

## Impact Objectives

- Gain greater understanding of the turnover of cell membrane using the lipidome profile (membrane fatty acid cluster) as a global health biomarker to individuate a molecular signature – connected to nutrition and metabolism – representing the person's overall health and wellbeing
- Devise personalised diagnostics so as to better understand an individual's balance reached in the specific health status by the cell membranes, and individuate the appropriated membrane therapy
- Further develop the customised FatProfile®-FatPharmacy® service, which reads the lipidomic profile of the mature erythrocyte, before making nutraceutical/nutrition strategy recommendations which allow the patient to make positive lifestyle changes

# Biotech and molecular medicine

*Founders of Lipinutragen, a biotechnology company utilising the latest molecular diagnostics, Dr Chryssostomos Chatgililoglu and Dr Carla Ferreri explain the history of the company and the future of the market*



From left: Dr Chryssostomos Chatgililoglu and Dr Carla Ferreri

### How have your research careers developed?

**CC:** After 20 years of foundational research in free radical chemistry, I began to work on the biomimetic chemistry of radical stress and related biomarkers. The discovery of the endogenous formation of trans-lipids was my entrance into the lipid world. We discovered the role of nutrition and the follow-up to the stress response by cell membrane lipidomics, and elucidated the connection with personalised health.

**CF:** For 18 years I taught organic chemistry to university students and then for 15 years I have been involved in researching free radical reactivity. Free radical effects on health and ageing have developed faster and faster over the last few decades, and I was able to connect my experience in chemistry with the knowledge in molecular interactions and biological pathways. Thereby, I built up the interdisciplinary environment needed for developing membrane lipidomics, a tool for understanding cellular stress and responses. Such stressors include lifestyle and nutritional habits. This research provided the expertise needed for starting a business based around personalised health and nutrition.

### How has Lipinutragen developed out of your academic research background?

**CC and CF:** Cell membrane lipidomics is at the crossroads of chemistry-biochemistry-biology-pharmacology-nutrition-medicine. The idea was to develop a company that focused on the membrane lipid profile as a global health biomarker. This comprehensive biomarker is directly connected to the nutrition and metabolism of each individual.

Using our expertise in synthetic and analytical chemistry, we developed a unique lipidomic laboratory that performs the isolation of the mature red blood cells (erythrocytes) and identifies the membrane fatty acid profile of each subject. This includes trans-lipids as biomarkers of radical stress (several patents & publications). All the important fatty acid families are represented in mature erythrocytes and a cluster of them (the lipidomic profile) provide a resource for personalised diagnostics. Lipinutragen was a spin-off company of the Italian National Research Council (CNR) from 2006 to 2012.

### How do you see Lipinutragen's future developing?

**CC:** We are in a post-launch period. Consolidating our client portfolio is one of our main objectives, along with looking into further expansion both in Italy and abroad. Cell membrane lipidomic profiling is expected to play a crucial role in health fields such as dietetics, nutrition, ageing, sportive activity, pregnancy and lactation, as well as in pathological situations such as dermatology, the immune system, cardiovascular, dislipidemia, metabolic disorders and obesity, amongst others. These directions must also be reinforced

with scientific publications. Therefore, we are working very hard to publish our studies of unhealthy persons with explanations of the role of membranes in the diseases.

**CF:** We successfully transferred to the Technological Park of Bilbao, Spain and a new brand was born, Lipigenia. We are trying to get Horizon 2020 small and medium-sized enterprise targeted funds in order to finance this on a larger scale. So far, we have secured H2020 funds for research (Eurostar-Eureka and Marie Skłodowska-Curie European Training Network). However, we do not expect to develop through grants, but rather through the market attractiveness and capabilities of the company.

### How does Horizon 2020 tie-in to the company's knowledge and expertise?

**CC:** From its inception, Lipinutragen built up its own laboratory. I was the Chairman of two European Co-operation in Science and Technology (COST) actions. One was on Free Radicals in Chemical Biology (2007–2011) and the other on Biomimetic Radical Chemistry (2013–2016).

Lipinutragen participated actively in this networking. The company collaborates with academic groups from several countries including Austria, Croatia, France, Greece, Ireland, Israel, Poland, Spain, Turkey and the UK. These collaborations, together with the EUROSTAR and Horizon2020 research projects, point to spreading the 'membrane lipidomic approach' as a molecular tool for personalised health.



# Profiling cell membranes

Biotechnology company **Lipinutragen** has the only service dedicated to cell membrane lipidomics, matching the membrane status with dietary and health conditions in a personalised manner. Lipinutragen's aim is to help with disease and healthy living by interpretation of the molecular composition of the cell membrane

The rise of diseases such as cancer and metabolic problems caused by lifestyle and genetics means the mass treatment medicine of the 20th century are no longer as effective. The 21st century marks the dawn of personalised medicine. An increasing capacity to collect and process large amounts of data has meant we are uncovering even more information about how disease presents itself, both across populations and within an individual. Instead of prescribing general treatments, the trend will be for a full analysis of the individual at a genetic and physiological level and tailored treatments devised. Genomic analysis, formerly used for personalised nutrition, has been

loose the natural balance among fatty acid moieties. The variability of membrane lipidome is attributed to a host of reasons, among them two key factors stand out: the capability to adapt to the on-going context of the body (physiological or pathological) and the nutrients available. It is the variability and adaptability of cell membranes that makes them a crucial site for evaluating the living balance, and finally an excellent candidate for molecular medical analysis.

Formed in Italy in 2006 by Dr Chrysostomos Chatgililoglu and Dr Carla Ferreri, Lipinutragen is a spin-off from their academic research. They both

more comprehensive results.

## STUDYING CELL MEMBRANES

Chatgililoglu and Ferreri identified erythrocyte (red blood cell) cell membranes as highly indicative of the overall health of an individual. Cells and their membranes are formed in each moment of life, and are not regenerated at the same rate; some are replaced very rapidly whilst others are more gradual. Erythrocytes are fully replaced roughly every four months. This makes them a good model for which to study the turnover of cell membranes. Erythrocytes display all the important lipid families, including those that act as biomarkers of free radical stress. They

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revolutionised thanks to epigenetics discoveries, therefore new research will clarify nutrition influences on DNA profiles.

## UNIQUE ANALYSIS SERVICE

At the forefront of the personalised medicine revolution is Lipinutragen, a biotechnology company providing a unique analysis service based on membrane lipidomics. Lipinutragen began with the lipid composition of cell membranes to develop the lipidomic phenotype. Knowledge of cell membranes as fundamental components of cells and life organisation, is well assessed. They are made of lipid molecules that create a bilayer, mediating the cell's interaction and response within itself and with the rest of the body. The exact composition of the bilayer is tissue specific and can vary within typical ranges or eventually

have a background in free radicals and organic chemistry. However, both have also spent decades applying their expertise to biochemistry and the field of lipidomics. They have been particularly motivated by a desire to understand what effects the composition of the cell membrane, and how that information can be used to improve people's health and wellbeing as Chatgililoglu explains: 'The principles that have been developed in Lipinutragen were derived from our own research on free radical stress, combined with the scientific publications on the great importance of membranes and lipids in the whole cell metabolism and fate, which is then reflected in the functioning of the tissues and the organism.' To this end, they have gathered an experienced team of experts at Lipinutragen to provide analyses and conduct research that will allow for ever

therefore offer a very detailed picture of the overall health of the cell and the stress it may be under. 'It is evident from basic studies in biochemistry, that membranes bring important information related to metabolism and nutrition, with four types of fatty acids (saturated, monounsaturated, polyunsaturated – PUFA – omega-6 and omega-3), not forgetting omega-6 and omega-3 precursors do not form endogenously, but we have to take them from the diet,' explains Ferreri. Based on this, together with the need to distinguish the lipidomic information which is sometimes overwhelming, Chatgililoglu and Ferreri developed a method to analyse the lipid composition of erythrocyte cell membranes, isolating the mature cell from the rest of the blood sample and selecting the lipidome cluster representative of the membrane organisation and properties.



The invention of robotics for cell selection and membrane work-up has added precision to the process and has made the method highly repeatable. They have now processed over 25,000 samples and use the profile database to increase the information and predictive value for the lipidome cluster of the future analyses. The company currently offers a fast, low-cost and non-invasive service with two analytical tools: FatProfile® through doctors and nutritionists, and FatPharmacy® through pharmacists.

#### FATPROFILE®

FatProfile® is the core service for medical doctors and nutritionists provided by Lipinutragen. The patient makes an appointment with their doctor for analysis. This is a swift process, well organised to answer background questions and take a small blood sample (0.5 mL). The sample is sent to the Lipinutragen lab where it is processed and results – including the calculation of the Membrane Unbalance Index – prepared within seven working days. The information is then relayed to the

and clinical treatments or create a healthy balance for disease prevention under physiological conditions.'

Some of the nutra-strategies arising from the FatProfile® and FatPharmacy® are also supplied by Lipinutragen. In fact, the nutritional requirements established by the analysis have offered an opportunity for the company to start its own nutraceutical development arm. Lipinutragen has developed several key products of the nutra-strategy targeted to reach the cell membranes. These take the form of the nutrient-based Nutragenika (for redox and fatty acid balance) and a line of food products, Nutraomic. Designed through the examination of the company's lipidomic database, these products aim to redress the equilibrium of the cell membrane. However, the long-term aim is always to get patients to positively alter their lifestyle themselves as Ferreri says: 'It is easily demonstrated that, when a person changes their dietary habits, membrane fatty acid composition changes and finds its optimal equilibrium.'

#### NEW GENERATION OF HEALTH PROFESSIONALS

Currently, Lipinutragen is based primarily in its home country of Italy. However, the business is expanding rapidly and they have already established a new partnership in Spain, deriving from a technological transfer through the Technological Park of Bilbao, under the brand Lipigenia. The potential market for the molecular diagnostics is huge – an overall estimate puts it at 5.5 billion euros – so there is plenty of room for expansion. Additionally, Chatgialloglu and Ferreri anticipate the market will create a new job role in healthcare – that of the molecular consultant. Ferreri explains how she envisages the role: 'We want to create a new generation of health professionals that are specialists in connecting the molecular status of a person with their own health and nutritional conditions, thereby customising clinical and therapeutic strategies.'

Lipinutragen also aims to continue to make a useful research contribution to the academic world. As more people sign up to use the service, the company will be able to collect large amounts of data on cell membranes under different pathologies and physiologies. Overall, Lipinutragen will provide multiple benefits both directly, to patients and academics, and indirectly, by being at the forefront of the molecular diagnostics industry.

*When a person changes their dietary habits, membrane fatty acid composition changes and finds its optimal equilibrium*

doctor who is trained by Lipinutragen to understand and explain the results to the patient and offer advice going forward. This advice includes personalised nutra-therapy and a nutritional strategy for the patient to follow. This nutra-strategy is aimed at re-balancing their lipidomics profile over four months through the natural turnover of cells and remodelling of cell membranes. In pharmacies, the analysis service is also offered, the idea being that membrane profiles can be unbalanced also in the absence of a real pathological conditions. Therefore, the FatPharmacy® service is used by pharmacists to address personalised prevention through nutraceutical and nutritional advices, ameliorating life quality and dietary habits. Chatgialloglu expands on the process: 'By defining the lipidomic profile of the individual, a customised nutraceutical/nutrition strategy can be suggested. This can either support pharmacological therapy

## Project Insights

#### AIMS

- Better understand the turnover of cell membrane
- Expand the FatProfile® service and complementing treatment strategy FatPharmacy®, as a prevention tool for personalised wellbeing
- Provide nuanced responses to individual health issues

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#### PROJECT COORDINATOR BIOS

**Dr Chrysostomos Chatgialloglu** is Research Director at the Italian National Research Council (CNR) in Bologna, Italy. He is also co-founder and President of the spin-off company Lipinutragen. He is author of more than 250 publications in peer-reviewed journals, 34 book chapters and six patents. He is the author or editor of several books, including Membrane Lipidomics for Personalized Health (Wiley 2015).

**Dr Carla Ferreri** is Senior Researcher at the Italian National Research Council (CNR) in Bologna, Italy. She is also co-founder and R&D director of the spin-off company Lipinutragen. She is author of more than 160 publications in peer-reviewed journals and various patents and co-author of the book Membrane Lipidomics for Personalized Health (Wiley 2015).



FAT PROFILE®

fatpharmacy®