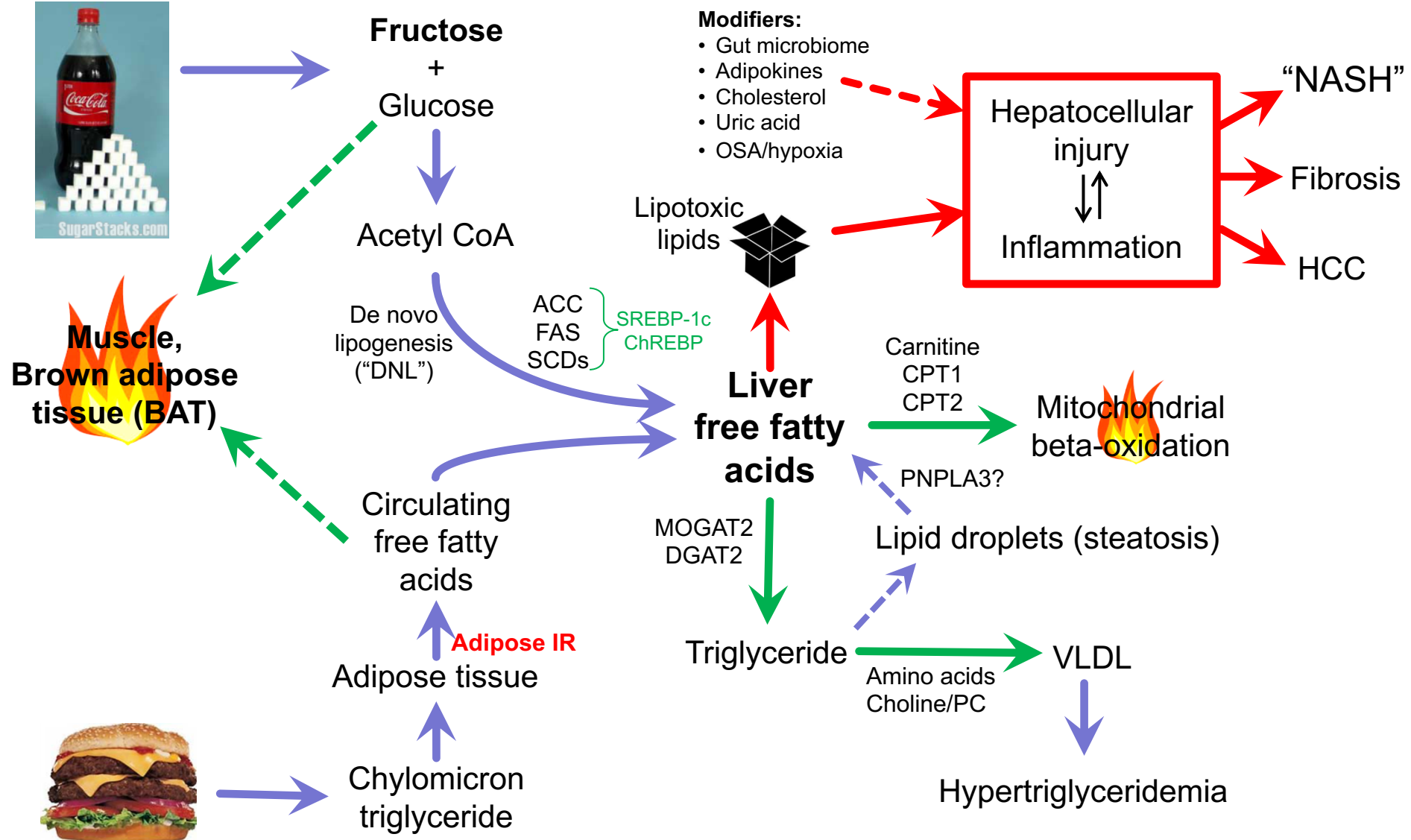
<sup>a</sup>Examples of multireceptor agonists being investigated for the treatment of type 2 diabetes mellitus and/or obesity. For each agent, the pharmacological profile and a representative clinical trial identifier is indicated if possible (clinicaltrials.gov). <sup>b</sup>NNC9204-0530 is being tested in combination with the GLP-1R agonist liraglutide in obese but otherwise healthy patients.



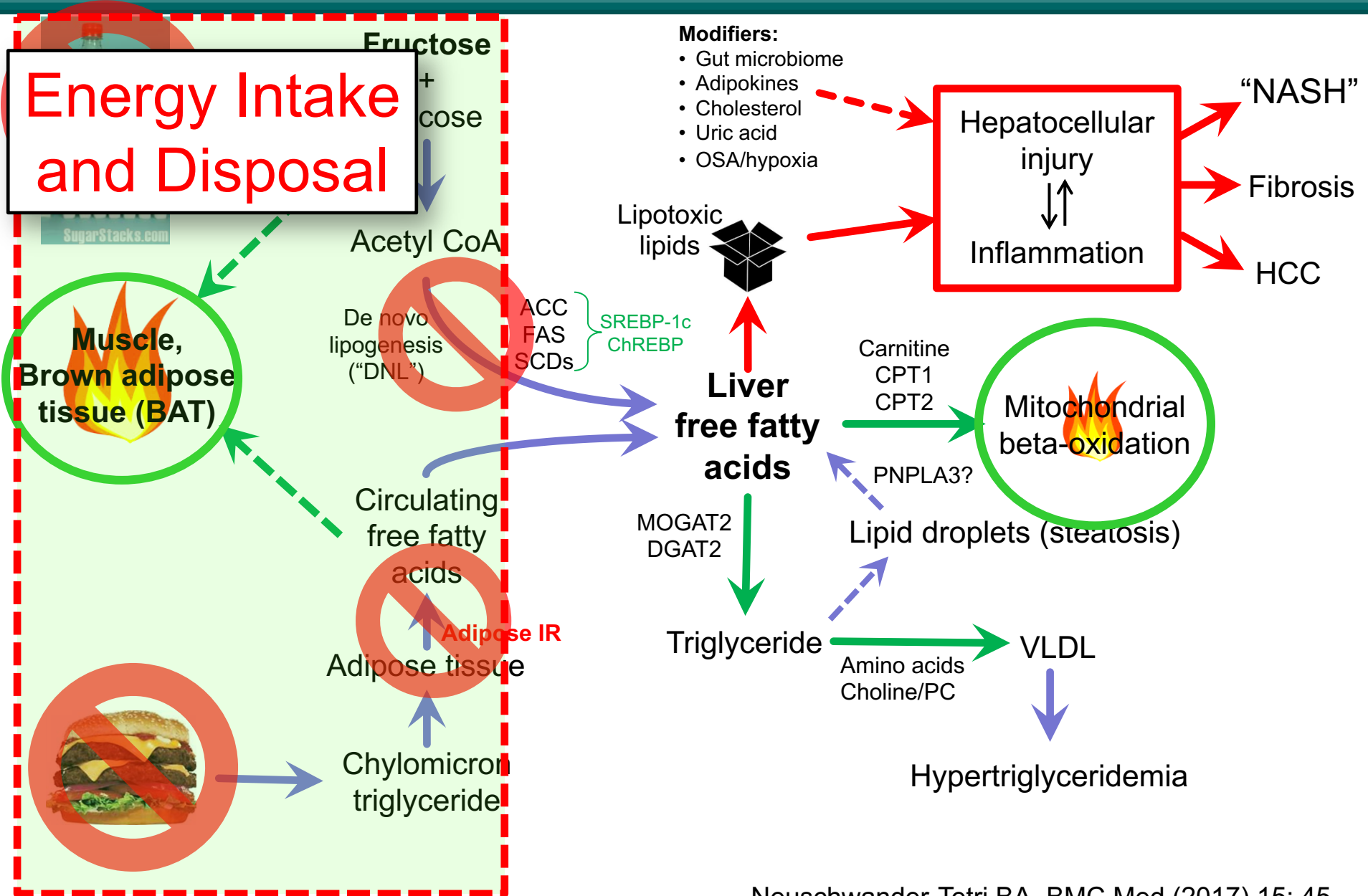
# FGF19 + FGF21 single peptide (= hypothetical “FGF1921”?)



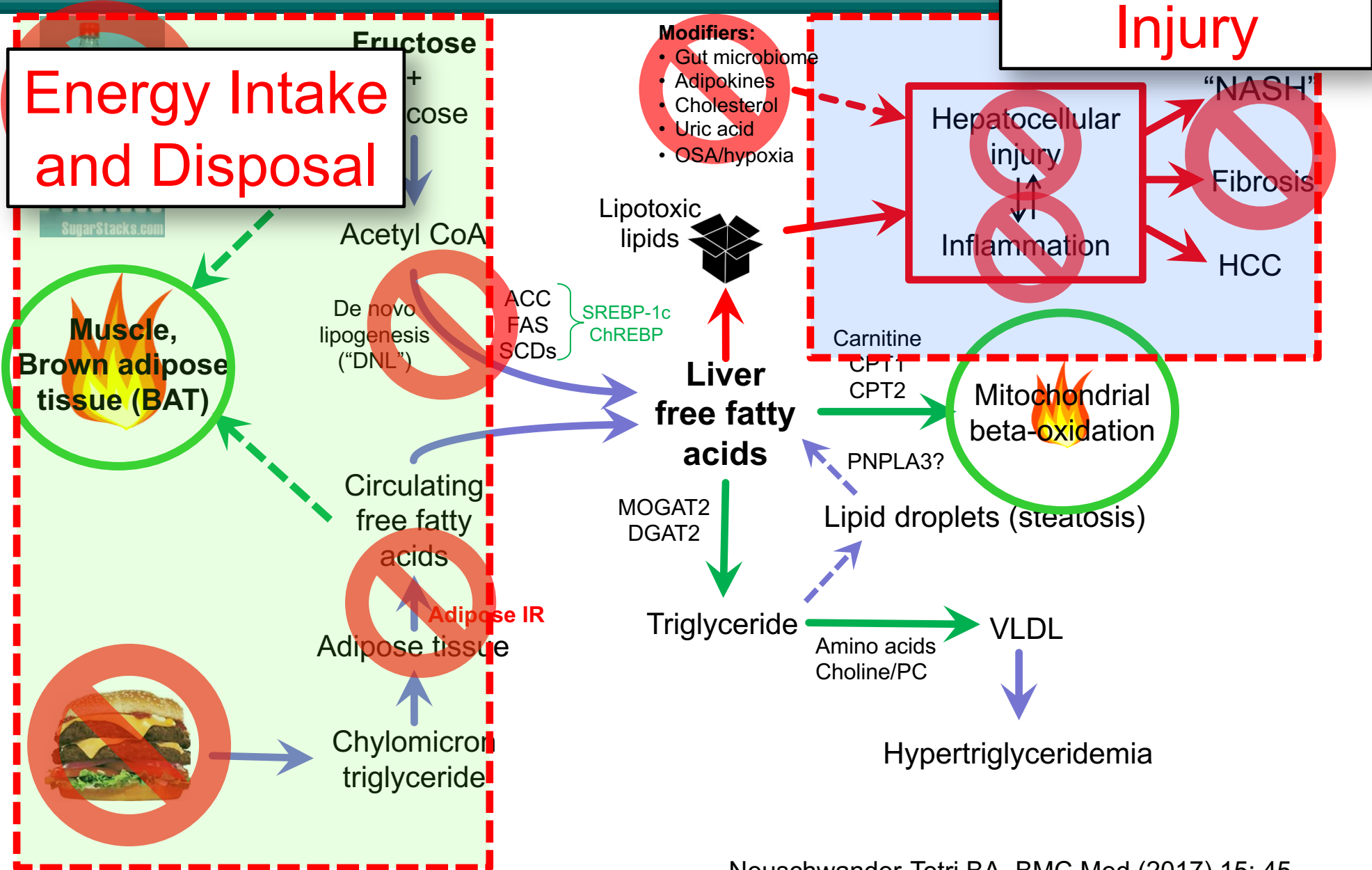
# Targets of combination therapies



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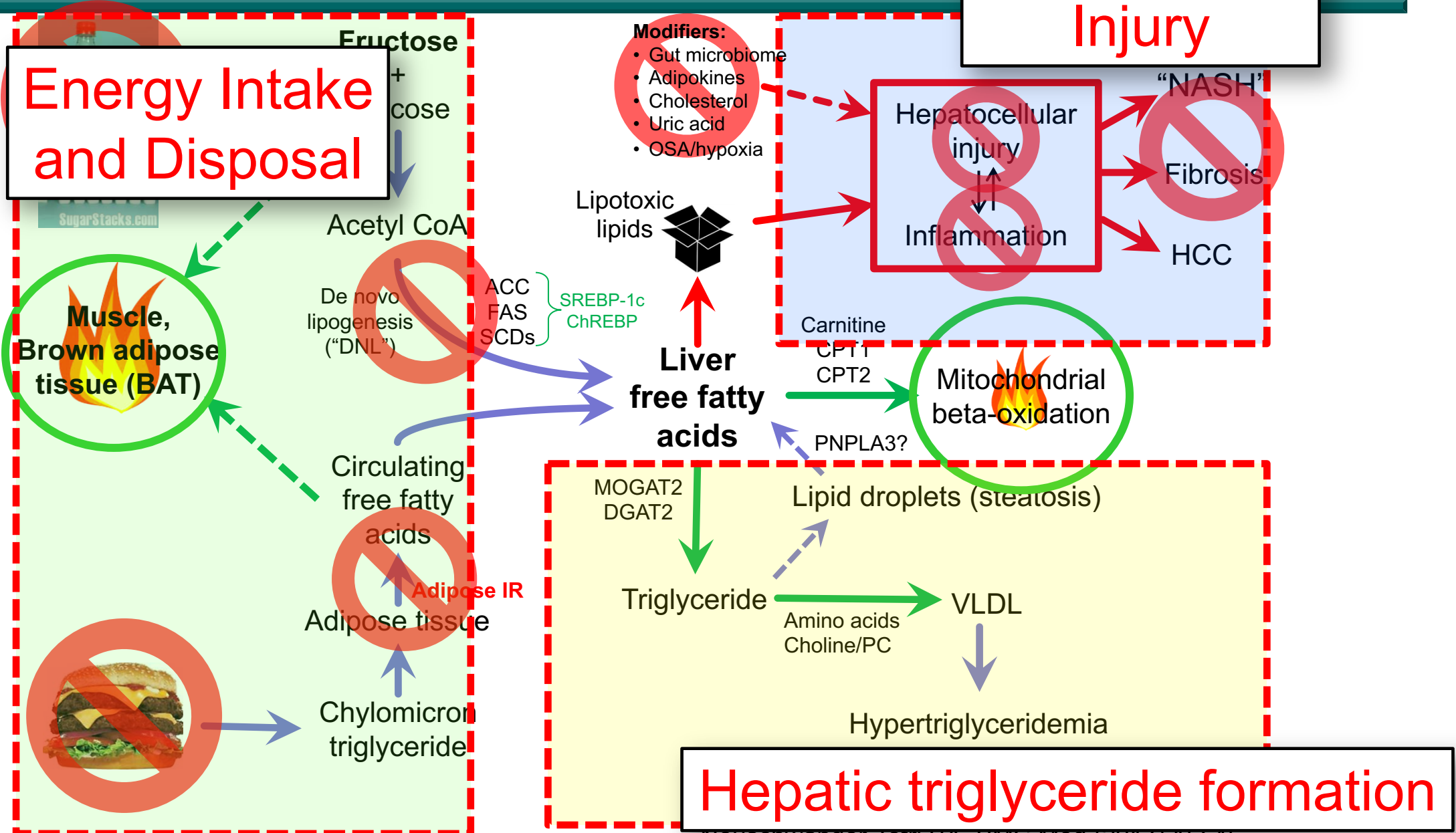


# Targets of combination therapies



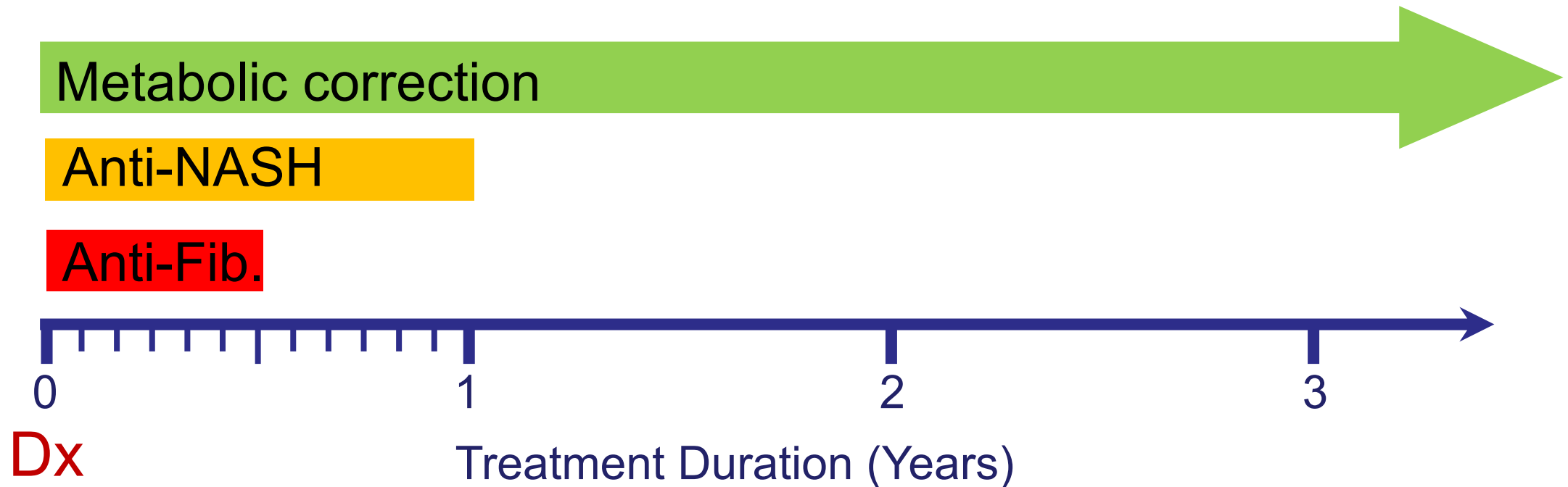


# Targets of combination therapies



**Hepatic triglyceride formation**

- For NASH with advanced fibrosis, target three broad processes:
  - Underlying/predisposing metabolic disease (metabolic correction): Indefinitely
  - Hepatocyte stress/inflammation (anti-NASH): 1 year?
  - Stellate cell activation (anti-fibrotic): 3-6 months?



- For NASH with
  - Underlying/pre
  - Hepatocyte str
  - Stellate cell ac

Metabolic co

Anti-NASH

Anti-Fib.

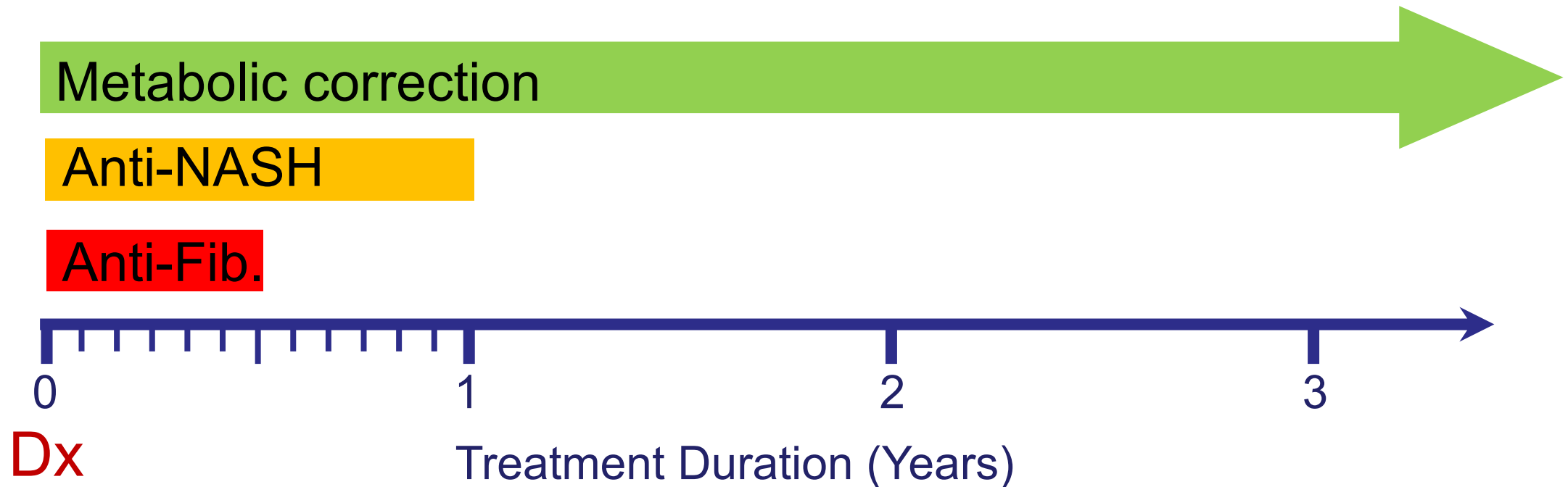
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- For NASH with advanced fibrosis, target three pathways:
  - Underlying/predisposing metabolic disease (metabolic correction): Indefinitely
  - Hepatocyte stress/inflammation (anti-NASH): 1 year?
  - Stellate cell activation (anti-fibrotic): 3-6 months?



- Given the multiple pathways involved in NASH
  - Combination therapy will likely have a role
  - But we still need get to rational individualized therapy
- Many combinations are in development for NASH and metabolic disease
  - Focus on rational mechanisms rather than convenience/expediency