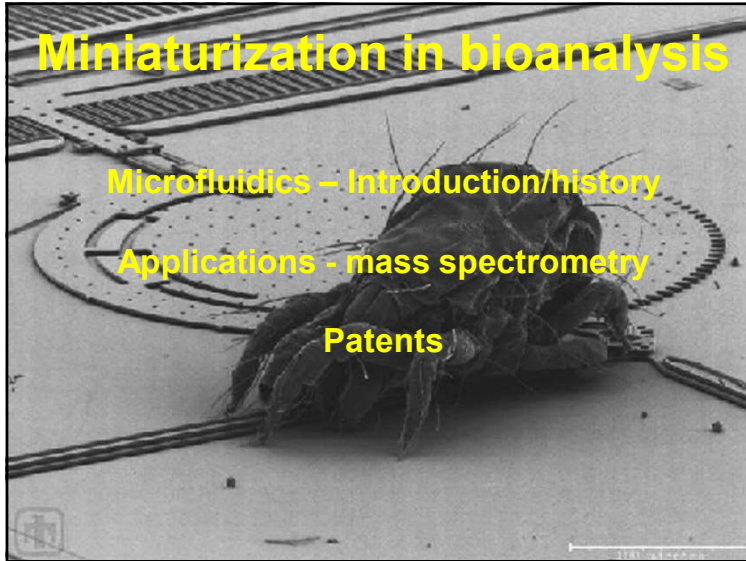


Miniaturization in bioanalysis

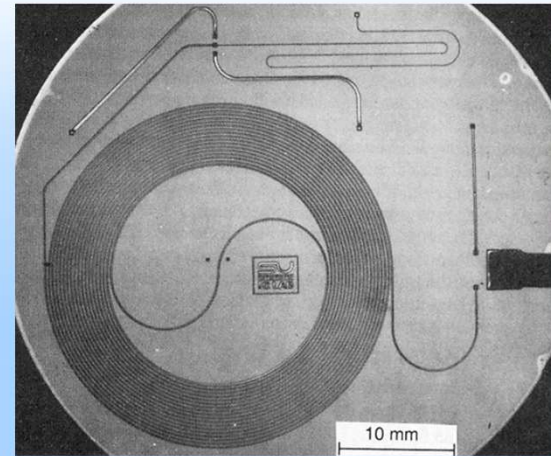
Microfluidics – Introduction/history

Applications - mass spectrometry

Patents



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

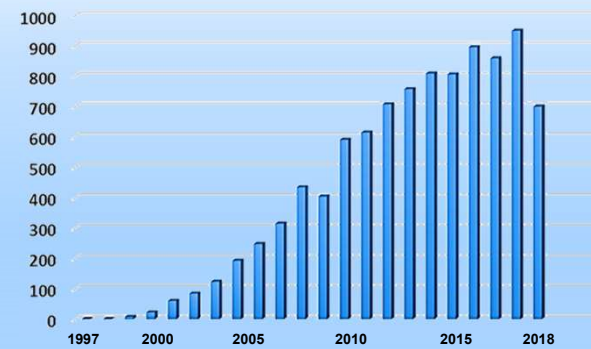
Prototype analog pneumatic computer to operate in a nuclear attack
NBS (now NIST) 1950's



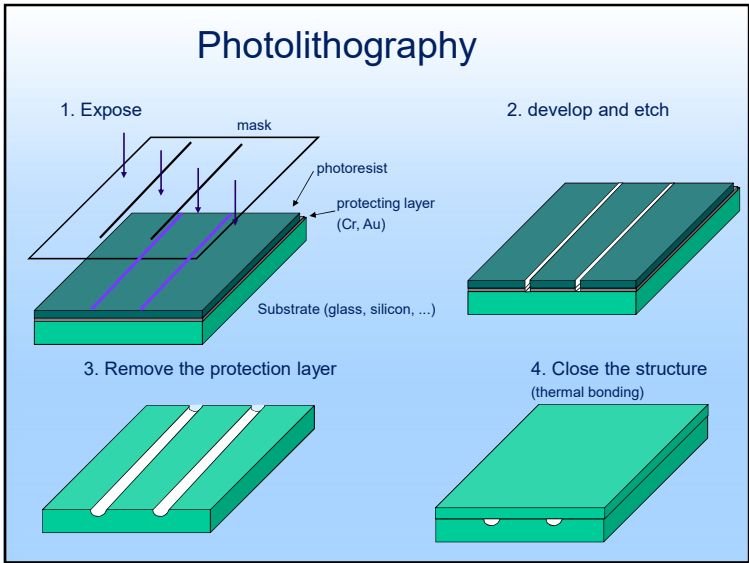
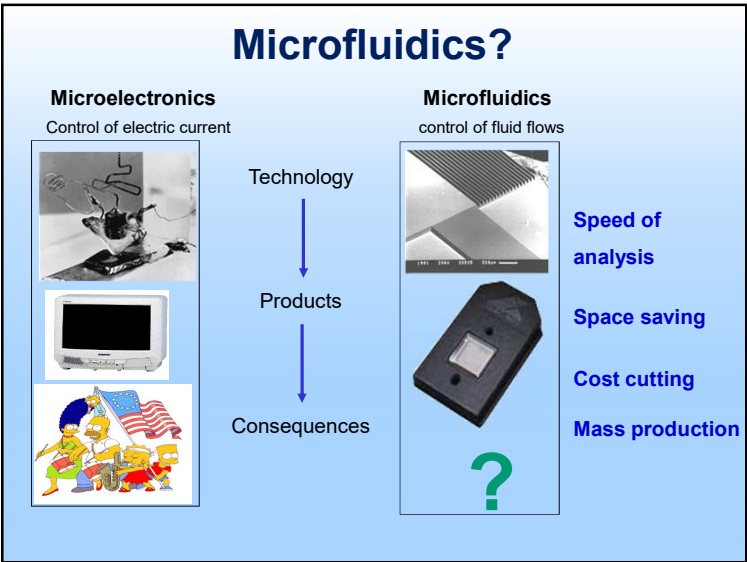
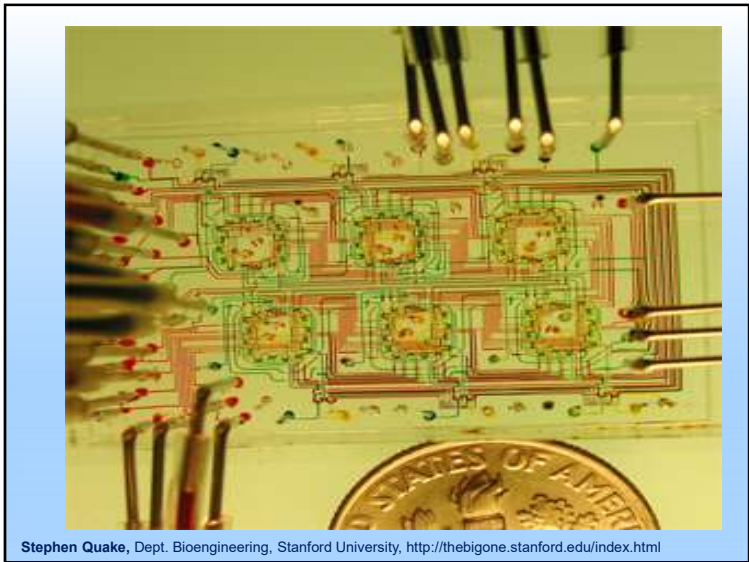
Picture by Wyatt Vreeland, NIST

Incidence of the word "MICROFLUIDIC" in PubMed

(as of August 2018)



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



Microfabrication technology

Micromilling	10 μm
Optical lithography	200 nm
e/ion beam lithography Multiple exposure techniques	10 nm
Etching (resist dependent)	\sim nm
Replication (mass production) Injection molding Hot embossing Casting	10's nm

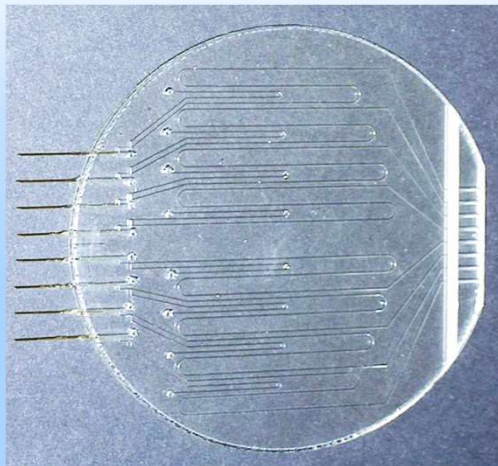
$\mu\text{PG 101}$ Tabletop Laser Pattern Generator

HEIDELBERG
INSTRUMENTS

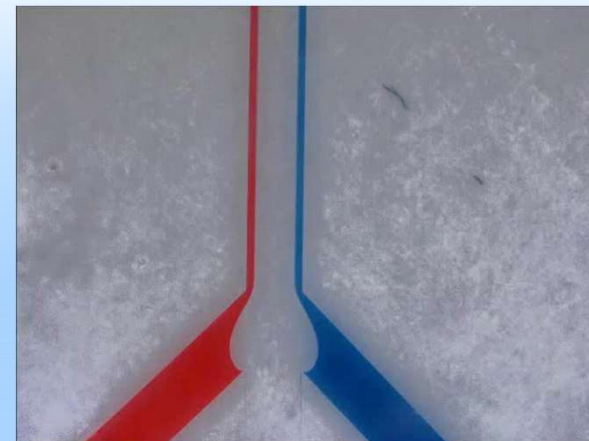


- Substrates up to 100 x 100 mm²
- Structures down to 1 μm
- Address grid down to 40 nm
- Standard or UV laser source

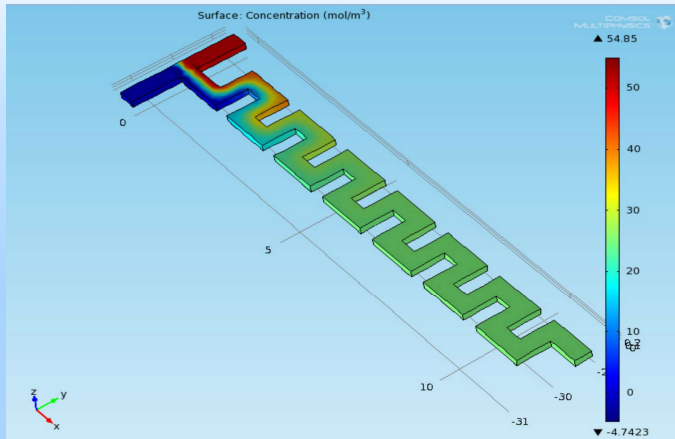
System Integration



Spatial flow focusing



Computational Analysis for Mixing of Fluids Flowing through MicroChannels

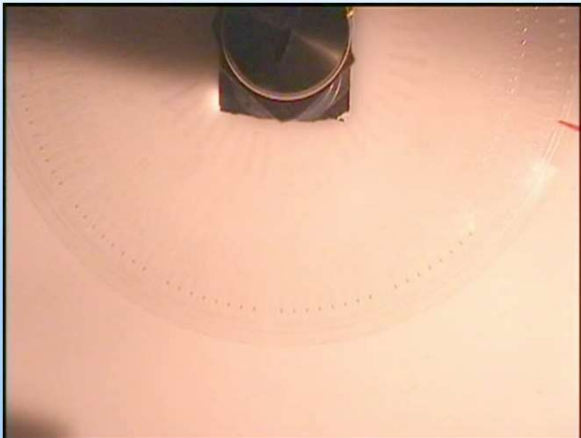


Sankha Shuvra Das, Binay Kumar Patawari, P.K. Patowari, S Halder
5th International & 26th AIMTDR 2014, December 12th-14th, 2014, IIT Guwahati, Assam, India 236-1

Diffusion limited mixing

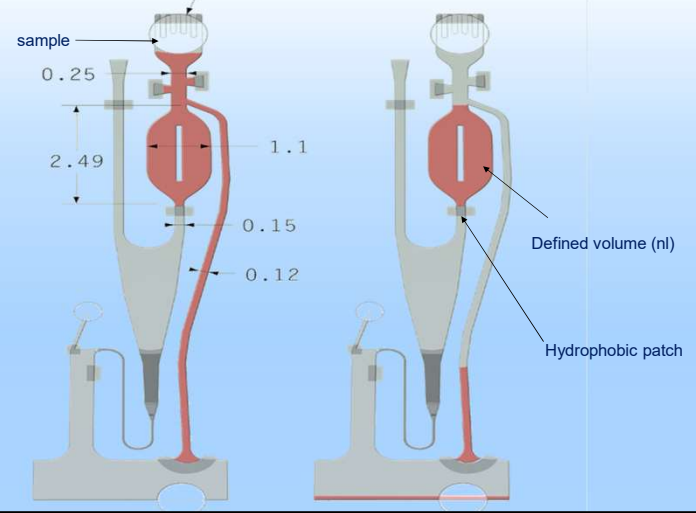


Capillary force filling

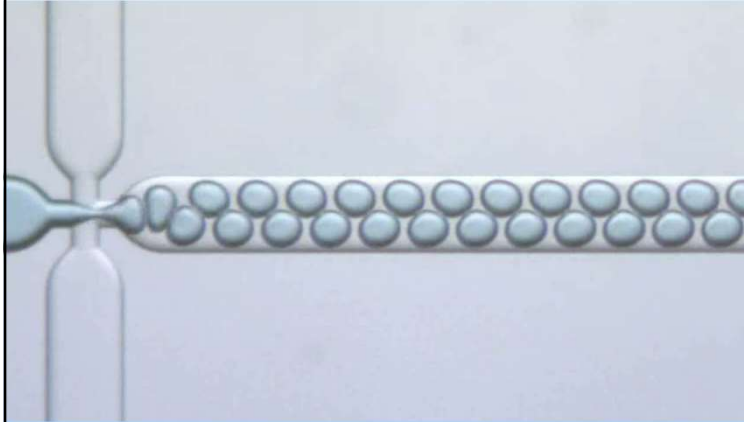


www.gyros.com

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

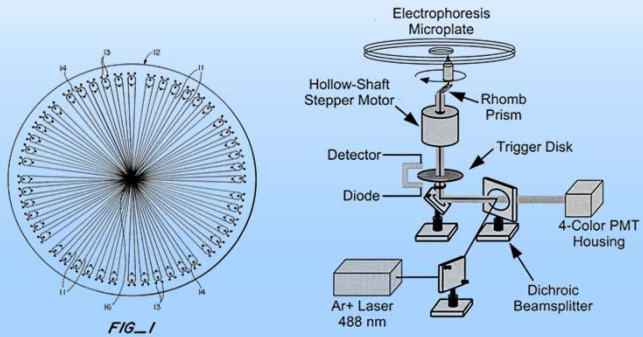
	2.15 mm	=>	10 μ l \sim 10^{-15} M
	1 mm	=>	1 μ l \sim 10^{-14} M
	0.1 mm	=>	1 nl \sim 10^{-11} M
	0.001 mm	=>	1 fl \sim 10^{-5} M

MICROFABRICATED DEVICES

- * **Sensors** - accelerometers, glucose monitors, ...
- * **Genomics** - next gen sequencing
- * **Proteomics** - sample processing separation

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

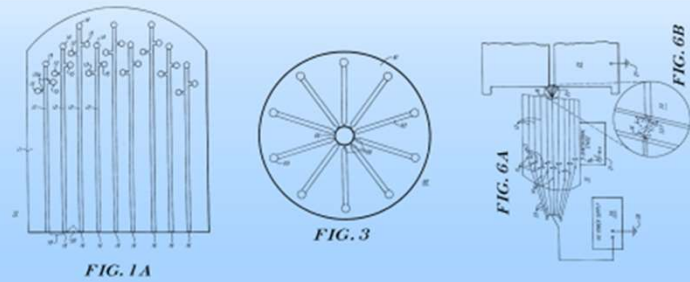
U.S. Patent Aug. 8, 2000 Sheet 1 of 6 6,100,535



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

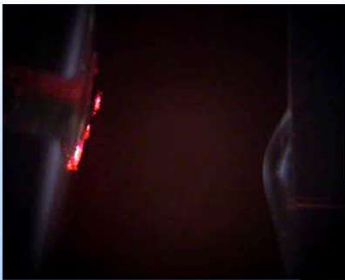
U.S. Patent Feb. 16, 1999 Sheet 1 of 10 5,872,010 U.S. Patent Feb. 16, 1999 Sheet 6 of 10 5,872,010 U.S. Patent Feb. 16, 1999 Sheet 8 of 10 5,872,010



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.

Electrospray

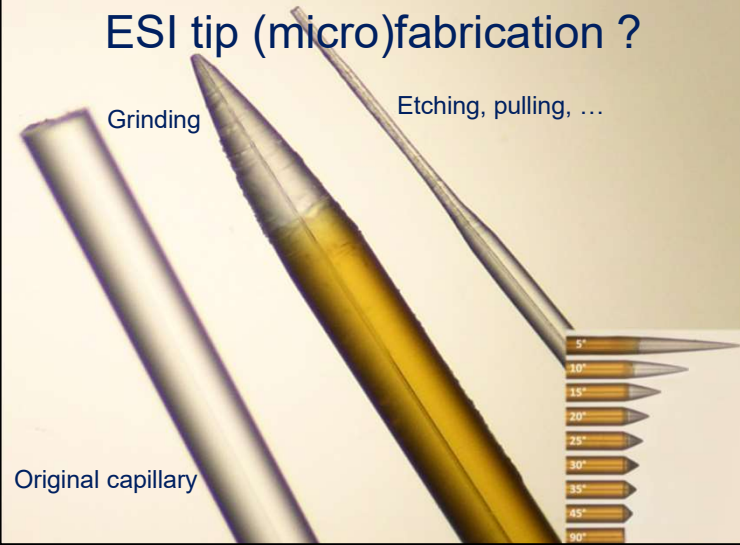


Flat surface - droplet



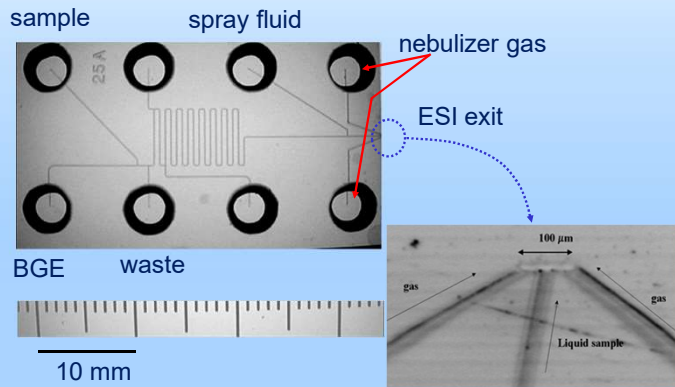
Capillary tip

ESI tip (micro)fabrication ?



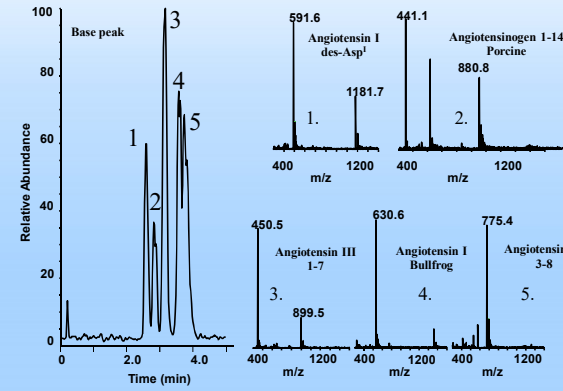
Original capillary

CE Microdevice with a Pneumatic Nebulizer

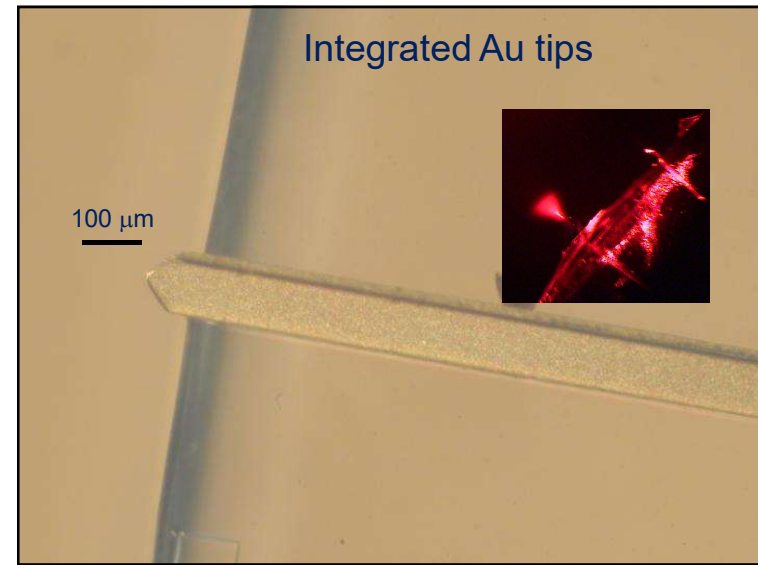
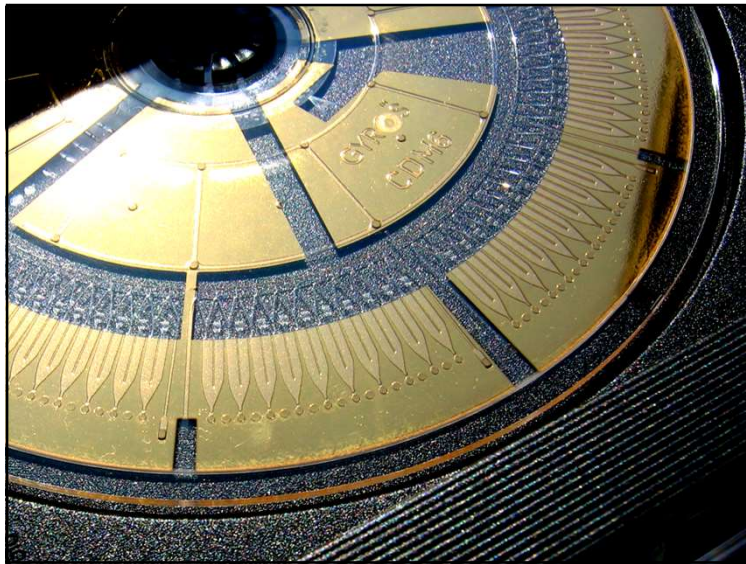


Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.*, 1999, 71, 3258-3264.

CE Microdevice with a Pneumatic Nebulizer

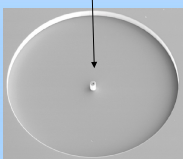
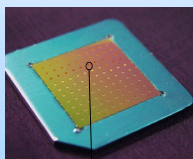


Zhang, B. Liu, H. Karger, B. L. Foret, F. *Anal. Chem.*, 1999, 71, 3258-3264.



ESI tip fabrication

DRIE in silicone



www.advion.com

Plasma etched in polyimide



www.diagnoswiss.com



www.agilent.com

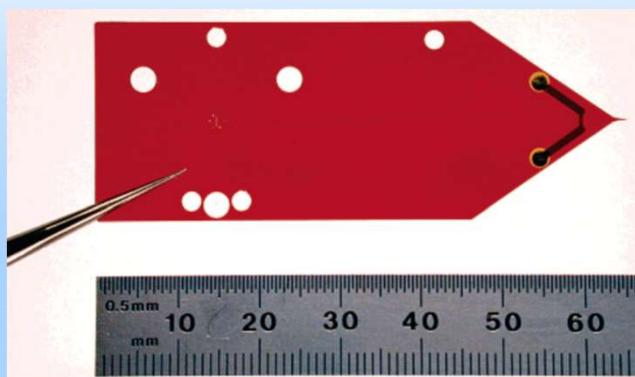
Injection molding in polypropylene



www.phoenix-st.com

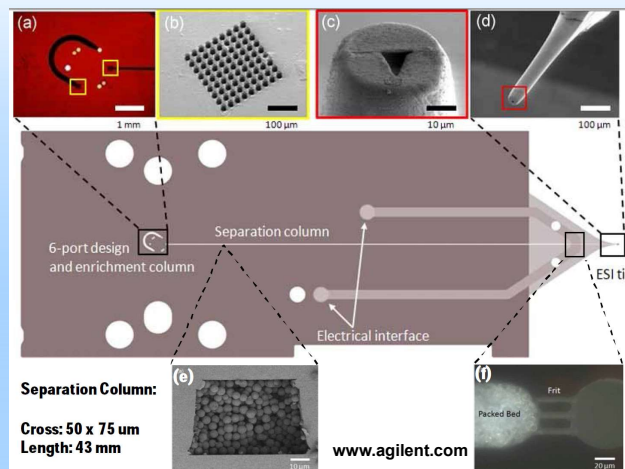
Applications Commercialization

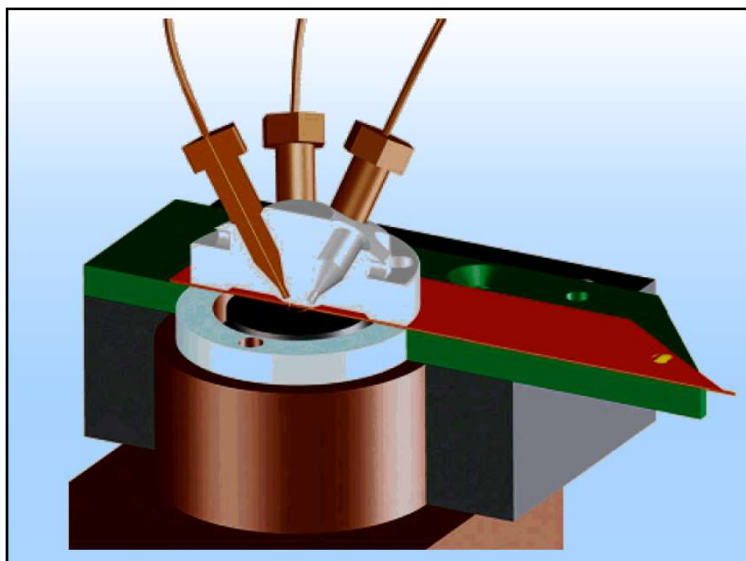
Microfluidic Chip for Peptide Analysis with an Integrated HPLC Column, Sample Enrichment Column, and Nanoelectrospray Tip



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 trapezoidal separation column



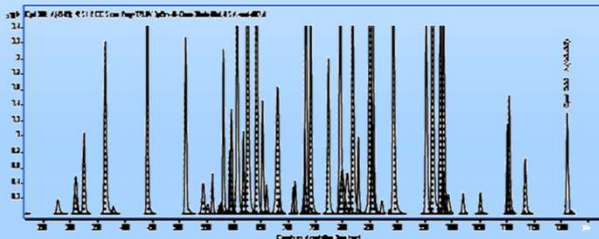


Segmented column HPLC/chip

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



Multi-segment three chip stack in enclosure.

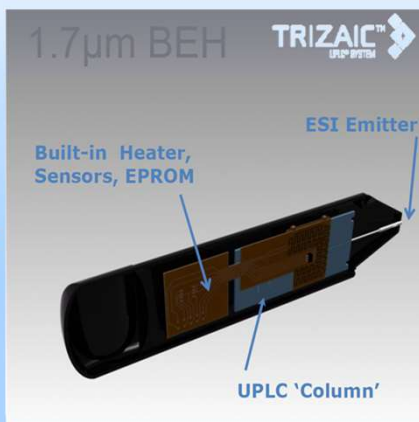


BSA digest separated with a 30min gradient on a 2 column segmented chip, packed with 3.5 μ m particles

www.agilent.com

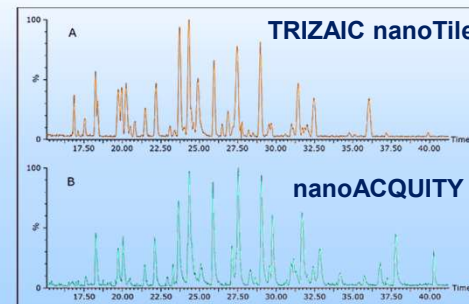
TRIZAIC nanoTile - Waters

- 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 μ m particles





Green tape

$\text{Al}_2\text{O}_3\text{-MgO-SiO}_2$ glass particles mixed with organic binders and solvents to form glass ceramic

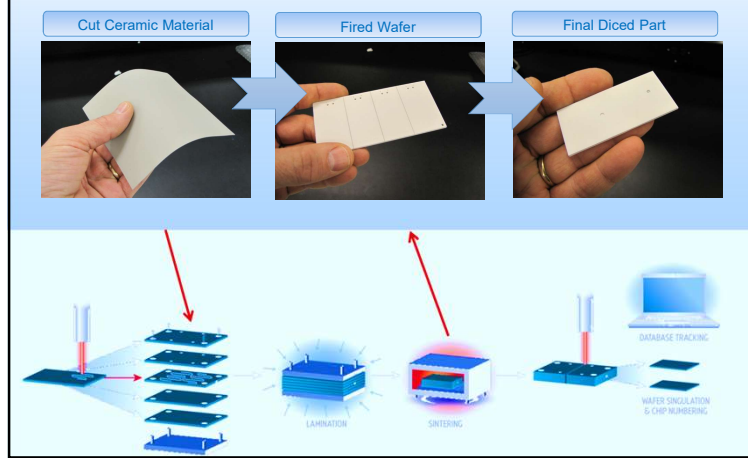
Product Description

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

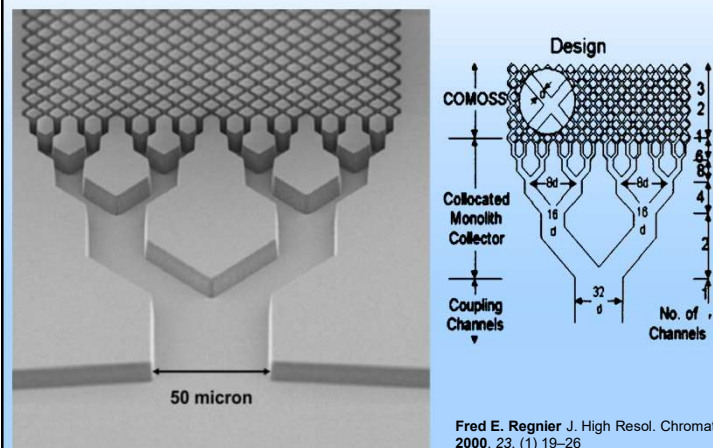
<http://www.dupont.com/mcm>

Ceramic Microfluidic Fabrication



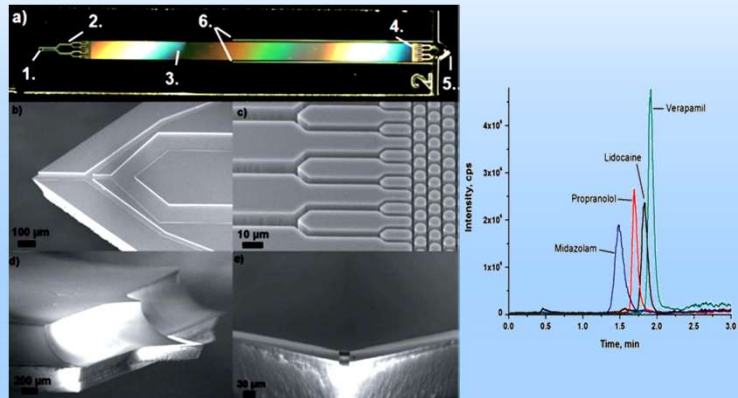
Microfabricated Monolith Columns for Liquid Chromatography

Sculpting Supports for Liquid Chromatography

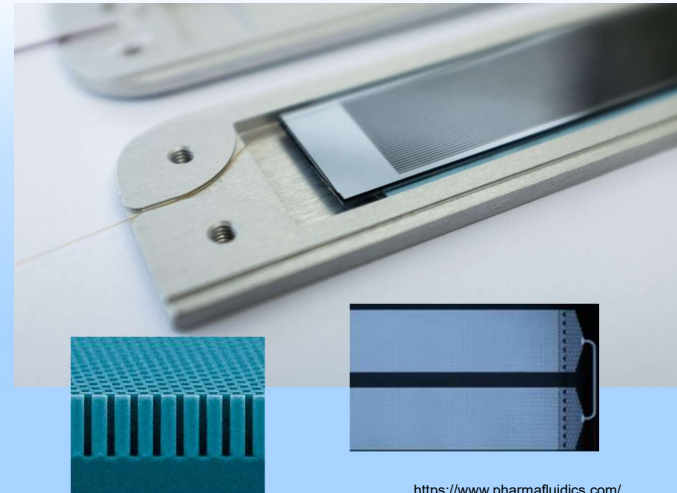


Fred E. Regnier J. High Resol. Chromatogr. 2000, 23, (1) 19–26

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



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



<https://www.pharmafluidics.com/>

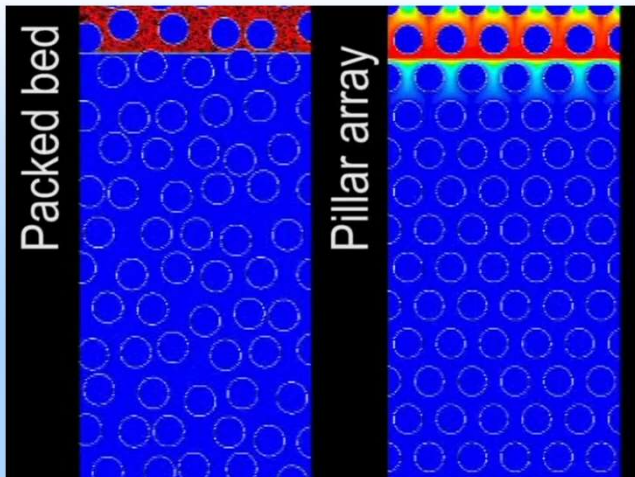
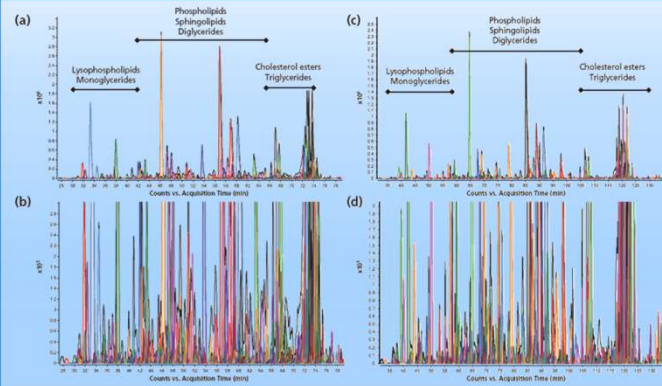
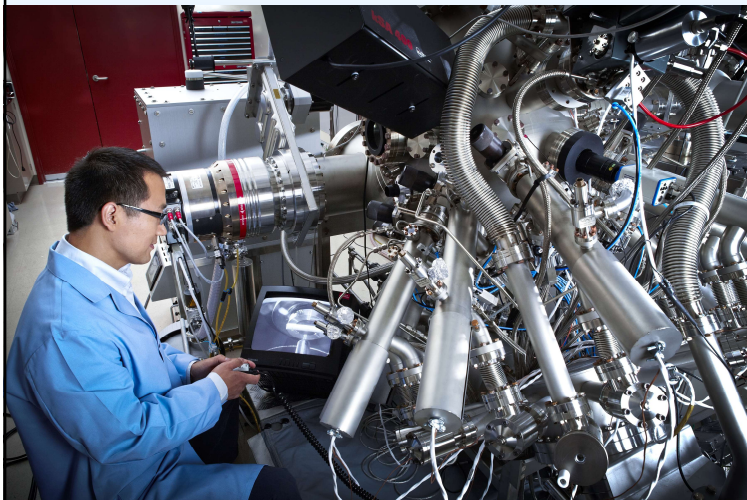


Figure 5: LC-MS compound chromatograms at different scaling (zoomed and unzoomed) obtained in the positive electrospray ionization mode for a human blood plasma lipid extract. (a) and (b) 60-min gradient, (c) and (d) 120-min gradient.



<http://www.chromatographyonline.com/evaluation-micro-pillar-array-columns-pac-combined-high-resolution-mass-spectrometry-lipidomics?pageID=5>

Miniaturized (microfabricated) mass spectrometers?

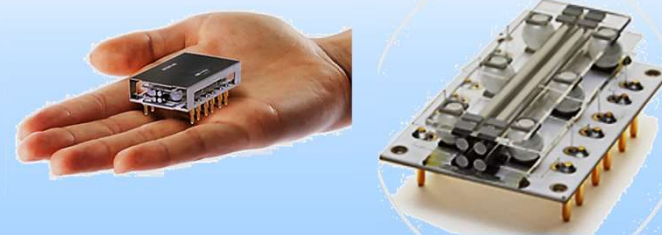
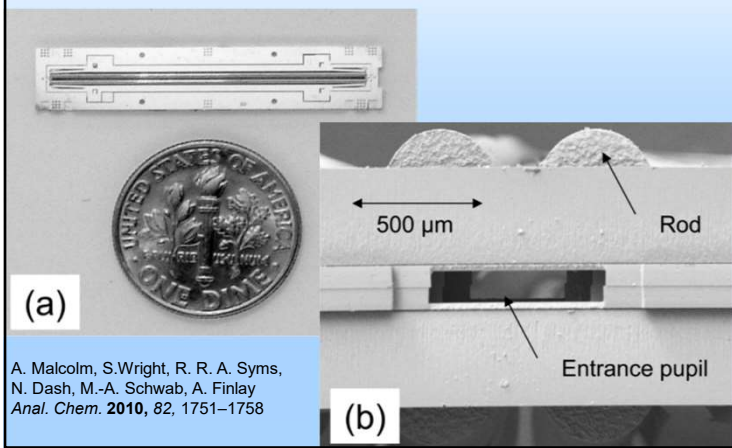


Applications of Miniaturized MS Instruments

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



Miniature Mass Spectrometer Systems based on a Microengineered Quadrupole Filter



Mass Analyzer ionchip® quadrupole mass spectrometer
Mass Range m/z 50-800 with ionchip®150
Mass Accuracy $\pm m/z$ 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)



Microsaic Systems



4000 MiD Bringing mass spectrometry down to size

www.microsaic.com

Advion expression Compact Mass Spectrometer



www.advion.com

Microscale Ion Trap

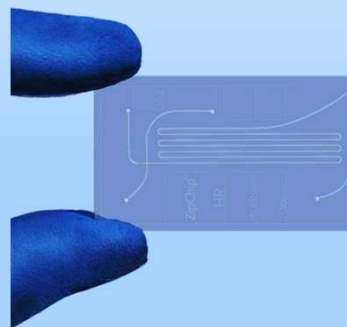


Internal glow discharge ionization
Mass Range 15-450 amu
Mass Resolution 1 amu



<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 vlastníkov 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 vylučné 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.

IMAGES (46)

DESCRIPTION
 RELATED APPLICATIONS AND INCORPORATION BY REFERENCE
 This application claims priority to U.S. provisional patent application 61/842,322, entitled CRISPR-CAS SYSTEMS AND METHODS FOR ALTERING

CLAIMS (20)
 What is claimed is:
 1. A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell containing and expressing a DNA molecule

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 CA2894688A1, 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

United States Patent [19] Patent Number: Des. 366,297
 Ford [45] Date of Patent: Jan. 16, 1996

4,497,751 16/983 Menap 446702
 FOREIGN PATENT DOCUMENTS
 01064 81911 France 446702
 73109 81983 France 446702
 Primary Examiner—Sandra L. Morris
 Attorney, Agent, or Firm—Lerner, Pitts, Lubliner & Becker, No.

CLAIM
 [57] The ornamental design for a finger puppet, as shown and described.

DESCRIPTION
 FIG. 1 is a reduced perspective view of a finger puppet, showing its one length. In broken line showing of FIG. 1 is the alternative purposes only, and forms no part of the claimed design.
 FIG. 2 is a front elevational view thereof.
 FIG. 3 is a rear elevational view thereof.
 FIG. 4 is a bottom plan view thereof.
 FIG. 5 is a top plan view thereof, in part.
 FIG. 6 is a side elevational view thereof, both sides being of like name appearance.

Reference Cited
 U.S. PATENT DOCUMENTS
 0, 16,640 81892 Simon 201/100
 0, 177,082 31956 Neuf 201/100
 1,235,709 21837 Shaw et al. 201/100
 1,764,436 31993 Ross 201/189
 4,203,576 31957 Kuhn 446702
 4,304,085 321981 Dixon 446702

1 Claim, 1 Drawing Sheet

CTT
 Centrum pro transfer technologii

Biomechanická obuv pro zdravotní chůzi

Domů
 Služby
 Duševní vlastnictví
 Příslušky práce
 Nabídka vzdělávání
 Ke stažení
 Novinky a akce
 Newsletter INTERFACE
 O nás
 Běžá pro komercializaci
 Fotogalerie
 Kontakt

Firmy a firemní zákazníci
 Novinky a akce
 Newsletter INTERFACE
 O nás
 Běžá pro komercializaci
 Fotogalerie
 Kontakt

Vědci a studenti univerzity

Centrum pro transfer technologii Masarykovy univerzity (CTT) bylo založeno v roce 2005 a jehož hlavním posláním: podporovat uplatnění výsledků vědy a výzkumu v praxi, budovat mosty mezi akademickou a podnikatelskou sférou, nastavovat podmínky pro transfer technologii a znalostí, chránit a spravovat duševní vlastnictví MU a poskytovat vědeckým i firemním profesionální podporu a servis ve všech souvisejících oblastech.

Tým CTT je tvořen business development manažery, projektovými manažery, právníky a ekonomicko-administrativním zázemím. Portfoliem svých služeb (tito specialisté ovládají jazyk více MU, tak konkrétní firmy, jako jsou základem úlohy pracovité)

- příměstí kontaktů místo Masarykovy univerzity pro firmy
- zprostředkování spolupráce akademické a podnikatelské sféry
- inovace vztahů mezi akademickou a podnikatelskou sférou
- ochrana a správa duševního vlastnictví
- propagace výzkumných aktivit Masarykovy univerzity
- vzdělávání a poradenství v oblasti transferu technologii a duševního vlastnictví

Více informací o transferu technologii na Masarykově univerzitě se dozvíte z brožury CTT. Příslušnou jazykovou verzi otevřete kliknutím na obrazy.

Česká verze brožury
 Anglická verze brožury

www.ctt.muni.cz

© 2008–2014 Masarykova univerzita | Centrum pro transfer technologii, Štepaňkova věž, 9, 602 77 Brno | Všechna práva vyhrazena. | Mapa stránek | Správa stránek | Přihlášení | Vytvoření uživatelského účtu

Novinky a akce
 04.11.2016
 Vychází druhý letovník INTERFACE
 Právě vychází druhý letovník Česko žurnálové INTERFACE. Hlavní vydává Centrum pro...
 21.11.2016
 TT Day 2016: Vstupte do světa inovací!
 Centrum pro transfer technologii si Vás dovoluje pozvat na 4. den otevřených dveří...
 31.10.2016
 Pátrá na podrobné profilování
 občanských známek!
 Na CTT MU opět příly dokumenty, které se týkají jako výzva a profesionální ochranné...
 03.10.2016
 MU spolupořádá konferenci o
 mezinárodních dotacích programech
 Masarykova univerzita zve jako spolupořadatel na konferenci s názvem
 "Heritage HE..."

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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*

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www.ce-ce.org

CECE 2019 16th International Interdisciplinary
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September 24-26th
Hotel Mercure Gdańsk Stare Miasto ****

CECE 2020 Siem Reap, Cambodia



ITP/CECE 2021 Brno, Czech Republic

