NanoScience Research Cluster - Proposal

Main objectives

The following proposal aims the establishment of a research cluster connecting Palestinian and German scientists in the interdisciplinary field of nanosciences. Nanosciences have gained international visibility and become a leading research focus in the last decades. The research interest of nanoparticles is intense as a result of the emergence and use of newly acquired size-dependent properties, including super-paramagnetism of magnetic materials, surface redox active properties or controllable colloidal behaviors (aggregation, dispersion, diffusion, and sorption). These nanoscale properties can be introduced into uncountable new nanomaterials justifying the application of nanoparticles in a wide range of socially and economically relevant fields.

Therefore, the cluster group of NanoSciences aims to focus on the fundamental aspects, fabrication, characterization, and applications of nanomaterials on industrial and biomedical fields.

Objectives of the NanoScience cluster include:

- development of novel nanoparticles
- characterization of those particles in a tight collaboration between partners
- tight and repeated interactions between experimental and theoretical scientists
- use of developed tools in medically-relevant scenarios

Reaching these goals requires a new generation of researchers highly skilled both in (i) cutting-edge experimental techniques and (ii) state-of-the-art theoretical methods for developing novel tools and strategies in the field of nanotechnology. The NanoScience cluster will address these challenges by means of highly interdisciplinary research through a dedicated team of chemists that will develop innovative nanoparticles and nanomaterials, experimental biologists who will collect data from living specimens and theoretical physicists and mathematicians to interpret and integrate data into models.

Research network

Our main objective is to bring scientists from Palestine and Germany into contact and establish a network of researchers with a permanent exchange of current knowledge of nanosciences. Our special aim is to interconnect complemental research groups, e.g. groups focusing on nanoparticle fabrication with partners specialized in one of the complementary fields e.g. material characterization or application. We believe that such research alliances with joined resources and knowledge create efficiencies to deliver great benefits to our future research. The cluster network is presented in Figure 1.

Continuous interdisciplinary feedback and collaboration will be essential for achievements with high relevance. In the early phase, the cluster plans to use the networking platforms provided by PGSB (e.g. workshops). Simultaneously, we aim to establish an internet platform for a permanent information exchange, as well as a network level staff exchange. The joint supervision of students introduced by PGSB also will tighten the scientific network.

The NanoScience cluster will provide excellent career prospects to the fellows due to their combined training in an interdisciplinary program. With this approach we aim to shape a new generation of young researchers that will no longer be hampered by the traditional boundaries of disciplines shaped centuries ago.

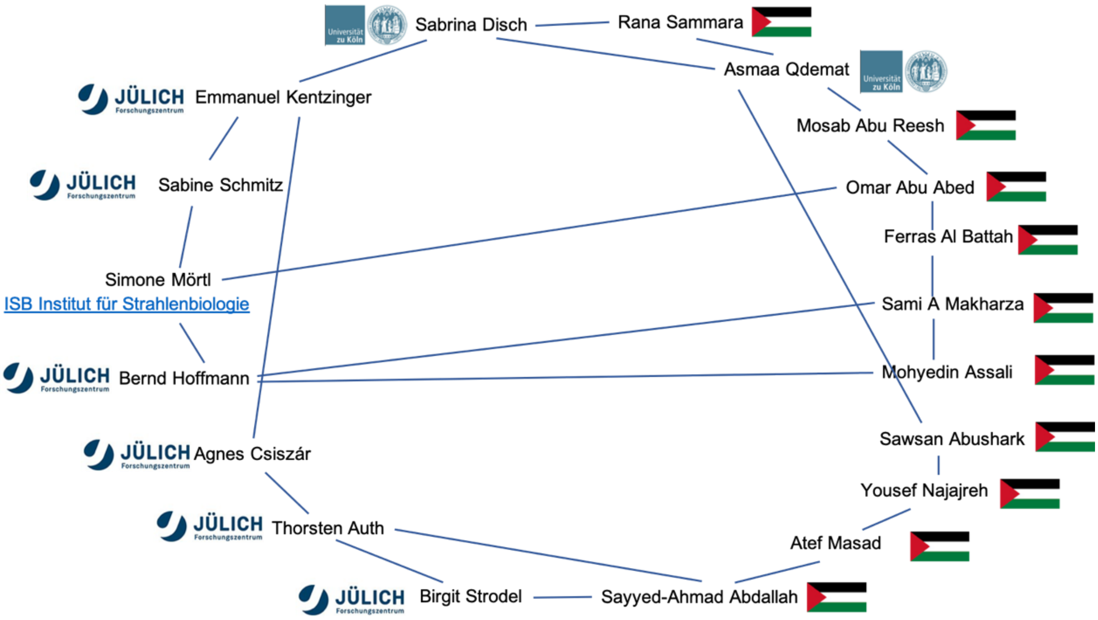

Figure 1: NanoScience cluster network

Research infrastructure

Nanoscience applications are highly relevant in several medical and industrial fields. In the last decades Palestinian scientists recognized the needs of such applications resulting in permanently growing research fields of nanotechnology. Several scientific groups have been specialized on nanoparticle and nanomaterial fabrication as well as their applications with special focus on medical therapy (cancer, radiation, Alzheimer, etc.) and agriculture (crop protection) (Table 1).

In order to fully understand the use and behavior of nanoparticles, it is necessary to characterize newly emerging materials by an array of physicochemical methods. The most common techniques will be used for structural characterization are **microscopy-based techniques** (e.g. **Transmission Electron Microscopy (TEM), High Resolution Transmission Electron Microscopy (HRTEM), Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM)**) which provide information on the size, morphology and crystal structure of the nanomaterials. **X-ray based techniques** such **as X-ray diffraction(XRD) or Small Angle X-ray Scattering (SAXS)** technique characterizing the crystalline structure, nature of the phase, lattice parameters and crystalline grain size or the particle size, size distribution, and shape, respectively. Furthermore, **Dynamic Light scattering (DLS)** technique will be used to access the hydrodynamic size and for detection of agglomerates. The characterization techniques employed to evaluate the magnetic properties of such nanoparticles are: **Superconducting quantum interference device magnetometry (SQUID)** which is a tool for measuring the magnetic properties of nanoscale materials, **Vibrating sample magnetometry (VSM)** a method used to record the M–H loops for magnetic nanomaterials and obtain parameters such as saturation magnetization (MS) and remanence magnetization (MR). Additionally, **polarized small angle neutron scattering technique (SANS)** will be applied to investigate the internal magnetic structure.

Palestinian researcher do not have any access to the above mentioned techniques therefore the NanoScience research cluster aims to provide such experimental setups. The associated neutron and X-ray scattering experiments will be performed at European large-scale facilities including **ILL in Grenoble, France**, and **MLZ in Garching, Germany** for neutron scattering, as well as **Forschungszentrum Jülich GmbH in Jülich, Germany** for X-ray experiments. For the longer term, the X-ray experiments can be conducted at the **Synchrotron-Light for Experimental Science and Applications in the Middle East (SESAME).**

Table 1: Participants of the NanoScience Cluster contributing to fabrication, characterization or application of nanoaprticles and nanomaterials.

Nanoparticle fabrication		Nanoparticle characterization		Nanoparticle application	
Participant	**NP**	**Participant**	**Methods**	**Participant**	**Field**
Abu Abed, Omar	Exosomes	Abdallah, Sayed-Ahmud	Advanced simulation	Abuabed, Omar	Cancer therapy
Abu Reesh, Mosab	Exosomes	Abusharkh, Sawsan	UV/VIS, FTIR spectroscopy	Al Battah, Ferras	Cancer therapy Neuronal networks
Abusharkh, Sawsan	Lipid NP Magnetic NP	Auth, Thorsten	Advanced simulation	Aliwani, Saeb	Cancer therapy
Assali, Mohyeddin	Carbon nanotubes	Csiszár, Agnes	Light microscopy Thermal analysis Light scattering	Hoffmann, Bernd	Neuronal networks
Csiszár, Agnes	Lipid NP	Disch, Sabrina	X-ray and neutron scattering	Makharza, Sami A	Cancer therapy
Disch, Sabrina	Magnetic NP	Kentzinger, Emmanuel	X-ray and neutron scattering	Masad, Atef	Cancer therapy
Najajreh, Yousef	Drugs to load into NP	Strodel, Birgit	Advanced simulation	Mörtel, Simone	Radiation therapy
Schmitz, Sabine	Exosomes	Qdemat, Asmaa	X-ray and neutron scattering	Samara, Rana	Agriculture
Qdemat, Asmaa	Magnetic NP Silica NP			Schmitz, Sabine	Radiation therapy

Current activities

The NanoScience cluster aims to integrate current research projects supported by the PGSB into his program (Table 2). Within the boundaries of running collaborations relevant for this cluster, two master students successfully finished their work until 2019. Four students started with their Ph.D. thesis in 2018 and 2019. Simultaneously, new project applications have been offered.

Table 2: NanoScience cluster relevant research projects currently supported by PGSB

Project title	Student	Time period	Supervisors
Development of novel fluorescent platinum(IV) derivatives and their delivery by fusogenic liposomes as nanocarriers into cancer cells	Alsharif, Sara (Ph.D.)	Oct. 2019 – Sept. 2022	Csiszár, Agnes; Najajreh, Yousef
Generation of neuronal tissue models in 3D for mechanobiological analysis	Ardah, Mahmud (MSc)	Oct.2018 – Apr. 2019	Al Battah Feraz; Hoffmann, Bernd
The simulation of amyloid aggregation under in vivo conditions	Fatafta, Hebah (Ph.D.)	July 2018 – June 2021	Abdallah, Sayyed-Ahmad; Strodel, Birgit
The simulation of amyloid aggregation under in vivo conditions	Khaled, Mohamed (Ph.D.)	Dec. 2019 – Nov. 2022	Abdallah, Sayyed-Ahmad; Strodel, Birgit
Nanoparticle-membrane interaction: the effect of electric charge	Othman, Sameh (MSc)	Oct.2017 – Sept. 2018	Abdallah, Sayyed-Ahmad; Auth, Thorsten
Generation of neuronal tissue models in 3D for mechanobiological analysis	Tarazi, Samar (Ph.D.)	Oct. 2018 – Sept.. 2021	Al Battah Feraz; Hoffmann, Bernd

Future activities

In the early phase, five scientific work packages address the major research challenge:

- Exosomes in medical applications
- Lipid nanoparticles in cancer therapy
- Nanoparticles in agricultural applications
- Magnetic nanoparticles in cancer therapy
- Carbon nanotubes in neuronal networks

Based on our first achievements, we also aim to develop new projects and extend our network in the middle phase of our working period.

A short summary of the individual work packages is given below:

Exosomes - a promising tool at the interface between basic research and applied research in a clinical context

Current research approaches reveal the great importance of exosomes due to their role in cell-cell communication for tumor, neuro- and radiation biology. We are proposing the establishment of a research cluster based on future collaborations with scientists working on exosomes.

Understanding how exosomes are composed and what components are contained in them offers numerous starting points for basic and applied research. It is known that they contain nucleic acids, fats and proteins and that they are taken up by cells (recipient cells), interact with them and as a consequence, change their phenotype. This knowledge makes exosomes a promising tool for radiation and neurobiology. The latter focuses on the analysis of the differentiation process of neural precursor cells, which can be influenced by exosomes. In radiation biology, the modulation of the radiation response to high and low doses of ionizing radiation is the subject of current research. The fact that exosomes can be both - secreted by tumor cells and taken up by them - offers new approaches for cancer therapy. Theranostic concepts are in the focus of attention based on the fact that exosomes can be used as vehicles for the introduction of anti-cancer drugs. Current considerations include the use of exosomes as a tool for the CRISPR/CAS system for genome editing in pancreatic or other cancer cells. Labelling of exosomes with fluorescent dyes and radioisotopes is one way to check whether the modified exosomes have found their target cells and what the distribution pattern and therapeutic response is. These questions will be analyzed by *in vitro* cell culture models (2D and 3D) as well as by *in vivo* studies. A decisive factor in these studies is the prior characterization of the exosomes in order to be able to chemically/pharmacologically modify them and to use them as a tool that fits the respective problem as precisely as possible.

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Lipid nanoparticles in cancer therapy

Cancer is one of the major causes of mortality today. More than 10 million people worldwide are diagnosed with this disease annually. Despite all invested efforts and high therapy costs, a limited number of cancers can be cured. Unfortunately, even for these cases patients generally experience severe side effects from the treatment. The efficient and targeted delivery of cancer therapeutics holds a great promise to address this issue. However, it is still a major pharmacological challenge.

We are proposing to establish a research cluster that aims to **develop novel cancer therapeutics** with improved efficiency and reduced toxicities. This will be achieved by utilizing lipid nanoparticles, called liposomes, which are increasingly used for these purposes due to their high bioavailability and low toxicity. This research cluster will also work on **developing novel therapeutic agents such as platinum(IV) derivatives as therapeutic agents for cancer treatment** that will be synthesized at the **Najajreh lab**. **Liposomes will be loaded with new platinum(IV) derivatives** at the **Csiszár lab** and **characterized at the Disch/Kenzinger lab**. In addition, we will characterize the uptake of lipid nanoparticles with various model-membrane systems and their delivery efficiency against different cancer cell lines.

The aforementioned experiments will be complemented by **theoretical calculations and computer simulations on the interaction of lipid nanoparticles with model membranes** using continuum models and molecular simulations that include oncogenic proteins. These calculations will be carried out by **Auth, Strodel and Sayyed-Ahmad labs** to predict the nanoparticle behavior in a biological environment.

In medical treatments, the intravenous administration of the liposomes is required where the liposomes inevitably interact with blood serum proteins building temporary complexes. Therefore, the third aim of this work is to **identify the principal molecular interactions**, structural, and functional properties **of the blood serum as a carrier for the**

drug-loaded lipid nanoparticles using different spectroscopic methods at the **Abushark lab** and **the Massad lab**.

Based on our in vitro results, the **in vivo analysis of the drug-loaded lipid nanoparticles** and the identification of the histological changes before and after treatment will be carried out at the **Massad lab** and the **Aliwani lab** to verify the improvement of the new treatment in mammalian organisms.

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Applications of nanoparticles in agriculture and in disease management

The most existing plant disease managements mainly depend on toxic pesticides being potentially harmful to humans and the environment. Moreover, the world demand for fertilizer and pesticides was forecast to increase. Therefore, there is an urgent need to tackle the excessive usage of pesticides and fertilizers by finding alternatives to current deployments. The above mentioned challenges can be overcome using Nanotechnology. Nanoparticles (NP) can be used as precise and targeted delivery vehicles for pesticides, herbicides or fertilizers. Their application offers advantages like increased solubility, improved shelf-life, and reduced toxicity of poorly water-soluble pesticides.

The main goal of this research proposal is to replace synthetic pesticides in **crop protection** using different alternative methods. Either **local indigenous microbial pesticides (entomopathogenic fungi, bacteria and viruses)** or **indigenous essential oils and plant extracts are proposed against insect and plant diseases**. Moreover, these methods might also be applied to control animal and human-related diseases.

The proposed research focuses on **the fabrication of inexpensive silica nanoparticles at the Disch/Qdemat lab** optimizing their physicochemical properties (size, porosity, surface charge, chemical activity, etc). The **loading of NP with bio-agents** such as fungi or their metabolites will be carried out **at the Samara lab**. We suppose that the new NPs will enhance the efficacy of the bio-agents due to higher surface area, sustained controlled release, induced systemic activity, and lower eco-toxicity due to higher solubility in water. The **bio-agent loaded NP will be tested at the Samara lab**.

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Magnetic nanoparticles for cancer therapy

One of the main challenges in the field of cancer therapy is to find efficient approaches in order to reduce the side effects of traditional cancer therapy and diagnosis. Magnetic nanoparticles (MNPs) offer a promising alternative for these purposes.

MNPs represent an important class of functional nanoparticles and have extensively been investigated for their interesting nanoscale magnetism and their demonstrated marked progress in technological applications. Several MNP technologies are routinely applied to biological systems with diagnostic or therapeutic purposes, such as magnetic resonance imaging (MRI), a technique that uses magnetic moments of the nanoparticles as a disturbance of the proton resonance to obtain images due to their magnetism. Moreover, their intrinsic magnetic property makes them the most promising nanomaterial to be used as contrast agents for magnetic resonance imaging (MRI) and induced magnetic hyperthermia. MNPs are a kind of intelligent nanomagnetic material since they absorb the heat generated by the electromagnetic wave in the alternating magnetic field. Also, they can convert electromagnetic energy into heat. Therefore, **the most popular application for MNPs is the destruction of tumor cells by heating them to their apoptosis threshold**. The most frequently used **MNPs in cancer diagnosis are superparamagnetic iron oxide nanoparticles (SPIONs)**, in particular magnetite (Fe_3O_4) and its oxidized form maghemite (γ-Fe_2O_3) due to their biocompatibility, low toxicity and cost and facile preparation.

The main aim of the proposed project is to utilize unique SPIONs to **pioneer a novel SPION-hybrid theranostic system to overcome the resistance mechanism of cancer cells to the available anticancer therapeutics.** Also, the proposed nanocarriers will target solid tumors, localize, and release drugs in sufficient amounts with minimal access to other sites. The project will **comprise of synthesis of SPIONs and their physical characterization, the development of the hybrid system, in vitro characterization by using (2D and 3D) cancer cell cultures, and animal studies.**

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Carbon nanotubes in neuronal networks

Neurodegenerative diseases are among the most complex diseases of the present day that are related to the progressive loss of nerve cells and their functions. Among these diseases are Alzheimer's disease, Parkinson's disease, brain stroke and others. There are huge efforts to understand underlying mechanisms to ultimately restore the functions of the injured neurons in these diseases. In order to achieve these goals, completely novel cell culture systems are necessary, which enable the best possible mimicking of neuronal systems.

In the latest years, the field of neural engineering has been energized by the design and fabrication of carbon nanomaterials such as nanotubes (CNT) and graphene sheets. These nanomaterials offer important physical and chemical advantages that make them extremely well suited for this purpose. The nanoscale roughness and porosity created by CNTs offer a unique neuronal interface that improves neuronal growth and can be beneficial for recording fine neural signals in dynamic systems. Furthermore, the surface of CNT can be functionalized with different bioactive molecules by covalent coupling, non-covalent wrapping or surface decoration to improve biocompatibility. This is of tremendous importance especially for neuronal networks since extracellular adhesion molecules in such tissues strongly differ from classical molecules used in cell culture.

The project proposed here will use carbon nanomaterials in tailor to develop novel cell culture systems. The aim is to break new ground in order to obtain the best possible information from carbon nanomaterial functionalized cell culture systems on natural tissue functions. Choosing the adequate topography, functionalization of the carbon nanomaterial surface, conductivity and ligand incorporation, we aim to build successful 3D carbon nanomaterial scaffolds of and to develop models that help to take a step towards better understanding, treatment and cure of neurodegenerative diseases.

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