

Publishable final activity report

SLIC-Biosensors in Molecular Diagnostics: Nanotechnology for the Analysis of species specific Microbial Transcripts

Acronym: SLIC

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STREP / Thematic Priority 1: Life Sciences, Genomics and Biotechnology for Health

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1 Project execution

Summary Description of Project Objectives:

The key aim of this project was the development of a novel biosensor-based device for molecular diagnostics for application in clinical microbiology. Current “state of the art” technologies for molecular diagnostics have technical limitations, are expensive and sometimes require highly skilled personnel and heavy infrastructure. It was a primary aim of the project to focus on post-genomic applications, i.e. non-DNA applications, which in our case was tmRNA. The simplification steps envisaged in the project would make RNA-based tests faster, easier to use, cheaper and thereby making them more globally accessible to both developing and developed healthcare markets. Towards achieving this objective, the SLIC consortium set out to accomplish the following key tasks:

- **Sample preparation** - Integration of cell lysis and RNA purification/extraction in one step. Normally these are several discrete steps that can be time consuming and are very prone to contamination and RNA material loss, thus making them very critical for the ultimate RNA yield and overall assay accuracy.
- **High-performance capture probe design** – The accuracy of any diagnostic assay rests considerably on the performance of the capture probe. Furthermore, probe hybridization typically requires certain stringent conditions, e.g. higher temperature, for it to work optimally, which adds to overall assay complexity and cost. The capability to design better probes that could even function close to body temperatures was another key objective of the project.
- **Ultrasensitive detection** – Typically, assays based on nucleic acid targets require amplification steps, in order to render them detectable with standard detection technologies. However, this adds appreciable complexity and cost to the overall assay, hence the project set out to substitute this with a novel ultrasensitive biosensor approach based on the SLIC technology.

Project State-of-the-art:

The global market for molecular diagnostics in 2006 was worth more than \$2 billion making it the 4th largest segment of the IVD market with infectious disease testing currently comprising the largest segment of molecular diagnostics testing. In 2006, world-wide sales of molecular diagnostic tests for infectious diseases were worth \$625 million and sales are expected to grow at a CAGR of more than 5% in the period 2006-2011 (Clinica report-Complete Guide to the Diagnostics Market 2007-2012, May 2007).

Molecular Diagnostics have the potential to impact positively in reducing healthcare costs by enabling timely diagnosis, timely intervention and monitoring of response to treatment. Push bottom automation is critical for diagnostic products. Emerging trends in the healthcare sector include consolidated workstations that offer labour cost savings and “point of care” testing particularly in the acute care setting. The opportunity exists for products with improved sensitivity and specificity, process simplification, cost-effectiveness and faster turn-around time.

Emerging markets such as telehealth will require simple and rapid tests. Application of biosensors that utilise direct-detection of nucleic acid targets, i.e. without requiring *in vitro* amplification, in medical diagnostics has the potential to meet the requirements of “point of care” and “telehealth” markets. In particular, the elimination of complicated and time-consuming DNA amplification steps, in order to reduce the complexity of genomic DNA, will facilitate the simplification of the device user-interface.

Technologies employed in direct detection are varied and include use of fibre-optic microarray bundles, surface plasmon resonance (SPR), quartz crystal microbalances (QCM), electron and dark-field microscopy, confocal fluorescence spectroscopy as well as more established technologies such as fluorescent in situ hybridisation (FISH). While some of these technologies are highly sensitive and specific (FISH, c-f spec) they can be time consuming and require highly skilled personnel. Some of the other technologies, such as SPR and QCM, are more amenable to automation but sensitivity remains an issue. Novel solutions are required to improve sensitivity for these sensors, which may involve the development of different types of transducer material for DNA and RNA recognition including electrochemical sensors of which SLIC is an example.

A major hurdle to be overcome in the transfer of these technologies to clinical settings, is the purification of sufficient amount of nucleic acid from more complex sample types including blood and sputum. Furthermore, the detecting biosensor must be robust enough in the face of interfering molecules/particles from clinical sample material, an area where a majority of otherwise elegant biosensor technologies typically fail.

Work Performed and Results:

The development of the novel biosensor-based device for application in molecular diagnostics was based on combining two proprietary technologies, the SLIC-Nanobiosystem, the biosensor platform and RiboSEQ, a molecular target technology. The SLIC-Nanobiosystem consists of a self-assembled lipid bilayer membrane that integrates a synthetic ligand-gated ion channel (SLIC). The SLIC comprises a capture molecule that can specifically bind a given analyte, a process that is monitored via electrical impedance spectroscopy (Fig. 1). It was shown recently that SLIC molecules can be designed to detect with high sensitivity antibody binding to antigens on a SLIC via modulation of the SLIC ion channel conductance [Angew. Chem. Int. Ed. **2001**, 40, 1740-1743; Langmuir, **2003**, 19, 5567-5569]. With this system, the effect from even a few channels can be resolved, thus providing an ultra-sensitive, highly stable and versatile biosensor platform.

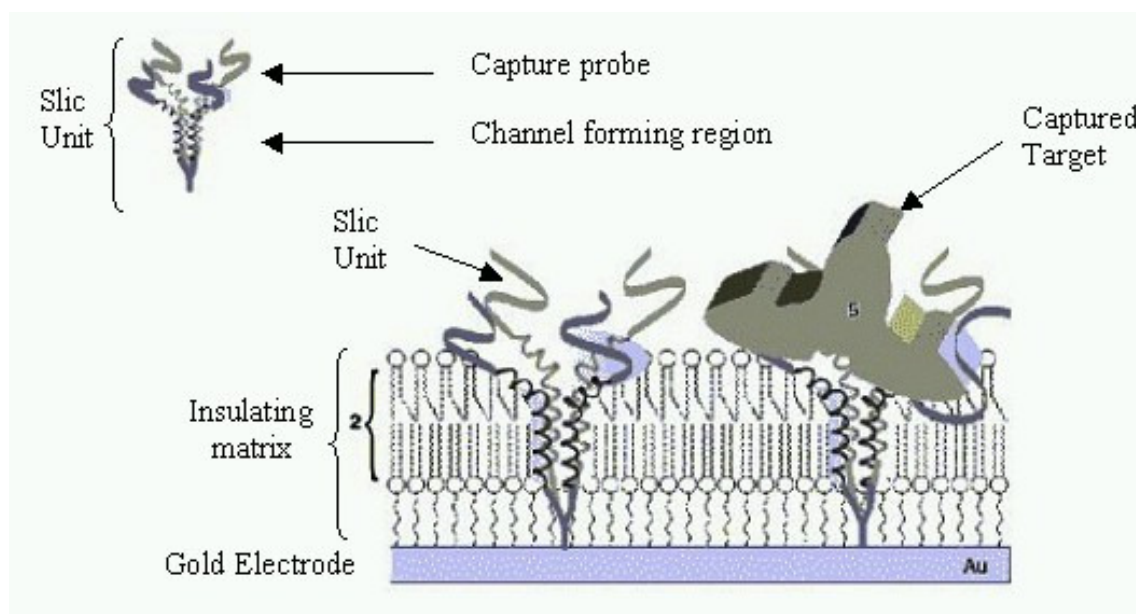


Figure 1: The SLIC Nanobiosystem

The **RiboSEQ platform** is based on the universal bacterial genomic target, tmRNA, which is encoded by the *ssrA* gene. It is a high copy number RNA target that has conserved and variable sequence signatures, which can be exploited to develop nucleic acid tests for microbial identification. *S. pneumoniae* was selected as the initial model system for the development of the biosensor-based device.

Since the capture probe also plays a key role in overall assay performance, a special effort was given to develop new tools for optimising tmRNA capture probes. These tools would also be used to develop probes that could simplify assay protocol, e.g. provide probes that can hybridize at lower temperatures (e.g. body or room temperatures).

Sample preparation is central to any diagnostic assay, but remains one of the areas that have been poorly addressed so far for RNA-based diagnostics. Therefore, significant effort was accorded for developing a novel platform that could carry out cell lysis, RNA purification in a rapid automated step. It was envisaged that such a novel sample preparation device would be integrated with the SLIC biosensor downstream, in order to provide a homogenous assay format.

The tasks towards these objectives was achieved through the various work-packages outlined below:

- Design of DNA probes for pathogen detection (WP1)
- Development and characterisation of SLIC detection platform (WP2)
- Optimisation of nucleic acid detection in the biosensor (WP3)
- Development of a sample preparation device for nucleic acid extraction (WP4)
- Performance evaluation of the biosensor-based device for clinical testing (WP5)

Overall, there was considerable collaboration and cross-fertilization of various skills and competences within the consortium. Virtually, all the consortium groups managed to interact and work with one another at some point during the project.

The consortium successfully developed panels of DNA probes based on the RiboSEQ technology for the model pathogen *S. pneumoniae* and other target pathogens, *H. influenzae* and *M. tuberculosis*. Specific DNA probes for *S. pneumoniae* were identified, selected and applied to develop and demonstrate various nucleic acid based diagnostic formats including biosensor, microarray and real-time in-vitro amplification based (NASBA) formats. The application of RiboSEQ as a molecular target technology for micro-organism identification was thus successfully demonstrated. Nucleic acid test formats including direct hybridisation dual probe sandwich assay were shown to be compatible with biosensor based detection, although detection of nucleic acids in this platform was not necessarily at clinically relevant levels. However, limits of detection relevant for clinical diagnostics (1-10 cell equivalents) were achieved, when biosensor-based detection using DNA probes was combined with an initial *in-vitro* amplification step of the target.

In order to modify and optimize capture probes so as to improve their sensitivity and specificity, various parameters, such as probe length, melting temperature and DG difference between true and false binding process, were studied. The results of these observations gave rise to a thermodynamics model, which was the basis for developing a software platform, SLICsel, for tmRNA capture probe design & optimisation. Towards improving hybridisation efficiency at lower temperatures, a novel strategy employing chaperones was devised. Through this approach, it was possible to demonstrate efficient hybridisation at 34°C, which would normally be achieved with hybridisation temperatures of over 46°C.

An elegant lab-on-chip technology for cell lysis and RNA purification was successfully developed and demonstrated. The principle of the approach is summarized in Fig. 2. Essentially cells are lysed thermo-electrically, and then directly followed by RNA isolation via an optimised electrophoretic purification. Subsequent detection can be done with the SLIC sensor or other detection platforms, such as real-time PCR.

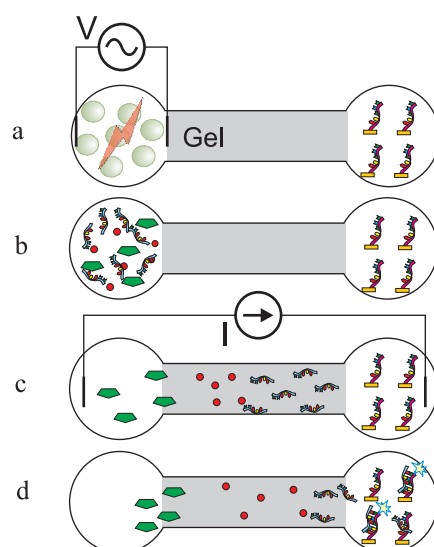


Figure2. Sample pre-treatment approach: (a), (b) cells are thermo-electrically lysed directly followed by (c) electrophoretic purification of RNA. After RNA elution, the RNA can directly hybridise to the SLIC sensor to diagnose and quantify the extracted RNA.

The combination of cell lysis and RNA isolation onto a single microfluidic cartridge minimizes the time between the two steps, thereby reducing the probability of RNase degeneration to a minimum. In order to arrive at such an integrated microfluidic cartridge, various novel techniques were developed. These included a new fabrication process based on the direct bonding of a dry film resist, in order to meet the demands of design flexibility, reduced fabrication times and cost. A microfluidic manipulation technique was also invented, which enabled better control on liquid handling and proper functioning of the electrophoretic actuation process. Figure 3 shows the microfluidic sample pre-treatment prototype chip. It contains two open electrodes for electrophoretic actuation and one passivated electrode for thermo-electric lysis. Capillary pressure techniques were developed to pattern the square gel in the centre of the chip and expel electrolytic gas bubbles. After gel cross-linking, two chambers are created: one for the bacterial cell sample and one for RNA elution.

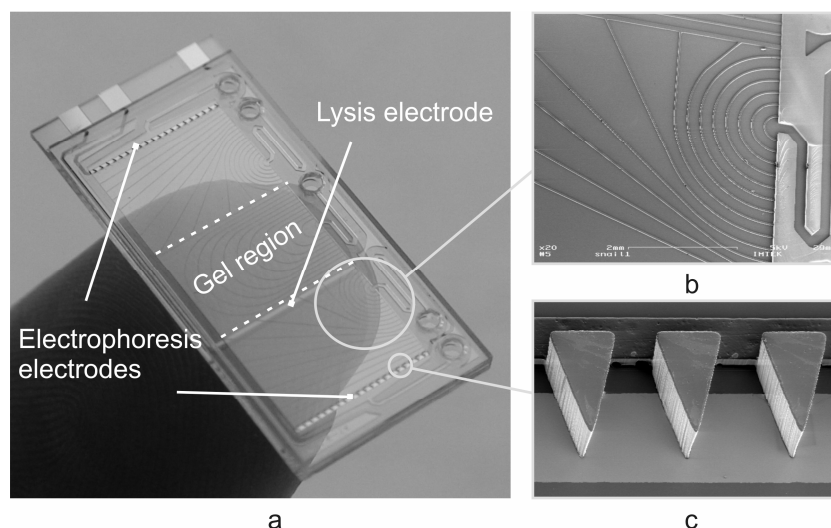


Figure 3. RNA isolation chip (a) containing (b) capillary pressure barriers for a controlled liquid and gel filling and (c) bubble expulsion structures to remove electrolytic gas.

The sample pretreatment chip has proven to be versatile and capable to quantify RNA for cell concentrations ranging from single cells to tens of billions of cells. The chip was capable of lysing and extracting RNA both from gram-negative and gram-positive bacteria, one of the toughest cells to lyse due to their cell wall. The microfluidic cartridge represents a fully automated sample pre-treatment approach that is unique in its simplicity. The combination of thermo-electric lysis and electrophoretic purification is the fastest RNA isolation method to date.

The aim of WP5 was the performance evaluation of the biosensor-based device for clinical testing. Because of technical challenges encountered in WP2, the biosensor-device only reached the stage where it could be evaluated for clinical testing at the very end of the project. Nevertheless, tests are ongoing to verify its ultrasensitive detection capability with nucleic acid targets. However, the robustness of the SLIC biosensor could be demonstrated when in contact with whole blood, one of the most complex/interfering clinical samples.

An important feature that was key to project success was the highly collaborative spirit that prevailed in the consortium throughout the project. For example, a member of ALU, who is a micro-engineer but was responsible for developing the sample preparation, spent time and received training on current molecular diagnostics techniques. A member of EBC and ALU at different times spent time at EPFL to gain an understanding of SLIC biosensor surface chemistry and function. Every time a technical hurdle arose, all the consortium members readily availed their expertise and resources.

Impact of project results in industry and research state-of-the-art:

The demonstration of the RiboSEQ technology as a diagnostic target is an important achievement. Due to its occurrence in high copy numbers, it represents an appreciable step towards reducing the burden/requirement of intermediate target amplification steps, especially as biosensor technologies continue to evolve and improve. In combination with the SLIC capture probe optimization tools (e.g. SLICsel), it promises to provide a powerful technology base for improved molecular diagnostics tests

for various key infectious diseases, such as respiratory diseases, and may also find relevance in bioterrorism diagnostics.

The SLIC RNA extraction platform represents a new breakthrough in the area of enabling tools for RNA analysis, especially small RNAs, one of the most intensely researched emerging domains. It is expected to attract interest primarily in drug discovery and biodiagnostics. In drug discovery, it provides equal or better small RNA recovery efficiency, but at a fraction of the time, than the leading products (e.g. Ambion) in the market does. In point-of-care testing (POCT), according to a recent review of emerging technologies for nucleic-acid POCT, currently all the instruments in the market focus on DNA detection (*Exp. Rev. Mol. Diagn.*, 7(4), 359-370, **2007**). Therefore, the SLIC RNA platform may have an opportunity to be one of the first RNA POCT devices in the market. A patent has been filed and will form the basis of a commercialisation plan that was elaborated by the SME partner in the consortium.

Project website: <http://www.fp6-slic.eu/>

2 Final plan for using and disseminating the knowledge

Section 1 – Exploitable knowledge and its Use

The SLIC project has generated the following exploitable knowledge:

1. Partner NUI Galway in collaboration with partner EBC designed species specific DNA probes for 3 pathogens (*S. pneumoniae*, *M. tuberculosis* and *H. influenzae*) based on the NUI Galway proprietary *RiboSEQ* platform for microbial identification. In the consortium agreement for this project, NUI Galway made the *RiboSEQ* technology available to the consortium for the development of DNA probes for the three pathogens *S. pneumoniae*, *M. tuberculosis* and *H. influenzae* for application and commercial exploitation in the SLIC biosensor. If the development work continues on the SLIC nucleic acid based biosensor then there may be an opportunity to exploit these probes linked to this specific biosensor platform for application in the IVD sector.

2. P. Vulto, G.A. Urban, **Integriertes mikrofluidisches Bauteil zum Aufreinigen von Analytmolekülen sowie Verfahren zum Aufreinigen**, PCT application No. 10 2006 050871.8, Pending

Partner ALU developed and patented a new principle for automated sample pre-treatment. The principle was demonstrated in the form of a microfluidic device that is now being prepared in collaboration with partner Ayanda for commercial exploitation. ALU proposes the integration of real-time PCR with the sample pre-treatment device. In addition ALU proposes to extend the functionality of the device from tmRNA to other small RNAs, messenger RNA and micro RNAs. Ayanda foresees a system in multiwell format.

Table 1: Overview table of exploitable knowledge

Exploitable Knowledge (description)	Exploitable product(s) or measure(s)	Sector(s) of application	Timetable for commercial use	Patents or other IPR protection	Owner & Other Partner(s) involved
1. Catalogue of DNA probes based on RiboSEQ tmRNA technology for <i>S. pneumoniae</i> , <i>H. influenzae</i> and <i>M. tuberculosis</i>	Pathogen specific DNA probes	Clinical IVD market	Not known	RIBOSEQ technology is covered by an international patent application, filed originally in 1999. The patent, WO 00/70086, is titled 'Nucleic acid probe-based diagnostic assays for prokaryotic and eukaryotic organisms'. It covers all major international jurisdictions and was published in November 2000. The Intellectual Property Rights are co-owned by NUI Galway and Enterprise Ireland. An agreement has been signed by the co-owners in relation to the commercial exploitation of the technology, and thus there is no impediment to the commercial exploitation of assays based on this technology.	Owner of IP- NUI Galway. Development of probes in this project performed in collaboration with partner EBC.
Patent on sample pre-treatment principle and device	Automated diagnostic device	Clinical, Research, Drug discovery	4 years	P. Vulto, G.A. Urban, Integriertes mikrofluidisches Bauteil zum Aufreinigen von Analytmolekülen sowie Verfahren zum Aufreinigen, PCT application No. 10 2006 050871.8, Pending	Owner: University of Freiburg Commercialisation partner: Ayanda Biosystems

Section 2 – Dissemination of knowledge

Each partner contributed to the dissemination of the results obtained in the SLIC project by attending conferences and publishing scientific papers.

Conferences:

Ayanda

- **Conference 1:** 20 June 2005: "SMEs in EC Projects: Finding the Holy Grail". Pizza Lunch Event at the PSE Parc Scientifique, EPFL Lausanne, CH.
- **Conference 2:** 16-19 January 2007: Infoweek - Official Swiss Launch of FP7, Bern, Switzerland.

- **Conference 3:** 23-24 April 2007: World Nano Economic Congress (www.world-nano.com), Pretoria, South Africa.
- **Conference 4:** 29-31 August 2007: BIOSURF VII - Functional Surfaces for Biomaterials (www.biosurf.ch), ETH Zurich, Switzerland.

EPFL

In period 2 the extension of the SLIC detection to nucleic acids was presented at Nano2life meeting at Cork, Ireland. Nano2life is the first European Network of Excellence in the field of nanobiotechnology supported by the European Commission under the 6th Framework.

ALU

- **Conference 1:** Microfluidic tools (phaseguides) and fabrication techniques were presented at microTAS 2005 in Boston. MicroTAS is the leading international conference on miniaturized analysis systems (Lab-on-a-Chip).
- **Conference 2:** Electrophoretic RNA purification was presented at microTAS 2006 in Tokyo. MicroTAS is the leading international conference on miniaturized analysis systems (Lab-on-a-Chip).
- **Conference 3:** Developed microfabrication processes using dry film resists and integrated electroplated electrodes were presented at Transducers 2007 in Lyon. Transducers is the leading international conference on microfabricated devices and microfabrication techniques.
- **Conference 4:** The principle of automated sample pre-treatment was presented at BMT 2007 in Aachen. BMT 2007 is a leading German conference new biomedical tools and techniques.
- **Conference 5:** The principle of automated sample pre-treatment was presented at microTAS 2007 in Paris. MicroTAS is the leading international conference on miniaturized analysis systems (Lab-on-a-Chip).
- **Conference 6:** The principle of automated sample pre-treatment by electrophoretic purification and thermo electric lysis will be presented at MSB 2008 in Berlin. MSB 2008 is an international conference on miniaturized separation systems.
- **Conference 7:** The sample pre-treatment device will be presented at the Lab-on-a-Chip World Congress in Barcelona. This is a new international conference in the field of Lab-on-a-Chip.
- **Conference 8:** The sample pre-treatment device will be presented at Biosensors 2008 in Shanghai. This is the international leading conference on biosensors and related systems.

NUI Galway: In period 2, NUI Galway presented some of the results from the EU SLIC project at two conferences.

- **Conference 1:** The work on the quantification of tmRNA copy number and its detection in biosensor platforms were presented at the European Conference for clinical microbiology and infectious diseases (ECCMID) in Munich in Mar-Apr 2007 (<http://www.eccmid-icc.org/>). This conference is very well attended by clinicians, researchers and reagent and test suppliers working the clinical microbiology space. The poster received good attention with many of those who viewed it were interested in to concept of rapid, high through-put low costs tests for application in the laboratory but also in the "point of care" setting.
- **Conference 2:** A poster was presented CHI conference "Nucleic Acid Technologies-Meeting the demands" Baltimore USA June, 2007 outlining the advantages of the *RiboSEQ* technology (tmRNA) as a molecular target for microbial identification. Because *RiboSEQ* is a platform technology, that is, tmRNA is universally present in bacteria and usually at reasonably high copy number the *RiboSEQ* technology is attractive for companies developing nucleic acid diagnostic tests for infectious diseases. The poster presented a range of different formats for nucleic acid diagnostic tests including biosensor platforms where *RiboSEQ* can be used and also presented some demonstrated applications of the technology relevant to the clinical IVD sector. The conference was attended mainly by American scientists and reagent and test suppliers. There was a small audience from Europe at the conference also. The poster was well received and interest in the *RiboSEQ* technology was expressed by a number of companies.

EBC: In period 2, partner EBC presented a poster describing a thermodynamics-based program called SLICSel for designing specific oligonucleotide probes for microbial detection at the "Nucleic Acid-based Technologies, Meeting the Demands" 2007 conference organized by Cambridge Healthtech Institute's in Baltimore, MA, USA.

Publications:

The published papers resulting from the SLIC project are listed in Section 3 – Publishable results. Below, only planned future publications are listed.

Ayanda and EPFL:

The detection of DNA hybridization on the SLIC platform resulted in a novel effect that was opposite to that observed for large proteins. This effect should be further analysed and compared with existing techniques in the field. In case of a positive evaluation we will write a paper in collaboration with the other partners of the consortium.

NUI and EBC:

- Glynn, B., et al-Application of NABSA and microarray-based detection for the detection of clinical pathogens. (planned pending outcome of experimental work and in collaboration with EBC).

ALU:

- Microfluidic cartridge for automated extraction of small and messenger RNA from *E. coli*, Targeted journal: Analytical Chemistry
- Phaseguides and bubble expulsion for automated RNA extraction from bacteria, Targeted Journal: Lab-on-a-Chip
- A microelectrophoresis cell with integrated bubble-free electrodes for automated RNA extraction, Targeted Journal: Electrophoresis
- RNA extraction from Gram positive and Gram negative pathogens on a microfluidic cartridge, Biological Journal (in collaboration with NUI, Galway)
- Full wafer fabrication process for glass microfluidic chips with integrated electroplated electrodes, Targeted Journal: Journal of Micromechanics and Microengineering

EBC:

- Palta P., et al., "SLICSel: program for designing specific oligonucleotide probes for microbial detection and identification", (manuscript in preparation)
- Scheler O., et al., "Labeling and using of NASBA products in microarray experiments", (manuscript in preparation with partner NUI)

Section 3 – Publishable results**Papers**

B. Glynn, K. Lacey, T. Barry, T. Smith, M. Maher, ***Reusable surface plasmon resonance assay for the specific detection of Streptococcus pneumoniae tmRNA***. Journal of Rapid Methods and Automation in Microbiology (accepted, in press).

B. Glynn, K. Lacey, J. Reilly, T. Barry, T. Smith, M. Maher, ***Quantification of Bacterial tmRNA using in vitro Transcribed RNA Standards and Two-Step qRT-PCR***. Research Journal of Biological Sciences 2, 2007: 564-570.

P. Vulto, G. Medoro, L. Altomare, G.A. Urban, M. Tartagni, R. Guerrieri, N. Manaresi, ***Selective sample recovery of DEP-separated cells and particles by phaseguide-controlled laminar flow***, J. Micromech. Microeng., 16, 2006, pp. 1847-1853

Conference talks

P. Vulto, G. Igel, G.A. Urban, ***Full wafer fabrication process for microfluidic glass chips with electroplated electrodes***, Proc. Transducers '07/EUROSENSORS XXI, Lyon, France, pp. 117-120.

P. Vulto, M. Weidmann, C. Klaunick, G.A. Urban, ***Fully automated RNA extraction on-a-chip by combined thermoelectric lysis and electrophoretic purification***, Proc. BMT 2007, Aachen, Germany, 1569050739.

P. Vulto, P. Zahn, G. Dame, G.A. Urban, ***Automated RNA Isolation On-a-Chip For Bacterial Diagnostics***, Accepted at Biosensors 2008, Shanghai, China.

P. Vulto, P. Zahn, U. Maier, G. Dame, G.A. Urban, ***Automated RNA Isolation By Electrophoretic Purification And Thermo-Electric Lysis***, Accepted at MSB 2008, Berlin, Germany.

P. Zahn, P. Vulto, U. Maier, G. Dame, G.A. Urban, ***Automated RNA Isolation By Electrophoretic Purification And Thermo-Electric Lysis***, Accepted at the Lab-on-a-Chip World Congress 2008, Barcelona, Spain.

Poster presentations

B. Glynn, K. Lacey, P. Palta, L. Kaplinski, M. Remm, T. Barry, T. Smith, M. Maher, ***Demonstration of the application of the tmRNA transcript of the bacterial ssrA gene as a molecular diagnostic target using a combination of NASBA and BiaCore technologies***. ECCMID, 2007, Munich, Germany

M. Maher, B. Glynn, M. Wernecke, J. O'Grady, K. Lacey, S. Lahiff, C. Mullen, S. Sedano, S. McGuinness, T. Smith, T. Barry, ***RiboSEQ-A nucleic acid test platform based on the bacterial ssrA gene for pathogen identification***. Cambridge Healthtech Institute's "Nucleic Acid- based Technologies, Meeting the Demands" 2007 Conference Baltimore, Maryland, USA.

P. Palta, L. Kaplinski, R. Andreson, A. Kurg, M. Remm, ***A thermodynamics-based program for designing specific oligonucleotide probes for microbial detection*** Cambridge Healthtech Institute's "Nucleic Acid- based Technologies, Meeting the Demands" 2007 Conference Baltimore, Maryland, USA.

P. Palta, L. Kaplinski, R. Andreson, S. Parkel, O. Scheler, K. Toome, B. Glynn, M. Maher, A. Kurg, M. Remm, ***A thermodynamics-based program for designing specific oligonucleotide probes for microbial detection and identification***. Cambridge Healthtech Institute's "Nucleic Acid-based Technologies, Meeting the Demands" 2006 Conference Washington DC, USA

S. Terrettaz, H. Vogel, ***Impedance Spectroscopy Measurements of Ion Channels in Tethered Lipid Bilayers***. Nano-2-Life Scientific Meeting. September 5-7, 2006. Cork, Ireland.

P. Vulto, C. Klaunick, G. Igel, G. Urban, ***tmRNA purification by electrophoretic filtration for genomic identification of bacteria on-a-chip***, Proc. of MicroTAS, 2006, Tokio, Japan, Vol. 2, pp. 377-379.

P. Vulto, C. Klaunick, M. Weidmann, P. Zahn, G. Dame, G.A. Urban, ***RNA Extraction On A Chip By Combined Thermo-Electric Lysis And Electrophoretic Purification***, Proc. μ TAS 2007, Paris, France, Vol. 2, pp. 1246-1248.

P. Vulto, P. Kuhn, G.A. Urban, ***Silver/Silver Chloride Electrodes For Bubble-Free Actuation In A Micro-Electrophoresis Cell***, Accepted at Biosensors 2008, Shanghai, China.

P. Vulto, P. Kuhn, G.A. Urban, ***A Micro-Electrophoresis Cell With Integrated Bubble-Free Electrodes***, Accepted at MSB 2008, Berlin, Germany.

P. Vulto, G. Medoro, G. Igel, J. Kieninger, G. Urban, M. Tartagni, R. Guerrieri, N. Manaresi, ***Phaseguide structures for pipette actuated laminar flow based selective sample recovery***, Proc. of MicroTAS, 2005, Boston, USA, pp. 1093-1095.