



University of Genova

**Department of Earth, Environmental
and Life Sciences**

**Doctorate Course in Earth and
Environmental Science and
Technology**



Curriculum in biology applied to agriculture and the environment

Research Theme n. 2

Titolo:

Implementazione di modelli in vitro avanzati 3D di tessuti polmonari umani per l'individuazione di biomarcatori specifici del potenziale infiammatorio e cancerogeno di fibre minerali e loro derivati

Title:

Implementation of advanced 3D in vitro models of human lung tissues for the identification of specific biomarkers of the inflammatory and carcinogenic potential of mineral fibers and their derivatives

Tutor:

-Prof. Sonia Scarfi (UNIGE)

Co-tutor:

-Prof. Alessandro F. Gualtieri (UNIMORE);
-Jan Markus, PhD, Senior Researcher (Mattek In Vitro Life Science Laboratories Bratislava, Slovakia)

Program description including the formation program abroad

The project focuses on the implementation and validation of 3D in vitro models of human lung tissues for the prediction of toxicity/carcinogenicity derived from the prolonged inhalation of mineral fibres. This type of particulate causes well known health pulmonary problems such as lung fibrosis, asbestosis, lung cancer and pleural mesothelioma. In nature, the occurrence of numerous minerals with asbestiform behavior has been widely documented. These are fibrous, friable silicates, able to split longitudinally into needle-like microfragments that can be inhaled, also containing heavy metal impurities (e.g. iron, manganese, chromium), resulting in different biodegradability in vivo, which ultimately cause environmental and workplace biosafety problems of great relevance.

The project will be developed in phases by testing in vitro models of increasing complexity, from simple co-culture systems of human lung cell types relevant to the development of inflammatory/carcinogenic pathways (i.e., alveolar macrophages, epithelial, endothelial, mesothelial cells) to the use of 3D lung reconstructed tissues such as the EpiAirway™ and EpiAlveolar™ models recapitulating faithfully the human bronchial and alveolar tissue architecture. In particular, the two latter models, although perfectly mimicking the micro-physiology of the lower respiratory tract and of the lung parenchyma, lack the immune cell component essential for the development of the acute and chronic inflammatory responses at the basis of the fibrotic and carcinogenic processes in the lung. As such in the last phase of the project the immune cells will be added to the 3D reconstructed

tissues to complete the in vitro model for the toxicity/carcinogenic predictive studies. The functionality of the models will be tested by using positive and negative mineral fibre controls of carcinogenicity in humans, namely crocidolite UICC and wollastonite NYAD G, together with other types of potentially harmful minerals (i.e., erionite, mordenite, chrysotile). The following parameters will be investigated to confirm/disprove the validity of the predictive model: short- and long-term cytotoxicity (24-48h and up to 14-21 days), oxidative stress, genotoxic stress, accumulation of heavy metals, production of acute and chronic inflammatory cytokines, expression of epithelial-to-mesenchymal transition markers and transformation potential.

If the models prove to be reliable, they could be used as predictive tools for the biosafety assessment of chemical substances, mineral fibres and environmental particulates potentially inhalable by humans, also helping to understand their mechanisms of toxicity.

Period abroad:

For a period of no less than three months, the PhD candidate will carry out part of the experimental thesis in the research laboratories of the Mattek in vitro Life Science Corporation (Bratislava, Slovakia), a leading company in the development of 3D human microtissue models, under the tutorage of Dr Jan Markus, for the implementation of the EpiAirway™ and EpiAlveolar™ models by the addition and further testing of the immune cell component to the respective in vitro systems.

Financial support:

PRIN2022 "SEEDS" overheads, 100022-2023-SS-PRIN_Bando2022, sufficient to cover the costs of a personal pc and of the reagents for the development of the research project.

Tutor's publications in the last 3 years:

-Di Giuseppe D, **Scarfi S**, Alessandrini A, Bassi AM, Mirata S, Almonti V, Ragazzini G, Mescola A, Filaferro M, Avallone R, Vitale G, Scognamiglio V, Gualtieri AF. Acute cytotoxicity of mineral fibres observed by time-lapse video microscopy. *Toxicology* 2022, 466: 153081. doi: 10.1016/j.tox.2021.153081

-Mirata S, Almonti V, Di Giuseppe D, Fornasini L, Raneri S, Vernazza S, Bersani D, Gualtieri AF, Bassi AM, **Scarfi S**. The Acute Toxicity of Mineral Fibres: A Systematic In Vitro Study Using Different THP-1 Macrophage Phenotypes. *Int J Mol Sci.* 2022, 23(5): 2840. doi: 10.3390/ijms23052840.

-Castellano M., Doderio A., **Scarfi S**, Mirata S., Pozzolini M., Tassara E., Sionkowska A., Adamiak K., Alloisio M., Vicini S. Chitosan–Collagen Electrospun Nanofibers Loaded with Curcumin as Wound-Healing Patches. *Polymers*, 2023, 15(13): 2931. DOI: 10.3390/polym15132931

-Mirata S., Asnaghi V., Chiantore M., Salis A., Benvenuti M., Damonte G., **Scarfi S**. Photoprotective and Anti-Aging Properties of the Apical Frond Extracts from the Mediterranean Seaweed *Ericaria amentacea*. *Marine Drugs*, 2023, 21(5): 306. DOI: 10.3390/md21050306

-Gualtieri A.F., Mirata S., Almonti V., Bassi A.M., Meo C., **Scarfi S**, Zapparoli M., Armeni T., Cianfruglia L., Marzioni D., Fantone S., Tossetta G., Stipa P., Laudadio E., Sabbatini S., Minnelli C., Di Valerio S., Vaia sicca S., Procopio A.D., Pugnali oni A. In vitro toxicity of short vs long chrysotile fibres. *Periodico di Mineralogia*, 2023, 92(2): 203-222. DOI: 10.13133/2239-1002/18012

-Bassi A.M., Mirata S., Almonti V., Tirendi S., Vernazza S., Fornasini L., Raneri S., Bersani D., Passalacqua M., Gualtieri A.F., **Scarfi S**. Cytotoxic and pro-inflammatory early effects of mineral fibres on human alveolar epithelial and immune cells. *Periodico di Mineralogia*, 2023, 92(2): 223-239. DOI: 10.13133/2239-1002/18082.

-Gualtieri A.F., Leoncini M., Fantone S., Valerio S.D., Tossetta G., Procopio A.D., Marzioni D., Pugnali oni A., Bassi A.M., Almonti V., Mirata S., Vernazza S., Tirendi S., Marengo B., Traverso N., Passalacqua M., **Scarfi S**, Raneri S., Fornasini L., Bersani D., Perchiazzi N., Ballirano P., Pacella A., Bloise A., Ottaviani M.F., Mattioli M., Giordani M., Ventura G.D. PRIN 2017 Fibres - A Multidisciplinary Mineralogical, Crystal-Chemical and Biological Project. What have we learned after four years of research? *Periodico di Mineralogia*, 2023, 92(2): 143-158. DOI: 10.13133/2239-1002/18021.

-Benvenuti M., Di Piazza S., Salis A., Cecchi G., Zotti M., **Scarfi S**, Damonte G. A novel method for the extraction and characterization of metabolites from Basidiomycota: *Pleurotus ostreatus* (Jacq.) P. Kumm., 1871 as a case study. *Sep Sci Plus*, 2023, 10(6): e2300116. <https://doi.org/10.1002/sscp.202300116>.

-Raneri S, Gianoncelli A, Bonanni V, Mirata S, **Scarfi S**, Fornasini L, Bersani D, Baroni D, Picco C, Gualtieri AF. The influence of cation exchange on the possible mechanism of erionite toxicity: A synchrotron-based micro-X-ray fluorescence study on THP-1-derived macrophages exposed to erionite-Na. *Environ Res.* 2024, 252: 118878. doi: 10.1016/j.envres.2024.118878.

- Almonti V, Vernazza S, Mirata S, Tirendi S, Passalacqua M, Gualtieri AF, Di Giuseppe D, **Scarfi S**, Bassi AM. Toxicity and inflammatory potential of mineral fibres: The contribute of released soluble metals versus cell contact direct effects. *J Appl Toxicol*. 2024, 44(8): 1166-1183. doi: 10.1002/jat.4610.
- Bassi S, Benvenuti M, Mirata S, Di Piazza S, Salis S, Damonte G, Zotti M, **Scarfi S**. Enhanced antioxidant and anti-inflammatory activity of the extracts of *Pleurotus ostreatus* edible mushroom grown on *Lavandula angustifolia* residues. *Food Bioscience*, 2024, 60: 104382. doi: 10.1016/j.fbio.2024.104382.
- Gualtieri AF, Ferrari E, Rigamonti L, Ruozzi B, Mirata S, Almonti V, Passalacqua M, Vernazza S, Di Valerio S, Tossetta G, Vaiasicca S, Procopio AD, Fazioli F, Marzioni D, Pagnaloni A, **Scarfi S**. Bridging the gap between toxicity and carcinogenicity of mineral fibres by connecting the fibre parameters to the key characteristics of carcinogens: A comprehensive model inspiring asbestos-induced cancer prevention strategies. *Curr Res Toxicol*, 2024, 7: 100202. Doi: 10.1016/j.crtox.2024.100202.
- Scarfi S**, Almonti V, Mirata S, Passalacqua M, Vernazza S, Prakash Patel J, Brook M, Hamilton A, Kah M, Gualtieri AF. In vitro cyto- and geno-toxicity of asbestiform erionite from New Zealand. *Env Res*, 2025, 265: 120415. Doi: 10.1016/j.envres.2024.120415.
- Mirata S, Almonti V, Passalacqua M, Vernazza S, Bassi AM, Di Giuseppe D, Gualtieri AF, **Scarfi S**. Toxicity of size separated chrysotile fibres: the relevance of the macrophage-endothelial axis crosstalk. *Toxicology*. 2025, 511: 154032. doi: 10.1016/j.tox.2024.154032.
- Ballirano P, Pacella A, Mirata S, Passalacqua M, Di Carlo MC, Arrizza L, Montereali MR, **Scarfi S**. Fibrous erionite modifications following THP-1 macrophage phagocytosis: An insight into the mechanisms of interaction with biological systems. *J Hazard Mater*. 2025, 489: 137546. doi: 10.1016/j.jhazmat.2025.137546.
- Giordani M, Mirata S, **Scarfi S**, Passalacqua M, Fornasini L, Drava G, Meli MA, Roselli C, Mattioli M. The cytotoxic/genotoxic role of impurities in soluble minerals: The case of natural (fibrous epsomite) versus synthetic (Epsom salt) magnesium sulphate. *Sci Total Environ*. 2025, 966: 178666. doi: 10.1016/j.scitotenv.2025.178666.