GA-Lct-40 – targeting cholesterol crystals for the prevention and treatment of vulnerable atherosclerotic plaque

Cholesterol crystals are one of the main culprits behind the rupture of atherosclerotic plaque and resultant thrombosis, the process responsible for the development of heart attack and ischemic stroke, the world's leading cause of mortality. Today there are no drugs or treatment able to target these crystals.

GA-Lct-40 is the first pharmaceutical candidate developed to prevent growth and facilitate disassembly of cholesterol crystals in persons with clinical complications of atherosclerosis.

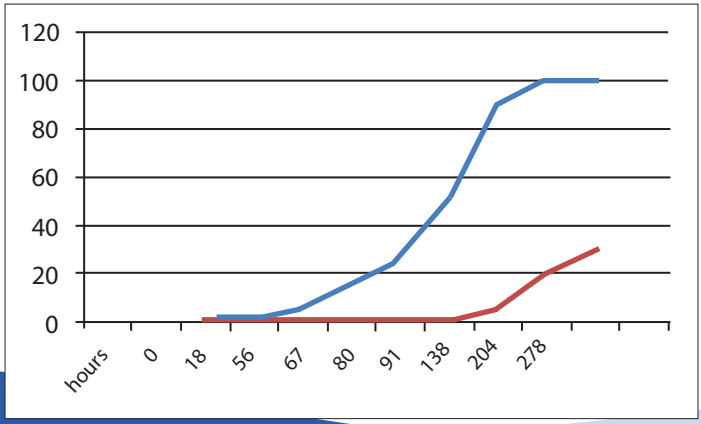
The product utilises a recent discovery of newly patented properties of carotenoids, which can create thermodynamically favourable complexes with lipids, including cholesterol, and trigger long-range ordering transition in their folding. This effect could be observed in a ratio of 1 molecule of a carotenoid to 1,000-10,000 molecules of cholesterol, subject to specific carotenoid structure [patent application, 7 February 2018].

GA-Lct-40 is a composite product based on a combination of a prime molecule, *trans*-Lycopene, designed to target cholesterol crystal folding, and two chaperones facilitating lycopene delivery and efficacy.

The Prime

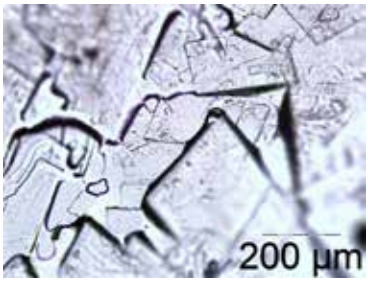
trans-Lycopene is representative of a new class of molecules, which can directly disrupt, slow down and facilitate reversal of the cholesterol crystallisation process. In *in vitro* experiments *trans*-Lycopene delayed the time of the beginning of cholesterol crystallisation by 8 fold and the rate of this process itself by 5 fold. In addition it was able to reduce the cholesterol mass involved into crystallisation by 60%, fig. 1.

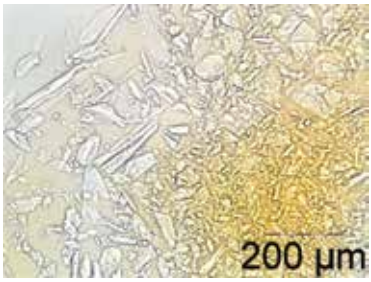
Fig. 1 Kinetics of cholesterol crystal growth; vertical axis – percentage of crystallisation
blue – control cholesterol, red - in presence of 0.1% of trans-Lycopene



Even when the cholesterol crystals were formed in the presence of *trans*-Lycopene, their size was significantly smaller than when the crystals grew undisrupted, fig. 2.

Fig. 2 Size of cholesterol crystals reduced by *trans*-Lycopene, *in vitro* - light microscopy

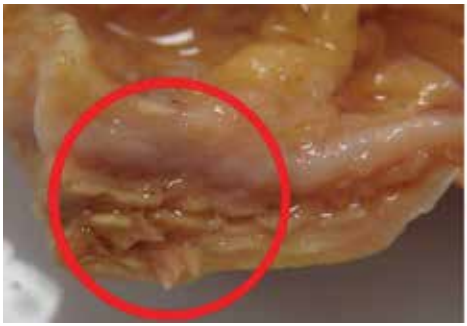


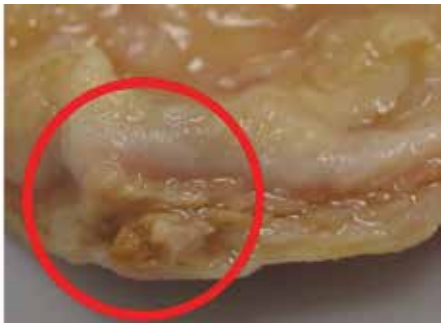


Control crystals **+ trans-Lycopene**

In an *ex vivo* experiment it was demonstrated that this carotenoid could disrupt already formed cholesterol crystals in a human atherosclerotic arterial wall, fig. 3.

Fig. 3 Disruption of cholesterol crystals by *trans*-Lycopene in human abdominal aorta *ex vivo*





Cholesterol crystals in aorta before experiment **12 days after exposure to trans-Lycopene**

1st chaperone – scaffolding

Since lycopene isomers are highly hydrophobic, they can be transported in the circulation only by lipoproteins. If their assembly, which predominately happens in the liver, is impaired, then the concentration of these molecules in the blood and in other organs will be reduced, therefore having poor bioavailability in middle-aged and older persons, and in those who have fatty liver, metabolic syndrome or who are overweight or obese (the categories to which the majority of patients with clinical complications of atherosclerosis belong).

To overcome this problem, the first chaperone molecule was added into the formulation, working as scaffolding to facilitate incorporation of the *trans*-Lycopene into newly assembling lipoproteins.

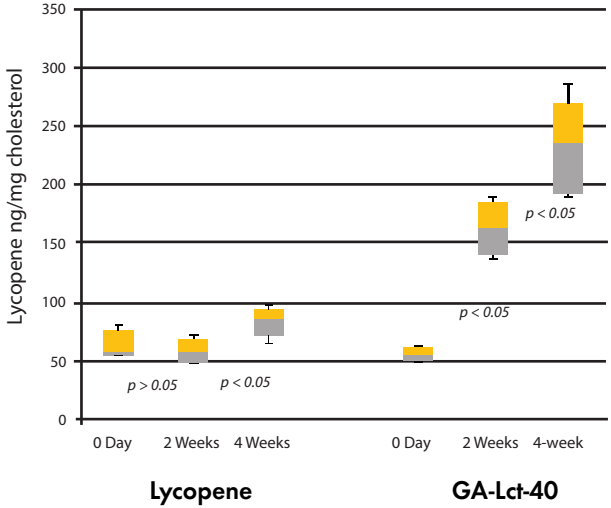
2nd chaperone – recovery cofactor

On-going inflammatory reactions, even on a sub-clinical level, which typically happen in patients with clinical complications of atherosclerosis, can accelerate lycopene oxidation and decomposition. Therefore, to extend the life of these molecules, it was beneficial to add a second chaperone molecule, which could facilitate a reverse conversion of their oxidised form back to the intact structure.

Pharmacokinetics

In a randomised double-blind clinical study on 142 patients with Coronary Heart Disease (CHD), it was demonstrated that administration of the GA-Lct-40 formulation provided a significantly higher concentration of lycopene in the blood than when it was taken in a conventional form, fig. 4.

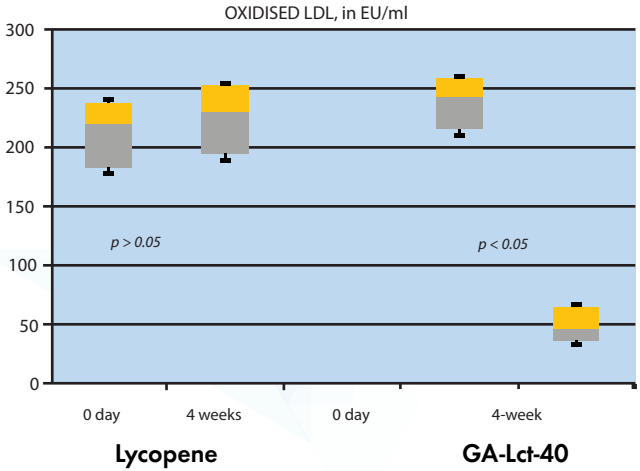
Figure 4. Comparative 4-week pharmacokinetics of 7mg lycopene ingested either in a conventional form, left, or as a part of GA-Lct-40, right



Pharmacodynamics

Better bioavailability and extension of the "life" of lycopene in CHD patients translated into significant performance of lycopene to inhibit LDL oxidation, fig, 5.

Figure 5. Comparative 4-week pharmacodynamics of 7mg lycopene ingested either in a conventional form, left, or as a part of GA-Lct-40, right



Ivan M. Petyaev, Pavel Y. Dovgalevsky, Victor A. Klochkov, Natalya E. Chalyk, Dmitry V. Pristensky, Marina P. Chernyshova, Ruzan Udumyan, Taron Kocharyan, Nigel H. Kyle, Marina V. Lozbiakova, Yuriy K. Bashmakov. - Effect of lycopene supplementation on cardiovascular parameters and markers of inflammation and oxidation in patients with coronary vascular disease. Food Science & Nutrition (2018), 6, 1770-1777.

Next Step

It was demonstrated that GA-Lct-40 is safe and can provide, in the specific metabolic and oxidative-inflammatory environment of CHD patients, a concentration of lycopene in the blood at a ratio of 1 molecule to 4,000 – 5,000 molecules of cholesterol, the sufficient level to provide an optimal interaction between these two molecules. This in turn resulted in the effective inhibition of oxidation of lipoprotein lipids, including cholesterol, which is the first step leading to its crystallisation.

The main objective at the next step will be a proof-of-concept clinical trial to assess whether the lycopene delivered to the vascular system at this level and in its active form, is able to affect the growth of cholesterol crystals in arterial atherosclerotic plaques.

Partnership

As part of preparation for a clinical efficacy Phase II clinical trial, Lycotec has established partnership with Professor Ik-Kyung Jang, from Harvard Medical School in Boston. Prof Jang is the world leader who pioneered the application of Optical Coherence Tomography for intravascular quantification of cholesterol crystals in atherosclerotic plaques in clinic. The Protocol for the Phase II trial on GA-Lct-40 has already been prepared.

Regulatory

All molecules comprising GA-Lct-40 are safe for humans, and do not require FDA or other countries' regulatory body approval for oral administration in their therapeutic dose-range.

IP Protection

A patent application on new properties of carotenoids as a new class of molecules, including GA-Ltc-40 and other relevant formulations, which are able to disrupt formation and facilitate disassembly of cholesterol crystals, was filed on 7 February 2018.

Lycotec is exploring different options either to seek a partnership and/or investment to take GA-Lct-40 to a clinical efficacy Phase II clinical trial, or to license it out for further clinical development.

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