出國報告（出國類別：其它-參訪交流）

台蒙計畫審查會、第4屆台以年會及台以研究計畫成果發表會出國報告

出國人員：行政院國家科學委員會 牟中原 副主任委員
行政院國家科學委員會 工程處 李清庭處長
行政院國家科學委員會 國合處 鄭慧娟研究員

派赴國家：蒙古、以色列
出國期間：101年6月26日至7月5日
報告日期：102年9月17日

目　錄

壹、目的

依據2007年8月本會與蒙古科學基金會所簽署之台蒙科技合作協議，為落實台蒙兩國實質合作及審議年度合作研究計畫，應定期召開工作會議及審議會。2013 年6月26至28日，本會工程處李處長偕國合處承辦人赴蒙國首府烏蘭巴托與蒙古科學基金會共同舉辦年度合作計畫審議會。

2013 年 6 月 29-7 月 5 日，本會牟副主委率團赴以色列耶路撒冷與以色列科技部召開第 4 屆台以年會、第二期台以共同研究計畫成果發表會及會後參訪活動。

本次訪以團成員包括牟中原副主委及國合處鄭慧娟研究員。

貳、過程與觀察

■主要行程/

1.本會(NSC)與蒙古教文部-科學基金會共同舉辦台蒙合作研究計畫聯合審查會

本會與蒙古教文科部科學基金會依據雙方合作備忘錄，為落實科技實質合作，除定期召開工作會議，每年亦在蒙國首府召開研究計畫聯合審查會，以討論合作計畫執行細節及研究計畫簽約儀式。本次聯合會議，由本會工程處李處長及教文科部科學基金會主任Kh. DONDOG 共同主持，本次會議共同核定自2013至2016年，為期3年之3項合作研究計畫及一場"Taiwan-Mongolia Advanced Nano-Science, Science Education and Humanity Sciences" 雙邊研討會。

2.參訪 ElMinda 公司及 Marvell 公司

ElMindA 公司主要是以腦波偵測為主，將腦波活動以圖像、數學等方式呈現，可用於偵測腦震盪、病變等，相當有實用性。接著是拜訪以 SAN 之儲存裝置控制 IC 出名之 Marvell 公司，也陸續參觀其 IC 設計、偵測、檢測、FIB 等實驗室與設備，是以色列少數以 fabless IC Design 為主的公司，但是其在全世界之排名可以到前十名內，研發能力驚人。

3.參訪 Ben-Gurion University of the Negev

訪團訪問以色列南部的Ben-Gurion University。Ben-Gurion University 由 Ilse Katz Institute for Nanoscale Science & Technology (IKI)主任 Yuval Golan 接待訪團進行簡報並參觀該中心。隨後並拜會該中心Department of Electro –Optic Engineering Dr. Yitzhaky、Electrical and Computer Engineer Dr. Amiel Ishaaya、Nano- Fabrication Center Head Erez Golan及The Atom Chip Lab Head Ron Folman。此大學之參訪重點是其光電與奈米技術中心，具有相當多之前瞻設備。同時，我們也瞭解以色列政府為了開發其國土南部而設立此一大學之意義。另一個令人注意的是該校為了結合產學與技轉，就在學校旁邊直接設立科學園區，打造科技城的概念。

4.拜訪 Bar-Ilan University

Bar-Ilan University由該校Research Authority 主任接待訪團。訪團參訪該校the Electromagnetic Brain Imaging Unit和Institute of Nanotechnology and Advanced Materials. 此一大學同樣以brain research為主，但是強調在影像方面；至於在奈米技術方面則是

以材料處理為主要領域。

5. 本會(NSC)與以色列科技部共同舉辦台以第二期研究計畫成果發表會

兩場研討會共同開幕式由本會牟副主委、以色列科技部 Vice Chief Scientist Dr. Victor Weiss 及科技部國際事務部主任Ilana Lowi Ms. Hana Lowi 分別致歡迎詞，展開了2場研究成果發表會，議程如下。

(1)Nanotechnology Session

13:30-14:30 - Optical and Electrochemical Biosensors Based on NAzymes and Quantum Dots (QDs)

Itamar Willner, Institute Chemistry, Hebrew University: *"Optical and Electrochemical Biosensors on DNAzymes and quantum Dots."*

Ja-an Ho, Bio-Analytical Chemistry Lab, Department of Biochemical Science and Technology, National Taiwan University: "*Electrochemical Sensors for Multiplex Screening of Genetically Modified DNA: Identification of Biotech Crops by Computational Biomolecular analysis.*"

14:30-15:30- Characterization of Relaxation on the Single Spin Level Using ESR-STM

Yishay Manassen, Physics Department, Ben- Gurion University: *"Electron spin resonance scanning tunneling microscopy on Si (111) containing C and O defects."*

Woei Wu Larry, Pai, Center for Condensed Matter Science, National Taiwan University: *"Development of a radio-frequency reflectometry based detection scheme for STM and electron spin resonance."*

16:00-17:00 - Nanoscale investigation of new Fe-based superconductors and Nanocrystals

Eli Zeldov, Condensed Matter Physics, Weizmann Institute: *"NanoSQUID-on-tip microscopy for study of vortex dynamics in superconductors on the nanoscale."*

Maw-Kuen Wu, President, National Dong Hwa University : *"Growth and Characterization of B-FeSe nanowires-Identification of Fe-vacancy order and the possible parent phase of the Fe-Se superconductors."*

(2)Medical devices Session

13:30-14:30-A Thermosensitive Hydrogel for Tissue Engineered Models of Chronic Wounds: Understanding Aetiology and Tarheting Treatments

Amit Gefen, Biomedical Engineering, Tel-Aviv University: *"A Thermosensive Hydrogel for Tissue Engineered Models of Chronic Wounds:Understanding Aetiology and Targeting Treatments."* Presented by Naama Shoham.

Feng-Huei Lin, Director, Division of Medical Engineering Research, National Health Research Institute: *"In situ*

forming Oxidized Hyaluronic Acid Hydrogel for Nucleus Pulposus Regeneration."

14:30-15:30- Sensory Substitution in Urban Environment

Ehud Ahissar, Neurobiology, Weizmann Institute:*" Vision to touch Substitution in the Real World."* presented by Amos Arieli

Sung-Nien Yu, Electrical Engineering, National Chung Cheng University: *"Sensory Substitution in Urban Environment."*

16:00-17:00-Implantable Spinal Cord Stimulator System Using Nano-technology with High-Efficiency Power Harvesting Device

Doron Shmilovitz , Physical Electronics Deptment, Tel-Aviv University: *" Implantable Spinal Cord Stimulator System Using Nano-technology with High-Efficiency Power Harvesting Device."*

Chua-Chin Wang, Department of Electrical Engineering, VLSI Design Lab: *"Implantable Spinal Cord Stimulator System Using Nano-technology with High-Efficiency Power Harvesting Device."*

6. 第4屆台以科技年會(Meeting of the Taiwan-Israel Joint Committee for Scientific and Technological Cooperation)

本次台以科技雙邊年會，是依2011 年5 月在台北召開，第3 屆科技年會決議辦理，於7 月3 日上午9 時30 分至12 時在以色列首都耶路撒冷以色列科技部會議室舉行。

台方由本會牟副主委率團，以方由科技部 Director General Menachem Greenblum 及 Chief Scientist Ehud Gazit 率團。

會議由以色列科技部總司長 Menachem Greenblum 致歡迎詞，對雙方在科技合作的努力表示肯定和期許，隨後由牟副主委致詞，除對以方本次的邀請及行程安排表達感謝，並期待藉由兩國政府與學者專家更廣泛的合作計畫及互動，共創雙贏契機。

會議議程主要如下:

(1) 由台以兩位學者報告前日舉辦之第二期研究計畫成果發表會會議摘要。

(2) 審查 2013-2015 年共同合作研究計畫。2013-2015 年之合作研究主題為"Effects of human activities on marine environments"及"Artificial intelligence and learning algorithms". 本年度共核定 6 項研究計畫，每件計畫台以雙方補助金額每年各以 US25,000 為限，為期 2 年。

(3) 討論第4期(2015-2017年)雙方合作重點領域為，Information Security和Nano Scale Bio Engineering。2014年在以色列舉辦前述領域的雙邊研討會，2015年在台灣召開第5屆台以年會。

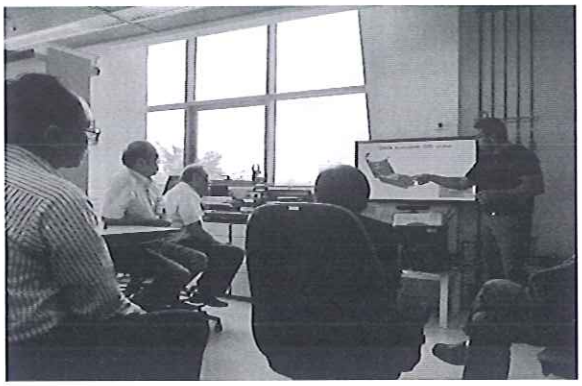
參、心得及建議

1.經由雙邊研究人員的合作、互動、互訪、交流，以及共同研究計畫成果發表會的機會進行參訪及互動，能激勵並提升雙方人員研究交流與情誼，對於提升台灣學術研究的視野及國際合作有加值的重要性。藉由共同研究計畫成果發表，可以驗收雙方推動該合作研究計畫的效益並瞭解所設定合作領域發展的現況，是否確已達到預期成果，並能配合國家科技發展政策訪向。本次研討會參與的學者，都是台以兩國近二年在奈米技術與醫療元件努力合作有成的學者；在前述兩領域中，以色列學者近年的研究成果都很傑出，甚至鼓勵專利申請，而非僅是發表論文而已。這樣的作法，有利於該國技術向下紮根，而不僅是進行曇花一現的研究，令人印象深刻。

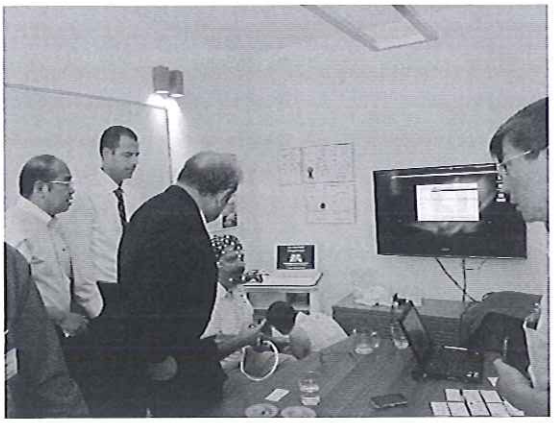
2.以色列政府正面鼓勵學校師生創業，甚至可出資達85%，讓師生沒有資金的憂慮。政府鼓勵創業，創業失敗也沒關係，這個觀點非常特殊。台灣目前的制度很難做到，亦幾乎不太可能。以色列的技術研發不是只有以論文篇數數量取勝，而是要具備質佳的論文篇數；更重要是IP的獲得與應用，這也是我國目前學界較為欠缺及不足的環節。

3.以色列政府鼓勵學校師生創業，並且出資協助，我國政府亦應多鼓勵學校或研究機構的研究創新，俾能縮短學用落差。政府可以政策利導讓研發成果可以為產業界所運用，以增進我國的產學合作效益。

◆附件--研討會及相關參訪行程照片



參訪以色列 Bar-Ilan University,
Institute of Nanotechnology and
參訪以色列 ElMindA Ltd.
Advanced Materials.



第 4 屆台以年會在以色列科技部舉行

台以第二期研究計畫成果發表會
牟副主委致詞

◆附件--研究成果發表會論文摘要

Nanotechnology Session

Optical and Electrochemical Biosensors Based on DNAzymes and Quantum Dots

Itamar Willner,[1] *Ronit Freeman,*[1], *Julia Girsh,*[1] *Amily Fang-ju Jou*[2] *and Ja-an Annie Ho*[2]

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Sequence-specific nucleic acids may exhibit specific binding sites toward low-molecular-weight substrates or proteins (aptamer), or may reveal catalytic properties (DNAzymes). While the catalytic properties of DNAzymes can be implemented for the development of amplified sensors, the recognition functions of aptamers can be used to selectively detect low-molecular-weight substrates or proteins. Different methods for the development of optical or electrochemical biosensors based on DNAzymes, and/or quantum dots (QDs) will be described, while emphasizing new amplification means and multiplexed analyses as innovative nanotechnology-based sensing platforms:

1. Biosensing with QDs will be exemplified with the fluorescence analysis of DNA,[1] the detection of aptamer-substrate complexes,[2] and the probing of enzyme activities, e.g., caseine kinase.[3]
2. DNAzyme machineries for the amplified detection of DNA through the autonomous synthesis of DNAzyme nanowires will be described.[4]
3. A new optical transduction paradigm, chemiluminescence resonance energy transfer (CRET) will be described using the hemin/G-quadruplex DNAzyme and QDs as hybrid systems. The use of this mechanism for the detection of DNA and aptamer-substrate complexes will be described, and the use of the CRET mechanism for multiplexed sensing will be addressed.[5]

4. A collaborative study between the Israeli and Taiwanese laboratories on the optical detection of Vascular Endothelial Growth Factor (VEGF) biomarker will be described.[6]

5. A series of electrochemical DNA sensors and aptasensors that implement the hemin/G-quadruplex as catalytic label will be introduced.[7]

6. Graphene oxide (GO) will be introduced as a new functional material for the fluorescence detection of DNA and aptamer-substrate complexes:

(a) The use of fluorophore-functionalized probes that bind to GO are used as hybrid supports for the detection of DNA or aptamer-substrate complexes. New methods to develop amplified sensing platforms through the regeneration of the analytes will be discussed. Also, multiplexed analysis of targets by modified GO will be addressed.[8]

(b) Ag nanoclusters (NCs) protected by nucleic acids provide a new class of luminescent QDs. The integration of the Ag NC-nucleic acids with GO yields functional hybrid materials for the optical detection of DNA, aptamer-substrate complexes, and multiplexed analysis of several targets.

References:

1. F. Patolsky, R. Gill, Y. Weizmann, T. Mokari, U. Banin and I. Willner, *J. Am. Chem. Soc.*, **125**, 13918-13919 (2003).
2. R. Freeman, Y. Li, R. Tel-Vered, E. Sharon, J. Elbaz and I. Willner, *Analyst*, **134**, 653-656 (2009).
3. R. Freeman, T. Finder, R. Gill and I. Willner, *Nano Lett.*, **10**, 2192-2196 (2010).
4. Y. Weizmann, M. Beissenhirtz, Z. Cheglakov, R. Nowarski, M. Kotler and I. Willner, *Angew. Chem. Int. Ed.*, **45**, 7384-7388 (2006).
5. (a) R. Freeman, X. Liu and I. Willner, *J. Am. Chem.. Soc.*, **133**, 11597-11604 (2011). (b) X. Liu, R. Freeman, E. Golub and I. Willner, *ACS Nano*, **5**, 7648-7655 (2011).
6. R. Freeman, J. Girsh, A. Fan-ju Jou, Ja-An A. Ho, T. Hug, J. Derenedde and I. Willner, *Anal. Chem.*, **84**, 6192-6198 (2012).
7. G. Pelossof, R. Tel-Vered, J. Elbaz and I. Willner, *Anal. Chem.*, **82**, 4396-4402 (2010).
8. X. Liu, R. Aizen, R. Freeman, O. Yehezkeli and I. Willner, *ACS Nano*, **6**, 3553-3563 (2012).

Electrochemical Sensor for Multiplex Screening of Genetically Modified DNA: Identification of Biotech Crops by Computational Biomolecular Analysis

Wei-Ching Liao, [1,2] *Itamar Willner,* [3] *Min-Chieh Chuang,* [1,4*] *Ja-an Annie Ho* [1,2*]

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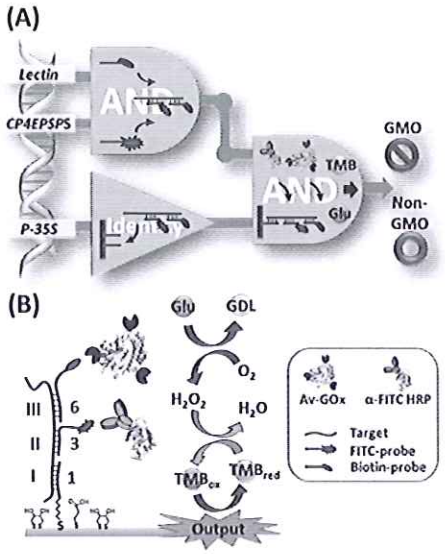
Genetically modified (GM) technique, one of the modern biomolecular engineering technologies, has been deemed as profitable strategy to fight against global starvation. Yet rapid and reliable analytical method is deficient to evaluate the quality and potential risk of such resulting GM products. We herein present a biomolecular analytical system constructed with distinct biochemical activities to expedite the computational detection of genetically modified organisms (GMOs). The computational mechanism provides an alternative to the complex procedures commonly involved in the screening of GMOs. Given that the bioanalytical system is capable of processing promoter, coding and species genes, affirmative interpretations succeed to identify specified GM event in terms of both electrochemical and optical fashions. The biomolecular computational assay exhibits detection capability of genetically modified DNA below sub-nanomolar level and is found interference-free by abundant coexistence of non-GM DNA. This bioanalytical system, furthermore, sophisticates in array fashion operating multiplex screening against variable GM events. Such the biomolecular computational assay and biosensor holds great promise for rapid, cost-effective, and high-fidelity screening of GMO.

KEYWORDS: Genetically Modified Organisms, Nucleic Acids, Biomolecular Assay, Multiplex Screening, Biosensors



C and O defects

Yishay Manassen, Physics Department, Ben- Gurion University

ESR-STM is a technique capable of single spin detection. In this seminar I shall describe the technical aspects of the detection, the main observations in the past and recent results: Paramagnetic defects related to oxygen and carbon in silicon were decteted. the first one is a broad 10MHz peak and the second a narrower triplet with a hyperfine splliting of 10MHz. This demostrates an ability to distinguish between 28 Si and 29 Si. A model that describes tunneling through a single spin in which the leeds are polarized in a mechainism similar to dynamic spin polarization is suggested. The tunneling of electrons through a spin polarized in a different direction gives a signal in the Larmor frequency. It is shown that the spectral intensity and the lineshape are in agreement with the predictions of the model. In addition initial experiments to detect signals from single nuclear spins using ENDOR type STM experiment were performed.

Development of a radio-frequency reflectometry based detection

scheme for STM and electron spin resonance

Dr. Woei Wu Pai, Mr. Chen I Jan, Center for condensed matter sciences,
National Taiwan University

The detection of electron spin resonance in a scanning tunneling microscope setup, called ESRSTM, has been typically done through examining the high-frequency component of tunneling current noise. When a spin resides in a magnetic field, it undergoes Larmor precession and gives rise to tunneling current noise at the corresponding frequency. Such a setup, however, has a major difficulty that the junction source impedance (over tens of Mohms) cannot be readily matched with the 50 ohms impedance of a detection circuit. This greatly reduces the detection sensitivity. To circumvent this situation, we work in collaboration with Prof. Yishay Manassen and develop a new ESRSTM detection scheme.
The new scheme is based on radio-frequency reflectometry in which a high-frequency (~1 GHz) RF signal is delivered to a pretuned low-pass L-leg LCR tank circuit with the shunt tunneling gap resistance as a perturbation. This tank circuit will be detuned when the STM tip engages tunneling to the surface. The minute change of RF reflection is post-processed through a gain/phase RF compensator that greatly enhances the detection sensitivity. In this way, we achieved several notable results. First, we obtained a very high detection bandwidth, e.g., >500 MHz. This represents a >5000 times of improvement to the conventional STM detection bandwidth. Second, we demonstrated the signal equivalence of RF reflectivity change and tunneling current. The RF signal gives atomic-resolved images on HOPG with excellent signal-to-noise ratio at >100 Mohms junction

resistance for the first time. With these two achievements, we set out to detect electron spins in two ways. One way is similar to convention ESR absorption. We detected ESR signal of stable free galvinoxyl radicals with our setup, with a sensitivity comparable to conventional ESR. Furthermore, our ESR detection is based on a proximal tip and therefore could render spatial resolution. The other way is to detect ESR signal when electrons tunneling through a gap with an electron spin. We have not yet achieved this but it is quite plausible that a superheterodyne mixing will occur with our carrier RF and Larmor frequency. To further detect ESR hyperfine

structure, we will use modulated carrier signal and study the dependence of reflectivity return loss as a function of modulation frequency. Our new detection scheme, once fully developed, will be uniquely suited for high-speed imaging, in-situ imaging of surface under electron excitation, and detecting electron spin resonance.

NanoSQUID-on-tip microscopy for study of vortex dynamics in superconductors on the nanoscale

E. Zeldov[1], Maw-Kuen Wu[2], and Ming-Jye Wang[2]

[1]Weizmann Institute of Sciences, Rehovot, Israel

[2]Institute of Physics, Academia Sinica, Taipei, Taiwan

A scanning probe microscope based on a nanoSQUID which is fabricated on the apex of a quartz tip has been developed. The nanoSQUID-on-tip device is fabricated by pulling a quartz tube into a sharp pipette with diameters down to 50 nm followed by deposition of a thin superconducting film onto the sides and the apex of the pipette. The devices operate at 4 K in applied magnetic fields of up to 1T and display an extremely low flux noise. As a result, a record spin sensitivity of better than 1 $\mu_B/Hz^{1/2}$ is achieved that is sufficient for detecting the magnetic moment of a single electron. Using a quartz tuning-fork based AFM technique the nanoSQUID can be scanned few nm above the surface of the sample. The combination of high sensitivity, high spatial resolution, wide bandwidth, and close proximity to the sample opens the pathway to direct imaging and investigation of vortex statics and dynamics in superconductors and of dynamic magnetic phenomena on the nanoscale.

Growth and Characterization of β-FeSe Nanowires—Identification of

Fe-vacancy order and the possible parent phase of the Fe-Se superconductors

Maw-Kuen Wu[1,2], Ming-Jye Wang[3], Hsian-Hong Chang[3], Ta-Kun Chen[2], Chung-Chieh Chang[2], and Chuan-Ming Tseng[2]

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2. Institute of Physics, Academia Sinica, Taiwan
3. Institute of Astronomy and Astrophysics, Academia Sinica, Taiwan

We have grown highly crystalline 刍-FeSe type iron chalcogenide nanowires (NWs) by annealing thin film that prepared by pulse laser deposition method. Three kinds of NWs with composition of $Fe_{0.8}Se$, $Fe_{0.88}Se_{0.32}Te_{0.68}$, and $Fe_{0.88}Te_{0.91}S_{0.09}$, have been prepared and carefully characterized by high-resolution transmission electron microscope (HRTEM). The NWs reveal ideal tetragonal structure with crystal growth along the [100] direction. The energy dispersive spectroscopy (EDS) studies and HRTEM images demonstrate good compositional uniformity, except the existence of a thin layer of oxide on the surface. No superconducting transition was observed in the $FeSe_x$ NWs, which is possibly caused by the highly Fe deficient. The other two types of NWs show relatively higher and sharper superconducting transition than that of their bulk counterparts. More detailed study of the non-superconducting $FeSe_x$ nanowires reveals that its stoichiometry is close to β-Fe_4Se_5 and exhibit $\sqrt{5}\times\sqrt{5}\times 1$ Fe-vacancy order, similar to that of the $K_xFe_4Se_5$ compound. Further investigations by analytical electron microscopy indicates that, at least three types of Fe-vacancy order were found: $\sqrt{2}\times\sqrt{2}$ with d_{100} shift every other (001) plane, for β-Fe_3Se_4, $\sqrt{5}\times\sqrt{5}\times 1$, for β-$Fe_4Se_5$, and $\sqrt{10}\times\sqrt{10}$ with ½d_{310} shift every other (001) plane, for β-Fe_9Se_{10}. These observations suggest that the rich-phases found in $A_{1-x}Fe_{2-y}Se_2$ may not be exclusive cases in iron-based superconductors. Furthermore, the magnetic and semiconducting β-Fe_4Se_5 or other β-$Fe_{1-x}Se$ phases with particular Fe-vacancy order may serve as the parent phase of the Fe-Se superconducting system. Our finding brings interests for future test, both experimentally and theoretically, on the role of Fe vacancies or dopants in iron-based superconductors.

Medical devices Session

A Thermosensitive Hydrogel for Tissue Engineered Models of Chronic Wounds: Understanding Aetiology and Targeting Treatments

Prof. Amit Gefen (Tel Aviv University) and Prof. Feng-Huei Lin (National Taiwan University)

Chronic wounds represent a major burden to patients and the healthcare system, affecting more than 1 in 10 hospitalized and 1 in 20 community patients. Treating these injuries is costly, exceeding ~1-billion USD annually, just in the United States. The severe type of these lesions often develops in ischemic soft tissues under sustained mechanical loads. In order to understand the aetiology, we developed ex-vivo wound models in monolayer cell cultures and tissue-engineered constructs, and studied the effects of ischemic factors on the migration behavior of fibroblasts, pre-adipocytes (3T3-L1), and myoblasts (C2C12), which are all involved in the injury and healing. Analyzing the kinematics of migration by a new image processing method revealed that acidosis slowed the migration of NIH3T3 fibroblasts but not of 3T3-L1 and C2C12 cells. Low temperature and low glucose conditions did not affect migration rates in our experiments. Examining these factors, together with mechanical loads, by a confocal-based finite element model, in combination with diffusion simulations, showed that the built-up of oxygen levels in isolated myoblasts is slightly but consistently hindered when cells are subjected to compressive deformations. Decreasing temperature further hindered the oxygen build-up in the cells.

We also tested the hypothesis that macroscopic tissue deformations translate to cell-level deformations in the plasma membrane (PM), which increases its permeability and could then disrupt vital transport processes. We measured uptake of fluorescein isothiocyanate (FITC)-labeled Dextran in deformed versus unreformed myoblasts, using a fluorescence activated cell sorting (FACS) method, and found that the uptake of the Dextran increase with the levels of cellular stretching.

In addition to the experimental work, we have also developed computational finite element models of compressed myoblasts and analyzed the deformation of the PM under the mechanical stress. We found that in order to induce large tensile strains (>5%) in the PM and in the nuclear surface area, there was a need to apply more than 15% of global cell deformation in cell compression tests, or more than 3% of

tensile strains in the elastic plate substrate in cell stretching experiments.

Considering tissue engineering (TE) strategies as a promising treatment approach in modeling and repairing tissue defects, particularly delivery of preadipocytes to sites were adipose tissue damage needs to be repaired, we have characterized the injectable hyaluronic acid/adipic acid dihydrazide (HA/ADH) hydrogel in terms of biological compatibility as well as mechanical behavior and found that the mechanical properties of the hydrogel, when subjected to compression, are in good agreement with those of native adipose tissue. Hence, we concluded that injectable HA/ADH hydrogel may serve as a vessel for protecting preadipocytes during, and at a short-term after delivery to native tissues, e.g. in research towards regenerative medicine in tissue reconstructions.

Moreover, we have developed experimental setup and fully-automated image processing algorithm for studying cell migration rates in the hydrogel. Our system allows quantifying directional migration of colonies in a HA/ADH three-dimensional matrix following fluorescent staining. Our method can be implemented in future TE studies where the influences of chemotaxis or mechanical stimuli are being investigated. Our experimental and computational models, at the cell and engineered-tissue scales, considerably expand the understanding regarding the aetiology and the healing process of chronic wounds, towards better prevention and treatment.

In situ Froming Oxidized Hyaluronic Acid Hydrogel for Nucleus Pulposus Regeneration

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1. Introduction

Encapsulation of nucleus pulposus (NP) cells within in situ forming hydrogels is a novel biological treatment for early stage intervertebral disc degeneration. The procedure aims to prolong the life of the degenerating discs and to regenerate damaged tissue. In this study, we developed an injectable oxidized hyaluronic

acid-gelatin–adipic acid dihydrazide (oxi-HAG-ADH) hydrogel. High molecular weight (1900 kDa) hyaluronic acid was crosslinked with various concentrations of gelatin to synthesize the hydrogels and their viscoelastic properties were analyzed. Interactions between the hydrogels, NP cells, and the extracellular matrix (ECM) were also evaluated, as were the effects of the hydrogels on NP cell gene expression. The hydrogels possess several clinical advantages including sterilizability, low viscosity for injection, and ease of use. The viscoelastic properties of the hydrogels were similar to native tissue, as reflected in the complex shear modulus (11~14 kPa for hydrogels, 11.3 kPa for native NP). Cultured NP cells not only attached to the hydrogels but also survived, proliferated, and maintained their round morphology. Importantly, we found that hydrogels increased NP cell expression of several crucial ECM-related genes, such as COL2A1, AGN, SOX-9, and HIF-1A.

2. Materials Preparation

HAG polymers were prepared by EDC/NHS chemical crosslinking (Tang et al., 2007). A series of 0.025, 0.25, and 0.5 mg/mL gelatin solutions were prepared by dissolving gelatin in 400 mL double-distilled water (DDW) at 60°C. HA at 5 mg/mL was then added to the solutions, which were stirred overnight at room temperature to generate HAG1 (5 mg/mL HA, 0.025 mg/mL gelatin), HAG2 (5 mg/mL HA, 0.25 mg/mL gelatin), and HAG3 (5 mg/mL HA, 0.5 mg/mL gelatin) solutions. Crosslinking was performed by adding EDC and NHS at a molar ratio of 2:1 to the HAG solutions for 30 min. The reactions were terminated by the addition of 5 mL glycine (40 mg/ml). The solutions were dialyzed to remove byproducts, and the final HAG1, HAG2, HAG3 polymers were obtained by lyophilization (FDU-1200, EYELA, Tokyo, Japan). Spectrum 100TM FT-IR (PerkinElmer, Massachusetts, USA) with a universal attenuated total reflectance accessory (UATR) was used to identify the functional groups of the polymers. HA and HAG polymers were dissolved in DDW at room temperature and oxidized with sodium periodate as previously described (Su et al., 2010). Briefly, 400 mL of 5 mg/mL polymer solution was gently mixed with 10 mL of sodium periodate (2.67%) and kept in the dark for 24 h. Ethylene glycol was added to stop the oxidation reaction. The final oxidized HA or HAG polymers (oxi-HA, oxi-HAG1, oxi-HAG2, and oxi-HAG3) were obtained by dialysis and lyophilization. Spectrum 100TM FT-IR with UATR was used to confirm the oxidation results.

3. Results & Discussion:

Gene expression was measured in NP cells cultured in hydrogels for 7 days (Fig. 1). The mRNA levels of HIF-1A and SOX-9 were increased significantly in hydrogel-cultured cells compared with monolayer-cultured cells ($p < 0.05$). There was no significant difference in HIF-1A gene expression among the hydrogel-cultured groups. Levels of SOX-9 mRNA were significantly lower in the cells cultured in oxi-HA-ADH and oxi-HAG3-ADH than in oxi-HAG1-ADH hydrogel (12.76 ± 0.1, $p < 0.05$). The highest SOX-9 mRNA level was found in cells cultured in the oxi-HAG2-ADH hydrogel (20.82 ± 3.36, $p < 0.05$). Fig. 1B shows the expression of small leucine-rich protein (SLRP)-related genes. BGN and DCN mRNAs were increased significantly in the hydrogel-cultured cells compared with the monolayer-cultured cells ($p < 0.05$). NP cells cultured in oxi-HAG1-ADH, oxi-HAG2-ADH, and oxi-HAG3-ADH hydrogels expressed much more DCN mRNA that those cultured in the oxi-HA-ADH hydrogel ($p < 0.05$). Moreover, the level of BGN was significantly higher in the oxi-HAG2-ADH hydrogel-cultured group (65.04 ± 12.83) than in other groups ($p < 0.05$). Fig. 1C shows the expression of ECM-related genes. AGN and COL2A1 mRNA levels were increased significantly in the hydrogel-cultured cells compared with monolayer-cultured cells ($p < 0.05$). Among the hydrogel groups, the highest AGN expression was observed in NP cells cultured in the oxi-HAG2-ADH hydrogel. AGN is the major proteoglycan of the IVD and is responsible for maintaining tissue hydration through osmotic pressure. The level of COL1A1 mRNA was decreased significantly in cells cultured on the hydrogels compared with monolayer-cultured cells ($p < 0.05$).

4. Conclusion

Encapsulation of NP cells in in situ forming hydrogels is a novel biological treatment for early stage IVD degeneration. In the present study, oxi-HAG2-ADH in situ forming hydrogel was developed using high molecular weight hyaluronic acid and gelatin. The hydrogel possesses several advantages such as sterilizability, low viscosity for injection, and ease of use. The shear modulus of the hydrogel was similar to native NP tissue. The hydrogel was biocompatible; encapsulated NP cells not only survived but also proliferated well. Importantly, the oxi-HAG2-ADH hydrogel also activated NP cell synthesis of COL2A1, AGN, SOX-9, BGN, DCN, and HIF-1A mRNA. Taken together, these results indicate that oxi-HAG2-ADH is a promising hydrogel for

future application in the treatment of early stage IVD degeneration.

References

Boedtker H, Doty P (1954) A study of gelatin molecules, aggregates and gels. J Phys Chem 58: 968-983.

Boyd LM, Carter AJ (2006) Injectable biomaterials and vertebral endplate treatment for repair and regeneration of the intervertebral disc. Eur Spine J 15: S414-421.

Chen WY, Abatangelo G (1999) Functions of hyaluronan in wound repair. Wound Repair Regen 7: 79-89.

Crawford JR, Jacobson BS (1998) Extracellular calcium regulates HeLa cell morphology during adhesion to gelatin: role of translocation and phosphorylation of cytosolic phospholipase A2. Mol Biol Cell 9: 3429-3443.

Cs-Szabo G, Ragasa-San Juan D, Turumella V, Masuda K, Thonar EJ, An HS (2002) Changes in mRNA and protein levels of proteoglycans of the anulus fibrosus and nucleus pulposus during intervertebral disc degeneration. Spine 27: 2212-2219.

Day AJ, de la Motte CA (2005) Hyaluronan cross-linking: a protective mechanism in inflammation? Trends Immunol 26: 637-643.

Delmage JM, Powars DR, Jaynes PK, Allerton SE (1986) The selective suppression of immunogenicity by hyaluronic acid. Ann Clin Lab Sci 16: 303-310.

Gibson JN, Grant IC, Waddell G (1999) The cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. Spine 24: 1820-1832.

Girish KS, Kemparaju K (2007) The magic glue hyaluronan and its eraser hyaluronidase: a biological overview. Life Sci 80: 1921-1943.

Hadjipavlou AG, Tzermiadianos MN, Bogduk N, Zindrick MR (2008) The pathophysiology of disc degeneration: a critical review. J Bone Joint Surg Br 90: 1261-1270.

Vision to Touch Substitution in the Real World

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Sensory substitution conveys information that is naturally perceived via one sensory modality to another sensory modality. The most common use of sensory substitution is the vision-to-touch substitution system for impaired vision. In most vision to touch (or hearing) substitution devices (VTSD/VHSD) the sensor and stimulator are attached to different body organs, and light intensity is translated to tactile/acoustic vibrations. Our goal was to develop and optimize a sensory substitution device based on the characteristics of both sensory receptors and perceptual mechanisms. We aimed to reveal the benefits of applying active sensing principles to a substitution system and, therefore, we examined the efficiency of a VTSD attached only to the hand and which translates light intensity to tactile pressure directly. Therefore, a stationary stimulus creates a constant pressure and sensory adaptation. To activate mechanoreceptors of the fingers, thus, the subject must move the hand much like during natural touch. . We explored the best strategies for using an active substitution device for interactions with the environment.

We have built an active sensing VTSD and tested the performances of blindfolded sighted participants in two series of recognition tasks: recognition of 2D images and of 3D objects. In each trial they were presented with 5 objects of ~ 15*15 cm size from a distance of ~1 meter. The participants succeeded in recognizing 2D and 3D shapes in less than 30s in 86% and 95% of the trials, respectively. Participants improved from one experimental day to another. Success rates increased while the recognition times decreased. Comparing participants' achievements in our experiment to other studies in the literature reveals the efficiency of our system especially when taking into account our short training period and steep learning curve. In 2D shapes recognition our averaged success rate was 0.75 – one of the highest success rates shown so far in the literature. Another experiment showing similar success rate has a much longer recognition time. The advantage of our system is even more notable when comparing the 3D objects recognition. Comparing to a similar study in the literature, our participants' averaged success rate is 1.5 times higher with a recognition time approximately half and a training period that is 1.5 times shorter.

Participants developed an ability to identify local features (e.g., orientations, curvatures, vertex, corners), and they were aware to their accomplishments as evident by the high correlation between their success rate and their self-confidence report. Tracking participants' movements while recognizing shapes and objects revealed different scanning strategies: (a) scanning along the border of the object, (b) scanning perpendicular to the border of the object and (c) feature-oriented scanning.

The common components of the motor-sensory strategies underlying the observed improved performance were investigated by analyzing scanning patterns and comparing correct and wrong trials. We found that the prominent scanning strategy is a feature-oriented strategy. In this strategy the participant scans a certain portion of the object more frequently than the other portions in order to find the unique characteristic of each object.

We conclude that using motion-dependent tactile sensation and having motion and sensation on the same organ can improve perception via a VTSD significantly, and that this improvement depends critically on the participant's active strategy. These results show the superiority of an active sensing vision to touch substitution system and suggest the focus scanning strategy as the best active strategy characterizing the successful trial.

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Sensory Substitution in Urban Environment

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A TVSS translates visual input, usually from a video camera, into the output of a tactile stimulation array. With the assistance of digital image processing techniques, the most significant features of the image could be extracted and provided as augmented sensation to the visually impaired. As a sequel, the users could more accurately distinguish foreground objects from the background.

Since the idea of sensory substitution was introduced, researchers gradually recognized the importance of actively moving the camera in the use of the TVSS. Because tactile resolution in the fingers is far more limited than the visual resolution (and so is the resolution of the arrays of tactile actuators relative to the number of process is termed "active sensing." The knowledge about how people develop effective strategies to actively sense the environment is also an important issue in the development of a TVSS.

This study stem from a cooperation project about sensory substitution between the Laboratory for the Study of Adaptive Perceptual Processing directed by Prof. Ehud Ahissar and the Active Sensing Laboratory directed by Dr. Amos Arieli at the Weizmann Institute of Science in Israel and the Biomedical Signal Processing and System Design Laboratory directed by Prof. Sung-Nien Yu at the National Chung Cheng University in Taiwan. The Israeli team set up experiments for active sensing with a TVSS while the Taiwanese team developed image processing algorithms aiming to enhance active sensing performance of the experiments. A trajectory tracking algorithm was jointly developed to understand participants' active sensing strategies.

The TVSS contains a tactile stimulation device and a camera. Tactile stimuli were provided by the VTMouse. The VTMouse is a standard size computer mouse for the blind, which consists three tactile stimulation arrays of 32 pins each (4x8) and provide tactile stimuli to the fingers at different heights (4 levels). A miniature video camera (active camera) was attached to the VTMouse as the visual input sensor. In parallel to the miniature camera is a red laser pointer (605nm) which provides a marker associated with the location of the VTMouse. A wide view camera (fixed camera; 1280x1024, RGB, 15Hz) was arranged in a fixed location to the left of the participant). With this arrangement, the movement of the active camera is

identifiable in the fixed wide image taken by the fixed camera for further analysis.

This system contains two parts, including an image processing and a trajectory tracking functional blocks. The image processing part converts the color images acquired from the active camera into lower resolution binary images with valuable features reserved, which designated to generate adequate output for the tactile device. The color video frames acquired by the active camera, originally represented with red, green, and blue (RGB) attributes, were first transferred into hue, saturation, and intensity (HSI) color space. Only the intensity part of the frame was reserved and represented as the grey-levels of the image. Image enhancement with histogram equalization followed to make the foreground objects more separable form the background. The enhanced image needed to be further processed with downsampling, low-pass filtering, thresholding, and morphological process in order to generate suitable output for the tactile stimulation array.

The trajectory tracking part, on the other hand, tracks the trajectory of the participant on the stimuli and provides information for the study of active sensing strategies to explore the environment, without vision, using only TVSS. Before tracking, the acquired images from the two cameras were downsampled to reduce the computational load of the following process. The laser pointer was used for identifying the location of the participant on the wide view image. We firstly identify the location of the red spot recorded by the fixed camera based on the difference image of the present and previous frames. The location was considered the probable center of the images acquired by the active camera. We then searched for the real center in the vicinity of the location for the most similar image region acquired by the fixed camera compared to the active camera image using the maximal index calculated from the cross-correlation function. As a result, the strategy used by the participants could be analyzed through tracking the trajectory of the participants on the stimuli during active sensing tasks.

During the period when we were working on the project with regular cameras, we noticed the potential of Microsoft XBOX Kinect 3D body sensor, which, beside of regular camera, has a pair of infrared (IR) sensors for obtaining depth information of the scene. We also tried to integrate the depth information provided by the 3D sensor into the TVSS. Techniques for depth information processing were developed to improve the quality of the signal. This part was not planed in the proposal. However, the outcome was exciting. The results confirmed the advantage of using

the 3D sensor to provide depth information of the objects that were not offered by regular camera.

The fulfillment of the project is founded on the cooperation between Prof. Ehud Ahissar and Dr. Amos Arieli's group in Israel and Prof. Sung-Nien Yu's group in Taiwan. We will continue the cooperation and friendship between the two research groups and hope the visually impaired people can benefit from this study in the near future.

Implantable Spinal Cord Stimulator System Using Nano-technology with High-Efficiency Power Harvesting Device

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Compared with the conventional medicine-based approach, SCS attains the following advantages, including no side effects, mobile, relatively low cost, no need to carry pain-killing medicine, and effective. Through this project, both Taiwan (NSYSU) and Israel (Univ of Tel Aviv) teams have further extended their long-term close and efficient collaboration to apply advanced nano-meter CMOS process and high-efficiency transcutaneous energy transfer (TET) into SCS devices enabling prolonged operation time with no surgical interferences .

We have realized that Ultrasonic TET (UTET) presents an attractive alternative to conventional methods such as electro-magnetic TET and implanted batteries, and also exhibits advantages such as better power transfer efficiency, compactness and improved electromagnetic compatibility. It is particularly suitable for the SCS where the required power levels are below a few hundred milliwatts .

The newly proposed UTET has been analyzed in full detail, and design considerations were developed to address issues such as tissue biosafety concerns, transducer's material selection, acoustic link matching, the design of the driving and rectifying electronic circuitry and sensing of the available energy in the implant for control of the external transmitter.