Nano2Life
Bringing Nanotechnologies To Life

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Book of Abstracts

N2L Scientific Meeting Cork

September 5th – 7th 2006

This book of abstracts was compiled by Dr. Eric Moore, Tyndall National Institute

Welcoming Note from the Organising Committee

Dear N2L members,

It's a great pleasure to welcome you to **Cork** for this new Summer Scientific meeting of the **Nano2Life Network of Excellence**. This summer meeting is part of our activity in organising scientific meetings to increase the matching probability among scientists in order both initiate and continue joint research projects. This matching activity has been proved fruitful in the past two years with nearly **20** joint projects then successfully funded by the EC, which have been initiated by meetings and discussions in some previous **Nano2Life** meetings.

Nano2Life is so far the **biggest** and most **organised European group** of **experts** in **Nanobiotechnologies**. Of course improvements can still be done and we welcome all suggestions to make N2L work better. So the Cork meeting is a very unique event where you can

- meet new partners of interest for your daily research
- meet new partners for future bi or multilateral projects, with or without EC funding
- find a specific expertise and/or equipment for future mobility
- get an overview of on going research activity in the N2L partners
- get news about the latest activity managed by Nano2Life
- …enjoy the so famous N2L spirit ☺

In the programme, plenary sessions are scheduled to provide you with latest news about Nano2Life and parallel sessions are dedicated to targeted projects or working groups. The **bazaar**, which has evolved into the **N2L speciality**, is open permanently to give you the opportunity to get news from partners, from the **Strategic Research Projects**, regarding on going joint projects.

The timing of the Cork meeting is particularly adequate in the sense that **FP6** is about to end while **FP7** will start in a few months (early 2007). This meeting will provide an excellent opportunity to both initiate long term projects like the intersections projects to be presented in the bazaar and also to see how the members of N2L could address the research priorities selected by the **European Technology Platform** on **Nanomedicine**, which will be presented on Thursday 7th September 2006.

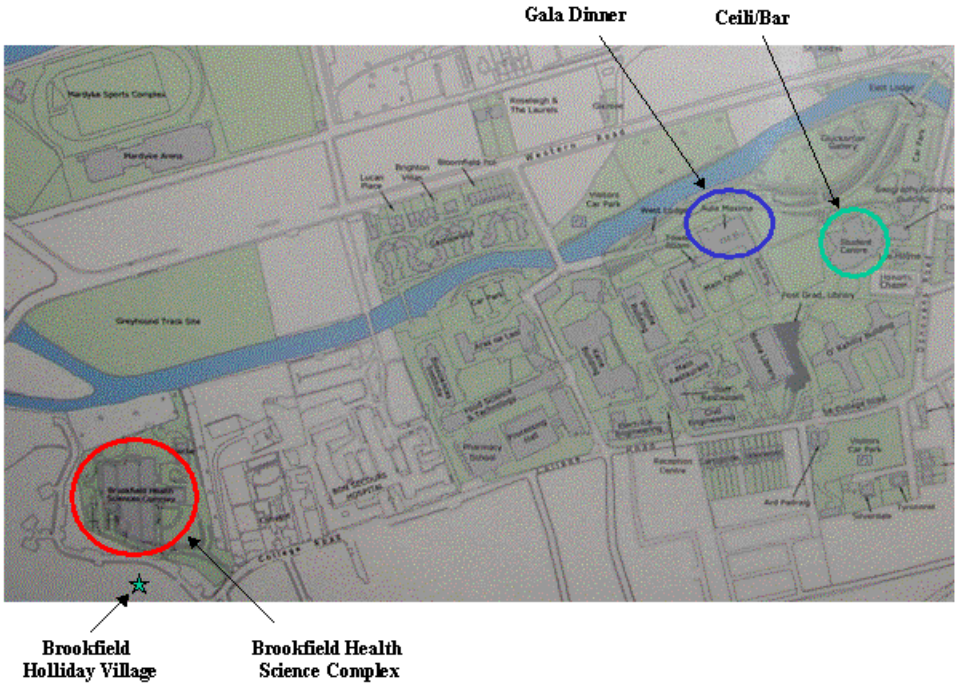
Nano2life is a living community where each partner and each member brings his own culture, expertise and vision. So this 2006 summer meeting will definitely have an Irish taste, not only during the sessions but also in the social programme. This is another nice way to address the European integration…

We would like to thank you for being in Cork with us, enjoy your stay during the sessions…and after!

Eric Moore
Paul Galvin
Patrick Boisseau
Mira Marcus
Klaus-Michael Weltring

Important Information

N2L Scientific Meeting – Venue & Activity Map



Accommodation:

Brookfield Holiday Village, College Road,
Cork, Ireland.

Tel: + 353 (21) 4344032
Fax: + 353 (21) 4344327
web: info@brookfieldcork.ie

★ **You can collect your room keys either at the reception desk or in the security hut after 6 pm**

Catering:

Breakfast is available in **Brookfield Hotel** from 7:30 am until 8:30.
Lunch and dinners will be provided during the day.

Important phone numbers:

- **Brookfield Health Science Complex (Reception +353 (21) 4344032)**
- **Tyndall National Institute (Reception +353 (21) 4904177)**
- **Taxis +353 (21) 4961961**
- **Cork Airport Information Desk +353 (21) 4313131**
- **Skylink (Bus service to airport) +353 (21) 4321020**

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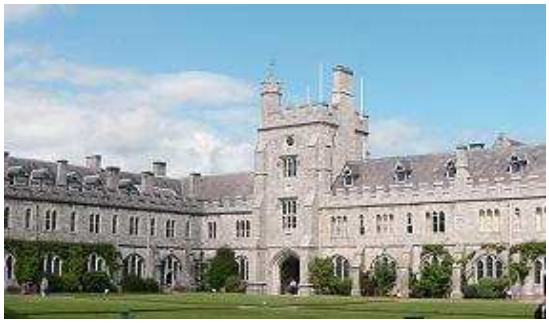
Nano2Life Scientific Meeting Agenda

	Tuesday (Sept 5th)	Wednesday (Sept 6th)	Thursday (Sept 7th)
09.00	Contact point meeting	SRP Explanation (P. Boisseau)	Intersection project: in vitro tox on chip (M.Whelan / P.Galvin) / Intersection project: optic nerve regeneration (A. Barzilai, P. Galvin) / Bazaar including SRP meetings
09.30		Invited speaker: Pr Bertrand Tavitian, (To be confirmed) NoE EMIL, molecular imaging	
10.00			
10.30		Break & Bazaar	
11.00			Break
11.30		Invited speaker: Pr Jean-Yves Blay, NoE Conticanet, sarcome cancers	Invited speaker: Regenerative medicine in FP7
12.00	Lunch		
12.30		Lunch	Lunch
13.00	EON / Tutorials		
13.30		Intersection project: in vitro tox on chip (M.Whelan P.Galvin) / Bazaar including SRP meetings	Intersection project: NBIC (M.Kalish) / Intersection project: Drug Delivery (R. Kornstein) / Intersection project: Cell Surfaces (J.Schnekenburger / P.Colpo)
14.00	Intersection project: NBIC		
14.30			
15.00	Break		
15.30	Intersection project: NBIC (M.Kalish)	Break	Break
16.00		Intersection project: optic nerve regeneration (A. Barzilai, P. Galvin) / Bazaar including SRP meetings	Invited speaker: Drug delivery in FP7
16.30			
17.00	Opening Session		Invited speaker: Diagnostics in FP7
17.30			
18.00			Conclusions: N2L towards FP7
18.30			
19.00	Opening Reception Vertigo Restaurant 17th Floor, Cork County Hall	Gala Dinner Aula Maxima University College Cork	Closing Reception Buses to BBQ in Hamlets, Kinsale

Agenda for Social Events

Welcoming Reception
7pm Tuesday 5th Sept
County Hall, Cork

Gala Dinner
7pm Wednesday 6th Sept
The Aula Maxima, UCC



The Aula Maxima

Special Event
9pm Thursday 7th Sept
BBQ in Hamlets, Kinsale

Aims of Meeting

Nano2Life set out to enable a durable integration of European researchers in nanobiotechnology. Initial efforts focussed on the development of joint research projects that would provide *cement* for researchers in different partners to start working together. Through a combination of brainstorming sessions and informal discussions on selected topics, new collaborative research projects were conceived and 15 of these have since been successfully developed into funded collaborative research projects.

As the network has evolved, the joint research activity has been iteratively refined and focussed based on extensive discussions with both academic and industry partners. This process has enabled **12** ***Strategic Research Programmes*** (SRPs) to be established providing a platform for researchers within the network to develop durable collaborations.

Six of the strategic research programmes have focussed on research in novel technologies (referred to as SRP-Ts), while the other six strategic research programmes, have focussed on elaboration of applications (referred to as SRP-As). Therefore, the research challenges defined by SRP-A groups, provide the basis for *Intersection Projects* between an SPP-A with an SRP-T. The Nano2Life scientific meeting in Cork will have dedicated sessions to four active intersection projects as follows:

(1) Novel technology platforms for in vitro cytotoxicity testing
(2) Novel technologies to promote optic nerve regeneration
(3) Cell surface interactions
(4) Drug delivery and theranostics

As a pre-requisite to participation within an intersection project meeting, each researcher is expected to bring a poster (based on the template provided) to the meeting, detailing how his/her technology / expertise / facilities / etc can contribute to finding solutions to the challenges of that intersection project. This could be a technique or technology developed for another application, which would need to be adapted and tested to evaluate its potential to solve problems within the selected intersection project.

The poster should clearly identify upstream and downstream needs, where N2L researchers could envisage opportunities for collaboration to add value to a potential solution to a research challenge.

Bazaar

The aim of the bazaar will be to enable Nano2life researchers to browse displays and posters of fellow scientists, identify opportunities for collaborations, and to discuss potential future research opportunities (e.g. FP7 projects). The bazaar area will be designed to maximise interaction among Nano2Life researchers.

Benefit of Strategic Research Programme for you

Based on detailed specification of the requirements to address the research challenge of the SRP-A (e.g. technology for cytotoxicity analysis), the SRP-T group will develop a master plan that will leverage from the extensive expertise and resources of participating individuals, research groups and institutions.

The implementation of the necessary research will, by definition, be complementary to existing ongoing strategic research activities of the participant institutions, and therefore, will not initially require additional resources to enable the necessary research. Instead, researchers will be afforded an opportunity to add value to existing funded research projects by exchanging protocols, materials and personnel as appropriate to accelerate the progress of their research and to avail of new applications for existing know-how and technologies.

As an example, it is envisaged that a novel sensor platform developed by one research group, could be optimised with respect to signal processing by another group, by chemically functionalised and patterned by other research group(s), characterised by another, provided with a novel assay by another, and packaged with a complimentary sample preparation platform by other group(s). In this way, the synergistic benefit of the collaboration is compatible with durable integration of the researchers within the network where:

- each individual and research group benefits directly with new research publications (and potentially patent(s)),
- new research outputs are generated with a highly efficient process in which technical challenges are rapidly resolved by involving the some of the most experienced researchers in the field for troubleshooting (i.e. no time wasted re-inventing the wheel)
- no new resources are required for the performance of the research (i.e. the only the additional costs involved are associated with networking activities).

Joint Research Program (WP7)

The N2L Joint research program goal is to Improve European scientific excellence and industrial competitiveness in NanoBiotech.

The need of better connection between the (nano) technology development on one hand (i.e. technologists) and the application in life sciences on the other hand, was identified in the informal brainstorming discussions with academia and industries formed in N2L previous meetings and lead to the Strategic Research Program - SRP, as a broad long term vision to meet the great challenges of Nano-bio.

The SRP goal is to create joint research groups at the intersection between the technologies oriented and the application oriented groups.

That's in order to meet the Nano-Bio future needs and challenges, as defined by the industries (WP6), and the N2L state of the art and forecasting report (WP5).

The SRP group interactions creates a platform for focused, solution driven joint research, that is essential in establishing multidisciplinary R&D, involving basic research and industries.

The **SRP approach** is based on 12 Strategic Research groups (SRPs) as a platform for researchers within the network to develop durable collaborations.

Six of the strategic research groups focus on research in novel technologies (referred to as SRP-Ts), while the other six strategic research groups, have focused on elaboration of applications (referred to as SRP-As).

These 6 technology-oriented SRPs and 6 application-oriented SRPs, are organized in the Matrix, (see enclosed) which is a visual representation of the interaction between the different SRPs to achieve more focus, and make Nano2Life more efficient.

Thus creates an intersection platform in which these two groups (technology-driven and application driven) can interact, and create new initiatives (new proposals, collaborations, etc…) That's following the ongoing process of assembling consortia and establishing **20** successful projects to gain EU funding.

The common goal for each SRP group and intersection project is to become an EU scientific excellence centre, for industry and science.

The Matrix consists of six rows and six columns. The 6 columns represent the technology-oriented groups, whereas the 6 rows represent the application-oriented groups.

Projects within the matrix can be found at any intersection between technology and application-oriented groups, which allows projects to have the full scope from technology development to a final application.

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SRPA	SRPT					
	bioanalytics instrumentation Peter-Katalinic	in vitro cell and tissue analysis Marin Bennink	in vivo imaging Pierre Le Ber	surface functionalisation Pascal Colpo	nano-assemblies Ehud Gazit	protein, DNA & cell chip Paul Galvin
Drug delivery incl theranostics Rafi Korenstein						
Cancer related diagnostics Jürgen Schnekenburger						
NBIC applied to neurodegenerative medicine Mira Markus-Kalish						
Environment monitoring & security Shimshon Belkin						
Cell biology Kristina Riehemann						
In vitro toxicology Maurice Wheelan						

SRP Descriptions

SRP – T: Surface Functionalisation

SRP Leader: Dr. Pascal Copola

JRC, Italy

Email: p.copola@jrc.it

Functionalization and nanopatterning of surfaces play a crucial role in medical diagnostics, in vitro toxicology, cell biology and biosensor developments. For instance, protein chips require well designed transducer surfaces with high specific binding of protein in an active state to guaranty specificity, sensitivity and selectivity of detection. Cell based analysis devices must rely on surfaces, which preserve cell integrity and promote cell growth and proliferation.

The SRP on surface functionalization and nanopatterning aims to gather the expertises present in N2L to address challenges/bottleneck commonly defined with the SRPA.
The expertise of N2L partners in this domain covers most techniques of surface functionalization and nanopatterning available worldwide :
- surface functionalization methods : self assembled monolayers, plasma polymers, polymer matrix…
- Nanopatterning : photolithography, e-beam lithography, ion beam.
- Bio nanopatterning : bio-functionalization (Protein, DNA… by soft lithography, dip pen lithography .).

Potential contribution of SRP4 have been identified in 3 intersection projects:

- Novel technology platforms for in vitro cytotoxicity testing (P. Galvin)
- Novel technologies to promote optic nerve regeneration (A. Barzalai)
- Cell surface interactions (J. Schnekenburger)

Cell surface interactions:
A project meeting has been organized during the Sitges N2L meeting.
During this meeting a workprogram has been proposed in agreement with the J. Schnekenburger (leaders SRP cancer diagnostics). Profiling of participants has been done.
A refinement of the group structure will be done during a dedicated poster session where people are asked their potential contribution to this project planned in the frame of Cork meeting. Restricted meetings are foreseen on demand.

Novel technology platforms for in vitro cytotoxicity testing

In the fame of this project, a working group on surface functionalization has been set up in Sitges. The definition of the project specification is on going and will be refined during Cork meeting.
Two sessions are foreseen in Cork for these intersections projects.

Novel technologies to promote optic nerve regeneration

The definition of the project specification is on going. A session is foreseen in Cork for this intersection project.

SRP – T: DNA, Protein and Cell chips

SRP Leader: Dr. Paul Galvin

Nanobiotechnology Team
Tyndall National Institute
Cork, Ireland

Email: paul.galvin@tyndall.ie

Mission: This Strategic Research Programme (SRP) will build a synergy among Nano2Life partners with research activities relating to DNA, protein and cell chips, by engaging in collaborative research to address specific application challenges.

Background: Many Nano2Life research groups have already developed significant know-how relating to novel samples preparation devices, sensors, and methodologies for surface functionalisation, data processing and system integration. The potential exists to add significant value to the research outputs of individual groups, through collaboration with other research groups with complementary expertise, technologies and know-how. The synergy expected will result from individual research groups focussing on their specific strengths, and by availing of existing solutions to research challenges where possible. This should significantly accelerate research progress and avoid duplication of effort by different groups with the network.

The focus of the collaborative research activities within this SRP will be driven by the needs of applications specialists including industry. An initial workshop was organised (Sept 9th in Amsterdam), together with leaders of the SRPA on *cancer related nanodiagnostics*, and SRPT on *Surface functionalisation* to define a set of research initiatives for this SRP.

Scope: The primary research goal of this SRP is to facilitate collaboration among research groups within N2L towards the development of integrated biochip platforms for DNA, protein or cell analysis. It is envisaged that the expertise, know-how and infrastructure required will include end-user requirements, sample preparation of DNA, cells and proteins, microfluidics, biophotonics, surface functionalisation and surface characterisation, various electronic detection platforms, signal processing, data analysis and interpretation, systems integration and packaging, etc. The specific requirements for each research initiative within this SRP will be dictated by the specific nature of the application chosen. In this regard, applications such as point-of-care diagnostics and environmental monitoring will have very different requirements with respect to the selection of performance priorities such as sensitivity, cost, durability, size, etc. Therefore, while the research is intended to be industry relevant, the scope is expected to span from short-term applied (based on new applications of existing infrastructure and know-how), to long-term fundamental (based on defined fundamental problems). The initial focus will be targeted towards the two intersection projects on *cytotoxicity,* and *novel technologies for stimulation of optic nerve regeneration* (see relevant intersection project descriptions for details).

Outputs: It is envisaged that this SRP will result in several dynamic collaborations involving two or more research groups addressing specific challenges, sharing know-how and resources, exchanging material, and with the aid of N2L WP1, exchanging researchers. As this SRP topic has the potential to be the core enabling technology for many different applications, it will be initially focussed on the two very specific challenges where the end user requirements can be well defined from within the Nano2Life network, and where the potential exists to combine available expertise and resources to generate a significant research momentum. It will later be possible to expand the applications to other challenges including environmental sensing and implantable drug delivery systems.
Publications, patents and new research proposals resulting from these collaborations will provide the basis for durable integration of the involved researchers and research groups.

SRP – A: Cell Biology

SRP Leader: Dr. Kristina Riehemann

CeNTech/Physikalisches Institut
University Munster
D-48149 Munster

Email: K.Riehemann@uni-muenster.de

Within the last months the cellbiology group is started to be built up. The first meeting of this group will be in Cork. Aim of this meeting is to collect the Cellbiology know-how within nano2life. The outcome shall be a state-of-the-art report which explains the research areas, aims and technical problems of the cellbiology scientist of this group. The report should help to establish contacts between the SRP-T groups and people from the cellbiology group. After the cellbiology survey of the know-how within N2L, external scientist with research areas fitting to the focus of the research groups within N2L will be contacted to strengthen the group. In a second meeting together with the SRP-T groups intersection projects will be discussed and started.

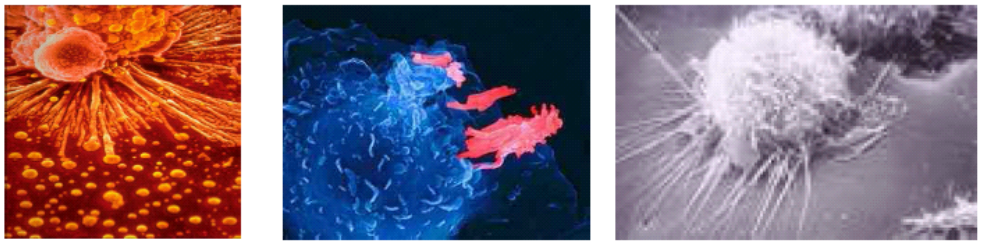

Fig 1.-3. Macrophages: components of the immunedefense (Nilson; Brinkmann; Boehringer)

Deliverables of the next months:

1. - complete European expert group cellbiology
2. - state-of-the-art-report "Cellbiology"
3. - generate intersection projects
4. - contacting industries to plan grant application

SRP – A: In Vitro Toxicology

SRP Leader: Dr. Maurice Whelan

JRC, Ispra, Italy

Email: m.whelan@jrc.it

SRPA structure and work programme

The work of the SRPA will involve the definition and execution of targeted research and demonstration projects, in partnership with SRPT groups. These 'intersection' projects will be tackled by different dedicated group of N2L partners drawn principally from the SRPTs. The work programme of an intersection project will be managed by task leaders, who will be supported by the SRPA and SRPT leaders.

The first intersection project entitled "Cytotoxicity on a chip" will address the scientific and technological challenges associated with the conception and design of an integrated device (loosely termed "chip") to carry out complete cytotoxicty assays based on mammalian cells. The initial focus will be on assays that determine the systemic or organ-specific cytotoxicity of chemicals, that when combined with biokinetic (ADME) data, can be used in the prediction of acute toxicity in lab animals or humans. This intersection project got underway during the N2L annual meeting in Sitges (27-29 March, 2006). In a plenary session, the SRPA leader for "In vitro toxicity" (M. Whelan) gave a presentation to put the intersection project in context, describing the political and commercial relevance, current trends and approaches, and the scientific and technical challenges to be tackled (presentation available on-line at http://nano2life.tau.ac.il/archive.html). The next sessions dedicated to this intersection project will take place during the N2L meeting in Cork in September 2006. Newcomers are very welcome, and are encouraged to present a poster (see meeting web-site for more information on the intersection project and instructions and the template for poster presentation).

It is foreseen that this SRPA will work closely with the SRPTs on "In vitro cell and tissue analysis" (leader M. Bennink), "DNA, Protein and Cell chips" (leader P. Galvin) and "Surface functionalisation" (leader P. Colpo). Examples of scientific challenges to be considered are as follows:

- Rapid, sensitive, non-invasive methods for detection of basal cytotoxicity
- Integrated systems for maintaining cell and tissue models from 1 to 90 days
- Improved techniques for quantitative morphological analysis of cells and tissue
- Sensitive, specific, non-invasive detection techniques for intracellular targets
- Multi-modal integrated biosensing for on-line monitoring of multiple parameters

Through interaction with end-user groups and in vitro toxicology experts the SRPA will guide the specification of the technical requirements and constraints associated with these challenges. The SRPA will organise inter-laboratory comparisons when appropriate to encourage a multifaceted, problem solving approach to tackling the research challenges. The new integrated facility at the JRC for automated ADME-Tox testing can be utilised if desired as a European platform for the evaluation and demonstration of novel nanotechnology devices.

Guidance from external bodies will be facilitated by the frequent consultation of the SRPA leader with European organisations such as ECVAM (http://ecvam.jrc.it), and entities that will participate in the "Prospective Workshop on Drug Development" being arranged by WP5. Together with WP6, the SRPA leader will also manage practical interactions with industrial partners and end-users already associated with N2L.

SRP – A: Converging Technologies applied to Neurodegenerative Medicine

SRP Leader: Dr. Mira Marcus-Kalish

Tel Aviv University, Israel

Email: miram@post.tau.ac.il

Vision

To become a meeting point of the various research areas, technologies, tools, and know-how, represented in NBIC – Nano-Bio Info Cogno. That is in order to enhance human performance in various application, mainly in neurodegenerative medicine. To relate to the whole human body and its surroundings as one, including Cognition, Psychology… etc., while bridging language, technology and other barriers.

Background

Converging Technologies (NBIC) was presented first on December 2001, as a synergistic combination of (a) nanoscience and nanotechnology; (b) biotechnology and biomedicine, including genetic engineering; (c) information technology, including computing and communications; and, (d) cognitive science, including cognitive neuroscience.

Converging Technologies CT- NBIC was recognized as a USA national initiative (1 Billion $ a year) and defined as "a broad, cross-cutting, emerging and timely opportunity of interest to individuals, society and humanity in the long term, which offers immense opportunities and represents a major new frontier in research and development". (Roco and Brainbridge, 2002).

Following that, the European Commission (EC), published on Sep 2004 the experts report on " Converging Technologies – shaping the future of European society" where the circles of Converging Technologies was widened towards "CTEKS: (Convergence Technologies for the European Knowledge Society), including Nano-Bio-Info-Cogno-Socio-Anthro-Philo" and set it as a priority area for FP7.

Focus

The focus is on creating infrastructure for research at the confluence of NBIC domains, in order to understand the unity of specific system at the Nano scale level, including brain multilevel functioning, neuronal networks as well as cognitive sciences and behavior.

Goals

To create a European Converging Technologies working group on Nano-Bio broad aspects based on N2L top researchers from various disciplines, like: Medicine, Life sciences, Cognitive sciences, engineering, psychology, ethics, environmental studies, exact sciences….etc.

Outputs

The group will develop powerful transforming tools at confluence of disciplines while focus on specific research questions/applications such as: cerebellum motor functions, regenerative nerve systems, neuronal functioning early detection and treatment of diseases.

Key success factors:
Understanding the structure and function of complex systems by creating:
1. Ongoing interdisciplinary working group applied to Neuro medicine, while:
- Bridging language and concept barriers
- Creating innovative approach to Nano-Bio, new concept, systems & process understanding, products.
- Establish collaboration with Industrial partners.
- Cooperation with ethics, educational and societal professionals.
- Being part of the EC policy framework.

2. Introduce major European workshops in the area,
3. Become a reference center in the area.

Needs
Cooperation with other SRPT (Technological) and SRPA (applications) groups. Involvement of N2L partners from various areas such as: engineers, Biologists, Nano-science, various technologies such as imagining, bio-informatics, cognitive sciences, psychology, ethics, medical doctors, Neuro-science, etc.
Looking for interested partners and projects from academia and industry.

Do you want to suggest a project / join one of the groups?
please contact
miram@post.tau.ac.il

Work Plan
➢Establish interdisciplinary working groups, such as the following projects:

- Nerve de/regeneration mechanism, for example axonal regeneration of optic nerve. (lead by Prof. Ari Barzilai – Tel Aviv University.)
  Please see intersection project in the conference site, www.tyndall.ie/n2l
- Investigating mechanism of dopaminergic neurodegeneration and neuroprotection. (lead by Prof. Maria Klapa – Forth – Greece)
- Rehabilitation of cerebellar functionality by Nano-interfaced model chip.

(lead by Prof. Matti Mintz – Tel Aviv University).

More information on the various projects- short presentations at:
http://www.tau.ac.il/video/Lectures/nano/n2L/Barcelona/day_3.html
User-id and password nano2life

Establish a professional board from academia and industry to identify and characterize the NBIC activities and relevant applications.
Scientific workshop – special meeting, on broad NBIC – Converging Technologies applications, 2.5 days planned in beginning 2007 in Israel.
Prospective workshop on Cognitive Sciences and Neurological rehabilitation, planned in Israel on 2007.
Establish a consortium of interested partners and industry, focused on NBIC commercial applications and tools.

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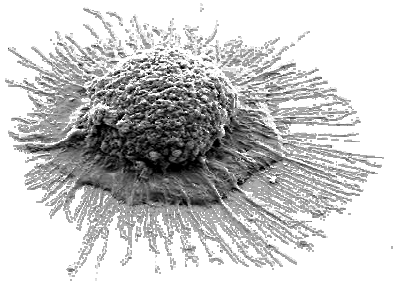

SRP – A: Nanotechnology and Cancer Diagnostics

Mission and Vision:

The general mission of the SRPA group Cancer Diagnostics is the development of new technologies for a cheap, reliable and early cancer diagnosis.

The SRPA group has 3 major objectives:

1. Strengthening of N2L research competence in cancer diagnostics by bilateral projects between N2L biomedical partners and technology developers. This objective has a focus on the support of SRPT partners with biological material, samples and biomedical expertise.
2. Generation of funded biomedical research projects for the development of new in vitro and in vivo devices and technologies for early cancer detection, rapid classification and decision support systems involving partners from outside of N2L, biomedical groups within N2L and technology developing N2L partners recruited for defined application driven projects.
3. Organisation of a European research area in nanotechnology and cancer diagnostics directed by N2L.

Group structure:

The core group are biomedical experts working in the field of cancer diagnostics from N2L (Uni Münster, CEA, INSERM). External partners for specific projects are hospitals with a broad experience in clinical studies, Bioinformatics researchers, Pharmaceutical industry, Diagnostics industry, Medtech industry, other networks or nanomedicine organisations.
The core group will acquire high competence in new nanotechnology development by own cooperative research projects and lab visits of technology partners. This expertise will be used for the set up of research projects with external partners and an influential participation in EU research organisations as the ETP nanomedicine.

Offers to N2L and external partners:

- A broad expertise in cancer biology and the application of new technologies in cancer research and diagnostics. Critical review and test of technology transfer to biomedical applications.
- Defined biomedical materials and probes (cell lines, tissue probes and serum samples from human and animal sources) for testing and development of new technologies for N2L partners including a list of possible preparation methods and transport conditions of the selected material.

- A catalogue of possible cooperation projects as example for N2L cancer research opportunities developed together with N2L strategy and foresight experts.
- Set up of projects on the area of nanotechnology and cancer research. Organizing consortia for the preparation of EU FP7 applications or industry funded projects.
- Running projects include the development of new diagnostic lab-on-a-chip systems, the development of surfaces selective for diagnostic markers or disease related cells or the application of new optical technologies in in vivo cancer diagnostics.

Biological and Bio-inspired Nano-assemblies

The development of novel biomaterials is a key area of research for advanced medical technology. Nano-scale biological and bio-inspired assemblies are emerging as materials for controlled drug release, tissue repair, molecular imaging, and tissue engineering. Due to the fact that many diseases cannot be treated solely by small-molecule drugs, cell-based therapy is emerging as an alternative approach. Several types of self-assembled nano-structures, their derivatives, and other biocompatible polymers showed great promise in this area.

Tubular nanostructures, particularly carbon nanotubes (CNT), are suggested to have a wide range of applications in nanotechnological devices and assemblies. CNT offer many advantageous due to their small size, high aspect ratio, and conductance. However, the integration of carbon nanostructures into functional devices is limited by major issues related to their production, uniformity, bioincompatibility, reproducibility, and cost. Furthermore, the chemical nature of the tube limits their covalent modification with biological and chemical reporters.

Self-assembling biopolymer systems are especially attractive for this purpose due to their ability to serve as biological compatible scaffolds and nano-vesicles. Most of the recent studies was based on peptide or peptide-hybrid molecules. However, other types of biomaterials could be used. Furthermore, biocompatible peptide-based material gained much interest as a building block in the bottom-up design and assembly of nano-scale devices for bio-nano-applications (such as cellular manipulation, bio-nano-machines, and nano-scale diagnosis and treatment). Fabricated biomaterial was shown to support cell attachment and differentiation, to support neurite outgrowth and the formation of functional synapses of primary and cultured neuronal cells. Other studies had demonstrated the utilization of nano-scale bio-assemblies in sensitive biosensors and as contrast agents in advance MRI imaging.

In the SRPT group, we intend to explore the properties and potential use of nano-structures that are based on biomaterials. This will include direction toward the characterization of the structures, their mechanism of assembly, the directions toward their modification. We will also discuss applications in the diverse fields such as material science, tissue engineering, biosensors, etc. The potential members of the group include both experts in the fields of self-assembly and molecular design as well as those interested in the specific applications (tissue engineering, drug release, contrast agents, biomaterials, etc.).

Intersection Project Descriptions

Title : Cell – Surface Interactions	
SRPT:	**In vitro cell and tissue analysis & Surface functionalisation**
SRPA:	**Cell biology Cancer Diagnostic**

1. What is the question that this research will address?

Analyzing cell function in a defined 3 dimensional environment
The objective of the intersection project is the development of artificial 3-dimensional (3D) structures with functionalized surfaces for the study and establishment of heterogeneous cellular systems. The 3D systems will be composed by nanostructured scaffolds arranged in a 3D platform for cell analysis.

The 3D platforms for studying cancer cells in a defined 3D environment will be used as a model for the migration, dedifferentiation of tumor cells and the development of heterogeneous tumor cell populations under defined conditions. The non linear development of tumor cell subtypes can be studied in great detail to establish a new test system for cancer drugs and combinations of cancer drugs addressing heterogeneous therapy-resistant tumors. The 3D platforms will establish for the first time a direct access to heterogeneous tumor systems and overcome the restrictions of studying clonal cell systems in vitro and in animal models. The system will open application areas using 3D cell systems with high positive biomedical impact as stem cell differentiation, dedifferentiation of adult stem cells, tissue engineering and the design of biocompatible implants. Nanostructured implantable 3D scaffolds are expected to be used for the induction of in vivo tissue regeneration. The 3D platforms developed within this project will solve previously unaddressable problems, the behaviour of heterogeneous cell populations in tumors and 3D structures involved in stem cell differentiation will become open to direct study. The characterization of heterogeneous tumor cell systems will generate new tools for the development of tumor therapeutics and reveal new parameters for tumor diagnostics and prognosis.

2. Why is the problem significant?

The treatment of cancers is one of the most challenging problems in gastroenterology and other medical fields. Pancreatic cancer as an example is a highly metastatic cancer which is resistant to all known therapies resulting in a poor mean survival of 5 % after 6 months from first diagnosis. The analysis of cell migration and metastasis is therefore a crucial issue to get insights in cancer progression and to develop new therapeutic concepts. Recent reports demonstrated the very essential need of yet unavailable, highly defined 3 dimensional (3D) environments for the study of cancer cell migration. Cancer cells in 3D systems reveal novel features, such as an amoeboid-like cell movement, not observed in widely used 2-dimensional cell culture plates. Moreover the development of heterogeneous cell systems reflecting the situation of a solid tumor requires a 3D environment with different functionalized surfaces exposed to cells. These surfaces will create different signals to the cell population inducing cells to change their phenotype to different directions.

3. What is needed to address the problem?

For the study of cancer cells in an environment reflecting the heterogeneity of an in vivo situation we have to develop novel 3 dimensional artificial nanostructured building blocks that will function as *in vitro* platforms for living cell studies, with radically increased complexity and flexibility. Among the important determinants and triggers for the behavior of cells in contact with solid surfaces, neighboring cells or extra cellular matrix components are chemical surface composition (ligand type, density and spatial distribution on the substrate, and the cell membrane), as well as topography and mechanical properties of the underlying substrate. Studies using 2D structured surfaces have already shown that the nano-scale distribution of (extra) cellular components on the single molecule level controls the macro-scale functioning of cells and corresponding in-out signaling processes. The platform will provide a fully controlled 3D environment reflecting extracellular matrix structures including additional cell types, such as fibroblasts, endothelial layers, leukocytes and epithelia. The nanopatterned functionalization of the surfaces should allow the analysis of the function of defined protein complexes, such as growth factors, angiogenesis factors, integrins and cadherins and the clustering of cell surface proteins by nanoscale structures.

4. How will the problem be addressed?

The platforms can be generated by targeted arrangement of nano- and microstructured micrometer-sized building blocks on prepatterned and structured surfaces. The immobilization of cell surface receptor ligands can be facilitated via hybridization of target oligo-DNA conjugated ligands with surface immobilized complementary probe DNA.

Cells will be analyzed by atomic force and fluorescence microscopy, the marker free and noninvasive recording of cellular processes will use the recently established method of digital holography of living tumor cells. Gene expression analysis will involve fluorescence-based measurement of tumor cell protein expression and single cell DNA arrays

WWU can contribute to this project defined and characterized cellular systems, tools and methods for the analysis of cell differentiation and tools and methods for the analysis and modulation of cell migration and cell-cell interaction.

Title : Novel Technology Platforms for in vitro Cytotoxicity Testing	
SRPT:	**Protein, DNA and Cell chips & Surface functionalisation**
SRPA:	**In vitro toxicology**

1. What is the question that this research will address?

This project will address the scientific and technological challenges associated with the conception and design of an integrated device or "chip" to carry out complete cytotoxicty assays based on mammalian cells. The initial focus will be on assays that determine the systemic or organ-specific cytotoxicity of chemicals, that when combined with biokinetic (ADME) data, can be used in the prediction of acute toxicity in lab animals or humans. Currently, the majority of testing laboratories in the EU carry out cytotoxicity assays manually, using typically 6 to 384 well microtiter plate formats. After seeding of the well-plates, the cell culture is treated with the test chemical and incubated for a number of hours or days. The degree of toxicity is then determined by measuring a particular cytotoxic "endpoint", such as membrane integrity or metabolism. Often the objective is to produce a dose-response curve from which, for example, an IC_{50} value can be extracted (i.e. the concentration of test chemical at which the viability of half of the cell population is compromised).

There are a number of commercial products that target the automation and miniaturisation of cell-based assays. Some of these utilise a micro-fluidic chip (e.g. desk-top analyser from www.home.agilent.com, Fig.1a) but their function is usually limited to the analysis of treated cells (e.g. cytometry), neglecting the preceding steps in the assay. A number of companies offer "workstation" solutions which can carry out many different assay steps and which can handle standard microtiter plate formats (e.g. cell-assay workstations from www.caliperls.com, Fig.1b). However, to achieve a more satisfactory level of functionality and throughput, users must resort to large, sophisticated and costly test platforms (e.g. JRC cytotoxicity test facility, Fig 1c).

This project will identify and demonstrate how selected nanobiotechnologies can be exploited to deliver more functionally rich, highly integrated, holistic solutions to carry out cytotoxicity testing of chemicals. Both existing know-how and the most radical of new ideas will be considered and elaborated, with the aim of making a quantum leap in the cell-on-chip concept.

Fig. 1 (a) Desk-top cell analyser from Agilent

Fig. 1 (b) Microtiter plate workstation from Caliper LS

Fig. 1 (c) Cytotoxicty testing facility at JRC.

2. Why is the problem significant?

There is a considerable, rapidly increasing demand from pharmaceutical, cosmetics and chemical companies for validated in vitro test methods and technologies. The demand stems from two main sources. Firstly, the new EU chemicals policy (REACH) and the Seventh Amendment to the Cosmetics Directive have placed a significant burden on industry to provide more comprehensive safety assessment data on their products, while in parallel requiring the reduction and eventual elimination of animal testing. Secondly, companies are committed to introducing in vitro toxicity

testing earlier in their discovery and development processes to reduce the huge costs associated with safety assessment and regulatory acceptance, usually carried out downstream.

State-of-the-art commercial solutions are not keeping pace with demand – there is a huge gap between what current devices can do and what is actually required to carry out comprehensive cytotoxicty testing of chemicals, in a modern industrial and regulatory context. Although many novel test methods and technologies are emerging from the scientific community, the impact of these has been very limited to date. Innovative assay technologies need to be specifically adapted for cytotoxicity testing, they need to be systematically assessed and demonstrated through comparison with standardised tests, and they should be coupled with a suitable standard operating protocol (SOP) as a first step in gaining regulatory acceptance.

3. What is needed to address the problem?

3(a) Although certain detailed technical requirements depend on the specific cytotoxicity assay being implemented, there are a number of general design criteria that should be considered when conceiving a cytotoxicity-on-chip solution. Firstly, the device should be able to carry out all the necessary steps in an assay, including conditioning and maintenance of the cell culture model, treatment and incubation of the cells with the test chemical, measurement of both test conditions and the response of the cell model, and output of the test data in a suitable format. Most cells used are adherent and thus should be cultured, treated and monitored in situ, although many assays use blood cells which can be suspended in a circulating biofluid or a stationary gel matrix. The surfaces to which cells adhere have an important role since cell morphology and function can be influenced in a beneficial or detrimental fashion. For example, suitable surface properties can ensure that hepatocytes and neural stem cells achieve a sufficient degree of differentiation, in order to function as viable cytotoxicity models.

The duration of an assay can vary significantly, from a couple of days with simple cell lines to many weeks with more complicated cell or tissue models, thus correct maintenance and nutrition of the culture is critical. Ideally cells should be monitored non-invasively over the duration of the assay, to register changes in cell mechanisms and function such as metabolism, protein turnover, gene regulation, intra- and intercellular signalling, glycolysis and the formation of reactive oxygen species. More organ-specific functions which are also important are transport and filtration, metabolic transformation, electrical conduction and neurotransmission. Monitoring of test conditions such as temperature, humidity, pH and dissolved oxygen would be also useful for process control and quality assurance.

Since it is better to base the cytotoxicity profile of a chemical on data derived from a number of different endpoints, when testing it on more than one cell type, an on-chip solution should support high content analysis in a parallel processing scheme. There are a number of practical reasons why the overall system should be small and compact, but more importantly the characteristic "size" or format of the assay itself should be as small as possible. That is, the minimum amount of cells, reagents and test chemicals should be used without compromising the quality and robustness of the assay. As an indication, it has been shown that for certain cell lines, a cytotoxicity assay is feasible using 100s if not 10s of cells, instead of the millions of cells used in larger microtiter plate formats. Finally, and not surprisingly, cost is a major factor for consideration, although appropriate cost-models and cost-benefit analyses should be devised that accurately describe the potential economic impact of a disruptive on-chip technology.

3(b) SRP-T leaders should then identify and detail in general the skill-set that would be needed (i.e. specific scientific research disciplines required, etc), infrastructure requirements (i.e. cell culture / surface characterisation tools / etc), technology requirements (e.g. sensors, fluidics, modified surfaces, etc).

(500 words *by March 15, 2006*)

Title : Novel Technologies to Promote Optic Nerve Regeneration	
SRPT:	**In vivo imaging and Surface functionalisation**
SRPA:	**NBIC for neurodegenerative disease**

1. What is the question that this research will address?

Our long-term goal is to devise ways for the improvement of functional axonal regeneration in adult animals following acute injury and chronic disease. However, it appears that the central nervous system (CNS) regenerative failure reflects both the intrinsic inability of adult CNS neurons to survive and reinitiate axonal growth, and the lack of a permissive environment for such growth. This led us to hypothesize that initiation of the retinal ganglion cells (RGCs') growth program by the expression of certain proteins, and the alteration from a non-permissive environment to a permissive mode could result in functional axonal regeneration. The purpose of this research is to generate a holistic treatment that will define the conditions that will permit preservation of RGCs, initiation of the growth program and generation of a permissive environment that will permit functional axonal regeneration of adult RGCs towards their target organ, namely, the lateral geniculate body (superior colliculus).

2. Why is the problem significant?

These studies should shed new light on the mechanism of neuronal degeneration and axonal regrowth in chronic eye diseases and during trauma. In addition, they may lead to the development of novel drugs that will confer long-term protection to the RGCs, and enable axonal regeneration in a way that maintains the already existing retinotypic maps.

3. What is needed to address the problem?

Axotomy of the optic nerve axons leads to the death of the RGC cell bodies and, consequently, to a Wallerian degeneration of injured axons. As a first step towards future treatments, one should analyze the molecular events associated with retinal degeneration and optic nerve injury and pave the way to treatments allowing retinal survival and axonal regeneration. In the first part of the project, we intend to continue our efforts in the analysis and characterization of the cellular and molecular events that underlie retinal and axonal degeneration and the generation, of the non-permissive environment. In parallel, alterations in the RGC growth program that allows growth initiation and the generation of a permissive environment will be examined. The research program is based on the following main foundations: a) Microsurgical techniques to create the basis for clean axotomy of optic nerve and methods for implantation of nanotechnological material and stimulating substances for regeneration; b) Usage of nanotechnologies and bioinformatics that will include metabolomics, proteomics and transcriptomics; c) An electrophysiological test to evaluate the activity of the regenerative response and its connection to the brain; d) Cognitive studies that will focus on the behavior of retinotypic maps after injury and during regeneration.
We hypothesize that holistic and comprehensive treatments that include re-ignition of the growth program, preservation of RGCs survival, the generation of a permissive environment

and the maintenance of target sites at the brain, are sufficient and necessary to enable functional axonal regeneration. Based on this hypothesis, we set out to explore whether re-ignition of the growth program and provision of the injured axons with the necessary support and removal of the non-permissive cues will result in enhanced functional axonal growth. Here we plan to focus on acute ON injury (axotomy in rats). Towards this goal, we intend to focus our efforts in the following directions: (i) Further analysis of the retinal and axonal degenerative processes. (ii) Generation of a permissive environment that will permit functional axonal regeneration. (iii) The maintenance of the visual tracts by nanostructures that are capable of activation of the visual pathways. (iv) A test of the efficiency of combined treatments by morpgological and electrophysiologic evaluations.

4. How will the problem be addressed?

Specific scientific research disciplines required;

1. Generation of various types of axonal promoting substrates. Here we require nanotechnologists who will develop these materials that can be injected into the injured nerve and support functional axonal regeneration.
2. The generation of microelectrodes and specific chips that will stimulate the injured optic nerve in order to enhance axonal growth. For this purpose we need scientists who specialized in nano-electrical engineering.
3. Generation of nano-particles that will allow spatial and temporal secretion of specific materials. Here we need scientists who are specialized in nano-particles.
4. Imaging analysis of the growth process. Here we need scientists who are specialized in various imaging techniques.
5. Electrophysiological analysis of the injured optic nerve-here we need electrophysiologists of the visual system.
6. Final analysis will be cognitive analysis of the optic nerve and optic tract.

The potential exists to develop dynamic substrates with a range of electrode designs, and a range of chemical release capabilities to enable an evaluation of various combinations of topographical, chemical and electrical stimuli to trigger the axonal growth promotion.

Therefore, N2L scientists who have already developed (or are in the process of developing) novel electrode designs, novel dynamic substrates with capabilities to selectively release molecules from the surface, novel nanopatterned surfaces, or any combination of the three might agree to provide samples for evaluation as potential axonal growth promoting devices.

Interaction with SRPs on *Surface Functionalisation* and *In Vivo Imaging* are envisaged.

For the electrophysiological and cognitive aspects, interested persons are required.

N2L members participating in the Cork meeting should prepare posters detailing how their chips / nanopatterned surfaces / dynamic surface chemistry / etc could have potential value for axonal promotion as the starting point for the intersection project discussions. Then it will be possible to get deep into more detailed aspects of how different approaches might work, and the next steps. Additional expertise can be sourced locally from medical professionals if necessary to provide additional input on biology of optical nerves etc.

Title : Drug Delivery and Theranostics	
SRPT:	**Surface functionalisation, Protein, DNA and Cell chips & Nanoassemblies**
SRPA:	**Nanobased drug delivery, Cancer related nanodiagnostics**

The improvement of drug delivery by employing novel types of nanocarriers constitutes one of the central goals of nanomedicine. A possible approach to supply on demand drugs linked to nanocarriers is the employment of **semi-implantable drug delivery systems**.

Taking into consideration the priorities of research in the area of drug delivery in the field of nanomedicine it has been decided concentrate on applications in two specific clinical topics:

(i) **Diabetes** – Develop a semi-implantable device which will carry out detection of glucose level in blood coupled to delivery of insulin, coupled to nanocarriers. The preferred strategy will incorporate an array of microneedles that penetrate the *stratum corneum* impermeable layer of skin. **Project leader** – Dr. Michael Loughran (Tyndall National Institute)

(ii) **Cancer** – Develop implantable or semi-implantable device for local electric stimulation of the site of primary tumor following local injection of nano-carriers linked to chemotherapeutic agents. **Project leader** – Prof. Rafi Korenstein (Tel-Aviv University)

Diabetes: Diabetes is a prevalent, costly condition associated with substantial morbidity and mortality. In 1997, approximately 15.7 million persons in the United States (5.9% of the total population) had diabetes. **(US Department of Health and Human Services, CDC, 2000).** An EU consensus in 2005 estimated that more than 25 million people live with diabetes. **(EU Diabetes Policy Puzzle, International Diabetes Federation, European Region, published June 2006).** All of them threatened by serious, disabling diabetes-specific complications leading to damage or even complete failure of target organs - kidneys, nervous system and the eyes. Diabetes is also major contributor to cardiovascular disease **(Diabetes and Cardiovascular Disease Scott M Grundy et al., Circulation. 1999;100:1134-1146)**. It is also estimated that up to 50 % of people with diabetes are undiagnosed or are unaware of their condition. Conventional self-monitoring of blood glucose (SMBG) with multiple daily injections or insulin pump therapy (continuous subcutaneous insulin infusion offered the possibility of controlling postprandial hyperglycemia and reducing the risks of severe hypoglycemia. However, most youths with type 1 diabetes only measure pre-meal blood glucose levels during the day and rarely

measure glucose levels during the night, the time of greatest vulnerability to hypoglycemia (Porter PA et al., *J Pediatr* 130:339–341, 1997). Therefore a continuous glucose Monitoring System is required to helps patients manage glucose fluctuations for 24h. Measurement of real-time glucose values is required to alert patients when glucose levels become too high or too low. A semi implantable insulin pump, which is designed to more closely mimic the function of a normal pancreas, offers potential treatment advantages to patients who have difficulty maintaining consistent glucose control. Our implantable pump is designed to deliver short, frequent pulses of insulin into the peritoneal cavity via a microneedle array, where it can be more rapidly and predictably absorbed versus in the subcutaneous tissue.

Cancer: Cancer is a complex multifactorial disease and it requires combinations of several therapeutic modalities to treat it effectively. Despite advances in the field of prevention and treatment of cancer, morbidity remains high, especially for tumors that cannot be completely removed, those that are highly recurrent, or highly metastatic.
A possible application of semi-implantable device in cancer therapy is to deliver the chemotherapeutic agent at high comcentration directly to the cancerous cells in the primary tumor. Based on studies on enhanced uptake of macromolecules into cells via endocytic pathways following exposure to low electric fields, a novel approach was recently developed for metastatic cancer cure founded on a treatment by local low electric field stimulation of the primary tumor combined with chemotherapy (Entin et al., **Clinical Cancer Res** 9: 3190-3197, 2003**;** Plotnikov et al., **Clin. Exper. Immunol.** 138: 410-416, 2004; Plotnikov et al., **Int. J. Cancer** 117: 816-824, 2005). It is intended to extend these studies by employing chemotherapeutic agents linked to nanocarriers. It is suggested to apply these chemotherapuetic agents in combination with electrical stimulation of the primary tumor. We expect that this treatment modality will be able, in future, to substitute the conventional surgery and chemotherapy treatment.

Required collaboration:

(1) **Diabetes:** Researchers engaged in fabrication and characterization of micro-needle arrays; Researchers studying novel approaches for a quantitative and repeatable detection of glucose.

(2) **Cancer:** Researchers who are engaged in production and employment of chemotherapeutic agents linked to nanocarriers in cancer treatment.

The discussion of these two intersection projects is planned to take place during the WP7 meeting in Cork on Thursday September 7th.

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   J. Rishpon
   Tel-Aviv University.

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3. **Bioassay Platform using Fibre-coupled Avalanche Photodiodes for Improved Biomolecule Detection**
   M. Mac Sweeney[1], F. Li[1], C. Jackson[2], A. Mathewson[1] and M. Manning[1]
   [1]Tyndall National Institute, Lee Maltings, Cork, Ireland.
   [2]SensL Technologies Ltd., Riverview Business Park, Blackrock, Cork, Ireland.

4. **Electroanalysis as a monitoring tool for cytotoxic conditions**
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   Chemical µAnalytics, Tyndall National Institute, Lee Maltings, Prospect Row, Cork, Ireland.

5. **Base-stacking Approach to SNP Detection on a Magnetic Sensor Platform.**
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   Tyndall National Institute, Lee Maltings, University College Cork, Ireland.

6. **Impedance Spectroscopy Measurements of Ion Channels in Tethered Lipid Bilayers**
   Samuel Terrettaz and Horst Vogel
   Laboratory of Physical Chemistry of Polymers and Membranes, Swiss Federal Institute of Technology in Lausanne (EPFL), 1015 Ecublens, Switzerland.

7. **Development of low cost miniaturised cell analysis system**
   B. Fogarty[1], P. Casaubieilh[1], M. Mc Carthy[2], S. Culloty[2], J. Davenport[2] and J. Alderman[1]*
   [1]Life Science Interface; Tyndall National Institute, Cork, Ireland.
   [2]Department of Zoology, University College Cork, Ireland.

8. **Functional analysis of Shiga toxin 1 interactions with human brain microvascular endothelial cells: a nanotechnology-based strategy for analyzing virulence factors of pathogenic bacteria**
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   [1]Institute for Hygiene, University of Münster,
   [2]Institute for Medical Physics and Biophysics, University of Münster,
   [3]Laboratory of Biophysics, University of Münster,
   [4]Institute for Medical Physics and Biophysics & CeNTech, University of Münster, D-48149 Münster, Germany.

9. On-Chip determination of Neurotransmitter Exocytosis

Christer Spégel[1,3]*, Arto Heiskanen[1], Jenny Acklid[1], Anders Wolff[2], Rafael Taboryski[3], Jenny Emnéus[1] and Tautgirdas Ruzgas[4]
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[3]Sophion Bioscience A/S, Baltorpvej 154, DK-2750 Ballerup, Denmark.
[4]Facutly of Health and Society, Malmö University, SE-20506 Malmö, Sweden.

10. Development of a biochip sensing platform for monitoring of cells in-vitro

Karen O Donovan, Terri Wood, John Alderman and Eric Moore
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[1]Department of Analytical Chemistry, Lund University, Sweden.
[2]Department of Restorative Neurology, Lund University, Sweden.
[3]Division of Solid State Physics, Lund University, Sweden.

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15. Kinetics of Protein Adsorption at Liquid/Solid interfaces

Christoph Gilow[1], Hubert Mantz[1], Anthony Quinn[1], Armin Nagel[1] and Karin Jacobs[1], Markus Bellion[2] and Ludger Santen[2]
[1]Saarland University, Experimental Physics, D-66041 Saarbrücken, Germany.
[2]Saarland University, Theoretical Physics, D-66041 Saarbrücken, Germany.

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[3]Faculty of Health and Society, Malmö University, SE-205 06 Malmö, Sweden.

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Department of Molecular Microbiology and Biotechnology, Tel Aviv University, 69978, Tel Aviv, Israel.

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Leibniz-Institute for New Materials Im Stadtwald, D-66123 Saarbrücken, Germany.

28. Cell surface interactions
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Ecole Polytechnique Fédérale de Lausanne (EPFL), Imaging and Applied Optics Institute, 1015 Lausanne, Switzerland.

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[1]Chemistry Department, University College Cork, Ireland
[2]Biophotonics & Microfluidics Research Group, Tyndall National Institute, Cork., Ireland.

36. Genetic and Environmental Mechanisms Underlying Alzheimer's Disease and Their Use for the Identificiation of Novel Therapeutic Approaches

Daniel M. Michaelson
Department of Neurobiochemistry, The George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv 69978, Israel.

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Karen Twomey, Julian Marchesi, Tanguy Crocy, Olivier Chevalerias, Pio Jesudoss, Frank Stam, Eva Alvarez and Damien Arrigan.
Tyndall National Institute, Cork, Ireland.

38. Molecular analysis of optic nerve degeneration and regeneration

[1]Arieh S. Solomon, [2]Anat Nitzan, and [2]Ari Barzilai
[1]Goldschleger Eye Research Institute, Chaim Sheba Medical Center, Tel Aviv University.
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39. Novel technologies to promote optic nerve regeneration

C. Depeursinge, F. Charrière, J. Kühn, Y. Delacretaz, P. Marquet, B. Rappaz
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40. Whole-cell biosensors for environmental and security monitoring applications

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41. TOXDROP Project

Béatrice Schaack
CEA, France.

42. Nonlinear optical filtering microscopy for in-vivo investigation of cell dynamics and analysis of micro fluid flows

M. Woerdemann, F. Holtmann, M. Eversloh, O. Grothe, H. Deitmar, V. Krishnamachari, and C. Denz
Institut für Angewandte Physik, Westfälische Wilhelms Universität Münster, 48149 Münster, Germany

43. Nanobiotechnological applications of biosilica enzymes from sponges

Thorben Link[1], Anatoli Krasko[1], Ute Schloßmacher[1], Muhammad Nawaz Tahir[2], Wolfgang Tremel[2], Heinz C. Schröder[1] and Werner E.G. Müller[1]
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[2] Institut für Anorganische Chemie und Analytische Chemie, Universität, Duesbergweg 10-14, D-55099 Mainz, Germany.

44. Digital Holographic Microscopy Applied for Dynamic Monitoring of Shiga Toxin 1 Treated Single Human Brain Microvascular Endothelial Cells

Patrik Langehanenberg[1], Björn Kemper[1], Gert von Bally[1], Andreas Bauwens[2], Martina Bielaszewska[2], Helge Karch[2], Johannes Müthing[3], Jasna Peter-Katalinic[3]
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[3]Institute for Medical Physics and Biophysics, University of Muenster, Robert-Koch-Str. 31 D-48149 Muenster, Germany.

45. Integrated Optofluidics for Bio-Analysis

Des Brennan, Maeve Curtin, Eric Moore and Paul Galvin.
Tyndall National Institute, Lee Maltings, Prospect Row, Cork, Ireland.

46. Fabrication and functionalization of nanochannels by electron beam induced silicon oxide deposition

Christophe Danelon,[†] Christian Santschi,[§,‡] Samuel Terrettaz,[†] Jürgen Brugger,[§] and Horst Vogel[†]*

47. Nanophosphors as Luminescent Labels for Bioanalysis

Torsten Vielhaber and Uwe Karst
Institute of Inorganic and Analytical Chemistry, University of Münster, Corrensstraße 30, D-48149 Münster, Germany.

48. Magnetic micro-actuator for biomolecule capture and mixing

Hervé Rostaing and Paul Galvin
Tyndall National Institute, Lee Maltings, Cork, Ireland.

49. Sedimentation Analysis of Human Erythrocytes by Multi Focus Digital Holographic Microscopy

Patrik Langehanenberg[1], Björn Kemper[1], Gert von Bally[1] Lyubomira Ivanova[2], Ingolf Bernhardt[2]
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[2]Laboratory of Biophysics, Faculty of Natural and Technical Sciences III, Saarland University, P.O. Box 151150, D-66041 Saarbrücken, Germany.

50. Chromosome Total Analysis System (C-TAS)

Jacob M. Lange[1], Maria Dimaki[1], Niels Tommerup[2] and Winnie Svendsen[1]
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51. Application of nanotechnologies in the analysis of gastrointestinal tumor cells

Ilona Bredebusch, Wolfram Domschke, Jürgen Schnekenburger
Department of Medicine B, Westfälische Wilhelms-Universität, Münster, Germany.

52. Micro-grippers for manipulation of nanowires and tubes
K. N. Andersen, D. H. Petersen, K. Mølhave, J. Kjelstrup-Hansen, P. Bøggild
MIC - Department of Micro- and Nanotechnology, Technical University of Denmark, Building 345E, 2800 Kgs. Lyngby, Denmanrk.

53. Recognition of individual bio-molecules by using Atomic Force Microscopy
D. Benayahu, A. Ron, N.Fishelson, R. Socher, And Y. Shacham-Diamand
Tel-Aviv University, Israel.

54. Biophotonics And Microfluidics Research
Michael Loughran and Alexandra Homsy
Tyndall National Institute, Cork, Ireland.

55. Biomedical Microsystems Research Team
Frank Stam, and Karen Twomey
Tyndall National Institute, Cork, Ireland.

56. HUNN – Hungarian Network of Excellent Centres on Nanosciences
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57. Tel-Aviv University Research Institute for Nano Science and Nano-technology
Yosi Shacham-Diamand
Faculty of Engineering – Tel-Aviv University, Israel.

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Tutorials

Dynamic Processes in Biological Membranes

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Our knowledge about the cell membrane has changed dramatically over the last decades. The lecture will start with an overview about the structure of the cell membrane. It takes into consideration the "fluid mosaic model" developed by Singer and Nicolson (1) and explains some extensions to this model. One focus of the lecture will be drawn on the understanding of the dynamics of membrane constituents (proteins, lipids). In addition, the nanostructure of the membrane surface including lipid rafts will be discussed.

Another major topic of the lecture will be the principal characterization of the ion transport pathways in biological membranes. It includes pumps, channels and carrier and explaines our current understanding of the partial movement of these transporters (2).

Finally, the process of the shape change of a cell will be analyzed. There are two general mechanisms known, which can lead to a shape change: (i) lipid redistribution between the two membrane leaflets (relatively slow process) and (ii) protein-based expansion of one of the membrane leaflets (relatively fast process) (3 – 5). A very fast shape change can be observed, e.g., when red blood cells get in contact with a glass surface. To study the process of such rapid shape changes of living (non-fixed) red blood cells, a new technique, the high resolution digital holographic microscopy, developed in the research group of G. von Bally (University of Muenster) has been applied (6). With this method it is possible to perform time-resolved quantitative microscopic measurements of changes in the lateral and axial shape under different experimental conditions.

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(6) Carl, D., Kemper, B., Wernicke, G., von Bally, G. Applied Optics 43 (2004) 6536–6544

Experiences in the Commercialisation of Equipment for Clinical Diagnostics

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In our laboratory, we have developed instruments that are, in principle, capable of changing radically the protocols used for the measurement of clinically important analytes. The two methods employed are based on the propagation of vibrational and electromagnetic fields: these are an ultra high frequency shear wave system and a scanning Kelvin nanoprobe. An exciting potential for both these techniques lies in the future avoidance of time-consuming ELISA assays involving the use of Western Blots and the like. In terms of commercialisation it has been relatively straightforward to acquire seed funding for proof–of- principle development. However, further enhancement of technical development has proven to be challenging in the uncompetitive technology transfer arena represented by Canada. This paper will discuss some strategies to avoid pitfalls in commercialisation of such machines and possible scenarios to establish a modicum of success. .

Micro and Nanofabrication Processes

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Semiconductor fabrication particularly in relation to silicon processing has been under continuous development since the fabrication of the first solid-state transistor in 1947. This development has followed what has become known as "Moore's Law" after the publication of an article by Gordon Moore[1] in 1965. The adherence to this law translates to a doubling of the complexity or the number of transistors on a chip every 18-24 months. At present the semiconductor industry is manufacturing with feature sizes of the order of 60nm and hundreds of millions of transistors on a single chip. Future developments in semiconductor technology are outlined for a forward window of 15 years in the ITRS roadmaps[2].

More recently the techniques used in the fabrication of silicon integrated circuits have been used to fabricate devices and structures of use in the areas of biological and biomedical sciences. These artefacts can be used for analysis, identification, isolation and replication of biological samples.

This tutorial will cover a simple review of the individual technologies that go to make up the full integrated circuit fabrication process[3]. It will identify a number of electronic devices that can be used in the area of the biological sciences as well as describing a number of non-electronic device structures that have potential in these areas.

References:

(1) Cramming more components onto integrated circuits, Gordon E. Moore, Electronics Volume 38 Number 8, April 19, 1965
(2) International Technology Roadmap for Semiconductors ITRS
(3) Silicon VLSI Technology Plummer, Deal & Griffin; Prentice Hall; ISBN 0-13-085037-3

N2L Programme Descriptions

The N2L Mobility Programme

A **key aim** of the Nano2Life Network of Excellence is to develop a durable **integration of nanobiotechnology researchers** working in all of the participant institutes. To support this aim, Nano2Life has developed a **mobility programme** to **support** exchange of **researchers** among the participating institutes. Two types of exchanges are envisaged as follows:

(1) **Short-term** visits of a few days up to two weeks to enable researchers to access resources (i.e. facilities, specialist equipment and/or expertise) in Nano2Life participating institutes. For some applications, more than one trip may be required for different stages of the process.

(2) **Medium-term** visits for a period of a few weeks up to six months. It is envisaged that a key objective of these exchanges should be the promotion of stronger linkages between participating Nano2Life members in nanobiotechnology related research, and the programme is open to researchers at all levels.

While the **maximum grant** for any one proposal will be **€10,000**, it is anticipated that proposals for short-term visits will normally be less than €2,000. Given the diversity of institutional structures and types of research being considered in this programme, each proposal will be considered on a case by case basis with respect to relevance to Nano2Life research excellence and integration goals (i.e. rather than providing specific guidelines).

Application Process

Access to the facilities and expertise within the Nano2Life Network is available to all research staff and postgraduate students of all full members of Nano2Life, and who have the approval of their department head to submit a project proposal.

Proposal forms can be downloaded either on the Nano2Life website in the mobility programme section (WP1) or are available from your local Nano2Life contact point.

Before submitting the proposal it is essential that the proposed project is discussed with the contact point of the host institute to establish agreement that the work proposed can be carried out there. On completion of this form (remember signature required) please electronically scan and email as attachment to **Dr. Eric Moore**: nano2life@tyndall.ie

You will receive an acknowledgement of receipt of your submitted proposal and will be updated on the decision of the evaluation committee. The evaluation committee will review submitted proposals on a monthly basis. For more information please contact:

Dr. Eric Moore, Tyndall National Institute, Cork, Ireland. Tel: +353 21 490 4451
eric.moore@tyndall.ie

The e-Mentor program

"A mentor is simply someone who helps someone else learn something that would otherwise have been learned less well, more slowly, or not at all." (Chip R. Bell, Managers as Mentors, 1997)
"An mentee is a person who wants to learn and educate him/herself personally and professionally, through conversations and co-operation with another person who at times has wider experience than he/she does."

Through the e-Mentor programme WP3 in Nano2Life aims to make use of the competence of colleagues by giving them the opportunity of acting as good examples and "learning anew". The programme is intended to facilitate a mutual give and take of knowledge and experience between the more experienced colleague (the mentor) and the less experienced one (the mentee), both of them belonging to Nano2Life. The e-Mentor programme is further intended as a flexible means of disseminating knowledge and addressing infrastructure problems in Nano2Life, which is a large and dispersed organisation.

· As a mentee you get additional information, encouragement, advice, and access to networks from a tenured faculty member in your field, from anywhere in Europe. You also have the opportunity to take part in specific interactive career promoting activities that you together with other mentees and mentors decide of what kind they should be (e.g. how to write a good EU proposal, patent etc).
· As a mentor you get a chance to help a less experienced scientist to succeed in an area of your scientific interest by providing supportive advice; something that feels good and is as well upgrading!

General information

Participants in the N2L e-Mentor programme e-mail each other for about 12 months, but face-to-face meetings are also possible, e.g. at the different meetings arranged by N2L.

Both mentors and mentees can get ideas and help through the interactive home page (e-Mentoring Nano2Life), which contains information material addressed to both parties. The material on this home page is meant to provide practical advice and hints on how to work as mentor and mentee, and will help structure the work of the paired mentor and mentee. The home page also serves as a "safe place" where no one else can access communication between the programme participants. The home page includes a chat forum where the different mentor-mentee couples can discuss general issues.

Why writing instead of seeing your mentor/mentee?
· The dialogue becomes more reflective, because you can take your time answering.
· You automatically acquire a logbook in which your personal development is easily traceable.
· It is efficient as you decide when a "meeting" may take place.
· Your mentor or mentee may come from the whole of Europe – so the experience gets an international touch!

So far we have 13 mentor-mentee couples active in the program. If you are interested in participating as a mentor or a mentee, please contact:

Elena Martinez, PCB, Barcelona, Spain: emartinez@pcb.ub.es
or
Jenny Emnéus, Lund University, Sweden: jenny.emneus@analykem.lu.se

PROGRESS – Progress in understanding groups and leaders

PROGRESS is a new European multi-cultural and equality oriented human resource management course that addresses leadership training in combination with empowerment. The aim of the program is to develop a common leadership- and group-orientated knowledge within the Nana2Life scientific community that promotes the fundamental value of equal treatment.

PROGRESS has been developed in collaboration between Nano2Life WP3 and WP8 and the consultancy firms Right Sinova (http://www.right.com/se/ - one of the largest in management and leadership in Sweden, and part of the global Right management consultants (http://www.right.com/) and Lund University Education AB (http://www.education.lu.se/eng/).

The course gives the participants an increased understanding of how group dynamics affect results and how leadership styles should be adapted to the group's maturity stage and specific tasks at hand. PROGRESS provides the participant with insight as to why people behave in certain ways in certain situations and why conflicts arise in a group. The goal is to convey knowledge concerning how the individual person, both as leader and member of a group, relate to the other individuals and the group in different process situations, for example formulation of goals, decision-making, dialogue/communication and conflict.

The vision of PROGRESS is that it will counteract alienation between sexes and therefore also lead to a more open, vivid and more strategic orientated dialogue between individuals within working groups of Nano2Life. This will in turn lead to organizational changes in order to accomplish enhanced equality, especially between sexes but also between groups with different nationality and background.

There are two certified course instructors (a woman and a man) who operate as facilitators, and the group always consists of 8-12 participants. The group members are put together based on as much diversity as possible (i.e. age, gender, etc.). The course is five days in length and requires full attendance (arriving on Monday morning and leaving Friday afternoon).

So far PROGRESS has been given at three different occasions in Hungary, Greece, and Sweden and has been extremely well received by the participants. It will be given again in Sept. 25-29 in Sweden. Support for participating to PROGRESS is granted by the N2L mobility program.

Have a look at the website and watch interviews with two PROGRESS participants at http://www.education.lu.se/o.o.i.s/3493. For more information please contact:

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Poster Abstracts

SRP Posters

Protein, DNA and Cell Chips
Surface Functionalisation
Bioanalytics Instrumentation
In Vitro Toxicology
Cell Biology
NBIC for Neurodegenerative Disease
Environment Monitoring & Security
In Vivo Imaging
Cancer Related Nanodiagnostics
In Vitro Cell & Tissue Analysis
Nanobased Drug Delivery
Nanoscale Assemblies

Institute/Team Posters

Application of nano technologies in electrochemical Biosensors

J. Rishpon, Tel-Aviv University, Israel.

Carbon nanotubes on amperometric electrodes

We have effectively exploited the unique electronic properties of carbon nanotubes (CNT) in electrochemistry as a means of promoting the electron transfer reaction for the development of enzyme based sensors. CNT were attached to gold or carbon electrodes and applied in a sensitive detection of hydrogen peroxide employing the enzyme horse reddish peroxidase immobilized on a CNT modified electrode. The detection limit was 10nM compared to 0.400mM in the absence of the CNT. This sensor was capable to measure enzymatic activity released from the *mycobacteria smegmatis* (a model system for *mycobacteria tuberculosis*). CNT attached to electrodes were also exploited in a highly sensitive electrochemical enzyme immunosrnsors.

Peptide nanotubes on amperometric electrodes

In addition, we have examined the possibility of employing peptide nanotubes (PNT) as catalytic elements in amperometric biosensors [1]. We used the diphenylalanine peptide that is readily self-assembled into well-ordered peptide nanotubes under mild conditions. PNT were attached to gold or carbon electrodes and this novel electrochemical biosensing platform was used for detection of hydrogen peroxide and glucose. Voltammetric and time based amperometric techniques were applied to demonstrate the significantly improvement electrochemical parameters by the PNT. Scanning electron microscopy analysis of the electrode after the electrochemical experiments showed that the tubular structures stayed attached to the modified working electrode. These findings clearly show that this novel class of peptide nanotubes provides an attractive component for future electroanalytical biosensors.

Lipid nanolayer on gold electrode

We have investigated interactions between receptors and hormone by following the impedance changes in 5-7nm thick lipid bilayers on gold electrodes. The system respond to estrogen or testosterone at physiological concentrations. Moreover, it enables the detection of xenohormones like xenoestrogens that are a health risk in the environment [2].

Lab on a Chip

We developed an innovative electrochemical 'lab on a chip' system that integrates the applicability of physiological reactions to serve as biosensors with the advantages of micro electro mechanical systems (MEMS). The novel specific design and process of the nano-biochip adjusted to an exclusive biochemical process enables highly accurate, sensitive and rapid diagnosis of physiological reactions by a hand held miniaturize device [3]. The device is composed from two units: a disposable silicon chip containing an array of nano-volume electrochemical cells integrating the biological material, and a reusable unit that includes a multiplexer and potentiostat connecting to a pocket PC for sensing and data analysis. Each electrochemical cell in the array can be electrochemically measured simultaneously and independently. This system was used in the detection the response of microorganisms to acute toxicity in water.

References:

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Silicon Sensor for Biomolecule Detection

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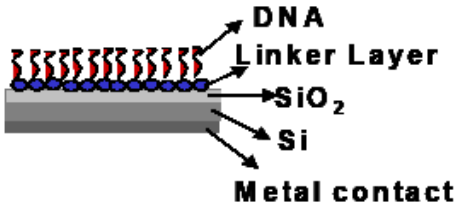
Bioanalytical microsystems show considerable potential for the applications requiring specific, rapid and cost effective interrogation of genetic information in areas as diverse as clinical diagnostics, detection of genetically modified foods, bioterrorism agents and monitoring of environmental pollutants[1] Most detection methodologies used for this at present require labelling of the target by means of external indicators or signalling probes with fluorescent dyes, redox indicators or metal complexes to confirm the hybridisation event. This is a costly, complex and long-term procedure for either sample preparation and target DNA detection. Therefore label independent methods such as impedance-based techniques are of considerable interest especially because these methods are compatible with modern micro- and nano- technologies expanding the possibilities for creating biosensor-on-chip devices or indeed an entire Lab-On-A-Chip system.

In this study, investigation of the silicon DNA sensor by application of an impedance spectroscopy approach and capacitive approach is reported.The structure of the sensor contains a thin SiO_2 insulating layer grown on a silicon substrate with an aluminium back contact for electrical connection. The assembly of probe oligonucleotides covalently immobilised to the top oxide of a Si/SiO_2 structure using a versatile attachment chemistry optimised in house were examined.



A flow injection analysis system was developed for the testing of two sensors simultaneously. A novel flow cell allows the exposure of the active area of 2 sensors to a reference and counter electrode while immersed in electrolyte. Complementary DNA (cDNA) can be injected into the flow cell an allowed to hybridise. Non-hybridised DNA can be washed out of the system thereafter.

Capacitance-Voltage (C-V) sweeps were performed on the sensors before and after hybridisation to detect variations in the capacitive characteristics of the sensor, due to the binding of cDNA to the surface. Impedance spectroscopy was performed by frequency sweeps with an Agilent 4284A LCR meter working under the control of a LabView program. Analysis of the electrical equivalent circuit shows that impedance changes are mostly due to variations in the Warburg impedance. Obtained results can be used for sensor optimisation and instrumentation development.

References:

Simonian et al., (2005) Analytica Chimica Acta 534, 69-77.

Bioassay platform using fibre-coupled avalanche photodiodes for improved biomolecule detection

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For future fully integrated sensing applications, a CMOS sensor will be required. New CMOS photon counting sensors have recently become available and these devices provide high quantum efficiency, photon counting sensitivity levels and low power consumption. Avalanche photodiodes can now be fabricated in arrays and with integrated on-chip electronics to produce minitaturised but highly sensitive optical tools. In biological applications, photon counting is focused on the detection of low intensity fluorescence signals from fluorophores conjugated to proteins or nucleic acid biomarkers from fluorescent proteins. We describe the development of a novel microtitre plate reader format, or bioassay platform that incorporates arrays of photon counting detectors for multiple parallel readout and data acquisition. We have designed and fabricated custom-made reaction wells using Pyrex and deep ion trench etched silicon, which produce optically clear structures to facilitate fluorescence detection in biological samples volumes of 2 nL to 2 μL. For initial verification of the system, a new photon counting detector from SensL is used to determine the effectiveness of the wells as the bioassay platform. The compact unit consists of a fibre coupled silicon photon counting sensor, thermoelectric cooler, thermoelectric controller, active quenching circuit, power supplies, and an USB interface to the operating software. Included in the module is a counter with time binning capability. Sensitivity increases of more than two orders of magnitude in fluorescence detection are expected over commercially available instruments. This system demonstrates that a miniaturized, low cost solution is possible for fluorescence bioassay detection, which can be used to meet growing demands in the in vitro diagnostics and Point of Care markets.

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Electroanalysis as a monitoring tool for cytotoxic conditions

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The application of lithographic techniques for the fabrication of microelectrode arrays results in an increase interest in the development and application of electrochemical device for in real time monitoring. Micrometer size electrochemical sensors present a number of advantages (mass transport rates, improved signal to noise ratio, reduction of uncompensated ohmic drop and independence from the hydrodynamic condition of the media) over conventionally macrometer sized electrochemical sensors. Moreover their reduce size also allows them to be able to work with small volume sample, to be integrated in small size devices (micro-fluidic devices or µ-TAS) and to be packaged, in limited space, as an array of sensors able to monitor in real time different parameters (for example different heavy metal). All these characteristics make electrochemical micro sensors very interesting tool for environmental monitoring.

In the case of cytotoxicity on chip micrometer size electrochemical sensors can find large application in the monitoring of the environment in which the experiment is carried out. Parameters as Na, K and phosphate concentration, oxygen content, pH can be monitored by using electrochemical devices. Moreover electrochemical sensors can be used to monitor small biological molecules (peptides) or heavy metal allowing, potentially, the monitoring of cell lysis. Finally electrochemical sensors can be used to monitor the concentration in the experimental media of electrochemically active toxic compounds as some mycotoxins or heavy metals.

In this poster some of the latest results, obtained at the Tyndall National Institute by the Chemical MicroAnalytics group, in the development of electrochemical sensors for heavy metals, phosphate and peptides/proteins will be presented. Moreover a prototype of a multi-parameter monitoring device will be presented.

Base-stacking approach to SNP detection on a magnetic sensor platform

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Genetic analysis based on single nucleotide polymorphisms (SNPs) provides the basis for point-of-care diagnosis and will be an enabling technology for personalised medicine. To achieve this end, new detection platforms are required which enable SNP genotyping on novel electronic biochip platforms to provide the real-time analysis required for point-of-care applications. Here we report a novel approach to SNP detection that is compatible with electronic (e.g. magnetic and optical) biochip platforms.

The microarray utilised consisted of a silicon surface modified with a silane anchor, with a homobifunctional cross linker to allow for covalent attachment of a collection of terminally aminated probe DNA molecules bound to a surface in a n x n array of spots. Using a short (12-mer) capture oligonucleotide probe anchored to an electronic microarray substrate, target complementary DNA (e.g. PCR amplified DNA) is "captured" by hybridisation. Hybridisation detection is enabled by labelling of the target DNA with a fluorophore. The stability of this double stranded DNA molecule is increased, through the addition of a short (12-mer) reporter oligonucleotide (CY3 labelled) complimentary to the target sequence immediately adjacent to capture probe sequence. Where full complementarity exists, base-stacking of the capture and reporter oligonucleotides results in a high level of thermal stability, while in the presence of a single base mutation at the junction of the capture and reporter oligonucleotides, the thermal stability is significantly reduced. Here, oligonucleotide capture probes were designed and synthesised with amino-modified 3' ends, printed in an array format on silicon slides, and immobilised using a covalent surface chemistry. Oligonucleotides were designed to simulate target DNA containing each of the eight possible interactions at the SNP site (i.e. A-A, A-C, A-G, C-C, C-T, G-G, G-T and T-T). Proof of concept of SNP identification was demonstrated following a wash stringency test where the Tm for the mismatched duplexes corresponded to the theoretical calculated denaturation temperatures observed through a loss in signal, as observed using epiflourescent microscopy. The thermal stability of double stranded nucleic acids corresponded to base composition of the DNA, where a 1% base mismatch between two DNAs lowers the T_m of the hybrid molecule by 1.4ºC.[1] This approach offers a multiplicity of potential reporter molecules for SNP detection such as labelling with paramagnetic beads to enable screening on a magnetic sensor platform.

References:

1. Marmur, J., and Doty, P., (1962) J. Mol. Biol., **5**, 109-118

Impedance Spectroscopy Measurements of Ion Channels in Tethered Lipid Bilayers

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Ion channels are crucial components of all living cells where they control ion fluxes. They play essential roles in cellular processes such as maintenance of the transmembrane potential difference, signal transduction and osmoregulation and are therefore directly or indirectly targeted by many clinically used drugs. In addition to their biological importance, ion channels are particularly interesting in the field of biosensors because they provide an intrinsic amplification of ligand binding. Tethered lipid bilayers provide a unique tool to reconstitute membrane proteins at surfaces, where they can be interrogated with several surface-sensitive techniques. The bilayers contact an aqueous environment on both sides of the membrane to accommodate the extramembraneous parts of the protein; they can be tuned to an appropriate fluidity and composition. The modulation of the ion channel activity by the selective binding of suitable ligands can be measured in tethered lipid membranes on gold electrodes by electrical impedance spectroscopy.[1]

A synthetic ligand-gated ion channel (SLIC) made of branched polypeptides has been reconstituted in a tethered lipid bilayer.[2] Conceptually, a SLIC comprises a ligand-binding and a channel-forming region. As a ligand-binding region we have chosen a peptide, the repetitive NANP sequence which is recognized by a specific monoclonal antibody. The NANP sequence is the major B cell epitope of the circumsporozoite protein of *Plasmodium falciparum*, the cause of human malaria. The channel-forming part is built by 4 melittin peptide segments that are chemically attached to the branched spacer. The melittin sequence was chosen because of its well-known channel-forming properties. Selective antibody binding to SLIC in the lipid bilayer increases the membrane resistance as a function of the concentration of the antibody Sp3E9 in the aqueous phase.

We recently reported lipid bilayers tethered to gold electrodes with electrical resistances approaching the values of freestanding membranes used for classical single-channel measurements in black lipid membranes and patch-clamp experiments.[3] SLIC was reconstituted in these highly insulating tethered membranes and specific channel gating was induced by the antibody Sp3E9. Due to the low density of defects of the tethered membrane, the effect of a few SLIC channels (less than 100) has been resolved in such layers. Recent developments include a further increase of the layer resistance in order to reach single channel sensitivity.

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Development of low cost miniaturised cell analysis system

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Flow cytometry is a state-of-the-art method for cell analysis and interrogation in clinical and biological laboratories. Advantages of this technology include high speed of analysis and the multi-parameter information that can be obtained in a single run including information on cell size, cell diameter, viability etc. Issues with the use of current commercial flow cytometry systems include the high cost of purchase and maintenance as well as the need for skilled operators and relatively large area of dedicated bench space. In addition the majority of commercial systems are not portable or amenable to use outside of the laboratory. Miniaturisation of conventional instrumentation could allow the development of low cost, 'turnkey' systems exhibiting a high degree of process integration, automation and portability[1].

This work aims to develop a micro fluidic-based flow cytometry system incorporating several novel design elements. Work-to-date has focused on the development of a microchip platform fabricated using inexpensive polymer components. Fluidic control is achieved using syringe pumps allowing metered delivery of sample and sheath fluids at precise flow rates. Initial tests have involved the use of fluorescent beads to characterize fluidic system operation. The integration and packaging of miniaturized optical elements developed in house to allow the development of rugged systems is currently under investigation [2,3]. Components include light emitting diodes for illumination and photodiode for detection.

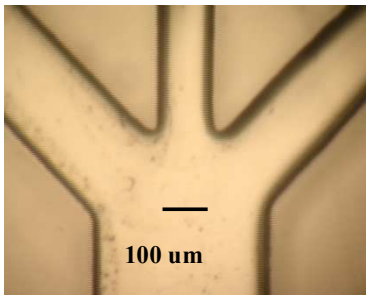

Fig. 1: Microfluidic channels fabricated in poly(dimethylsiloxane)

The first generation prototype unit will focus on the detection of E. Coli due to the availability of commercial immunoassay kits for system comparison. Developed protocols will be validated using a commercial system incorporating immunological labelling for cell identification. It is envisioned that following thorough system evaluation, modification of the immunoassay protocol will allow the detection of other targets of interest. The poster will outline results to-date including packaging and testing of optical elements with progress towards integrated electronic control of system components.

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Functional analysis of Shiga toxin 1 interactions with human brain microvascular endothelial cells: a nanotechnology-based strategy for analyzing virulence factors of pathogenic bacteria

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Shiga toxin-producing *Escherichia coli* (STEC) strains, especially of serotype O157:H7, are responsible for life-threatening zoonotic food- or water-borne illness consisting of diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome (HUS). Serious systemic complications of STEC infection such as HUS, and the ability of these organisms to cause large outbreaks make these bacteria one of the most important emerging pathogens. HUS is histopathologically characterized by microvascular lesions in the renal glomeruli, the gastrointestinal tract, and other organs, e.g., pancreas, lungs, and brain, which result from the injury of microvascular endothelial cells by Shiga toxins (Stx), the major virulence factors of STEC. It is now evident that, when death occurs during HUS, it is most commonly associated with the damage to the brain. Specific therapeutic or preventive strategies are presently not available.

The integrity of the blood-brain barrier is critical for normal brain function. Human brain microvascular endothelial cells (HBMECs) form a unique, tightly interconnected, cellular monolayer. This highly selective impermeable barrier strictly controls the exchange of material between the blood circulation and the brain. Several studies suggest that Stx1 is involved in manifestation of neurological dysfunction, which is associated with endothelial cell injury in microcapillaries of the central nervous system. The processes by which Stx1 causes these pathological changes are not well understood.

Stx1 is a member of the so-called AB_5-class of bacterial toxins, consisting of a single A subunit (~33 kDa) and a pentamer of identical B subunits (~7.7 kDa each). The catalytic A subunit has RNA N-glycosidase activity and inhibits eukaryotic protein synthesis. The pentameric B subunit is responsible for binding to the functional cell-surface receptor glycosphingolipid (GSL) globotriaosylceramide (Gb3Cer/CD77). Gb3Cer (Galα1-4Galβ1-4Glcβ1-1Cer) consists of a lipophilic ceramide and a hydrophilic trisaccharide moiety. This oligosaccharide with the unusual terminal Galα1-4Gal-sequence represents the binding structure for Stx1.

Due to the clinical importance of this life-threatening toxin, a cooperation was established connecting biological and biophysical nanotechnologies for the *in vitro* and *in vivo* receptor-based functional analysis of Stx1-mediated interaction with HBMECs. The nanotechnologies used were (i) High-resolution Mass Spectrometry (Fourier transform ion cyclotron resonance mass spectrometry, FT-ICR MS), (ii) 4Pi Fluorescence Microscopy, (iii) High-resolution Scanning Electron Microscopy, and (iv) Modular Digital Holographic Microscopy.

On-Chip determination of Neurotransmitter Exocytosis

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Characterization of single cells and small ensambles of cells is important since all cells differ in their composition and function. These differences are very important in medical science.

Microchips (Fig. 1) have been designed and manufactured using standard clean-room lithographic processes. In brief, silicon oxide is deposited on both sides of the wafer, electrodes are defined by photomasking and evaporation of titanium and gold onto the substrate followed by lifting off the photomasking material and the excess metal in aceton and finally the active electrode area and contact pads are defined by depositing and pattern an insulating layer of the epoxy based resist SU8.

When electrochemically detecting dopamine (**DA**) on clean gold surfaces, the amperometric response will decrease with time due to irreversible polymerisation of **DA** on the gold surface. To prevent this electrode fouling, the electrode surfase has been modified with self assembled monolayers (**SAM**) of thiols. A total of eight thiols, differing in chain length as well as the functional group have been tested using electrochemical impedance spectroscopy (**EIS**) and cyclic voltammetry (**CV**). It was found that mercaptopropionic acid (**MPA**), carrying a weak acidic functional group decreased electrode fouling and improved the electrochemistry of **DA**. The improved eclectrochemistry of **DA** on **MPA** modified gold is ascribed to a favourable orientation of **DA** on this surface. Stripping voltammograms revealed that the surface coverage of **MPA** was 1.1 nmol/cm^2, corresponding to a densly packed monolayer. CV in **DA** solution of **MPA** modified microchip electrodes confirmed the increased stability of the electrode. Also **EIS** experiments performed with the microchips confirmed a succesfull immobilization of **MPA**. Neurotransmitter exocytosis from PC12 cells was succesfully monitored using the **MPA** modified microchip electrodes.

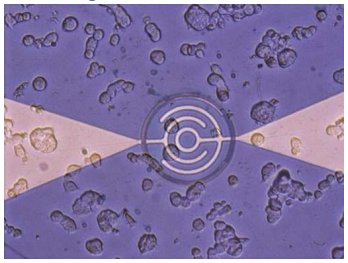

Fig. 1. *Image of PC12 cells sedimented on a microchip*

Analysis of a biochip sensing platform for monitoring of cells *in-vitro*

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Cell-based biosensors (CBBs), which treat living cells as sensing elements are able to detect the functional information of biological active analytes and also provide quantificational analysis. In general, they can keep living cells under constant observation to study cellular physiological action when cells are subjected to stimulus and verify the presence and the concentration of these stimuli. CBBs characterise with high sensitivity, excellent selectivity and a fast response time. With the rapid development of micro-fabrication technology of semiconductor, miniaturisation of analytical technology has offered a powerful tool for analysis of the cellular microenvironment. CBBs have been applied in areas such as environmental monitoring, pharmaceutical screening and biomedicine[1].

Impedance measurements on cellular systems[2] with inter-digitated electrode structures (IDES) have been shown to be an effective way of monitoring cellular behaviour on-line and in real-time. In this study the biocompatabilty and performance of IDES sensors comprised of indium tin oxide (ITO) and gold were compared. ITO and gold were used as the impedance sensors. ITO was used due to its conductive, biocompatible and transparent characteristics.

The presence of intact cell membranes on the electrodes determines the current flow and thus the sensor signal[3]. Growth behaviour, adhesive properties and the physiological state of adherent cells can be monitored during cultivation. The cells show significant, cell type specific fluctuations in the impedance signal over the course of a day. However, a more complete description of cellular behaviour is only possible when arrays of different sensors are utilised in parallel with each other.

The flow-through bioimpedance measurement system comprised of an IDES mounted on a 4.4cm x 1cm PCB, with the IDES flip-chip bonded to the underside of the PCB. Adherent cell lines were immobilised onto the IDES structure and placed in a flow-through device, which is connected to a gravity feed cell media reservoir. The combination unit was placed in a sterile incubator with electrical connections for monitoring to occur. The ITO IDES sensor measured the impedance and images were also viewed and photographed using a microscope coupled with a camera.

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Genomic and molecular genetic tools for monitoring gene expression, pathogenic bacteria and toxic compounds.

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Our group has the know-how and infra-structure in molecular genetic, micro-arrays, proteomics, real time PCR and mass spectrometry. Recently we acquired and started to use the 454 genome sequencing technology.

Our research interests are:

1. Control of gene expression, especially under environmental stress or presence of toxic compounds. The global analysis of gene expression by genomics, micro-arrays and proteomics enables the monitoring of changes in gene expression by designing and constructing general, as well as specific, biosensors.
2. We have developed electrochemical on line biosensors for gene expression, for general toxicity and for specific toxicants
3. We can detect specific bacteria, including pathogens, by online electrochemical biosensors, or by the use of real time PCR.
4. In a joint project with R. Popovtzer, J. Rishpon and Y. Shacham we succeeded to monitor samples using a nano-system connected to a hand-held computer

We can provide:

1. Molecular genetic infrastructure for constructing tools to monitor gene expression, toxicants and bacteria
2. Infra-structure and assistance in "omics", molecular genetics and mass spectrometry.
3. Develop on line and *in situ* monitoring systems, which can be miniaturized to nano-scale.

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