P4 Inclusive Cosmetics - Deciphering skin longevity biomarkers through the innovative P4I Cosmetics approach.

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The use of accurate, actionable and specific Predictive biomarkers of skin health & longevity is essential to support the transition in the direction of Precision and Personalised cosmetics, including consumers contributions through Participatory cosmetics, paving the way towards P4 Inclusive Cosmetics. In recent years, important advances have been evidenced in personalized medicine, precision medicine, and P4 medicine. This concept refers to the practice of customizing medical treatment and/or products to each individual patient (1). P4 medicine is an approach to make medicine more Predictive, Preventive, Personalised and Participatory, and its two main objectives are to underscore wellbeing and health (2).

P4 Inclusive Cosmetics (Predictive, Preventive, Personalised, Participatory) is our innovative approach inspired by personalised medicine, precision medicine or P4 medicine, applied and adapted to Cosmetics interventions. Methods for developing Personalised cosmetic formulas range from mobile apps, online questionnaires about your skin requirements and skin consultations, to scientific methods involving epigenetics and Omics approaches, cellular metabolism and biomarkers of skin longevity. A new path is already open: P4 Inclusive Cosmetics has only just begun.

Preventive cosmetics focus on targeting the early molecular events related to skin aging, protecting our skin cells and macromolecules (proteins, lipids and nucleic acids) from the toxic effects of the skin exposome, preventing premature skin ageing. Preventive ageing is becoming a trend in the cosmetics industry, as many of us believe that prevention is more effective than cure. Beauty is being refined for Generation Z, who are looking for preventative anti-ageing treatments, and Millennials are not waiting to get old either, younger Millennials are looking for preventative cosmetics products. Consumer focus has shifted seeking prevention versus cure.

Exciting advances in personalised medicine have been seen in the area of dermatology, taking account genetic backgrounds profiles of patients for the treatment and management of dermatosis, such as psoriasis, acne treatments and atopic skin (3). In this context, the identification of specific skin biomarkers associated with particular skin conditions may play a key role in order to drive more targeted approaches, taking into consideration the patient's genetic profile and phenotypic parameters of the patient (microbiome composition, lifestyle, diet and other environmental factors). Personalized cosmetics, also known as bespoke or custom-made cosmetics, are products that are tailored to the specific skin needs and preferences of the individual consumer. One of the main benefits of personalized cosmetics is that they are designed to address specific skin concerns and issues. For example, a personalized skincare routine may include products that target acne, fine lines, or uneven skin tone.

The new concept of inclusive cosmetics or personalised beauty products is growing in recent years. The Cosmetics industry will experience revolutionary changes in the science of ageing in 2023, and skin care product trends will focus on preventing skin ageing damage caused by cellular processes and external factors. Scientific research has shown that most signs of ageing and skin problems are primarily epigenetic, and many formulators are already working on "Predictive, Preventive and Personalised" Cosmetic formulations with repairing actives that can help change our genetic expression patterns to make our skin look younger from the inside out by boosting the skin cells longevity.

Next generation personalised or customised beauty products are emerging technologies that provide an alternative to conventional "one-size-fits-all" products. Cosmetics companies involved in the manufacturing of personalized beauty products utilize biological information and behaviour of a person to design personalized beauty products for the consumer. Next-Generation Personalized Beauty includes various personalized products such as Skincare, Haircare, Make-up, Fragrances, and Others. In recent years, Rapid Development in Omics sciences coupled with deep learning and AI data analyses have pave the road for the development of personalized beauty products which is expected to show significant market opportunities in upcoming years (4).

Recently, the Nuclear factor erythroid 2-related factor 2 (NRF2) pathway, a master regulator of the cellular anti-oxidant response has been used for the design of personalised inner beauty products and a new concept of participatory cosmetics, including consumers, by implementing a Direct-

To-Consumer (DTC) testing approach in the non-face-to-face era that is evolving after the global pandemic (5). Brands that offer customized products allow the consumer to find the right product for their skin needs. This 2023, a personalised sunscreen formula for a girl with a rare genetic light disorder has been developed (6), other brands have been pioneers in the development and manufacture of scientifically proven skin care products to improve quality of consumers life with specific skin conditions (7, 8).

Because our skin is exposed to a combination of internal and external stressors, people's chronological and biological ages can differ markedly. The design of precise dermo-cosmetic approaches targeting the main causes of aging can help slow down the deterioration of the skin's structure and functionality and keep our skin in better condition despite chronological age, a term commonly called "Healthy Skin". For this purpose, the identification of reliable biomarkers of skin longevity is key. Oxidative stress due to reactive oxygen species (ROS) in the skin plays a key role in the ageing process. Chronic micro-inflammation (coined as inflamm'aging) also appears to be a driver of accelerated skin ageing. Both inseparable processes are cross-cutting in different phenotypes of "unhealthy skin": such as atopic skin, sensitive skin, and photoaged skin, eventually lead to blemishes, clogged pores, dry skin, and wrinkles. Extrinsic stressors such as photodamage, urban pollution, microbiome dysbiosis, as well as internal factors such as neurogenic inflammation or mood disorders have negative effects on skin wellbeing by altering the innate functions of the skin barrier and delaying its repair and renewal, making it more sensible to external aggressions.

In recent years, skin ageing research has experienced a renaissance, and new advances are rapidly emerging. Multiple types of data can be used to predict age and link the prediction to key biological processes, such as epigenetic alterations, loss of protein homeostasis or proteostasis, deregulation of nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell reduction and altered intercellular communication. Among these, and in the context of identifying reliable biomarkers of longevity, modifications of the skin proteome appear crucial. Over time, the skin's protein homeostasis or proteostasis network becomes burdened with proteins modified by reactive oxygen species (ROS) exacerbate skin aging and inflammation, and metabolites that induce oxidative damage. These by-products can react with cellular proteins and cause morphological alterations (misfolding) and loss of function of key skin proteins involved in skin structure and function. Overall, the understanding of the molecular mechanisms implicated is important to prevent physiologic skin aging and to compensate for functional deficits implicated in premature skin aging. However, the major challenging point is the definition of preventive strategies capable of sustaining the cutaneous intrinsic defence system (9).

The most relevant morphological and anatomical changes in skin ageing occur at the single cell level, in the stratum corneum, epidermis and dermis; changes in natural moisturising factor (NMF), cellular lipids and ceramides in the epidermis, and a reduction in collagen and elastin proteins that are generated in the matrix of the cells that make up the dermis. Interestingly, in an investigation of human skin ageing using single-cell analysis of upper eyelid skin, most of the mechanisms underlying skin ageing are found in specific cell types: fibroblasts, endothelial cells and pericytes (10). To this purpose, our scientific team has set-up a novel targeted proteomics approach for the assessment, quantification and identification of oxidatively damaged (carbonylated) proteins at the proteome level using direct in situ labelling coupled to mass spectrometry approaches. Distinct signatures of biomarkers (i.e., specific proteins) have been observed upon skin exposition to different types of stressors. Recent in vivo studies underscored the benefits to be gained from increased protection or the stimulation of carbonylated proteins elimination by the amelioration of parameters related to skin appearance.

Personalisation is a trend in our lives, and we want the same for our skin care. We are confident that the P4 Inclusive Cosmetics concept will REVOLUTIONISE SKIN CARE, where an ideal product tailored exactly to the skin needs of each individual or a group of individuals will be applied in many innovative cosmetic formulation researches using data from distinctive biomarker signatures. It is now a challenge for many brands that have started to work under the tailor-made skin care approach based on proper skin characteristics and scientific analysis to deliver what your skin needs to look better and healthier.

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