

## ***THE CONCEPT OF LOW DOSE MEDICINE***

**Low Dose Medicine (LDM)** was born from the merging between Molecular Biology and Psycho-Neuro-Endocrine-Immunology (P.N.E.I.), and was developed thanks to research results in the field of **Low Dose Pharmacology**.

**Low Dose Medicine** is a person-centered Medicine, based on three guiding principles:

- to treat the human being and not only the disease;
- to act on the causes and not only on the symptoms;
- to consider the human being as a unique whole mind-body network

**LDM** is grounded on the fundamental principle represented by the centrality of the human being as a whole mind-body entity. The individuality of each patient is always considered during the design of a specific therapy, while the inner disease etiology (instead of the symptoms) represents the real target of Low Dose Therapy.

**The restoration and/or preservation of the original physiological (homeostatic) condition is the first fundamental pillar of LDM approach.**

### ***P.N.E.I. VISION AND LDM***

**LDM** starts from an original idea in the medical field: to return an unhealthy body to the original physiological condition through the use of the same biological molecules (neuropeptides, hormones, cytokines, along with growth factors) normally present in the body and which, in healthy conditions, monitor and guide bodily functions.

Besides the signaling molecules, **LDM** pharmacology refers to the immense patrimony of knowledge on natural substances (vegetal, animal and mineral origin), investigated under the magnifying lens of Molecular Biology.

In tandem with the knowledge on the signaling molecules, in recent years we have witnessed, in the medical field, the gradual abandonment of the separatist conception of biological functions giving way to become a more unified one in accordance with the guiding principles of P.N.E.I.

**This unified vision of the human body is the second pillar of LDM.**

### ***P.N.E.I. SYSTEMS AND BIDIRECTIONAL CROSS-TALK***

**The main unifying P.N.E.I. element is identified in the cross-talk between the psycho-neuro-endocrine systems and the immune system.** This sophisticated cross-talk is mediated by a complex network of signaling molecules (cytokines, hormones, neuropeptides and growth factors) which are the vehicles of the biological information necessary for the complex and efficient regulation of cellular responses to stimuli.

An altered cross-talk due to an imbalance between specific signaling molecules is crucial, for example, in inflammatory, allergic, and autoimmune diseases. **Administering biological molecules which control and drive cellular functions in order to restore the original physiological conditions is the third pillar and the core of LDM.**

## ***THE MATTER OF SIGNALING MOLECULES ORAL BIOAVAILABILITY IS SOLVED BY SKA TECHNOLOGY***

A critical point of signaling molecules oral administration is represented by their low bioavailability; an effective drug delivery system is mandatory in order to improve this key parameter. **The utilization of physiological low doses *per os* in LDM is enabled by the application of SKA technology (Sequential Kinetic Activation)**, a sophisticated drug delivery system. The SKA technology is based on the principles of Quantum Physics, in particular on the *release activity* that is the ability of the basic substance to release its activity in the aqueous milieu. The SKA technology allows the nano-concentrations to be active even below the actually considered minimum effective dose, with therapeutic results comparable to those induced by high concentrations.

**SKA technology represents the *technical core* that allows the production of innovative medicines whose *functional core* is represented by Low Dose signaling molecules. This modern technological approach enables the availability of synergistic, effective and safe medicines that are cornerstones of LDM.**

### ***SKA SIGNALING MOLECULES: MECHANISM OF ACTION***

The action mechanism of SKA Low Dose cytokines, hormones, neuropeptides and growth factors consists in the sensitization and the activation of some units of cellular (or plasmatic) receptors in virtue of their high dilution (in their physiological working range between micrograms/milliliter for hormones and picograms/milliliter for the other signaling molecules). **SKA Low Dose molecules work by bringing to the whole P.N.E.I. system information able to activate auto-regulation mechanisms.**

The ability to correct, for example, alterations of the immune system administering the right cytokines or alterations of endocrine disorders administering the right hormones, represents one of the most fascinating and innovative research fields in Molecular Biology applied to Medicine.

### ***LDM AND SCIENTIFIC RESEARCH: A WINNING PARTNERSHIP***

**Low Dose Medicine is not a novel therapeutic theory based only on hypothesis.** A growing body of experimental evidence continuously add new data on SKA Low Dose signaling molecules mechanisms of action, clarifying the physiologic and biochemical concepts underpinning the use of Low Dose signaling molecules.

In November 2009, the journal Pulmonary Pharmacology & Therapeutics published the first paper on the effects of SKA Low Dose cytokines in a animal model of allergic asthma: Gariboldi et al. *Low dose oral administration of cytokines for treatment of allergic asthma*. Pulmonary Pharmacology & Therapeutics 22 (2009) 497-510; **this paper represents the milestone of LDM research. Since 2009, new publications have followed the paper published by Gariboldi and colleagues extending available data regarding LDM therapeutic design, efficacy and safety.**

Six years of scientific research on LDM allowed the researchers to deeply evaluate some pivotal aspects linked with LDM:

- the validity of the theoretical concepts underpinning the LDM approach
- the centrality of the SKA pharmaceutical technique
- the immunomodulatory and immunostimulatory effectiveness of the experimental and clinical administration of SKA Low Dose signaling molecules

### ***LDM: A NEW ERA IN THE POSSIBILITY OF CLINICAL THERAPIES***

Biological molecules, pharmacologically active at low dosage which are obtained applying SKA technology, are able to re-modulate the neuro-endocrine-immune network imbalances that underlie many diseases. The possibility of using biological molecules with immunological modulating properties opens the way for a highly effective treatment of high social impact pathologies whose current treatment is still widely symptomatic and not definitive.

LDM provides the tools to integratively support the treatments currently considered as the *gold standard* for many diseases. The ability to use low-dose SKA signaling molecules without adverse events gives us the opportunity to intervene on several networks in a physiological and pleiotropic way, acting simultaneously on the crucial points of pathology onset mechanisms.

The most modern techniques in the production of human recombinant proteins has enabled the achievements of a very high quality production standards along with effective medicines. The SKA pharmaceutical technology (designed, developed and standardized in Guna Laboratories, Milan) allowed to produce Low Dose drugs that demonstrate the same therapeutic effects as those drugs containing high doses of signaling molecules but without adverse effects.

The SKA production method opens a new era of possibilities in clinical use of signaling molecules of biotech origin. Constantly attracting the attention of the scientific world, preclinical and clinical scientific research is drawing up new scenarios in the treatment of many diseases, giving a new hope to millions of patients.

From the era of *Evidence Based Medicine* LDM has definitively shifted into the era of *Efficacy Based Medicine*.