Palestinian-German ScienceBRIDGE
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Thesis Project Offer

Joint Research and Education Programme "Palestinian-German Science Bridge PGSB"
Forschungszentrum Jülich GmbH & Palestine Academy for Science and Technology

Thesis type*

☐ BSc	☒ MSc	☐ PhD	Intended starting date (approx.): November 2020

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Project description*

Carbon nanotubes for establishing biomimetic neuronal 3D systems

Our nervous system consists of more than a billion of neurons which form over a trillion of synaptic connections. These connections are responsible for the intelligence of humans and are continuously adapted and newly formed. Especially in the case of injuries, both, neuronal extensions and the underlying connections between neurons are destroyed. New formation of the corresponding neuronal extensions would be an absolute necessity for healing and full functionality. Unfortunately, neuronal growth as well as their re-connection are often severely impaired since nerves have only a limited ability to regenerate. In addition, developing scar tissue most often results in altered tissue elasticity, topography and density and therefore represents hurdles that impair or even completely prevent complete neuronal healing. Probably the most massive impairment in this context is paraplegia.

Recent finding at the IBI-2 in Juelich showed that neurons respond to mechanical strain with growth enhancement, a different morphological appearance and that the direction of neuronal outgrowth can be controlled by cyclic mechanical strain. So far, these experiments were conducted in a two dimensional environment on flexible elastomer chambers. Therefore, the elastomer chambers are fabricated in our laboratory. Primary cortical rat cells are isolated from rat embryo (E18) and

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cultivated on these chambers. The chambers are linear elastic and by stretching these substrates, adhered cells can be subjected to well-defined mechanical forces. Here, we specially focus on a functional neuronal network formation and changes under mechanical cyclic strain.

At the same time it was shown, that carbon nanotubes (CNT) are ideal scaffolds for nerve tissue engineering. Such artificial nanomaterials do not only improve neuronal membrane potential dependent activity, but also facilitate growth along nanotubes and enhance synaptic connectivity for ultimate network formation. With Prof. Assali we have an expert in CNT formation and application in biological systems. Single-wall and multi-wall carbon nanotubes as well as graphene sheets can be produced. Furthermore, surface functionalization is well established in his institute and can be performed with non-covalent as well as covalent coupling procedures.

In order to direct neuronal growth by chemical, topographical and mechanical signals in parallel, we plan to combine natural stretch signals with carbon nanotube paths. Experiments will be performed on 2D cell monolayers as well as in 3D stretchable culture systems. While 2D systems will mainly serve as internal control for proper cell adhesion to carbon nanotubes and their response to cyclic stretching, 3D culture systems will be formed as biomimetic system. Here, neurons are embedded in matrigel, which mostly consists of laminin, the most abundant extracellular matrix protein in the brain. Upon use of a “sandwich” method layers of neurons are separated by cell-free matrices. These matrices can be either formed by ECM proteins or by other gel-forming molecules. Cell-free layers mimic neuronal injuries that separate neuronal networks. Neuronal cells are able to survive many days in these systems and are able to form new extensions for network formation within their layer but also cross cell free matrices to some extent. By use of different types of CNTs, we will analyse if such nanomaterials direct neurite growth to ultimately form functional networks between cell layers. Functional connectivity will be characterized by Ca2+ signalling using Fluo-4 as Ca2+ sensitive fluorescent dye. Experiments will be performed in the presence and absence of stretch. Stretch parameters will be chosen in a way that additive, supportive grwoth effects will be induced. For optimisation, different CNT surface functionalisation will be analysed.

Ultimately, our goal is to develop functional systems for directing neuronal cell growth with subsequent functional synapse formation using a combinatory approach of nanomaterial sciences with mechanobiological approaches. By this, biomimetic systems might pave the way for better treatment of neuronal injuries in human.

Date*	**Signature***
18.09.2020	Bernd Hoffmann

* required field