Glycation of apoB100 by methylglyoxal reduces hepatic catabolism of LDL and increases the risk of coronary heart disease in type 2 diabetes

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Team IV

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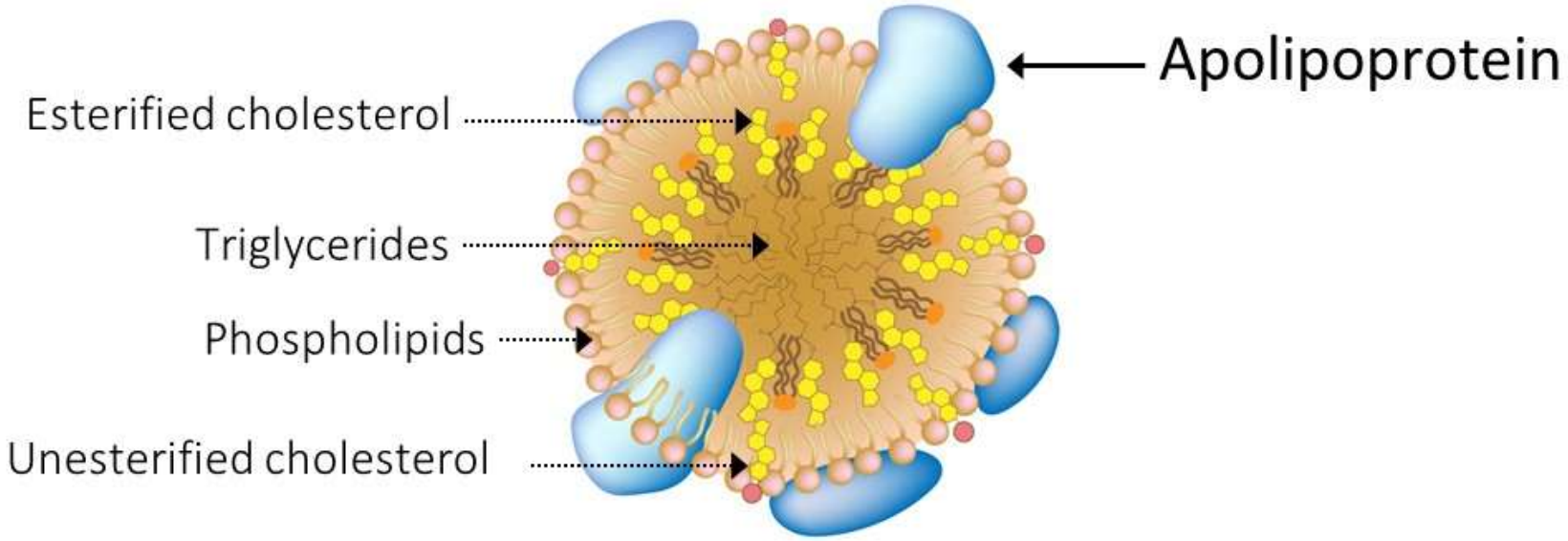
Inserm UMR 1087 / CNRS UMR 6291
Nantes, France

50 ans del'AE2BM, 2 Octobre 2025

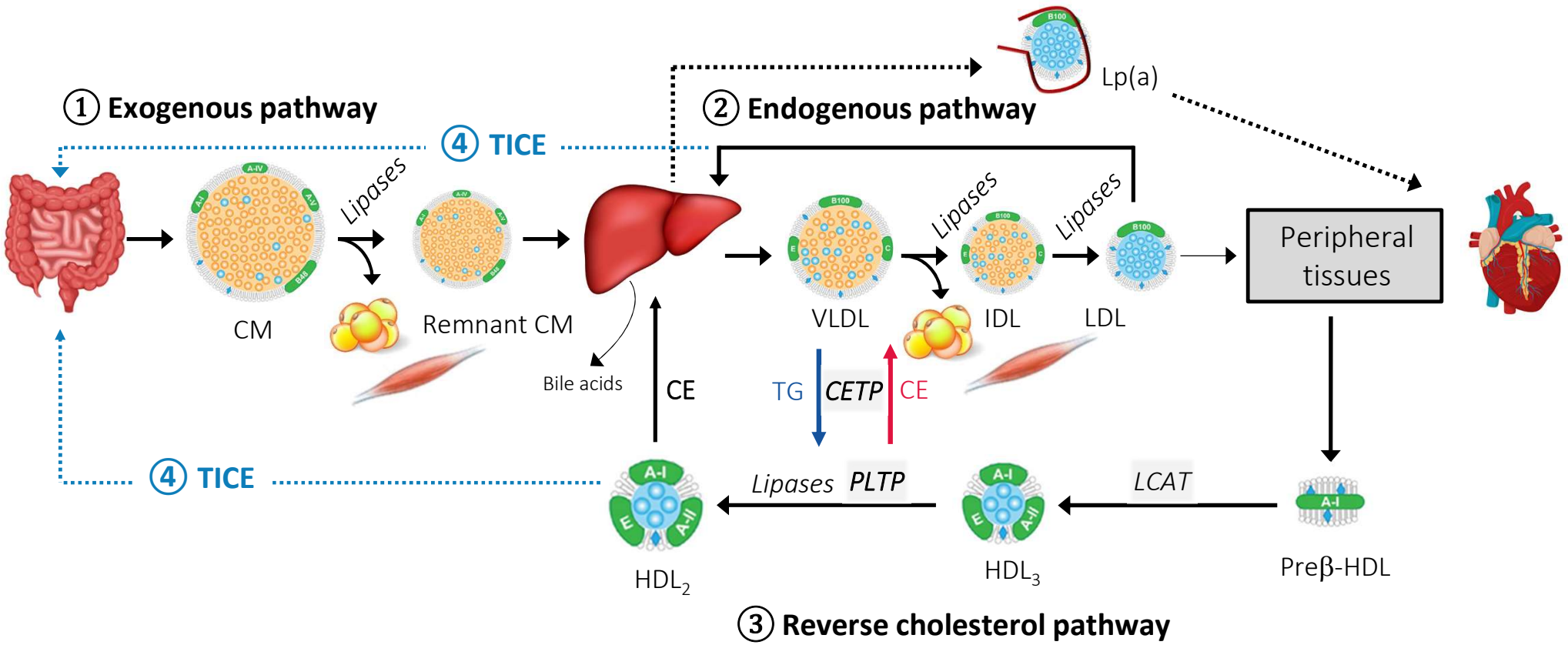
Apolipoproteins and lipoproteins



Apolipoproteins govern lipoprotein metabolism

Dominiczak & Caslake, *Ann Clin Biochem*, 2011 - Van den Broek *et al.*, *Proteomics*, 2017

Lipoprotein metabolism

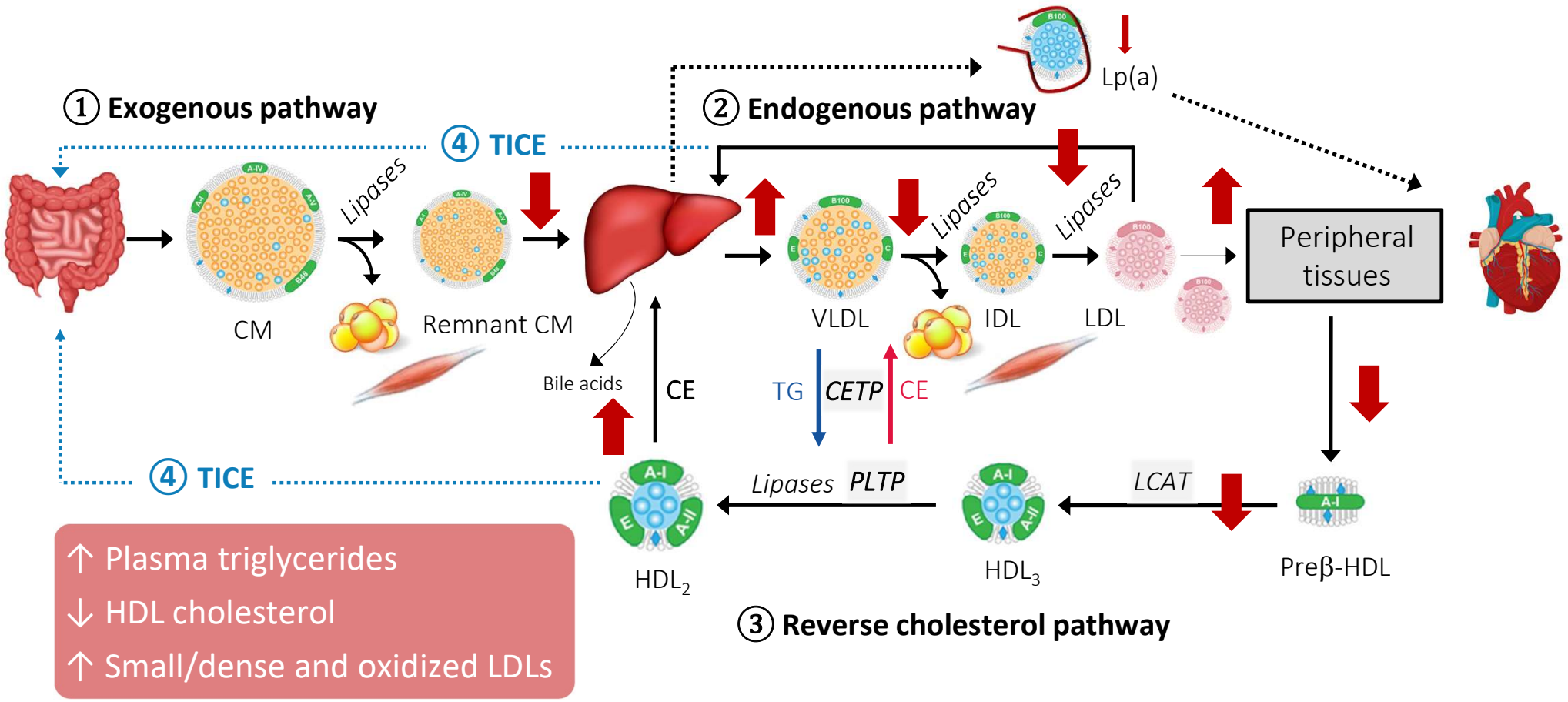


UC: unesterified cholesterol
CE: cholesterol ester
TG: triglyceride

CM: chylomicron
VLDL: very-low-density lipoprotein
IDL: intermediate-density lipoprotein

LDL: low-density lipoprotein
HDL: high-density lipoprotein

Lipoprotein metabolism in type 2 diabetes



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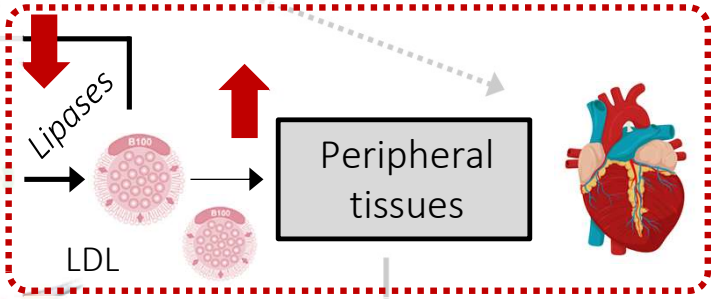
Vergès, *Diabetologia*, 2015

Lipoprotein metabolism in type 2 diabetes

In contrast to LDL-lowering drugs (statins, iPCSK9), therapies targeting HDL and triglyceride plasma concentrations (fibrates) failed to demonstrate benefits in CVD outcomes.



↑ Plasma triglycerides
↓ HDL cholesterol
↑ **Small/dense and oxidized LDLs**

Vergès, *Diabetologia*, 2015

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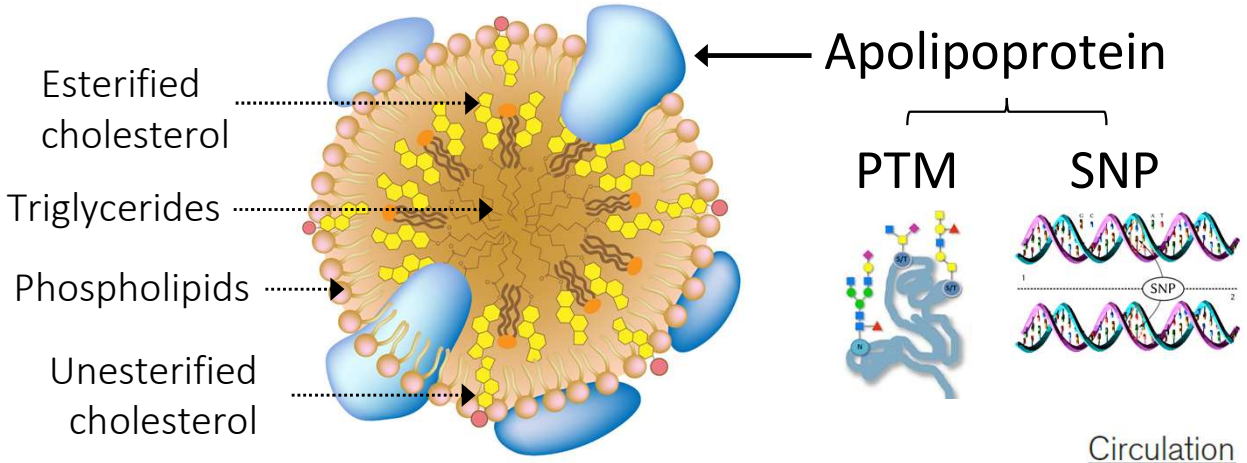
Apolipoproteins are powerful biomarkers of lipoprotein metabolism and CVD



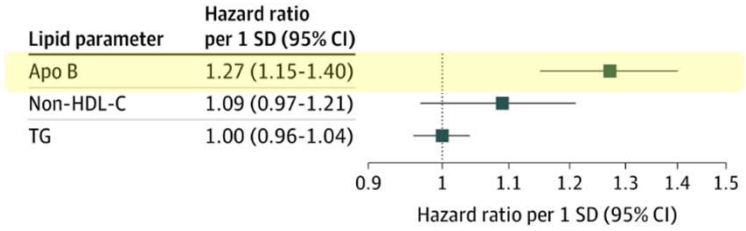
Structural component of lipoproteins

Ligand for cell-surface receptors

Activator/inhibitor of specific enzymes

Circulation

Apolipoprotein plasma concentrations predict ASCVD better than plasma lipids



FRONTIERS

Apolipoprotein B: Bridging the Gap Between Evidence and Clinical Practice

Diana De Oliveira-Gomes, MD; Parag H. Joshi, MD, MHS; Eric D. Peterson, MD, MPH; Anand Rohatgi, MD, MSCS; Amit Khera, MD, MSc; Ann Marie Navar, MD, PhD

ABSTRACT: Despite data suggesting that apolipoprotein B (apoB) measurement outperforms low-density lipoprotein cholesterol level measurement in predicting atherosclerotic cardiovascular disease risk, apoB measurement has not become widely adopted into routine clinical practice. One barrier for use of apoB measurement is lack of consistent guidance for clinicians on how to interpret and apply apoB results in clinical context. Whereas guidelines have often provided clear low-density lipoprotein cholesterol targets or triggers to initiate treatment change, consistent targets for apoB are lacking. In this review, we synthesize existing data regarding the epidemiology of apoB by comparing guideline recommendations regarding use of apoB measurement, describing population percentiles of apoB relative to low-density lipoprotein cholesterol levels, summarizing studies of discordance between low-density lipoprotein cholesterol and apoB levels, and evaluating apoB levels in clinical trials of lipid-lowering therapy to guide potential treatment targets. We propose evidence-guided apoB thresholds for use in cholesterol management and clinical care.

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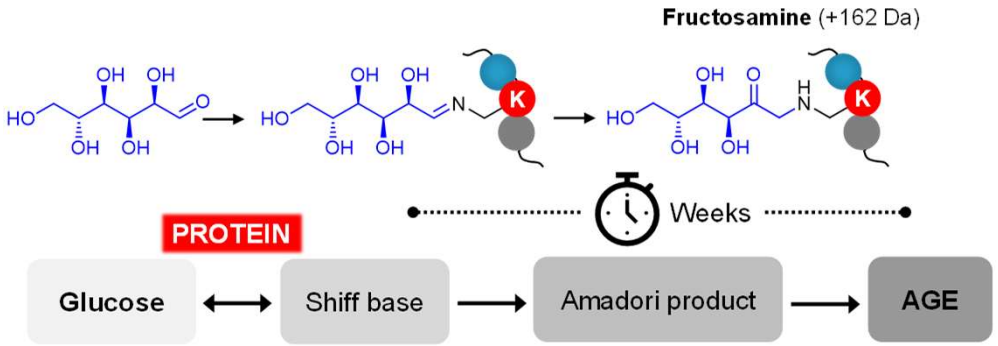
Dominiczak & Caslake, *Ann Clin Biochem*, 2011 - Van den Broek *et al.*, *Proteomics*, 2017 – Martson *et al.*, *JAMA Cardiol.*, 2021 – McQueen *et al.*, *Lancet*, 2008.

Chronic hyperglycemia promotes the irreversible and non-enzymatic glycation of proteins



Schalkwijk & Stehouwer, *Physiol Rev*. 2019 - Hanssen *et al., Diabetes Care*. 2018 - Rodrigues & Chevalier *et al.*, *Clin Chem*. 2025

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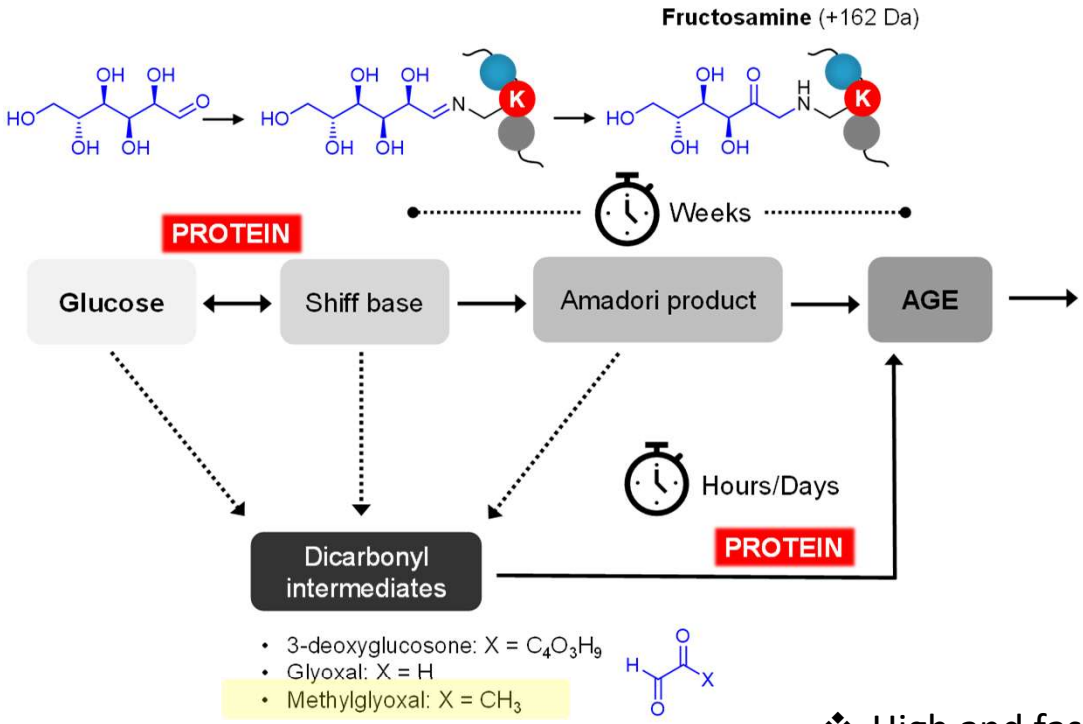

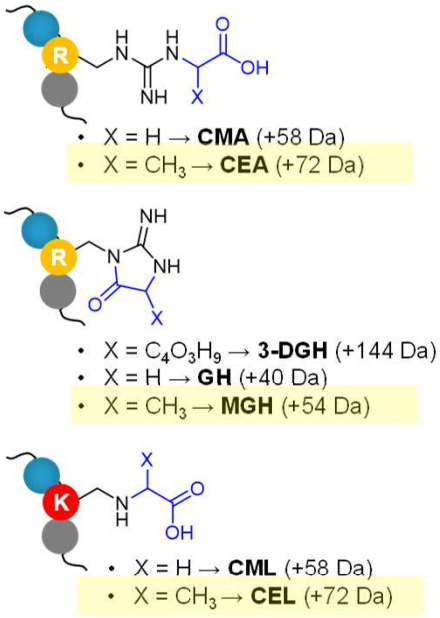

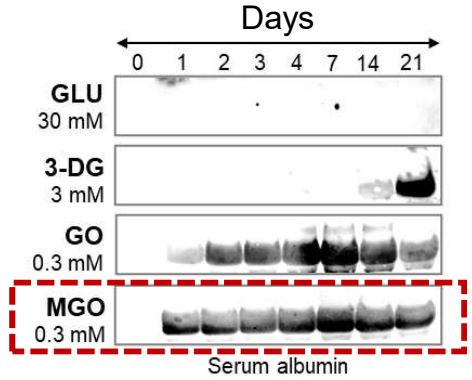

❖ High and fast reactivity of dicarbonyl intermediates *vs.* reducing sugar

❖ Half-life of apolipoproteins = a few days

❖ ↑Methylglyoxal (MGO) plasma concentrations = ↑ risk of CVD in T2D

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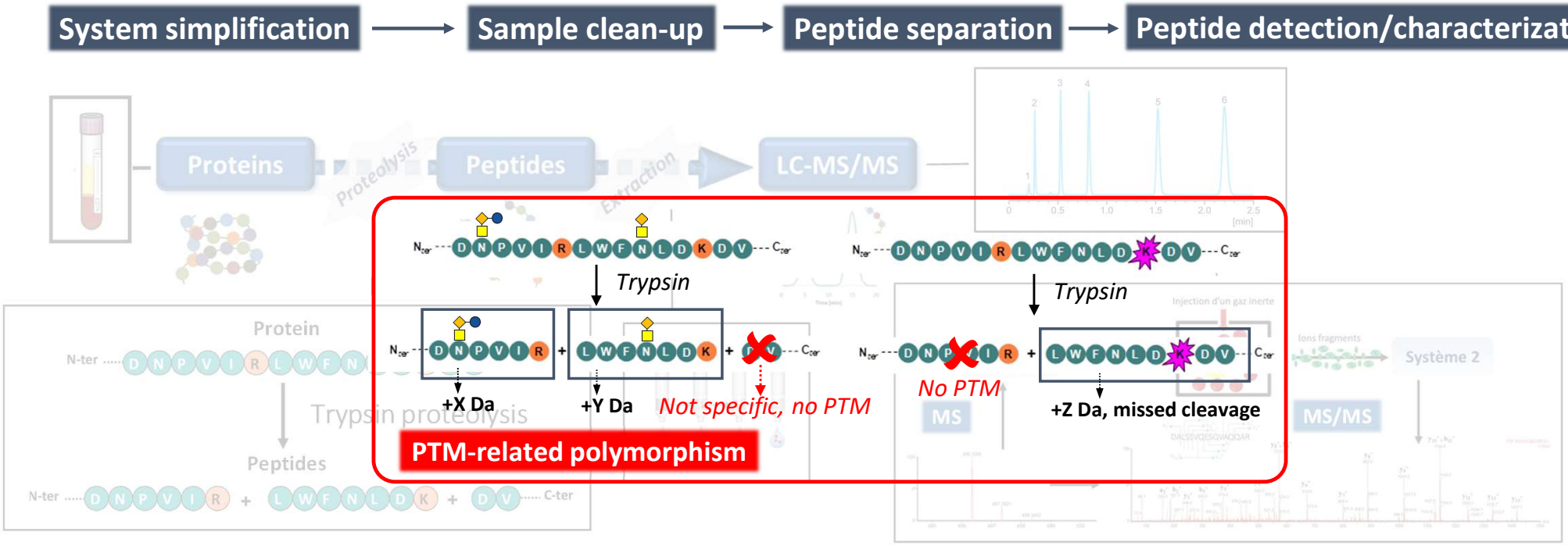
Schalkwijk & Stehouwer, *Physiol Rev*. 2019 - Hanssen *et al., Diabetes Care*. 2018 - Rodrigues & Chevalier *et al., Clin Chem*. 2025

Mass spectrometry-based proteomics (bottom-up)



- MS enables the absolute quantification of apolipoproteins, the assessment of apolipoprotein turnover from stable isotope kinetic studies and the determination of specific polymorphisms.

Blanchard *et al.*, *J Lipid Res*, 2020

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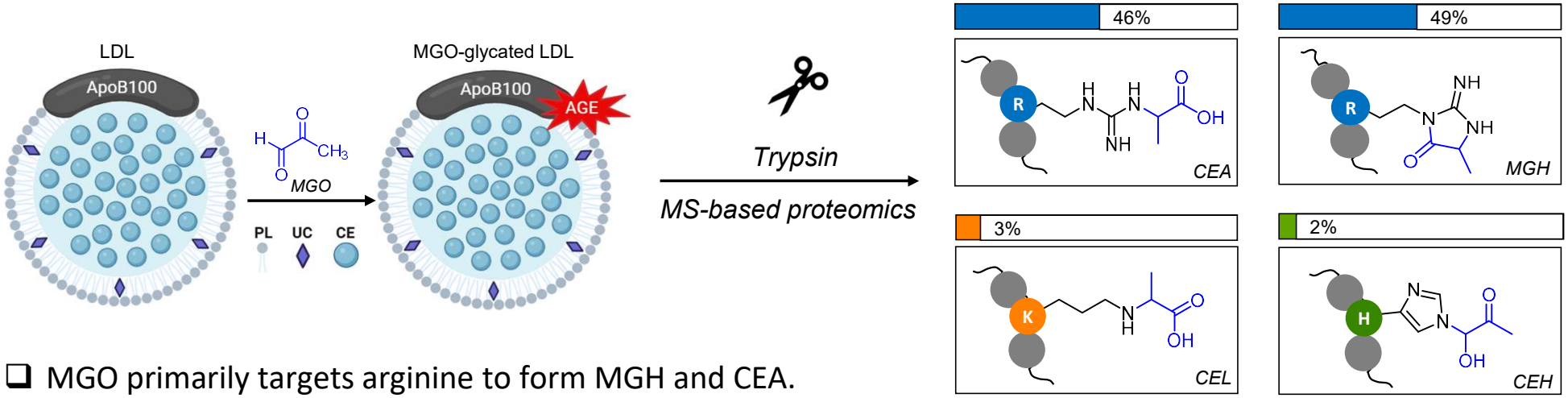
Identification of a proteolytic peptide representative of apoB100 glycation by MGO



- MGO primarily targets arginine to form MGH and CEA.

Apolipoprotein B100

MDPPRPALLALLALPALLLLLLAGARAEEEMLENVSLVCPKDATRFKHLRKYTYNYEAESSSGVPGTADSRSATRINCKVELEVPQLCSFILKTSQCTLKEVYGFNPEGKALLKKTKNSEEFAAAMSRYELKLAIPEGKQVFLYPEKD
EPTYILNIKRGIISALLVPPETEEAKQVLFLDTVYGNCSTHFTVKTRKGNVATEISTERDLGQCDRFKPIRTGISPLALIKGMTRPLSTLISSSQSCQYTLDAKRKHVAEAICKEQHLFLPFSYKNKYGMVAQVTQTLKLEDTPKINS
RFFGEGTKKMGLAFESTKSTSPPKQAEAVLKTLQELKKLTISEQNIQRANLFNKLVTELRGLSDEAVTSLLPQLIEVSSPITLQALVQCGQPQCSTHILQWLKRVHANPLLIDVVTYLVALIPEPSAQQLREIFNMARDQRSRATLYA
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VASHIANILNSEELDIQDLKKLVKEALKESQLPTVMDFRKFSRNYQLYKSVSLPSLDPASAKIEGNLIFDPNNYLPKESMLKTTLTAFGFASADLIEIGLEGKGFEPTLEALFGKQGFFPDSVNKALYWVNGQVPDGVSKVLVDHFGY
TKDDKHEQDMVNGIMLSVEKLIKDLKSKEVPEARAYLRILGEELGFASLHDLQLLGKLLLMGARTLQGIPQMIGEVIRKGSKNDFFLHYIFMENAFELPTGAGLQLQISSSGVIAPGAKAGVKLEVANMQAELVAKPSVSVEFVTNMG
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TQAEGAKQTEATMTFKYNRQSMTLSSEVQIPDFDVDLGTILRVNDESTEGKTSYRLTLDIQNKKITEVALMGHLSCDTKEERKIKGVISIPRLQAEARSEILAHWSPAKLLLQMDSSATAYGSTVSKRVAWHYDEEKIEFEWNTGTNV
DTKKMTSNFPVDLSDYPKSLHMYANRLLDHRVPQTDMTFRHVGSKLIVAMSSWLQKASGSLPYTQTLQDHLNSLKEFNLQNMGLPDFHIPENLFLKSDGRVKYTLNKNSLKIEIPLPFGGKSSRDLKMLETVRTPALHFKSVGFHLPS
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VKEVKIDGQFRVSSFYAKGTYGLSCQRDPNTGRLNGESNLRFNSSYLQGTNQITGRYEDGTLSLTSTSDLQSGIIKNTASLKYENYELTLKSDTNGKYKNFATSNKMDMTFSKQNALLRSEYQADYESLRFFSLLSGSLNSHGLELNA
DILGTDKINSGAHKATLRIGQDGISTSATTNLKCSLLVLENELNAELGLSGASMKLTTNGRFREHNAKFSLDGKAALTELSLGSAYQAMILGVDSKNIFNFKVSQEGLKLSNDMMGSYAEMKFDHTNSLNIAGLSLDFSSKLDNIYSS
DKFYKQTVNLQLQPYSLVTTLNSDLKYNALDLTNNGKLRLEPLKLHVAGNLKGAYQNNEIKHIYAISSAALSASYKADTVAKVQGVEFSHRLNTDIAGLASAIDMSTNYNSDSLHFSNVFRSVMAPFTMTIDAHTNGNGKLALWGEHT
GQLYSKFLLKAEPLAFTFSHDYKGSTSHHLVSRKSISAALEHKVSALLTPAE~ 280 peptide candidates!!LDSPIKVPLLLSEPINIIDALEMRDAVEKPQEFTIVAFVKYDKNQDVHSINLP
FFETLQEYFERNRQTIIVVLENVQRNLKHINIDQFVRKYRAALGKLPQQANDNEKLSQLQTYMIQFDQYIKDSYDLHDLKIAIANIIDEIIEKLKSLDEHYHIRV
NLVKTIHDLHLFIENIDFNKSGSSTASWIQNVDTKYQIRIQIQEKLQQLKRHIQNIDIQHLAGKLKQHIEAIDVRVLLDQLGTTISFERINDILEHVKHFVINLIGDFEVAEKINAFRAKVHELIERYEVDQQIQVLMDKLVELAHQY
KLKETIQKLSNVLQQVKIKDYFEKLVGFIDDAVKKLNELSFKTFIEDVNKFLDMLIKKLKSFDYHQFVDETNDKIREVTQRLNGEIQALELPQKAEALKLFLEETKATVAVYLESLQDTKITLIINWLQEALSSASLAHMKAKFRETL
EDTRDRMYQMDIQQELQRYLSLVGQVYSTLVTYISDWWTLAAKNLTDFAEQYSIQDWAKRMKALVEQGFTVPEIKTILGTMPAFEVSLQALQKATFQTPDFIVPLTDLRIPSVQINFKDLKNIKIPSRFSTPEFTILNTFHIPSFTID
FVEMKVKIIRTIDQMLNSELQWPVPDIYLRDLKVEDIPLARITLPDFRLPEIAIPEFIIPTLNLNDFQVPDLHIPEFQLPHISHTIEVPTFGKLYSILKIQSPLFTLDANADIGNGTTSANEAGIAASITAKGESKLEVLNFDFQANA
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NKINSKHLRVNQNLVYESGSLNFSKLEIQSQVDSQHVGHSVLTAKGMALFGEGKAEFTGRHDAHLNGKVIGTLKNSLFFSAQPFEITASTNNEGNLKVRFPLRLTGKIDFLNNYALFLSPSAQQASWQVSARFNQYKYNQNFSAGNNE
NIMEAHVGINGEANLDFLNIPLTIPEMRLPYTIITTPPLKDFSLWEKTGLKEFLKTTKQSFDLSVKAQYKKNKHRHSITNPLAVLCEFISQSIKSFDRHFEKNRNNALDFVTKSYNETKIKFDKYKAEKSHDELPRTFQIPGYTVPVV
NVEVSPFTIEMSAFGYVFPKAVSMPSFSILGSDVRVPSYTLILPSLELPVLHVPRNLKLSLPDFKELCTISHIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLLSSSSSVIDALQYKLEGTTRLTRKRGLKLATALSLSNK
FVEGSHNSTVSLTTKNMEVSVATTTKAQIPILRMNFKQELNGNTKSKPTVSSSMEFKYDFNSSMLYSTAKGAVDHKLSLESLTSYFSIESSTKGDVKGSVLSREYSGTIASEANTYLNSKSTRSSVKLQGTSKIDDIWNLEVKENFAG
EATLQRIYSLWEHSTKNHLQLEGLFFTNGEHTSKATLELSPWQMSALVQVHASQPSSFHDFPDLGQEVALNANTKNQKIRWKNEVRIHSGSFQSQVELSNDQEKAHLDIAGSLEGHLRFLKNIILPVYDKSLWDFLKLDVTTSIGRRQ
HLRVSTAFVYTKNPNGYSFSIPVKVLADKFIIPGLKLNDLNSVLVMPTFHVPFTDLQVPSCKLDFREIQIYKKLRTSSFALNLPTLPEVKFPEVDVLTKYSQPEDSLIPFFEITVPESQLTVSQFTLPKSVSDGIAALDLNAVANKIA
DFELPTIIVPEQTIEIPSIKFSVPAGIVIPSFQALTARFEVDSPVYNATWSASLKNKADYVETVLDSTCSSTVQFLEYELNVLGTHKIEDGTLASKTKGTFAHRDFSAEYEEDGKYEGLQEWEGKAHLNIKSPAFTDLHLRYQKDKKG
ISTSAASPAVGTVGMDMDEDDDFSKWNFYYSPQSSPDKKLTIFKTELRVRESDEETQIKVNWEEEAASGLLTSLKDNVPKATGVLYDYVNKYHWEHTGLTLREVSSKLRRNLQNNAEWVYQGAIRQIDDIDVRFQKAASGTTGTYQEW
KDKAQNLYQELLTQEGQASFQGLKDNVFDGLVRVTQEFHMKVKHLIDSLIDFLNFPRFQFPGKPGIYTREELCTMFIREVGTVLSQVYSKVHNGSEILFSYFQDLVITLPFELRKHKLIDVISMYRELLKDLSKEAQEVFKAIQSLKT
TEVLRNLQDLLQFIFQLIEDNIKQLKEMKFTYLINYIQDEINTIFSDYIPYVFKLLKENLCLNLHKFNEFIQNELQEASQELQQIHQYIMALREEYFDPSIVGWTVKYYELEEKIVSLIKNLLVALKDFHSEYIVSASNFTSQLSSQV
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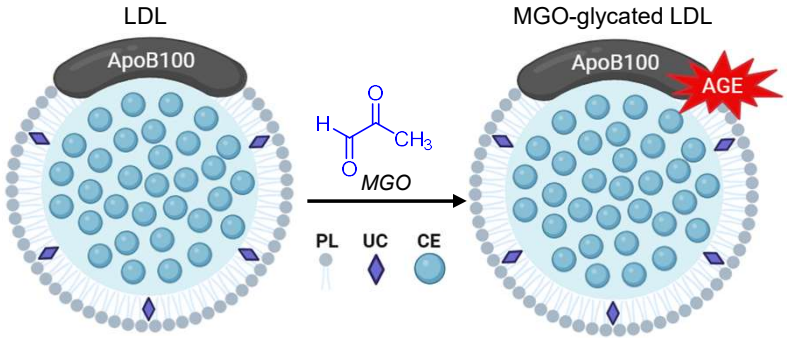
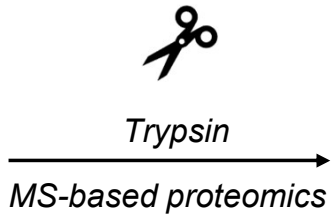
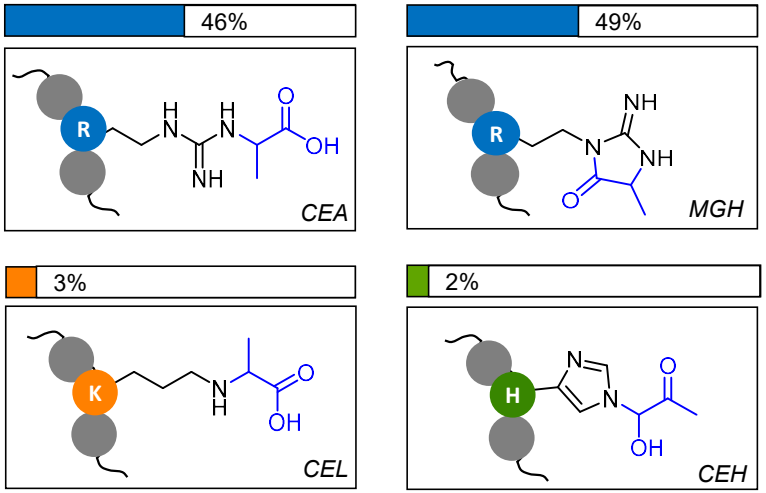
Apolipoprotein B48

Identification of a proteolytic peptide representative of apoB100 glycation by MGO



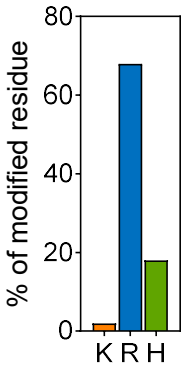




- MGO primarily targets arginine to form MGH and CEA.

Human apoB100: domains 4 and 5

H_2N~~K[2833]YLR*TEHGSEMLFFGNAIEGKSNTVASLHTEKNTLELSNGVIVKINNQLTLDSNTKYFHK
LNIPKLDFSSQADLR*NEIKTLLKAGHIAWTSSGKGSWKWACPRFSDEGTHESQISFTIEGPLTSFGL
SNKINSKHLR*VNQNLVYESGSLNFSKLEIQSQVDSQHVGHSVLTAKGMALFGEGKAEFTGRHDAHL
NGKVIGTLKNSLFFSAQPFEITASTNNEGNLKVRFPLR*LTGKIDFLNNYALFLSPSAQQASWQVSAR
FNQYKYNQNFSAGNNENIMEAHVGINGEANLDFLNIPLTIPEMRLPYTIITTPPLKDFSLWEKTGLKEF
LKTTKQSFDLSVKAQYKKNKHRHSITNPLAVLCEFISQSIKSFDRHFEKNR*NNALDFVTKSYNETKI
KFDKYKAEKSHDELPRTFQIPGYTVPVVNVEVSPFTIEMSAFGYVFPKAVSMPSFSILGSDVRVPSYTL
ILPSLELPVLHVPR*NLKLSLPDFKELCTISHIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVA
HLLSSSSSVIDALQYKLEGTTRLTRKRGLKLATALSLSNKFVEGSHNSTVSLTTKNMEVSVATTTKAQ
IPILR*MNFKQELNGNTKSKPTVSSSMEF[3460]~~CO_2H



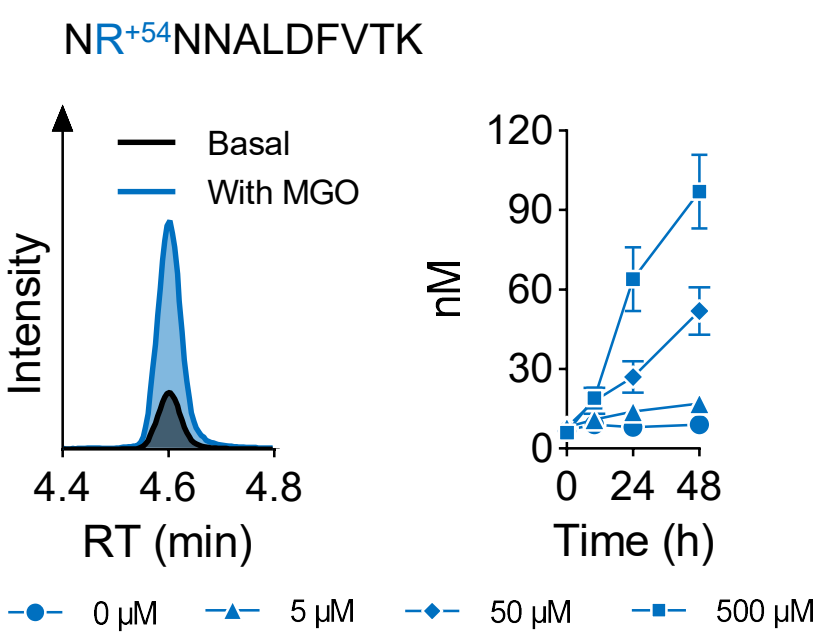
* Sensitive to other glycating agents

- In the apoB100-to-LDLR interaction domain, MGH and CEA levels are positively correlated.
- Two peptides were detected *in vivo* (plasma) but only one (NR[+54]NNALDFVTK) has been validated for high throughput analyses.

Reimund *et al., Nature,* 2024

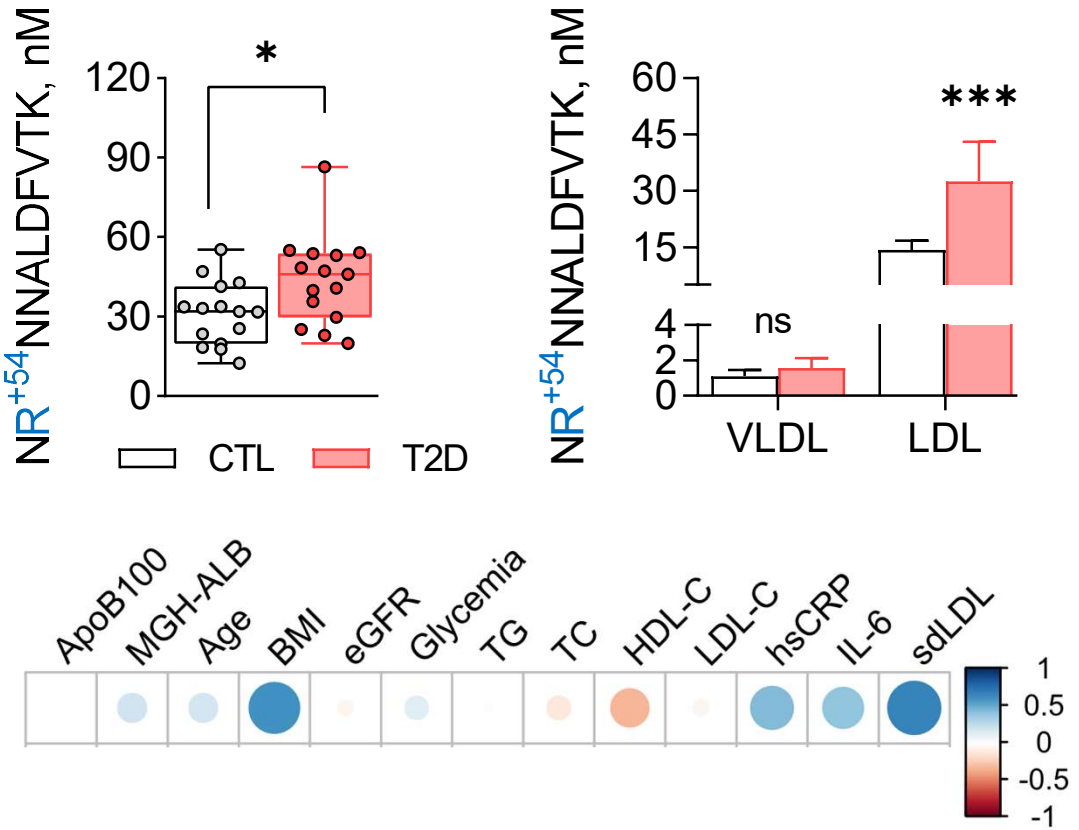
Identification of a proteolytic peptide representative of apoB100 glycation by MGO

1 *Ex vivo*



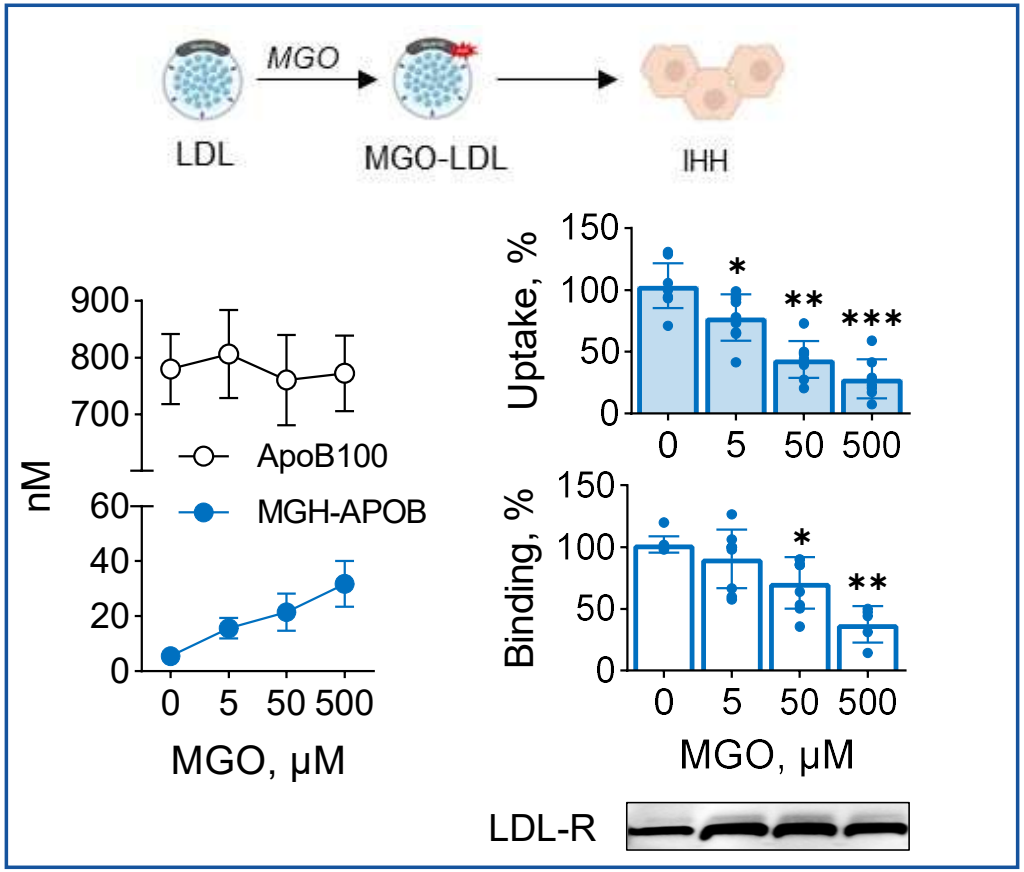
Plasma levels of NR^{+54}NNALDFVTK (called MGH-APOB) are increased in T2D patients and primarily detected in LDL particles.

2 *In vivo*

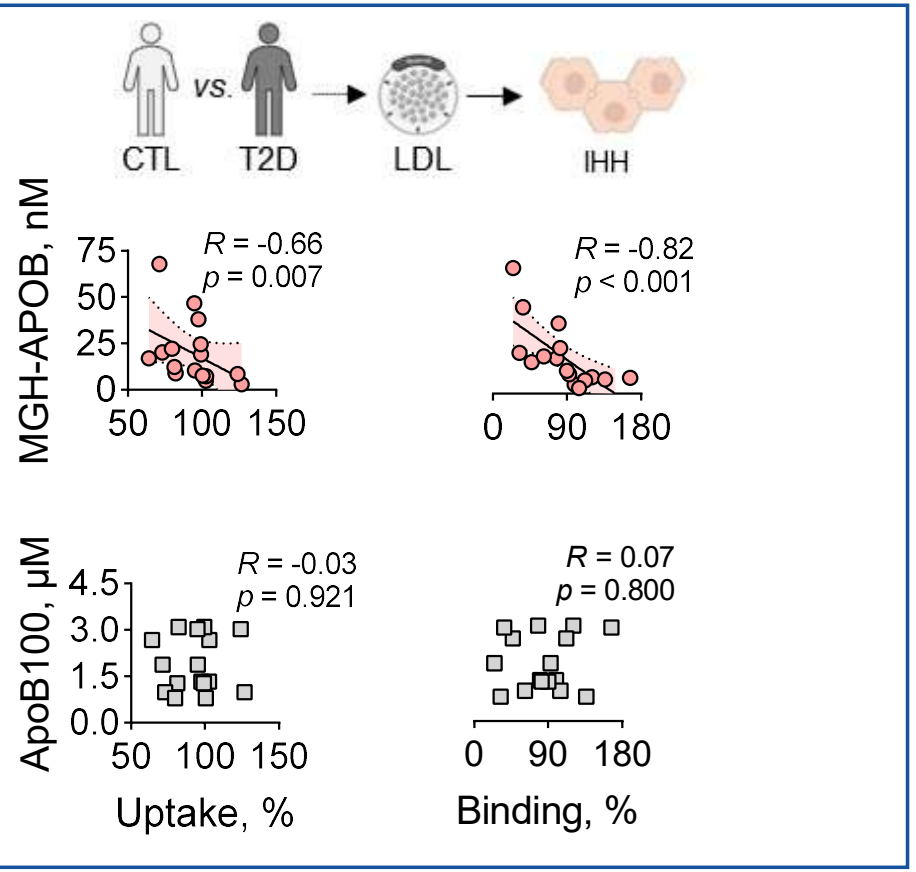


ApoB100 glycation by MGO reduces the hepatic catabolism of LDL

1 *In vitro*



2 *Ex vivo*



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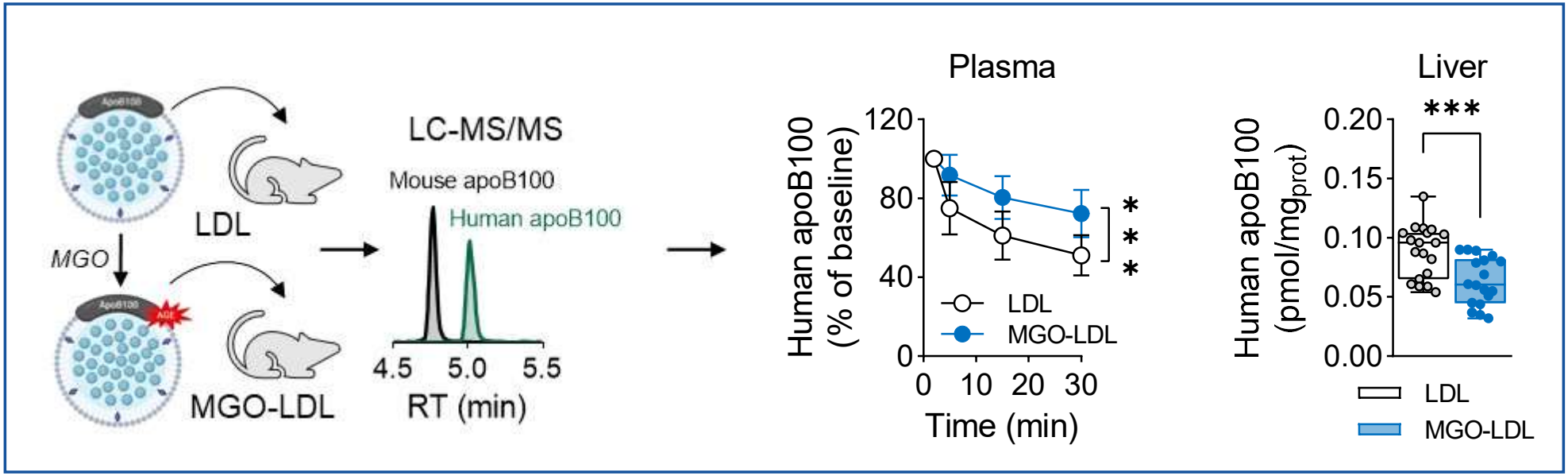
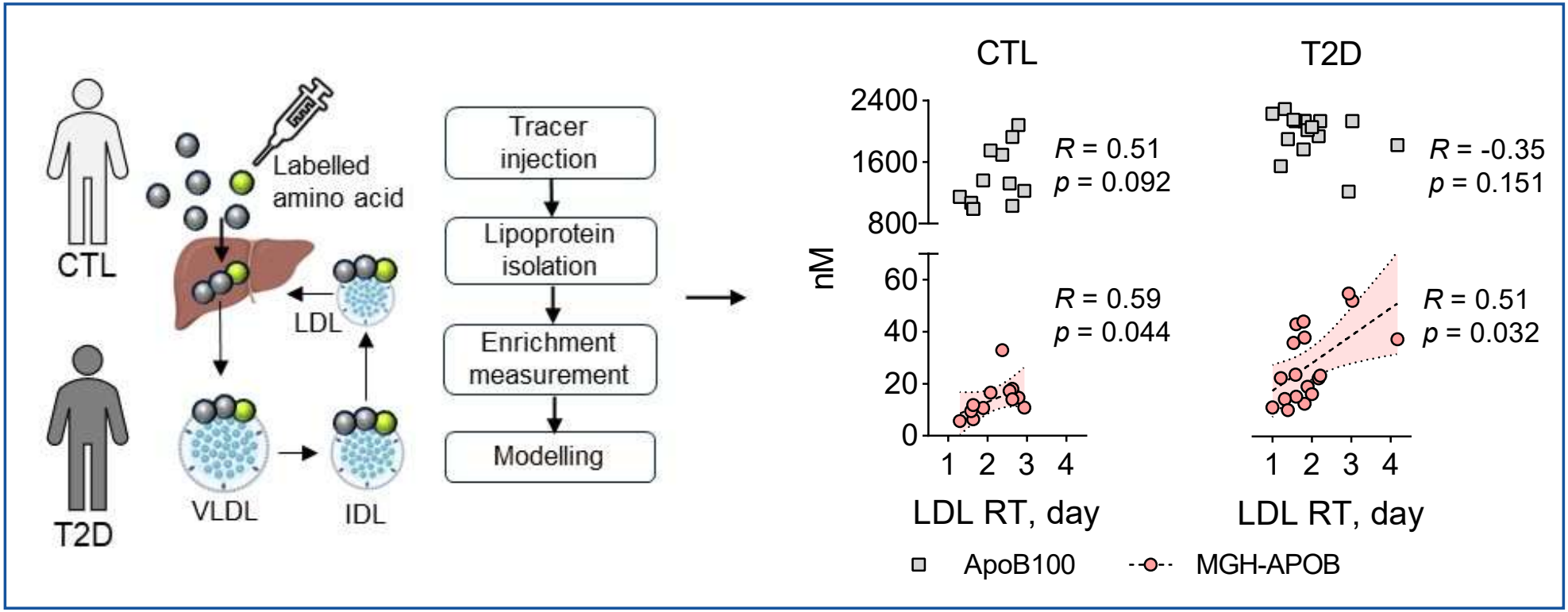
ApoB100 glycation by MGO reduces the hepatic catabolism of LDL

3 *In vivo in mouse (C. Le May)*



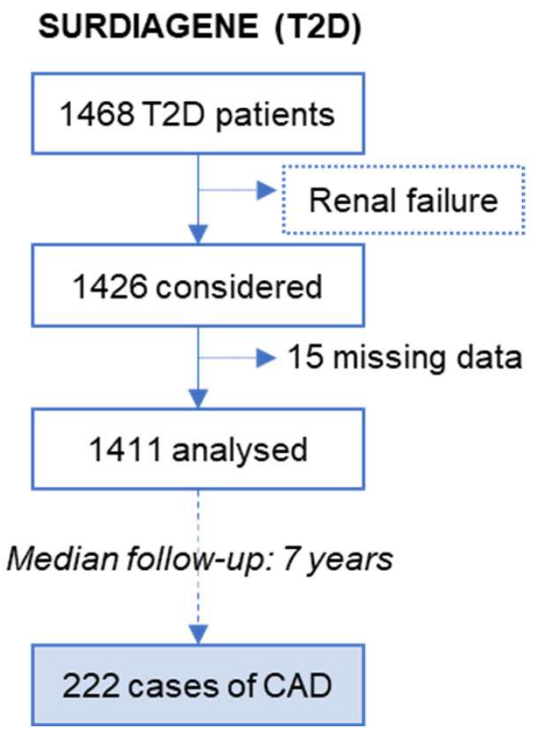
ApoB100 glycation by MGO reduces the hepatic catabolism of LDL

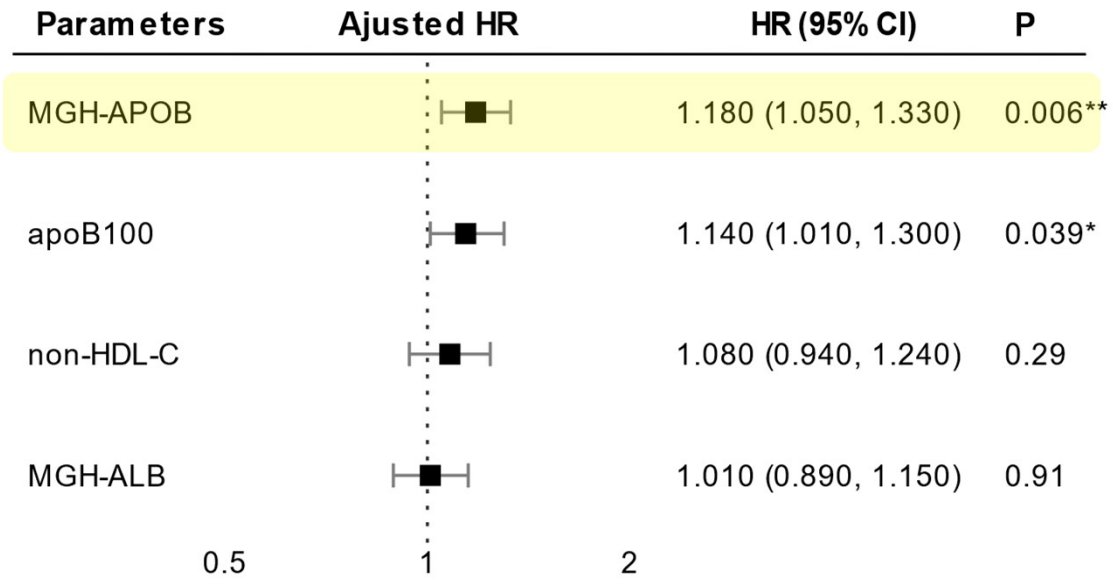
4 *In vivo in human (stable isotope kinetic study, B. Vergès)*



Association of MGH-APOB plasma concentration and incident CAD in T2D

► *Longitudinal & prospective studies (S. Hadjadj, PJ. Saulnier, M. Wargny)*





HR per 1 SD adjusted for sex, age, BMI, uACR, eGFR, history of CAD, HbA_{1c} and HDL-C

❑ MGH-APOB remains significant after adjustment for non-HDL-C, apoB100 and MGH-ALB : **HR 1.16 [1.03 – 1.31]; *p = 0.015***

► *To be replicated (in progress): DIABHYCAR, D.E.S.I.R.*

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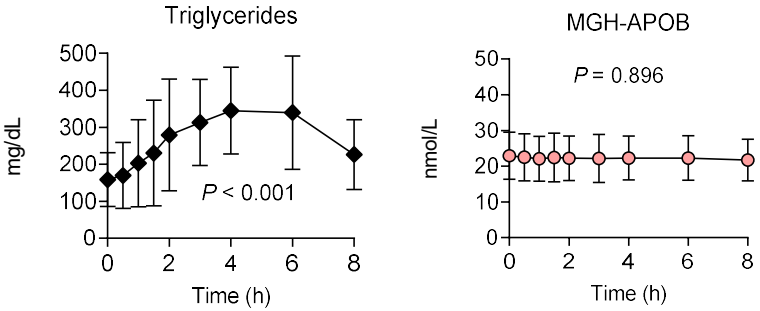
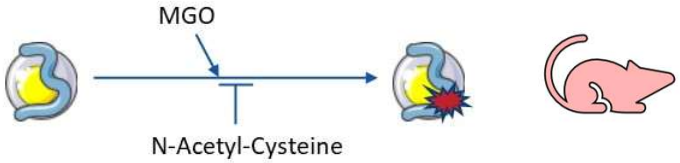
Effects of lipid- or glucose lowering treatments

1 *Impact of food intake (B. Cariou)*

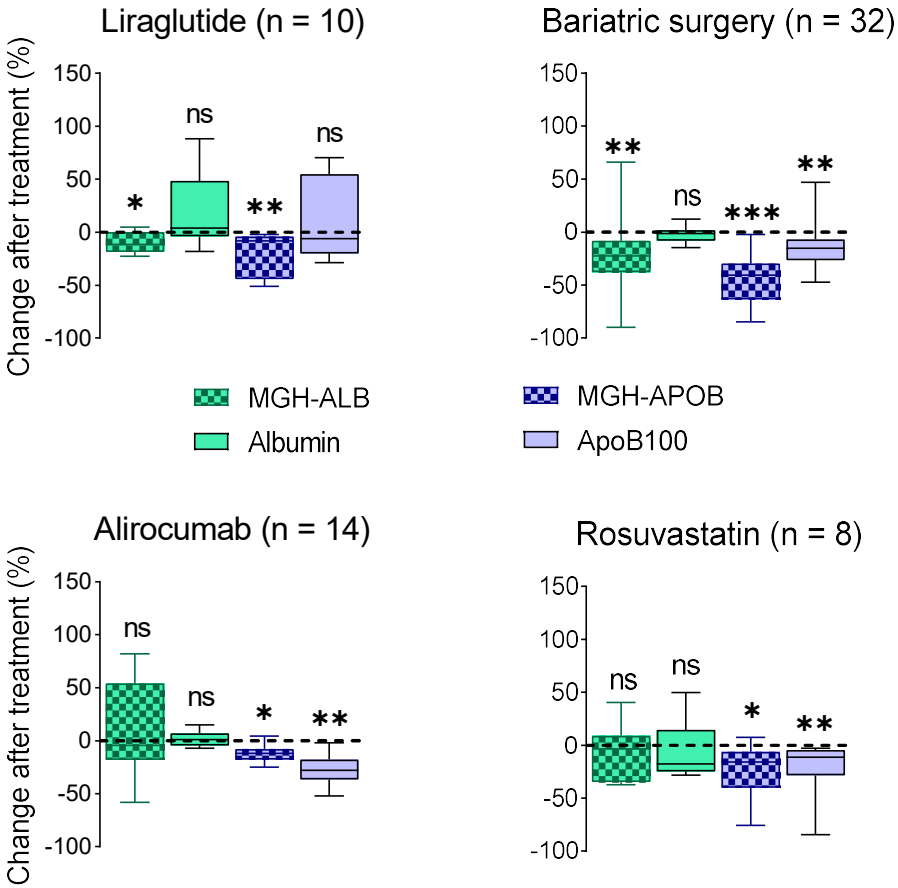


3 *Treatments (C. Le May)*



Effect of drugs capable of neutralizing MGO in progress

2 *Treatments (B. Cariou, B. Vergès, R. Valéro)*



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General conclusion

▶ Take-home message

Proteins are biomarkers for early disease detection. **PTMs give key insights into organ dysfunction** and cellular stress, but remain **complex to analyse**. Chronic hyperglycaemia, dyslipidaemia, and nephropathy alter PTM dynamics and some **specific PTMs are implicated in the pathogenesis of chronic diseases**.

▶ Future directions

Develop multiplexed assays to quantify diverse apolipoprotein proteoforms; focus on clinically relevant, functionally impactful biomarkers to improve CV risk stratification.

▶ Translational approach

Bridge basic science with clinical application to clarify links between metabolic dysregulations, lipoprotein metabolism, and CVD.

▶ Ultimate goal

Improve care for high-risk patients, identify **novel therapeutic targets** through apolipoprotein PTMs, consider PTMs as direct therapeutic targets in the future.

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Thank you for your attention

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