CISAS

Centro Internazionale di Studi Avanzati su ambiente, ecosistema e Salute umana

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WP 5
Molecular Epidemiology

WP leader: Fabio Cibella
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UNIVERSITÀ DEGLI STUDI DI PALERMO

Istituto di Biomedicina e Immunologia Molecolare "Alberto Monroy" - CNR

ISTITUTO SUPERIORE DI SANITÀ

Task 5.1

Bio-accumulation of environmental contaminants in placenta, maternal and newborn tissues and their association with placental transcriptome, pregnancy and long-term infant outcomes

Task leader: Fabio Cibella IBIM-CNR

Task 5.1 - Background

The present research program is aimed at studying impact of environmental pollution on ecosystem and its connection with human health.

Generally epidemiologic studies tend to assess the potential toxicity of pollutants using a multi-disciplinary approach, focusing on vulnerable groups, e.g., children.

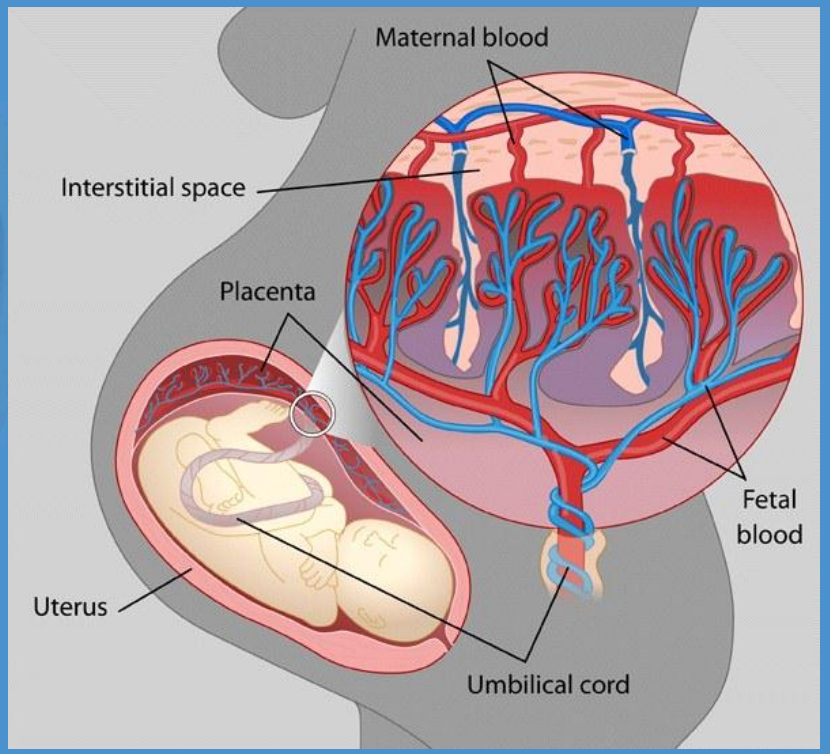
In the last years a great deal of effort has been made in the evaluation of the effects of environmental contaminants on children's health.

More recently, the theory of **"intrauterine origins of health and disease susceptibility"** states that adult diseases may have an in utero origin, when suboptimal intrauterine conditions - including exposure to environmental contaminants - induces irreversible changes, which manifest themselves in post-natal and adult life.

Placental Functions

Placenta is posed at the interface between maternal/external environment and fetus. It is essential in many aspects of embryo development:

- **Respiratory**
- **Excretory**
- **Nutritive**
- **Barrier function**
- **Immunological function**

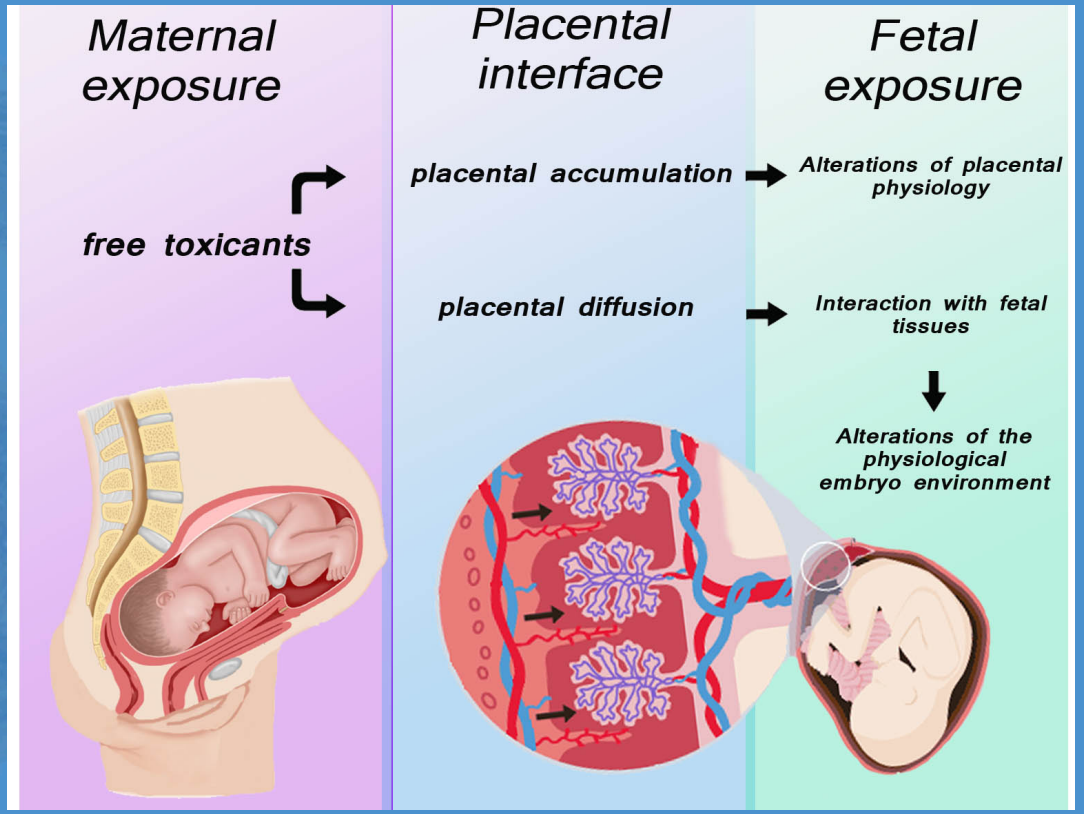


Environmental contaminants may alter placental physiological function with early and late negative consequences on child's health.

Placenta as a study model

Placental tissue is:

- a noninvasive exposure biomarker for different organic and inorganic pollutants
- usually discarded after birth
- easy to obtain
- an exposure model of both mother and fetus.



This tissue offers abundant material useful for the identification of possible exposure biomarkers

Mothers and child pairs birth cohort

Combined residential and Hospital-Based recruitment of healthy pregnant women

General criteria for inclusion will be:

- To be residence in the study areas at least two years,
- To be able to speech and understand Italian language,
- To be aged between 18 to 40 years old at the time of delivery,
- To not have followed any program of assisted reproduction,
- Absence of serious chronic diseases, such as diabetes, hypertension, etc.
- Absence of any evident complications during pregnancy diagnosed previously of the signature of informative consensus.

Task 5.1 objectives

1) Evaluating the risk of toxicants contamination during pregnancy in a cohort of mother-child pairs resident in highly polluted areas;
2) evaluating the bioaccumulation features and patterns of toxicants by examining their distribution among maternal, placental and fetal tissues;
3) determining whether the bio-accumulation of toxicants might impact placental mRNA expression;
4) understanding whether prenatal exposure to toxicants might cause negative pregnancy outcome and long-term effects on children health and disease predisposition;
5) defining the association of placental contamination and gene expression patterns with long-term infant health outcomes, to evaluate the validity of placental analysis in predicting future infant health outcomes.

Task 5.1 deliverables

D 5.1.1: Epidemiologic survey in study and control areas: evaluation of reproductive health (M6)

D 5.1.2: “Ecologic” evaluation of selected pollutants in maternal and fetal tissues (M15)

D 5.1.3: Comparative estimate of genome-wide mRNA expression in placenta between high and low exposure areas (M28)

D 5.1.4: Long-term comparative evaluation of child health between high and low exposure areas (M34)

D 5.1.5: Identification of exposure placental biomarkers related to late-onset diseases (M36)

Task 5.2

Cellular models and environmental pollutants in biochemical and biomolecular mechanisms of airway diseases

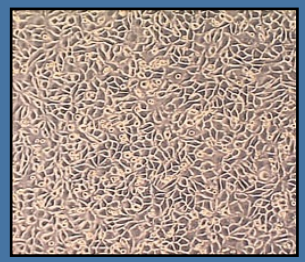
Task leader: Mirella Profita IBIM-CNR

Task 5.2 objectives

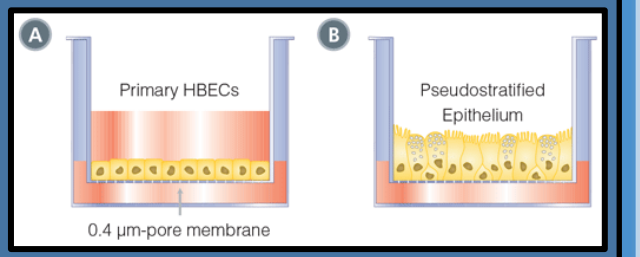
Development of experimental models of ex vivo/in vitro cell culture of cell lines and normal human primary cells and cancer of bronchial and nasal epithelium (single-layer, two-dimensional and three-dimensional).

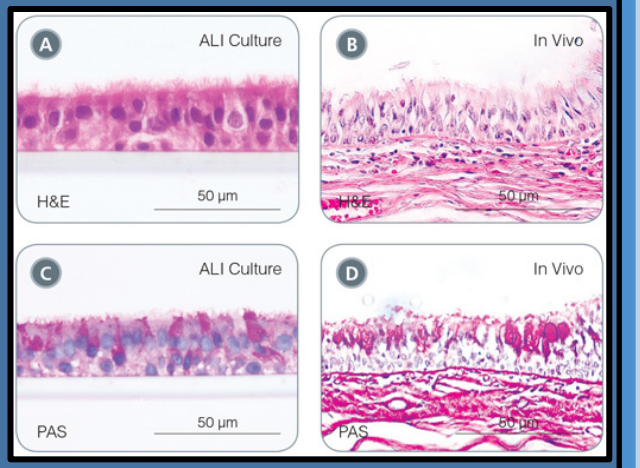
Development of knowledge on the interaction mechanisms at the biochemical and molecular levels of contaminants (heavy metals, emerging pollutants, PBDEs, POP) in experimental models ex vivo / in vitro differentiated cells and tissues in the laboratory.

Culture for Respiratory Research



Monolayer Nasal or bronchial epithelial cells





2D Bronchial or nasal epithelium

3D Lung or nasal tissue

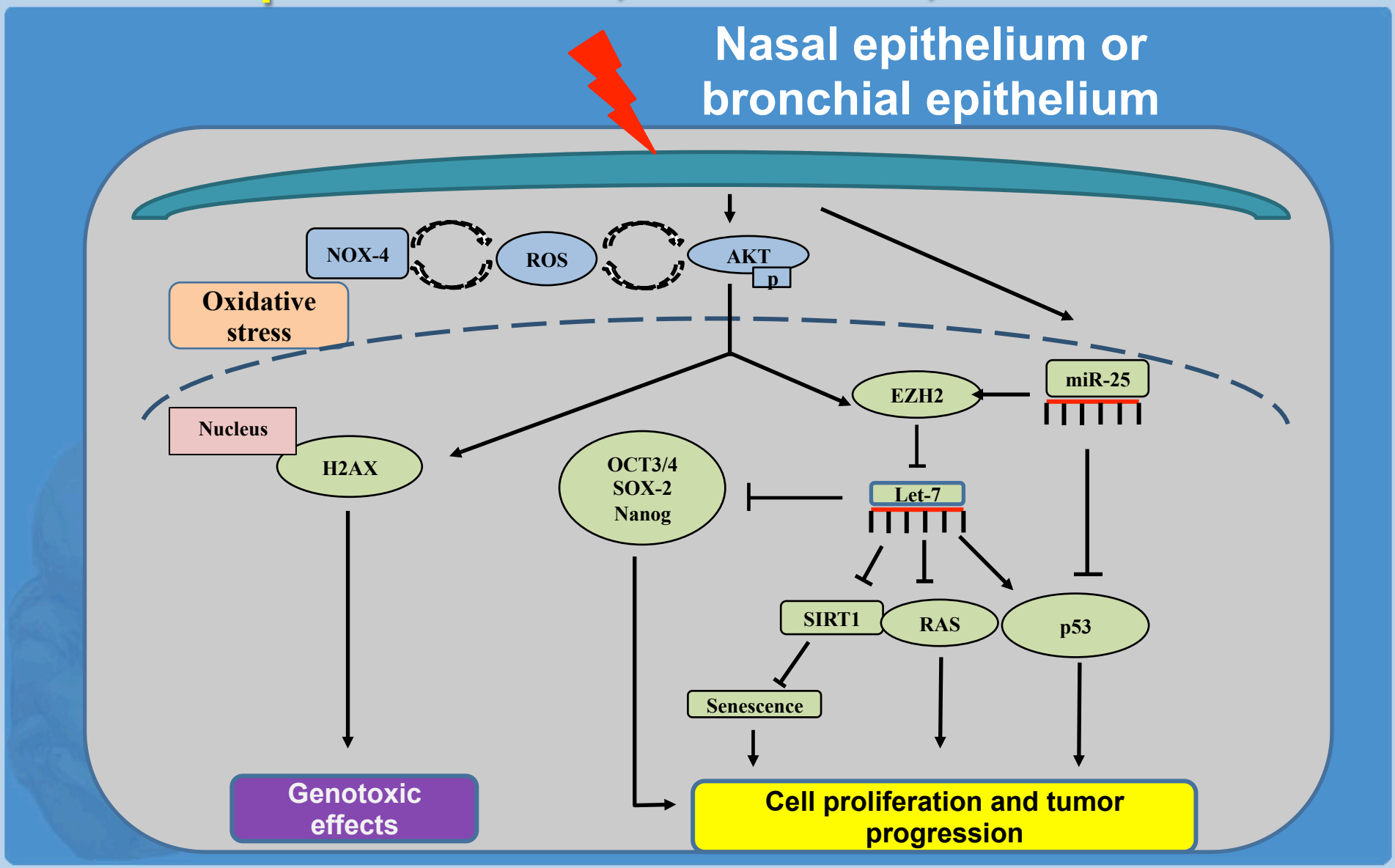
Task 5.2 objectives

Development of scientific research to understand the effects of environmental pollution on human health concerning respiratory diseases.
Identification of pathogenic mechanisms by which environmental pollutants interfere with normal cellular activities:

1) induction of oxidative stress,
2) interference with DNA repair mechanisms,
3) deregulation of cell proliferation,
4) genotoxic effects,
5) cellular mechanisms that promote carcinogenesis,
6) cellular mechanisms that involve the activation of several genes,
7) biomarkers, proteins, and other factors.

The knowledge of these mechanisms is important to counteract the negative effects of pollutants.

Effect of heavy metals, emerging pollutants, PBDEs, POP



Task 5.2 deliverables

D 5.2.1: Development of ex vivo/in vitro experimental models of disease (related to exposure to target contaminants) (M18)

D 5.2.2: Comparative analysis of the data (M24)

D 5.2.3: Dissemination of scientific results (M30)

Task 5.3

In vitro and in vivo studies of mechanisms of immunomodulation and immunotoxicity

Task leaders: Paolo Colombo IBIM-CNR
Gabriella Di Felice ISS

Task 5.3 objectives

It has been shown that exposure to contaminants in the environment via different routes can cause adverse effects on biological systems, such as the central nervous system, liver, reproductive and endocrine systems.

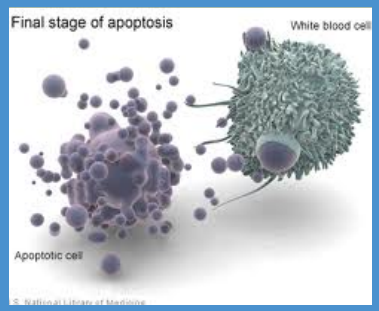
Although the information on the impact on the immune system is limited, recent studies in animal models have shown immunosuppressive and immunomodulatory effects suggesting that contaminants present in the environment can display a potential immunotoxic effect.

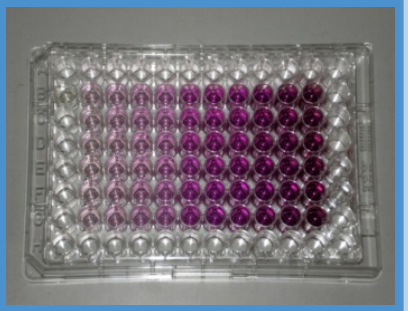
Effect of heavy metals, emerging pollutants, PBDEs, POP

In vitro/ex vivo toxicity tests using different cell types

Ex vivo and in vitro assays with human and mouse primary cells or cell lines (supervised by IBIM-CNR/ISS)

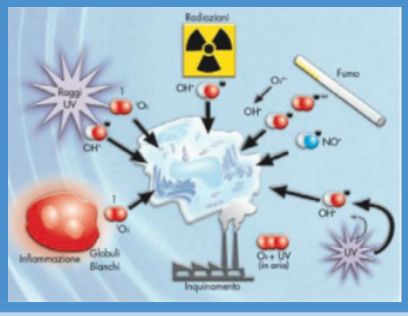
Subtask 5.3.1

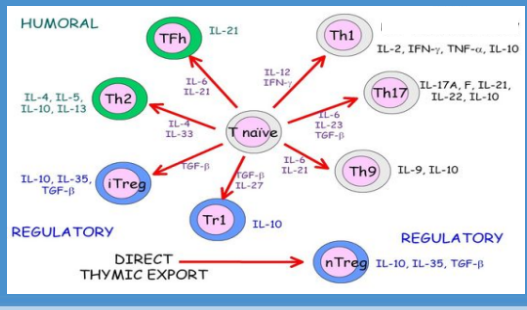




1) Modulation of cell viability (i.e., cell proliferation, cytotoxicity, cell death, etc):

2) Modulation of inflammatory properties (i.e. cytokine production, ROS production, modulation of immunological response by both innate and adaptive immune cell populations):





Effect of heavy metals, emerging pollutants, PBDEs, POP

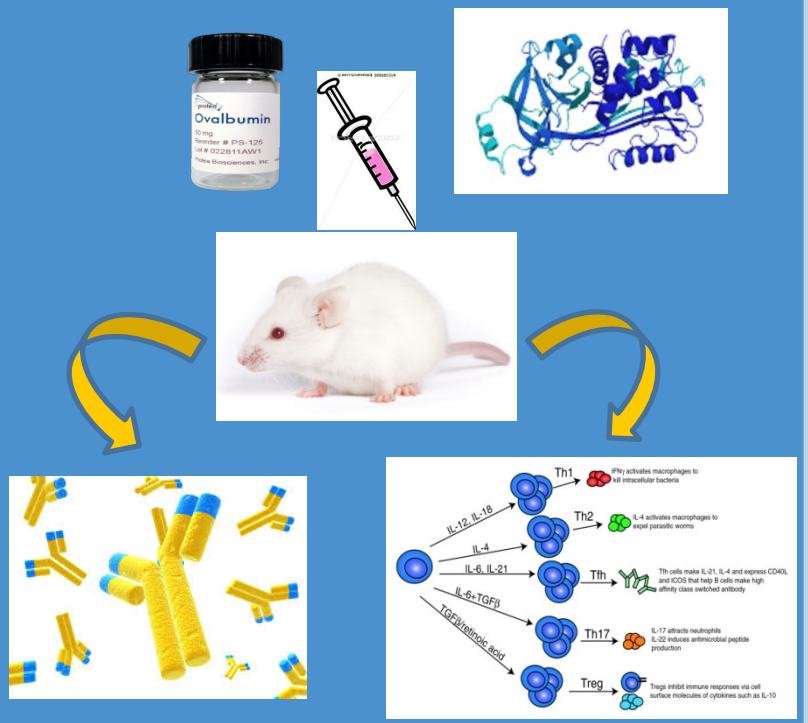
In vivo toxicity tests

Animal system: Balb/c mice
(supervised by Gabriella Di Felice - ISS)

Subtask 5.3.2

1) Modulation of *in vivo* immune responses (*in vivo* studies to define the impact on complex immune responses, i.e., antibody and cell responses to standard antigen immunization)

2) Correlation among *ex vivo*/*in vitro* studies and functional *in vivo* studies



Task 5.3 deliverables

D 5.3.1 Development of human and murine experimental models of immunotoxicity: Cell cultures assays

D 5.3.2 Development of experimental in vivo animal models

Task 5.4

Biomolecular markers related to exposure in vitro and cancer

Task leader: Concetta Maria Messina
DiSTeM - UniPA

Task 5.4 objectives

UniPa – DiSTeM (Dept Earth and Sea Science, Marine Biochemistry and Ecotoxicology lab).

Specific objective: in vitro evaluation of cancer promotion of the combined actions of the contaminants selected in WP2.

By evaluating: signal transduction, biochemical markers related to toxicity, inflammation, oxidative stress, cell cycle control, angiogenesis and apoptosis.

Task 5.4

Model systems	Hepatoma, retinoblastoma, osteosarcoma, cancerstem cells, melanoma, fibroblast
Biomarkers	- Antioxidant/pro-oxidant switch and related signal transductions pathways - Dose-time dependent toxicity - Biomarkers of oxidative stress - Cell cycle modulation, inhibition or promotion of apoptotic pattern, or proliferative effect - Markers of inflammation - Markers of angiogenesis

Task 5.4 deliverables

D 5.4.1: Evaluation of molecular sensors related to exposure to target contaminants, stress, signal transduction related to cancer (M30)

Grazie per l'attenzione