

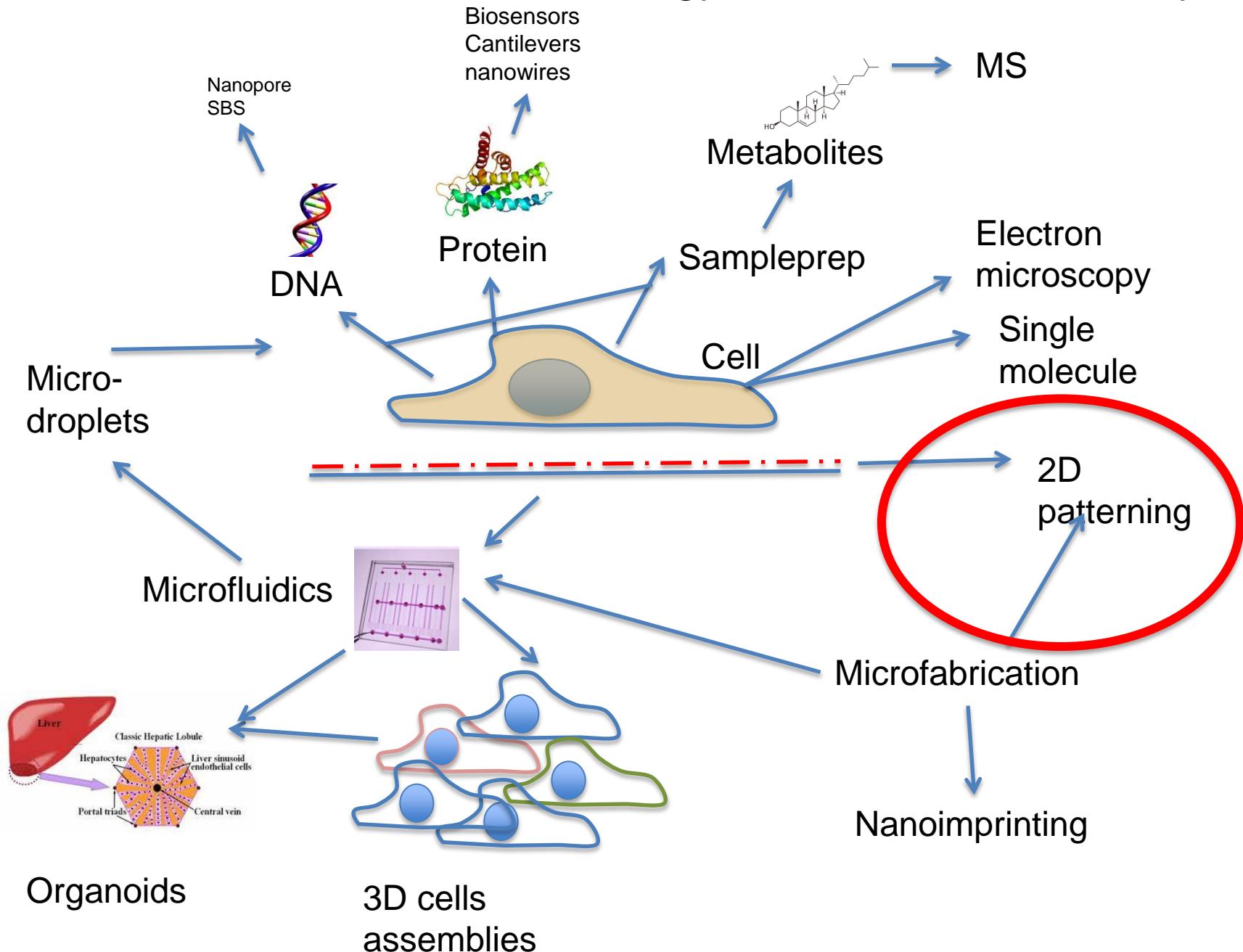
# Biopatterning

creating and controlling  
bioactive surfaces

# This lecture

- Functionalizing surfaces
- Creating patterns
- Characterizing patterns
- Using devices

# Course outline : nanotechnology for biomedicine : analysis



# Why functionalize and pattern..

- Protein probes
  - AFM (force measurements)
  - Protein chips (quantitative measurements)
- In vitro assays
- Stem cell differentiation
- Cell interaction
- Cell patterning
- Little spatial control in 3D
- Enhanced function by microfluidics

# Traditional cell biology

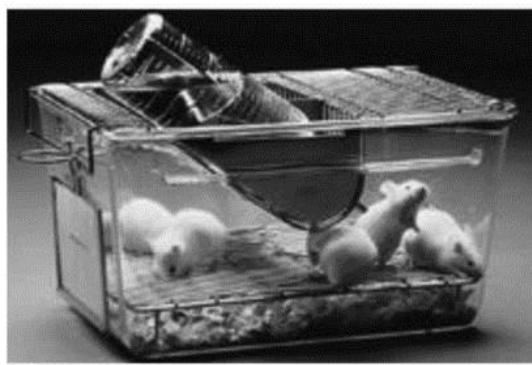
Large numbers of cells and supplies



Human labor



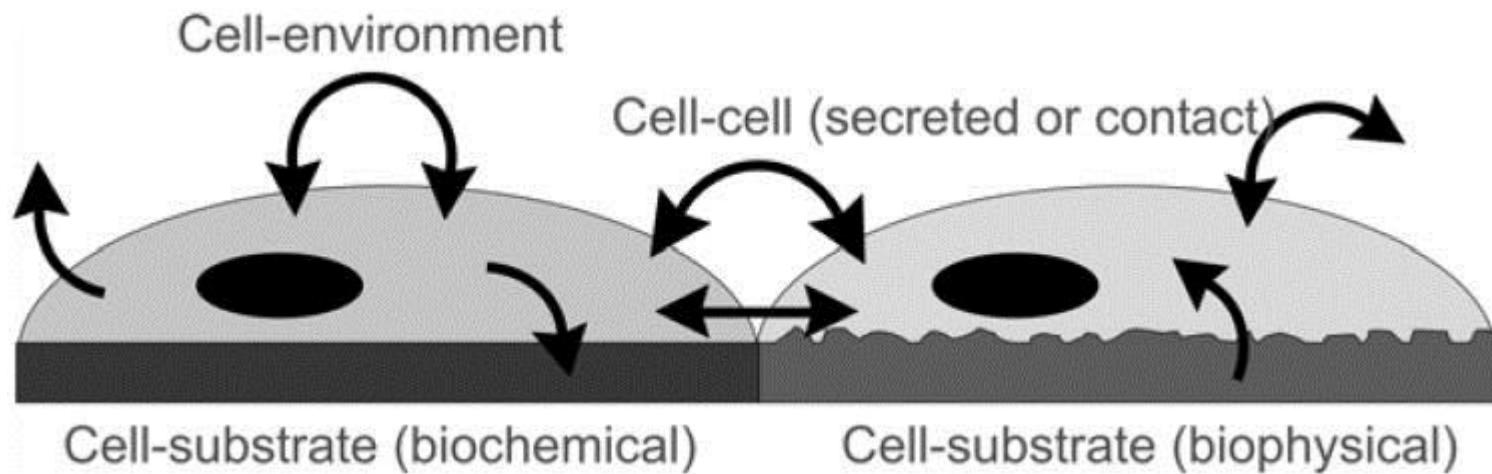
Animal suffering



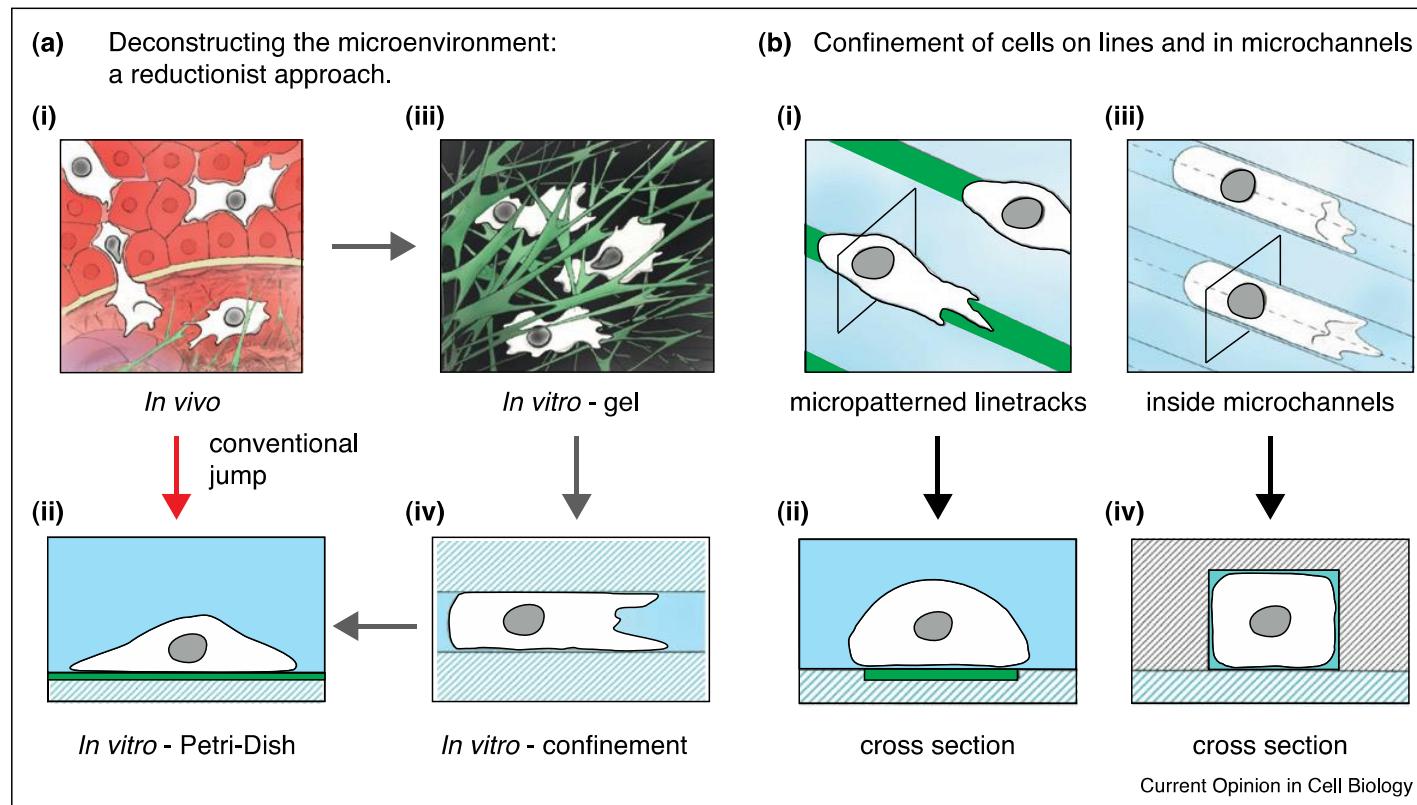
Expensive equipment



# What lacks control in traditional cell biology



# Cells in a petri dish is no longer good enough: Why? “because we can”



**Table 1** Selected Studies on Stem Cells Using Lab-on-a-chip Devices

Stem Cell Application	Selected Studies
Control of Soluble Factors	Dynamic exposure to soluble drug Design for controlled-diffusive mixing Microfluidic based multi-injector method 'Microbioreactor' system for human embryonic stem cell differentiation Paracrine and autocrine signaling control
Control of ECM Interactions	Combining soluble and insoluble factors in microarray 3D microenvironment to study stem cell fate
Control of Cell-Cell Interactions	Design to control cell-cell interactions Design for cell pairing Design for co-culture of mES cells with other cell types Design for temporal control of cell-cell signaling
Control of Mechanical Signals	Design for heterotypic cells with different shear sensitivities Controlled elasticity geometry through PDMS patterns Control of elasticity using magnetic nanoposts Controlling nanoscale symmetry and disorder in cues Designs for surface pattern geometries Design for study of role of topography Control of 3D topography by electrospun nanowires Control of shear stress as a mechanical cue Shear control for long term culture
High Throughput Screening	High throughput integrated microfluidic systems 'High-content screening' with combinatorial stimuli Design to study high throughput temporal responses Design to screen effects of drugs in long term cultures
Novel Studies for Potential Stem Cell Research	Slow perfusion by osmotic pump for long term culture Design for reversible bonding of microfluidic device to cell culture containing cover slip by vacuum Design for reversible bonding of microfluidic device by magnetic force

## Uses of cell substrate patterning

Subcellular organization (standardization)

Cell-patterning and guided cell motility

Cell:cell communication

Cell:substrate interaction

Cell differentiation

Axon guidance

Patterned cultures

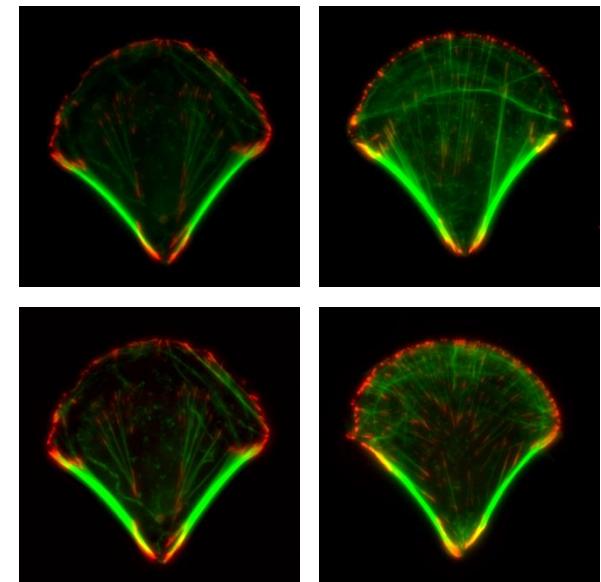
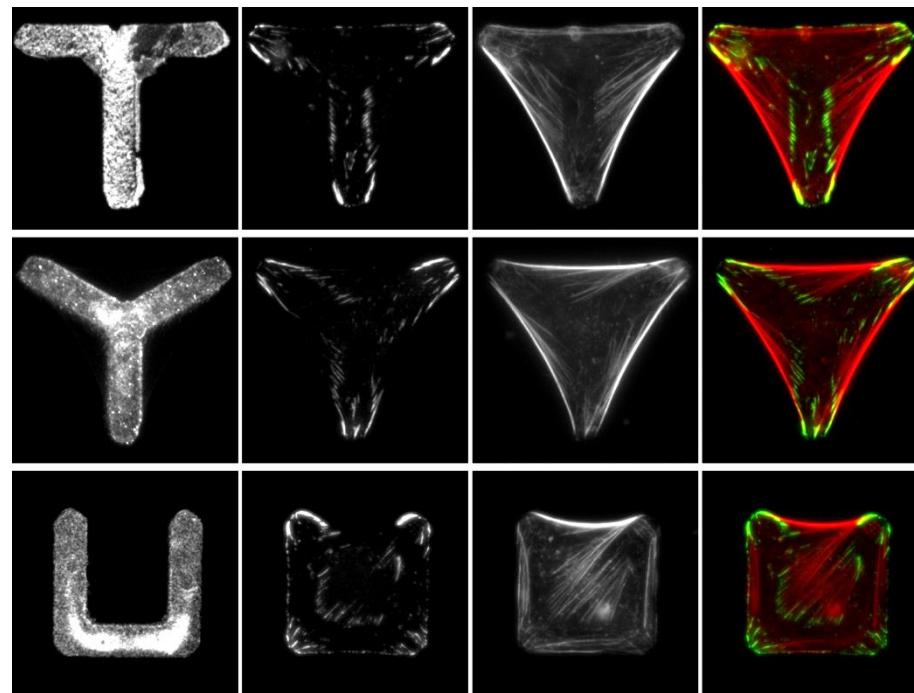
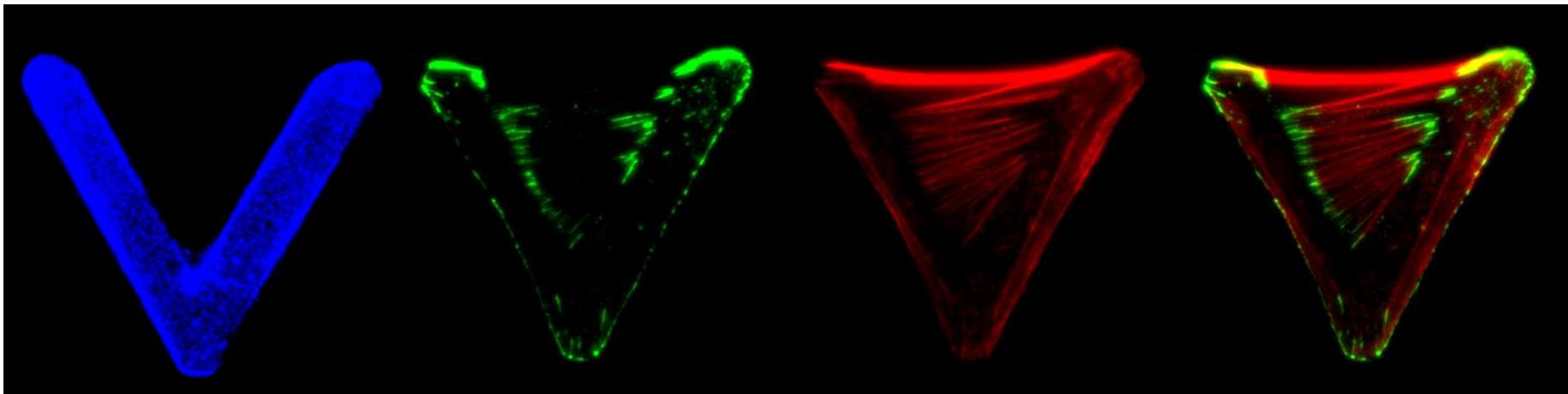
++++

# Cells form stress fibers over non adhesive edges

fibronectin

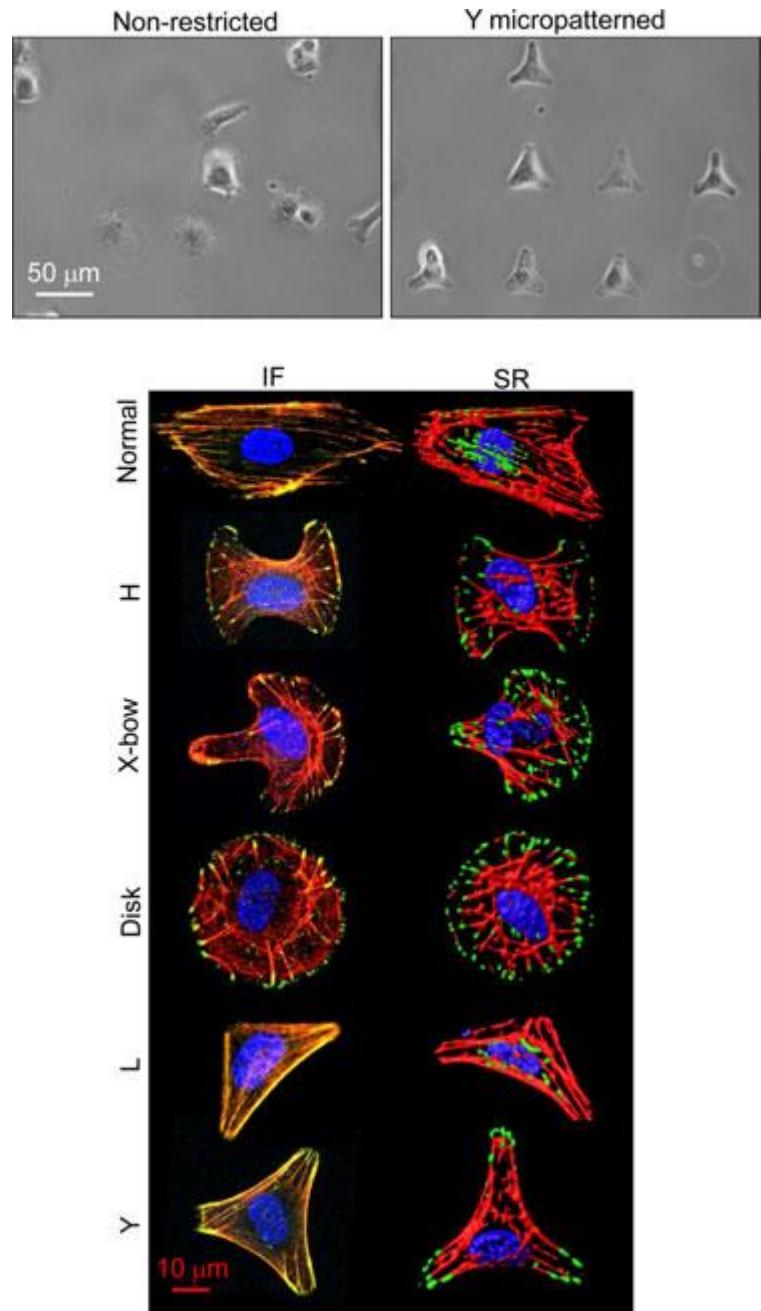
vinculin

actin



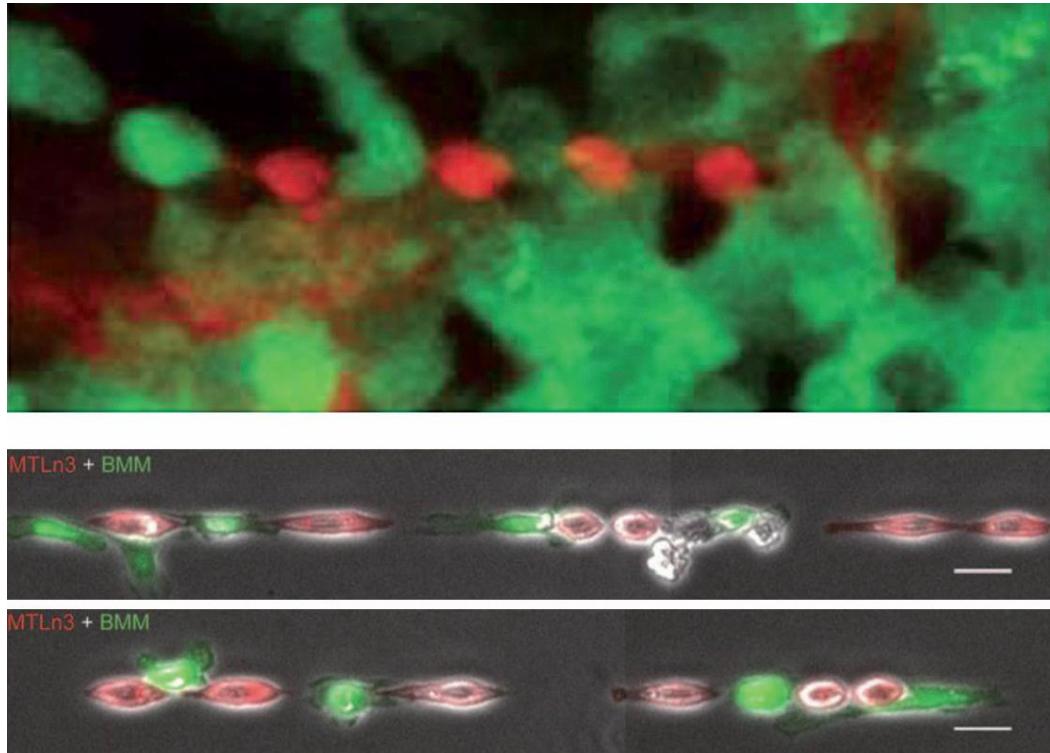
Thery et al., CMC and PNAS, 2006

## Standardization of cell organization



<http://cytoo.com/>

# Migratory highways

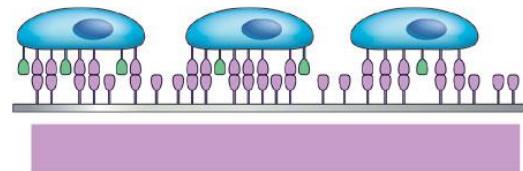


<http://cytoo.com/CYTOO-applications-cell-migration.php>

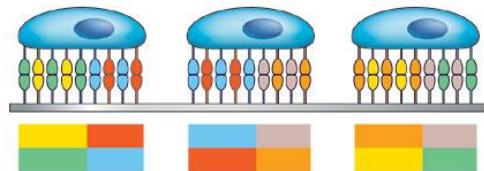
# Printed growth factors and stiffness structure determines stem cell fate

2D

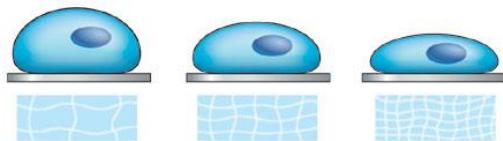
a Individual signals



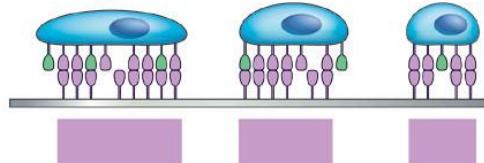
b Combinatorial signal mixtures



c Modular substrate stiffness

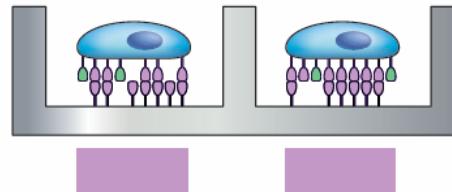


d Printed signal islands

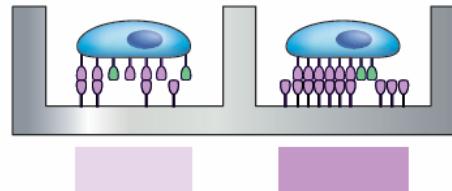


pseudo3D

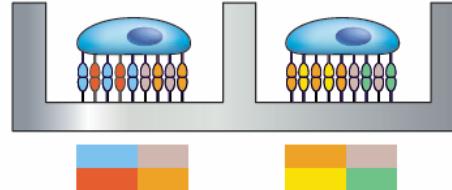
a Individual signals



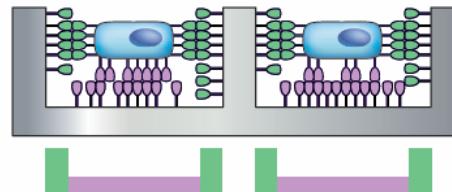
b Individual signal gradients



c Combinatorial signal mixtures



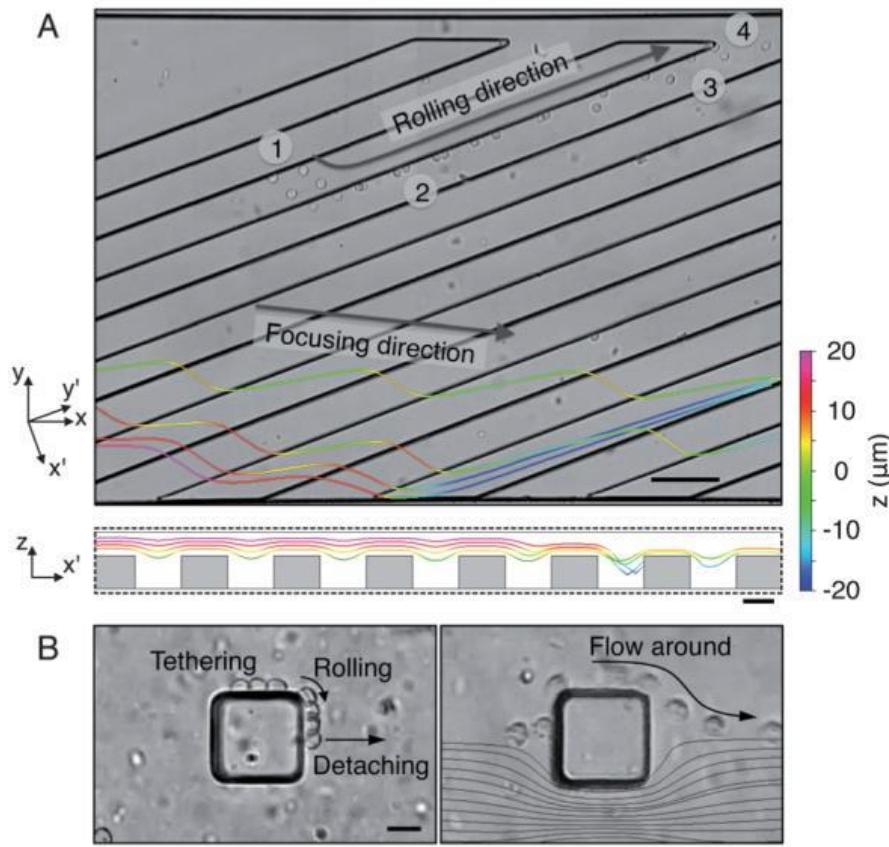
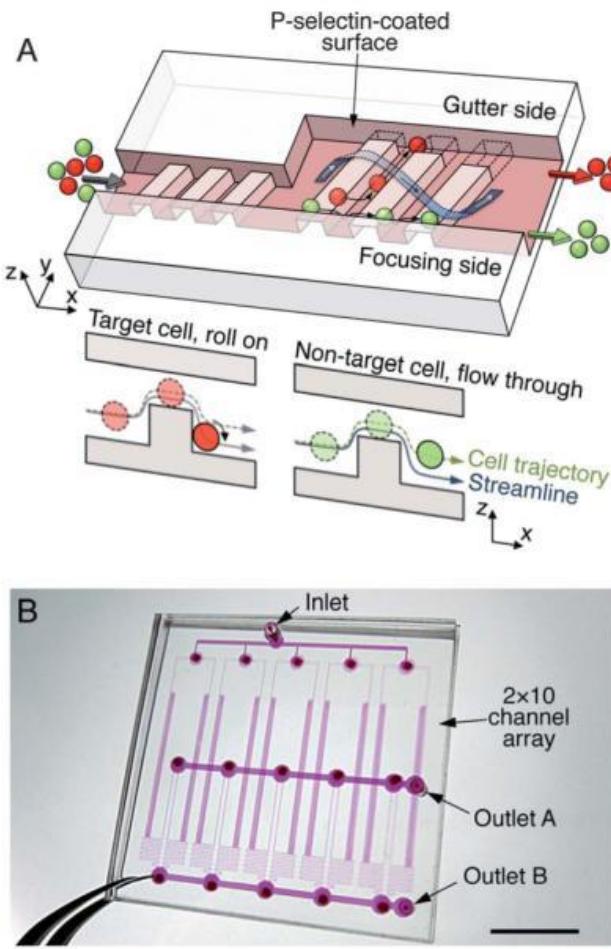
d Spatial control of signals



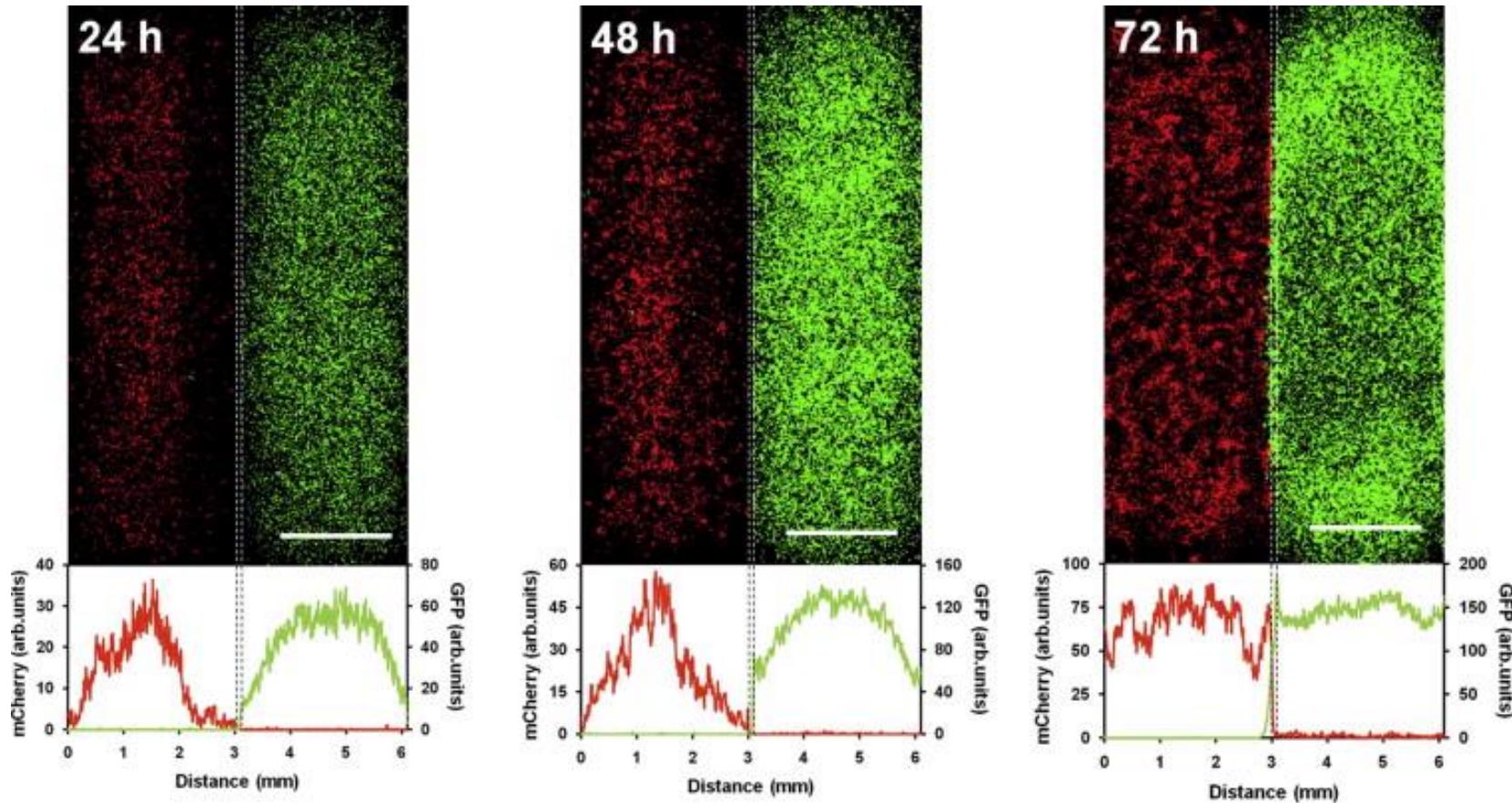
Designing materials to direct stem-cell fate

Matthias P. Lutolf, Penney M. Gilbert & Helen M. Blau  
Nature 462, 433-441(26 November 2009)

# Cells interacting dynamically with surfaces, microfluidic sorting

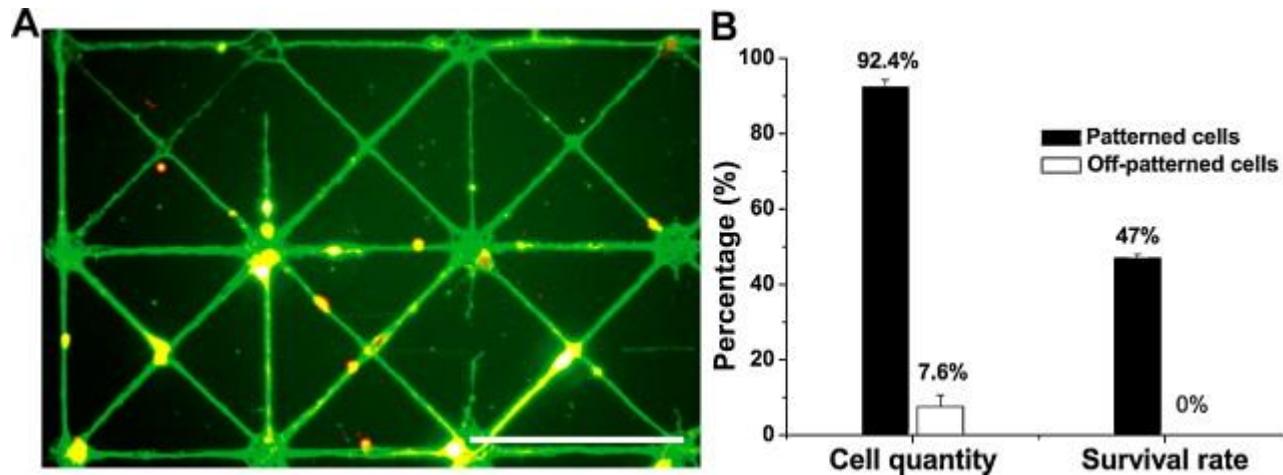


# Segregated and patterned cell co-cultures a new beginning in tissue engineering and cancer research

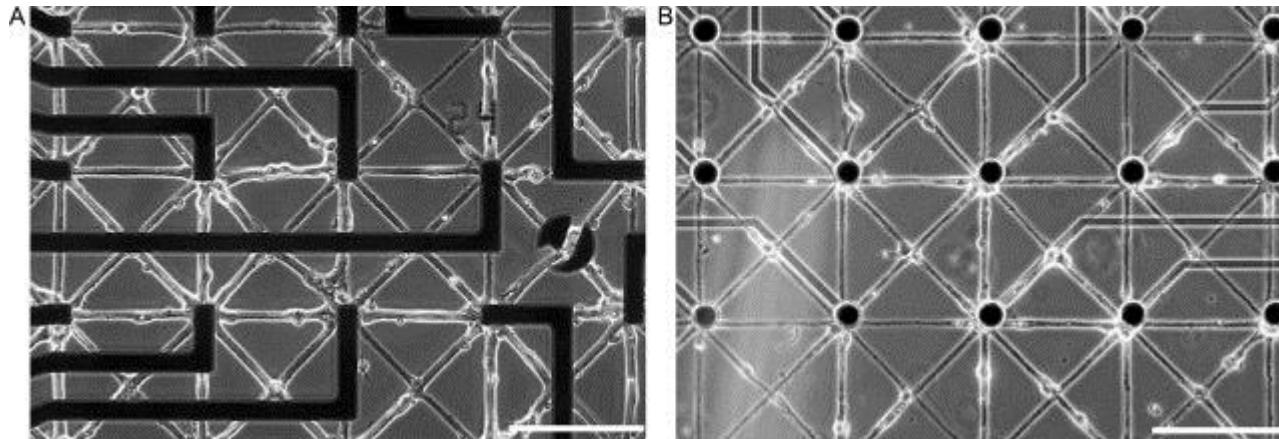


# Building neuronal networks with electrodes

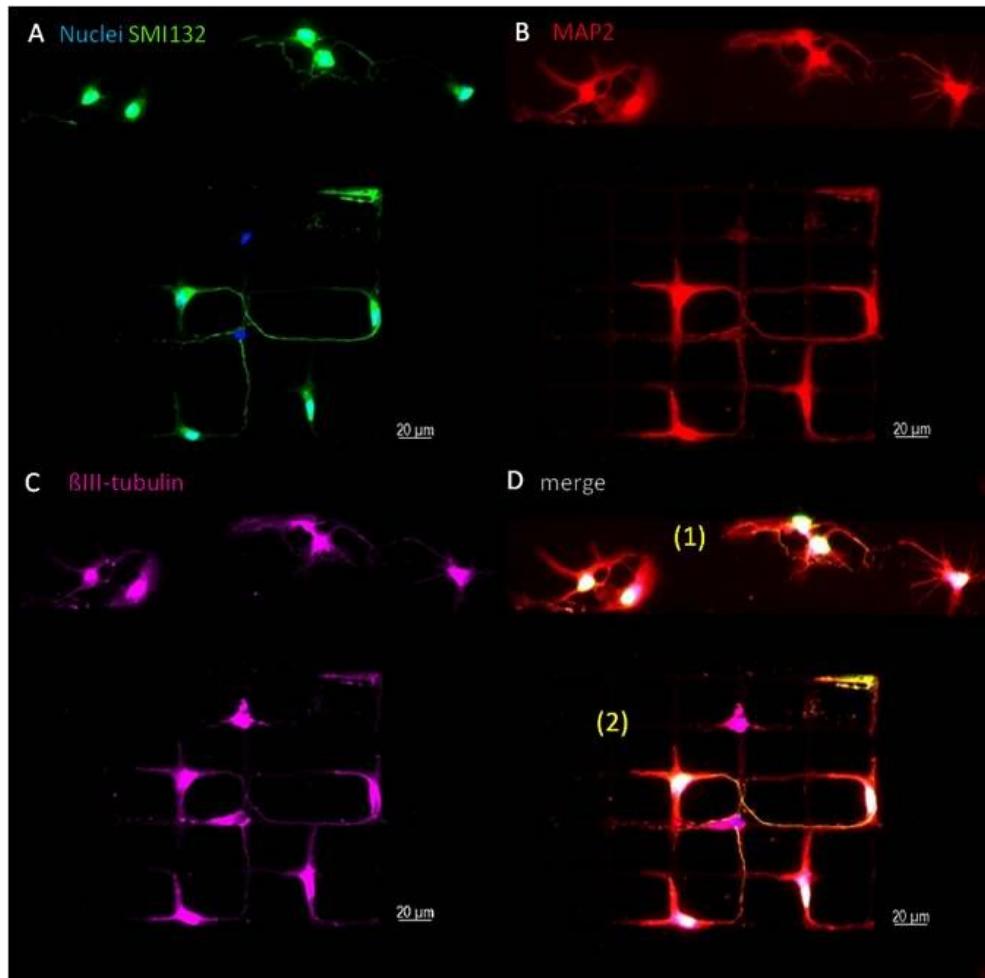
Forming networks based on adhesive patterns



Monitoring neuronal activity by embedding electrodes in custom-built neuronal networks

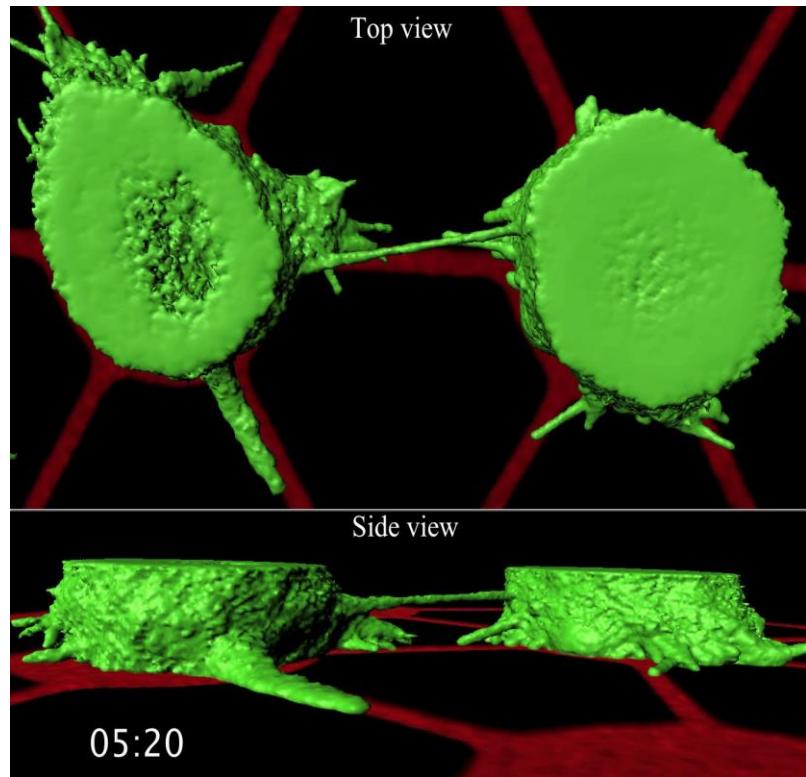
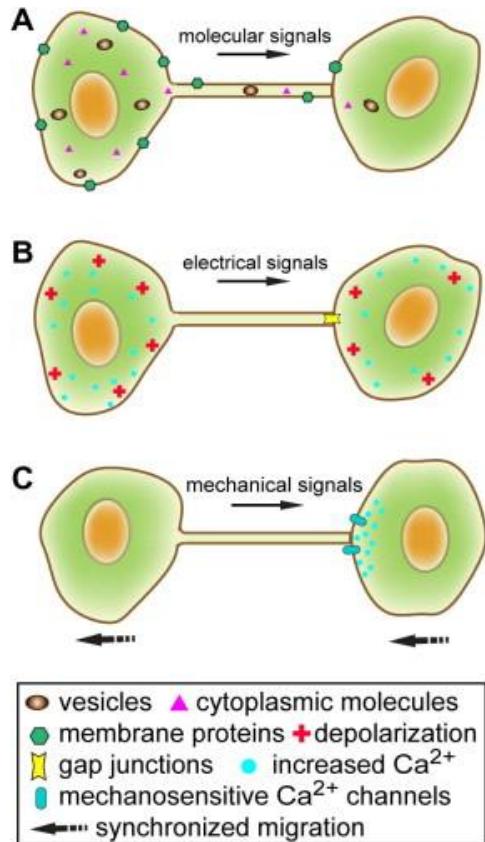


# Neuronal patterning

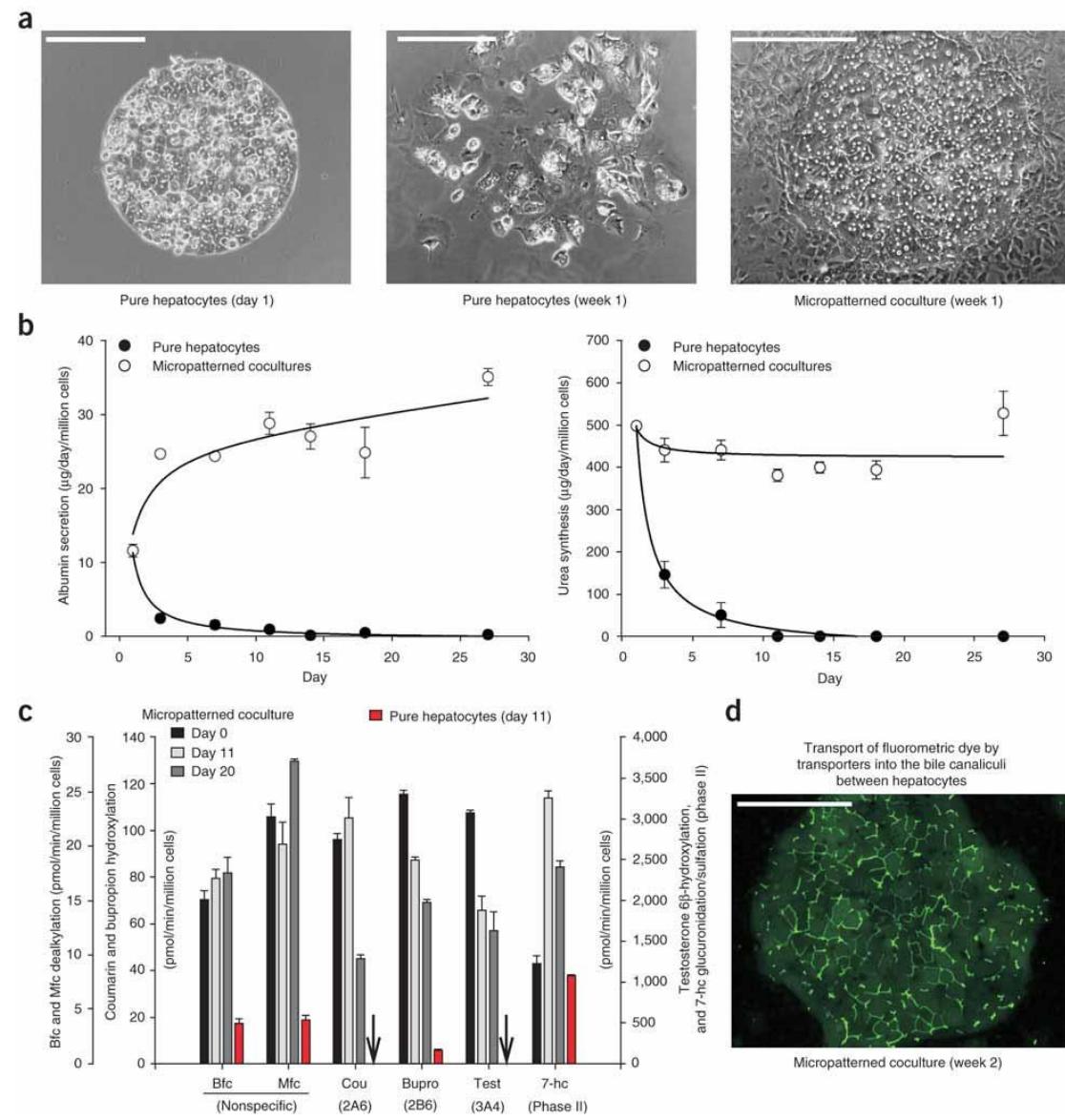
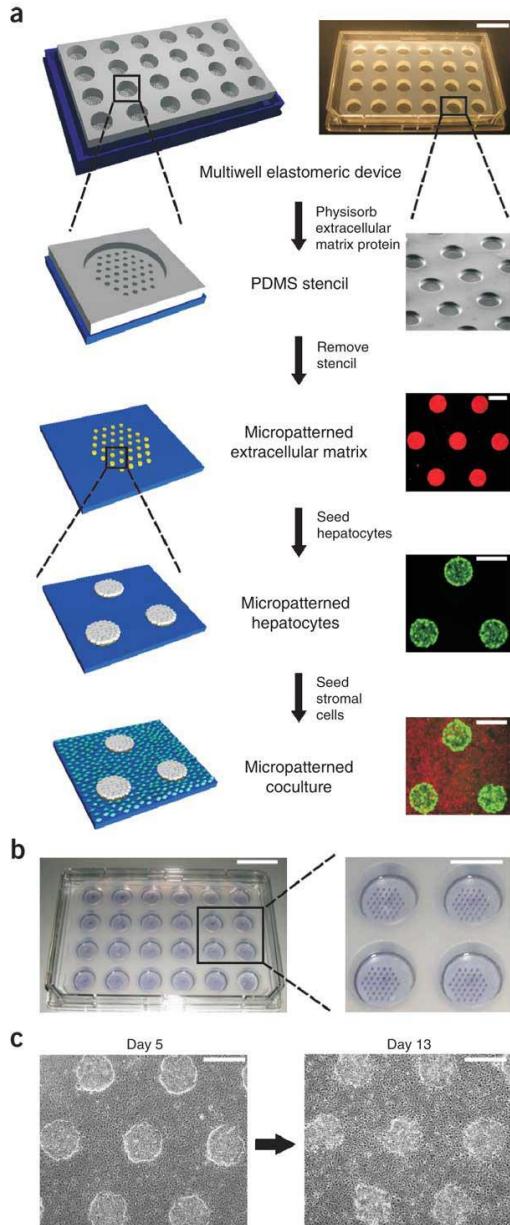


<http://cytoo.com/CYTOO-applications-neuron-networks.php>

# Facilitated cell:cell communication



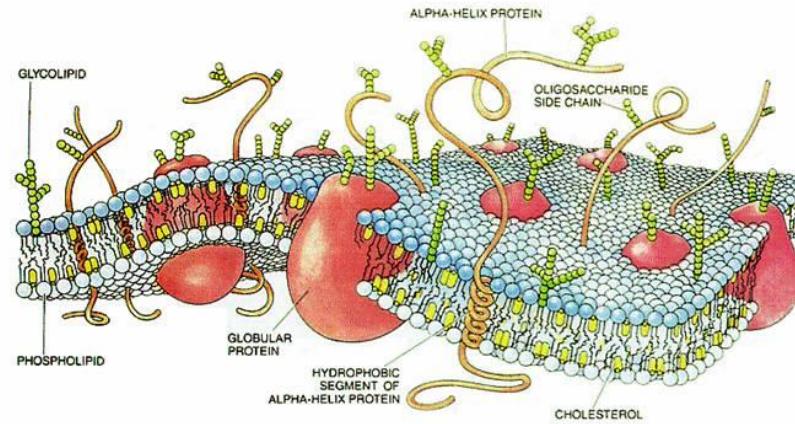
# Micropatterned –co-cultures for HCV virus



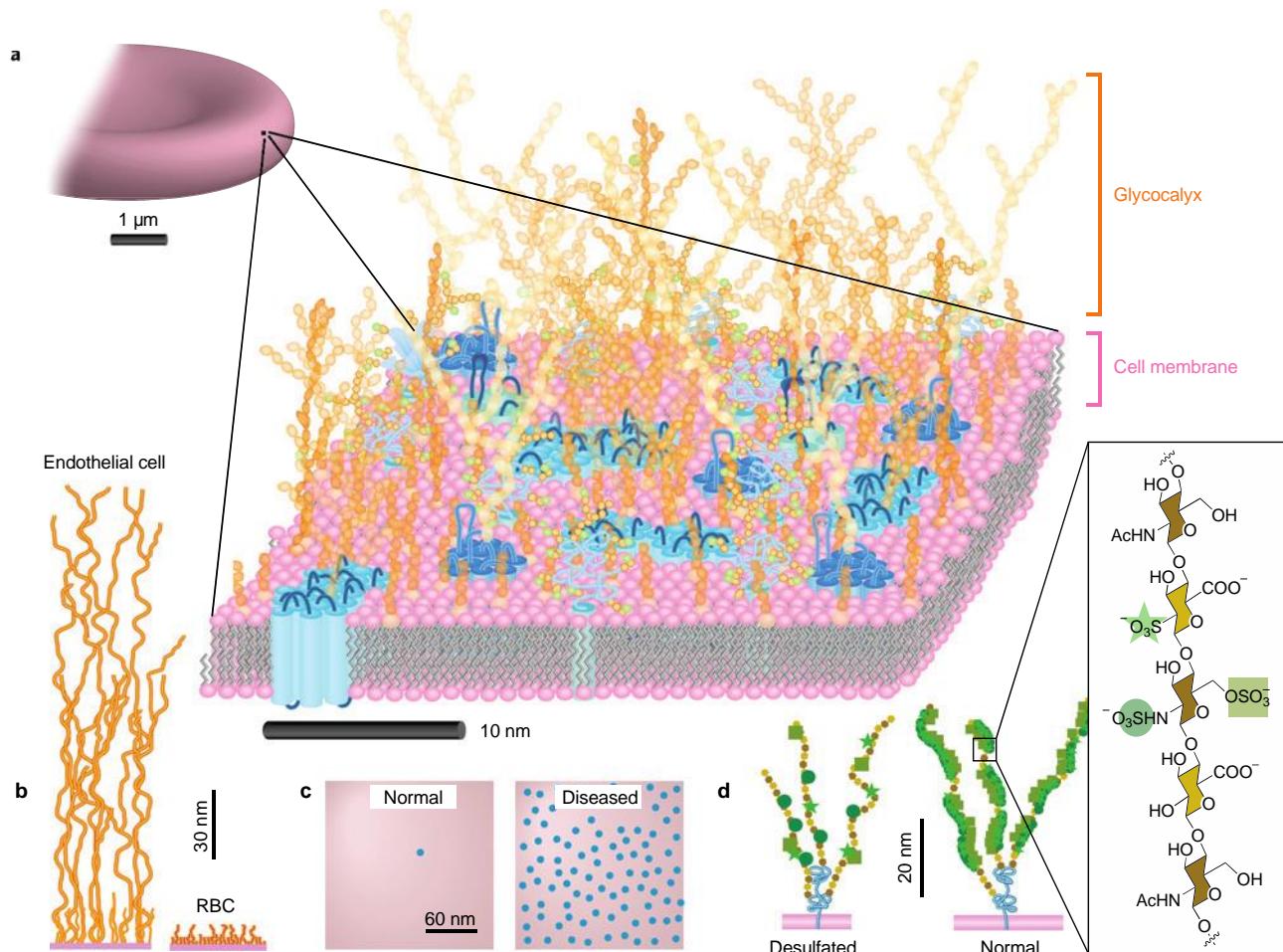
First, the membrane and cell-cell interaction  
The membrane contains x000 different molecules ranging from millions to thousands in number

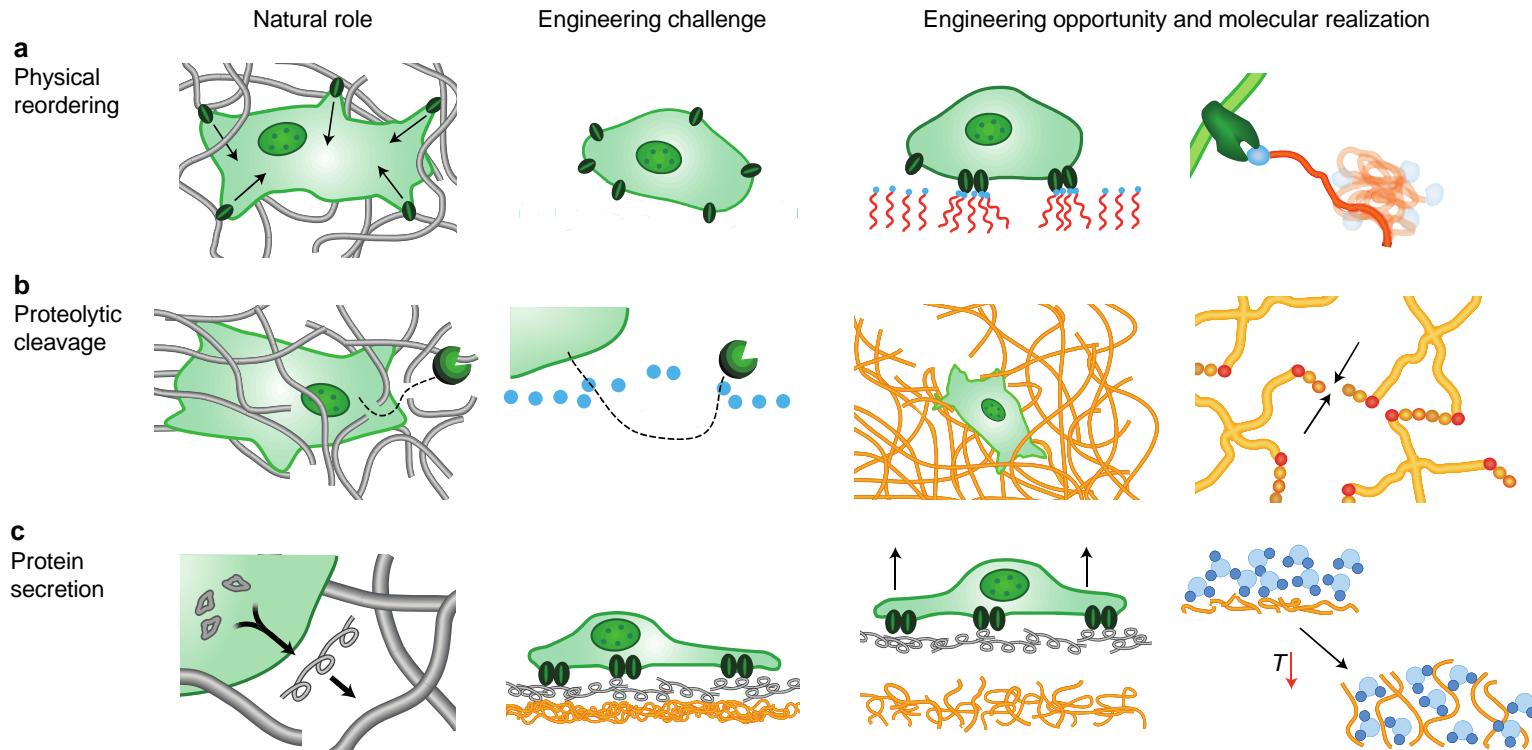
It is on or through the membrane where cell action is initiated

- Activation
- Multiplication
- Differentiation
- Migration
- Organization



# What does a cell surface look like?

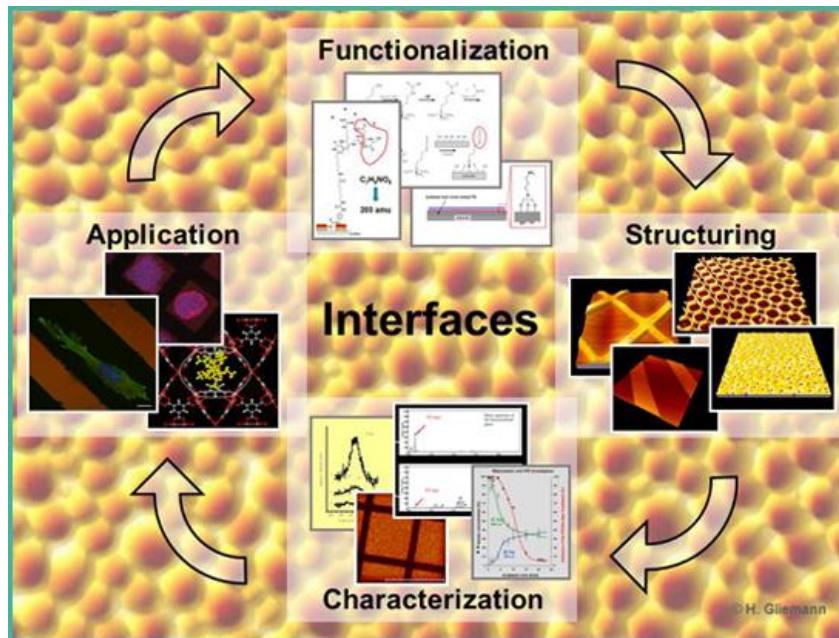




Exploring and exploiting chemistry at the cell surface  
**Morgan D. Mager, Vanessa LaPointe & Molly M. Stevens**  
*Nature Chemistry* 3, 582–589 (2011) doi:10.1038/nchem.1090

# The general idea

- 1) coat/pattern surface/tip/bead with functional organic groups  
(NH<sub>2</sub>, COOH, SH, CHO)
- 2) Conjugate bioactive molecules to pattern  
(proteins, peptides, nucleotides, sugars, fats, drugs)
- 3) Backfill with bioinert material  
(PEG, Pluronic, PVA, BSA)



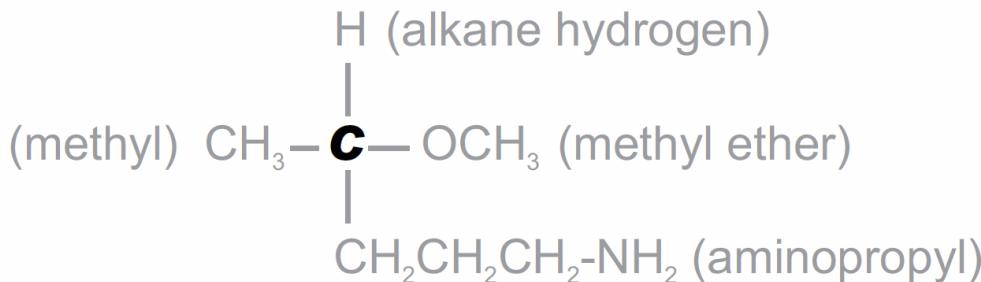
# The substrate

- Optics used for detection and monitoring
- Preferred substrate is glass
- Other options such as Silicon (silicium), PMMA (plexi-glass, transparent), PDMS (Elastomeric metallo-organic-polymer, transparent), COC (transparent, massproducible)

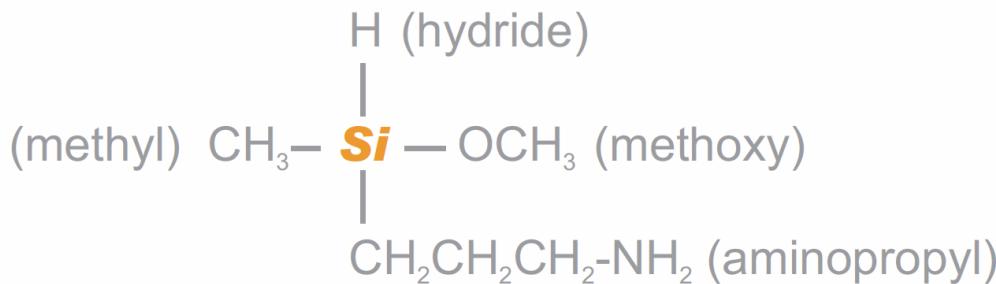
# Surfaces can be functionalized with similar chemistry as life chemistry : Organic (carbon) vs. Silanes (metal)

Figure 1. Carbon vs. silicon chemistry.

## Organic (Carbon-Based) Chemical



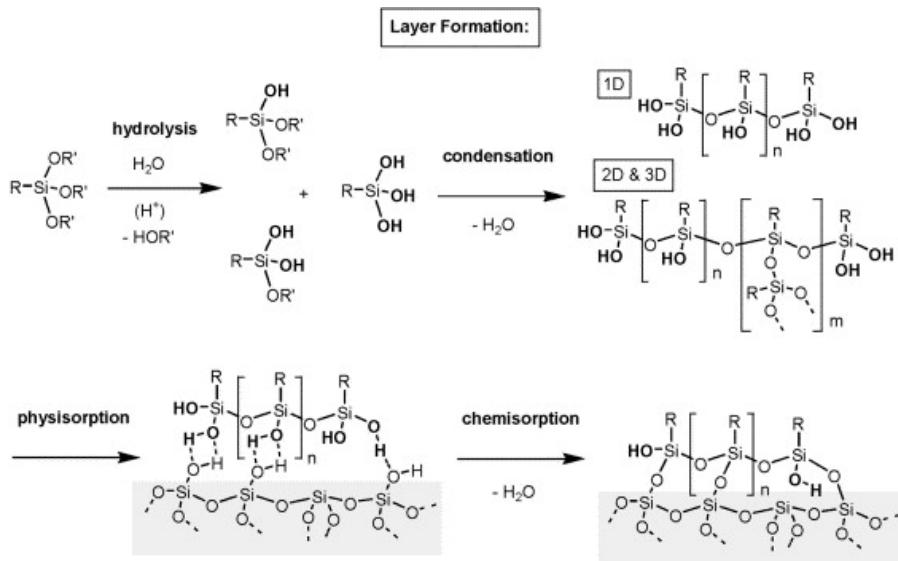
## Silane (Silicon-Based) Chemical



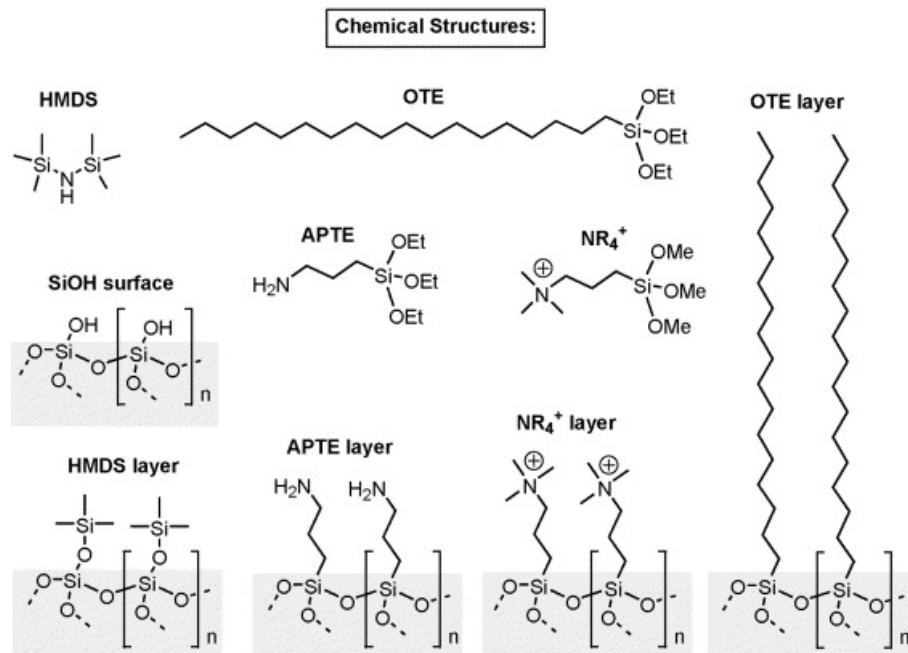
# Silanization

## (in EtOH solution or as chemical vapor deposition)

Silanization reaction



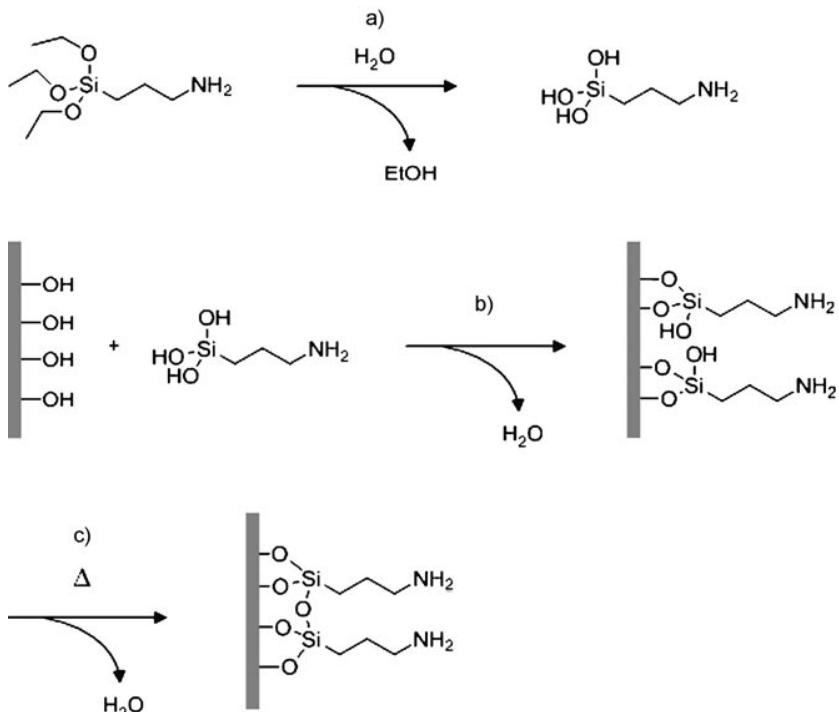
Novel surface (examples)



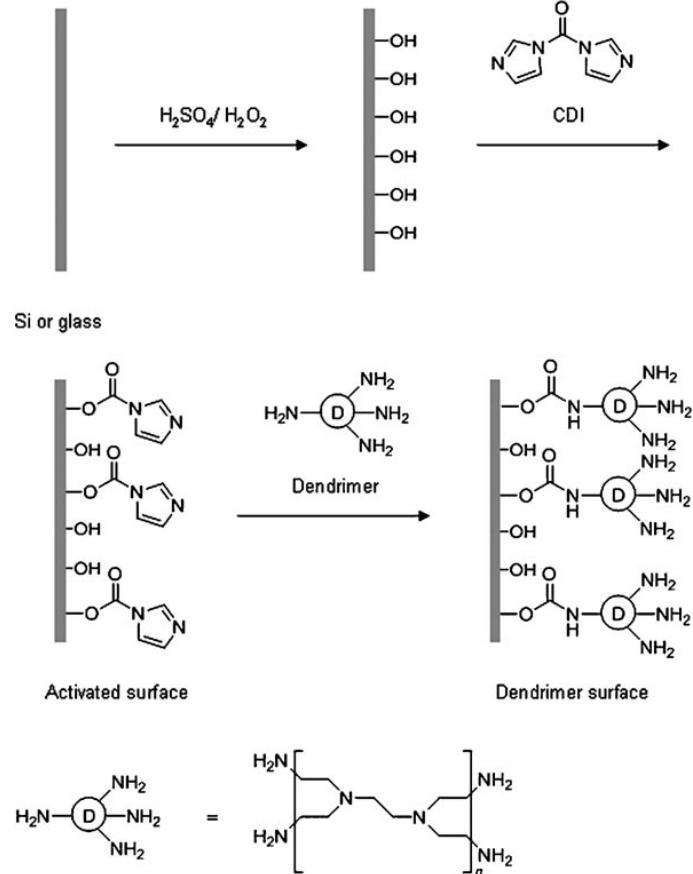
For a list see

<http://www.sigmaaldrich.com/chemistry/chemistry-products.html?TablePage=16246303>

# Compare silanization with other surface activation

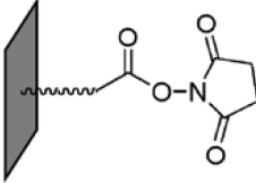
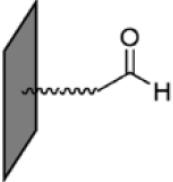
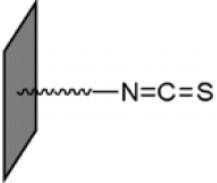
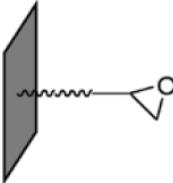
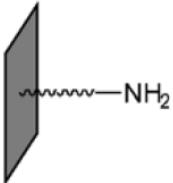


**Scheme 1.** Proposed mechanism for the silanization with aminopropyltriethoxysilane (APTES): Hydrolysis of the reactive siloxanes (a), which can take place in solution or on the substrate surface, allows condensation with surface silanol groups (b). Thermal curing of the resulting film causes further cross-linking (c).<sup>[41–45]</sup>



**Scheme 2.** Production of dendrimer-functionalized chips using poly(propylene imine) dendrimers: After cleaning with piranha solution, the glass or silicon surface can be activated with carbonyldiimidazole (CDI), for example. Dendrimers can then be immobilized through their peripheral amine groups.<sup>[51]</sup>

**Table 2:** Methods used for nonspecific covalent protein immobilization.

Surface functional groups	Protein functional groups	Product
NHS ester <sup>[126–130]</sup>	 <chem>H2NR-C(=O)OCC1=CC=C1</chem>	<chem>H2NR-C(=O)NH-R</chem> amide
aldehyde <sup>[7, 9, 131–138]</sup>	 <chem>H2NR-C(=O)H</chem>	<chem>H2NR-C(=N)H-R</chem> imine
isothiocyanate <sup>[99]</sup>	 <chem>H2NR-C(=S)N</chem>	<chem>H2NR-C(=S)NH-R</chem> thiourea
epoxide <sup>[133, 139, 140]</sup>	 <chem>H2NR-C1=CC=O1</chem>	<chem>H2NR-CH(OH)CH2N-R</chem> aminoalcohol
amine <sup>[121, 157] [a]</sup>	 <chem>H2NR-NH2</chem>	<chem>H2NR-C(=O)NHR</chem> amide

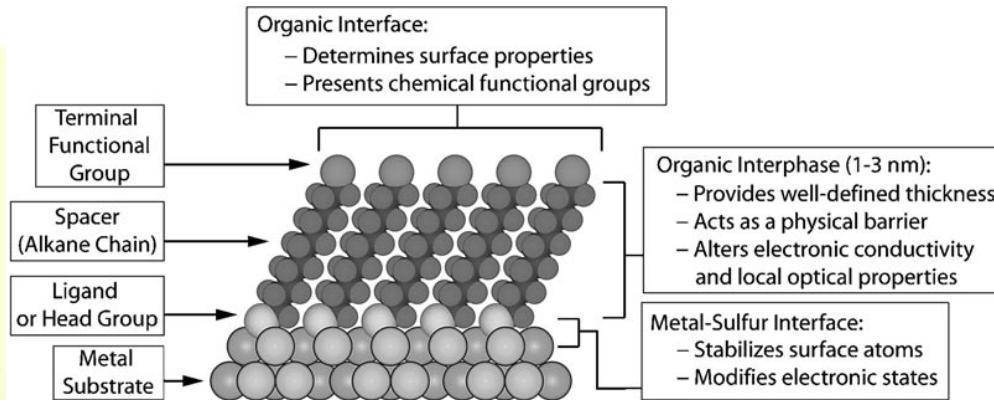
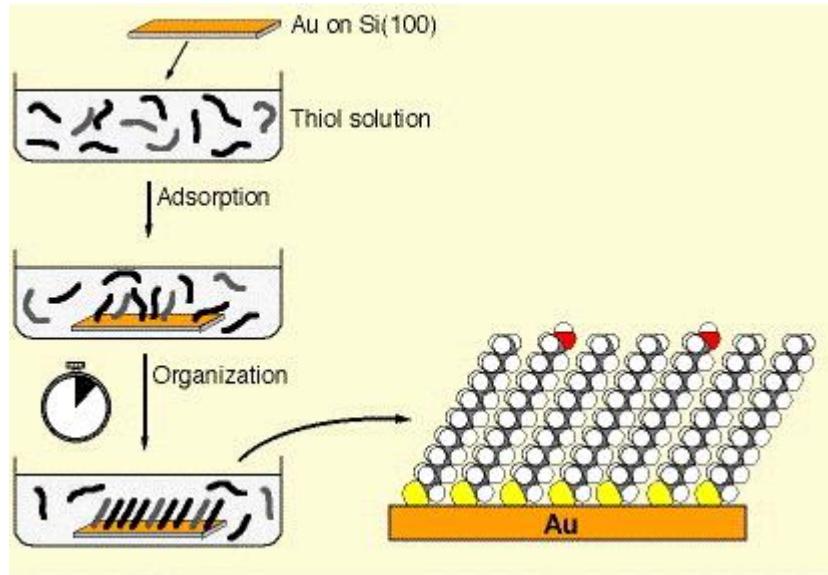
[a] With coupling reagent (e.g. CDI).

**Table 3:** Overview of photoreactive groups and heterobifunctional linkers.<sup>[161–171]</sup>

	Photoreactive groups	Heterobifunctional linkers
arylazide		
diazirine		
benzophenone		
azidophenylalanine		
disulfide		
nitrobenzyl <sup>[a]</sup>		

[a] Photocleavable protecting group.

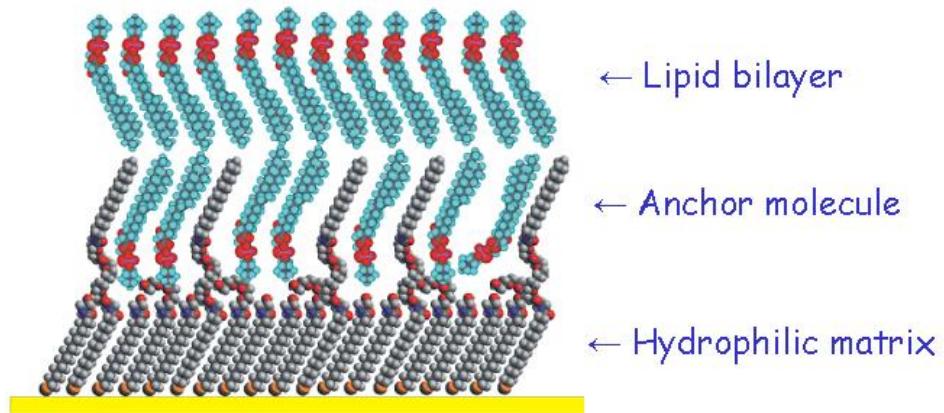
# Self assembled lipid bilayers on gold surface



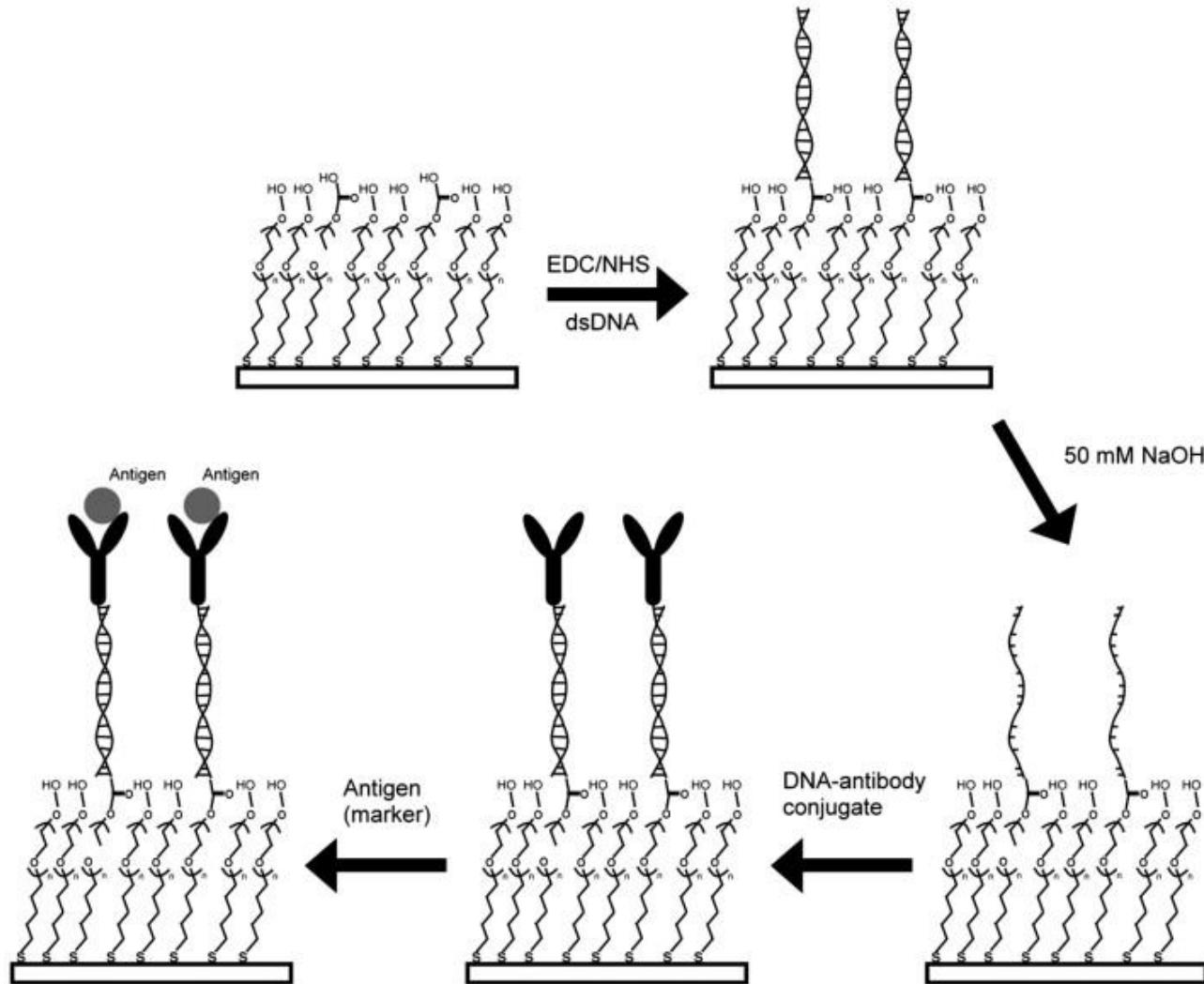
**Figure 1.** Ideal self-assembled monolayer (SAM) of terminally functionalized alkylthiolates bound to a Au(111) surface, showing the alkyl chains in the characteristically tilted orientation.<sup>[66]</sup> Reproduced with permission from ACS.

Gold at <100nm is transparent(ish), at least for larger structures such as cells

Lipidated surface

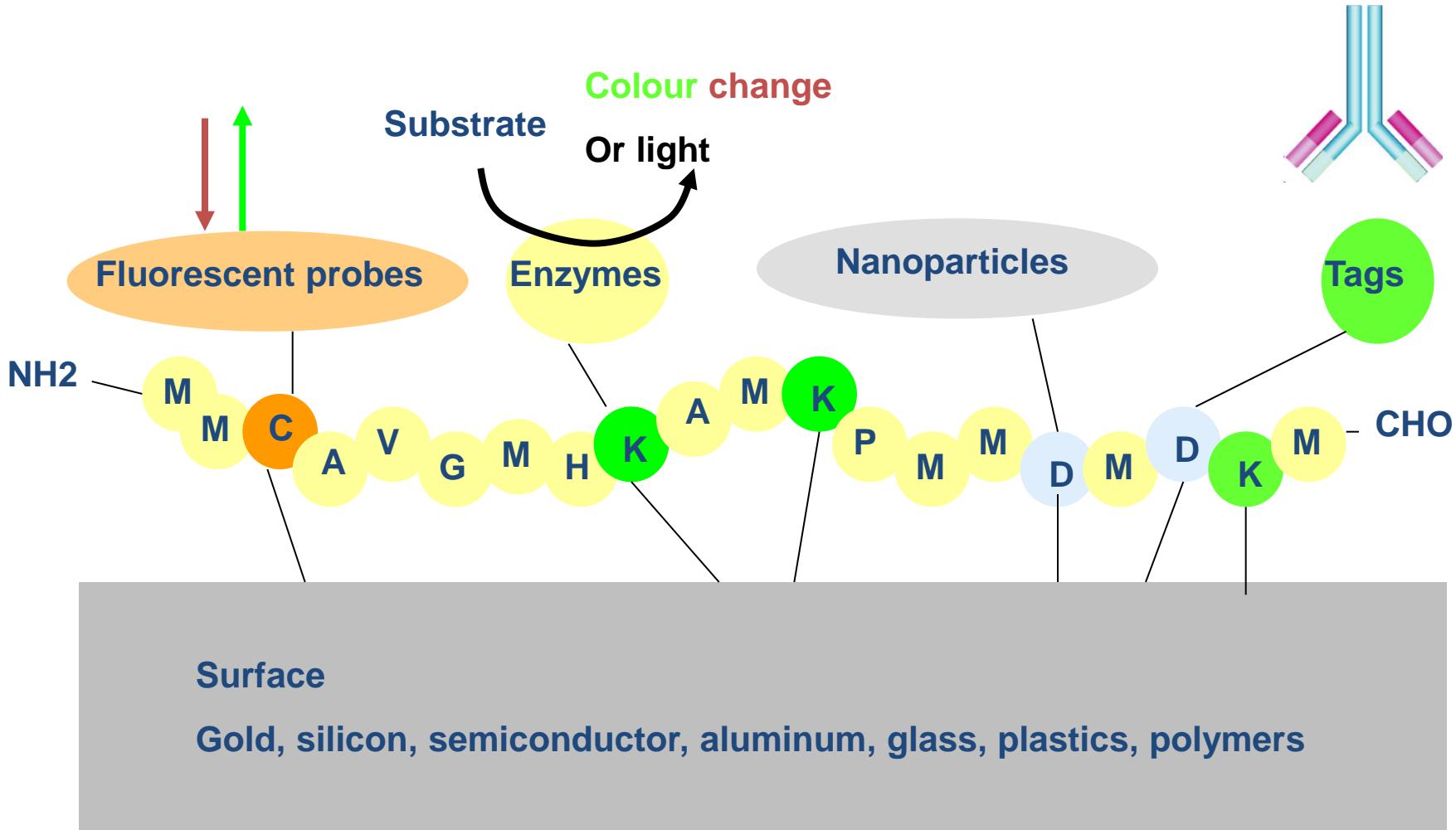


# Using immobilized oligo-DNA hybridisation to site specifically immobilize proteins



# **Protein conjugation and immobilization**

# Protein conjugation



# Crosslinker options

**Homobifunctional**

**Heterobifunctional**

**Functional group interchange**

**Spacer arms (Polyethylenglycol, PEG)**

**Photoactivable (UV)**

**Conjugation to other proteins**

**Conjugation to activated surfaces and solid support (e.g QD)**

**Conjugation to small molecule derivatives (fluorescence, biotin etc)**

## **Chemical groups in proteins available for labeling and modification**

**Primary amines ( $-NH_2$ ):** In the N-terminus of each polypeptide chain and in the side chain of lysine (Lys, K) residues.

**Carboxyls ( $-COOH$ ):** In the C-terminus of each polypeptide chain and in the side chains of aspartic acid (Asp, D) and glutamic acid (Glu, E).

**Sulfhydryls ( $-SH$ ):** This group exists in the side chain of cysteine (Cys, C).

**Carbonyls ( $-CHO$ ):** These aldehyde groups can be created by oxidizing carbohydrate groups in glycoproteins.

**Protein crosslinker reactive groups.** Functional groups in proteins and the reactive groups that target them, listed from most popular (top) to less common (bottom). Reactive group names link to specific sections of this article.

Functional Group Target	Reactive Group
Carboxyl (directly to amine)	<a href="#">Carbodiimide (e.g., EDC)</a>
Amine	<a href="#">NHS ester</a> <a href="#">Imidoester</a> PFP ester Hydroxymethyl phosphine
Sulfhydryl	<a href="#">Maleimide</a> <a href="#">Haloacetyl (Bromo- or Iodo-)</a> <a href="#">Pyridyldisulfide</a> Vinyl sulfone
Aldehyde (Carbonyls) i.e., oxidized carbohydrates	<a href="#">Hydrazide</a>
Any Group (Nonselective)	<a href="#">Diazirine (Photo-reactive)</a> <a href="#">Aryl Azide (Photo-reactive)</a>
Hydroxyl (non-aqueous)	Isocyanate

**Table 1:** Structures of commonly used spacer/linker molecules (SATA, MSA, SADP, PMPI, SMCC, SPDP, SIAB from Pierce).

	Spacers	
Homobifunctional		Heterobifunctional
<b>Amine-reactive</b>		
glutaraldehyde		glutaric anhydride
1,4-butanediol diglycidyl ether		SATA (protected thiol)
1,4-phenylene diisothiocyanate		MSA (protected acid)
dimethylsuberimidate		SADP (photoreactive)
divinylsulfone		
disuccinimidyl carbonate		PMPI
terephthalaldialdehyde		
bis(sulfosuccinimidyl)suberate		SMCC
<b>Thiol-reactive</b>		SDPD
2,2'-dipyridyl disulfide		SIAB
<i>N,N'</i> -carbonyldiimidazole		
<b>Amine-reactive</b>		
<b>Amine- and hydroxy-reactive</b>		
<b>Amine- and thiol-reactive</b>		

# Visualization of conjugation sites on IgA

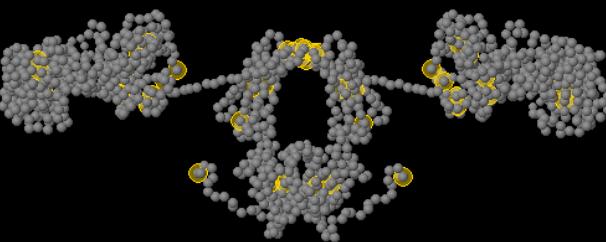
All proteins have multiple conjugation sites

Therefore one chooses chemistry/concentration/time that produces 1-5 conjugates per protein STATISTICALLY

Immunoglobulin A

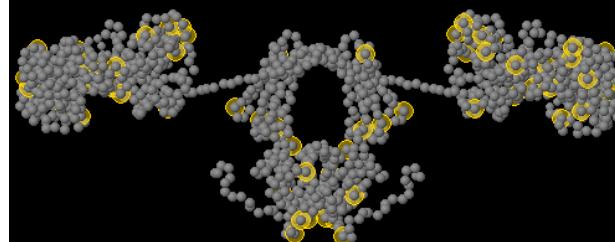
1378 aa

Cystein -SH (44aa)



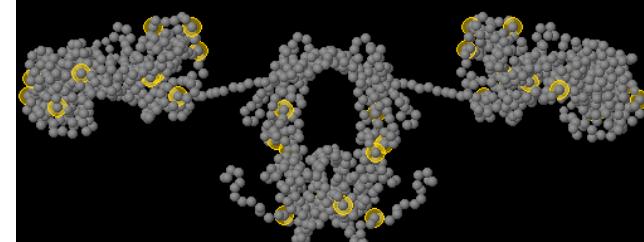
Jmol

Lysine -eNH<sub>2</sub> (66aa)



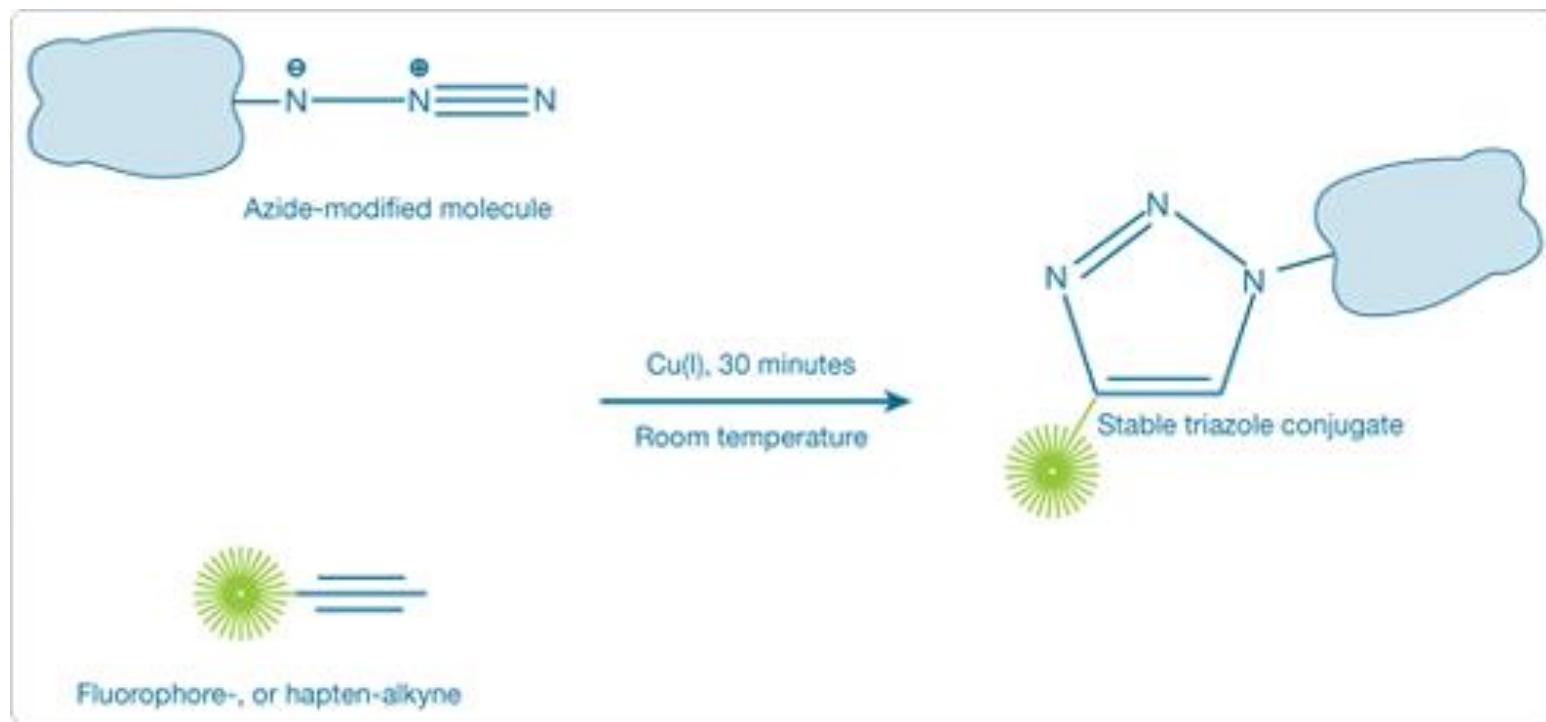
Jmol

Glutamate -COOH (66aa)



Jmol

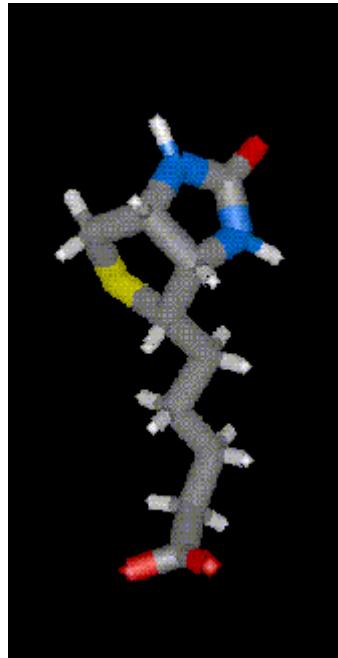
# Click-chemistry azide-alkyne has many potential applications



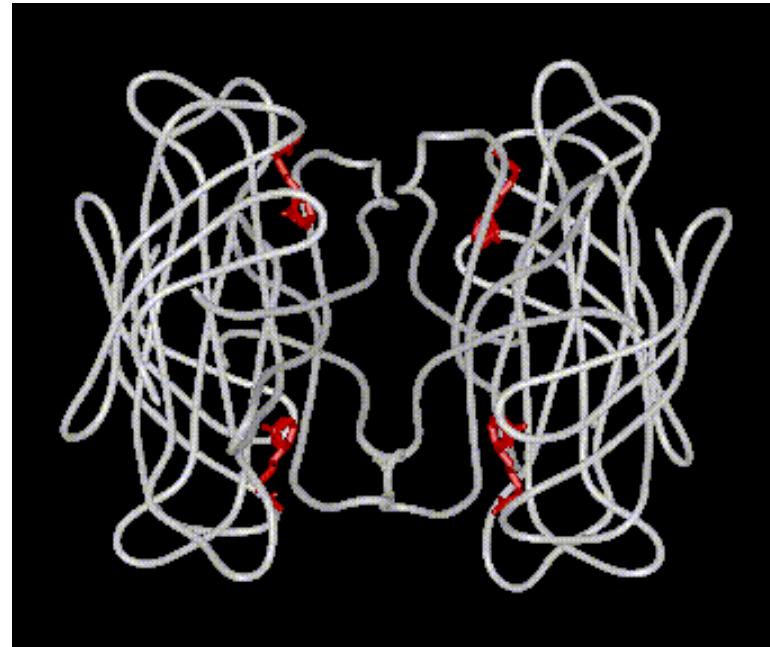
Isotope(s)	Click-iT™ alkyne	Click-iT™ azide	Biotin	Alexa Fluor® 488	Streptavidin	IgG antibody	
MW	3	25	42	~300	500	~68,000	~150,000
Both required for detection						Both biotin and streptavidin required for detection	

# Biomolecules can be conjugated to biotin

Biotin bind streptavidin with the highest known non-covalent affinity ( $K_{assoc} = 10e14$ ) and is extremely stable

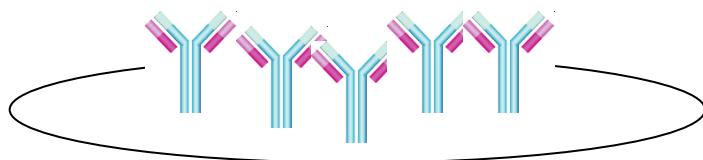


biotin

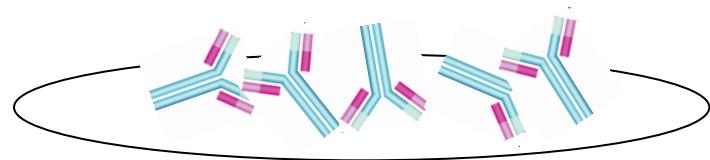


Straptavidin + 4 biotin

**What you want**



**What you get**



**Current protocols: ng added = 1000000000 molecules which yields good enough orientation using current methods. Including a standard with known concentration essential**

**Novel nanotech devices need higher degree of orientation, but statistically immobilized surfaces should be >250nm**

**Several layers of linkers are necessary**

# **Oriented immobilization**

# Orientation through secondary antibodies with affinity for Fc portion of species specific antibody subclass

Showing Secondary Antibodies  Search within these results

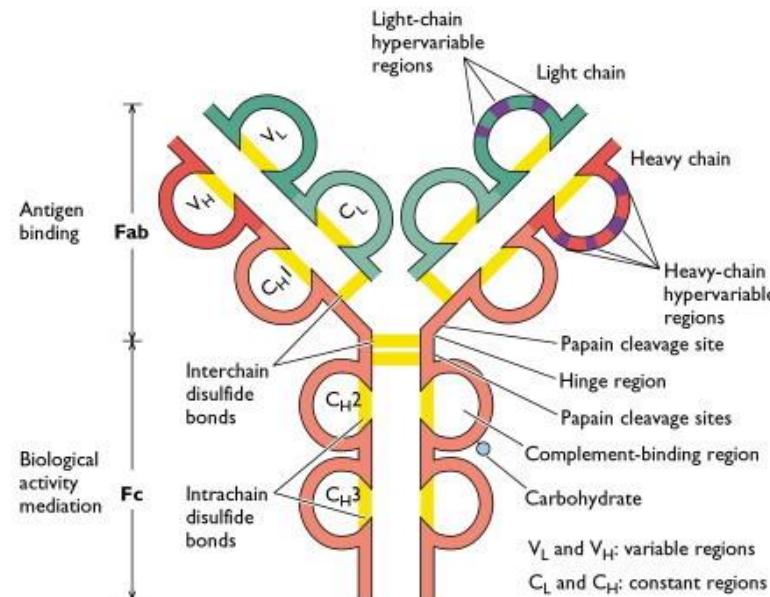
**Secondary Antibodies**

Target Ig Class	Host	Reactivity	Conjugate Type	Regulatory Status	Antibody Form
Ig (all classes) (9)	Chicken (12)	Ch (9)	Alexa Fluor dyes (244)	ASR (94)	F(ab')2 (139)
IgA (33)	Donkey (38)	Ch, Turkey (5)	Biotin (66)	IVD (4)	Fab' (6)
IgD (6)	Goat (578)	Gp (10)	Classic Dyes (107)	RUO (706)	Whole Ab (659)
IgE (12)	Mouse (65)	Gt (43)	Dual/Mixture (9)		
IgE (Fc region) (3)	Rabbit (82)	Ha (11)	Enzyme Labeled (162)		
IgG (465)	Rat (24)	Hu (227)	Other (22)		
<a href="#">+ All Target Ig Class</a>	<a href="#">+ All Host</a>	<a href="#">+ All Reactivity</a>	<a href="#">+ All Conjugate Type</a>		

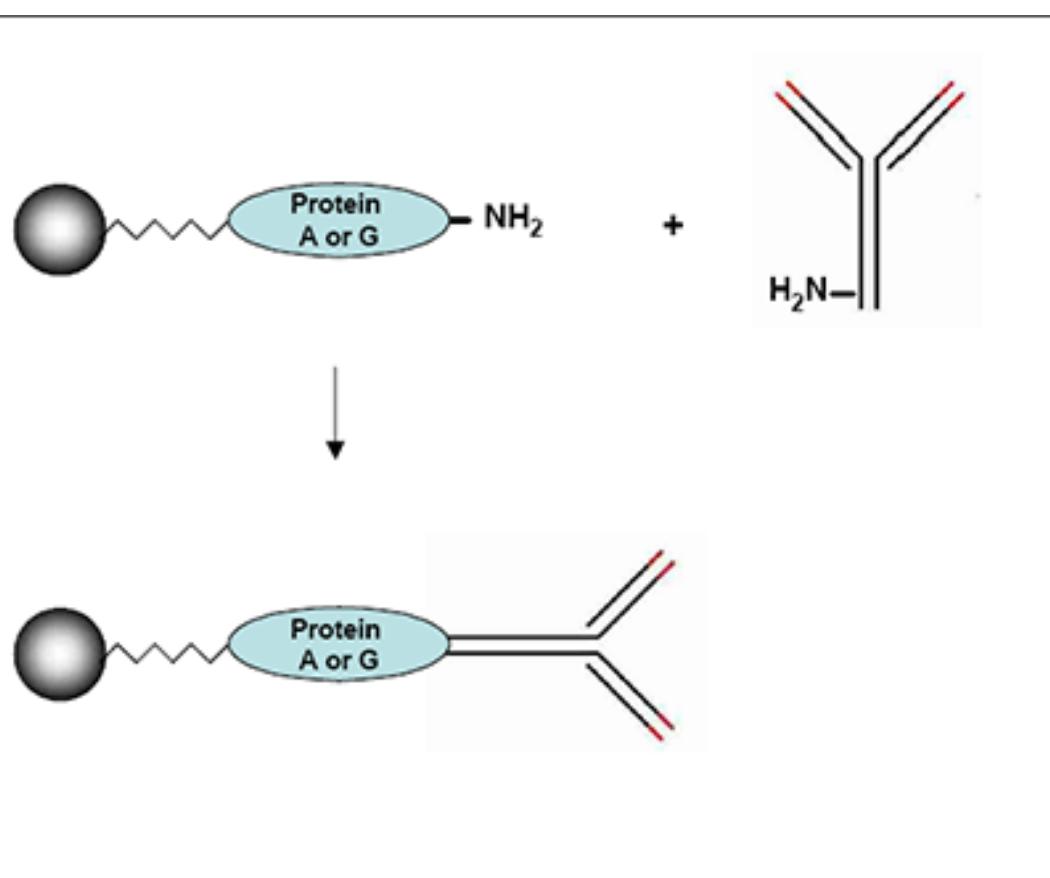
804 Results Returned

6 7 8 9

Invitrogen/zymed



Surface proteins on bacteria bind immunoglobulins –Fc-part in self defence, in molecular biology we exploit this



Protein A  
*Staphylococcus aureus*

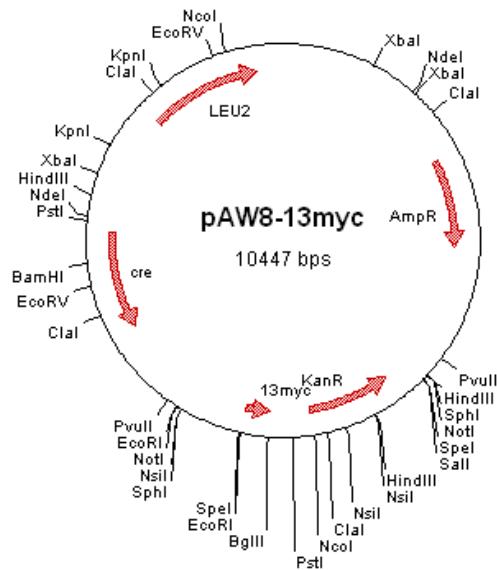
Protein G  
*Streptococcus*

Ig Origin	Protein A	Protein G
Human IgG1,2,4	Strong	Strong
Human IgG3	No binding	Strong
Human IgA,D,E,M	Weak	No binding
Mouse IgG1	Weak	Strong
Mouse IgG2a,2b,3	Strong	Strong
Mouse IgM	Weak	No binding
Rat IgG1	Weak	Weak
Rat IgG2a	No binding	Strong
Rat IgG2b	No binding	Weak
Rat IgG2c	Strong	Strong
Bovine IgG1	Weak	Strong
Bovine IgG2	Strong	Strong
Chicken IgY	No binding	No binding
Dog IgG	Strong	Weak
Goat IgG1	Weak	Strong
Goat IgG2	Strong	Strong
Guinea pig IgG	Strong	Weak
Hamster	Weak	-
Horse IgG	Weak	Strong
Monkey IgG	Strong	Strong
Porcine IgG	Strong	Strong
Rabbit IgG	Strong	Strong
Sheep IgG1	Weak	Strong
Sheep IgG2	Strong	Strong

# Proteins can be genetically functionalized with tag using recombinant DNA technology

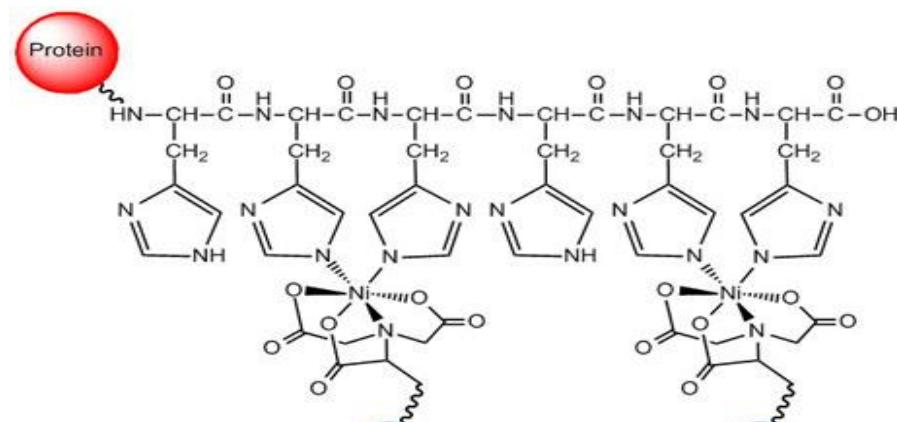
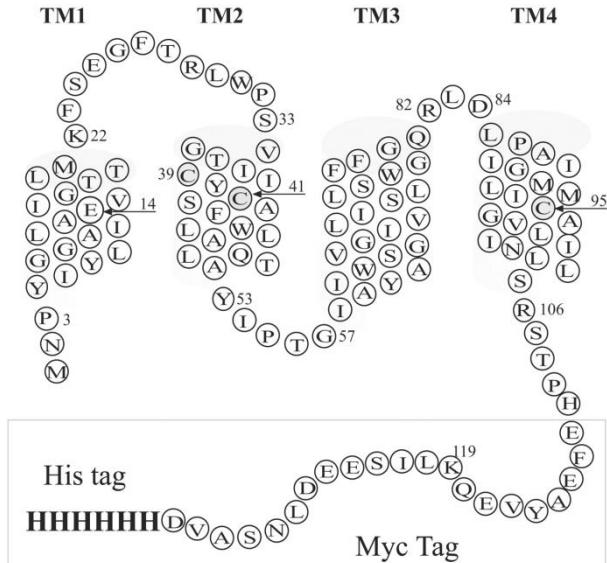
**Table 1** Matrices and elution conditions of affinity tags

Affinity tag	Matrix	Elution condition
Poly-Arg	Cation-exchange resin	NaCl linear gradient from 0 to 400 mM at alkaline pH>8.0
Poly-His	Ni <sup>2+</sup> -NTA, Co <sup>2+</sup> -CMA (Talon)	Imidazole 20–250 mM or low pH
FLAG	Anti-FLAG monoclonal antibody	pH 3.0 or 2–5 mM EDTA
Strep-tag II	Strep-Tactin (modified streptavidin)	2.5 mM desthiobiotin
c-myc	Monoclonal antibody	Low pH
S	S-fragment of RNaseA	3 M guanidine thiocyanate, 0.2 M citrate pH 2, 3 M magnesium chloride 150 mM imidazole or low pH
HAT (natural histidine affinity tag)	Co <sup>2+</sup> -CMA (Talon)	
Calmodulin-binding peptide	Calmodulin	EGTA or EGTA with 1 M NaCl
Cellulose-binding domain	Cellulose	Family I: guanidine HCl or urea>4 M Family II/III: ethylene glycol
SBP	Streptavidin	2 mM Biotin
Chitin-binding domain	Chitin	Fused with intein: 30–50 mM dithiothreitol, $\beta$ -mercaptoethanol or cysteine
Glutathione S-transferase	Glutathione	5–10 mM reduced glutathione
Maltose-binding protein	Cross-linked amylose	10 mM maltose



Terpe, K:  
Appl Microbiol Biotechnol. 2003 Jan;60(5):523-33.

# Orientation through genetically modified His tags on Ni



NTA-Ni surface

# Bio-Patterning

Placing molecules at will

# Resolution of different techniques for patterning

**TABLE I. Techniques for Patterning at the Nanoscale (Adopted With Permission From Ref. 25)**

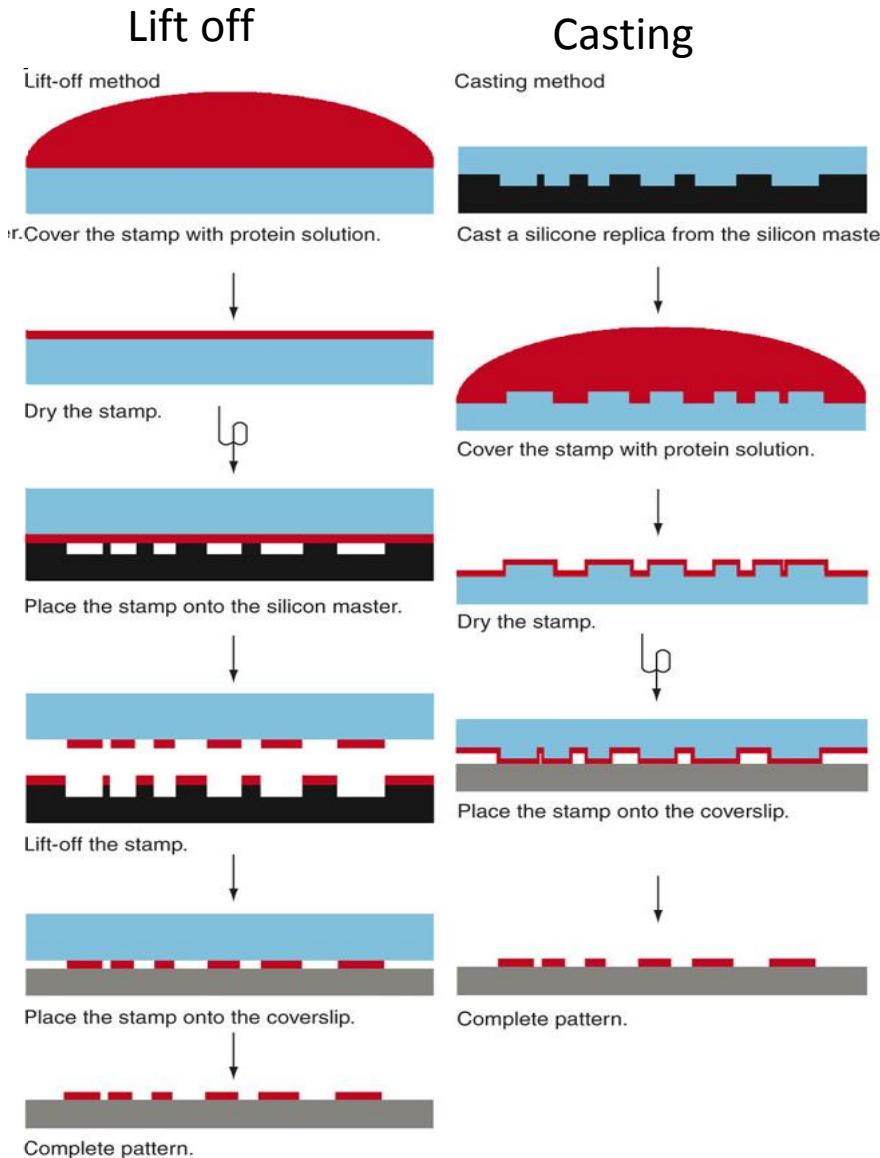
Technique	Modification of Topography	Modification of Chemistry	Lateral Resolution	Advantages	Disadvantages
<b>Topographical patterning</b>					
Photolithography	Yes	No	40 nm (EUV)	Widely used, any shape possible	Best resolutions require a synchrotron and are expensive
Transfer from self-assembled polymer film	Yes	Can be avoided	50 nm	Different substrates possible	Usually only one type of shape: hexagonally packed pegs
Polymer demixing	Yes	Yes, but there are ways this can be avoided	Sub-micron	Very easy to make, nanometric heights	Little shape control, only worm-like or island structures
Nanoimprint lithography	Yes	No	100 nm	Topography without chemistry	Low resolution
Colloidal lithography	Yes	No, but possible if desired	50 nm	Even spacing	Lack of shape flexibility, can only have hexagonally packed structures
Surface roughening	Yes	No	Not easily controlled, nanometric range	Uniform surface with controlled chemistry	The surface structure cannot be controlled
Anodic oxidation of metals	Yes	No	15 nm for nanotubes	Controlled chemistry, easily tunable sizes	Small range of structures that can be produced
Electrospinning	Yes	No	Dependent on fibre size	Can use a wide variety polymers, mimics ECM	Only one type of shape: bed of fibres
E-beam lithography	Yes	No	15 nm	Good resolution	Very slow because each feature has to be made separately; expensive
<b>Chemical patterning</b>					
Micro-contact printing	Can be avoided with back-filling	Yes	40 nm linewidth	Easy, variety of inks possible	Induces some topography
From nanoparticle arrays	Yes	Yes	Dots with 28 nm spacing	Small features, tunable sizes	Induces some topography
Molecular-assisted patterning by lift-off	Could be avoided	Yes	100 nm linewidth	Can obtain a variety of surface chemistries	Resolution
Supra-molecular nanostamping	Molecule height	Yes	14 nm dots spaced 77 nm apart	Tunable chemistry, aqueous conditions	
LB films/spin-coated block co-polymers	Yes	Yes	50 nm	Aqueous conditions, tuneable sizes	Limited chemistry, LB difficult, limited shapes
Dip-pen nano-lithography	Yes	Yes	Down to 15 nm	Great control over feature size and shape	Slow as each feature has to be made separately

# Microcontact printing (approx 1 $\mu$ m) to get substrates localized on a surface

Creating positive or negative patterns

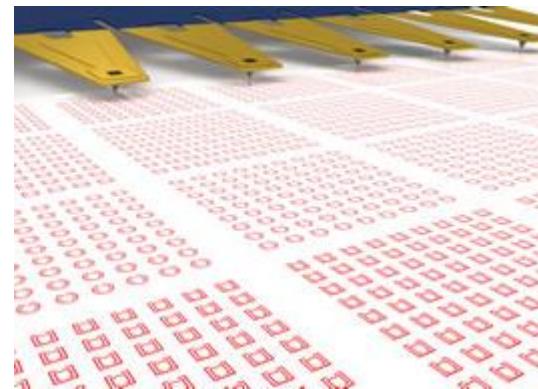
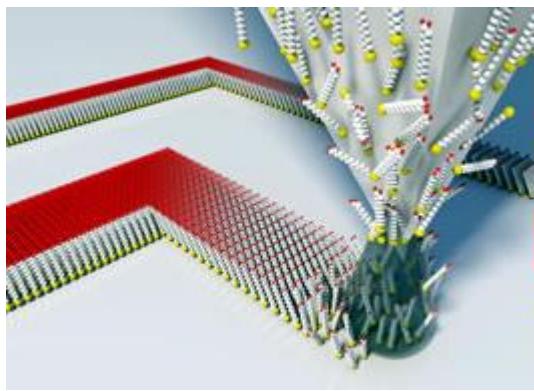
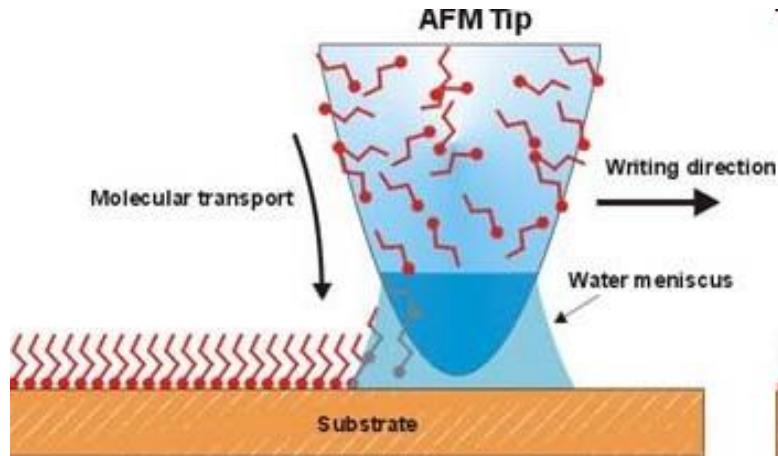
Backfilling is necessary  
(As in standard ELISA,  
PEG, BSA etc)

Nanoimprinting and  
fabrication startegies in  
coming lectures



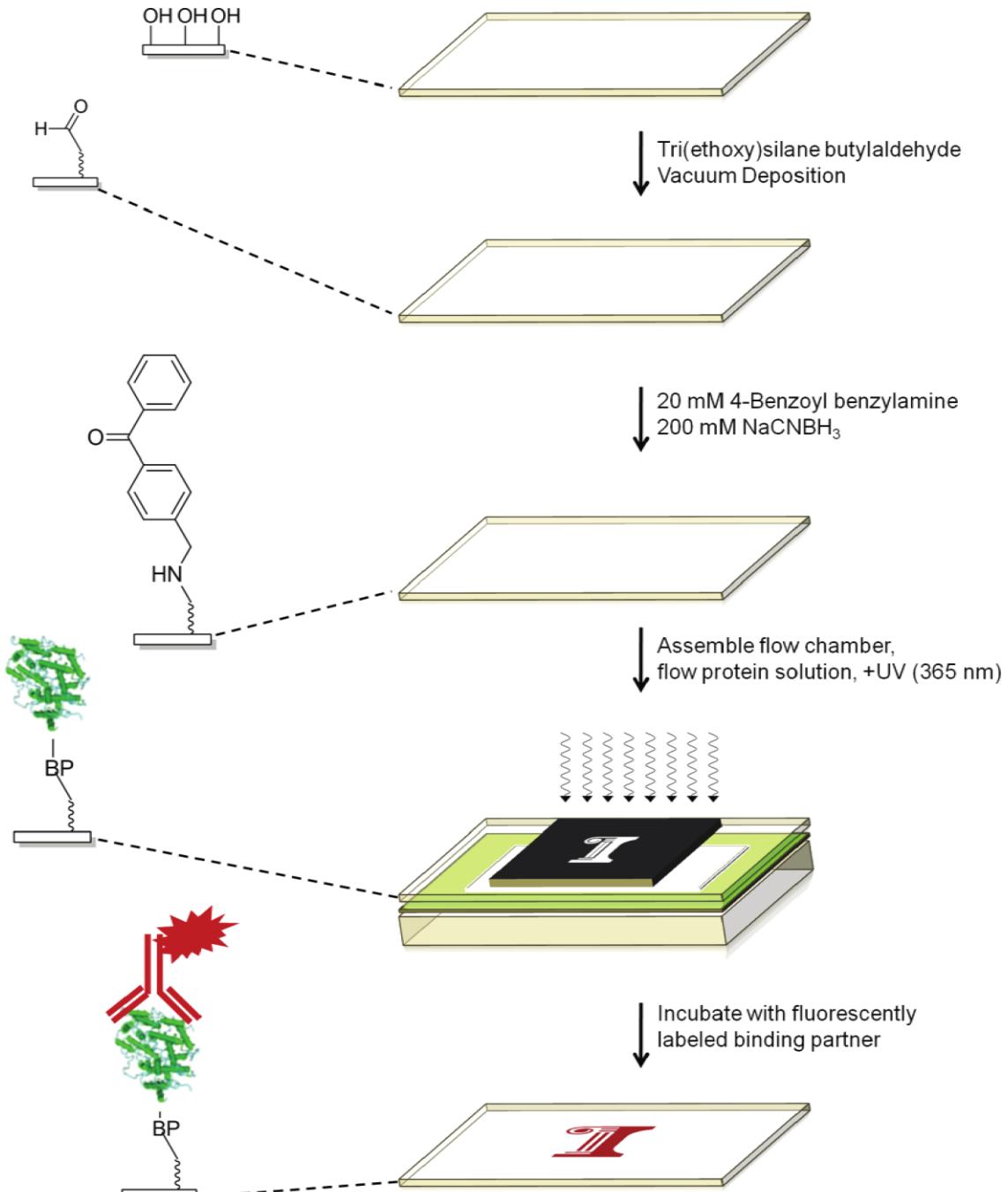
# Writing with biomolecules

Using scanning probes (AFM) for deposition of proteins with 100nm features : Dip-pen lithography



Scheme 1. Schematic Diagram Showing the Preparation of BP-Modified Substrates and Subsequent Biomolecule Photoimmobilization<sup>a</sup>

Patterning by  
immobilizing photo-labile  
linker

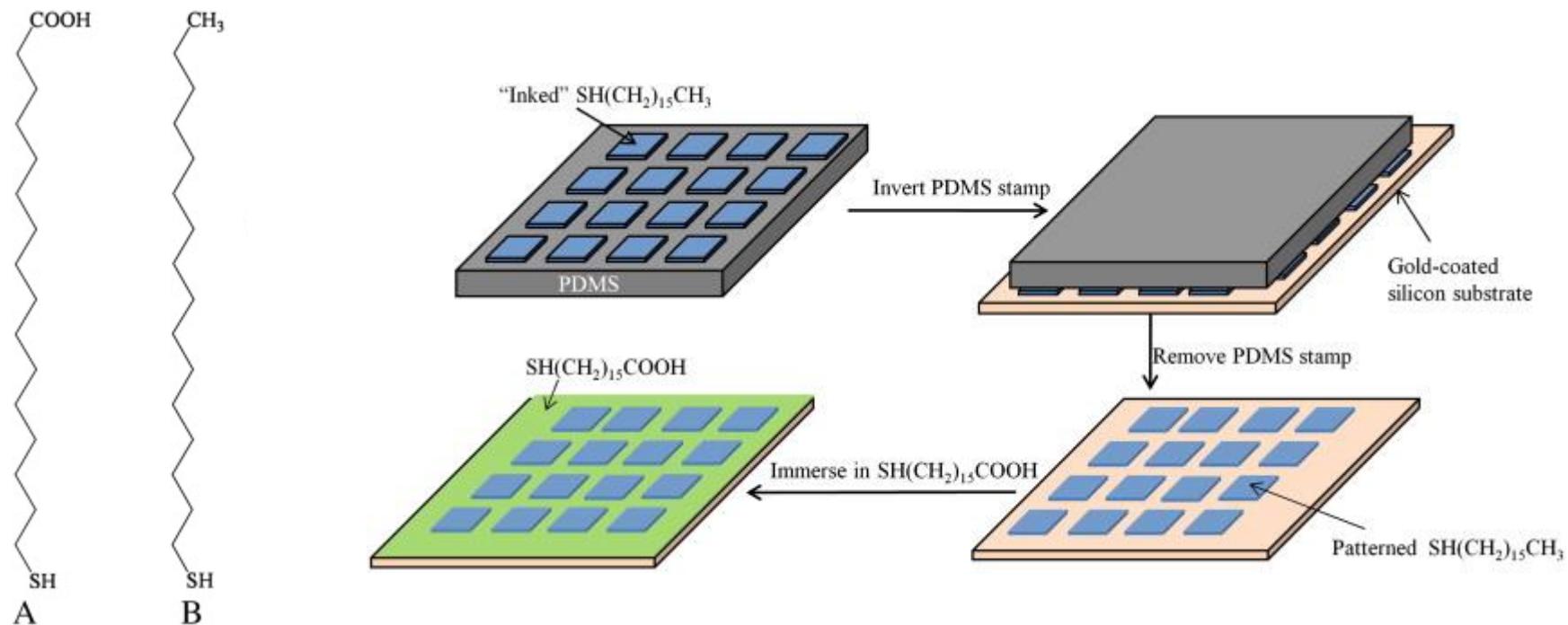


# Microcontact printing on gold surfaces

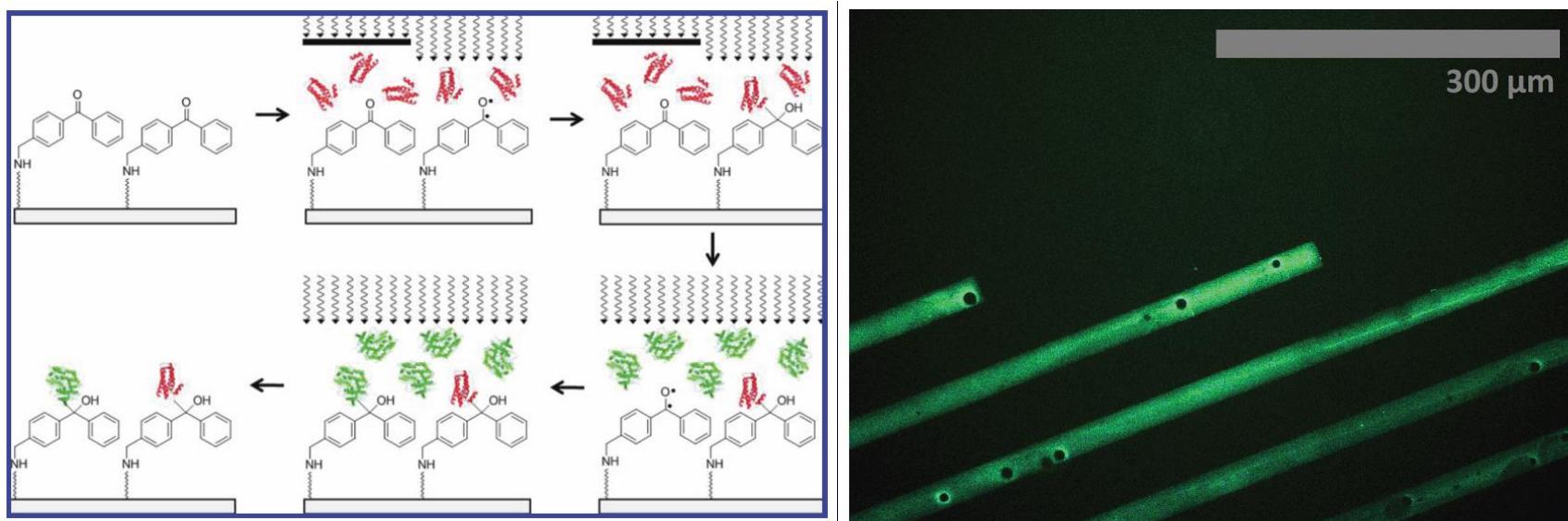
Coat surface with gold (vapor deposition)

Stamp functionalized alkane-thiol

Backfill with inert alkane-thiol



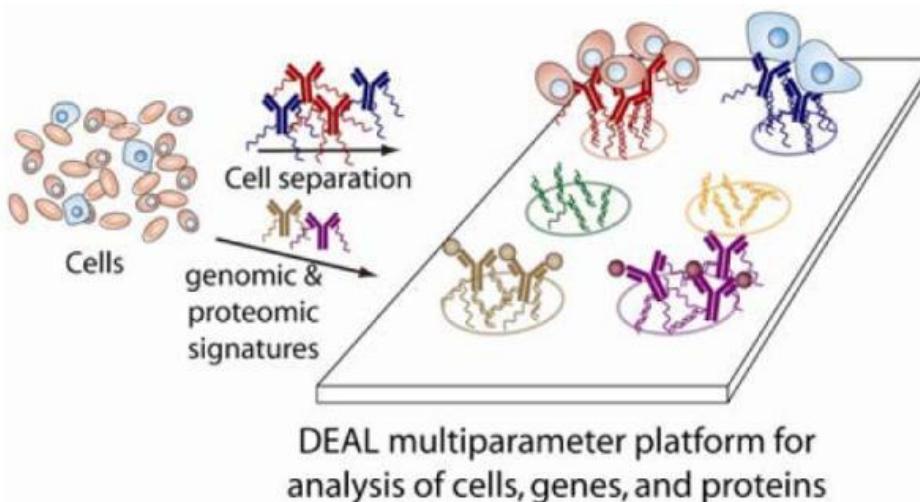
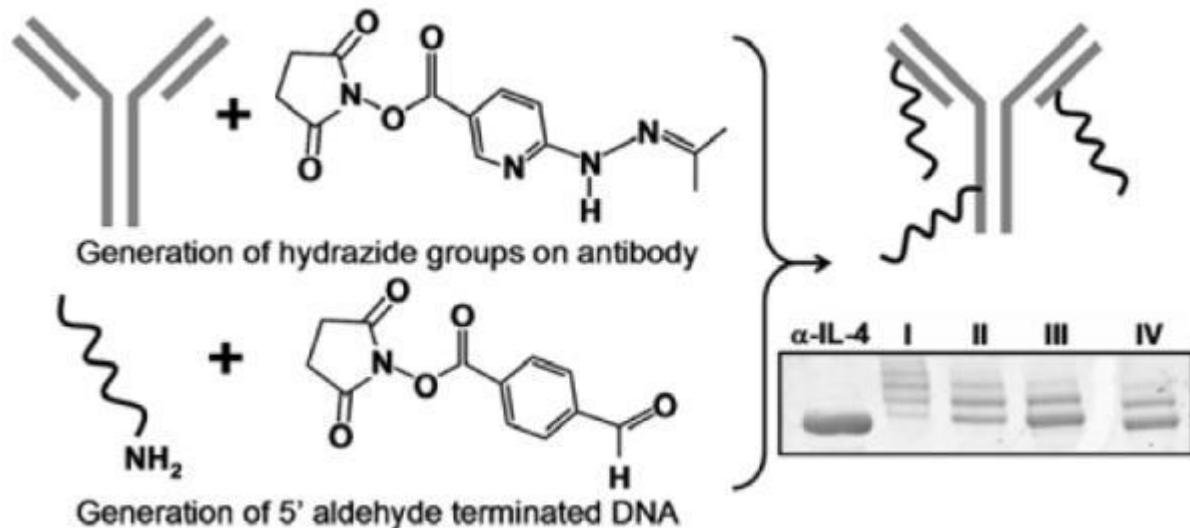
# Using photochemistry for site-specific immobilization of proteins



Direct biophotolithographic method for generating substrates with multiple overlapping biomolecular patterns and gradients. Toh CR, Fraterman TA, Walker DA, Bailey RC. Langmuir. 2009 Aug 18;25(16):8894-8.

# DNA-encoded antibody libraries (DEAL) for patterning

Requires spotting  
of ssDNA probes



# Characterization of molecular deposition

Contact angle

Crystal quartz microbalance

AFM

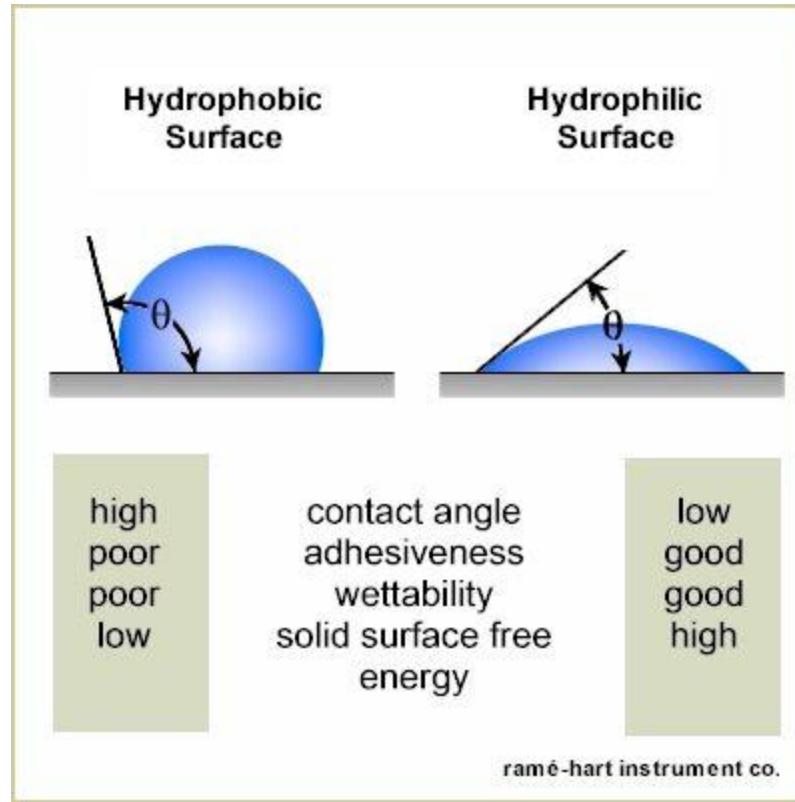
Fluorescence Microscopy

Radioactivity

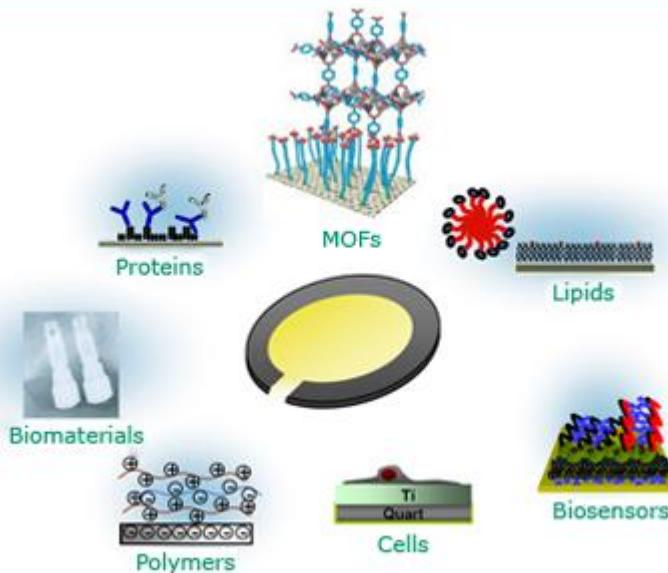
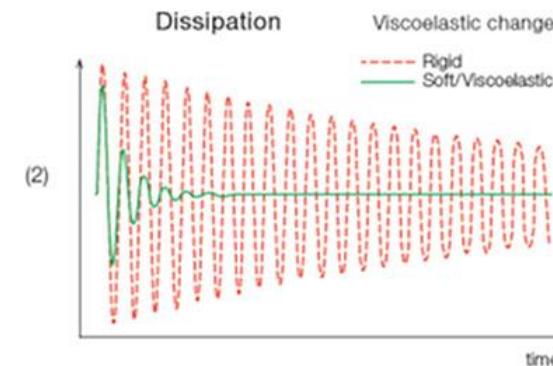
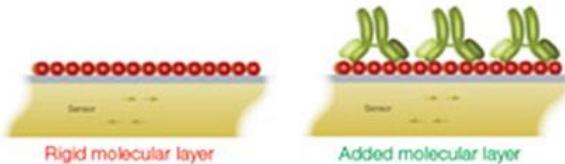
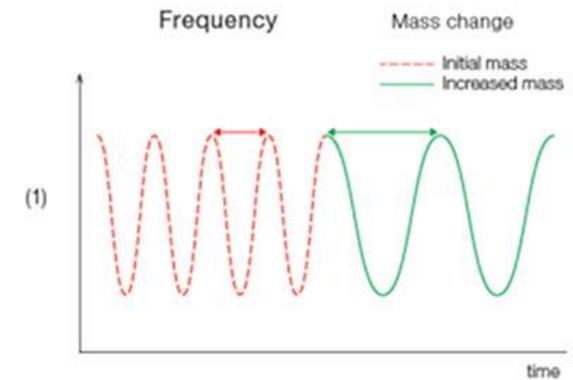
# Contact angle measurement

No spatial resolution, little chemical information

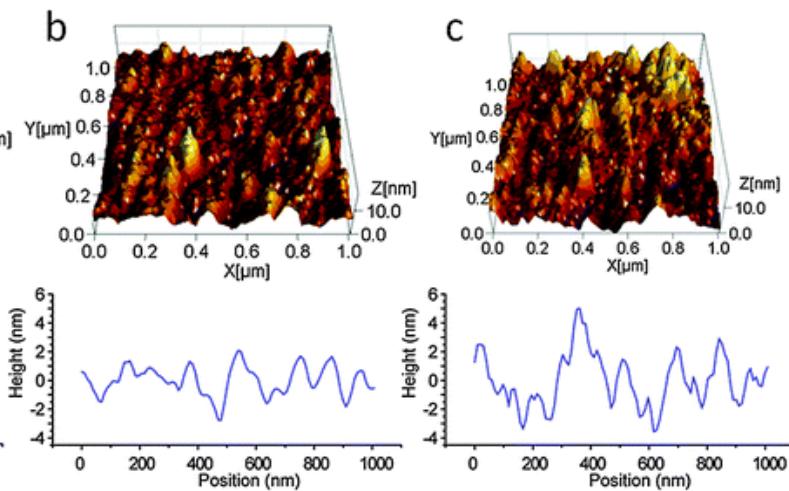
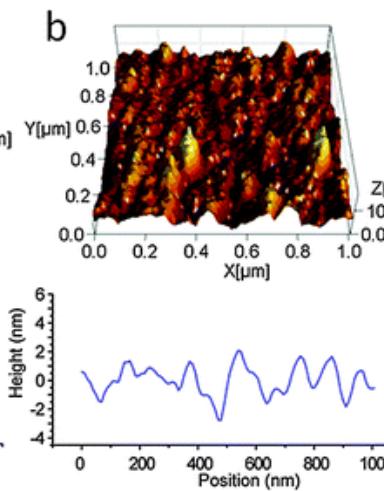
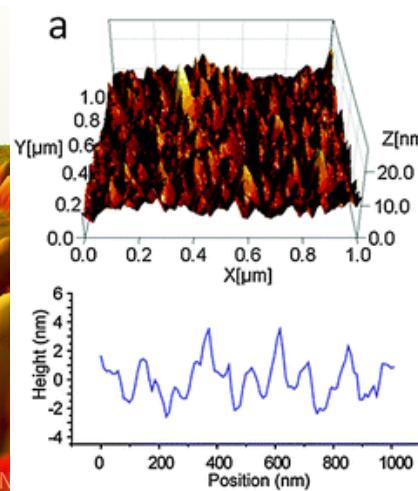
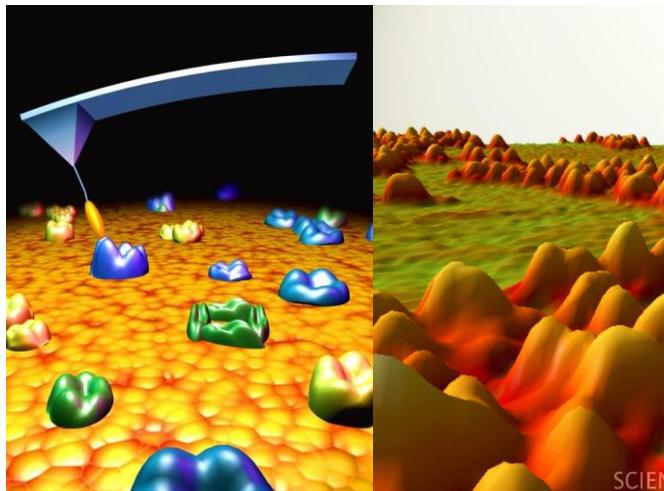
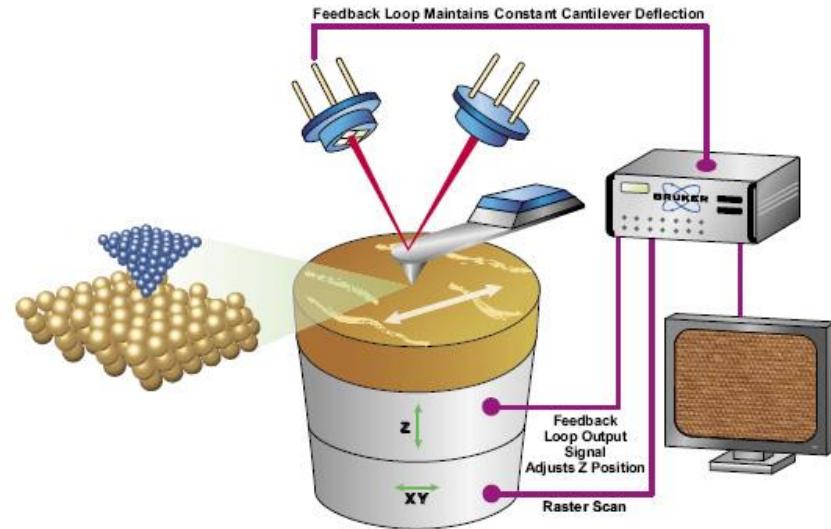
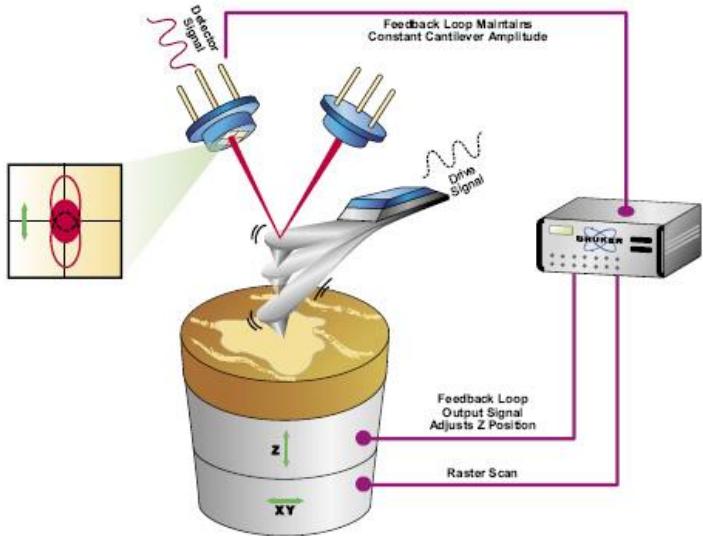
But nice as routine monitoring of chemical processes



# Monitoring adsorption and optimizing chemistry through Crystal Quartz Microbalance (no spatial resolution, high mass resolution)



# Feeling the surface with a scanning probe AFM (previous lecture)(low area)



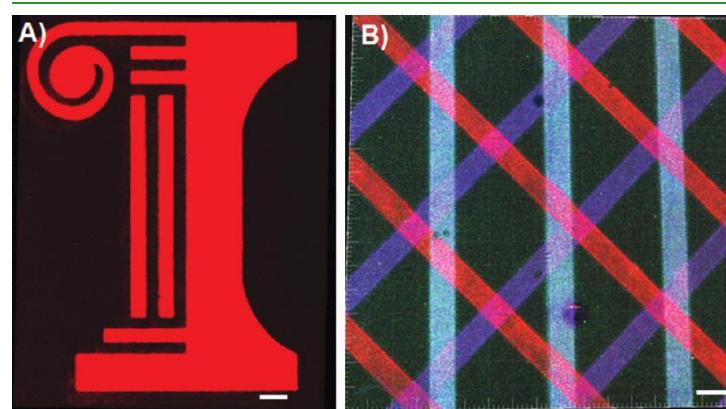
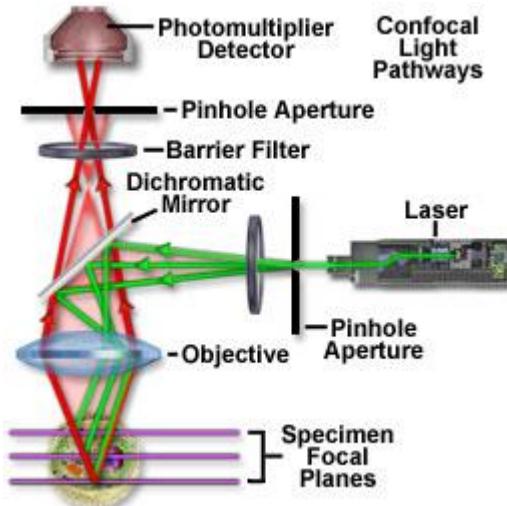
# Non-specific characterization of surface, comparing AFM/contact angle

Table 1. Surface Characterization of BP-Modified Substrates<sup>a</sup>

	Glass	Aldehyde silane	BP functionalization	Post-Protein Conjugation
Contact Angle (H <sub>2</sub> O)	0°	44.8 ± 1.9°	53.4 ± 1.1°	30.2 ± 2.1°
RMS Roughness (AFM)	352 pm	915 pm	833 pm	775 pm
Chemical Structure				

<sup>a</sup> Surfaces were characterized using contact angle goniometry and AFM to determine changes in hydrophobicity and surface roughness. Contact angle data represent the average of  $n = 9$  substrates ( $\pm$  standard deviation) from two batches of slides made on the same day. AFM was done after each reaction and the RMS roughness was determined.

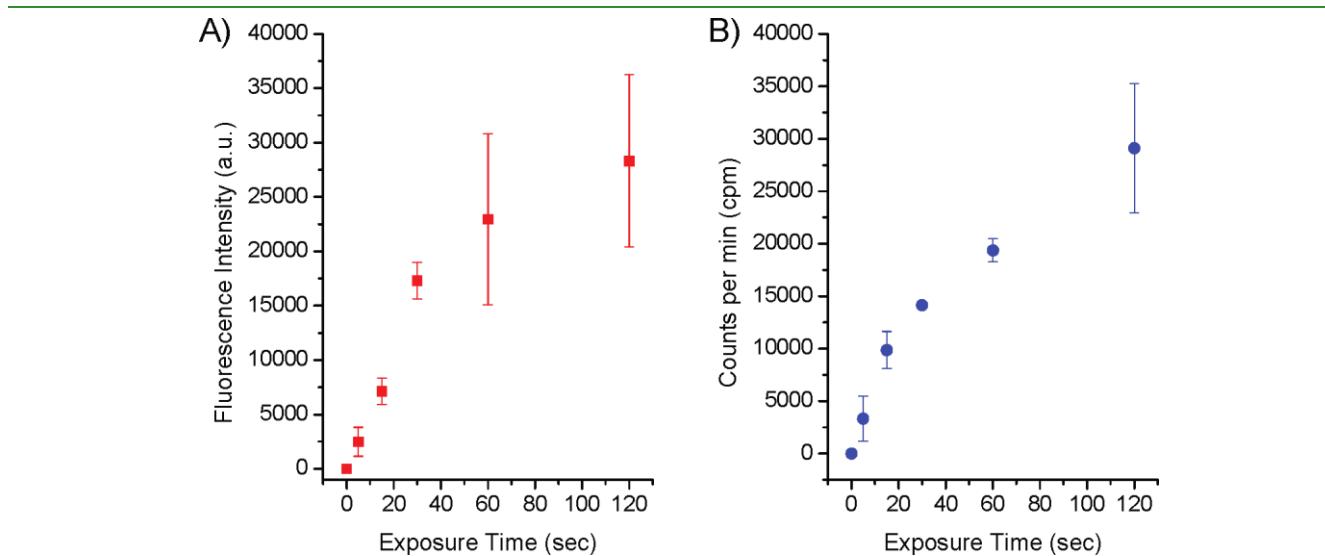
# Using confocal fluorescence (non-quantitative, spatial resolution approx $1/2\lambda$ (wavelength))



**Figure 1.** One-component and three-component patterns of biomolecules on BP-modified substrates. (A) Photoimmobilization of biotinylated ConA in the “Illinois logo” pattern, visualized with fluorescently labeled streptavidin. (B) Three-component pattern of mannan (blue, stripes running from top right to bottom left), P-selectin (red, stripes running from top right to bottom left), and Fibronectin (green, vertical stripes) photoimmobilized sequentially on BP-modified substrates with a  $100 \mu\text{m}$  stripe pattern with mask rotation between exposures. Scale bars:  $100 \mu\text{m}$ .

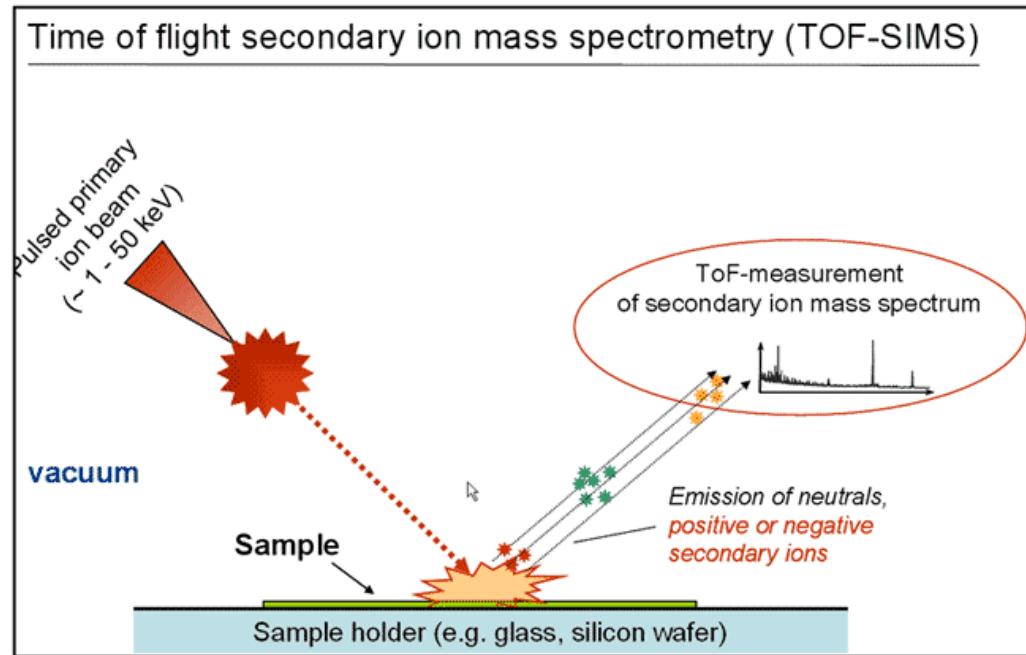
«Qualitative research is  
20% better than  
quantitative»

## Correlating Fluorescence (non-quantitative) to radioactivity (quantitative).



**Figure 2.** Protein loading is positively correlated with UV exposure time. Biotinylated ConA ( $5 \mu\text{g}/\text{mL}$ ) was uniformly photopatterned onto BP-modified substrates for 5, 15, 30, 60, or 120 s. The signal from subsequent (A) fluorescence analysis and (B) radioimmunoassays show the increase of signal as a function of UV exposure time ( $\sim 365 \text{ nm}, 17 \text{ mW}/\text{cm}^2$ ). Control substrates were employed to account for nonspecific binding of antibodies. Data represents the average of  $n = 3-4$  ( $\pm 95\%$  C.I.).

# TOF-SIMS for surface molecular analysis



## • Surface Spectroscopy

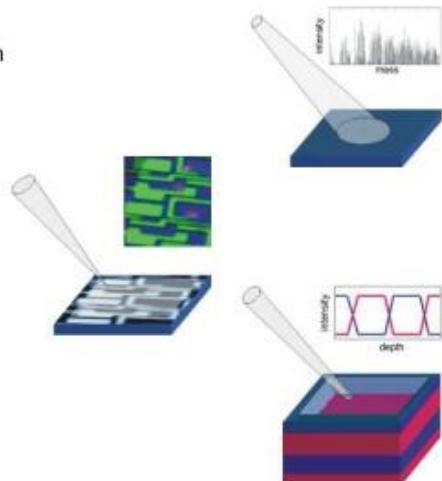
- elemental and molecular information
- unlimited mass range
- ppm sensitivity
- mass resolution > 10,000

## • Surface Imaging

- lateral resolution < 100 nm
- parallel mass detection

## • Depth Profiling

- depth resolution < 1 nm
- thin layers from 1 nm to > 10  $\mu\text{m}$
- ideal for insulators



# Suggested reading and PENSUM

## Pensum

### **Micropatterning as a tool to decipher cell morphogenesis and functions**

Manuel Théry . J Cell Sci 2010 123:4201-4213; doi:10.1242/jcs.075150

### **Microfabricated devices for cell biology: all for one and one for all**

Franziska Lautenschläger and Matthieu Piel

Current Opinion in Cell Biology 2013, 25:116–124

### **Designing materials to direct stem-cell fate**

Matthias P. Lutolf, Penney M. Gilbert & Helen M. Blau

Nature 462, 433-441(26 November 2009)

### **Exploring and exploiting chemistry at the cell surface**

Morgan D. Mager, Vanessa LaPointe & Molly M. Stevens

Nature Chemistry 3, 582–589 (2011) doi:10.1038/nchem.1090

### **Chemical strategies for generating protein biochips**

Jonkheijm P, Weinrich D, Schröder H, Niemeyer CM, Waldmann H.

Angew Chem Int Ed Engl. 2008;47(50):9618-47.

### **Recent developments in the site-specific immobilization of proteins onto solid supports.**

Camarero JA.

Biopolymers. 2008;90(3):450-8. Review.

<http://www.sciencedirect.com/science/bookseries/0091679X/121>