**Stimuli-Responsive Nucleic Acid-Functionalized Nano-Carriers and Materials for Biomedical Applications**

*Itamar Willner, Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel*

The base sequence comprising nucleic acids, allows, besides dictated formation of duplex structures, the triggered reversible reconfiguration. Auxiliary triggers such as pH, metal ions, light or heat, reconfigure random nucleic acids into organized structures such as, i-motif, triplexes, G-quadruplexes or chemically stabilized duplex structures. These switchable properties of nucleic acids provide useful keys and tools to develop stimuli-responsive nanomaterials for various biomedical applications. This will be exemplified with:

(i) The development of stimuli-responsive nano-/micro-carriers for controlled drug release. Specifically, drug-loaded nucleic acid-gated metal-organic framework nanoparticles (NMOFs) and drug-loaded nucleic acid-gated microcapsules will be introduced as stimuli-responsive nanocarriers for controlled drug release. The uncaging of nucleic acid gates by means of cancer biomarkers, such as pH, VEGF, ATP, or miRNA, and the selective release of chemotherapeutic drugs will be demonstrated. Means to target the carriers and promote their permeation into cancer cells will be discussed.

In addition, the development of glucose-responsive, insulin-loaded, nucleic acid-functionalized carriers acting as “Artificial Pancreas” nanodevices for the controlled release of insulin will be addressed.

(ii) The synthesis of stimuli-responsive nucleic acid-functionalized hydrogels (polyacrylamide, carboxymethyl cellulose) will be introduced. The switchable, and reversible control over the stiffness of the hydrogels by means of triggered reconfiguration of nucleic acid crosslinking units will be demonstrated.

Different triggers such as pH, K+-ion/crown ether, donor-acceptor complexes, or light are used to switch reversibly the stiffness of the hydrogels. The use of the stimuli-responsive hydrogels as shape-memory materials and self-healing matrices for tissue engineering will be addressed. The stimuli-responsive hydrogels are, also, applied for the controlled switchable drug release.

In addition, the fabrication of bi-layer nucleic acid-based stimuli-responsive hydrogel assemblies allows the dictated triggered control of the stiffness and stress in the bilayer systems. Triggered reversible mechanical bending of the structures is demonstrated, suggesting the potential use of these materials as actuators and robotic devices.