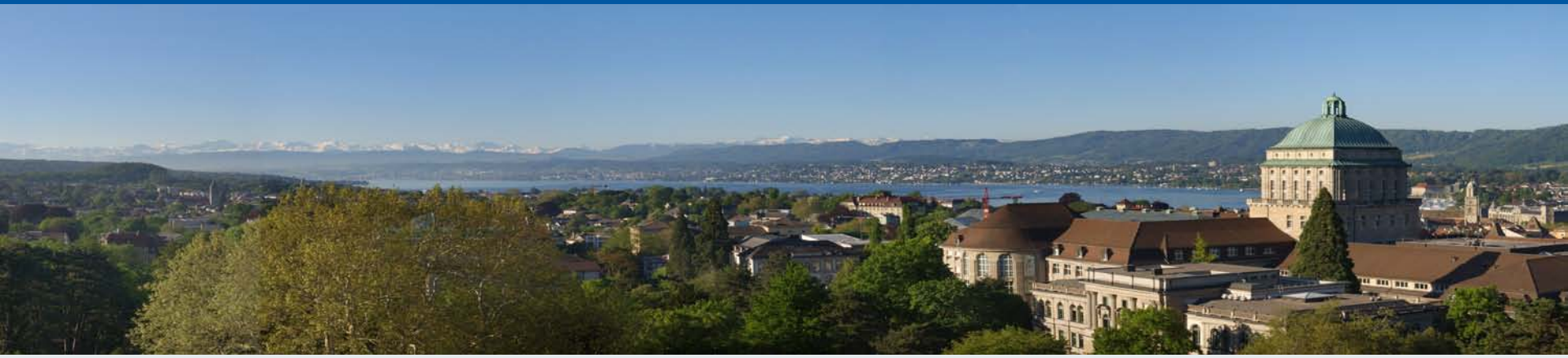

Comments on HPS2-THRIVE

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UniversityHospital Zurich

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U.Landmesser - Disclosures

Speaking or consulting: Roche, MSD, Pfizer

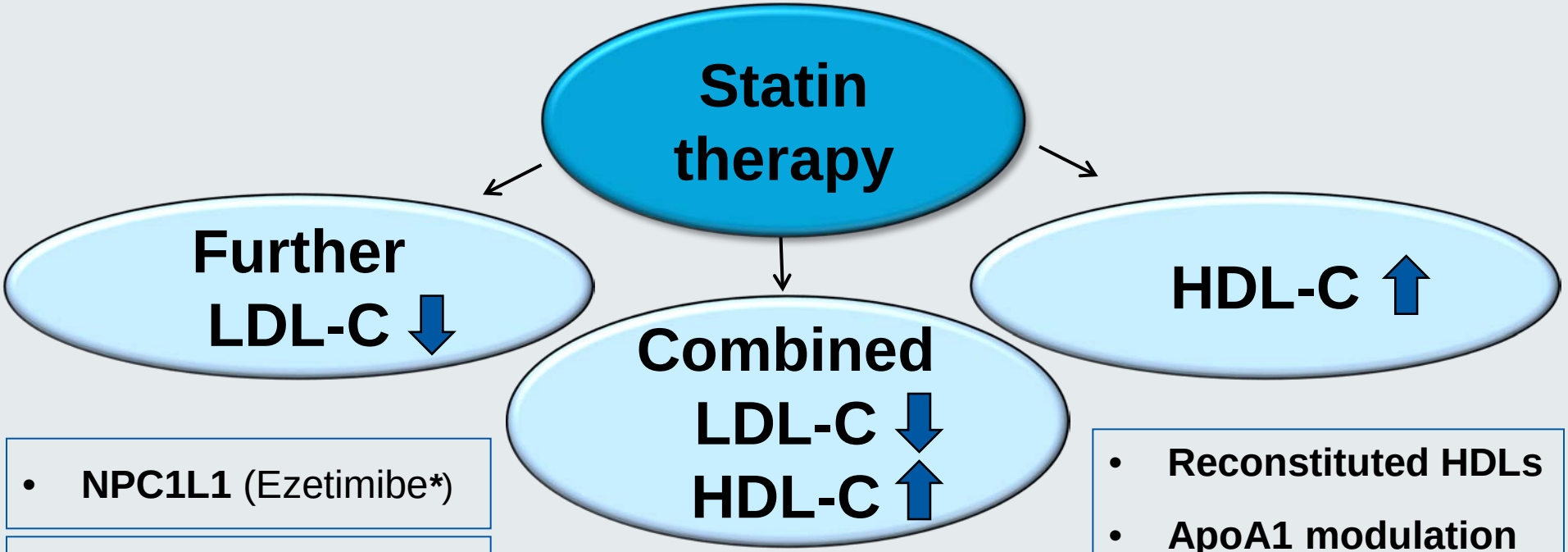
Research grants: Roche, Merck

Comments on HPS2-THRIVE

Treatment of HDL to Reduce the Incidence of Vascular Events

1. **Lipid-targeted therapies – what should be added to statins ?**
2. **Niacin – the first lipid-modifying drug - what have we learnt ?**
3. **Comments on HPS2-THRIVE analysis**
4. **Comparison between AIM-HIGH and HPS2-THRIVE**

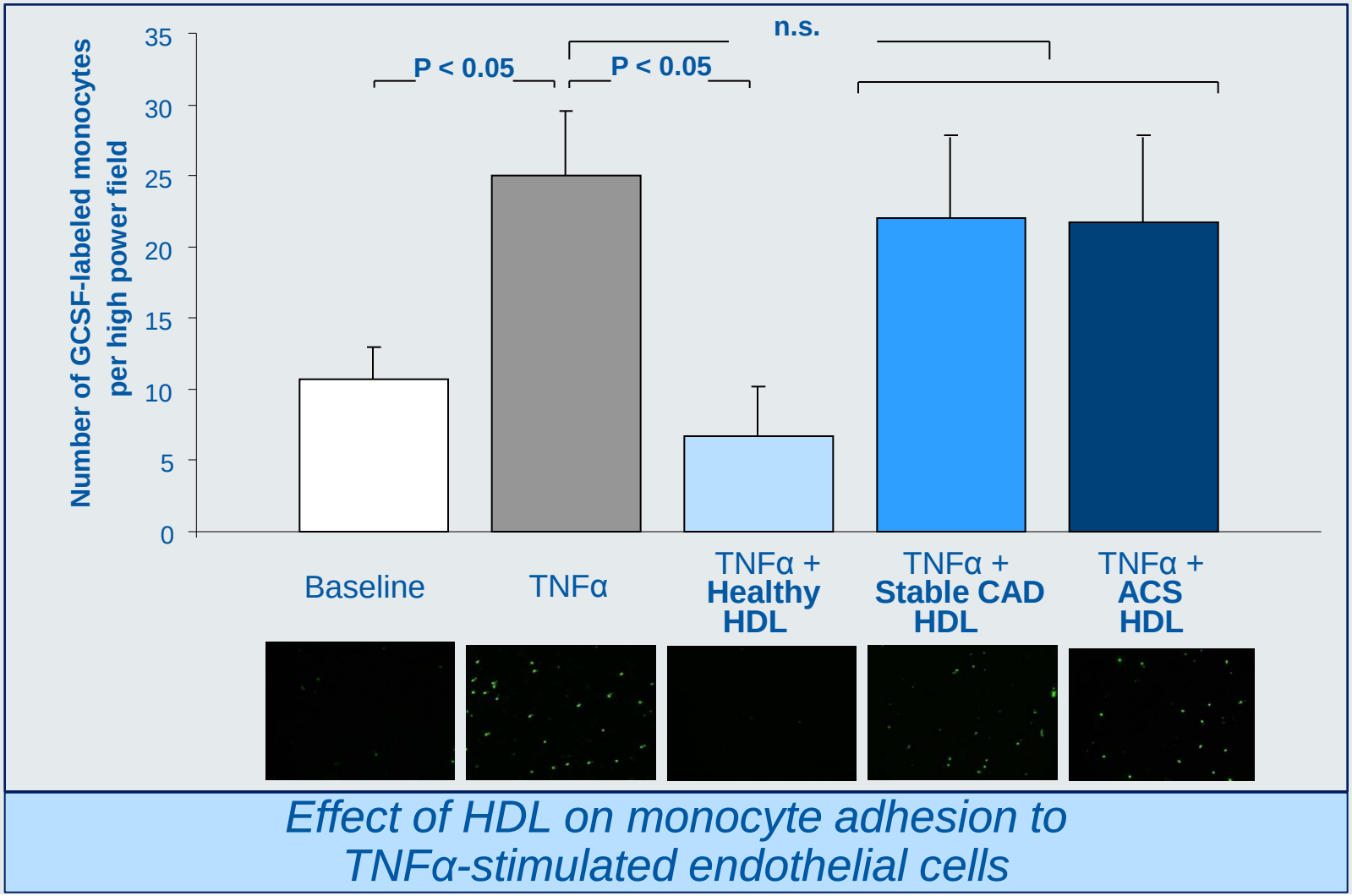
Lipid-targeted Therapies - What should be added to statins in patients with high vascular risk ?



*****Clinical outcome trials ongoing*

Role of HDL function versus HDL cholesterol levels ?

Different effects of HDL from patients with CAD on inflammatory activation

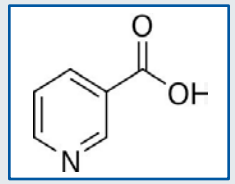


Effect of HDL on monocyte adhesion to TNFα-stimulated endothelial cells

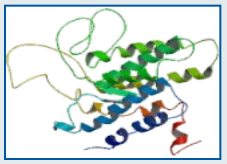
Besler C et al. *J Clin Invest* 2011;121: 2693-708

Niacin – the first lipid-modifying drug

1955 Niacin (vitamin B3) - first antidyslipidemic agent
(>50 years of clinical use)

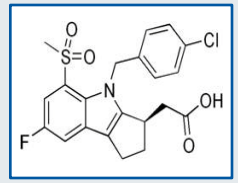


1975 Coronary Drug Project
(1,119 patients on niacin)

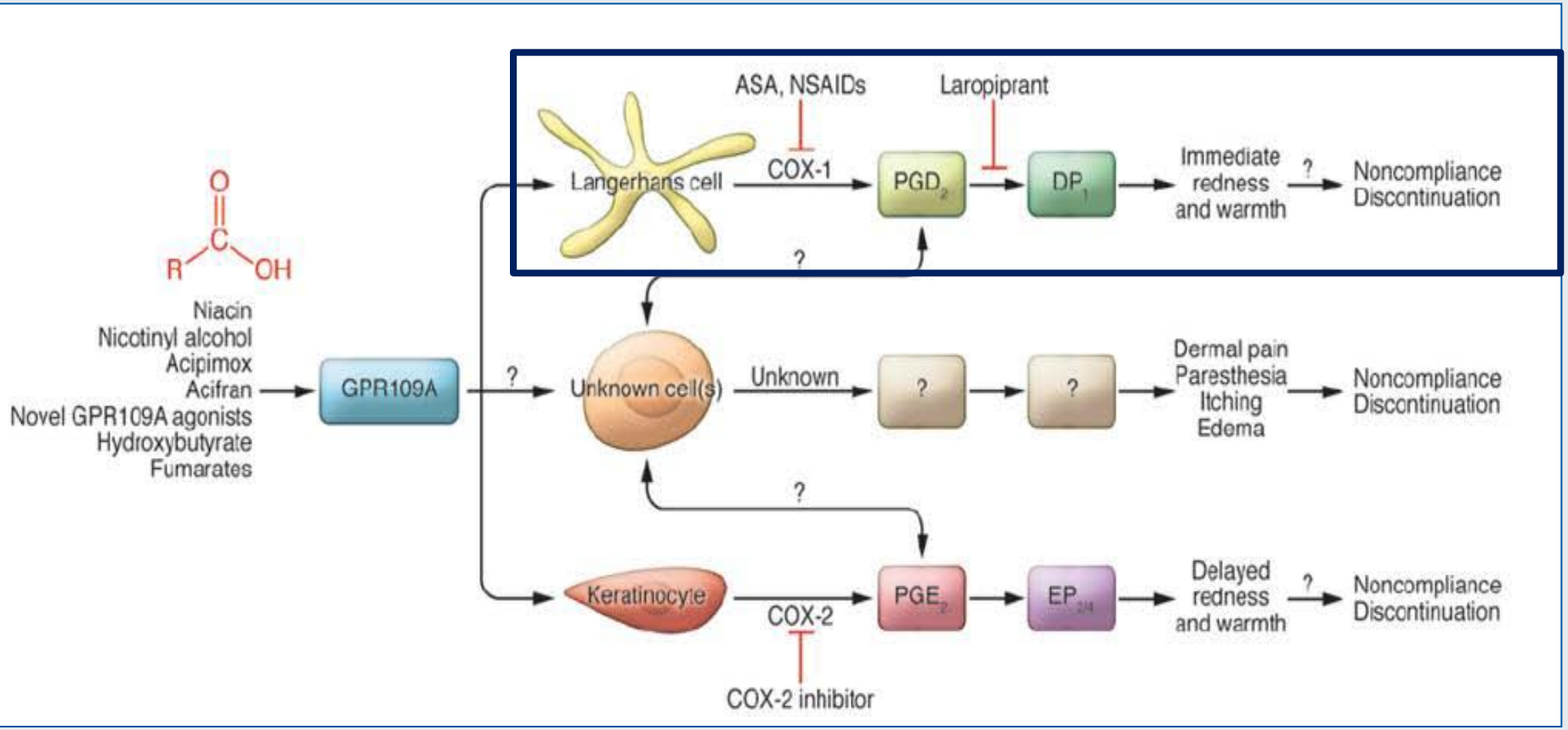


2003 Discovery of niacin receptor (GPR109A)

2009 Coadministration of DP_1 antagonist laropiprant reduces flushing (1,455 patients)



Proposed model of niacin-associated adverse skin effects



Dunbar RL, Gelfand JM. *J Clin Invest* 2010;120: 2651-5

Comments on HPS2-THRIVE

Withdrawal of active ER-Niacin/laropiprant before randomization:

For any medical reason: 25.4 %
- Skin (11.3. %)
  (Pruritus, rash, flashing)
- GI symptoms (5.5%)

Withdrawal in randomized treatment phase:

- Skin symptoms (5.1 vs. 1.2 %)
  (mostly pruritus)
- GI symptoms (3.6 vs. 1.6 %)
  (upper and lower GI)

Approximately 2/3 of patients can tolerate ER-Niacin/ laropiprant therapy

Comments on HPS2-THRIVE: Safety analyses

Myopathy increased: 62/69 (0.5%) vs. 10/12 (0.1%)

Largely in patients with Chinese descent

Rhabdomyolysis: 7 (0.05%) vs. 3 (0.02%)

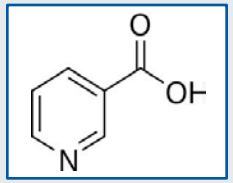
Severe liver disease
(3x ULN + bilirubin ≥2x ULN): 15 (0.1 %) vs. 18 (0.1 %)

FDA approved label change for simvastatin:
”Patients of *Chinese descent* should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products. Caution is recommended when such patients are treated with simvastatin 40 mg or less in combination with cholesterol-modifying doses of niacin-containing products.”

Caution in patients with chinese descent (myopathy)

Niacin – the first lipid-modifying drug

1955 Niacin (vitamin B3) - first antidyslipidemic agent
(>50 years of clinical use)



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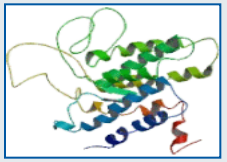

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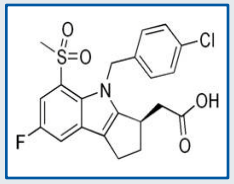


2011 AIM-HIGH Study

2013 Clinical outcome data of HPS2-THRIVE

Comparison of AIM-HIGH and HPS2-THRIVE

AIM-HIGH trial

(*N Engl J Med* 2011)

- Pre-randomisation phase with niacin(1.5/2g)
  ➡ exclusion: 20.1 %
- Aiming to have similarly low LDL-C in both treatment groups
  ➡ LDL: - 5.5 %, HDL: + 13.2 %
  ➡ **More patients on high-dose statin and ezetimibe in control-group**
- Randomization (n): 1718 vs. 1696 patients
- Mean FU - 3 years (556 events)

HPS2-THRIVE trial

- Pre-randomisation phase with ER-niacin (2g)/ laropiprant ➡ exclusion: 25.4 %
- No further adjustment of LDL-C levels after randomization
  ➡ LDL: -20 %; HDL + 17 %
- Randomization (n): 12838 vs. 12835 patients
- Mean FU - 4 years (? events)
- **Addition of laropiprant (Antagonist of PGD2 receptor DP1)**

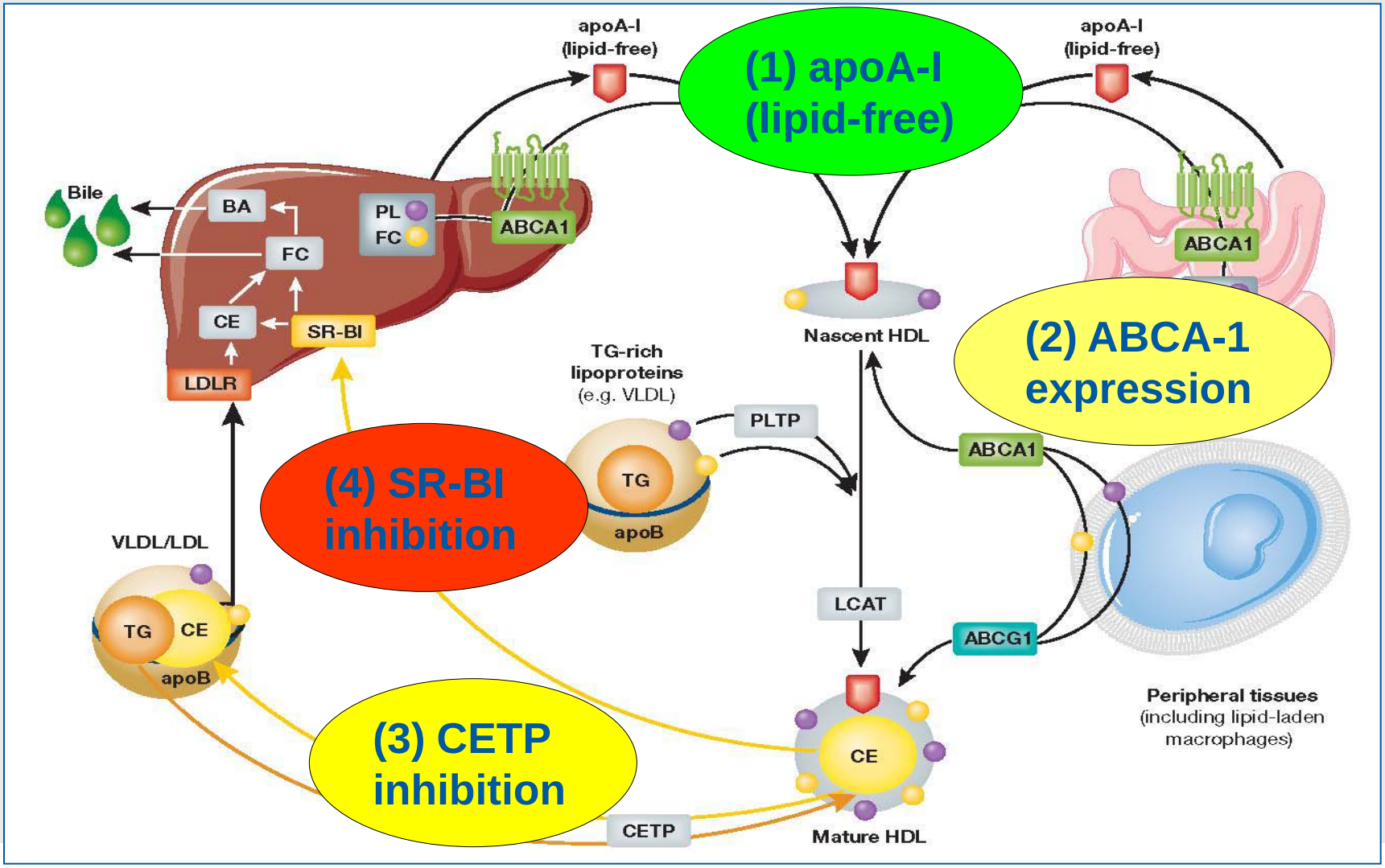
➡ **HPS2-THRIVE clinical outcome data (presentation expected in 2013)**

Thank you

UniversityHospital Zurich

University of Zurich[UZH]

(I) HDL-C raising can be due to increased production and/or reduced catabolism



Besler C, Luscher T, Landmesser U. *EMBO Mol Med* 2012; 4(4):251-68