Opposite Effects of Plasma From Human Apolipoprotein A-II Transgenic Mice on Cholesterol Efflux From J774 Macrophages and Fu5AH Hepatoma Cells

Natalie Fournier, Anne Cogny, Véronique Atger, Danièle Pastier, Dominique Goudouneche, Antonino Nicoletti, Nicole Moatti, Jean Chambaz, Jean-Louis Paul, Athina-Despina Kalopissis

Abstract—Overexpression of human apolipoprotein A-II (hAIItg mice) induced marked hypertriglyceridemia and low levels of plasma high density lipoprotein (HDL) with a high hAII content. We sought to determine whether cholesterol efflux to plasma and HDL from these mice would be affected. In the Fu5AH cell system, plasma from hAIItg mice induced a markedly lower cholesterol efflux than did control plasma, in accordance with the dependence of efflux on HDL concentration. Moreover, HDLs from hAIItg mice were less effective acceptors than were control HDLs. In the J774 macrophage cell system, pretreatment with cAMP, which upregulates ATP binding cassette transporter 1, induced a marked increase in the efflux to hAIItg plasma as well as to purified hAII and hA-II, whereas it had no effect on cholesterol efflux to control plasma. A strong positive correlation was established between percent cAMP stimulation of efflux and plasma hA-II concentration. The cAMP stimulation of efflux to hAIItg mouse plasma may be linked to the presence of pre-β migrating HDL containing hA-II. Thus, despite lower HDL and apolipoprotein A-I contents, the increased ability of plasma from hAIItg mice to extract cholesterol from macrophage-like cells may have an antiatherogenic influence. (Arterioscler Thromb Vasc Biol. 2002;22:638-643.)

Key Words: human apolipoprotein A-II transgenic mice ■ Fu5AH rat hepatoma cells ■ J774 mouse macrophages ■ cholesterol efflux ■ ATP binding cassette transporter 1

The negative correlation between plasma HDL concentration and the risk of cardiovascular disease has been partly attributed to the ability of HDL to stimulate reverse cholesterol transport (RCT) from peripheral tissues to the liver for recycling.1,2 The first step of RCT is efflux of free cholesterol from cell membranes to the extracellular medium. A major research effort these last decades has established that at least 3 mechanisms are involved: a nonspecific and relatively inefficient aqueous diffusion pathway, which operates in all cells, and 2 regulated pathways, which are modulated by phospholipid (PL)-containing acceptor particles (such as HDL) or lipid-poor apolipoproteins.3 On the other hand, controversial results were obtained regarding the effect of the apolipoprotein composition of HDL, with some studies reporting a stimulation of cholesterol efflux by HDLs containing only apoA-I4 and other studies reporting HDL carrying apoA-I and apoA-II.5 Recently, the type of the acceptor particles was linked to the type of the receptors present in the various cells,6 thus identifying the following 2 specific efflux mechanisms involving (1) the scavenger receptor class B type I (SR-BI) and (2) the ATP binding cassette transporter 1 (ABCA1). Cholesterol molecules that desorb from cell membranes rich in SR-BI diffuse through the aqueous phase and associate with PL-containing acceptor particles, in proportion to PL content.6 Moreover, the ability of HDL and serum to stimulate cholesterol efflux from different cell types was correlated with the expression level of SR-BI.7 SR-BI is equally efficient at mediating the import and export of cholesterol to and from cells to lipoproteins and other acceptors.7,8 By contrast, the unidirectional efflux of membrane cholesterol and PL of cells expressing ABCA1 is promoted by apolipoproteins in lipid-poor form but is little affected by HDLs, small unilamellar vesicles, bile acid micelles, or cyclodextrin.9–11

ApoA-I is the major apolipoprotein component of HDL, and its role in RCT has been extensively studied. ApoA-II is the second most abundant HDL apolipoprotein, but its contribution to the function of HDL is controversial and poorly understood. We recently generated transgenic mice overexpressing human apolipoprotein (hAII) A-II, which display a marked hypertriglyceridemia and a great decrease in plasma HDL and apoA-I concentrations.12 HDLs from our transgenic mice are characterized by an enrichment in triglycerides, the predominance of smaller sized particles (7.8- versus 10-nm

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diameter), a low apoA-I/apoA-II ratio, and the presence of pre-β HDLs containing apo A-II.13

Our aim was to investigate the ability of plasma from hAIIgt transgenic (hAIIgt) mice to promote cholesterol efflux from 2 cell types representative of SR-BI–mediated or ABCA1-mediated cholesterol efflux. Fu5AH rat hepatoma cells, which have a high expression level of SR-BI and lack ABCA1,7,10 were used to assess the contribution to cholesterol efflux of plasma PL-rich acceptors.14–16 The ability of plasma with a high hA-II content to promote cellular cholesterol efflux was assessed by use of the J774 mouse macrophage cell system, which expresses SR-BI at very low levels.7 Exposure of J774 cells to cAMP upregulates the expression of ABCA1, which is closely correlated with increased cellular cholesterol efflux to several unassociated apolipoproteins, such as apoA-I,17 apoE,18 and apoA-IV.9 Therefore, we compared the efflux capacity of purified hA-II with that of hA-I.

Methods

The Methods section can be accessed online at http://www.atvb.ahajournals.org.

Results

Plasma and HDL From hAIIgt Mice Decrease Cholesterol Efflux From Fu5AH Cells

Because of the low plasma HDL content of hAIIgt mice (two individual lines δ and λ), we compared its ability to promote cholesterol efflux with that of control mouse plasma. After 4-hour incubations with 2.5% diluted plasma from animals fed ad libitum, the fractional cholesterol efflux was 36% and 57% lower in plasma from δ and λ mice, respectively, than in plasma from control mice (Table 1). To determine whether the low plasma concentration or the different properties of HDL from transgenic mice were responsible for the decreased cholesterol efflux, we compared HDL from transgenic and control mice fed ad libitum at the same HDL-PL concentration. HDL from transgenic mice displayed increased protein and triglyceride contents and decreased cholesterol ester, resulting in a lower ratio of HDL–total lipid to protein (Table 2). Cholesterol efflux was greatest to control HDL and was inversely related to the level of hA-II expression in transgenic mice, displaying 25% and 50% decreases in HDL from δ and λ mice, respectively (Figure 1).

Plasma From hAIIgt Mice Stimulates Cholesterol Efflux From J774 Cells

In a first attempt, we tested the same plasma pools used in Fu5AH cells for their capacity to promote cholesterol efflux from J774 cells. Surprisingly, we obtained the opposite effect, inasmuch as plasma pools from δ and λ mice exhibited a greater efflux capacity from cAMP-treated cells (0.72±0.02%, 1.18±0.05%, and 2.46±0.09% for control, δ, and λ mice, respectively). Therefore, we precisely documented this effect with plasma from individual mice and used the feeding-fasting

### Table 1. Plasma and HDL Parameters and Efflux Capacity of Plasma From Control and hAIIgt Mice in Fu5AH Cells

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>hAIIgt-δ</th>
<th>hAIIgt-λ</th>
</tr>
</thead>
<tbody>
<tr>
<td>hA-II g/L</td>
<td>...</td>
<td>0.44</td>
<td>0.52</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>0.68</td>
<td>2.94</td>
<td>10.56</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.57</td>
<td>0.41</td>
<td>0.24</td>
</tr>
<tr>
<td>HDL-PL, mmol/L</td>
<td>0.65</td>
<td>0.47</td>
<td>0.20</td>
</tr>
<tr>
<td>Fractional efflux (%/4 hours)</td>
<td>20.1±0.4</td>
<td>12.9±0.8</td>
<td>8.7±0.9</td>
</tr>
</tbody>
</table>

Each plasma pool was prepared by using 20 individual mice fed ad libitum. Human apoA-II and triglyceride (TG) were measured in the plasma pools before ultracentrifugation to isolate HDL. The fractional efflux (%/4 hours) to 2.5% hapo A-II transgenic plasma was the average (mean±SD) of triplicate wells, as described in Methods and was representative of 2 independent experiments, each testing separate plasma pools.

### Table 2. Mass Composition of HDL Isolated From Control and hAIIgt Mice

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>hAIIgt-δ</th>
<th>hAIIgt-λ</th>
</tr>
</thead>
<tbody>
<tr>
<td>% PL</td>
<td>22.3</td>
<td>21.6</td>
<td>20.5</td>
</tr>
<tr>
<td>% FC</td>
<td>1.4</td>
<td>2.2</td>
<td>3.3</td>
</tr>
<tr>
<td>% CE</td>
<td>27.1</td>
<td>15.9</td>
<td>13.3</td>
</tr>
<tr>
<td>% TG</td>
<td>1.0</td>
<td>3.5</td>
<td>7.0</td>
</tr>
<tr>
<td>% protein</td>
<td>48.2</td>
<td>56.8</td>
<td>55.9</td>
</tr>
<tr>
<td>PL/protein</td>
<td>0.56</td>
<td>0.38</td>
<td>0.36</td>
</tr>
<tr>
<td>FC/protein</td>
<td>0.03</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>CE/protein</td>
<td>0.60</td>
<td>0.34</td>
<td>0.24</td>
</tr>
<tr>
<td>TG/protein</td>
<td>0.02</td>
<td>0.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Lipid/protein</td>
<td>0.96</td>
<td>0.76</td>
<td>0.79</td>
</tr>
<tr>
<td>hapo A-II/protein</td>
<td>...</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>hapo A-II/PL</td>
<td>...</td>
<td>1.43</td>
<td>1.73</td>
</tr>
</tbody>
</table>

Values correspond to 1 representative HDL preparation isolated from pooled plasma (20 mice fed ad libitum per group) and are expressed as a percentage of total protein and lipid in HDL. Ratios are calculated as mass ratios. FC indicates free cholesterol; CE, cholesteryl ester.

Figure 1. Efflux capacity of HDLs from control and hAIIgt mice in Fu5AH cells. Values are mean±SD of 3 separate experiments, each using different HDL preparations (from 20 to 24 mice fed ad libitum per group). For each HDL-PL concentration, the fractional cholesterol efflux (%/4 hours) was the average of triplicate wells, as described in Methods. aP<0.05, bP<0.01, and cP<0.001 for transgenic vs control mice. xP<0.01 and yP<0.001 for hAIIgt-δ vs hAIIgt-λ mice. Solid square indicates control mice; solid circle, δ mice; and solid triangle, λ mice.
transition as a means to modulate the plasma concentrations of hapo A-II, mouse apo A-I (mapo A-I), and HDL. Indeed, plasma hapo A-II from animals in the fasted state is decreased 2-fold, leading to concomitant increases in plasma HDL levels and in the ratio of apoA-I to A-II in HDL; conversely, hypertriglyceridemia is normalized. When cells were not pretreated with cAMP, each fractional cholesterol efflux value is the mean of triplicate wells. Percent stimulation of efflux by pretreatment of cells with cAMP was calculated as described in Methods. Statistical analysis of the results was performed by using the t test for nonpaired samples after analysis of variance.

Table 3: Efflux Capacity of Plasma From Control and hAIItg Mice in J774 Cells

<table>
<thead>
<tr>
<th>Nutritional Status</th>
<th>Genotype, n</th>
<th>TG, mmol/L</th>
<th>hapo A-II, g/L</th>
<th>Efflux (%) cAMP (−)</th>
<th>Efflux (%) cAMP (+)</th>
<th>cAMP Stimulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed</td>
<td>Controls, 10</td>
<td>0.72±0.61</td>
<td>...</td>
<td>1.03±0.28</td>
<td>0.96±0.20</td>
<td>2±4</td>
</tr>
<tr>
<td>Fed</td>
<td>hAIItg-δ, 10</td>
<td>3.73±4.84</td>
<td>0.66±0.26</td>
<td>0.98±0.17</td>
<td>1.40±0.54*</td>
<td>40±36†</td>
</tr>
<tr>
<td>Fed</td>
<td>hAIItg-λ, 10</td>
<td>10.09±4.19</td>
<td>0.92±0.43</td>
<td>1.30±0.56</td>
<td>2.27±1.08§</td>
<td>73±2.5$</td>
</tr>
<tr>
<td>Fasted</td>
<td>Controls, 7</td>
<td>0.30±0.12</td>
<td>...</td>
<td>0.94±0.26</td>
<td>0.95±0.16</td>
<td>6±8</td>
</tr>
<tr>
<td>Fasted</td>
<td>hAIItg-δ, 9</td>
<td>0.48±0.60</td>
<td>0.38±0.09#</td>
<td>0.78±0.37</td>
<td>0.95±0.33¶</td>
<td>32±47</td>
</tr>
<tr>
<td>Fasted</td>
<td>hAIItg-λ, 8</td>
<td>0.74±0.79**</td>
<td>0.41±0.17#</td>
<td>0.79±0.51</td>
<td>0.96±0.52#</td>
<td>31±3.5#</td>
</tr>
</tbody>
</table>

Values are mean±SD for (n) individual mice. The 0.5% diluted plasma was incubated 2 hours with J774 macrophage cells pretreated without or with 0.2 mmol/L cAMP. Each fractional cholesterol efflux value is the mean of triplicate wells. Percent stimulation of efflux by pretreatment of cells with cAMP was calculated as described in Methods. Statistical analysis of the results was performed by using the t test for nonpaired samples after analysis of variance.

and because plasma from hAIItg mice has elevated concentrations of hapo A-II, we compared the efflux capacities of lipid-free hapo A-II and hapo A-I. In 3 separate experiments, marked cAMP stimulations of efflux were promoted by both apolipoproteins to similar degrees (Table 4). These values were very close to those previously obtained for hapo A-I and hapo A-I IV.

### Pre-β Migrating HDLs Containing Hapo A-II Are Present in Plasma of Transgenic Mice

Because pre-β HDL is an efficient acceptor of cellular cholesterol, we analyzed the proportions of α and pre-β HDL in control and transgenic mice (Figure 2). In plasma from control mice either fed or fasted, the bulk of apoA-I was present in large-sized α HDL and a very small amount in pre-β HDL, whereas hapo A-II was present only in α HDL (not shown). Plasma from fed or fasted δ mice contained 2 main HDL subpopulations with α mobility; apoA-I was present in the larger α HDL and in pre-β HDL (not shown), whereas hapo A-II was present in all α HDL subpopulations as well as in pre-β HDL. Irrespective of nutritional state, plasma from δ mice contained little apoA-I in α HDL (not shown), whereas hapo A-II was abundantly present in all α

Table 4: Efflux Capacity of Human Lipid-Free ApoA-II and ApoA-I in J774 Cells

<table>
<thead>
<tr>
<th>Cholesterol Efflux From J774 Incubated Without cAMP, %</th>
<th>Cholesterol Efflux From J774 Incubated With 0.2 mmol/L cAMP, %</th>
<th>cAMP Stimulation of Cholesterol Efflux, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-free hapoA-II</td>
<td>0.16±0.01</td>
<td>450</td>
</tr>
<tr>
<td>Lipid-free hapoA-I</td>
<td>0.13±0.01</td>
<td>531</td>
</tr>
<tr>
<td>Experiment 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-free hapoA-II</td>
<td>0.14±0.02</td>
<td>629</td>
</tr>
<tr>
<td>Lipid-free hapoA-I</td>
<td>0.17±0.01</td>
<td>476</td>
</tr>
<tr>
<td>Experiment 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-free hapoA-II</td>
<td>0.11±0.03</td>
<td>636</td>
</tr>
<tr>
<td>Lipid-free hapoA-I</td>
<td>0.12±0.04</td>
<td>625</td>
</tr>
</tbody>
</table>

Values are mean±SD from triplicate wells. Lipid-free hapoA-II and hapoA-I were tested at the concentration of 10 μg/mL. The 2-hour fractional cholesterol efflux from cells incubated without or with 0.2 mmol/L cAMP is calculated as described in Methods, and the results are expressed as percent stimulation of efflux by cAMP pretreatment.
HDL subfractions, especially in the smaller ones. For the fed state, pre-β HDL with hapo A-II was more abundant in λ than in δ mouse plasma. Of note, pre-β HDL with hapo A-II was not detected when δ and λ mice were fasted overnight.

Absence of Atherosclerotic Lesions in Transgenic Mice
Aortic sections from chow-fed control mice (not shown) and hapo A-II high-expressing λ mice stained with oil red O were totally devoid of lipid infiltrations (Figure II, which can be accessed online at http://atvb.ahajournals.org). “En face” specimens of the thoracic aorta from chow-fed control and high-expressing λ mice were stained with oil red O and were also totally devoid of lipid infiltrations (data not shown).

Discussion
The present study shows for the first time opposite effects of plasma from mice overexpressing hapo A-II on SR-BI-mediated and ABCA1-mediated cholesterol efflux. The lower cholesterol efflux from SR-BI–expressing Fu5AH cells to plasma from hAlltg mice can be attributed to their decreased plasma HDL level, whereas the greater cholesterol efflux from ABCA1-expressing J774 macrophages may result from the high content of hapo A-II, probably in the form of pre-β HDL.

In the Fu5AH system, cholesterol efflux correlates best with HDL-PL.\(^{15,16} \) The markedly reduced cholesterol efflux capacity of plasma from hAlltg mice is consistent with the major decrease in HDL.\(^{12,13} \) Plasma from independently established mice overexpressing hapo A-II has also displayed lower HDL-PL concentrations and a reduced ability to efflux cholesterol from fibroblasts.\(^{19} \) The lower efflux capacity of HDL from hAlltg mice compared with HDL from control mice may be attributed to their high hapo A-II content. Indeed, cholesterol efflux from Fu5AH cells to human HDL, was negatively correlated with their apoA-II/apoA-I+apoA-II ratio.\(^{20} \) Our results are also in accordance with the lower cholesterol efflux capacity from Fu5AH cells of HDL from hapo A-I/hapo A-II transgenic mice compared with HDL from hapo A-I transgenic mice.\(^{21} \) Furthermore, we have demonstrated by use of a large number of human serum samples that LpA-I is a better acceptor than LpA-I/A-II of cholesterol effluxing from Fu5AH cells.\(^{14} \)

Hapo A-I and hapo A-II bind to rodent SR-BI,\(^{22} \) and this binding is essential for cholesterol efflux.\(^{23} \) However, although apoA-II–enriched HDLs bind to human SR-BI with higher affinity than apoA-I–rich HDLs, they display a lower capacity to deliver cholesterol esters to human adrenal cells.\(^{24} \) By analogy, the lower efflux capacity of hapo A-II–rich HDL from our hAlltg mice may indicate that hapo A-II is a negative modulator of SR-BI–mediated cholesterol efflux. This negative effect of hapo A-II may be related to the altered cholesterol distribution in plasma membrane domains induced by SR-BI.\(^{25} \)

Apart from the greater apoA-II/apoA-I ratio, some of the other HDL modifications of our transgenic mice may contribute to their lower efflux capacities from Fu5AH cells. It is unlikely that the smaller particle size explains their reduced efflux effectiveness, inasmuch as smaller particles, at a given PL concentration, more efficiently remove cellular cholesterol.\(^{26} \) However, the triglyceride enrichment of HDL may affect cholesterol efflux because, at a given PL concentration, triglyceride-enriched HDLs isolated from hypertriglyceridemic subjects were less efficient in extracting cholesterol.\(^{27} \)

The major finding of the present study was that cAMP treatment of J774 cells, which upregulates ABCA1,\(^{10,11} \) markedly increased cholesterol efflux to the plasma of hAlltg mice, in a manner directly proportional to the plasma concentration of hapo A-II; conversely, no variation in efflux to the plasma of control mice was observed. Exposure of macrophages to cAMP stimulated the release of cholesterol and PL to lipid-free apoE,\(^{18} \) apoA-I,\(^{17} \) and apoA-IV.\(^{9} \) Our hapo A-II transgenic mice have small amounts of apoE and apoA-IV, which are comparable to those of control mice, whereas HDL and apoA-I are greatly decreased.\(^{12,13} \) On the other hand, plasma from hAlltg mice contains small-sized α HDLs rich in hapo A-II as well as pre-β HDLs with hapo A-II.\(^{13} \) The greater cAMP stimulation of efflux to plasma from fed relative to fasted λ mice may be linked to the appreciable amount of hapo A-II–containing pre-β HDLs in the fed animals. Moreover, in the present study, free hapo A-II stimulated cholesterol efflux to the same extent as did...
free hapo A-I. Accordingly, similar efflux stimulations were reported for unassociated apoA-II and apoA-I from human fibroblasts that express ABCA1,28 whereas expression of ABCA1 in Hela cells markedly increased specific binding of apoA-I and apoA-II to a common binding site.29 Therefore, the greater efflux ability of plasma from hapo A-II transgenic mice may be attributed to the pre-β HDLs containing hapo A-II and/or to the high total hapo A-II content.

Studies of cholesterol efflux from cultured cells ultimately aim to assess the efficacy of the first step of RCT as a predictor of atherogenic risk.2 Thus, it is of interest to compare the results on cholesterol efflux elicited by plasma from various types of mice overexpressing hapo A-II with the degree of aortic lesions developed by the corresponding mice.

Transgenic mice with a high hapo A-II expression did not develop lesions when they were fed a chow diet,30 whereas their plasma displayed a 40% lower efflux capacity from fibroblasts than did plasma from chow-fed control C57BL/6 mice.19 Conversely, plasma from hapo A-II transgenic and control mice fed the atherogenic diet had similar efflux capacities,19 although the former developed more aortic lesions than did the latter.30 Independently, established transgenic mice with a moderate expression of hapo A-II developed less aortic lesions on a cholesterol-rich diet than did control mice, although their plasma elicited less cholesterol efflux from Fu5AH cells.31 On the other hand, apoA-I knockout (AI-KO) mice have very low plasma HDL levels but are not at increased risk of aortic lesion development, even after administration of the atherogenic diet.32 Chiesa et al53 expressed hapo A-I, hapo A-II, and both hapo A-I and A-II in the AI-KO background, and they measured cholesterol efflux from Fu5AH cells. Efflux was equally low in plasma from Al-KO and AI-KO/hAIItg mice, whereas it increased appreciably in plasma from AI-KO/hAIItg mice, with or without the concomitant expression of hapo A-II. In the present study, the hypertriglyceridemic high-expressing λ mice did not develop atherosclerotic lesions, although their HDL and plasma displayed lower efflux capacities from Fu5AH cells than did HDL and plasma from control mice.

Taken together, the results of the above studies clearly show that variations in the ability of plasma and HDL to induce cholesterol efflux from Fu5AH cells is not predictive of aortic lesion development of the corresponding mice. To what extent SR-BI–expressing cells display appreciable cholesterol efflux in vivo has not been established at present. Conversely, it is well known that SR-BI mediates selective uptake of cholesteryl esters in steriodogenic tissues and the liver.34 Because SR-BI is equally efficient at mediating the import and export of cholesterol to and from cells to lipoproteins and other acceptors,7,8 the specific metabolic conditions in vivo favoring cholesteryl influx or efflux remain to be established.

By contrast, expression of a nonfunctional ABCA1 protein leads to increased atherosclerotic risk in patients with Tangier disease,35 whereas the expression of a partially functional ABCA1 is correlated with HDL deficiency in humans.2,36 In this case, lack of cholesterol efflux is correlated with greater atherosclerotic risk, thus providing evidence that strengthens the link between HDL, RCT, and atherosclerosis.35 Plasma from our hAIItg mice markedly stimulated cholesterol efflux from J774 macrophages pretreated with cAMP, which up-regulates ABCA1 expression,10,11 whereas the coronary arteries of hAIItg mice were totally devoid of lipid infiltrations.

In conclusion, our data demonstrate opposite effects of plasma from hapo A-II transgenic mice on cholesterol efflux from Fu5AH hepatoma cells and from J774 macrophages. Because macrophages are implicated in the early steps of atherogenesis, the increased ability of plasma with a high hapo A-II content to extract cholesterol from such cells indicates an antiatherogenic influence of hapo A-II.

Acknowledgments

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References


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cAMP stimulation of efflux (%) vs. hapo A-II (g/L)

$R = 0.53; P = 0.001$