LYCOCARD: Investigating the role of lycopene for the prevention of cardiovascular diseases

Volker Böhm (Co-ordinator)

Institute of Nutrition, Friedrich Schiller University Jena, Dornburger Str. 25-29, 07743 Jena, Germany (Volker.Boehm@uni-jena.de)

Cardiovascular diseases and cancer are the main mortality causes in Europe and all developed territories. Lycopene is a plant pigment found among others in tomatoes, Europe's second-most important agricultural crop. Strong supportive data from several epidemiological studies suggest that lycopene may provide important protection against cardiovascular diseases and cancer. However, lycopene content of tomatoes and processed tomato products and lycopene's beneficial effects have not been sufficiently linked so far.

LYCOCARD, an Integrated EU-funded Project (6th Research Framework Programme) that has started in April 2006, investigates the role of lycopene in reducing the risk of cardiovascular diseases, adopting a "total food chain" approach by addressing each link in a "farm to fork" approach for future projects to increase the understanding of diet and health. Specifically, LYCOCARD's multidisciplinary, intersectorial consortium (15 partners from 6 countries) of scientists, technologists, and patient organisations will clarify the following points: Effects of technological processing on lycopene, interactions between different food ingredients, molecular aspects of absorption and metabolism of lycopene, biological effects of lycopene isomers and lycopene metabolites. This information will lead to improved nutritional guidelines and healthy new foods based on tomatoes and other dietary sources containing lycopene. These novel dietary guidelines will help consumers to select specific diets which protect them against disease risk. LYCOCARD will therefore improve the health of European consumers and reduce the costs of health systems, while also significantly advancing the state of the art. In addition, the position of the European food industry will be strengthened by increasing the demand for health-related tomato products and other newly developed healthful foods.

The project will end on March 31st 2011. Results produced by the different work packages (introduced to the participants of the congress separately according to project pillars) will be available regularly during this period and will be added on the LYCOCARD website www.lycocard.com.

Lycopene, its metabolites and its oxidative/degradative products: biological activities in *in vitro* models

Paola Palozza (Project Pillar Leader of the *in vitro* studies within LYCOCARD)

Institute of General Pathology, Catholic University Rome, Largo F. Vito 1, 00168 Rome, Italy (p.palozza@rm.unicatt.it)

Dietary intake of tomatoes and tomato products containing lycopene have been shown to be associated with decreased risk of cardiovascular diseases in numerous studies. However, the mechanisms of action by which lycopene exerts its beneficial effects and the role of its metabolites and derivatives are poorly known. The LYCOCARD European project is focusing the attention on understanding the genetic, molecular, biochemical and physiological functions of lycopene and related compounds in protecting human body against cardiovascular diseases.

In particular, the *in vitro* section of the project, by using several *in vitro* models, including acellular and cellular systems, is investigating the following aspects in lycopene field: (1) lycopene bioavailability, including isolation and characterization of lycopene (Z)-isomers/metabolites and identification of enterocyte transporters/receptors and their changes in relation to polymorphisms; (2) formation of lycopene oxidative metabolites, generated spontaneously or through lycopene interactions with chemical oxidants, cigarette smoke condensate, cholesterol/oxysterols and oxidized LDL; (3) antioxidant efficiency of lycopene, its isomers and metabolites in protecting isolated proteins, lipids, LDL and intact cells against oxidative stress induced *in vitro*; (4) lycopene modulation of cell signalling pathways involved in endothelial functions and in the regulation of cell proliferation, differentiation and apoptosis of vascular cells.

All the studies take into account several problems related to lycopene administration to *in vitro* models, including the solubility of the carotenoid and its derivates *in vitro*, the comparison with doses achieved *in vivo* by dietary means and the possible interactions with other antioxidants. Such studies should provide more insight into the molecular mechanisms underlying the bioactivities of lycopene metabolites and determine what dose of lycopene (or its metabolites) combined with other antioxidants provides optimal protection while not increasing the risk of formation of undesirable metabolic by-products (especially in smokers and hypercholesterolemic subjects).

In vivo investigations on biological activities of lycopene

Patrick Borel (Project Pillar Leader of the *in vivo* studies within LYCOCARD)

INSERM, U476 « Nutrition Humaine et Lipides », Marseille, F-13385 France; INRA, UMR1260, Marseille, F-13385 France; Univ Méditerranée Aix-Marseille 2, Faculté de Médecine, IPHM-IFR 125, Marseille, 13385 France (Patrick.Borel@medecine.univ-mrs.fr)

Epidemiologic studies suggest that lycopene-rich foods, i.e. tomatoes and tomato products, may provide protection against cardiovascular diseases. However, there are many details regarding bioavailability, metabolism, and molecular mechanisms involved in lycopene biological activities that are still unknown. LYCOCARD's *in vivo* studies consist of both animal and human trials aiming to answer the main following questions:

- do genetic polymorphisms in putative intestinal transporters of lycopene affect lycopene absorption efficiency ?
- does absorption efficiency depend on lycopene cis-trans isomerisation ?
- what are the main lycopene metabolites produced in the body ?
- what is the concentration of lycopene and its metabolites in tissues ?
- what is the role of lycopene on gene activation ?
- what is the effect of lycopene on redox status ?
- does lycopene improve endothelial function ?

In vivo studies have been organised into work packages listed in the table below.

WP 15	Determination of nuclear receptor activation by lycopene, lycopene (Z)-isomers/metabolites and tomato preparations in transgenic animals *(Dr R. Rühl, Debrecen University, Hungary)*
WP 16	Analysis of the redox status of mononuclear cells isolated from chronic smokers and hypercholesterolemic patients before and after supplementation of a tomato-rich diet *(Dr P. Palozza, Rome University, Italy)*
WP 17	Effect of polymorphisms in intestinal lycopene transporter(s) on lycopene bioavailability *(Dr P. Borel, INRA/INSERM/Marseille University, France)*
WP 18	Evaluation of oxidative stress and lipid status in human plasma: influence of smoke exposure and lycopene supplementation *(Dr G. Lowe, Liverpool University, UK)*
WP 19	Study of lycopene isomerization in human plasma by isotopically labelled lycopene *(Dr V. Böhm, Jena University, Germany)*
WP 20	Evaluation of atherosclerosis prevention by lycopene in animal models *(Dr V. Stangl, Charité Berlin, Germany)*
WP 21	Effects of lycopene and different tomato products on endothelial function in humans *(Dr V. Stangl, Charité Berlin, Germany)*
WP 22-23	*In vivo* effect of diets enriched with traditional and newly developed tomato products on obese and normal weight subjects *(Dr A. Mordente, Nutriunit Rome, Italy)*

Lycopene and other antioxidants in tomato and tomato products

Maria Periago (Project Pillar Leader of the food product studies within LYCOCARD)

Department of Food Technology, Food Science and Nutrition, Murcia University, Murcia 30071, Spain (mjperi@um.es)

Tomato and tomato-derived products are considered the main source of lycopene in the human diet, and several epidemiological studies have reported that lycopene-rich diets show beneficial effects for human health. Tomatoes also contain widely-varying amounts of phenolic compounds, which enhance their antioxidant properties. A number of studies have shown that flavonoids and hydroxycinnamic acids are the major phenolics in tomatoes. Moreover, tomatoes contain moderate amounts of ascorbic acid, whose consumption contributes a good proportion of the recommended dietary allowance of vitamin C. Antioxidant activity in tomatoes is derived from the synergistic interaction of numerous antioxidant compounds; thus, any study of antioxidant activity must measure levels of all such compounds.

Folate is also present in tomatoes as 5-methyltetrahydrofolate (5-MTHF) and its biological activity is related to the protective effects against cancer, cardiovascular disease and impaired foetal development. Although tomatoes are not generally considered a rich source of folates in the human diet, they are widely consumed in all diets, and folate content may thus contribute to the overall beneficial effects of the tomato, particularly in preventing cardiovascular disease. Due to the bioactive compounds tomatoes and derived products are considered beneficial for the prevention of cardiovascular disease.

However, many factors affect the content of antioxidants during growing and also during food processing. The activities of LYCOCARD Food Product Studies focus on the evaluation of the effect of different agronomic conditions and industrial processing on the content of lycopene and other antioxidants in tomato and tomato products.