Editorial

Dear Colleague,

In this issue of the Lipid Club Letter Jean Ducobu reports further on presentations from the latest DALM meeting in the US. These are interesting contributions to the challenging field of reverse cholesterol transport and HDL metabolism. They also fit well in the agenda of the forthcoming meeting of the Belgian Lipid Club on June 10th 2008, completely devoted to HDL and arteriosclerosis.

I received several interesting submissions for the Lipid Club Fellowship. The jury will have a difficult job!

I invite all our members to contribute to these Lipid Club Letters with information or study results that may interest our Society. Do we have to go to the EAS meeting in Istanbul to learn what is happening in our research labs in Belgium? Let us try to make the Lipid Club letters also a newsletter regarding ongoing studies or local initiatives of general interest.

In the meantime, enjoy this letter and I hope to see you all on June 10th at our next Lipid Club meeting.

Cordially

Guy De Backer
President
Reverse cholesterol transport (RCT) is an antiatherosclerotic process (Fig 1 and Table 1). Multiple genes/proteins are involved in this process, leading to the identification of several targets, whose pharmacological modulation may provide antiatherosclerotic, beneficial effects. Compounds that promote lipid efflux may result in a substantial protective effect related to the reduction of cholesterol content of peripheral cells.

This effect is gained by PPAR and LXR agonists that increase cellular lipid release through up-regulation of ABCA1 and contribute to the formation of nascent HDL. The LXR synthetic agonists T0901317 and GW3916 have shown to promote the in vivo RCT that specifically occurs from macrophages. A possible mechanism related to this effect is the increased cholesterol efflux via passive diffusion and SR-BI-mediated mechanisms.

Since HDLs play an active role in several steps of RCT, factors that increase their level could promote the whole process. Despite torcetrapib failure, inhibition of CETP is currently a possible target for RCT.

Table 1:

<table>
<thead>
<tr>
<th>4 STEPS OF R.C.T. (REVERSE CHOLESTEROL TRANSPORT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cholesterol efflux from cells</td>
</tr>
<tr>
<td>2. Cholesterol uptake by the liver</td>
</tr>
<tr>
<td>3. Cholesterol excretion into bile</td>
</tr>
<tr>
<td>4. Sterol elimination into the feces</td>
</tr>
</tbody>
</table>
promising approach. Modulation of hepatic lipid uptake may be achieved by agents that stimulate SR-BI activity, as agonists of thyroid hormone receptors, whose administration in mice resulted in an improved fecal sterol excretion. The stimulation of the last step of RCT represents a novel approach, supported by the recent discovery that in vivo stimulation of LXR promotes the elimination of sterols into the feces through a biliary cholesterol independent pathway.

Many studies with mice have dissected the respective roles of receptors and enzymes in the RCT (Table 2).

Table 2:

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect on RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRB1 KO mice</td>
<td>no effect on RCT</td>
</tr>
<tr>
<td>ABCG1 KO mice</td>
<td>↓ RCT</td>
</tr>
<tr>
<td>ABCG1 Tg mice</td>
<td>↑ RCT</td>
</tr>
<tr>
<td>ABCA1 KO MICE</td>
<td>↓ RCT</td>
</tr>
<tr>
<td>CETP Tg mice</td>
<td>↑ RCT</td>
</tr>
</tbody>
</table>

ADVANCES IN THE MEASUREMENT OF CHOLESTEROL EFFLUX AND REVERSE CHOLESTEROL TRANSPORT (RCT)

Marc K. Hellerstein, Berkeley.

The functional significance of RCT remains controversial, largely because fluxes have not been measurable in vivo. But the laboratory of M.K.Hellerstein has developed a double isotope “in vivo” assay that is able to quantify the different fluxes. In summary, 1) C efflux from tissues is routinely measurable in vivo in humans and is of an order of magnitude greater than LDL delivery of C to tissues (suggesting a potent target); and 2) potential flux generating steps in RCT are now testable (e.g. ABCA1), as are drug effects (e.g. CETP inhibitors) and functional differences in HDLs (e.g. A1-Milano). The central questions concerning RCT can now be addressed: are RCT fluxes relevant to atherosclerosis (i.e. reflect macrophage events) and is efflux per se, without altering whole-body excretion, a therapeutic target?

HDL

ANTIATHEROGENIC PROPERTIES OF HDL

Philip Barter, Sydney

An inverse relationship between the concentration of cholesterol in high density lipoproteins (HDLs) and the development of premature coronary heart disease (CHD) has been observed in many large-scale prospective studies. In several of these, the level of HDL cholesterol (HDL-C) has been the single most powerful lipid predictor of future CHD events. In support of these human population studies, there are numerous intervention studies in animals showing that an increase in the concentration of HDLs inhibits the development of atherosclerosis. Evidence in humans that increasing the concentration of HDLs protects against cardiovascular disease is more limited but growing (Table 3). There are several properties of HDLs that have the potential to protect against the development of atherosclerosis. The best documented is the ability of HDL to promote the efflux of cholesterol from cells in the artery wall. However, HDLs have a number of additional potentially anti-atherogenic properties that may be unrelated to their role in plasma lipid transport. For example, HDLs bind lipopolysaccharide, promote endothelial repair by enhancing the migration of cells from neighbouring undamaged tissue and by recruiting progenitor endothelial cells from plasma into damaged endothelium. HDLs inhibit the synthesis...
of the platelet-activating factor by endothelial cells. HDLs are anti-thrombotic. They modulate endothelial function, probably by stimulating endothelial NO production. HDLs also possess antioxidant and anti-inflammatory activities. The degree to which any or all of these non-lipid transport functions of HDL contribute to a protection against atherosclerosis is still uncertain, although evidence is mounting that at least some of them may be of substantial importance.

But in many situations (systemic inflammation, diabetes, metabolic syndrome, ...), the HDL loses its protective functions (less paraoxonase) or becomes more aggressive (more myeloperoxidase).

So the “good” HDL becomes the “bad” HDL: this dysfunctional HDL is very important to understand the proatherogenic nature of HDL in systemic inflammation and metabolic syndrome (Fig 2).

Table 3: BENEFITS OF RAISING HDL

- **Animal studies**
  Raising HDL-C either by infusing HDL or by increasing the synthesis of apoA-I by genetic manipulation greatly inhibits the development of atherosclerosis in both mice and rabbits.

- **Human studies**
  Raising HDL-C with either niacin or fibrates in intervention trials is associated with a slowing of progression of atherosclerosis and a reduction in CV events

Infusion of reconstituted HDL reduces the atherosclerosis burden as assessed by IVUS.

Figure 2:
LOW HDL-C IS A SIGNIFICANT INDEPENDENT CVD RISK FACTOR AND THERAPEUTIC TARGET FOR REDUCING CVD RISK

Intervention trials using statins to lower LDL cholesterol (LDL-C) have consistently shown substantial reductions in major cardiovascular events (MCEs) in both primary and secondary prevention, in those with and without diabetes or hypertension and in people with a wide range of baseline lipid levels. Furthermore, the magnitude of the reduction in events is a function of the extent of LDL lowering, with each 40 mg/dl decrease in LDL-C equating with a 24% reduction in Major Cardiovascular Events (MCEs). This benefit has been demonstrated with reductions of LDL-C down to levels as low as 70 mg/dl. However, in all of the statin trials, including those in which a proportion of subjects achieved low levels of LDL-C, there is a substantial residual risk of MCEs despite adequate treatment with statins. In part, this reflects the residual risk associated with a low level of HDL-C. The fact that a low HDL-C remains predictive of MCEs during statin therapy supports the view that HDL-C should be considered as a therapeutic target, independent of achieved levels of LDL-C. This view was further supported by the results of the Treating to New Targets (TNT) study of more than 10,000 subjects, of whom many achieved an on-treatment LDL-C of less than 70 mg/dl (recently published in the New England Journal of Medicine (Oct. 2007). There was an inverse relationship between the incidence of MCEs correlated inversely and significantly with the on-treatment (3 months) level of HDL-C in the overall study. This inverse relationship remained apparent in the group with LDL levels less than 70 mg/dl (Fig 3).

Figure 3:

HDL, REVERSE CHOLESTEROL TRANSPORT, AND NUCLEAR RECEPTORS

Jean-Charles Fruchart, Lille.

High density lipoprotein (HDL) cholesterol levels are a strong increase predictor of cardiovascular events. PPARα (peroxisome-proliferator activated receptor α) and LXRα (liver receptor α) are transcription factors that regulate the expression of genes that control lipid and lipoprotein metabolism as well as the inflammatory response. PPARα and LXRα control the first steps of reverse cholesterol transport by acting on macrophages in different ways. PPARα agonists enhance the expression of the ABC transporter ABCA1 by an indirect mechanism involving the stimulation of LXRα expression. LXRα agonists promote cholesterol efflux from macrophages through the induction of ABCA1, ABCG1 and ABCG4. PPARα and LXR agonists increase the expression of NPC1 and NPC2 leading to an enrichment of cholesterol in the plasma membrane and to a stimulation of cholesterol mobilization by PPARα and LXR activation (Table 4). On the basis of these findings, the development of new molecules targeting selectively these nuclear receptors provide exciting opportunities to reduce atherosclerosis and its complications. They have developed selective nuclear receptor modulators with characteristic cofactors binding patterns in order to activate desirable target genes and to repress the transcription of undesirable genes. Ex.: GFT 505 is a PPARα agonist, a hundred times more potent than fenofibrate. It has showed protection against atherosclerosis in apo E2/E2 mice.

Table 4:

<table>
<thead>
<tr>
<th>EFFECTS OF LXR AGONISTS</th>
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<tbody>
<tr>
<td>➤ Macrophage cholesterol efflux (ABCA1, ABCG1)</td>
</tr>
<tr>
<td>➤ Liver bile synthesis</td>
</tr>
<tr>
<td>➤ Intestinal cholesterol absorption</td>
</tr>
<tr>
<td>➤ Macrophage inflammation</td>
</tr>
</tbody>
</table>

At this stage, a growing body of evidence from in vitro and in vivo study in animals and humans, indicates that these drugs are safe and could have beneficial effects in atherosclerosis.
HDL has been proposed to protect against atherosclerosis by several mechanisms including reverse cholesterol transport, protection of LDL from oxidation, as an anti-inflammatory agent, and by modulation of endothelial function with increased NO production. A major advance in HDL metabolism has been the elucidation of a dual pathway for HDL mediated cholesterol efflux. These pathways include poorly lipided apoA-I the preferred cholesterol acceptor for the ABCA1 transporter which leads to nascent HDL that facilitates efflux by the SR-BI receptor and ABCG1 transporter. Current drug therapy to increase HDL includes statins, fibrates, and niacin. Future approaches to increase HDL include both acute HDL infusion therapy for acute coronary syndrome (ACS) patients and chronic oral HDL therapy for stable cardiovascular disease patients (Table 5).

**Table 5:**

<table>
<thead>
<tr>
<th>HDL THERAPY:</th>
<th>Stable Coronary Heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Coronary Syndrome</strong></td>
<td><strong>Oral therapy</strong></td>
</tr>
<tr>
<td>Infusion therapy</td>
<td>- Fibrates</td>
</tr>
<tr>
<td>- Apo A1 Milano</td>
<td>- Niacin</td>
</tr>
<tr>
<td>- Delipidated HDL</td>
<td>- CETP inhibition</td>
</tr>
<tr>
<td>- Apo A1 mimetics.....</td>
<td>- New PPAR agonists</td>
</tr>
<tr>
<td></td>
<td>- Combination</td>
</tr>
</tbody>
</table>

Of clinical interest is the use of acute HDL infusion therapy to potentially decrease cardiac events in ACS patients. The initial clinical study with acute HDL therapy utilized apoA-I Milano/ phospholipids complexes and was associated with regression in coronary artery atherosclerosis (Table 6).

Recently, infusions of autologous delipidated HDL have been initiated to further establish the efficacy of apoA-I infusions to reduce coronary atherosclerosis. ApoA-I mimetic peptides are also being developed as an approach for infusions in ACS patients. Further clinical studies will be required to definitively establish whether acute HDL infusion therapy with apoA-I/ phospholipid complexes and apoA-I mimetic peptides will result in regression of coronary atherosclerosis and decreased cardiac events.

**Table 6:**

**INFUSION OF ApoA-I Milano RESULTED IN REGRESSION OF ATHEROSCLEROSIS IN PATIENTS WITH THE ACUTE CORONARY SYNDROME:**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>46 Acute Coronary Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusions</td>
<td>5 Weekly Infusions</td>
</tr>
<tr>
<td>33 ApoA-I Milano Infusion</td>
<td>(15mg/kg, n=12; 45mg/kg, n=24; 11 Saline Infusions)</td>
</tr>
<tr>
<td>Results</td>
<td>Decrease in Atheroma</td>
</tr>
<tr>
<td>Volume</td>
<td>-4.2%</td>
</tr>
</tbody>
</table>
A BI-HELICAL APOA-I MIMETIC PEPTIDE: EFFECT ON CHOLESTEROL EFFLUX AND ON ATHEROSCLEROSIS IN MICE

Alan T. Remaley, Bethesda.

ApoA-I peptide mimetics that mediate cholesterol efflux by the ABCA1 transporter are currently being investigated as therapeutic agents. A potentially limiting property is that these peptides can also remove cholesterol by a cytotoxic microsolvabilization process. A single injection resulted in a 45% increase of HDL-C at 6 h and a 165% increase in the ability of mouse serum to efflux cholesterol by ABCA1. At the end of the study, there were no apparent signs of toxicity from the peptide treatment, as assessed by liver and renal function tests, and the treated mice gained weight the same as controls. Analysis of the aorta in the treated mice had a 53%(P<0.002) reduction in atherosclerosis. In conclusion, the ApoA-I mimetic peptide showed the greatest ABCA1 specificity and the lowest cytotoxicity, and treatment with the peptide can increase HDL-C levels and reduce the progression of atherosclerosis in apoE K/O mice.

USE OF COMBINATION THERAPY WITH STATINS TO PROVIDE OPTIMAL REDUCTION IN RESIDUAL CVD RISK

Karol E. Watson, Los Angeles.

Current guidelines for the prevention and treatment of coronary heart disease focus on LDL-C as the primary target of therapy. However, there has been growing interest in raising HDL-C as a secondary target of therapy, based on strong epidemiologic data suggesting that HDL-C levels are inversely related to the development of atherosclerosis.

In the Framingham Heart Study, patients with the highest HDL-C levels had the lowest risk of developing coronary artery disease during the ensuing 35 years. Data from Framingham suggests that each 1% increase in HDL-C was linked to a 2% reduction in the development of coronary artery disease.

Lifestyle modification remain the first line of therapy for patients with low HDL-C. Obesity, cigarette smoking, high saturated fat intakes, and sedentary lifestyle all reduce HDL-C levels, and altering these risk factors can increase HDL-C. For many patients however, lifestyle modification may not be enough to achieve optimal HDL-C levels. A number of medications also impact HDL-C levels. Statins, which are the most efficacious LDL-C lowering medications, have a modest HDL-C raising effect. Fibric acid derivatives (fibrates) are effective therapy for patients with high triglycerides and low HDL-C, as is nicotinic acid (niacin). Niacin is the most potent drug currently available for raising HDL-C and has been shown to reduce the risk of cardiovascular events (Table 7). In clinical trials that have combined an LDL-C lowering strategy with an HDL-C raising strategy, clinical event reduction and atherosclerosis regression has been seen. The use of combination lipid lowering therapy is probably the best way focusing on the efficacy of this approach as well as the safety issues and practical applications.

Recently, a great meta-analysis of 23 trials by B.G. Brown has demonstrated the importance of raising LDL and decreasing HDL to obtain optimal CVD reduction (Fig 4 and table 8).
### Table 7: Existing HDL-Raising Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>5 - 15%</td>
</tr>
<tr>
<td>Statins</td>
<td>3 - 12%</td>
</tr>
<tr>
<td>Niacin</td>
<td>10 - 30%</td>
</tr>
</tbody>
</table>

### ADA LIPID TARGETS

- **LDL cholesterol**
  - <100 mg/dl
- **Triglyceride**
  - <150 mg/dl
- **HDL cholesterol**
  - > 40 mg/dl men
  - > 50 mg/dl women

### Strategies for Raising HDL in Humans

**Lifestyle**
- Weight reduction
- Increased physical activity
- Stop smoking
- ? Alcohol

**Drugs**

### Existing HDL-Raising Drugs

- Fibrates: 5 - 15%
- Statins: 3 - 12%
- Niacin: 10 - 30%
**Effect of various drug classes on trial primary clinical event rate**

**CONCLUSIONS:**

- A lower level of HDL-C is predictive of CV events even when the level of LDL-C is very low.
- There are several actions of HDLs with the potential to protect against CV disease.
- Evidence is mounting that increasing the plasma level of HDLs translates into a reduction in CV risk.
- Major trials are currently underway to test the effects of therapies that increase HDL and decrease LDL:
  - **Accord Study** with simvastatin and fenofibrate (Table 9).
  - **AIM High Study** with simvastatin and niacin (Table 10).

The results will not be available before 2010.

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**ACCORD** Action to Control Cardiovascular Risk in diabetes (Lipid Arm)

- 5800 patients
- Men and women
- Aged 40-79 years
- Type 2 diabetes, high risk for CVD events
- 70 clinics in US and Canada

**Primary End Point**
- First occurrence of major CVD Event (nonfatal MI, non fatal Stroke, or CVD death).

**Key Secondary End Point**
- Other CVD outcomes
- Total mortality
- Microvascular outcomes
- Quality of life
- Cost effectiveness

**AIM HIGH** Action to Control Cardiovascular Risk in diabetes (Lipid Arm)

- 3300 patients
- Men and women
- Aged ≥ 45 years
- Established vascular disease
- Atherogenic dyslipidemia
- Low HDL-C and high triglycerides

**Primary End Point**
- Composite of CHD death, Nonfatal MI, ischemic stroke or hospitalization for high-risk ACS with objective evidence of ischemia

**Key Secondary End Point**
- Composite of CHD death, nonfatal MI, or ischemic stroke

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**Table 9:**

<table>
<thead>
<tr>
<th>Variables</th>
<th>β Coefficient</th>
<th>95% confidence interval</th>
<th>P value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔHDL-C</td>
<td>-1.653 (0.696, 0.104)</td>
<td>0.04</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>%ΔLDL-C</td>
<td>-1.791 (0.529, 0.664)</td>
<td>0.01</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>%ΔHDL-C</td>
<td>-1.388 (0.695, 0.481)</td>
<td>0.01</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>%ΔLDL-C</td>
<td>-1.977 (0.643, 0.328)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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**Table 10:**

<table>
<thead>
<tr>
<th><strong>Simultaneous LDL-C Lowering and HDL-C Elevation for Optimal CVD Reduction</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 23 Lipid Trials</td>
</tr>
<tr>
<td>• The cardiovascular event rate reductions associated with a decrease in LDL-C and an increase in HDL-C are statistically independent.</td>
</tr>
<tr>
<td>• Meta-analysis revealed that the sum of % increase in HDL-C and % decrease in LDL-C (% ΔHDL + % ΔLDL) predicts cardiovascular benefits more effectively than either component alone.</td>
</tr>
<tr>
<td>• This analysis supports the notion that a readily attainable 40% reduction in LDL-C and a 30% augmentation of HDL-C will result in ~ 70% CHD risk reduction and a revolution in cardiovascular prevention.</td>
</tr>
</tbody>
</table>

The aim of the study was to determine the effects of the fenofibrate/pravastatin (FENO/PRA) fixed combination on atherogenic lipoprotein subfractions in high risk patients with mixed hyperlipidemia.

After an 8-week pravastatin (PRA) 40mg and diet run-in period, high-risk patients (n =248) with LDL-cholesterol ≥ 100mg/dl and triglycerides ≥ 150 and ≤ 400 mg/dl, were randomized to a double-blind, multicenter, 2 parallel arms, 12-week comparison of FENO/PRA160/40 mg versus PRA 40mg alone followed by an open-label, 52-week safety phase of the combination therapy. This study reports the effects on lipoprotein subfractions at the end of the double-blind phase.

After 12 weeks of double-blind treatment, the LDL, the TG and the non HDL decreased and the HDL increased more with FENO/PRA than with PRA alone (Fig 5). The ApoB/ApoA1 ratio was decreased (p<0.0001) with FENO/PRA (-16.2 %) compared with PRA (-6.1 %). LpB:E and LpB:CIII were significantly reduced with FENO/PRA (respectively – 23.8 % and 12.4 %) compared with PRA (respectively – 0.2 % and 7.4 %). The mean LDL size was increased in the FENO/PRA group (+1.54 %) compared with the PRA group (-0.16 %) (p<0.0001). The FENO/PRA fixed combination was generally well tolerated.

The combination of fenofibrate 160mg and pravastatin 40mg in patients with mixed hyperlipidemia provided significant improvements in atherogenic lipoprotein parameters compared with pravastatin 40mg monotherapy.
Ezetimibe (EZE) is a cholesterol absorption inhibitor that reduces plasma LDL-C by selectively binding to the intestinal cholesterol transporter, Niemann-Pick C1-Like 1 (NPC1L1). Mice deficient in NPC1L1 are protected from high fat/cholesterol diet-induced fatty liver and hypercholesterolemia. The object of the study was to determine if EZE treatment could reduce hepatic steatosis in diet-induced obese (DIO) mice.

Mice were fed a diet containing high fat and cholesterol [HFC; 45% (Kcal) fat and 0.12% (w/w) cholesterol] from six weeks of age. After seven months of exposure to the HFC diet, mice (n=12/group) were treated with EZE (0, 0.5, 1.6, or 5 mg/kg/day) admix in the HFC diet for four weeks.

Compared to age matched chow fed mice, C57BL/6J mice chronically fed a HFC diet had significantly higher body weights (+60%), and enlarged livers (+180%) with elevated liver to body weight ratio (+75%). The DIO mice had 35, 24, and 3.8 fold higher levels of hepatic triglyceride (TG), cholesteryl ester (CE) and free cholesterol (FC), respectively. The livers of mice fed the HFC diet developed hepatic steatosis, with varying degree of fibrosis and steatohepatitis. 87% of the mice on the HFC diet for seven months had elevated plasma ALT activity, a biomarker for Non Alcoholic Fatty Liver Disease (NAFLD). Four weeks of EZE treatment (5 mg/kg/day in diet) was able to reduce 40% of the TG, 80% of the CE and 50% of the FC that had accumulated in the liver after seven months of HFC feeding. Chronic EZE treatment also significantly decreased plasma ALT activity.

These data suggest that reducing FC, CE and TG levels with EZE may be a novel treatment for NAFLD.

**EZETIMIBE IMPROVES HIGH FAT AND CHOLESTEROL DIET-INDUCED NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN MICE**

S. Zheny, Kenilworth

Nicotinic acid (NA) inhibits adipocyte triglyceride lipolysis, thereby lowering plasma free fatty acids (FFA). Decrease in FFA flux to the liver has been postulated to entrain the beneficial effects of NA: reduction of triglycerides, LDL cholesterol and Lp(a), and elevation of HDL cholesterol.

However, NA also induces cutaneous flushing, limiting patient compliance. A *Gi-coupled 7-transmembrane domain receptor expressed in adipocytes and macrophages, GPR109A, has been shown to mediate both NA-induced anti-lipolysis and cutaneous flushing in mouse models*. The goal of the study was to identify a GPR109A ligand that maintains anti-lipolytic activity while avoiding flushing.

MK-0354, a pyrazole tetrazole, acted as a partial agonist in cell-based assays in GPR109A-expressing CHO cells (reduction of intracellular cAMP). Whereas MK-0354 inhibited lipolysis in primary adipocytes to the same extent as NA, it failed to stimulate MAPK phosphorylation in transfected cells or primary macrophages. Consistent with these in vitro findings, MK-0354 had a marked therapeutic window between plasma FFA reduction and cutaneous flushing in mouse and dog. The pharmacological profile of MK-0354 in rodents and dogs suggested potential advantages over the currently available “low-flush” NA formulations. MK-0354 was therefore nominated for further examination in clinical trials.

**DISCOVERY AND CHARACTERIZATION OF A PARTIAL AGONIST OF THE NICOTINIC ACID RECEPTOR GPR109A**

E. Carballo-Jane, San Diego
4th SYMPOSIUM
LIPIDES ET ATHEROSCLEROSE
CHU Charleroi, ULB
Auditoire Point Centre Charleroi
Saturday 27 September 2008

08:30  Accueil

08h55  « Introduction »  
       J. DUCOBU (ULB)

09h00  « HDL : Chameleon of the 21st Century »  
       J. CHAPMAN (Inserm Paris)

09h30  « Nouvelles approches dans l’étude de la myéloperoxydase et de son rôle dans l’athérosclérose »  
       Karim ZOUAOUI (CHU Charleroi) et P. VAN ANTWERPEN (ULB)

10h00  « Athérosclérose et inflammation (modèle de la vasculopathie du rejet) »  
       O. THAUNAT (Lyon)

10h30  Pause

11h00  « Imagerie de l’athérosclérose par IRM. »  
       R. MULLER (U. Mons Hainaut)

11h30  « Syndrome métabolique : l’épidémie du XXIème siècle. »  
       L. VAN GAAL (U. Antwerpen)

12h00  « Hypercholestérolémie. Qui dépister ? Comment traiter ? »  
       O. DESCAMPS (C.H. Jolimont)

12h30  Conclusions

Renseignements : jducobu@skynet.be ou jean.ducobu@chu-charleroi.be

Avec le soutien du Belgian Lipid Club et du Fonds de la Recherche Médicale dans le Hainaut (FRMH)