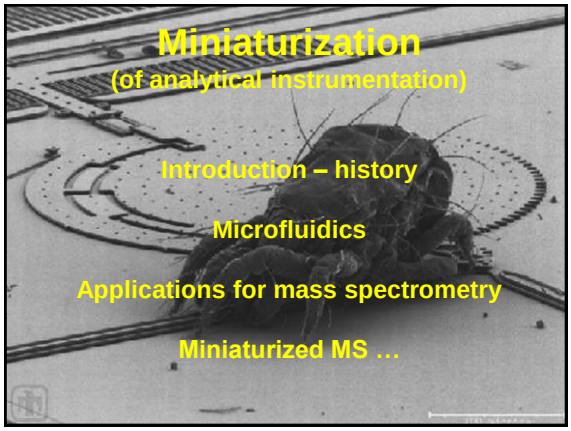
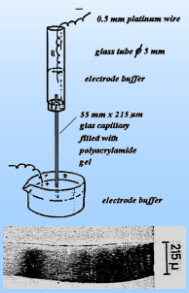
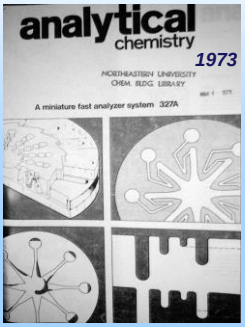



## Instrumentation Miniaturization

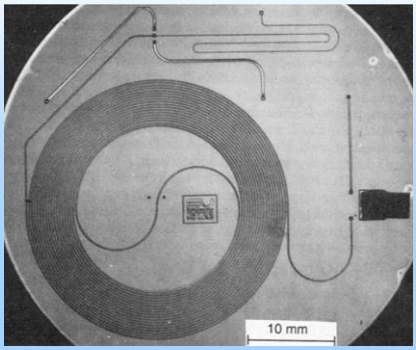



Capillary gel electrophoresis
Separation of nerve cell proteins

H. Hydén et al. Anal.Biochem, 17, 1-15, 1966.

## A Gas Chromatographic Air Analyzer Fabricated on a Silicon Wafer



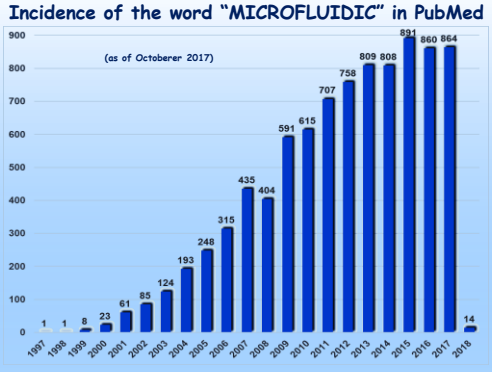

Terry, S.C., Jerman, J.H., Angell, J.B. IEEE Transactions on Electron Devices, 1979, 26, 1880-86.

## There really is nothing new under the Sun

Prototype analog pneumatic computer to operate in a nuclear attack
NBS (now NIST) 1950's


Picture by Wyatt Vreeland, NIST

## Incidence of the word "MICROFLUIDIC" in PubMed




https://www.ncbi.nlm.nih.gov/pubmed?term=Microfluidic%5BTitle%5D

## Microfluidics?

**Microelectronics**
Control of electric current

Technology
Products
Consequences

**Microfluidics**
control of fluid flows

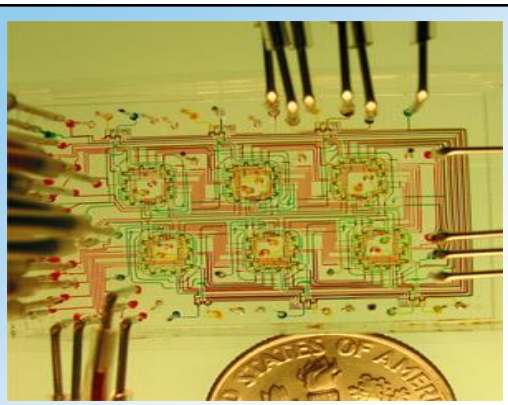
**Speed of analysis**

**Space saving**

**Cost cutting**

**Mass production**

?

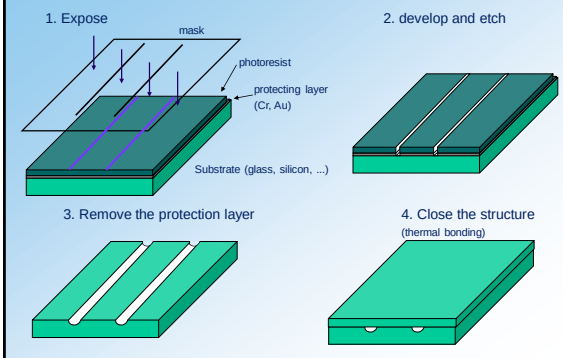


**Stephen Quake,** Dept. Bioengineering, Stanford University, http://thebigone.stanford.edu/index.html

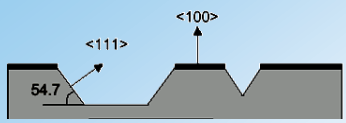
## Microfabrication technology

| | |
|---|---|
| Micromilling | 10 μm |
| Optical lithography | 200 nm |
| e/ion beam lithography<br>Multiple exposure techniques | 10 nm |
| Etching (resist dependent) | ~ nm |
| Replication (mass production)<br>Injection molding<br>Hot embossing<br>Casting | 10's nm |

## Photolithography




## SILICON - ANISOTROPIC ETCHING




* Anisotropic etching – direction dependent etch rate

* Etch rate slower perpendicularly to the crystalline planes with the highest density

* Typical etches: KOH, Tetramethyl Ammonium Hydroxide (TmAH) Ethylene Diamine Pyrocatechol (EDP)

Making and inspecting semiconductor chips requires pushing laser techniques deeper into the ultraviolet.

by Hank Hogan, Contributing Editor

As semiconductor feature sizes shrink, manufacturers need a light touch — and at the right wavelength. A look at three areas — lithography, metrology and assembly — shows how photonics-based innovations are tackling some of the semiconductor industry's most pressing problems.

Steppers are among the most critical tools used for semiconductor manufacturing and are at the heart of the photolithographic process, which transfers the features that are on a mask onto the photoresist material on a wafer. Subsequent processing reproduces that transferred layout in layers of conductors and insulators that eventually comprise a functioning integrated circuit. Today, state-of-the-art features are as small as 65 nm. Soon, they will be 45 nm, and the generation beyond that, 32 nm. The latter two scales are several years away, although the equipment needed for them is being rolled out now.

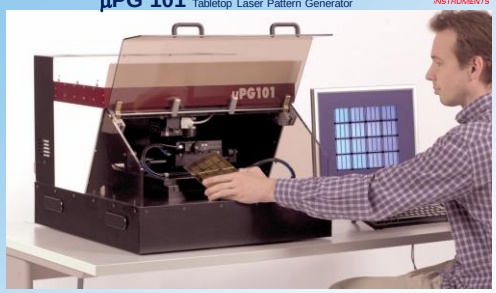
Although designed for manufacturing on a microscopic scale, the latest lithography stepper lens from Carl Zeiss SMT AG of Oberkochen, Germany, is not small. The Starlith 1900i weighs more than a metric ton, stands several feet tall and is as big around as a tree trunk. A catadioptric lens consisting of reflecting mirrors and refractive optics, it enables volume semiconductor production

The device pictured is a catadioptric lens that, according to the manufacturer, can achieve 40-nm-resolution lithography on semiconductor chips. Courtesy of Carl Zeiss SMT.

82 PHOTONICS SPECTRA DECEMBER 2006

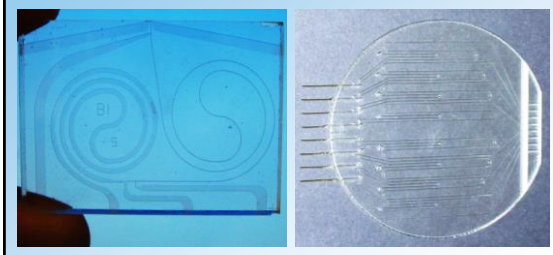
**μPG 101** Tabletop Laser Pattern Generator

HEIDELBERG INSTRUMENTS

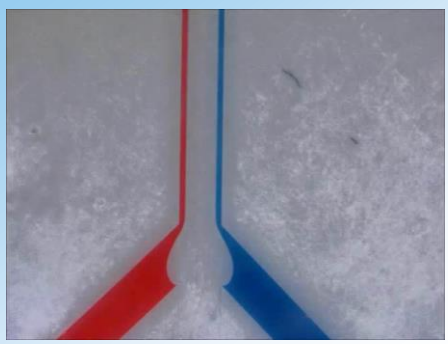



- **Substrates up to 100 x 100 mm2**
- **Structures down to 1 μm**
- **Address grid down to 40 nm**
- **Standard or UV laser source**

## System Integration



## Spatial flow focusing

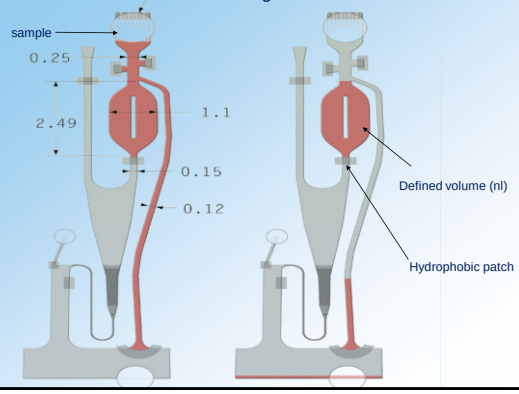


## Diffusion limited mixing

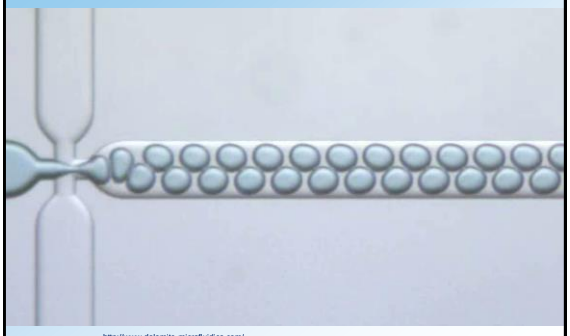
## Capillary force filling

www.gyros.com

## Exact volume metering on the nl level




## Droplet generation in nl-pl volumes



http://www.dolomite-microfluidics.com/

Seth Fraden et al., J. AM. CHEM. SOC. 2007, 129, 8825-8835.

## Benefits and Issues

Size - space saving
Low reagent/sample consumption
Smaller size – faster analysis
Microchannel junctions without dead volume
Parallel systems for high throughput
Disposable parts - point-of-care devices

**BUT**

Scaling issues
Fabrication limitations
Surface chemistry
Concentration limits of detection
Phenomena unimportant on the macro scale may dominate

## Small volume problem

Example: LOD = 1000 molecules

2.15 mm => 10 μl ~ $10^{-15}$ M

1 mm => 1 μl ~ $10^{-14}$ M

0.1 mm => 1 nl ~ $10^{-11}$ M

0.001 mm => 1 fl ~ $10^{-5}$ M

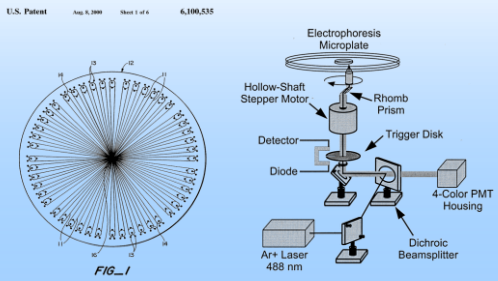
## MICROFABRICATED DEVICES

* **Sensors - accelerometers, glucose monitors, ...**

* **Genomics - first commercial applications**

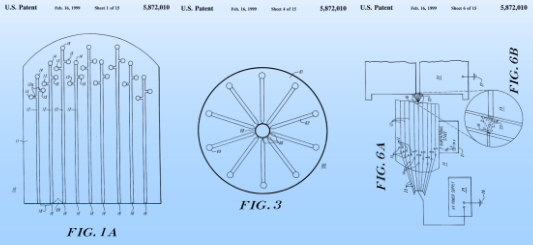
* **Proteomics - sample processing separation**

## Radial Capillary Array Electrophoresis Microplate and Scanner for High-Performance Nucleic Acid Analysis.




Yining Shi, Peter C. Simpson, James R. Scherer, David Wexler, Christine Skibola, Martyn T. Smith, and Richard A. Mathies. Anal. Chem. 1999, 71, 5354-5361

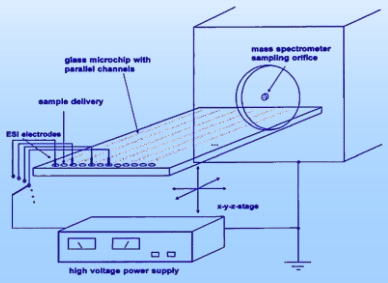
## Microscale Fluid Handling System




What is claimed is: 1. A liquid handling system, comprising a microscale liquid handling substrate having one or more channels integrally formed therein, for conducting a liquid sample in said substrate, said one or more channels terminating in one or more exit ports in an outer surface of said substrate for transfer of a microscale quantity of a liquid sample off said substrate by **droplet, spray or stream**;

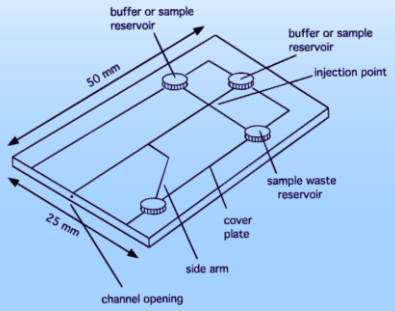
Karger, B.L., Foret, F., Qifeng, X., Dunayevski, Y., Zavracki, P., McGruer, N. U.S. Patent # 5,872,010, 1999.

## Multichannel Microchip Electrospray Mass Spectrometry



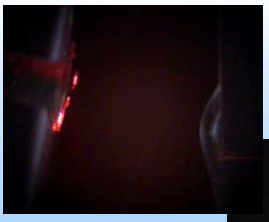

Xue, Q., Foret, F., Dunayevskiy, Y.M., Zavracky, P.M., McGruer, N.E., Karger, B.L. Anal.Chem., 69, 1997, 426-430.

## Generating Electrospray from Microchip Devices Using Electroosmotic Pumping




J. M. Ramsey, R. Ramsey Anal. Chem., 1997, 69, 1174-1178.

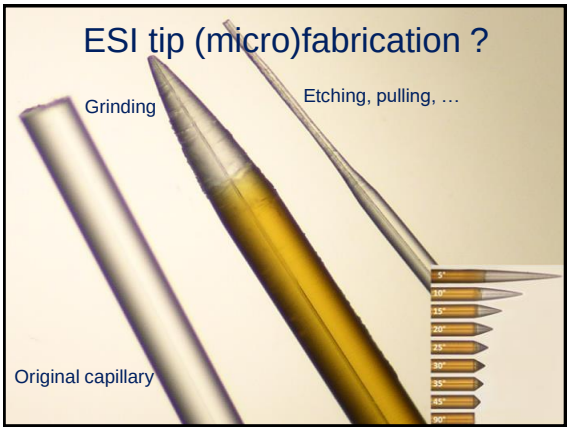
## Electrospray



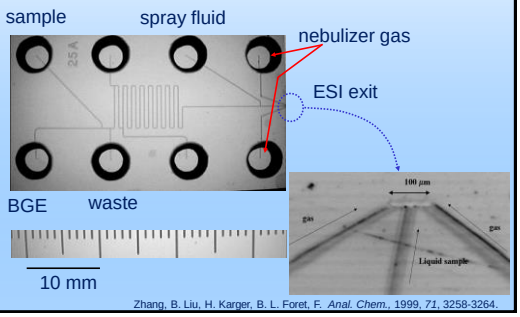
Flat surface - droplet

Capillary tip

## ESI tip (micro)fabrication ?

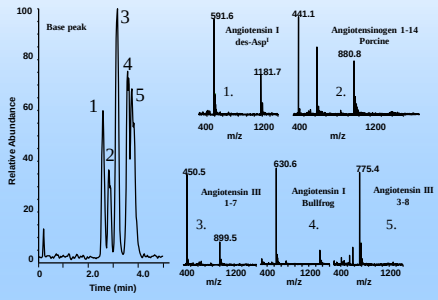



## CE Microdevice with a Pneumatic Nebulizer




Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.*, 1999, *71*, 3258-3264.

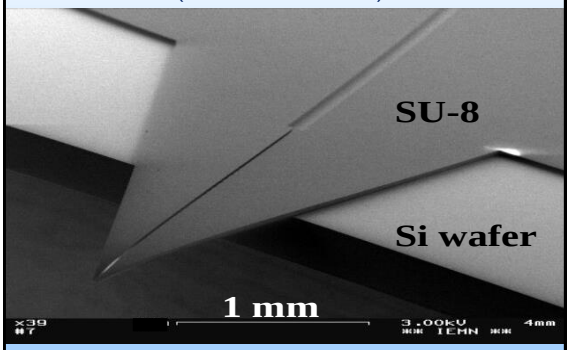
## CE Microdevice with a Pneumatic Nebulizer




Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.*, 1999, *71*, 3258-3264.

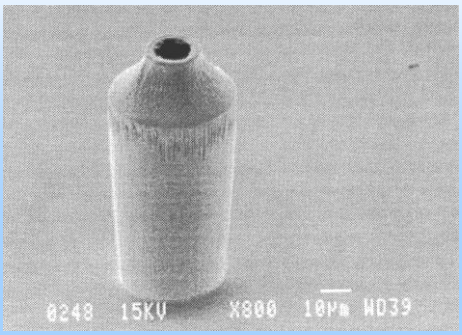
## Micro-nib electrospray source

(SU-8 on a silicon wafer)



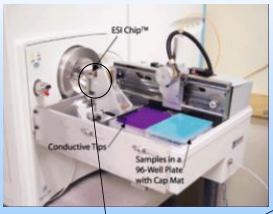

Le Gac S., Arscott S., Rolando C. ELECTROPHORESIS 2003 , 24, 3640-3647.

## ESI tips produced by DRIE in silicon

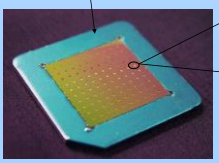


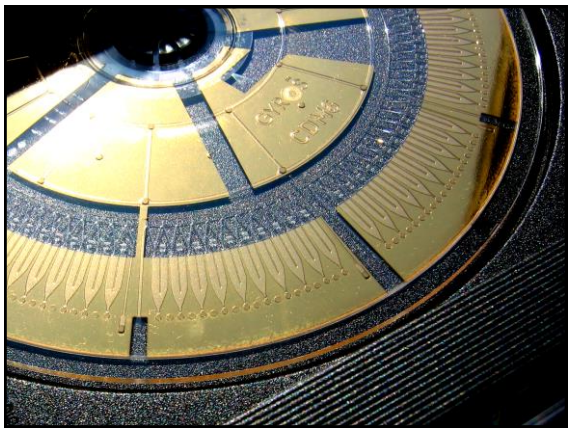

Sjödahl, J., Melin, J., Griss, P., Emmer, A., Stemme, G., Roeraade, J. Rapid Commun. Mass Spectrom. 2003, 17, 337—341.

## Infusion ESI Tip Array

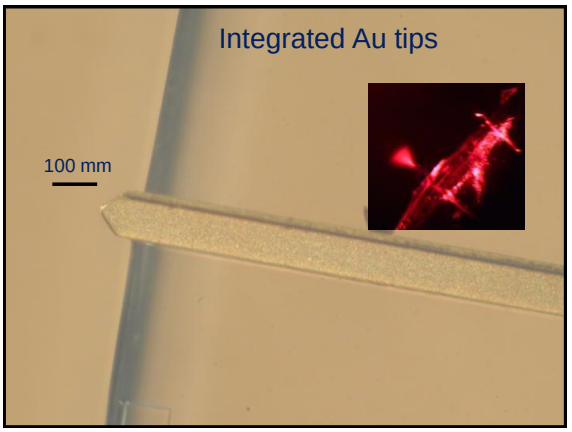



www.advion.com



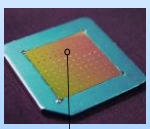


## Integrated Au tips




## ESI tip fabrication

DRIE in silicone



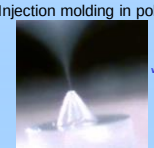
www.advion.com

Plasma etched in polyimide

www.diagnoswiss.com

www.agilent.com

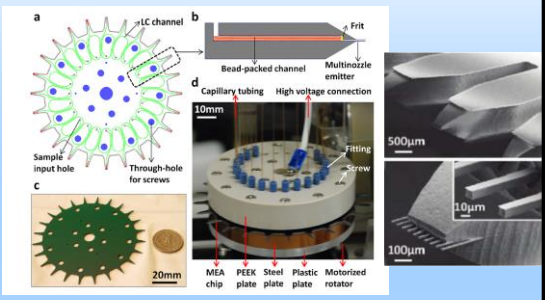
Injection molding in polypropylene



www.phoenix-st.com

## Applications

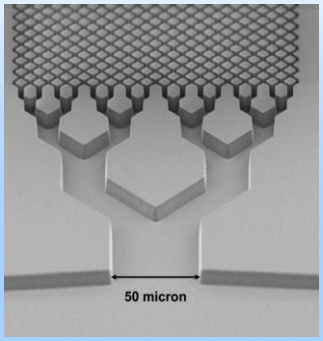
## Multinozzle Emitter Array Chips for Small-Volume Proteomics

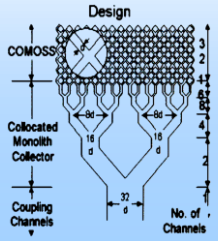



Mao, P; Gomez-Sjoberg, R; Wang, DJ. Anal. Chem. 2013, 85, 816-819.

## Microfabricated Monolith Columns for Liquid Chromatography

**Sculpting Supports for Liquid Chromatography**

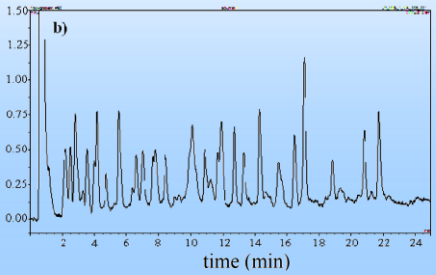



**Fred E. Regnier** J. High Resol. Chromatogr. **2000**, *23*, (1) 19–26

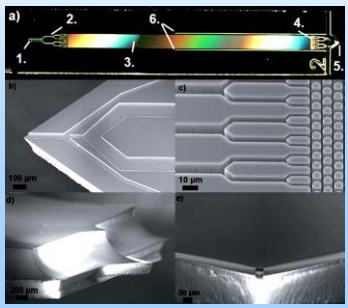
## Gradient LC separation of albumin digest

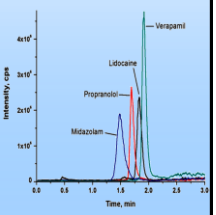
**(4µl/min, 1 mg/ml, UV detection)**




De Malsche W., De Bruyne S., Op de Beeck J., Eeltink S., Detobel F., Gardeniers H., Desmet G. Journal of Separation Science 2012, 35, 2010-2017

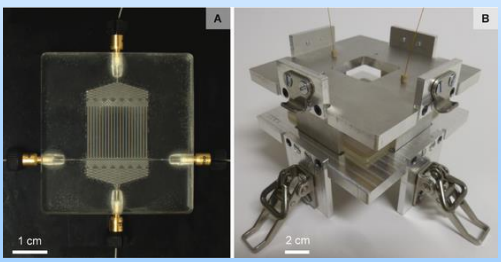
## A microfabricated micropillar liquid chromatographic chip Monolithically integrated with an electrospray ionization tip



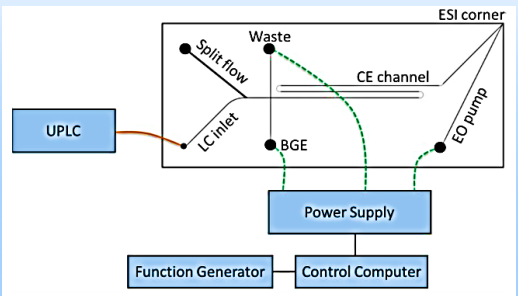

Lauri Sainiemi, Teemu Nissilä, Risto Kostiainen, Sami Franssila and Raimo A. Ketola Lab Chip, 2012, 12, 325

## Design of a microfluidic device for comprehensive spatial two-dimensional liquid chromatography



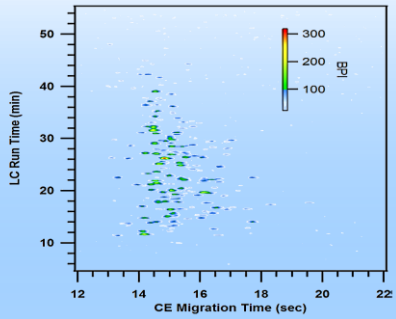

S. Eeltink, et al., J. Sep. Sci. 2015, 38,1123-1129.

## Hybrid Capillary/Microfluidic System for Comprehensive Online Liquid Chromatography-Capillary Electrophoresis-ESI-MS



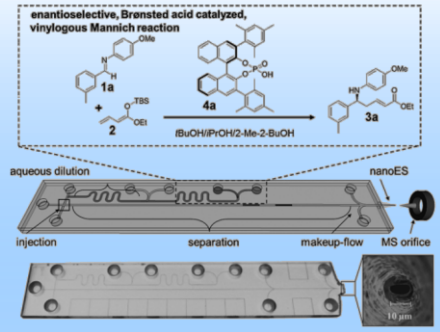

Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

## Hybrid Capillary/Microfluidic System for Comprehensive Online Liquid Chromatography-Capillary Electrophoresis-ESI-MS



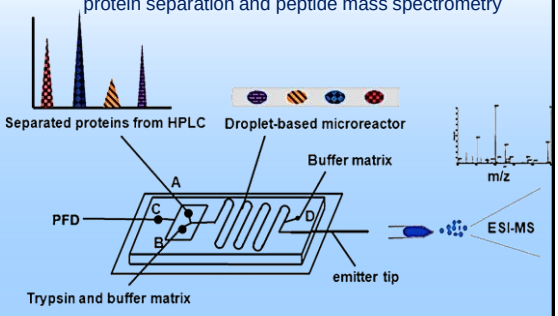

Mellors, JS; Black, WA; Chambers, AG; Starkey, JA; Lacher, NA; Ramsey, JM. Anal. Chem. 2013, 85, 4100-4106

## Asymmetric Organocatalysis and Analysis on a Nanospray Chip



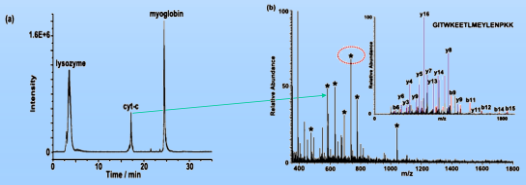

S. Fritzsche, S. Ohla, P. Glaser, D. S. Giera, M. Sickert, C. Schneider and D. Belder Angew. Chem., Int. Ed., 2011, 50, 9467-9470.

## Proteolysis in microfluidic droplets: an approach to interface protein separation and peptide mass spectrometry




J. Ji, L. Nie, L. Qiao, Y. Li, L. Guo, B. Liu, P. Yang and H. H. Girault, Lab Chip, 2012, 12, 2625-2629.

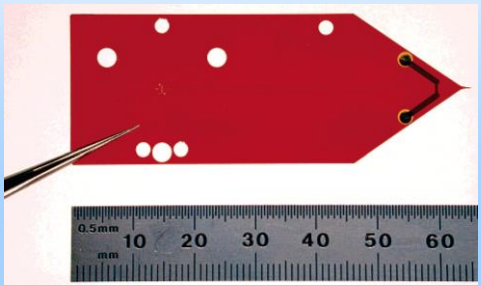
## Proteolysis in microfluidic droplets: an approach to interface protein separation and peptide mass spectrometry




J. Ji, L. Nie, L. Qiao, Y. Li, L. Guo, B. Liu, P. Yang and H. H. Girault, Lab Chip, 2012, 12, 2625-2629.

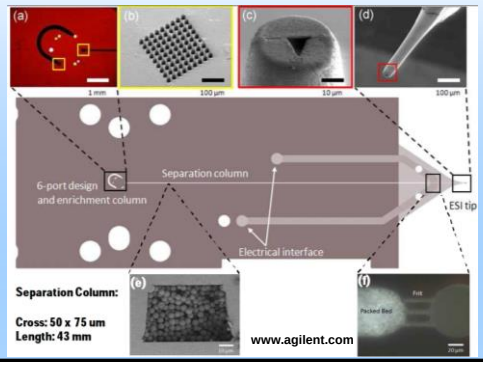
# Commercialization

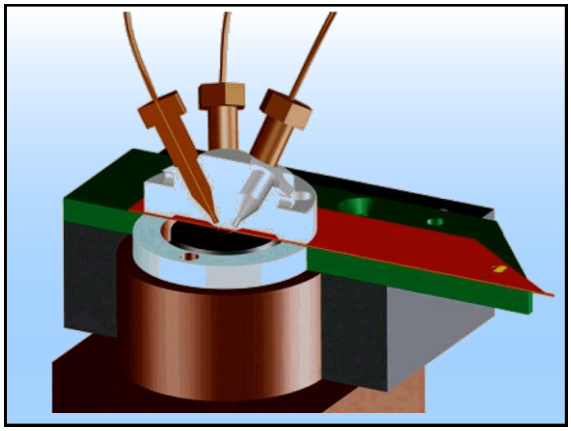
## Microfluidic Chip for Peptide Analysis with an Integrated HPLC Column, Sample Enrichment Column, and Nanoelectrospray Tip




H. Yin, K. Killeen, R. Brennen, D. Sobek, M. Werlich, T. van de Goor Anal. Chem. 2005, 77, 527-533

**Polyimide HPLC-chip, integrating an enrichment column, frits, a laser ablated ESI tip and trapazoidal separation column**

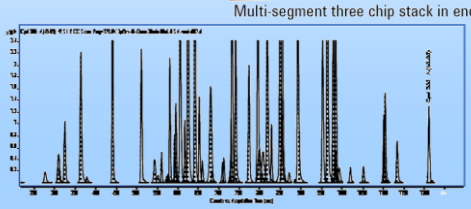


## Segmented column HPLC/chip

Three LC columns – length 130 mm
Each segment individually packed.

Multi-segment three chip stack in enclosure.

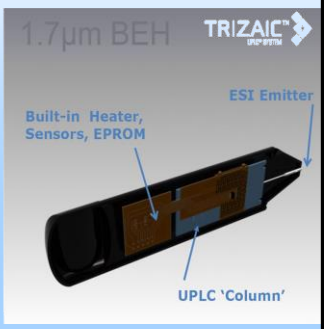


BSA digest separated with a 30min gradient on a 2 column segmented chip, packed with 3.5µm particles

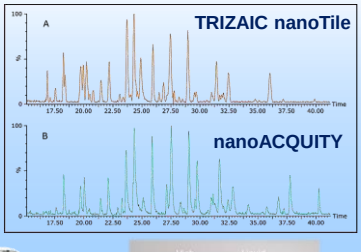
www.agilent.com

## TRIZAIC nanoTile - Waters

- UPLC Performance
- All fluidic connections are pre-made & factory tested
- Integrated ESI Emitter
- Low System Volumes
- Decreased Band Broadening
- Higher Sensitivity
- Incorporates:
  - Heater & Sensor
  - EPROM
- Increased Reproducibility




**Enolase digest**
70 fmol, 2 µm particles






- 150 µm ID Channel
- Sub-2-µm UPLC® Chemistries
- 10,000 psi Pressure Capability
- 1–7 pH Range
- Plug and Play Design
- Built-in eCord™
- Built-in Emitter
- Embedded Column Heater

## Green tape

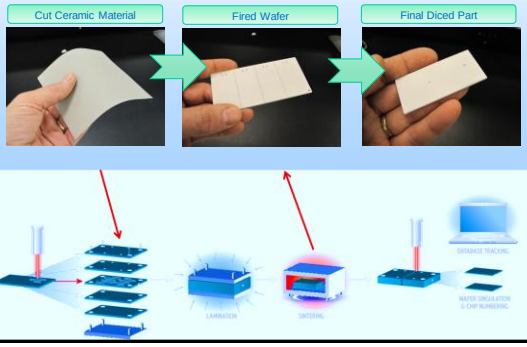
$Al_2O_3$–MgO–$SiO_2$ glass particles mixed with organic binders and solvents to form glass ceramic

**Product Description**
951 Green Tape is a low-temperature cofired ceramic tape.
The 951 system comprises a complete cofireable family of Au and Ag metallizations, buried passives, and encapsulants.
951 is available in multiple thicknesses for use as an insulating layer in:

- Multichip modules
- Single chip packages
- Ceramic printed wiring boards
- RF modules

http://www.dupont.com/mcm

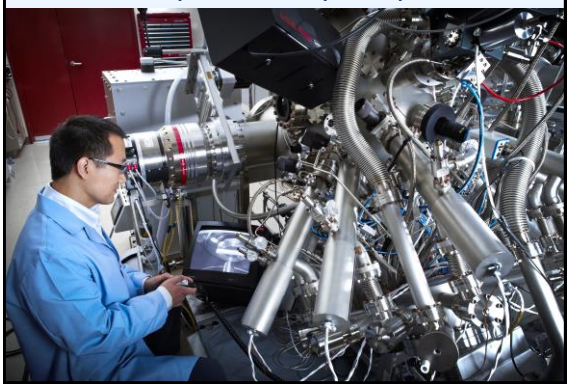
## Ceramic Microfluidic Fabrication




## Packed glass LC chip


Eksigent, part of AB SCIEX, www.eksigent.com

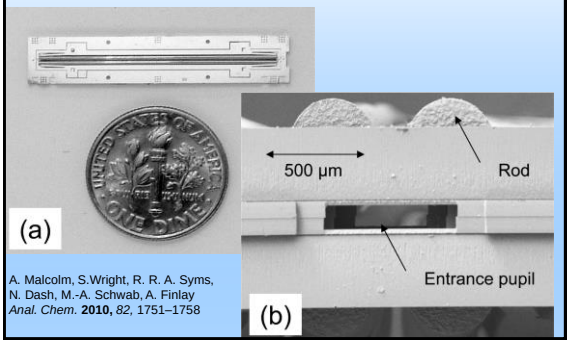
## Miniaturized (microfabricated) mass spectrometers?



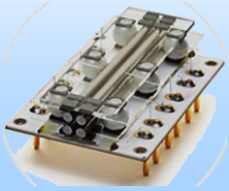
## Applications of Miniaturized MS Instruments

- trace explosive detection and airport security
- space exploration
- environmental monitoring
- point-ofcare medical applications

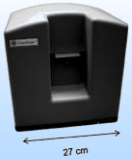
## Miniature Mass Spectrometer Systems based on a Microengineered Quadrupole Filter

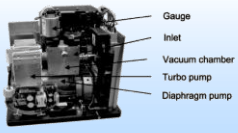



A. Malcolm, S.Wright, R. R. A. Syms, N. Dash, M.-A. Schwab, A. Finlay *Anal. Chem.* **2010,** *82,* 1751–1758

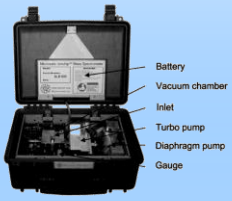


Mass Analyzer ionchip® quadrupole mass spectrometer
Mass Range m/z 50-800 with ionchip®150
Mass Accuracy ± m/z 0.3 in full scan
Mass Resolution m/z 0.7±0.1 FWHM
Sensitivity 10pg of reserpine in SIM mode S/N ratio of 10:1 (RMS)






27 cm



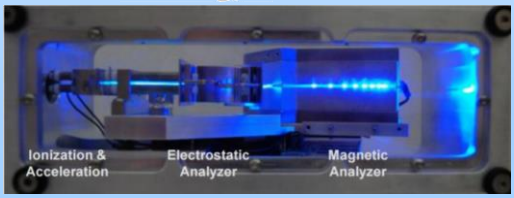

38 cm

Microsaic Systems

4000 MiD Bringing mass spectrometry down to size

www.microsaic.com

Self-contained instrument
Embedded PC
Vacuum inlet flow 2 mL/min
24V input (battery operation)




OI Analytical, www.oico.com

**Advion expression Compact Mass Spectrometer**

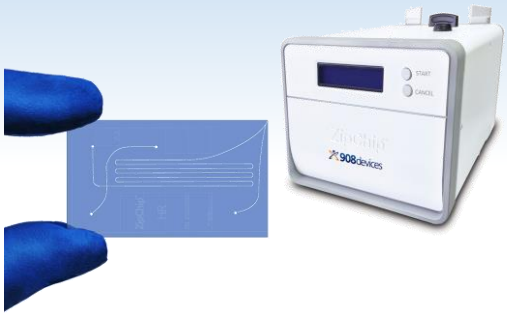

www.advion.com

Microscale Ion Trap

Internal glow discharge ionization
Mass Range 15-450 amu
Mass Resolution 1 amu

http://908devices.com/

## Automated CE-MS on a glass chip




## Patent? Patent!

- What is a patent
- Invention disclosure
- Does it make sense to patent?
- Patent search
- Resources

## What Is a Patent?

A patent for an invention is the **grant of a property right to the inventor**, issued by the United States Patent and Trademark Office. Generally, the **term of a new patent is 20 years** from the date on which the application for the patent was filed in the United States or, in special cases, from the date an earlier related application was filed, subject to the **payment of maintenance fees.** U.S. patent grants are effective only within the United States, U.S. territories, and U.S. possessions. Under certain circumstances, patent term extensions or adjustments may be available.
What is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention. Once a patent is issued, the patentee must enforce the patent without aid of the USPTO.

There are **three types of patents**:

1) **Utility patents** may be granted to anyone who invents or discovers any new and **useful process, machine, article of manufacture, or composition of matter**, or any new and useful **improvement thereof**;

2) **Design** patents may be granted to anyone who invents a new, original, and ornamental **design for an article of manufacture**; and

3) **Plant patents** may be granted to anyone who **invents or discovers and asexually reproduces any distinct and new variety of plant.**

## Patentable subject

1. **Does not fall under the laws of nature, natural phenomena or abstract ideas**
2. **Utility requirement - invention must be useful in association with machines, human-made products, compositions of matter or processing methods**
3. **Novelty the idea must not be presented to the public before the filing**
4. **Nonobviousness – it must be unrecognizable to a skilled person in the field of invention**
5. **Clarity of the description included in the application**

## Patent je zákonná ochrana vynálezů zaručující vlastníkovi patentu výhradní právo k průmyslovému využití vynálezu.

V České republice udělování patentů upravuje zákon 527/1990. Podle něj se patenty udělují na vynálezy, které **jsou nové, jsou výsledkem vynálezecké činnosti a jsou průmyslově využitelné**.
Vynález se považuje za nový, jestliže není součástí stavu techniky.

Stavem techniky je všechno, co bylo zveřejněno přede dnem přihlášení patentu, ať již v České republice nebo v zahraničí.

**Za vynálezy se naopak nepovažují zejména :**

**objevy, vědecké teorie a matematické metody,**
**pouhé vnější úpravy výrobků,**
**plány, pravidla a způsoby vykonávání duševní činnosti,**
**programy počítačů,**
**pouhé uvedení informace**

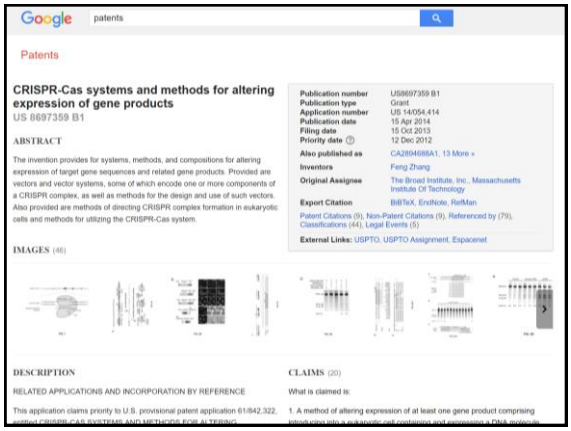
Majitel patentu má výlučné právo vynález využívat (tj. výrobek vyrábět, uvádět do oběhu nebo upotřebit postup), dále poskytnout souhlas k využívání vynálezu jiným osobám (např. licenční smlouvou) a má právo převést patent na jinou osobu.
Proto, aby patent zůstal v platnosti, je nutno platit tzv. udržovací poplatky, a to v každém státu zvlášť. Maximální možná délka patentové ochrany je 20 roků.

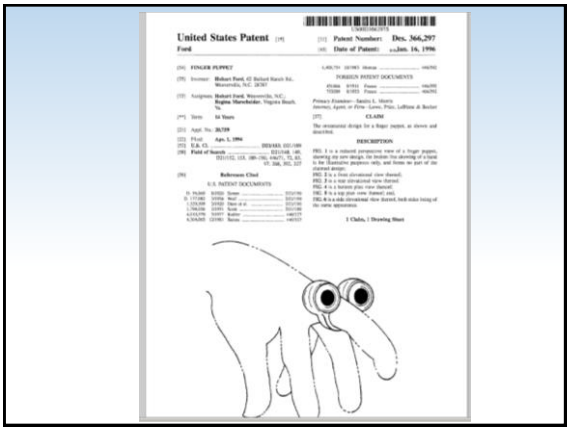
http://cs.wikipedia.org/

## United States Patent and Trademark Office
www.uspto.gov

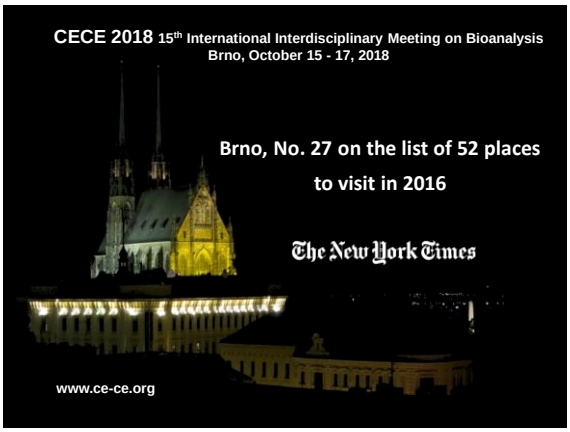
## European patent office
www.epoline.org

## Úřad průmyslového vlastnictví
www.upv.cz


Google
patents
Patents
CRISPR-Cas systems and methods for altering expression of gene products
US 8697359 B1
ABSTRACT
The invention provides for systems, methods, and compositions for altering expression of target gene sequences and related gene products. Provided are vectors and vector systems, some of which encode one or more components of a CRISPR complex, as well as methods for the design and use of such vectors. Also provided are methods of directing CRISPR complex formation in eukaryotic cells and methods for utilizing the CRISPR-Cas system.
Publication number US8697359 B1
Publication type Grant
Application number US 14/054,414
Publication date 15 Apr 2014
Filing date 15 Oct 2013
Priority date 12 Dec 2012
Also published as CA2894686A1, 13 More »
Inventors Feng Zhang
Original Assignee The Broad Institute, Inc., Massachusetts Institute Of Technology
Export Citation BiBTeX, EndNote, RefMan
Patent Citations (9), Non-Patent Citations (9), Referenced by (79), Classifications (44), Legal Events (5)
External Links: USPTO, USPTO Assignment, Espacenet
IMAGES (46)
DESCRIPTION
RELATED APPLICATIONS AND INCORPORATION BY REFERENCE
CLAIMS (20)
What is claimed is:


United States Patent
Ford
Patent Number: Des. 366,297
Date of Patent: Jan. 16, 1996
FINGER PUPPET
DESCRIPTION


CTT
Centrum pro transfer technologií
Firmy a firemní zákazníci
Vědci a studenti univerzity
Novinky a akce
Kontakt
www.ctt.muni.cz


CECE 2018 15th International Interdisciplinary Meeting on Bioanalysis
Brno, October 15 - 17, 2018
Brno, No. 27 on the list of 52 places to visit in 2016
The New York Times
www.ce-ce.org