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eHealth

Monthly Focus

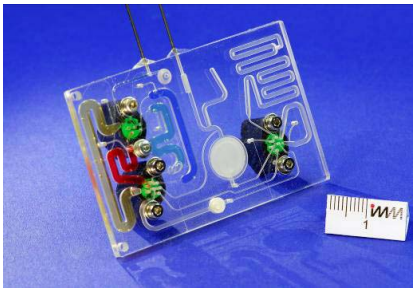
MicroActive

Improving cancer diagnosis in Europe and the US

European Commission
Information Society and Media

Recent developments in the area of "point of care" diagnostics may allow the transfer of molecular diagnostics from central laboratories to the doctor's office and to the homes of the patients.

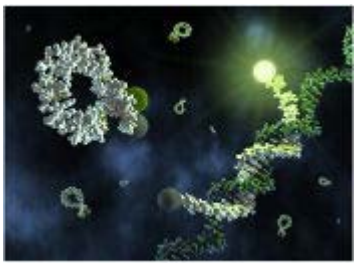
Currently, molecular diagnostic methods often require a number of steps, such as laborious sample preparation, creation of master-mixes and the performance of several assays concurrently, each with their own complexities. Such is the complexity of current molecular assays that they cannot be adapted to simple dipstick formats such as the currently used pregnancy tests or glucose meters.



The device accepts 3 ml of sample and performs the extraction in a disposable polymer chip of credit card size. Tests performed using cancer cell lines and cervical liquid based cytology specimens confirm the extraction of HPV-mRNA by the system.

The vision of the European funded project **MicroActive** has been to develop an **integrated system based on microtechnology and biotechnology for automated diagnosis** of a wide range of diseases. In the project, the developed system was tested successfully for the "proof-of-principle" detection of biomarkers indicative of cervical pre-cancer. Specifically the system was designed for the ion of transcription of oncogenic HPVE6/E7. The analysis detects mRNAs[1] (messenger ribonucleic acid), which are indicative of a biologically significant HPV[2] (**Human Papillomavirus**) infection. On-chip biological procedures have been compared to "gold standard" laboratory procedures.

MicroActive has developed two instruments and two microfluidic chips that can be joined together into one system for a full analysis of a patient sample. The analysis is miniaturized and the analysis procedure for diagnostics of HPV is more automated than those currently used in the laboratories. The procedure starts with metering up 3 ml of the buffer with patient cervical smear containing cells and mucus from a standard test container into a syringe. The syringe with the sample is then placed into the instrument with the sample preparation microfluidic chip. The extraction of mRNA, with a sufficient high quality for later NASBA[3] (Nucleic Acid Sequence Based Amplification), is performed automatically in the chip and the output is about 50 microliter of elute. This elute is mixed with reagents and then transferred to the amplification/detection chip in the second instrument where the liquid is automatically pulled into the chip, and split into separate amplification volumes. The mRNA for a specific HPV is amplified if the patient sample was positive for that active HPV virus, and then a fluorescent signal is monitored real time in the reaction chambers. From the signal a HPVE6/E7 mRNA positive result is determined.



Functional instruments and functional microfluidic chips have been used for tests on clinical specimens, in total **more than 300 biological analyses on clinical samples were performed**. Using clinical cervical cytology smear specimens from an established biobank, the functionality of the developed nucleic acid extraction with following on-chip amplification was demonstrated. Both instruments and chips are developed for production and for future use in a commercial system.

The project has achieved state-of-the-art scientific results in all of the disciplines involved. This has been proven by accepted publications on microfluidics, on-chip sample reparation, and miniaturized nucleic acid

[1] http://en.wikipedia.org/wiki/Messenger_RNA
[2] http://en.wikipedia.org/wiki/Human_papillomavirus
[3] http://www.pcr-encyclopedia.com/sequence-based-amplification-1480.html

amplification and on clinical comparison of HPV detection technologies in international journals and at international conferences. **Four publications are under preparation at the closing of the project**: A paper on the method for biocompatible lamination of polymer microchips, a paper on automatic sample preparation on-chip, one on parallel actuation of nanoliter sized plugs and spotting in micro-channels and one paper on the total analysis system.

Why targeting HPV?

Human Papillomaviruses ("HPVs") are a group of more than 100 related viruses, of which many types are considered relatively harmless, as they may only result in benign warts, or Papillomas. However, a few types of HPV are carcinogenic viruses that may result in cervical cancer. There currently exists an unmet medical need for further prevention of ICC (Invasive Cervical Cancer). Pap-smears and liquid based cytology lack the required sensitivity to further reduce the incidence of ICC. Diagnostic tests detecting presence of HPV are generally more sensitive than Pap smears and liquid based cytology, but much less specific - presence of HPV virus is not an ideal marker since more than 97% of HPV infections are dealt with by the immune system and do not lead to ICC.

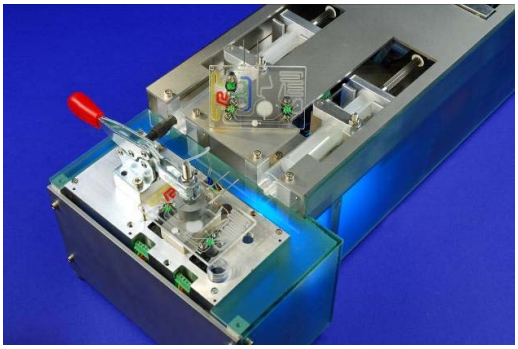
In summary, current standard of care diagnostics do not detect the oncoproteins responsible for the carcinogenesis. **NorChip's** commecial **macroscale tests** provide equivalent sensitivity to other next-generation genetic tests, but with significantly greater specificity, thereby **providing higher diagnostic accuracy to doctors and patients**.

What has been the progress to date?

NorChip achieved its first CE-marked product in 2003 and then in 2007 an international license agreement was signed with the French diagnostic group bioMérieux for the sale and distribution of their **macroscale PreTect HPV-Proofer technology world-wide**.

What does the future hold?

To date, NorChip has pioneered the development of cost-effective, miniaturized, disposable, and fully automated in vitro diagnostic devices that concentrate, extract, and detect RNA and DNA targets on an integrated micro-fluidics platform. The current status is a prototype system where **proof-of-principle analyses of patient specimens have been performed**. We believe that the development and deployment of certain diagnostic tests, in particular for certain cancers, will necessitate advanced technology for the high-throughput and highly multiplexed detection of RNA. NorChip therefore expects to co-develop proprietary tests based on micro-technologies, license out the technology, and manufacture its own systems.



They will present their recent technological advances during the next **pHealth2009** conference to be held in Oslo on **25 June**. More information in the June Oslo Bio Update Newsletter (http://www.norbiobase.no/no/Information/Oslo_Bio-Update/).

Partners:
- SINTEF (NO)
- NorChip AS (NO)
- Institut für Mikrotechnik Mainz GMbH (DE)
- IMTEK, University of Freiburg (DE)
- BioFluidix GmbH (DE)
- The Coombe Lying-in Hospital (IE)

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Instrument: STREP
Project Identifier: FP6-IST-2005-017319

Important Links:

Project website: www.sintef.no/microactive
Project publications: http://www.sintef.no/Projectweb/Microactive/Publications/
eHealth Research: http://ec.europa.eu/information_society/activities/health/research
eHealth FP6 Projects: http://ec.europa.eu/information_society/activities/health/research/fp6projects
pHealth2009: http://www.sintef.no/Projectweb/pHealth2009/programme

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