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The Epicholesteryl Betulinate and the Pegylated 3' α-Cholesteryl Betulinate are Active Against Liver Carcinoma. A Case Study.

E. Couché [1], M. Gelbcke [2], A. Burny [3] and J.C.Leunis[4,*]

[1]Ecole Européenne de Luxembourg,Blv Konrad Adenauer 23, L-1115 Luxembourg
[2]Faculty of Pharmacy, ULB, Free University of Brussels
[3]Molecular and Cellular Biology, University of Liège
[4]Jean Monnet Research Center - 1, Jean Monnet Avenue B - 1348, Louvain-la-Neuve

***Corresponding author:** J.C.Leunis, Jean Monnet Research Center - 1, Jean Monnet Avenue B - 1348, Louvain-la-Neuve; Tel: +00-32-10-810 460 ; E-mail:jleunis@hotmail.com

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Introduction

e potential value of triterpenoids, especially pentacyclic triterpenes like betulin, betulinic acid and betulonic acid in the induction of apoptosis in malignant tumor cells has been recognized for some years now [1,2].

Betulinic acid (BetA) and betulin come from a variety of botanical sources such as the bark from Betulaceae like *Betulae species, Alnus glutinosa, Corulus avellana Carpinus betulus,* as well as Platanaceae like *Platanus orientalis* and from Rhamnaceae like *Ziziphus species* [3,4]. BetA and betulonic acid are thus found in many plant species, although in a low concentration compared to betulin [5]. Betulinic acid (BetA) induces apoptosis of many types of cancer cells without toxicity towards normal cells in vitro and in vivo [6].

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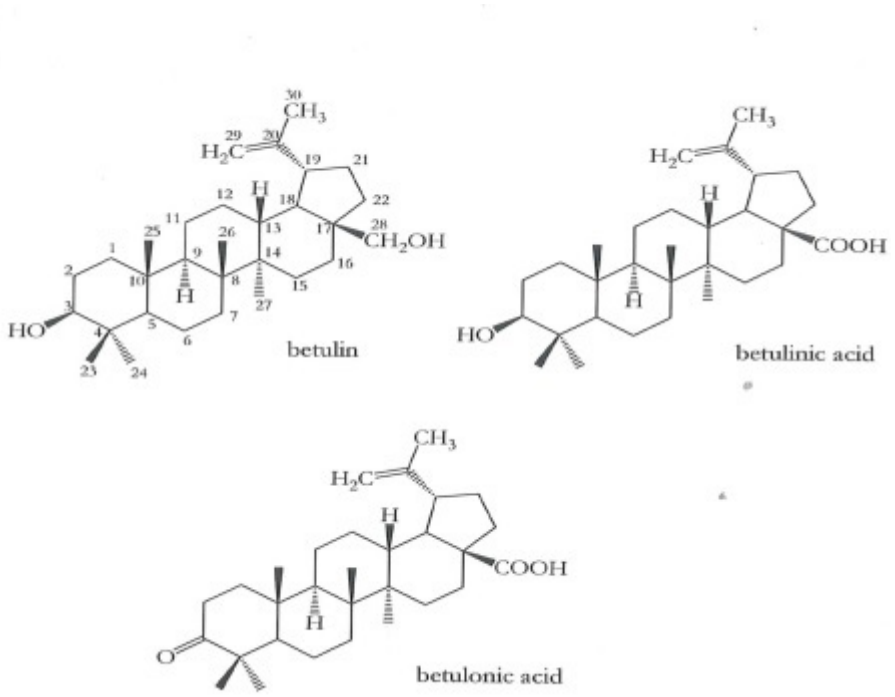


Figure 1: Structure of the natural active compounds

Methods of synthesis of many derivatives of BetA and betulonic acid have been described, including amino acid, amide as well as glycosides derivatives [7,8]. Several patents on BetA analogs for the chemotherapy of cancer have been reported. Most of these patents deal with modi cations at positions C-3, C-20, and C-28 [9].

In this study, we tested the anti liver carcinoma activity of two cholesteryl ester derivatives of betulinic acid in C-28: the epicholesteryl betulinate is oil-soluble and its pegylated form is water-soluble [10].

Why cholesterol as cancer recognized epitope?

Cancer cells proliferate rapidly and require high cholesterol concentration [11].

Mullauer FB et al described that betulin, here the lesser active of the three triterpenes, is a potent anti-tumor agent that is enhanced by cholesterol [12].

Cholesterol is indeed essential for the development of the cell membrane and it is found in the lipid ra s of all our cells.

It is, therefore, an essential nutrient for the cancer cell.

e antitumor pharmacological e ects consist of triggering apoptosis via the mitochondrial pathway, regulating the cell cycle and the angiogenic pathway via a variety of factors, including di erent transcription factors [13].

A case study

The alcoholic patient, B.H. born 06 April 1956, suffering from liver cancer developed on cirrhosis was, the 24 of Dec.2015, considered as lost for the medicine.

During hospitalization in December 2015, decompensated cirrhosis on hepatocarcinoma with the presence of ascites was diagnosed with the invasion of the portal vein.

The abdominal CT scan performed showed a 12 cm hepatocarcinoma in the right lobe.

Given the lack of therapy, the patient, Dr. in veterinary medicine, refused palliative care and decided on an experimental treatment by oral intake of two derivatives of betulinic acid. The Epicholesteryl betulinate and the Pegylated 3' α-cholesteryl betulinate.

Structure of the two derivatives used in this case study

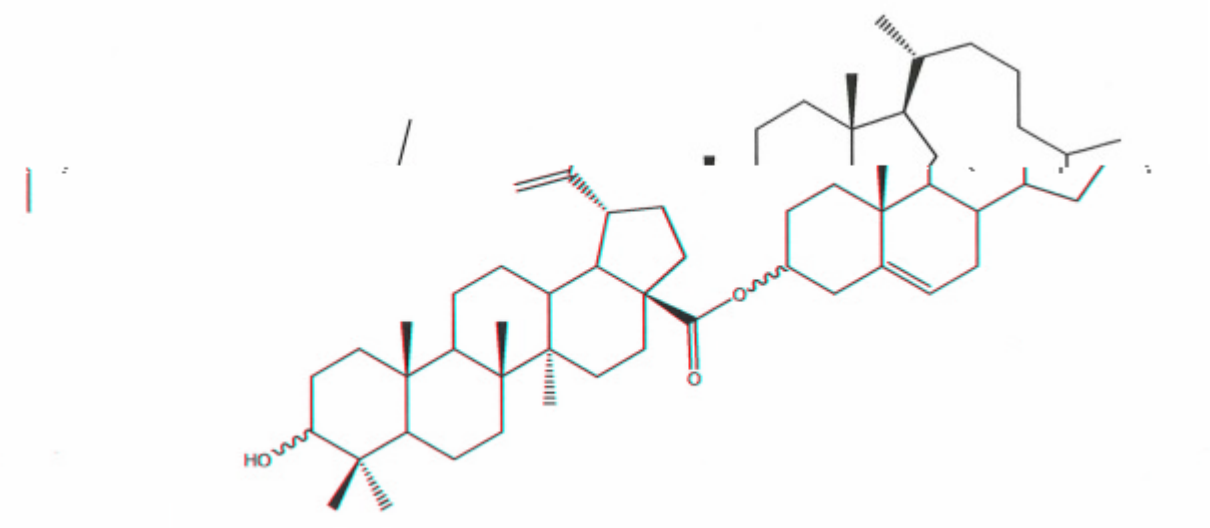


Figure 2: e Epicholesteryl betulinate

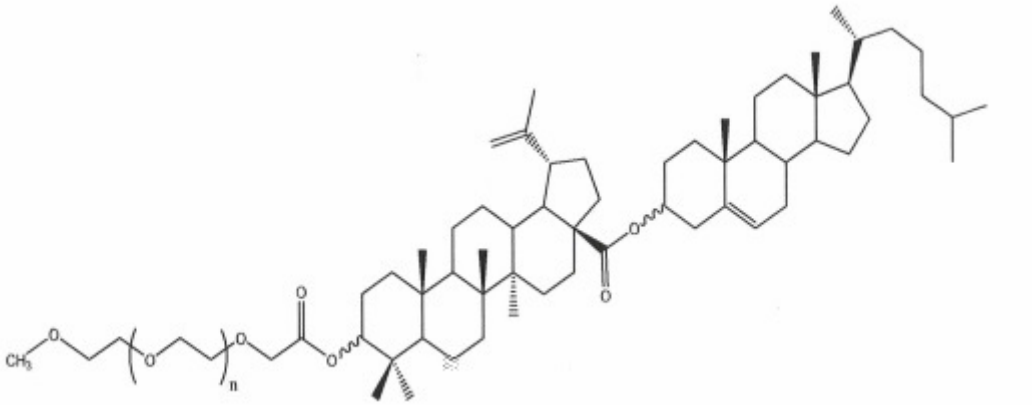


Figure 3: e pegylated 3' α-cholesteryl betulinate

e synthesis of those derivatives is described in the patents [7].

	AFP	D-Dim	NSE
28-12-2015	34258	16658	13,1
11-01-2016	6300	6494	
18-01-2016	2363	2221	
25-01-2016	1133	1330	
1-02-2016	814	1096	7,92
8-02-2016	596	993	

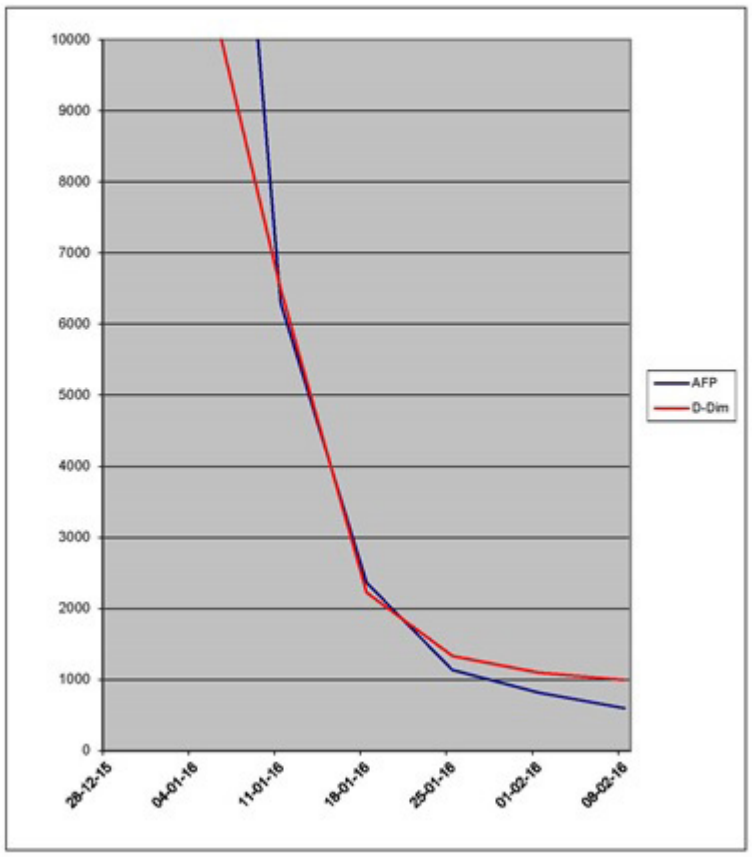


Figure 4

On the Monday 28.12.15 his alpha-fetoprotein (AFP) level was at 32258 ng/ml and the D-dimers at 16658 ng/ml.

During January 2016, he took per os the cholesteryl ester BetA derivative soluble in oil described in the patent. In February, for personal reasons, he took the water-soluble form.

e patient went back to work for a year but due to persistent alcohol abuse, treatment with a single drug [14] and the now well-documented tumor heterogeneity, resistance to treatment appeared, AFP levels reincreased and the patient died in February 2017. According to his caring doctors, the positive impact of the treatment is unquestionable. No negative side e ect was observed.

In the following graph, we document the observed values of AFP and D-dimers and their evolution until February 2016.

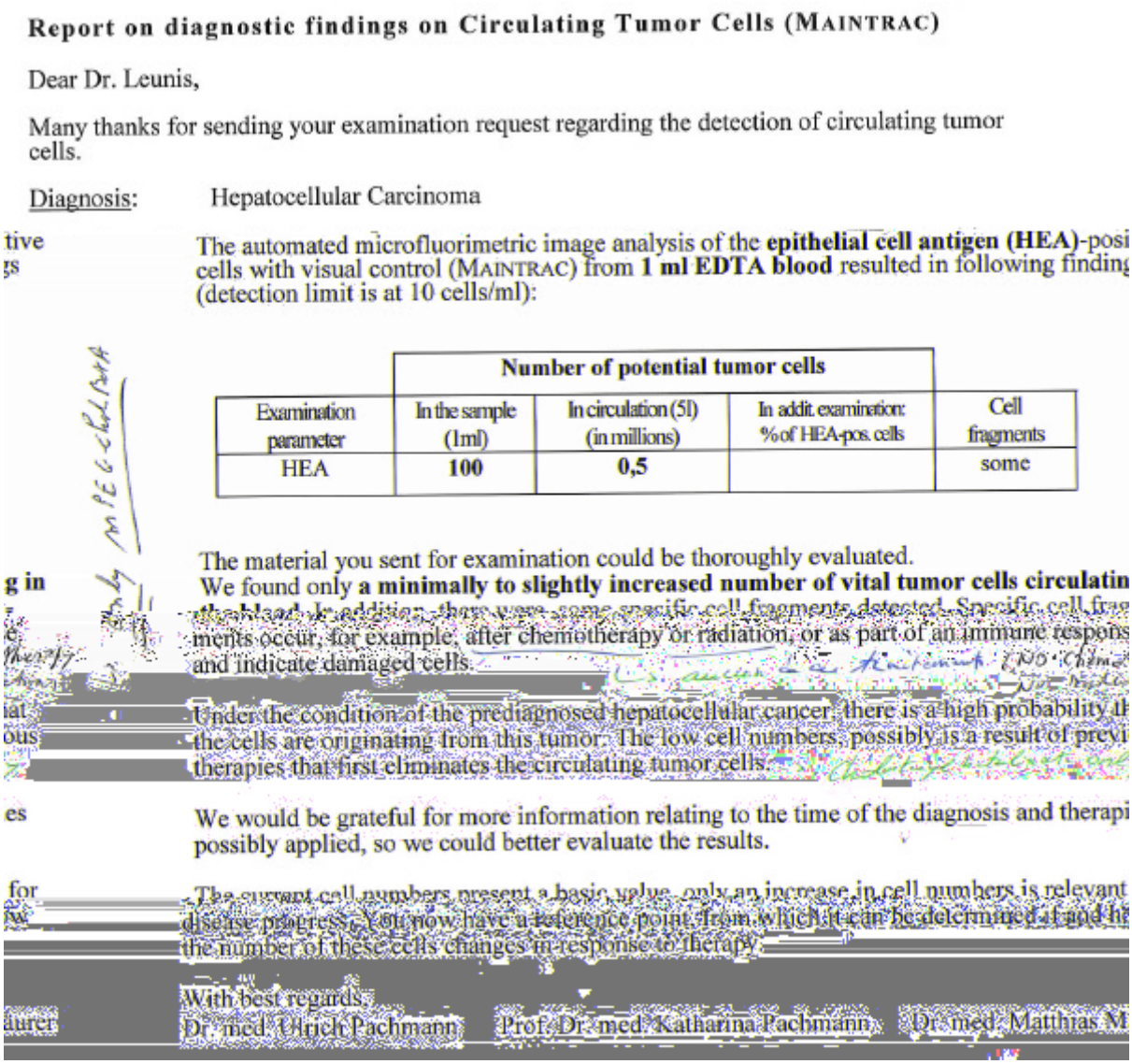
e normal physiological values for the parameters shown in the graph are as follows :

Alpha-fetoprotein - AFP : < 8 µg / L

D-Dimers : < 500 ng / ml

Neuro sensitive enolase - NSE - here not drawn : < 12 µg / L

Report of the diagonistic nding are show in gure 5



Report on diagnostic findings on Circulating Tumor Cells (MAINTRAC)

Dear Dr. Leunis,

Many thanks for sending your examination request regarding the detection of circulating tumor cells.

Diagnosis: Hepatocellular Carcinoma

The automated microfluorimetric image analysis of the **epithelial cell antigen (HEA)**-posi cells with visual control (MAINTRAC) from **1 ml EDTA blood** resulted in following findin (detection limit is at 10 cells/ml):

	Number of potential tumor cells			
Examination parameter	In the sample (1ml)	In circulation (5l) (in millions)	In addit. examination: % of HEA-pos. cells	Cell fragments
HEA	**100**	**0,5**		some

The material you sent for examination could be thoroughly evaluated.
We found only **a minimally to slightly increased number of vital tumor cells circulatin** ments occur, for example, after chemotherapy or radiation, or as part of an immune respons and indicate damaged cells.

Under the condition of the prediagnosed hepatocellular cancer, there is a high probability t the cells are originating from this tumor. The low cell numbers, possibly is a result of previ therapies that first eliminates the circulating tumor cells.

We would be grateful for more information relating to the time of the diagnosis and therapi possibly applied, so we could better evaluate the results.

The current cell numbers present a basic value, only an increase in cell numbers is relevant disease progress. You now have a reference point from which it can be determined if and h the number of these cells changes in response to therapy.

With best regards,
Dr. med. Ulrich Pachmann Prof. Dr. med. Katharina Pachmann Dr. med. Matthias M

Figure 5

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