These research projects, undertaken in partial fulfillment of the requirements for the MD degree at Sackler Faculty of Medicine, Tel Aviv University in 2010–2011, were considered the most outstanding of the graduating class

Animal models for the assessment of the activity of the neuroprotective peptides NAP and D-SAL

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Background: The neuroprotective peptides NAP (davunetide) and D-SAL are derived from endogenous proteins secreted by glial cells. The parent proteins, activity-dependent neuroprotective protein (ADNP) and activity-dependent neurotrophic factor (ADNF) respectively, are important for the formation and maintenance of the brain. Beneficial effects of these small peptides were proven in vivo and in vitro in models of Alzheimer's disease, stroke, electrical blockade and excitotoxicity.

Objectives: This work aims to examine the effects of these peptides in new models to assess their breadth of neuroprotection and potential use in neurodegenerative and neuropsychiatric conditions in humans.

Methods: Two transgenic mouse models were used to assess the neuroprotective properties of the aforementioned peptides. Firstly, partial *ADNP*-deficient mice which exhibit tau hyperphosphorylation and cognitive impairment were used as a tauopathy model. Secondly, a new model of schizophrenia, heterozygous deficient *STOP (stable tubule only protein)* mice, was characterized for future testing of these peptides. Behavioral testing in this study included the odor habituation-dishabituation, social recognition and open field tests.

Results: Chronic D-SAL treatment improved behavioral outcomes in the odor habituation-dishabituation test and the social recognition paradigm in the partial *ADNP*-deficient model. In addition, heterozygous *STOP*-deficient mice exhibited behavioral disturbances compatible with those of the homozygous group, validating a new schizophrenia model. Later experiments pointed to a positive effect of NAP treatment in this model.

Conclusions: These and other results confirm the potential of NAP (davunetide) and D-SAL (AL-309) as drug candidates in human tauopathies such as Alzheimer's disease and other human microtubule dysfunction diseases, such as schizophrenia. Studies in humans are in progress with promising results.

Determination of serum thymidine kinase activity level in children with acute lymphoblastic leukemia and correlation with clinical parameters and prognosis

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Background: Thymidine kinase (TK) is involved in nucleic acid synthesis and is therefore considered to be an important proliferation tumor marker. TK has been shown to be elevated in the serum of patients with a variety of human solid and hematological malignancies, and has been shown to correlate with stage of the disease, response to treatment, and prognosis.

Objectives: Our main goal was to measure the levels of TK activity in serum (STK), and correlate the levels with disease progression and response to treatment in children with acute lymphoblastic leukemia (ALL).

Methods: STK was determined by ELISA (DiviTum kit, Biovica) in serum samples from 46 children who were diagnosed with ALL and 20 healthy children. For all patients who were included in the study, STK was measured at diagnosis, and/or relapse and during follow-up and compared to the levels of healthy children. STK levels were correlated with clinical parameters.

Results: A significant negative linear correlation between STK level and age was detected in healthy children ($P < 0.001$). A significant difference was detected between mean age corrected STK in different stages of the disease (at diagnosis, remission, bone marrow relapse) and in the controls: high at diagnosis, low during remission and high again in samples taken during bone marrow relapse. We detected a significant correlation between STK level and risk groups, age and white blood cells count at diagnosis.

Conclusions: STK level was found to be a potential tool during follow-up of the disease and to monitor response to therapy in ALL patients.

Use of weight-bearing MRI for evaluating wheelchair cushions based on internal soft tissue deformations under ischial tuberosities*

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Background: Pressure ulcers are a major cause of morbidity and mortality, especially in bedridden or wheelchair-bound individuals. The classical understanding of the pathophysiologic mechanism was that the injury starts at skin level and progresses to deeper tissues. The classification of pressure ulcers was based on this understanding. It has been shown in recent years that a large percentage of what were previously defined as "high grade pressure sores" are actually a distinct entity which was named Deep Tissue Injury (DTI). Its pathophysiologic mechanism is completely different – the insult begins in the deeper tissues, close to the weight-bearing bone. These injuries are common under the weight-bearing pelvic bones – the ischial tuberosities (sitting) and sacrum (lying supine). In use today are a number of cushions or mattresses intended to prevent, or at least delay, pressure ulcers. Their current standard of quality is their contact pressure, the pressure between the patient and the surface he/she is sitting on, when used. However, there is no unanimous threshold for the contact pressure in the literature. Furthermore, the measurement of pressures is on the *skin*, while the tissue at risk (and therefore the one to be assessed) is deeper, namely the tissue adjacent to the bone. Internal tissue pressures cannot be measured directly and non-invasively.

Objectives: This study tested the influence of different types of cushions on the deformations in soft tissues (muscle, fat) under the pelvic bones. The relationship between the cushion's "stiffness" – i.e., its elastic modulus – to its prevention of deformation in the different tissues was studied. Also examined was the assumption that deformations in muscle tissue are higher than in fat tissue.

Methods: This "pilot" study tested qualitatively and in real-time four different types of cushions with different elastic moduli. Ten healthy volunteers of both genders were recruited. Exclusion criteria were inability to undergo magnetic resonance imaging, as well as pressure ulcers, an illness-limiting mobility and past pelvic fractures or operations. Age, weight, height and body mass index were recorded. While the subjects' pelvic bones were not bearing weight and afterwards were bearing weight with different supports under the pelvis, the subjects were scanned in the MRT ("open MRI", which enables imaging while the subject is sitting). Sitting contact pressures on the different supports were also measured using pressure sensors.

Results: Deformations were maximal in muscle tissue (mean ~70%), more than twice that in fat (~30%). Effective (fat and muscle together) soft tissue deformations were ~50–60%. The stiffest cushion provided the best overall results.

Conclusions: Although using cushions only mildly reduced muscle deformations, by an order of 10%, our interpretation suggests a considerable addition, theoretically ~50%, of safe sitting time.

Importance: This is the first report of measuring soft tissue deformations in the pelvis using different cushions. This study demonstrated that weight-bearing MRI is applicable for evaluating wheelchair cushions, and in the future, after further research, may serve as a tool to improve design and selection of cushions.

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