

Cancer nanomedicine: forging a path to the clinic

Book of abstracts

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A workshop organised within the activities of the EIC Pathfinder project:

2D material-based multiple oncotherapy against metastatic disease using a radically new computed tomography approach - PERSEUS

Selenoproteins and reductive enzyme pathways in control of cell fate and as anticancer drug targets

Elias S.J. Arnér - Invited

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Selenoproteins are typically reductive enzymes utilizing selenocysteine (Sec, U) as the catalytic residue. Their intricate translation machineries necessitate genetic engineering for recombinant selenoprotein production at higher yields, which we employ using *E. coli* as expression host. In a cellular context, potent antioxidant defense systems as well as a wide range of intracellular signaling pathways are controlled by key selenoproteins, including thioredoxin reductases (TXNRD) and glutathione peroxidases (GPX). The development and use of inhibitors of these enzymes will thus trigger increased oxidative stress as well as perturbed signaling, the outcome of which will always be context dependent. Intriguingly, we recently found that signaling through tyrosine phosphorylation cascades, such as upon stimulation of the receptor for Epidermal Growth Factor (EGFR) is tightly controlled of the cytosolic thioredoxin system, dependent upon TXNRD1, as well as by glutaredoxins dependent upon glutathione (GSH), seemingly acting in parallel in control of protein tyrosine phosphatases such as PTP1B. Inhibitors of both TXNRD1 and GPXs have been proposed for anticancer treatment, but the effects *in vivo* may vary depending upon tumor subtypes as well as differential effects on the immune system. These examples of how selenoproteins and reductive enzyme pathways can be anticancer targets while also controlling intracellular signaling pathways, ultimately determining cell fate, will be discussed.

Nature-inspired nanovesicles enable RNA delivery to the breast cancer microenvironment

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Lipid nanoparticles (LNPs) have emerged as clinically validated nonviral RNA delivery systems; however, their limited tumor targeting remains a major challenge in oncology. In this work, LNPs were functionally integrated with cancer cell membrane components to enhance their targeting capability. The natural composition of tumor cell membranes was leveraged to promote both homotypic and heterotypic adhesion, exploiting cancer cell self-recognition and interactions with stromal cells within the tumor microenvironment. A biomimetic nanocarrier was developed by cloaking RNA-loaded LNPs with nanovesicles derived from the membrane of triple-negative breast cancer cells (CCMNVs). These nanovesicles were dye-labeled and comprehensively characterized in terms of size, surface charge, protein composition, and membrane sidedness. The correct orientation of CCMNV membrane-associated proteins enabled homotypic binding with 4T1 cells and heterotypic recognition of a cancer-associated fibroblasts model developed and validated in this study. mRNA-LNPs were incorporated into CCMNVs via ultrasound-assisted fusion, yielding stable biomimetic LNPs (BLNPs) characterized by a multilamellar RNA-LNP core surrounded by a nanovesicle shell, as confirmed by Small-Angle X-ray Scattering. While uncoated LNPs showed negligible interaction with either homotypic and heterotypic cells, BLNPs displayed a strong affinity, enabling efficient internalization and RNA transfection, as confirmed by flow cytometry and confocal microscopy. This work provides proof of concept that RNA-LNPs can be effectively integrated into biomimetic carriers to enable dual targeting of tumor and stromal cells. The enhanced selectivity and delivery performance of biomimetic LNPs highlight their

therapeutic potential for overcoming stromal barriers in desmoplastic tumors such as triple negative breast cancer.

Industrial production of 2D materials: safety rules for scale up and standardisation

Francesco Bonaccorso - Invited

BeDimensional SpA, Genova, Italy.

We will present an overview of the challenges facing the industrialization of two-dimensional materials. In the first part of the presentation, we will present our industrial, scalable, reliable, and inexpensive production of 2D materials,^[1-3] involving a balance between final product quality and ease of fabrication. We will show the efficiency of the manufacturing of high-quality 2D materials by wet-jet milling^[2] and, in particular, the path towards industrial production of few layer graphene (FLG) and few layer hexagonal boron nitride (FLh-BN). Afterward, we will provide some insights on the hazard characterization of FLG and FLh-BN and how is critical to ensure safety for both consumers and workers^[4,5]. We will present the cytotoxicity effect of FLG on human monocytes and macrophages^[6]. Finally, we will show the investigation of the microglial response and the therapeutic efficacy of a dual-cell membrane-coated and doxorubicin-loaded FLh-BN, tested on human microglia and Glioblastoma multiforme cells^[7].

References

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Cutting-edge biofunctionalized nanoparticles: a step toward technological innovation

Miriam Colombo - Invited

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Multifunctional nanoparticles are promising tools for different kinds of applications in medicine. Most of the studies with nanoparticles in medical field focused on the development of new innovative tools. One of the greatest challenges in designing nanoparticles functionalized with bioactive molecules to optimize molecular recognition resides in the possibility to finely control the ligand orientation on the nanoparticle surface.

On the other hand, many efforts have been dedicated to the study of different administration routes alternative to the intravenous one. To support the research in new drug delivery nanosystems, in the past few years, I focused my research on the exploration of new innovative approaches for nanoparticle administration that combine the nanoparticle features with the potential of innovative formulations in order to obtain a synergistic effect.

Fragility as a Design Principle in Silica Nanoparticles for Nanomedicine

Alessandro Bertucci - Invited

Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Italy.

Nanoparticles for biomedical applications derive their unique potential from the possibility of integrating multiple functionalities within a single nanoscale platform, including targeting capabilities, tunable morphology and porosity, controlled cargo release, biocompatibility, and programmable degradation. Among these parameters, biodegradability is emerging as a critical design feature to improve safety, tolerability, clearance, and dosing flexibility of nanomedicine formulations. While lipid nanoparticles have recently revolutionized the field of drug delivery, silica-based nanomaterials represent a highly complementary class of systems owing to their structural robustness, synthetic versatility, high loading capacity, and precise control over physicochemical properties. Here, I will discuss the concept of “fragility by design” as a strategy to engineer advanced silica nanomaterials with programmable degradation and bioresponsive behavior. I will present work on hybrid organosilica nanoparticles in which cleavable molecular motifs are directly embedded into the silica framework, transforming otherwise inert silica architectures into dynamic and degradable systems. Breakable organosilica nanocapsules containing disulfide bridges within the shell architecture enable intracellular degradation and triggered release of protein cargos under reducing biological conditions. This concept was subsequently extended to mesoporous silica nanoparticles and other silica nanoarchitectures with controlled dimensions and degradation profiles, including organosilica cages whose structural disassembly can be directly monitored through spectroscopic signatures arising from confinement effects of fluorescent molecular payloads, providing insight into nanoparticle degradation dynamics. Finally, the lecture will focus on a new generation of bioresponsive organosilica nanoparticles in which nucleic acids are integrated as constitutive structural elements of the silica framework. In these systems, biomolecular recognition events, strand displacement reactions, enzymatic degradation, and aptamer-target interactions can directly induce morphological transformations, framework destabilization, and nanoparticle disassembly. By combining sol-gel chemistry with the programmability of supramolecular nucleic acid interactions, these materials introduce a new conceptual framework in which silica nanoparticles evolve from passive carriers into adaptive and stimuli-responsive systems capable of interacting dynamically with biological environments.

CRISPR-Cas Detection of Protein Biomarkers Powered by DNA Nanotechnology

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CRISPR-Cas systems have revolutionized molecular diagnostics by enabling ultrasensitive detection of nucleic acids through programmable enzymatic signal amplification. Extending these technologies toward clinically relevant non-nucleic-acid biomarkers, however, requires innovative strategies capable of translating protein recognition events into nucleic acid signals compatible with CRISPR processing. In this context, DNA nanotechnology offers a powerful molecular engineering framework to construct dynamic, programmable transduction mechanisms that bridge proteins and CRISPR enzymes. I will present a series of DNA-based molecular architectures developed to enable CRISPR-Cas sensing of diverse classes of protein biomarkers, including proteases, antibodies, and transcription factors. I will discuss a synthetic protein-to-DNA input exchange strategy for activity-based detection of matrix metalloproteinase 2 (MMP2), a clinically relevant cancer-associated protease biomarker. In this system, peptide-PNA chemical translators convert proteolytic cleavage events into nucleic acid

activators for CRISPR-Cas12a, enabling amplified fluorescence detection in the low picomolar range. I will then present the platform MARPLE (Modular Antibody Recognition via Proximity-triggered Linker Exchange), a CRISPR-Cas13 platform for ultrasensitive antibody detection based on antibody-induced proximity effects and dynamic strand displacement reactions. In MARPLE, antibody binding brings antigen-functionalized DNA strands into close proximity, triggering release of an RNA activator for Cas13-mediated collateral cleavage amplification. The modular architecture enables femtomolar detection of clinically relevant antibodies, including anti-MUC1 autoantibodies, anti-viral antibodies, and therapeutic monoclonal antibodies, while operating under isothermal one-pot conditions even in complex matrices such as human serum. Finally, I will describe the development of synthetic CRISPR networks regulated by transcription factors through engineered structure-switching DNA translators. These dynamic DNA systems convert transcription factor binding into programmable activation of CRISPR-Cas12a, enabling artificial biomolecular communication pathways between proteins, nucleic acids, and CRISPR enzymes. Overall, the lecture will highlight how dynamic DNA nanotechnology can function as a programmable molecular interface between protein biomarkers and CRISPR systems, opening new opportunities for precision diagnostics in oncology

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Radiation-induced cell damage enhanced by high-Z nanomaterials at low X-ray dose

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X-rays are non-selective cytotoxic agents, damaging both tumor and healthy tissues. Thus, minimizing the dose delivered outside the tumor volume is essential to reduce normal tissue toxicity and the risk of secondary cancers in radiotherapy.

X-rays interact with matter through ionization and excitation processes. In biological tissues, radiation damage arises from both direct effects on biomolecules, such as bond breaking and structural rearrangements, and indirect effects mediated by reactive oxygen species (ROS) generated by water radiolysis. Although radiation interactions are not intrinsically targeted to specific biomolecules, DNA represents the most critical cellular target. Double-strand breaks (DSBs) and clustered damage are among the most deleterious DNA lesions. Due to their low linear energy transfer (LET), X-rays produce relatively few complex DNA lesions.

A promising strategy to reduce healthy tissue toxicity is the internalization of high-Z nanomaterials by cancer cells. These materials enhance local photoelectric interactions and secondary electron generation, leading to increased complex biomolecular damage and localized energy deposition. Here, we present Monte Carlo simulations of dose enhancement induced by WS₂ nanosheets decorated with Au nanoparticles.

Synthesis of novel multicomponent hybrid nanosystems for cancer treatment under low energy X-ray irradiation

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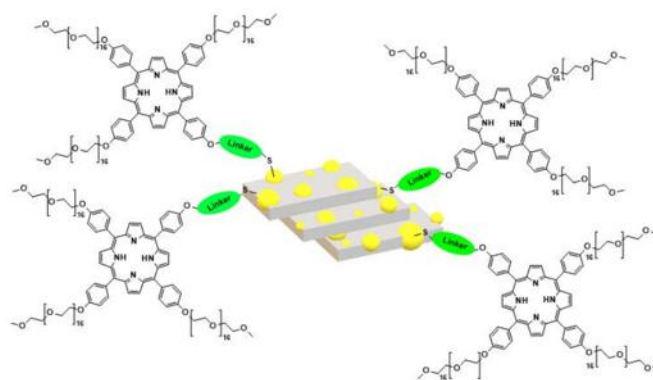
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Cancer is one of the leading causes of death in western countries, driving the continuous pursuit of innovative therapeutic strategies. Over the last decades, the rapid development of nanotechnology has also affected the medical field. Nanomedicine is a recent, interdisciplinary science which covers a wide range of applications, including imaging, drug delivery, tissue engineering, theranostics. Two-dimensional (2D) nanomaterials such as transition metal dichalcogenides have attracted considerable interest in cancer therapy. However, traditional X-ray-based radiotherapy often relies on high-energy X-ray beams (1-10 MeV) which may lead to unwanted damage to the surrounding healthy tissues. Here, we present the synthesis of novel multicomponent nanosystems (NS) to boost low energy (40 KeV) X-ray irradiation mediated cancer cell killing. The multicomponent hybrid NS consist of 2D nanocrystals of WS₂ functionalized with Au nanoparticles and conjugated with THPP porphyrin with PEG based linkers (WS₂@Au@THPP). Lipophilic THPP was conveniently derivatized to make it soluble in water and able to bind Au nanoparticles, giving water dispersible NSs. These were completely characterized by UV-Vis, fluorescence, Raman, ICP-OES spectroscopies and TEM microscopy. The NS stability in various media was proven, and its ability to produce ROS under X-ray excitation was demonstrated using DPBF as a chemical probe. In vitro experiments evidenced the activity of the NS in killing HT29 cancer cells.



Multicomponent nanosystem activated by low-dose irradiation in human cancer cells in 2D monolayers and 3D spheroids models

Gloria Cenci

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Cancer remains one of the leading causes of mortality worldwide, and conventional treatments such as photodynamic therapy (PDT) and radiotherapy often suffer from limited efficacy and significant side effects. To address these challenges, we developed a biocompatible hybrid nanosystem composed of

two dimensional tungsten disulfide (WS₂) nanoflakes grafted with Au nanoparticles and functionalized with a porphyrin derivative. This platform was designed as a radiosensitizer capable of being activated by low energy, low dose X ray irradiation to selectively enhance cancer cell killing. The nanosystem was evaluated in vitro using HT 29 human colorectal cancer cells in both 2D monolayers and 3D spheroid models. In conventional 2D culture, we assessed cellular internalization and therapeutic response following low dose irradiation (2 Gy, 40 keV) through analyses of gene expression (SOD1, HMOX1, BAX, and BCL2), cell cycle modulation, apoptosis induction, and clonogenic survival. In 3D spheroids, treatment efficacy was monitored by quantifying spheroid area reduction over time, as well as apoptosis and cell proliferation (Ki-67 staining), while nanosystem internalization was determined using two-photon excitation (TPE) microscopy. Furthermore, preliminary results using 2D cultures of the triple negative human breast cancer cell line MDA MB 231 confirmed the broader applicability of the approach. Overall, our findings demonstrate the promising potential of this novel hybrid nanosystem as an effective radiosensitizer for low dose radiotherapy.

Using nature to battle cancer

María C. Rodríguez-Argüelles - Invited

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Nature provides us with excellent tools for obtaining nanomaterials that can be used in different fields such as industry, environmental, agriculture, energy and medicine. In addition, to the simplicity and cost-effectiveness of using natural resources, these materials are affordable and environmentally friendly, allowing us to combine their intrinsic properties with those of the nanomaterials derived from them. Our research group has focused on the natural resources available in our region, such as shellfish, algae, and native plants. After obtaining and characterizing these nanomaterials, we evaluated their activity against different types of tumors and microorganisms.

Title Synthesis of Metal Nanoparticles by naturally-derived compounds for Photodynamic Therapy applications

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Photodynamic therapy (PDT) represents a minimally invasive and highly selective strategy for cancer treatment, based on the activation of photosensitizing agents by light to generate cytotoxic reactive oxygen species (ROS) capable of inducing cell death. Among the various classes of photosensitizers explored, naturally-derived compounds have gained increasing attention due to their intrinsic bioactivity, favorable safety profiles, and structural diversity. Natural photosensitizers can themselves act as reducing and capping agents in the synthesis of metal nanoparticles, enabling the development of multifunctional systems in which the photosensitizer remains associated with the nanoparticle surface and retains its photodynamic activity. The biological efficacy of these nanoparticles, developed by our collaborators, was assessed across multiple tumor cell lines. Dark viability assays showed that Hyp-NPs can reduce cancer cell survival in a concentration-dependent manner, depending on the cell line. Notably, some formulations did not show toxicity at the concentrations used for the assay. PDT effects were evaluated in 2D cell cultures, where metal nanoparticles showed an enhanced photodynamic response compared to free Hyp, attributed to the localized surface plasmon resonance

(LSPR) effect. However, only one type of nanoparticle and a limited number of tumor cell lines showed a significant response to light irradiation. PDT efficacy was further evaluated on three-dimensional multicellular tumor spheroids. Quantitative analysis of spheroid area over time revealed a significant reduction in growth in treated and irradiated spheroids compared to non-irradiated controls, demonstrating the ability of Hyp-NPs to penetrate and exert photodynamic effects within a more physiologically relevant tumor model. Finally, preliminary data on the applicability of this platform to other photosensitizers will be presented, highlighting its potential as a versatile strategy for novel PDT-based nanomedicines

Lipid Nanoformulations for Photodynamic- and Radiotherapy for Pancreatic Cancer

Måns Broekgaarden - Invited

French National Institute for Health and Medical Research (Inserm) and Institute for Advanced Biosciences, Grenoble-Alpes University, France.

Increasing the permeability of the pancreatic cancer stroma is of prime importance to increase treatment efficacies, yet existing strategies have been found unsafe or ineffective in clinical trials. Photodynamic priming (PDP) is an emerging modality that uses light-activated dyes to eradicate tumor- and stromal cells, denature the extracellular matrix, and increase vascular permeability with high precision. This has been shown to dramatically increase the efficacy of neoadjuvant chemotherapeutics. In this presentation, our work on elucidating the PDP kinetics and its exploitation to improve chemotherapy efficacies will be discussed. Moreover, to overcome the limited penetration depth of light in tissue, new strategies to prime the cancer microenvironment with radiotherapy-responsive nanomaterials will be discussed.

Graphene and other advanced materials: focus on inflammation

Bengt Fadeel - Invited

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Understanding the interactions of graphene and other advanced materials with the immune system is of key importance for the clinical implementation of such materials. This lecture will provide examples of studies conducted in the EU-funded Graphene Flagship on immune interactions of graphene-based materials such as graphene oxide, focusing on macrophages and neutrophils, storm troopers of the innate immune system.

Biological impact of multicomponent nanosystems using primary human macrophages: evidence for biotransformation in living

Pragati More

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Two-dimensional (2D) nanomaterials – including graphene family materials, transition metal dichalcogenides (TMDs), and others – have attracted considerable interest for their unique physicochemical properties and promising applications. However, a thorough understanding of their interactions with the immune system is required for clinical translation. Here, we performed a comprehensive evaluation of novel multicomponent nanosystems (NS) comprised of WS₂ nanosheets conjugated with gold nanoparticles which, in turn, were decorated with polyethylene glycol to improve

dispersibility of the NS in aqueous media. Biocompatibility was assessed using primary human peripheral blood mononuclear cells (PBMCs) and human monocyte-derived macrophages (HMDMs). Cellular uptake was evaluated by transmission electron microscopy (TEM) and inductively coupled plasma mass spectrometry (ICP-MS). No cytotoxicity was observed despite evidence of cellular uptake. We also investigated whether the NS affected M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophage phenotypes based on flow cytometry of the surface markers CD86 and CD206 and RT-PCR analysis of NOS2 and ARG1 mRNA expression. NS exposure triggered measurable alterations in polarization markers. Finally, biodegradation was addressed using both acellular and cellular model systems. In the presence of the peroxynitrite donor SIN-1 and artificial lysosomal fluid (ALF) (pH 4.5), the WS₂ nanosheets displayed a time-dependent reorganization or transformation, as evidenced by Raman spectroscopy and transmission electron microscopy-energy dispersive X-ray spectroscopy (TEM-EDX). Moreover, a similar transformation behaviour was noted in M1 and M2 macrophages, and pharmacological inhibition studies indicated that this was mediated by lysosomal acidification, consistent with the lysosomal localization in macrophages. Taken together, these findings have demonstrated the biocompatibility of novel multicomponent NS and the propensity of these materials to undergo biotransformation, highlighting their potential application as safe platforms for cancer therapy.

The evolution of radiation therapy: where we stand now.

Salem Billan - Invited

The Joseph Fishman Oncology Centre, Rambam Health Care Campus, Haifa, Affiliated to the Rappaport Faculty of Medicine, Israel Institute of Technology-Technion, Haifa.

Radiation oncology has become a central component of modern multidisciplinary cancer care, integrating advanced technology with precise clinical decision-making. This presentation reviews the expanding role of radiotherapy across a broad range of clinical settings, including definitive organ-preserving treatment, neoadjuvant and adjuvant therapy, palliative symptom control, and stereotactic ablative treatment for selected primary tumors and metastatic lesions. The therapeutic effect of radiotherapy is primarily mediated by ionizing radiation-induced DNA damage, resulting in tumor cell death while aiming to minimize injury to surrounding normal tissues. Over the past decades, major technological advances have transformed radiation delivery from simple two-dimensional techniques to CT-based three-dimensional planning, IMRT, VMAT, stereotactic radiosurgery, stereotactic body radiotherapy, image-guided radiotherapy, adaptive radiotherapy, and proton therapy. These developments have substantially improved dose accuracy, treatment reproducibility, organ-at-risk sparing, and daily treatment verification. Importantly, advances in imaging, motion management, dose modulation, and adaptive planning have translated into better toxicity control, reduced exposure of healthy tissues, safer dose escalation, and improved quality of life for patients. Artificial intelligence-based auto-contouring is also emerging as an important tool to shorten planning time, enhance consistency, reduce inter-observer variability, and support adaptive workflows. Finally, radiotherapy is increasingly recognized as a biologically active treatment that may interact with systemic therapies and immunotherapy. Emerging applications, including stereotactic arrhythmia radio-ablation, further demonstrate the expanding therapeutic potential of radiation technology. Overall, modern radiotherapy represents far more than a local treatment modality; it is a precise, safe, biologically active, and highly innovative pillar of contemporary oncology, with the potential to improve tumor control, reduce treatment-related morbidity, and help reshape the future of cancer care.

Optimal X-ray source peak voltage for treatment of tungsten disulfide based hybrid nanoparticle sensitized mouse tumor

Jakab Árpád

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Identifying irradiation parameters that maximize dose deposition within the tumor is essential for optimizing in vivo study design and reducing the number of mice required for experimental validation. Here, we use Monte Carlo simulations performed with GATE 9, a Geant4-based particle transport platform, to evaluate dose deposition in the tumor volume for the spectra of a reflection-type tungsten-anode X-ray source equipped with a 1 mm aluminum filter and operated at peak voltages of 50, 100, and 320 kV. The mouse morphology, anatomical geometry, and X-ray attenuation properties are derived from CT images. We aim to determine the optimal compromise between two competing requirements: (i) maximizing dose enhancement, defined as the increase in absorbed dose in the presence of nanoparticle-mediated radiosensitization relative to irradiation without nanoparticles, and (ii) delivering a therapeutically relevant dose within a limited irradiation time. The latter constraint is particularly important for in vivo experiments, where exposure durations must be minimized to reduce anesthesia-related stress and harm to the animals. As shown in the presentation, these two objectives favor different X-ray source settings. For near-surface tumor regions at depths of approximately 0–2 cm, the largest dose enhancement is expected for X-ray photon energies below 100 keV. In contrast, assuming identical tube current, operation at 320 kV provides the highest absolute delivered dose. Thus, the optimal irradiation protocol must balance radiosensitization-driven dose enhancement against practical constraints on dose rate, treatment duration, and normal tissue damage limitations.

X-Ray-Triggered Luminescence in Transition Metal-Doped Spinel Nanocrystals: Toward Precision Nanomedicine Applications

Dávid Beke - Invited

HUN-REN Wigner Research Centre for Physics, Budapest, Hungary.

X-ray-triggered optical luminescence offers a compelling pathway for deep-tissue bioimaging, dosimetry, and theranostics, as X-rays penetrate biological tissue far more effectively than UV or visible light. Here we present a systematic investigation of two spinel-family nanocrystal systems — Mn^{2+} -doped ZnGa_2O_4 (ZGO:Mn) and $\text{Mn}^{2+}/\text{Cr}^{3+}$ co-doped ZnAl_2O_4 (ZAO:Mn,Cr) — engineered for optimized X-ray excited optical luminescence (XEOL) through precise control of host composition and dopant interactions.

ZGO:Mn nanocrystals were synthesized hydrothermally at 230 °C with systematically varied Zn/Ga precursor ratios, followed by post-annealing treatments up to 1100 °C. We demonstrate that the Zn/Ga molar ratio profoundly governs particle morphology, phase purity, and emission efficiency, with an optimal ratio of approximately 1.1 and an annealing temperature of 600 °C yielding peak XEOL performance. Crucially, electron paramagnetic resonance (EPR) spectroscopy reveals that the local crystal field environment of Mn^{2+} — rather than its bulk concentration — is the primary determinant of luminescent output, with XEOL and photoluminescence (PL) showing distinct optimal synthesis windows due to their different excitation mechanisms.

In the ZAO:Mn,Cr system, Mn^{2+} (tetrahedral sites) acts as an energy sensitizer for Cr^{3+} (octahedral sites), enhancing Cr^{3+} XEOL and PL emission up to an optimal Mn concentration, beyond which concentration quenching dominates. Combined EPR and optical studies uncover a previously unreported magnetic (spin-exchange) interaction between Mn^{2+} and Cr^{3+} centers, manifesting as systematic shifts in the Cr^{3+} low-field EPR resonance, linewidth modifications, and redistribution of zero-field splitting environments — effects that collectively suppress non-radiative relaxation and amplify radiative recombination. Together, these results establish that host-composition engineering and inter-dopant magnetic coupling are powerful, underexplored levers for tuning X-ray-to-photon transduction efficiency in spinel nanophosphors. The multimodal (green, red, NIR) emission profiles and the sensitivity of these materials to X-ray excitation make them promising platforms for next-generation radioluminescent nanomedicines.

Multi-Functional 2D Nano-Systems for Precision Oncotherapy Triggered by Low Energy X-Rays

Yasmin Habib

Technion – Israel Institute of Technology, Haifa, Israel.

Radiotherapy (RT) remains a cornerstone of cancer treatment, however, its efficacy is often limited by damage to surrounding healthy tissue and by intrinsic tumor radioresistance. In this work, we investigate a multifunctional nanosystem (NS) composed of two-dimensional tungsten disulfide (WS_2) nanosheets decorated with gold nanoparticles (AuNPs) for low-energy X-ray-triggered radiosensitization. The system integrates principles from radiation physics, nanomaterials engineering, and cancer biology. Its high-Z components are designed to enhance radiation-induced reactive oxygen species (ROS) generation through increased local X-ray energy absorption and secondary electron emission. Cell-free ROS quantification assays demonstrated enhanced ROS generation under low-energy X-ray irradiation. In vitro studies using Panc02 cells, a pancreatic ductal adenocarcinoma (PDAC) cell line, further showed enhanced radiation-induced cytotoxicity and reduced clonogenic survival following combined NS and X-ray treatment. Cellular interaction studies revealed efficient and concentration-dependent NS uptake using live-cell imaging and flow cytometry approaches. Current work focuses on preclinical in vivo evaluation of treatment efficacy, tumor microenvironment modulation, and safety in PDAC-bearing mice, using PDAC as a model of highly radioresistant disease.

Multi-Functional 2D Nano-Systems for Precision Oncotherapy Triggered by Low Energy X-Rays

Xu Jing

Department of Microbiology, Tumor and Cell Biology, Biomedicum, Karolinska Institutet, Stockholm, Sweden.

We evaluated nanovehicle (NV)-assisted radiotherapy in metastatic cancer models within the PERSEUS project. We demonstrate that NVs accumulate primarily in liver and lung and exhibit no acute toxicity. Using both spontaneous and experimental metastasis models, combination treatment with NVs and low-dose X-ray irradiation significantly reduced metastatic burden across models. Mechanistic analysis suggests a dual effect, involving both direct tumor suppression and immune microenvironment remodeling, including increased macrophage infiltration especially CD86 recruitment. These results support NV-assisted radiotherapy as a promising strategy for targeting metastatic disease.

Unique Features and Collateral Adverse Effects of mRNA-LNP Nanoparticles: Focus on COVID-19 Vaccines and Cancer

János Szebeni - Invited

Nanomedicine Research and Education Center, Department of Clinical Pathophysiology, Semmelweis University, Budapest, Hungary

Reassessment of the risk-benefit balance of LNP-based mRNA vaccines, including Pfizer's Comirnaty and Moderna's Spikevax, is ongoing, partly because of the broader spectrum and increased incidence of severe adverse events (SAEs). Although such events are rare, the enormous scale of global vaccination has led to recognition of "post-vaccination syndrome," encompassing a wide variety of acute and chronic diseases temporally associated with mRNA vaccination. This presentation will examine the unique features of mRNA-LNPs and their plausible links to post-vaccination syndrome, including prolonged or uncontrolled spike-protein expression, chemically modified and stabilized mRNA, spike-associated toxicity, LNP-driven innate immune activation, off-target transfection, PEG-related immunogenicity, complement activation, GC enrichment, prefusion stabilization, and possible contaminants. With a focus on cancer, the presentation will discuss the controversial concept of "turbo cancer," referring to unusually rapid cancer progression or recurrence potentially associated with immune dysregulation after immunization with mRNA vaccines. Although a causal relationship has not been established, proposed mechanisms include inflammatory signaling and impaired immune surveillance, which could contribute to tumor acceleration in susceptible individuals. Another mRNA-LNP-relevant issue in cancer therapy is the in vivo generation of chimeric antigen receptor (CAR)-modified T cells. Conventional CAR-T therapy involves ex vivo reprogramming of T cells from tolerogenic to tumor-killing phenotypes, but this personalized procedure is not widely available. The new LNP-based approaches aim to restore cytotoxicity by transfecting T cells in vivo with mRNA-LNPs encoding CAR constructs. However, despite encouraging clinical data in hematologic malignancies and solid tumors, major challenges associated with mRNA-LNP technology remain. The lessons learned from COVID-19 mRNA vaccines may help clarify the alleged phenomenon of turbo cancer and support the development of safer and more effective mRNA-LNP-based anticancer therapies.