Mobile Microscopy, Sensing and Diagnostics using Computational Photonics

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Digital Diagnosis

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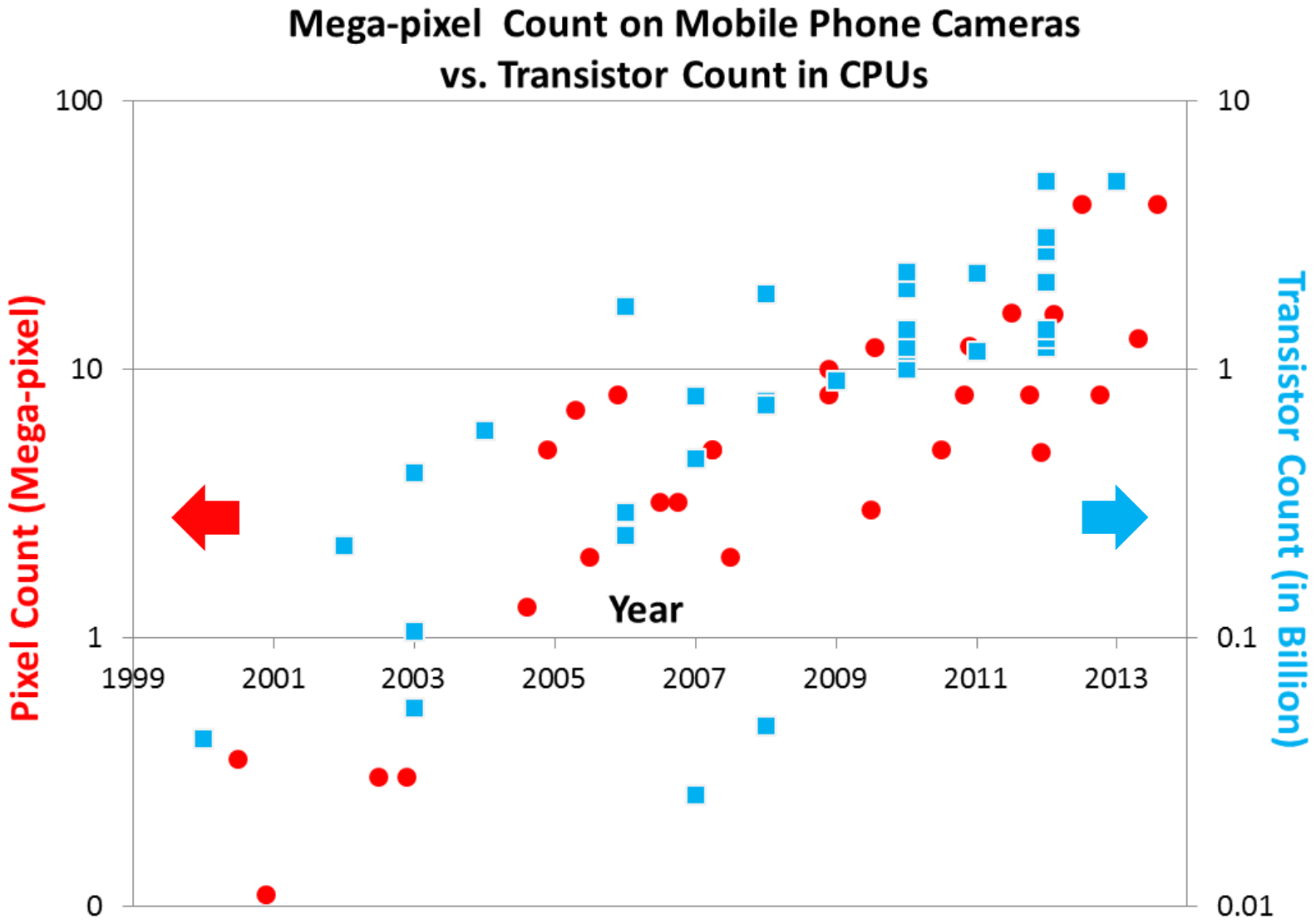
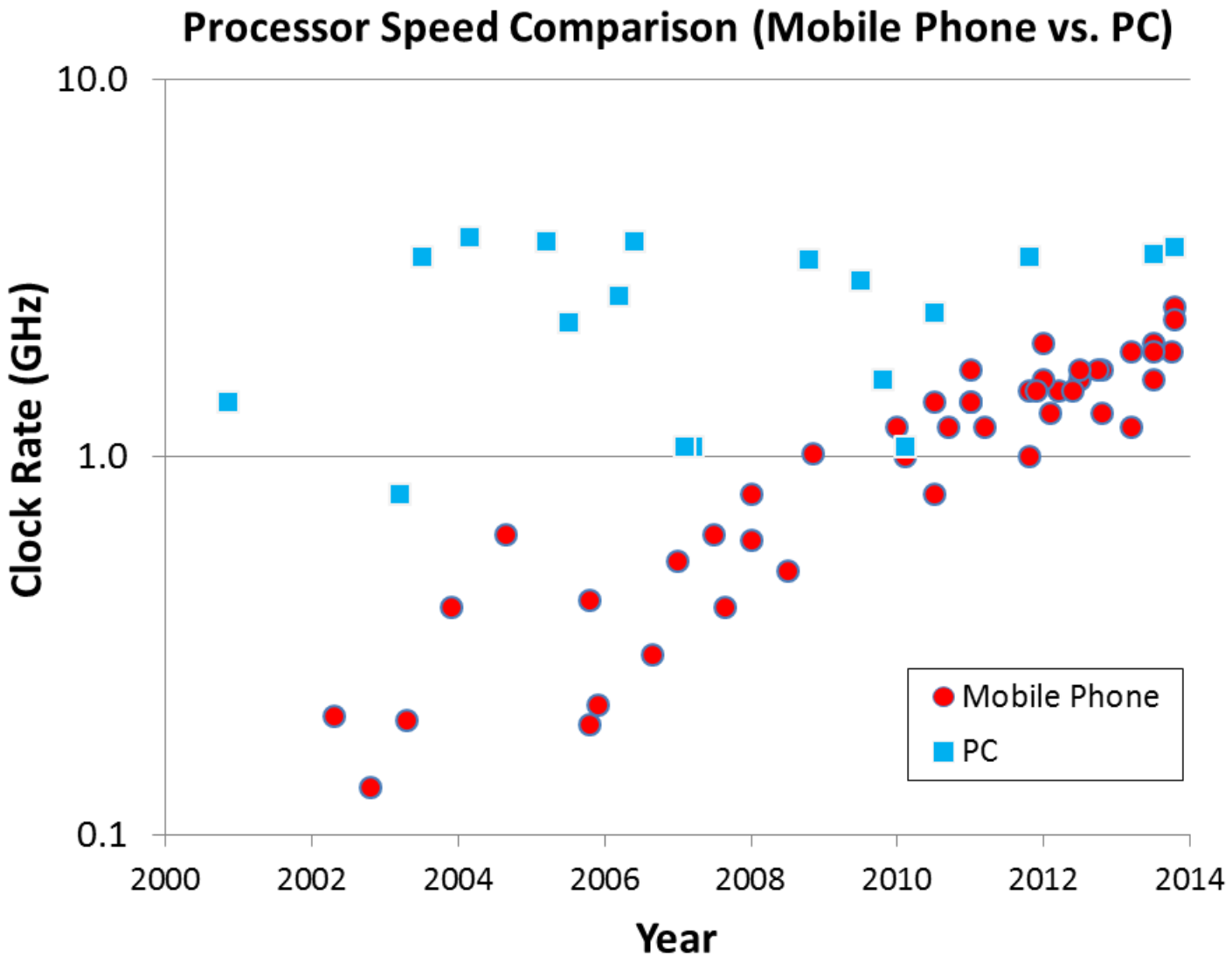
2016

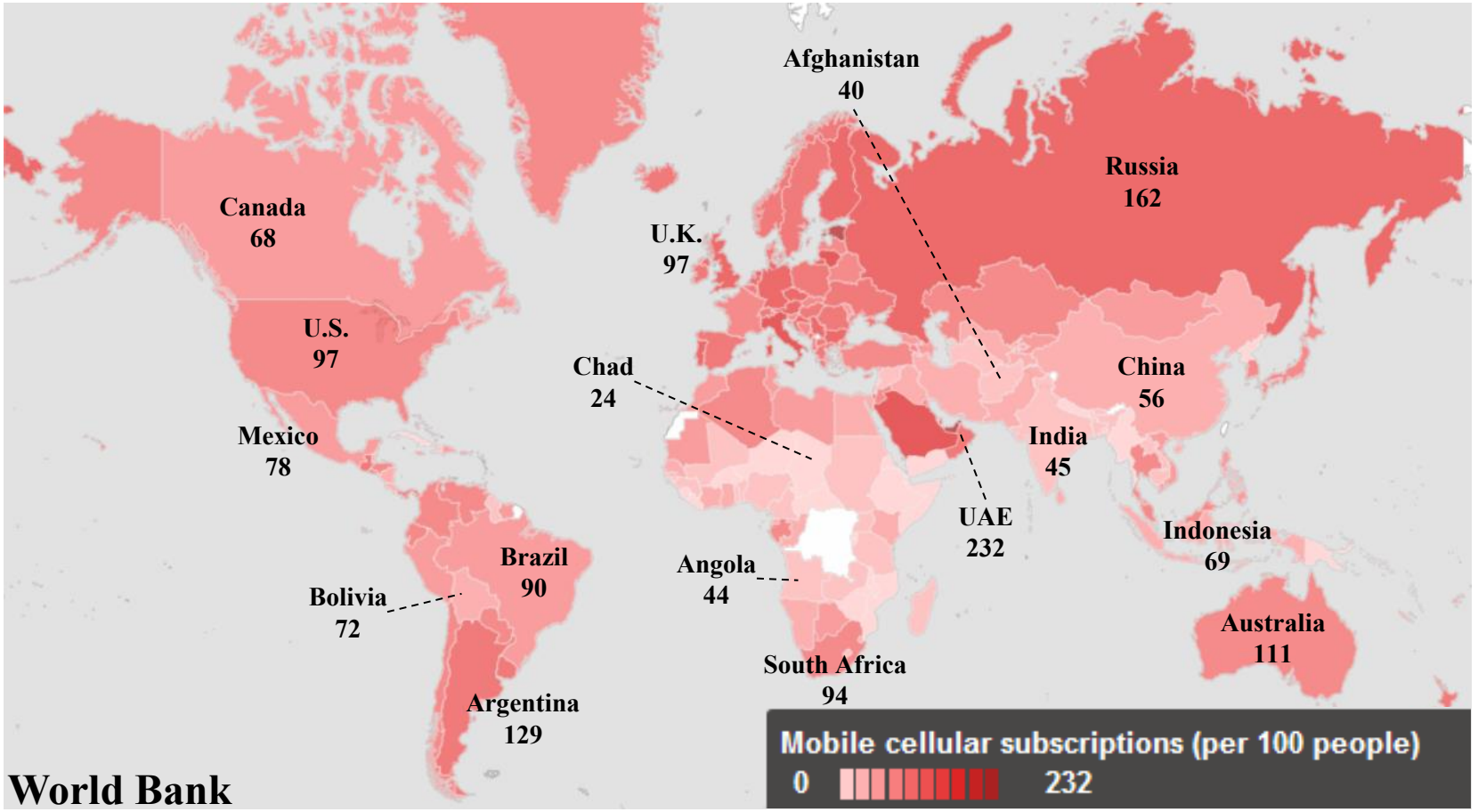
A different view of the Moore's Law



Smart-phones as super-computers

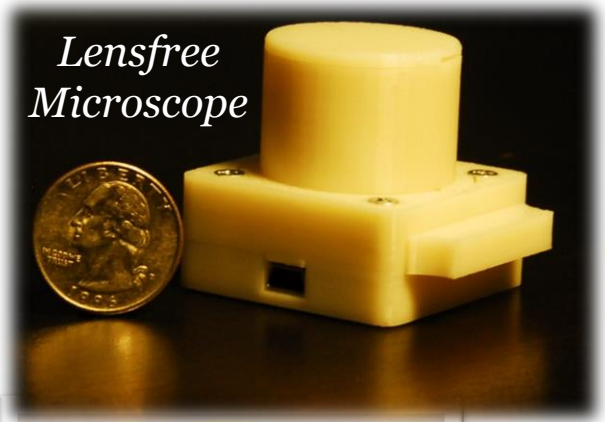


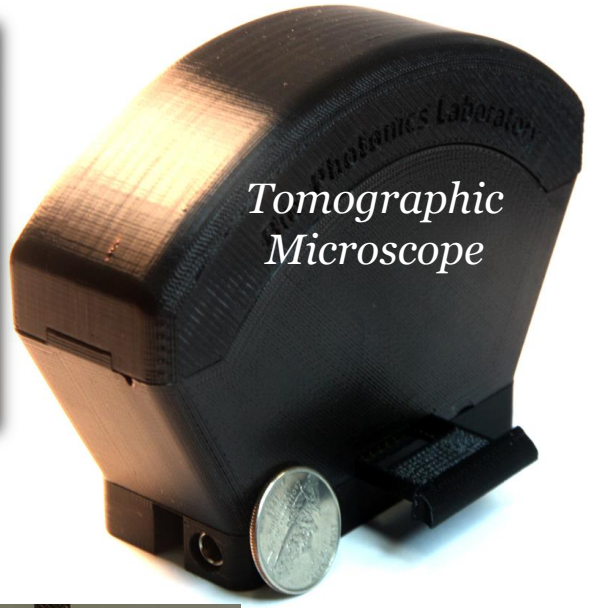
Cell phones are now everywhere: A great potential for Telemedicine needs

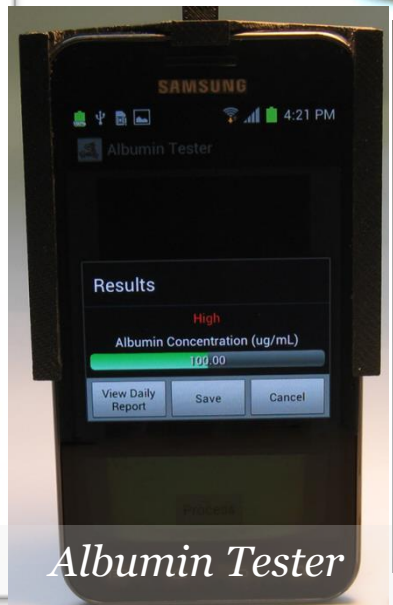


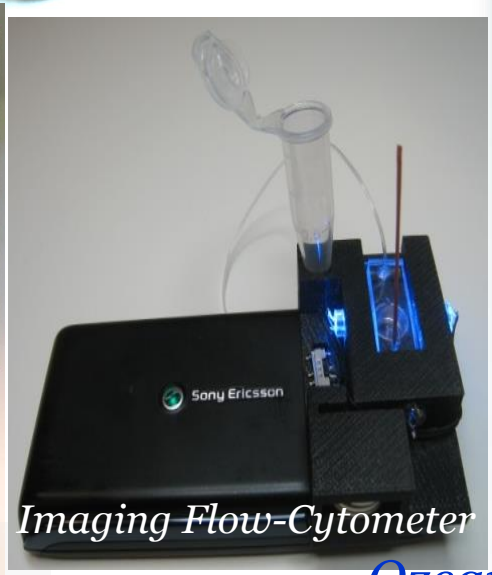
- ~7 billion cell phones are being used worldwide.
- ~15 billion cell phones have been sold so far.
- ~80% are in developing countries. (International Telecommunication Union)

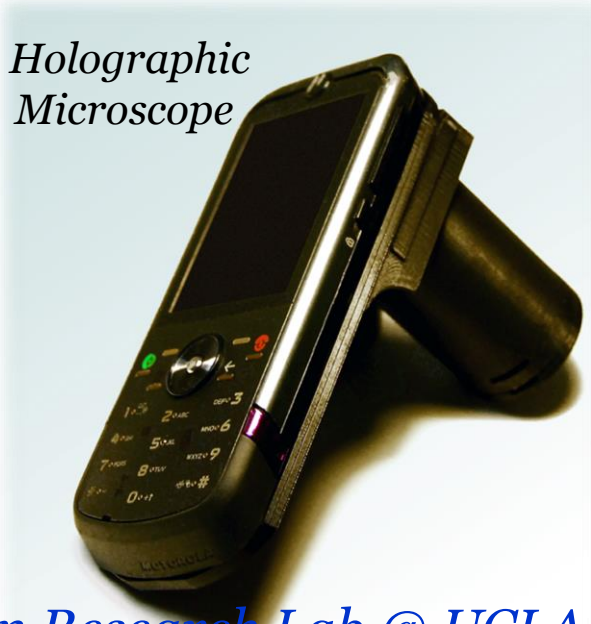
Providing a new platform for telemedicine











Ozcan Research Lab @ UCLA

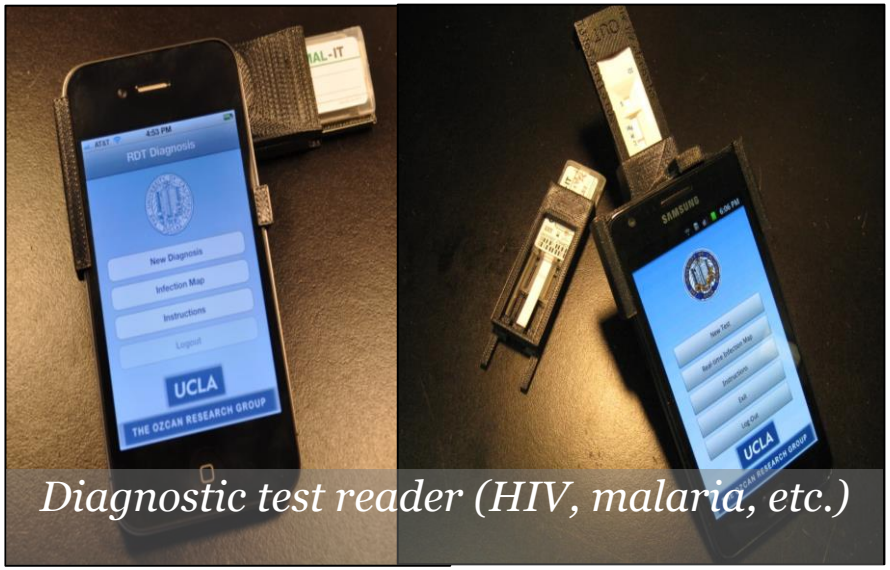
Providing a new platform for telemedicine

E. coli sensor

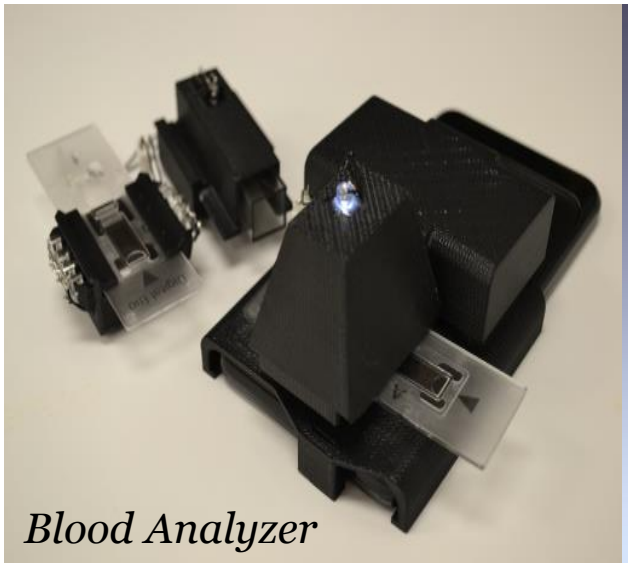
Allergen detector

Heavy metal detector

Google Glass based Diagnostics



Diagnostic test reader (HIV, malaria, etc.)



Blood Analyzer

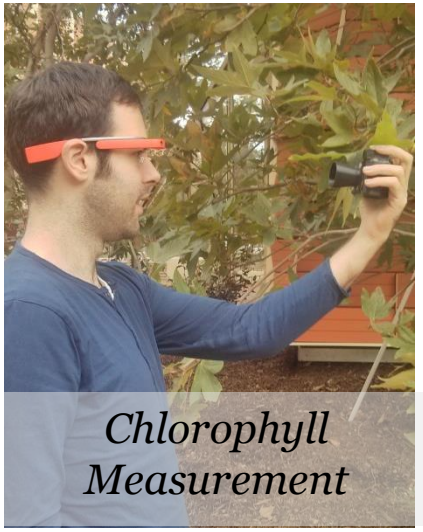
Blood Analyzer

Providing a new platform for telemedicine

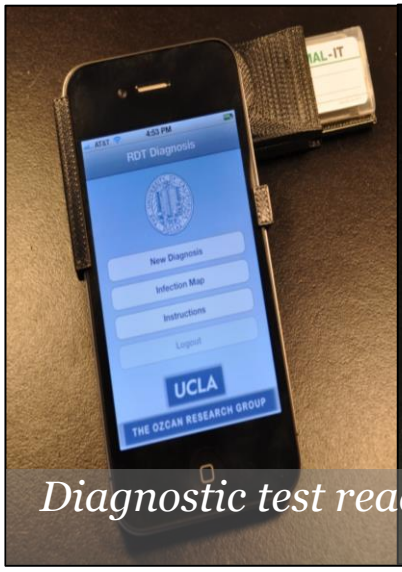
E. coli sensor

Allergen detector

Heavy metal detector



Chlorophyll Measurement



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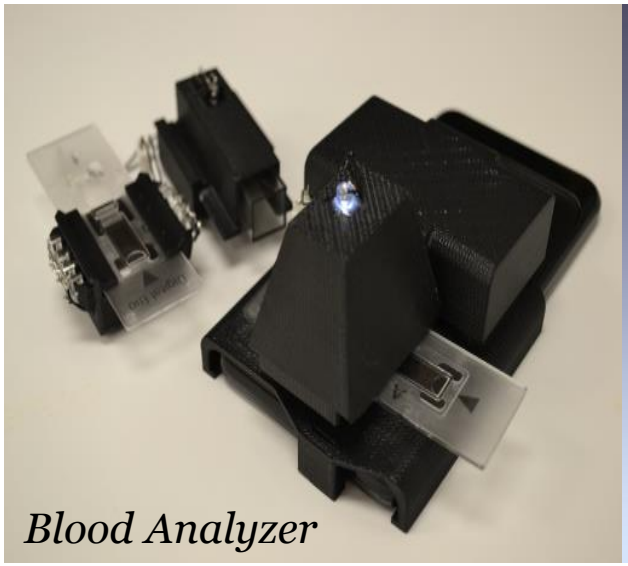


Blood Analyzer

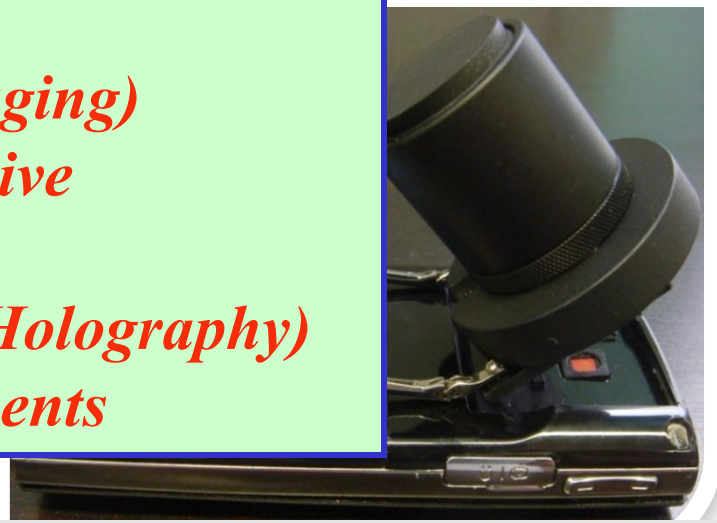
Blood Analyzer

The μ-Internet

Big Data

New opportunities in micro-analysis, medical diagnostics and epidemiology

Providing a new platform for telemedicine



LUCAS:

Lensfree (On-Chip Imaging)

Compact, Cost-effective

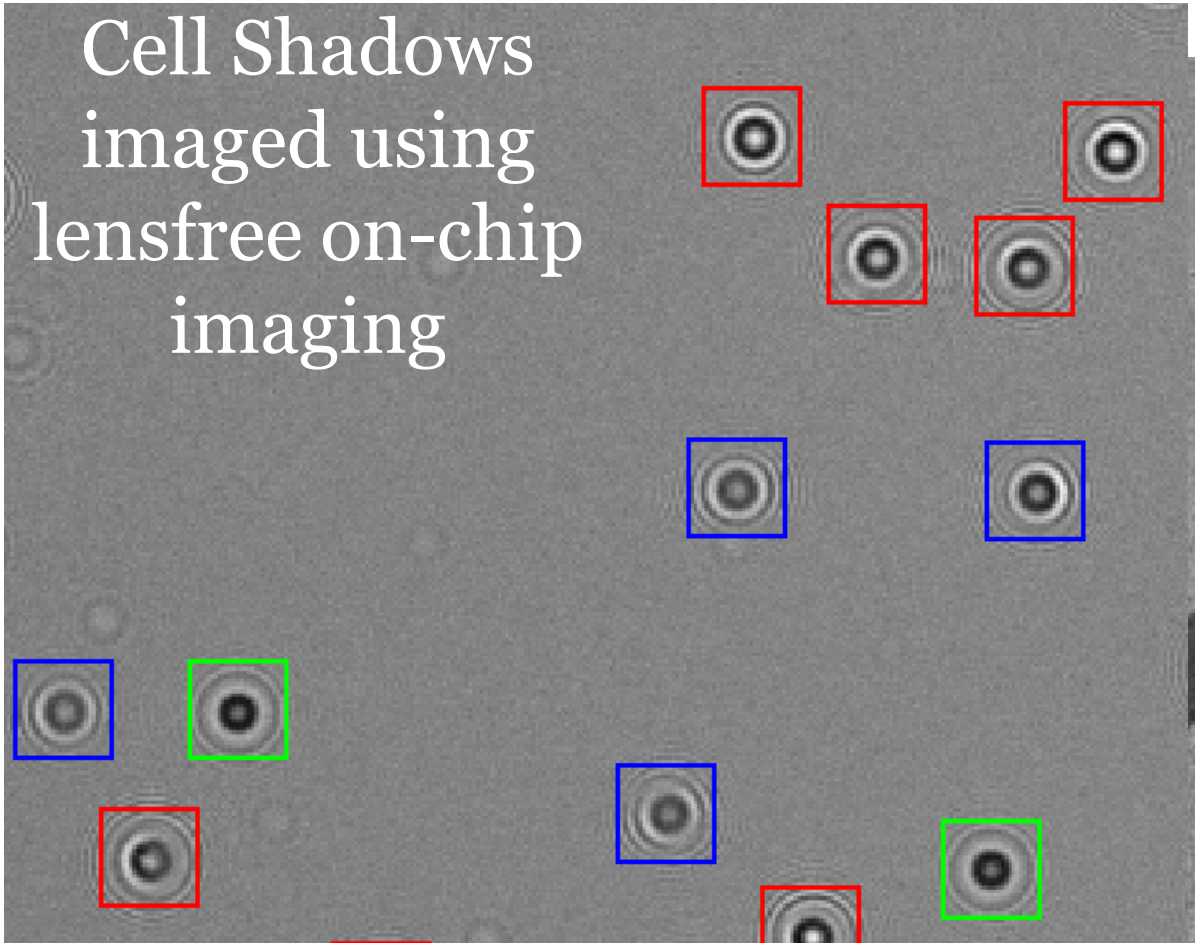
High-throughput

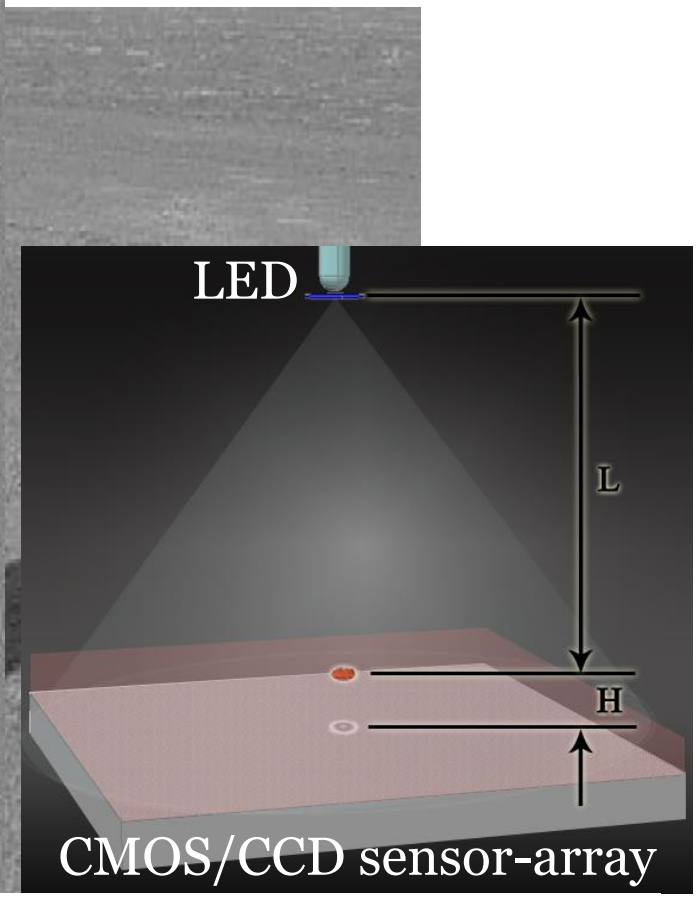
Highly sensitive (Incoherent Holography)

Tolerant to Misalignments

LUCAS: ***L***ensless, ***U***ltra wide-field ***C***ell monitoring ***A***rray platform based on ***S***hadow imaging

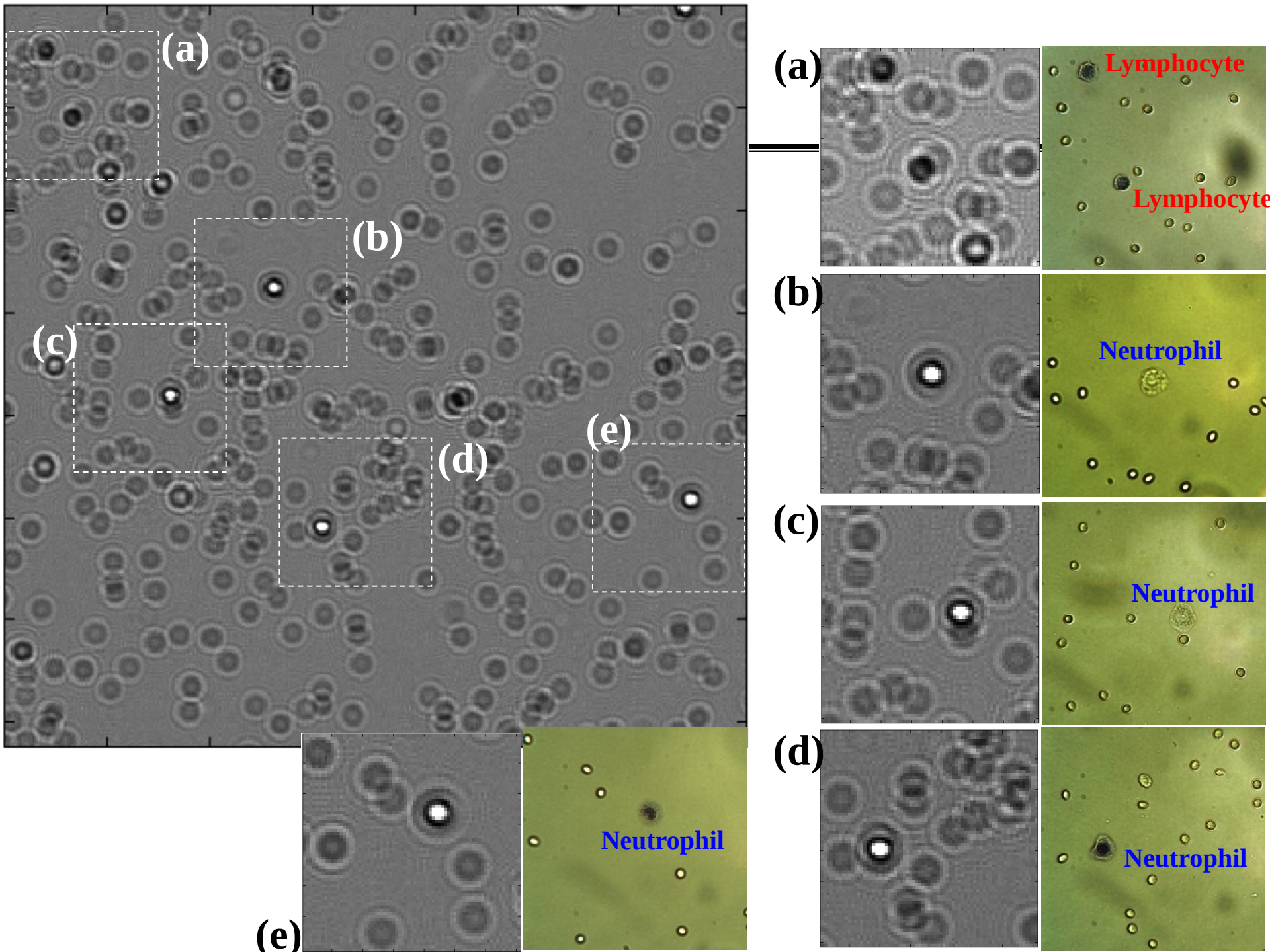
Imaging of shadows



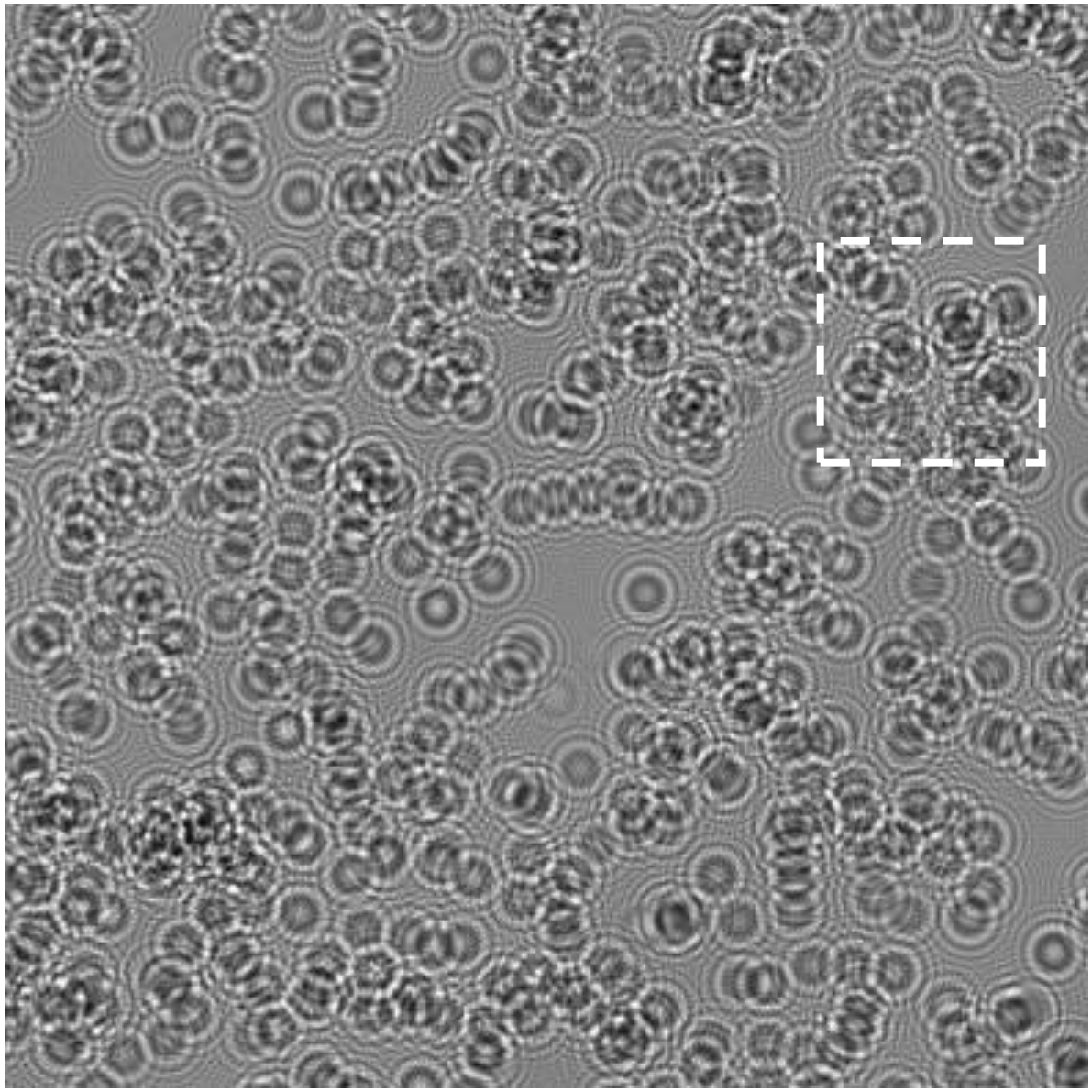


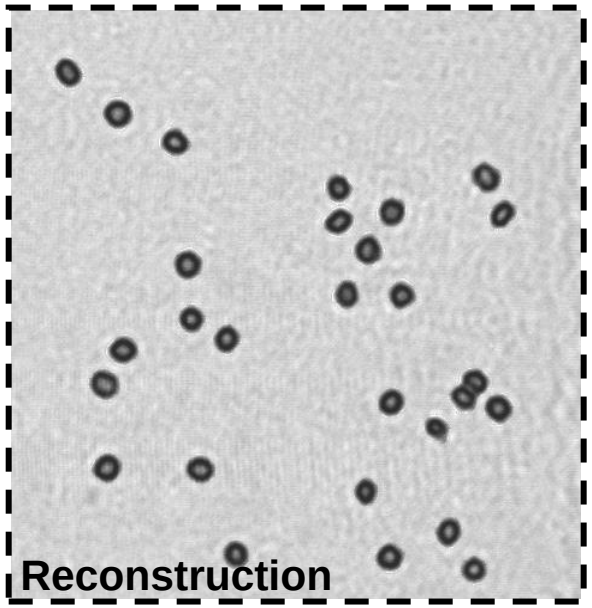
H<1-2 μm → contact on-chip imaging

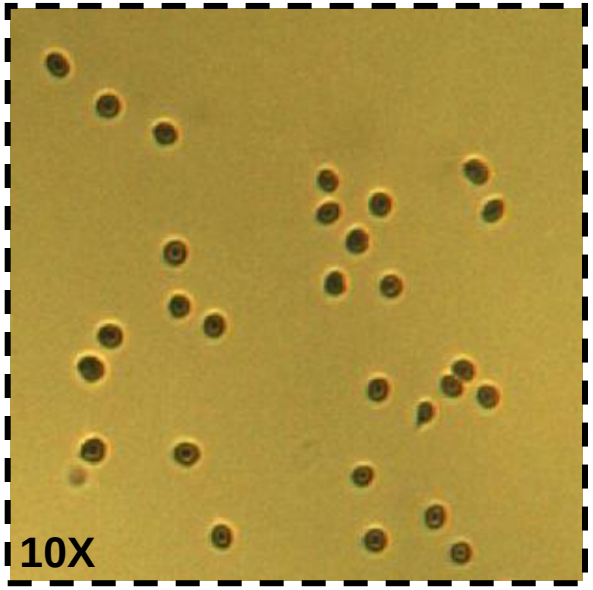
H ~ 10 - 1,000 μm → holographic on-chip imaging

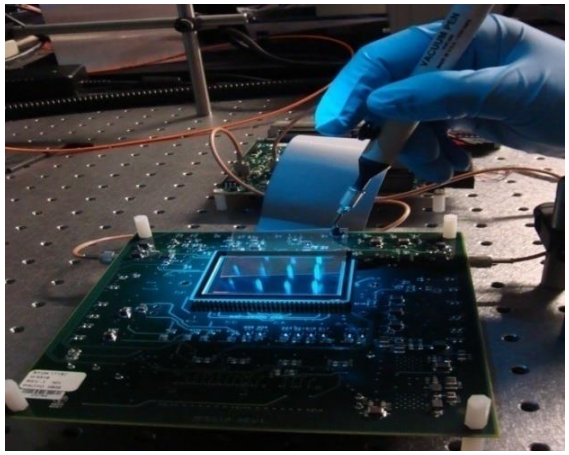

(a)
(b)
(c)
(d)
(e)
(a)
Lymphocyte
Lymphocyte
(b)
Neutrophil
(c)
Neutrophil
(d)
Neutrophil
(e)
Neutrophil

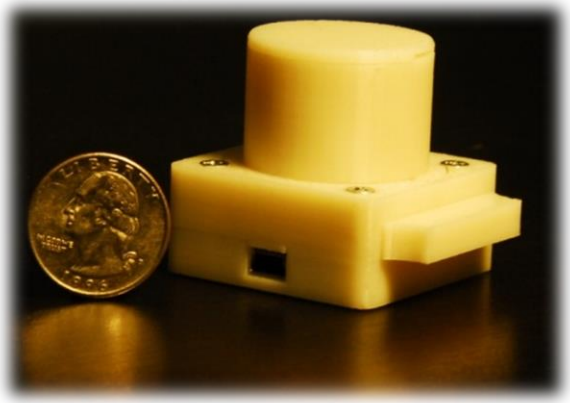
Cell Density: 102K [Cells/uL]

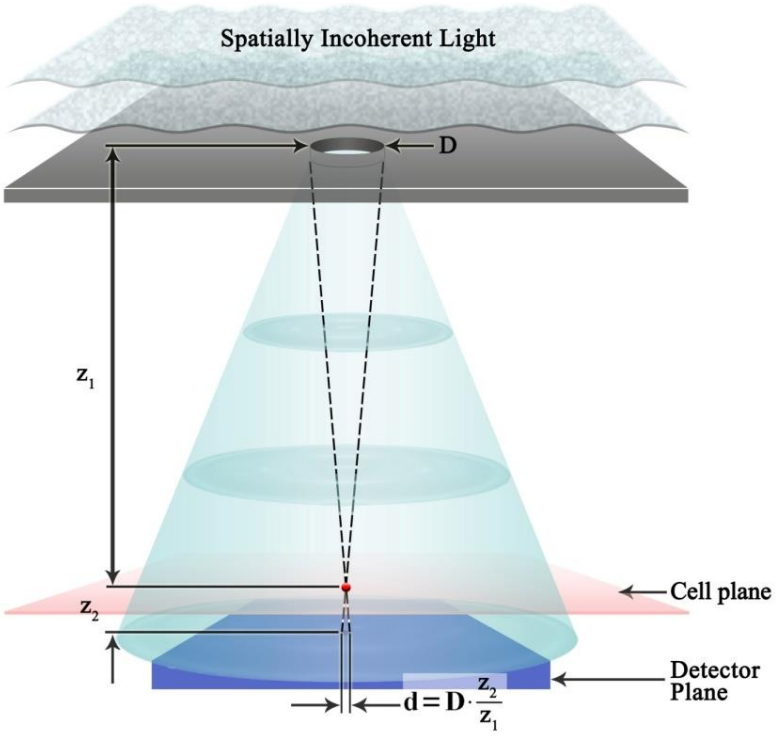












Incoherent Lensfree Holography Using Large Apertures:

-Reduced speckle noise and multiple interference noise

-Reduced cross-talk among cells

-Tolerant to misalignments; No need for coupling optics

-No need for lasers; LEDs would be sufficient

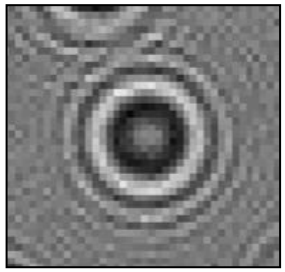
-Significantly larger field of view

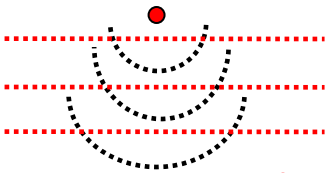
Iterative phase recovery eliminates the twin image: Exact transfer function enables convergence with <20 iterations

$$U_{-z_2}^{i+1}(x,y) = \begin{cases} m \cdot D_{-z_2}(x,y), & x,y \notin S \\ U_{-z_2}^{i}(x,y), & x,y \in S \end{cases}$$

$$m = mean(U_{-z_2}^{i}(x,y)/mean(D_{-z_2}(x,y)$$

Measured Hologram (red blood cell)





$[i(x_D,y_D)]^{0.5}$

Support constraint

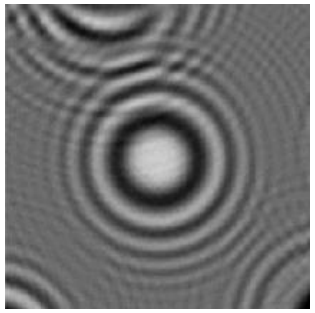
Digital propagation to object plane

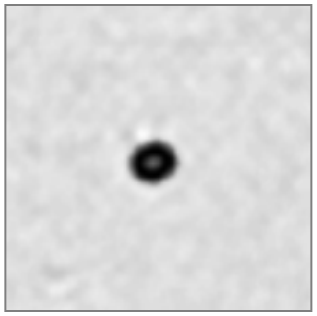
Digital propagation to hologram plane

Update Phase

N: number of iterations (e.g., <20)

Recovered Hologram Phase



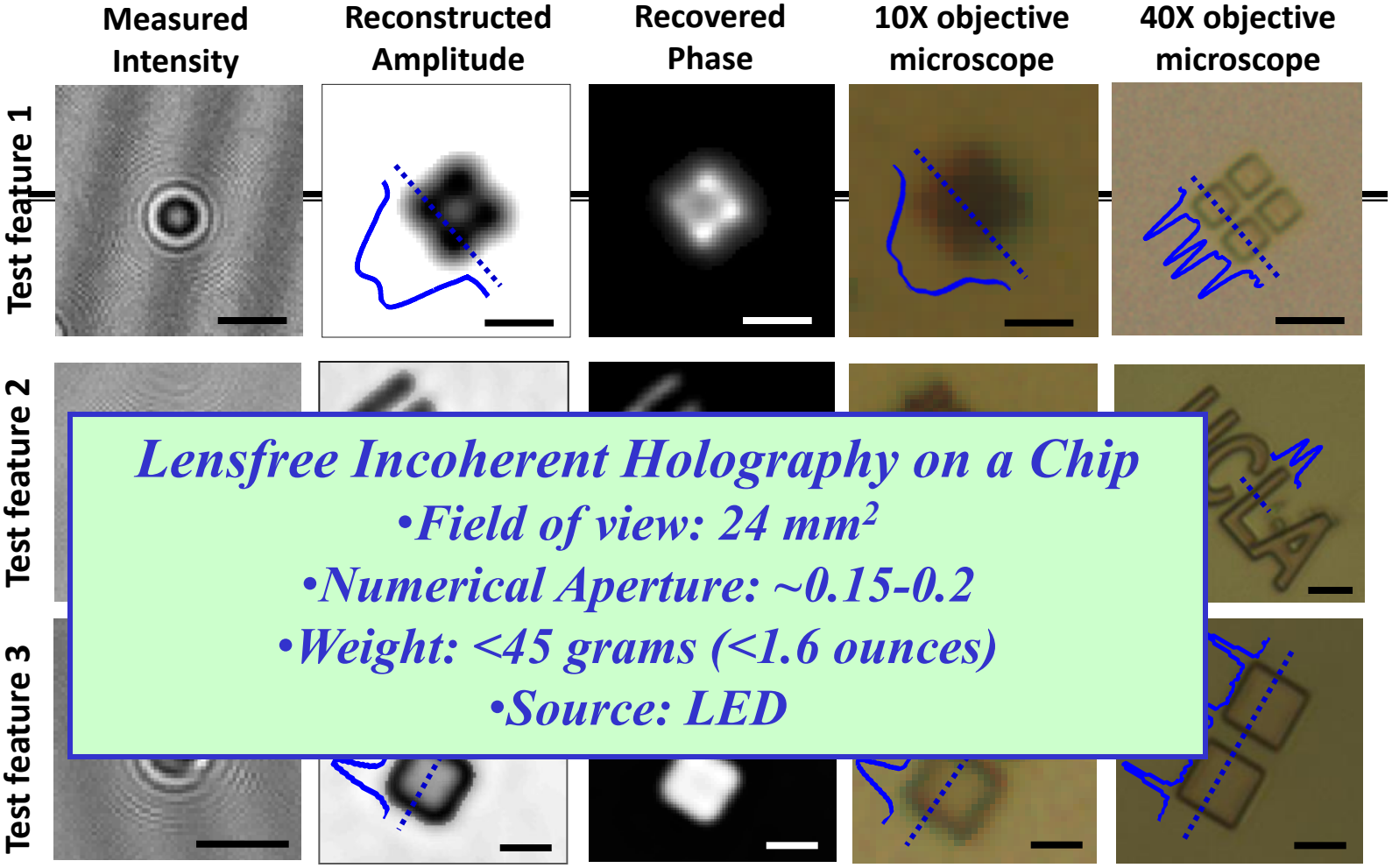


Lensfree image (red blood cell)

$$H_z(f_x,f_y) = \exp\left(j\frac{2\pi}{\lambda}z\right)\sqrt{1-(\lambda f_x)^2-(\lambda f_y)^2}$$

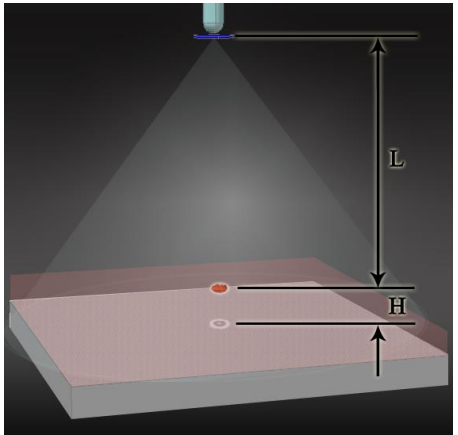
$$where \quad \sqrt{f_x^2+f_y^2} < \frac{1}{\lambda}$$

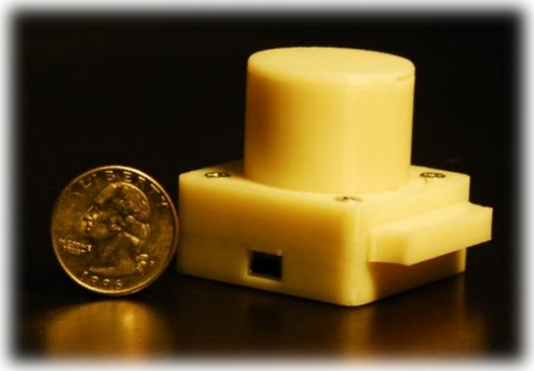
Scale bar - holograms: 50um
Scale bar - all others: 5um

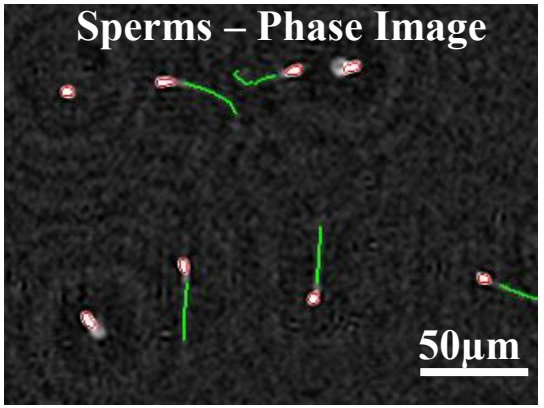


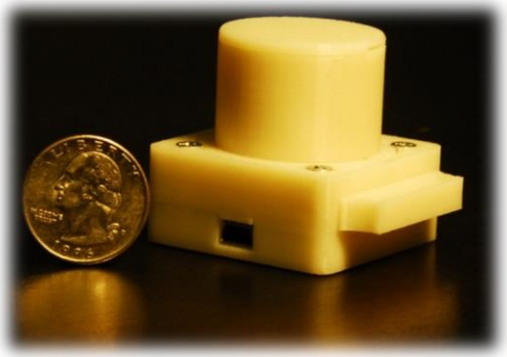
Lensfree Incoherent Holography on a Chip

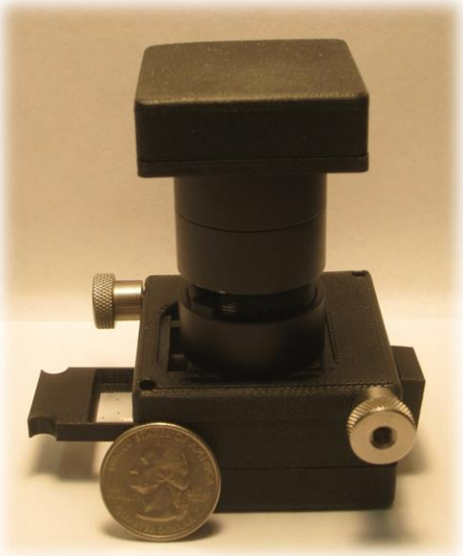
- ***Field of view: 24 mm²***
- ***Numerical Aperture: ~0.15-0.2***
- ***Weight: <45 grams (<1.6 ounces)***
- ***Source: LED***





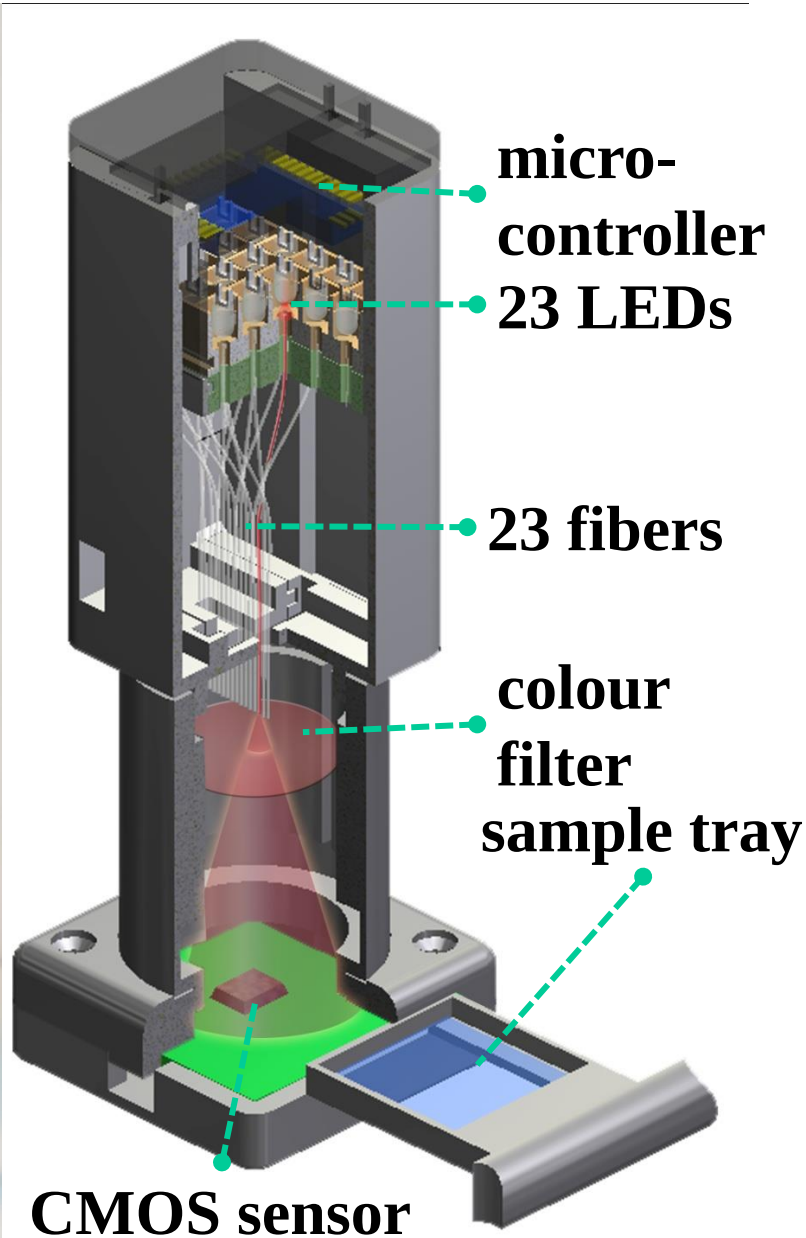


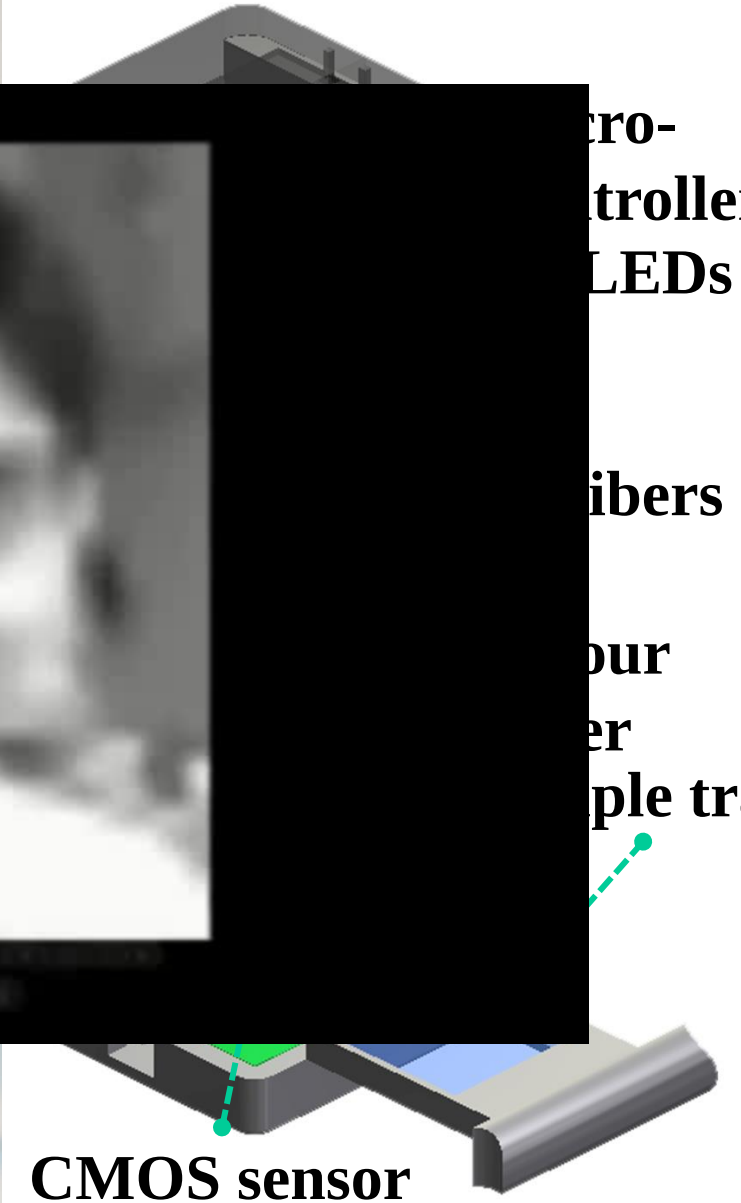




Super-resolution in lensfree on-chip imaging

Sub-micron resolution over 30 mm² field-of-view


micro-
controller
23 LEDs
23 fibers
colour
filter
sample tray
CMOS sensor



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LEDs

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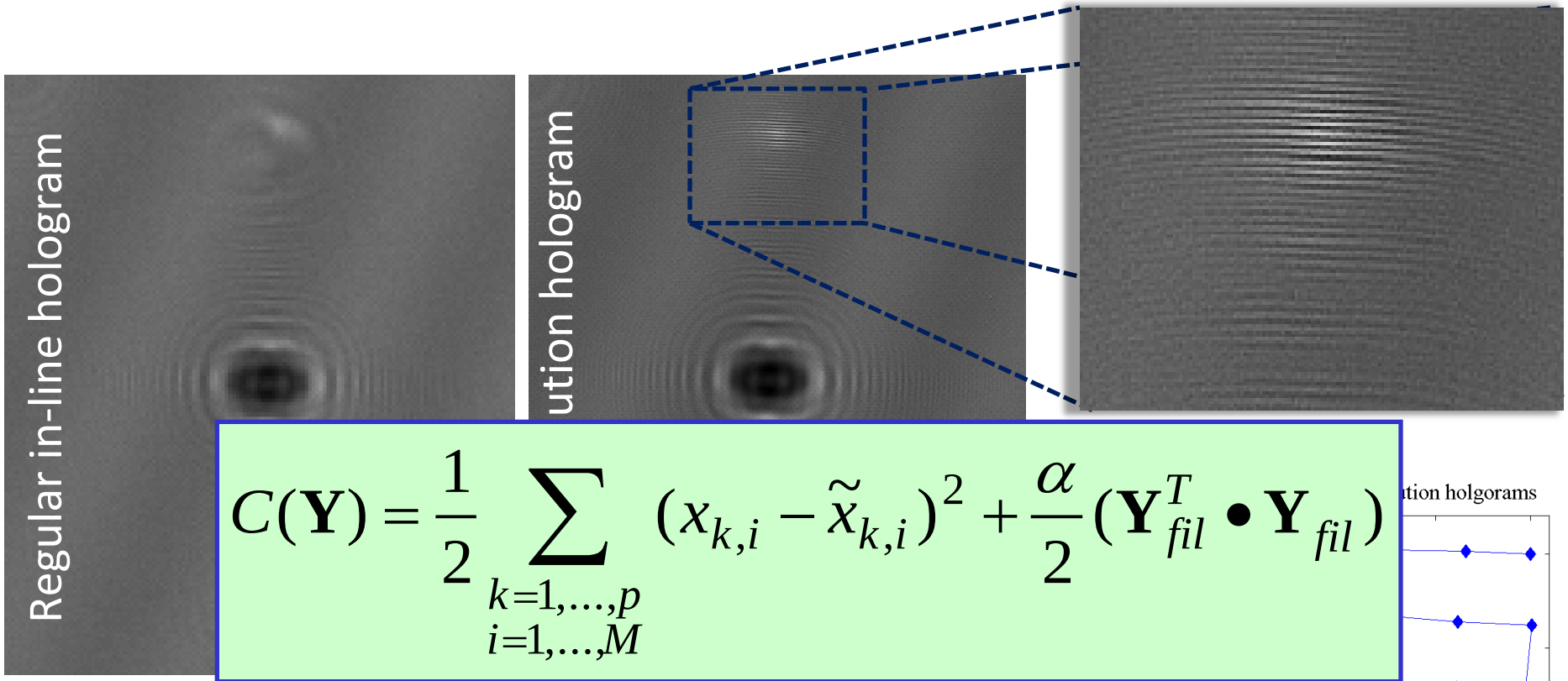
ple tray

CMOS sensor

Improving resolution to sub-micron

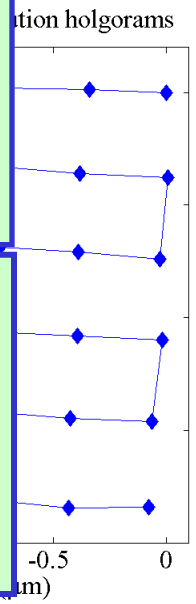


$$C(\mathbf{Y}) = \frac{1}{2} \sum_{\substack{k=1,\ldots,p \\ i=1,\ldots,M}} (x_{k,i} - \tilde{x}_{k,i})^2 + \frac{\alpha}{2} (\mathbf{Y}_{fil}^T \bullet \mathbf{Y}_{fil})$$

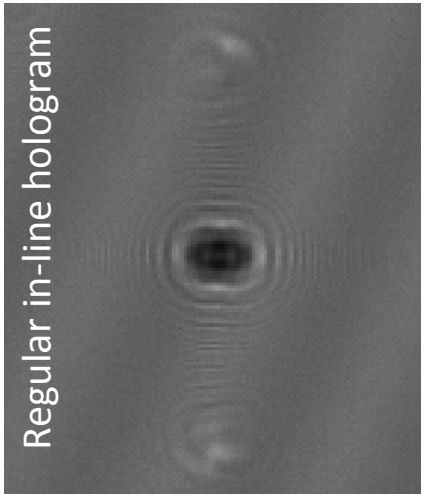
- *k=1:p --- Sub-pixel shifts*
- *i=1:M --- Pixels of the lower resolution hologram*
- *Y : High resolution hologram to be estimated*
- Y_{fil} *: High-pass version of Y*

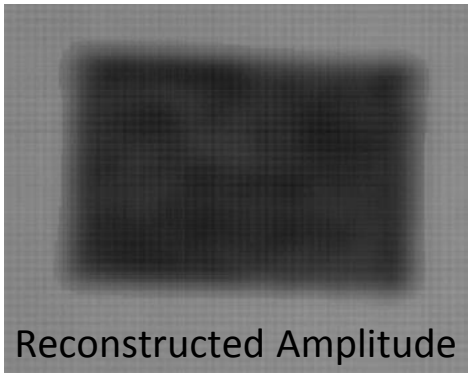
Pixelsi

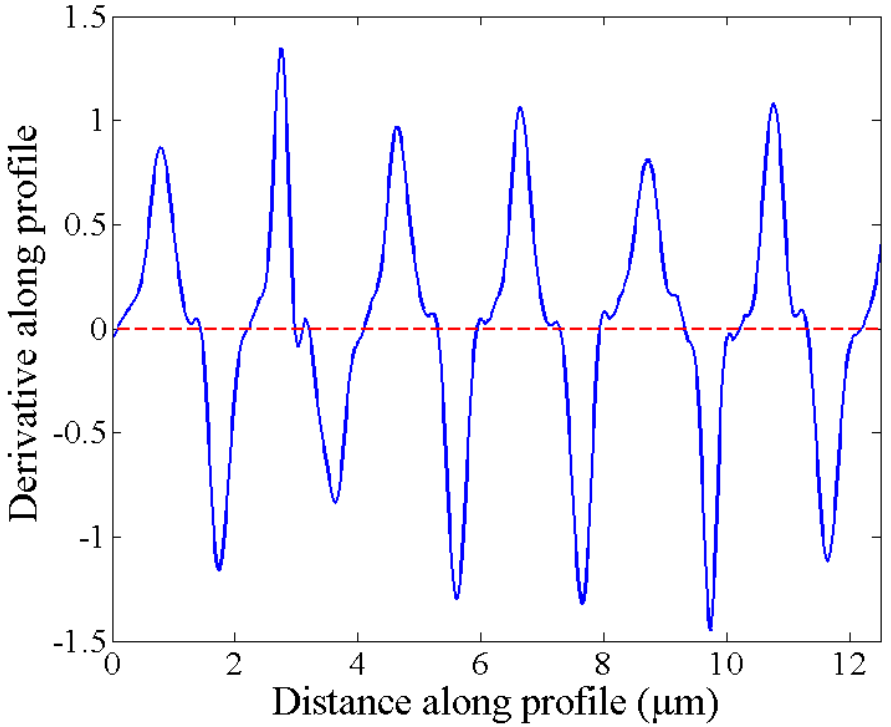
5M

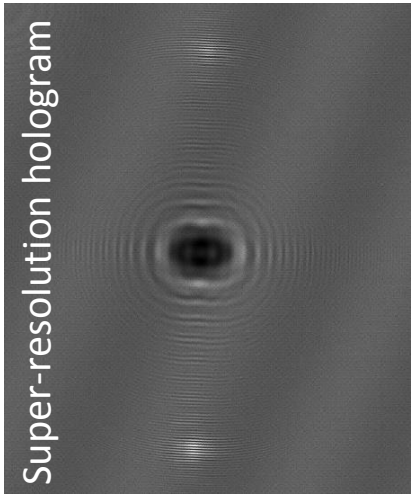


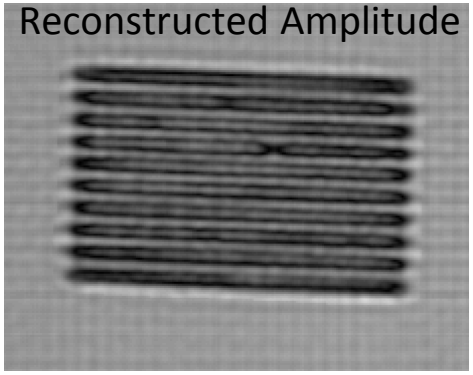
A numerical aperture of ~0.9 and a half-pitch resolution of <250 nm is confirmed

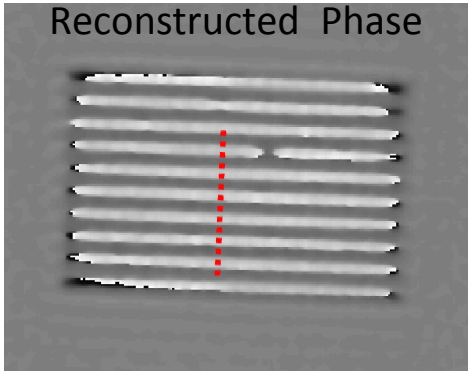


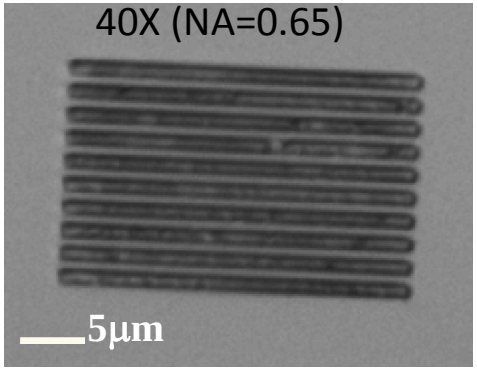




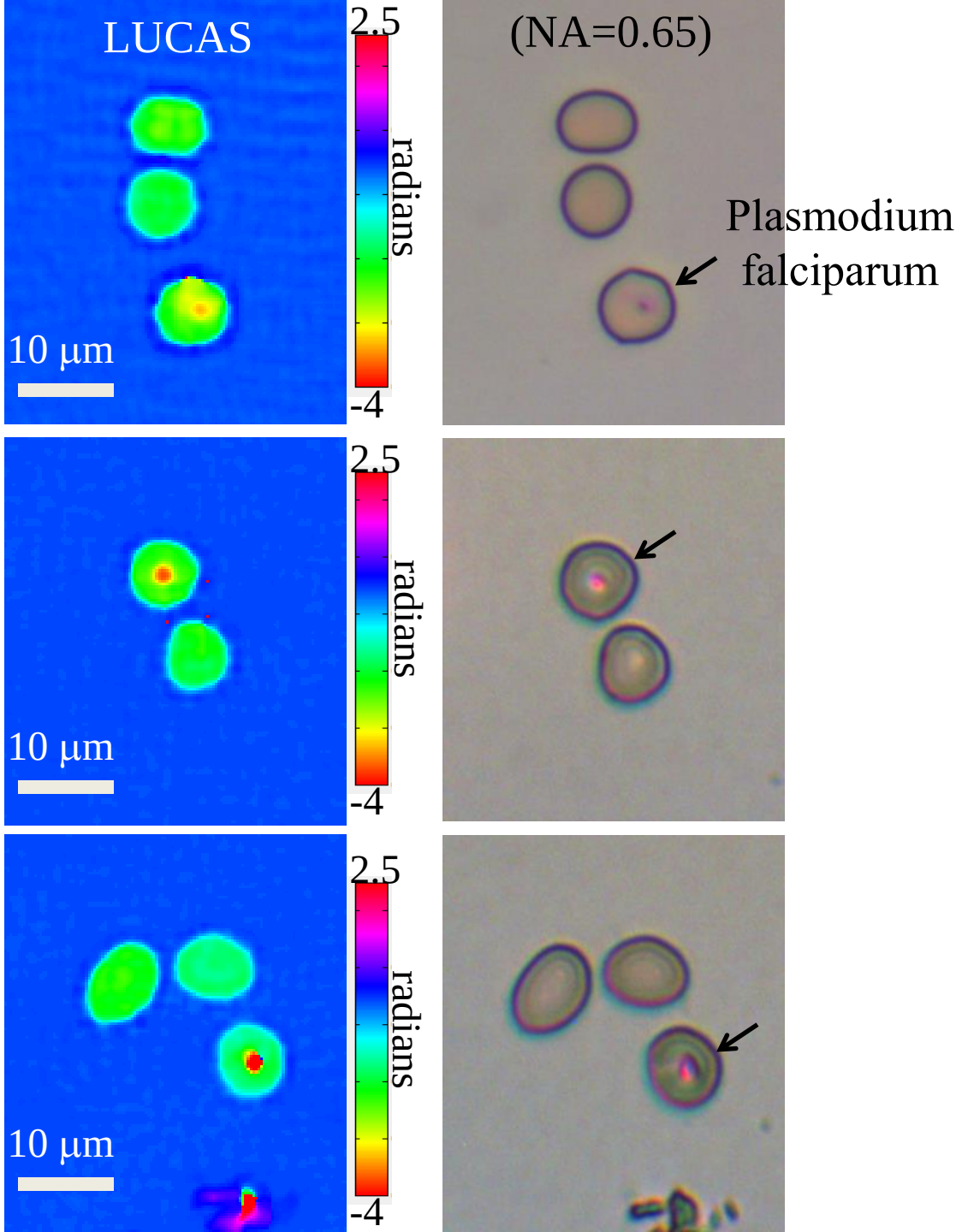




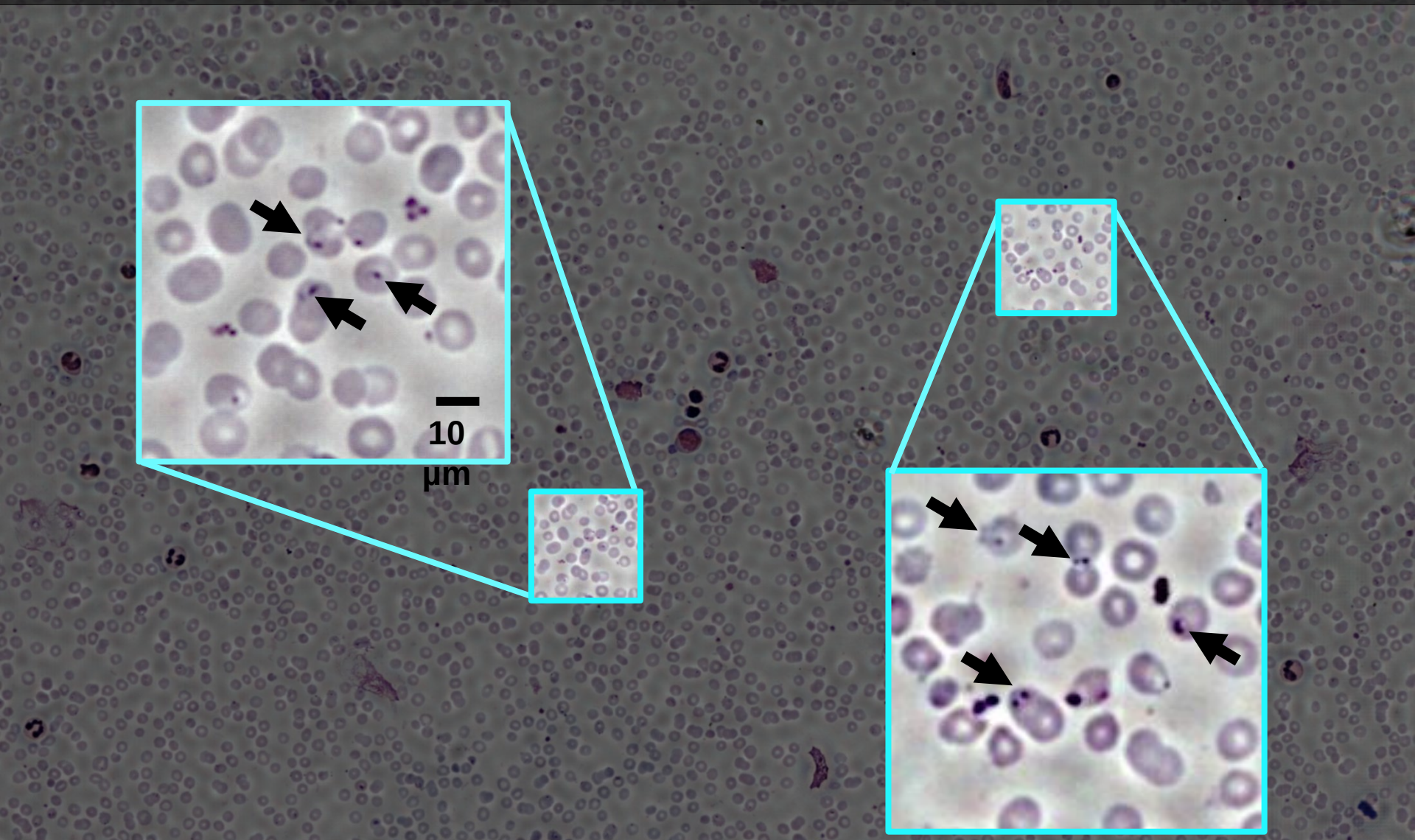




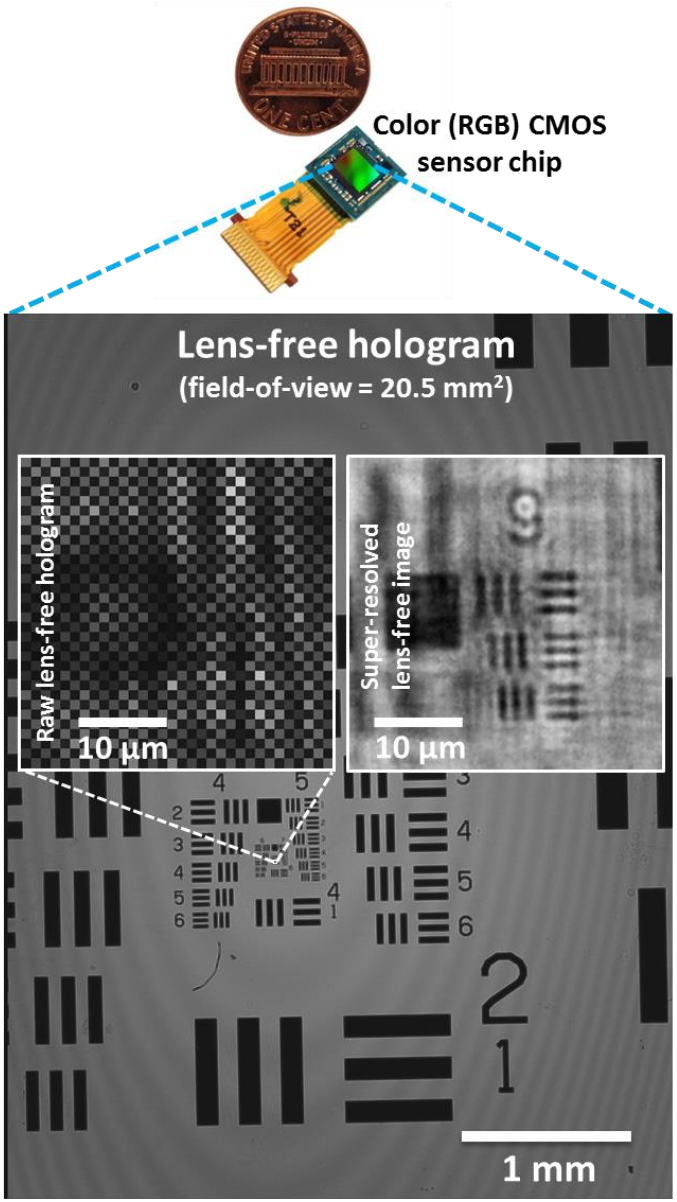
5 Megapixel
CMOS imager

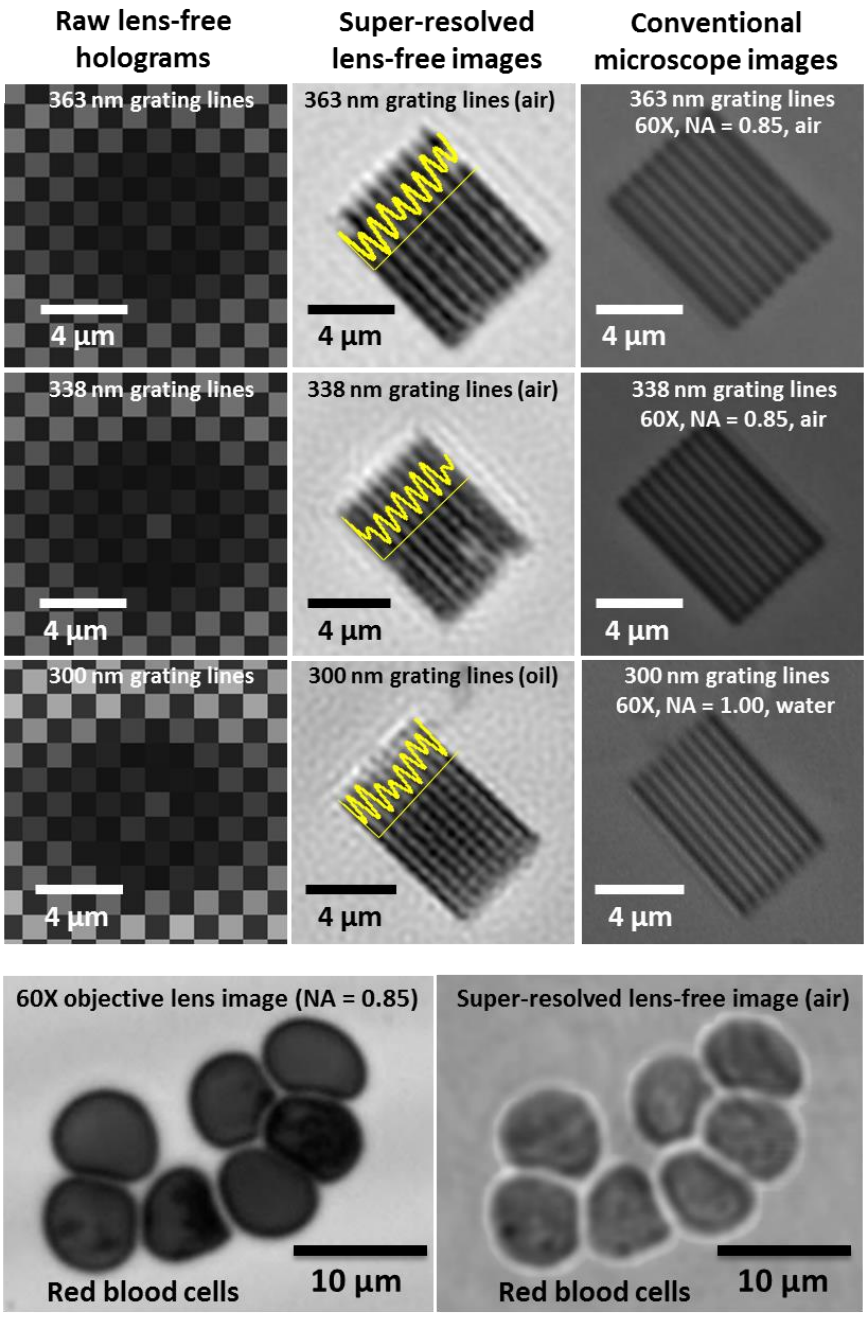


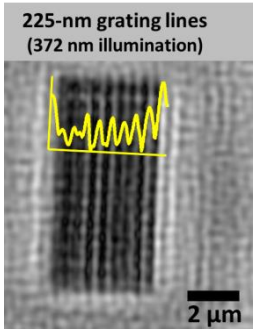
Malaria-infected blood sample



NA=0.9-1.0 FOV>20 mm^2

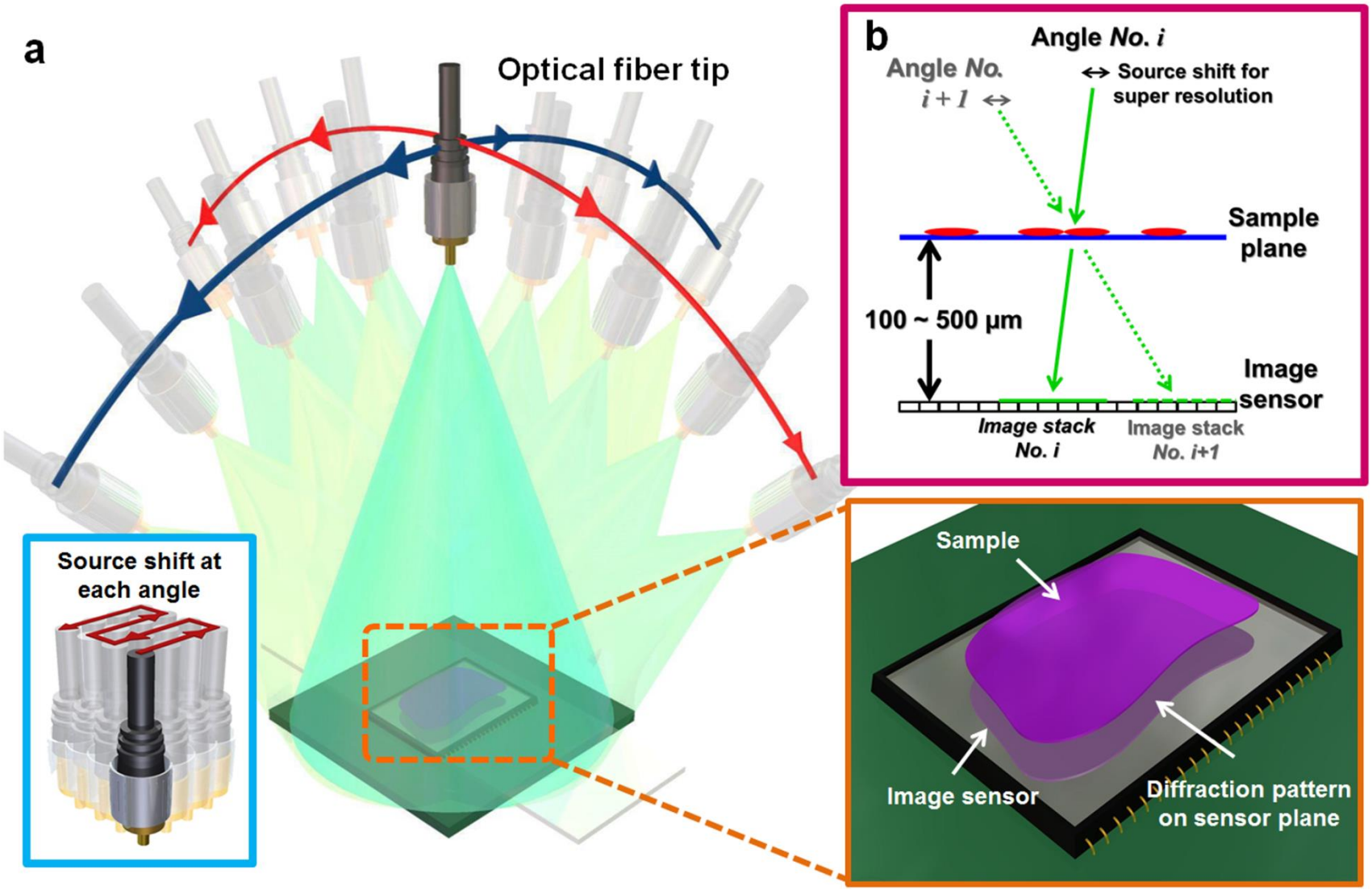






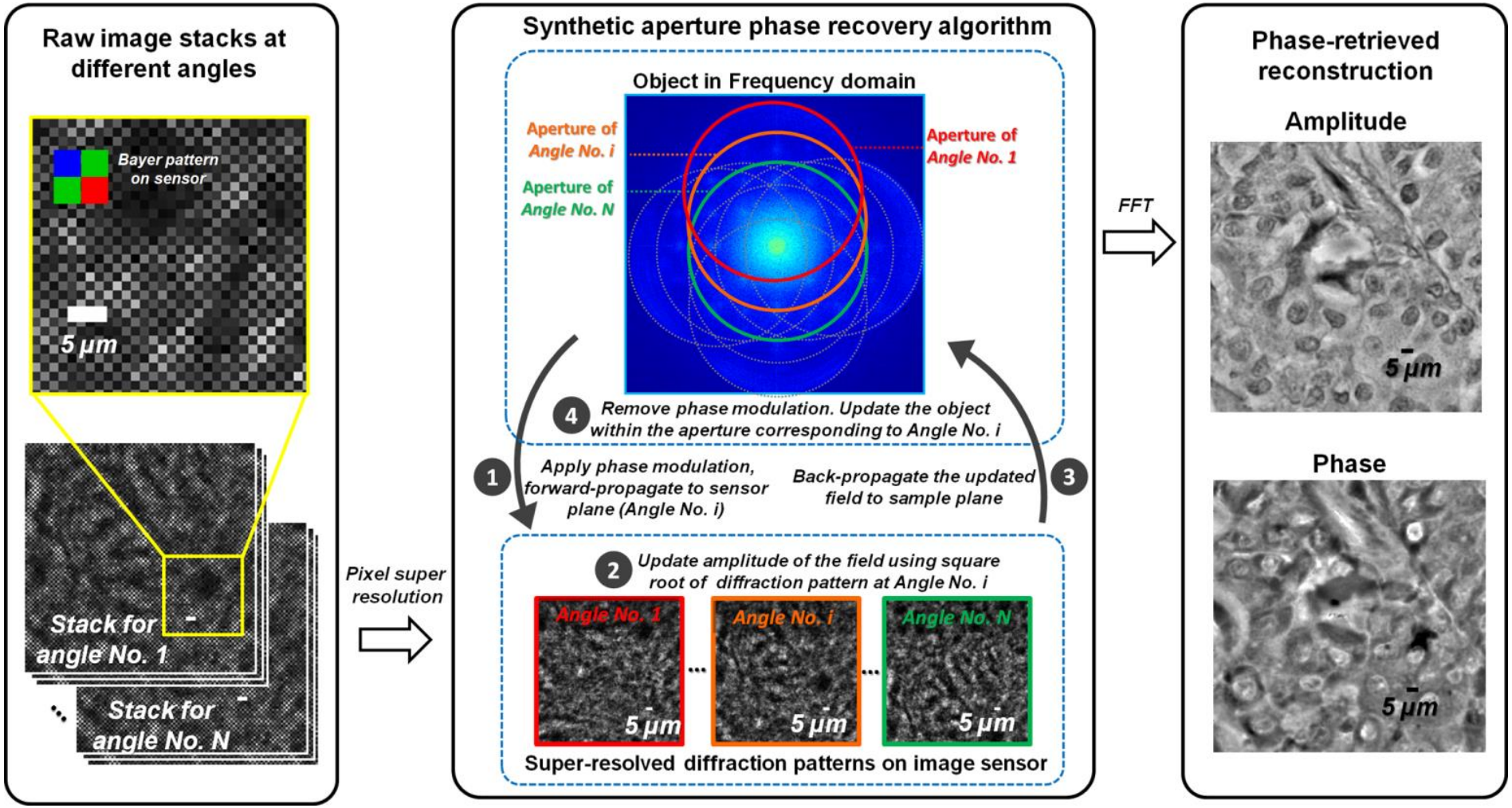
Nature Methods (2012)

Synthetic aperture based on-chip microscopy

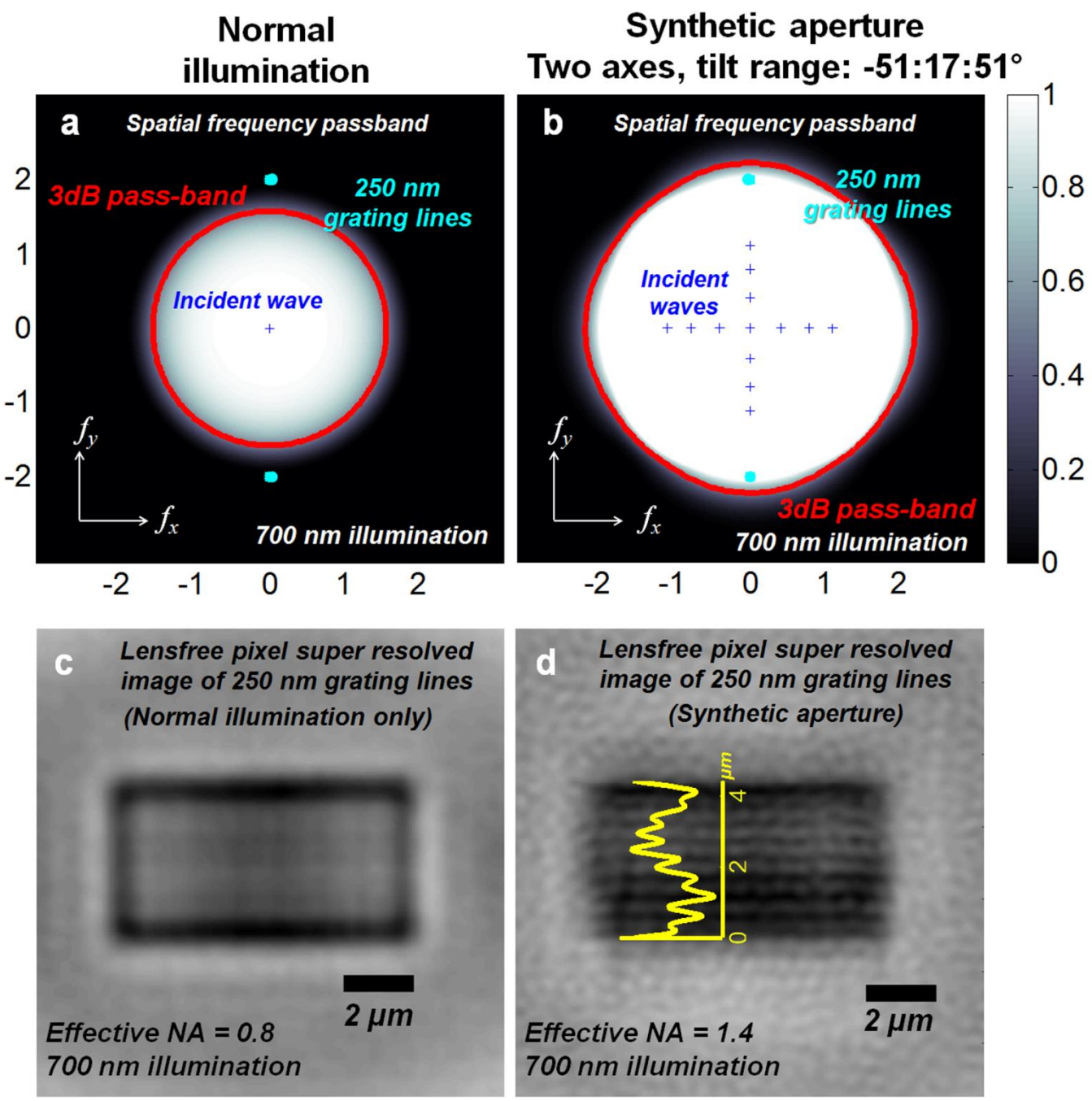


Nature Light: Science & Applications (2014)

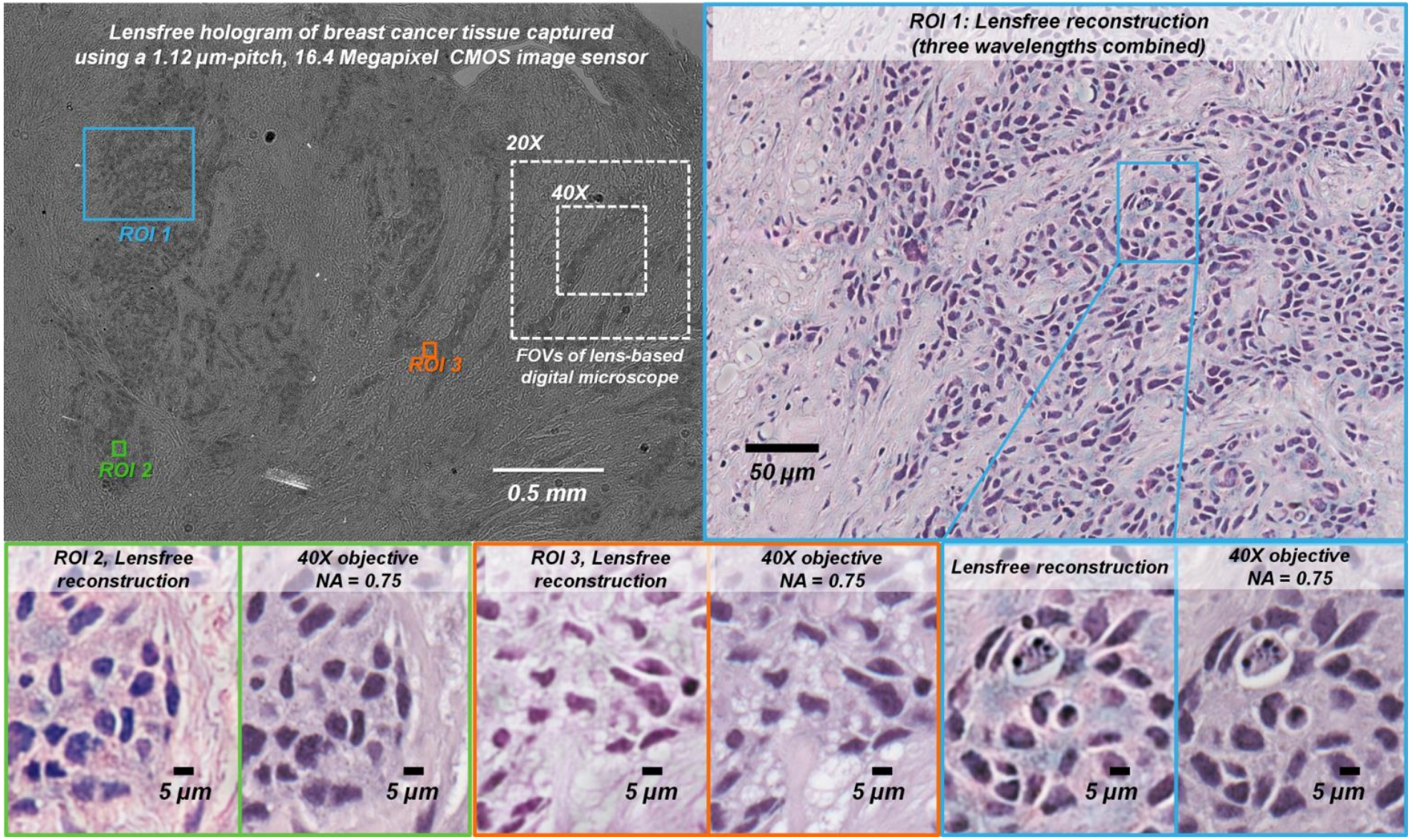
Synthetic aperture based on-chip microscopy



Nature Light: Science & Applications (2014)

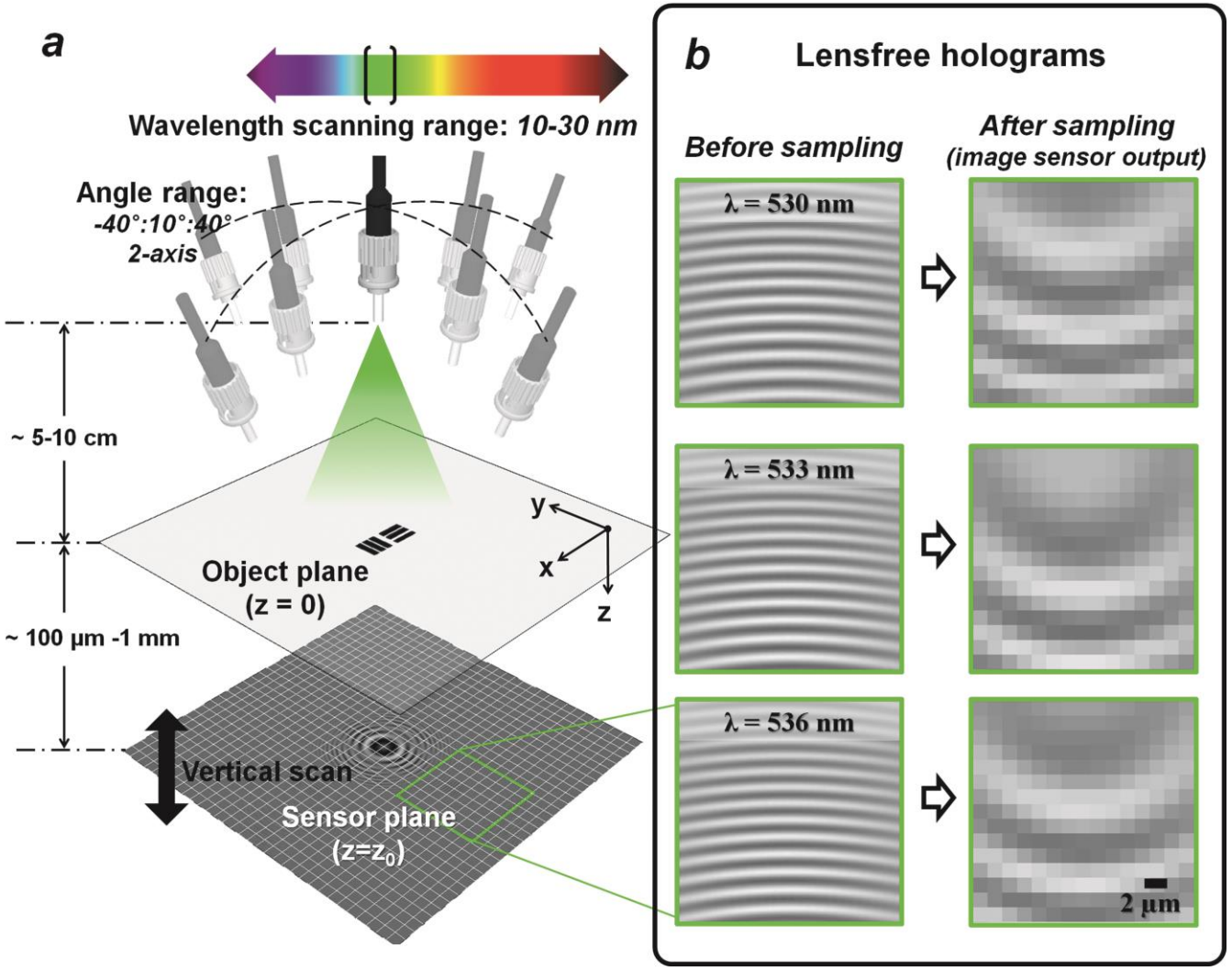


Nature Light: Science & Applications (2014)



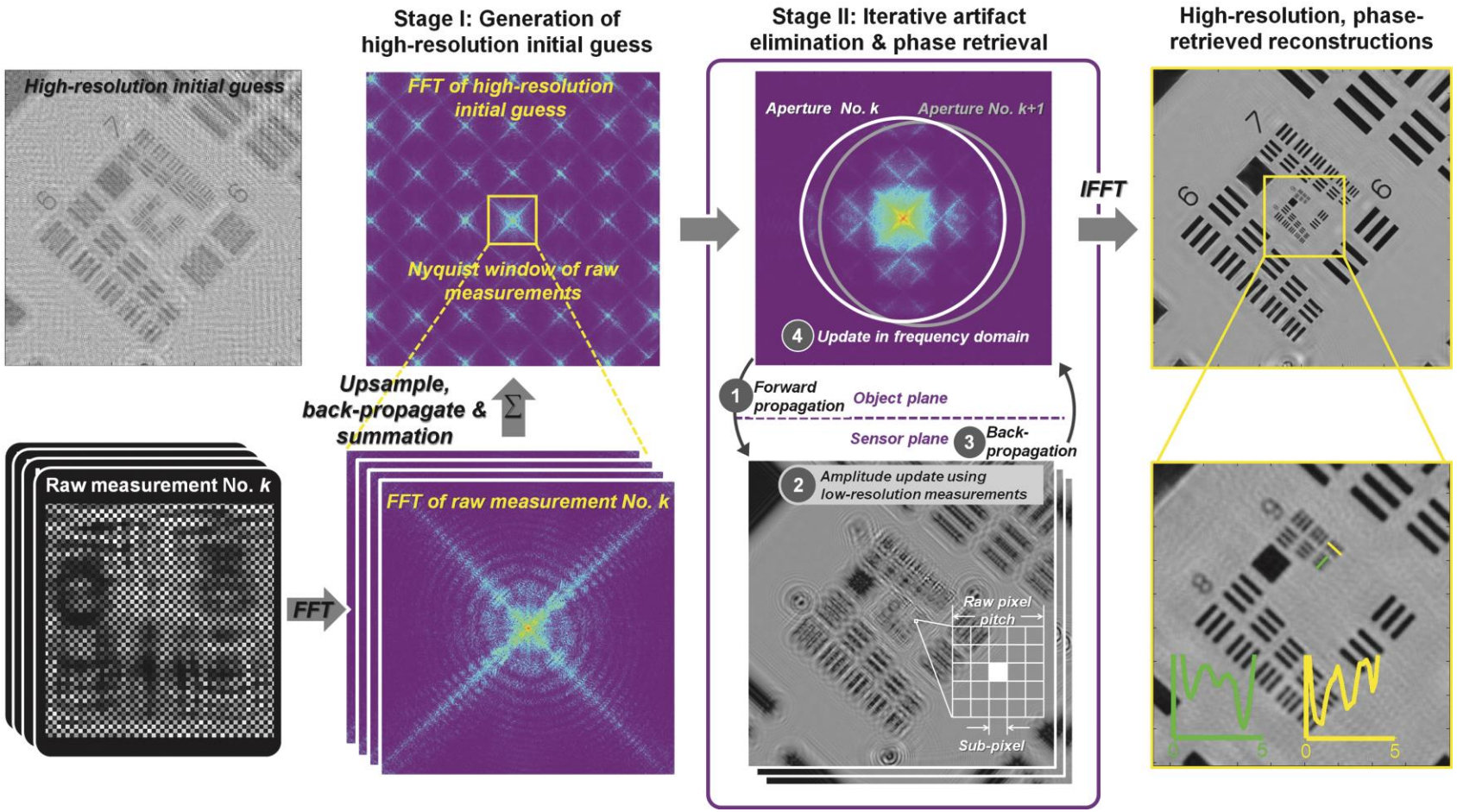
Nature Light: Science & Applications (2014)

Pixel super-resolution using wavelength scanning



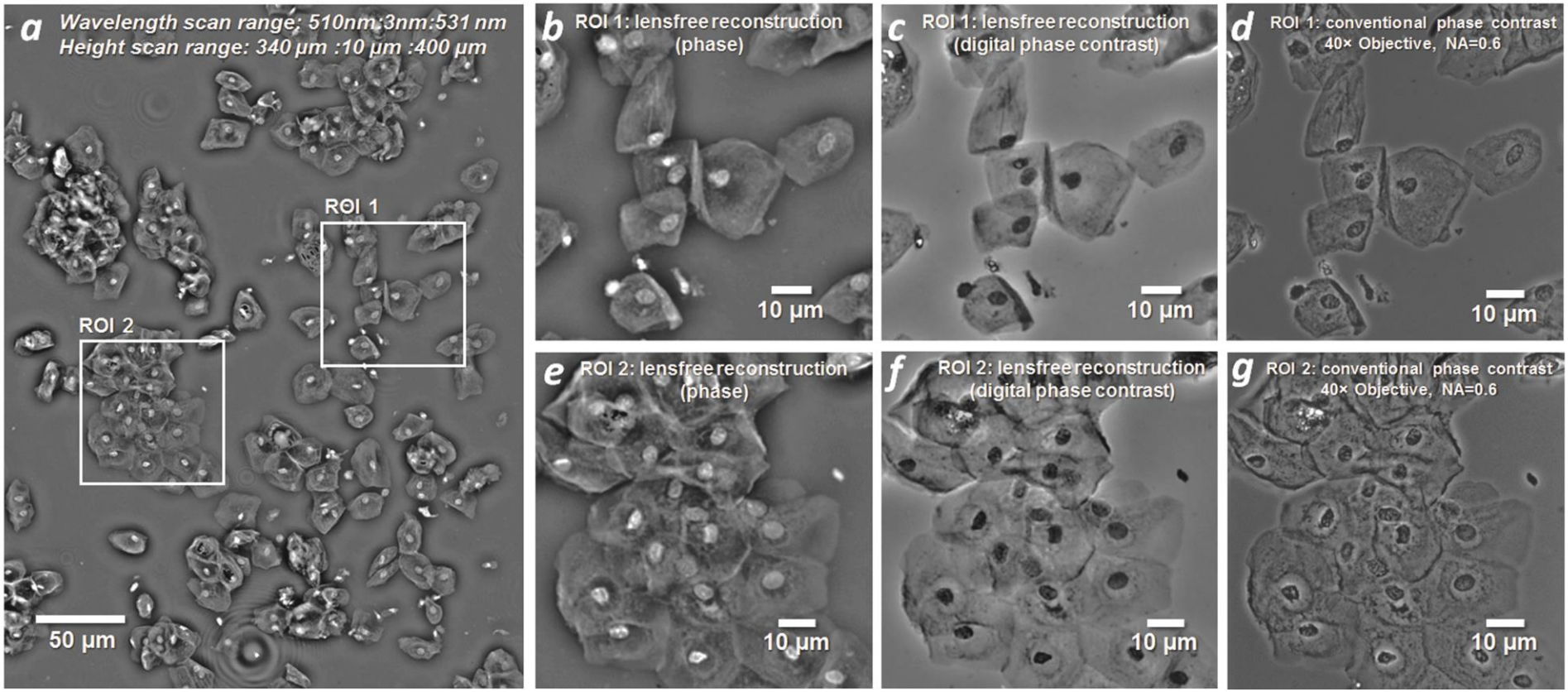
Nature Light: Science and Applications (2016)

Pixel super-resolution using wavelength scanning

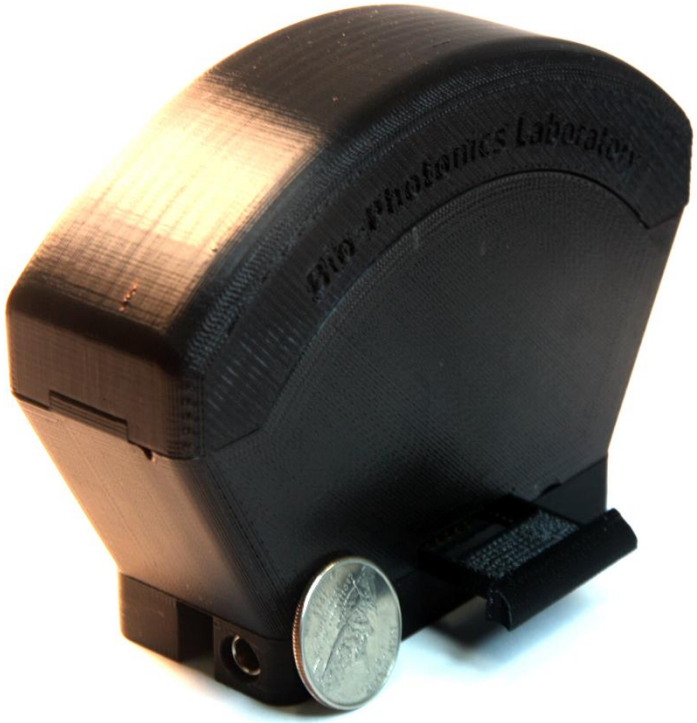


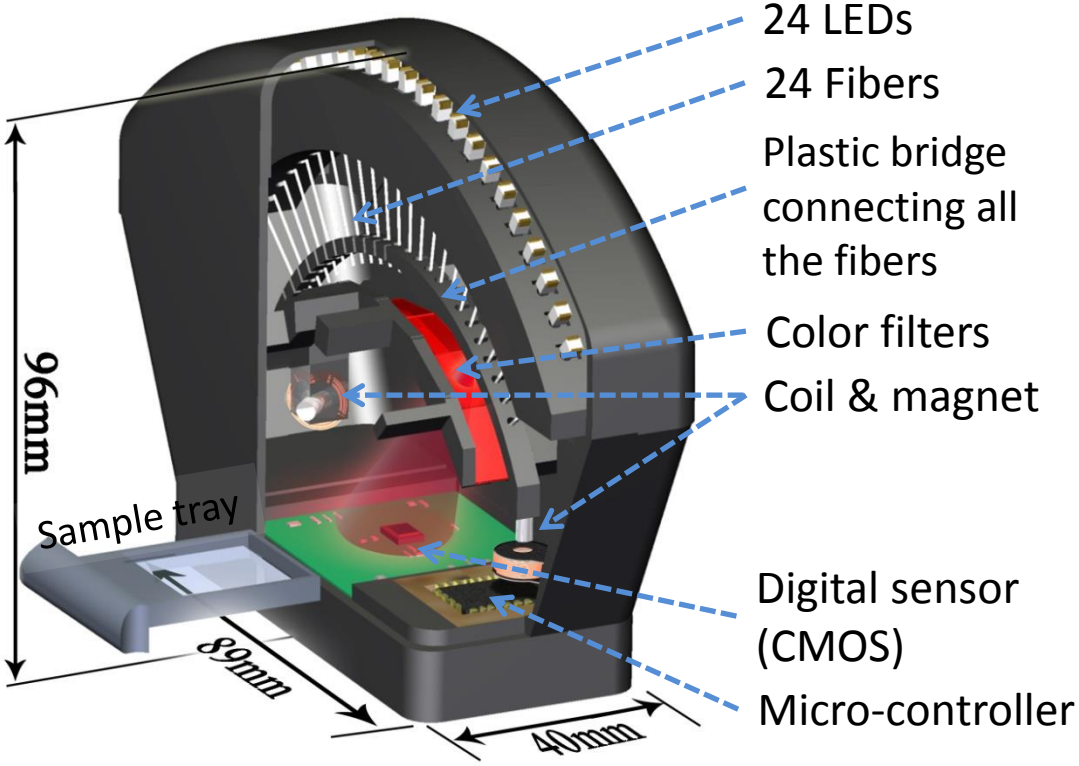
Nature Light: Science and Applications (2016)

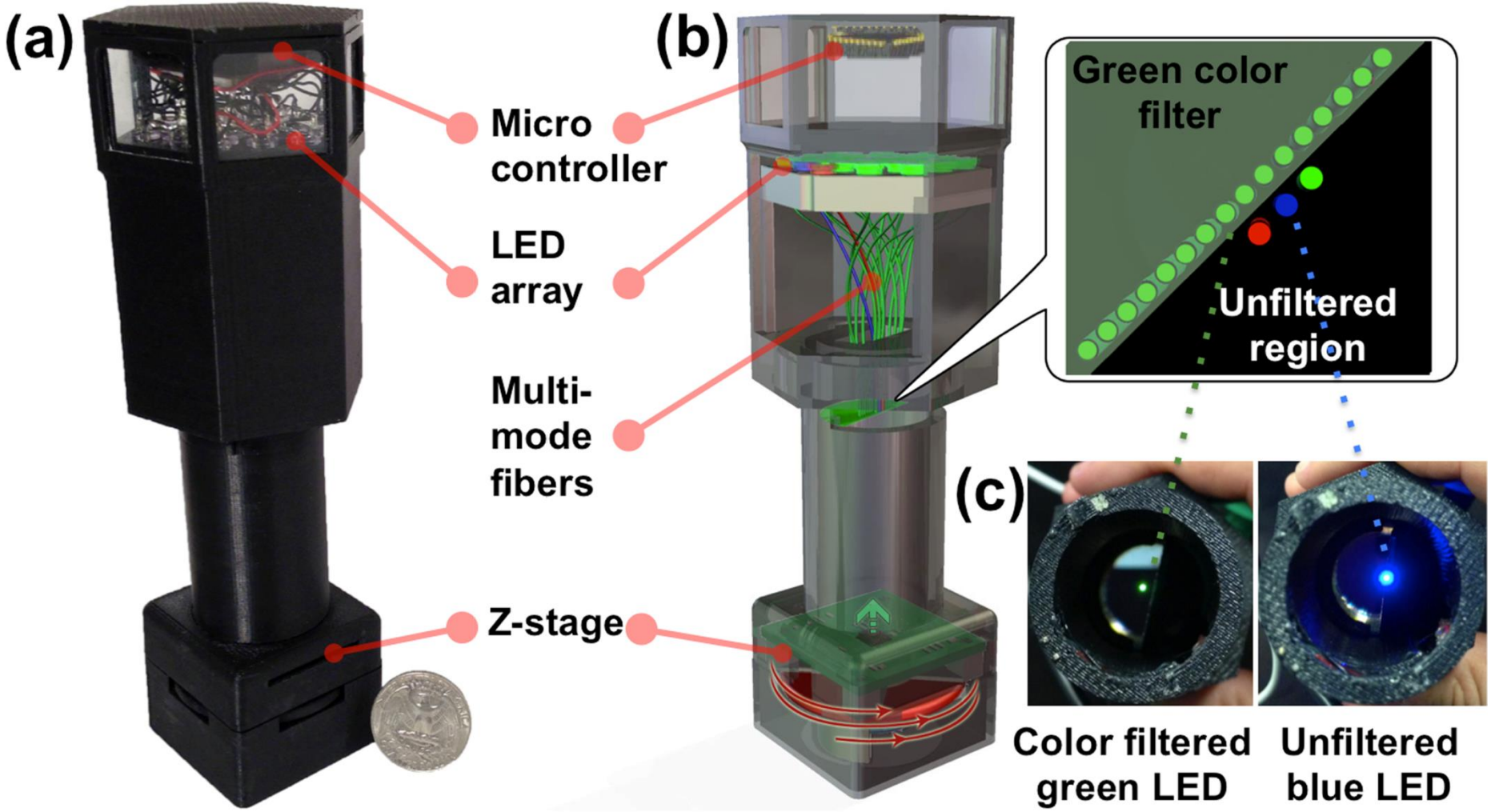
Pixel super-resolution using wavelength scanning

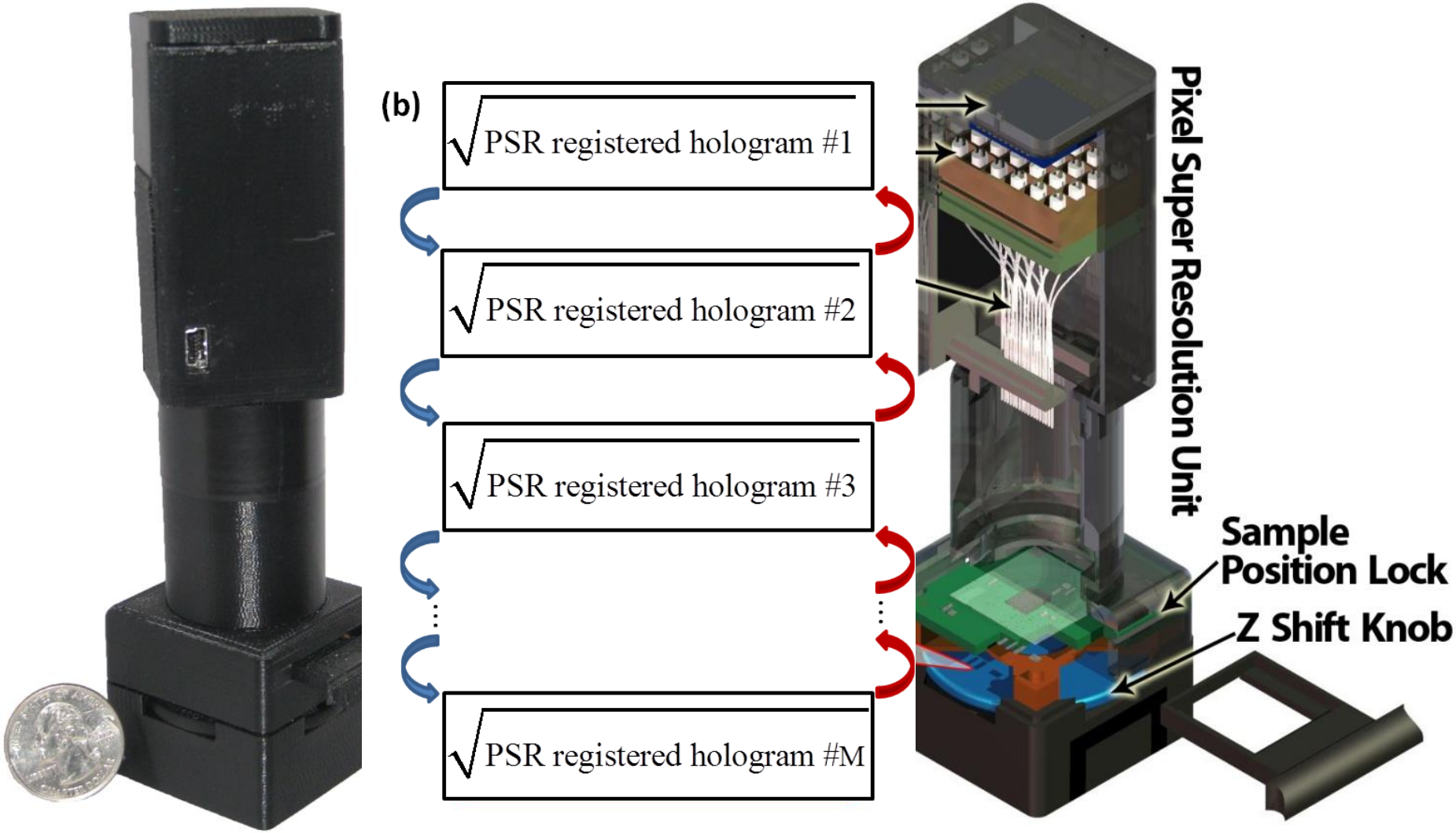


Nature Light: Science and Applications (2016)

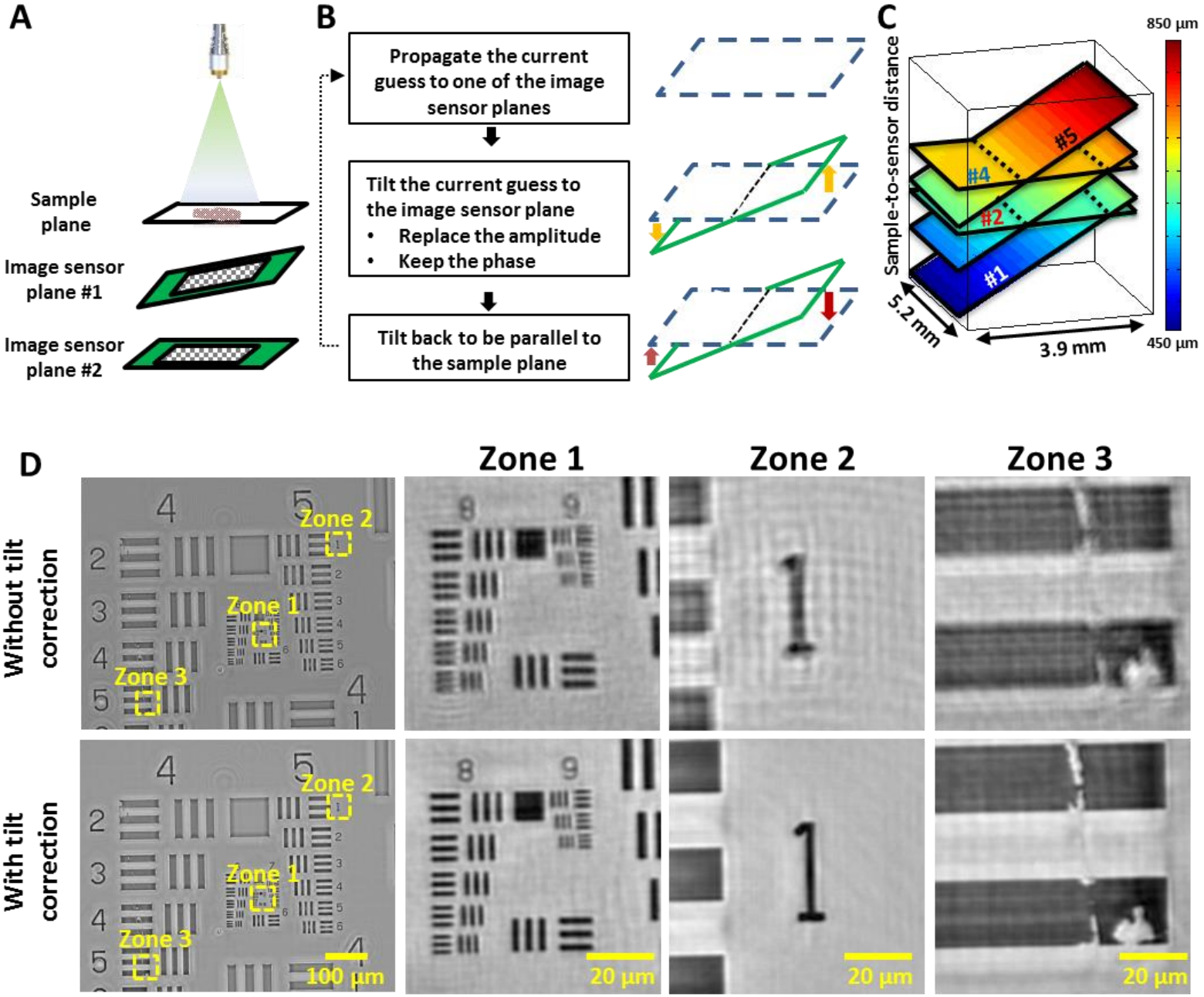

Bio-photonics Laboratory


24 LEDs
24 Fibers
Plastic bridge connecting all the fibers
Color filters
Coil & magnet
Digital sensor (CMOS)
Micro-controller
96mm
Sample tray
89mm
40mm

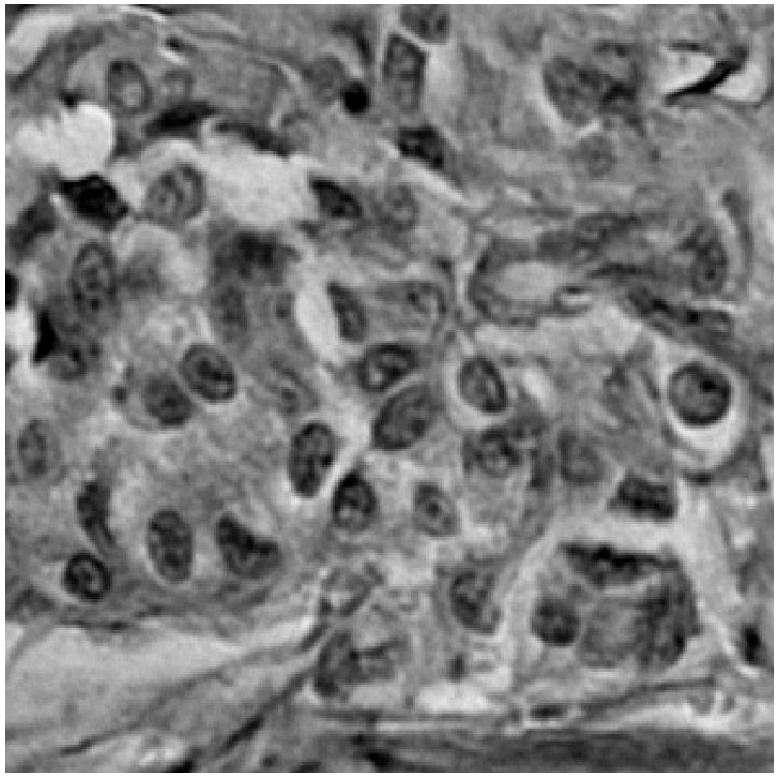

(a)
Micro controller
LED array
Multi-mode fibers
Z-stage
(b)
Green color filter
Unfiltered region
(c)
Color filtered green LED
Unfiltered blue LED

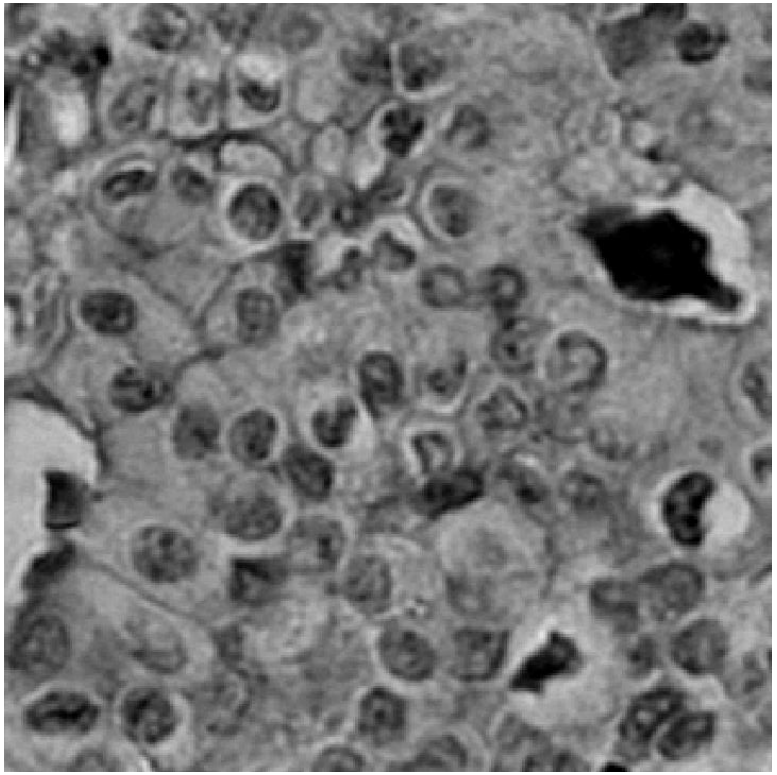

(b)
√PSR registered hologram #1
√PSR registered hologram #2
√PSR registered hologram #3
√PSR registered hologram #M
Pixel Super Resolution Unit
Sample Position Lock
Z Shift Knob

Tilt corrections through field rotations



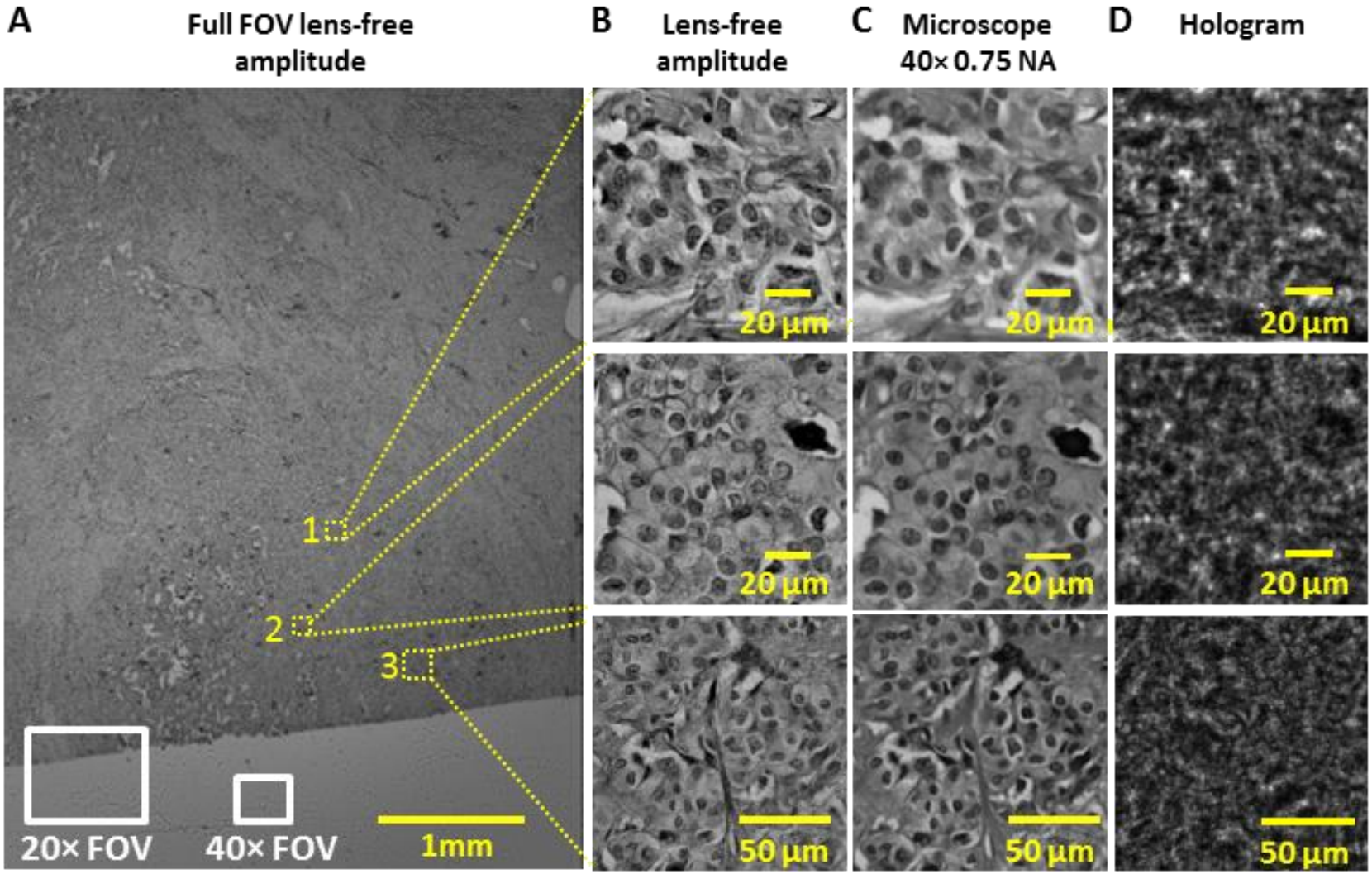
Lensfree imaging of histopathology slides



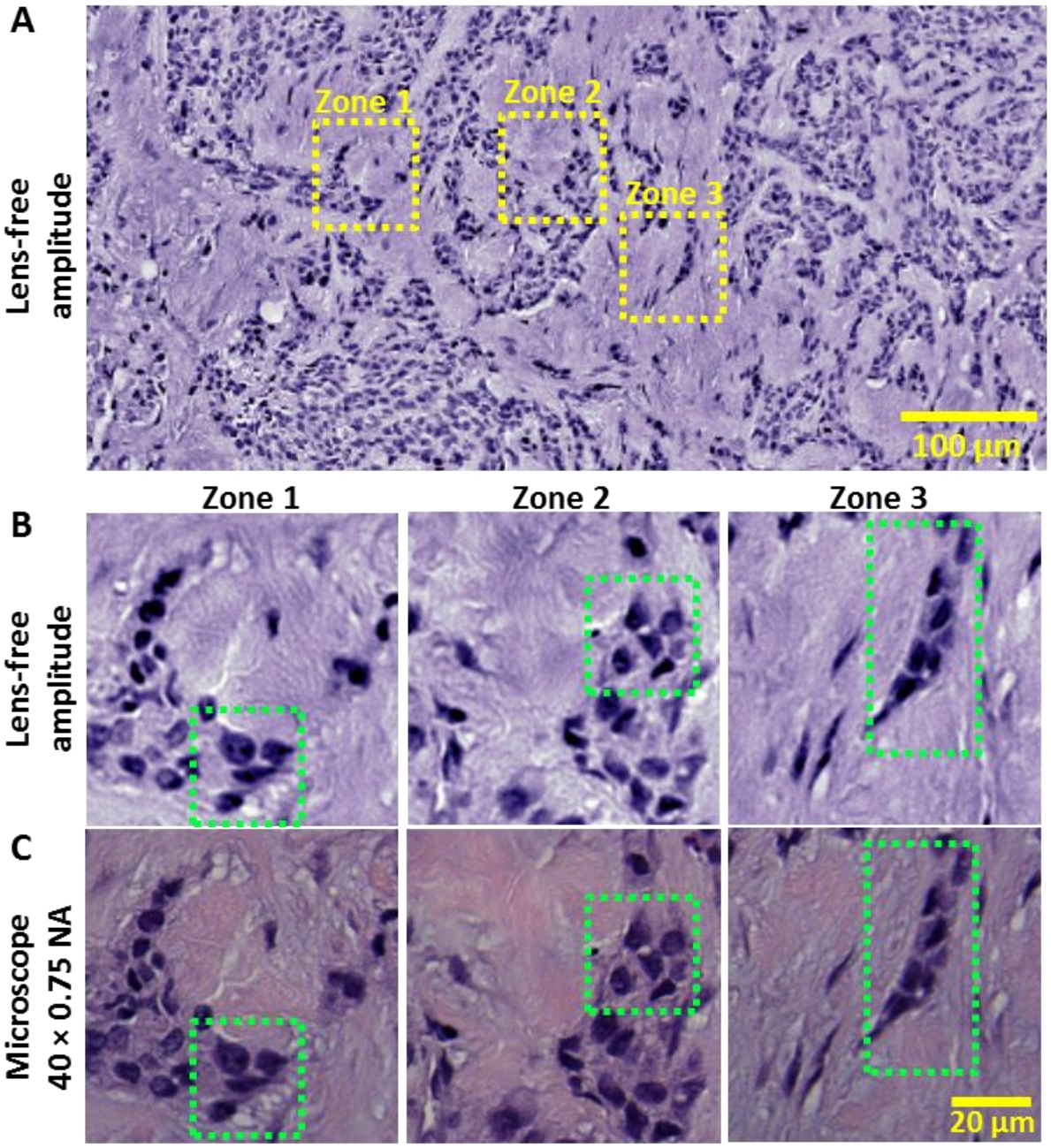


Breast Cancer Tissue

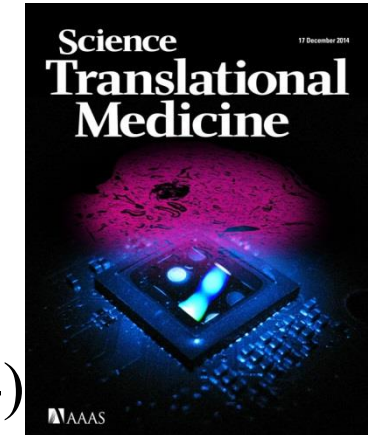
Lensfree imaging of histopathology slides

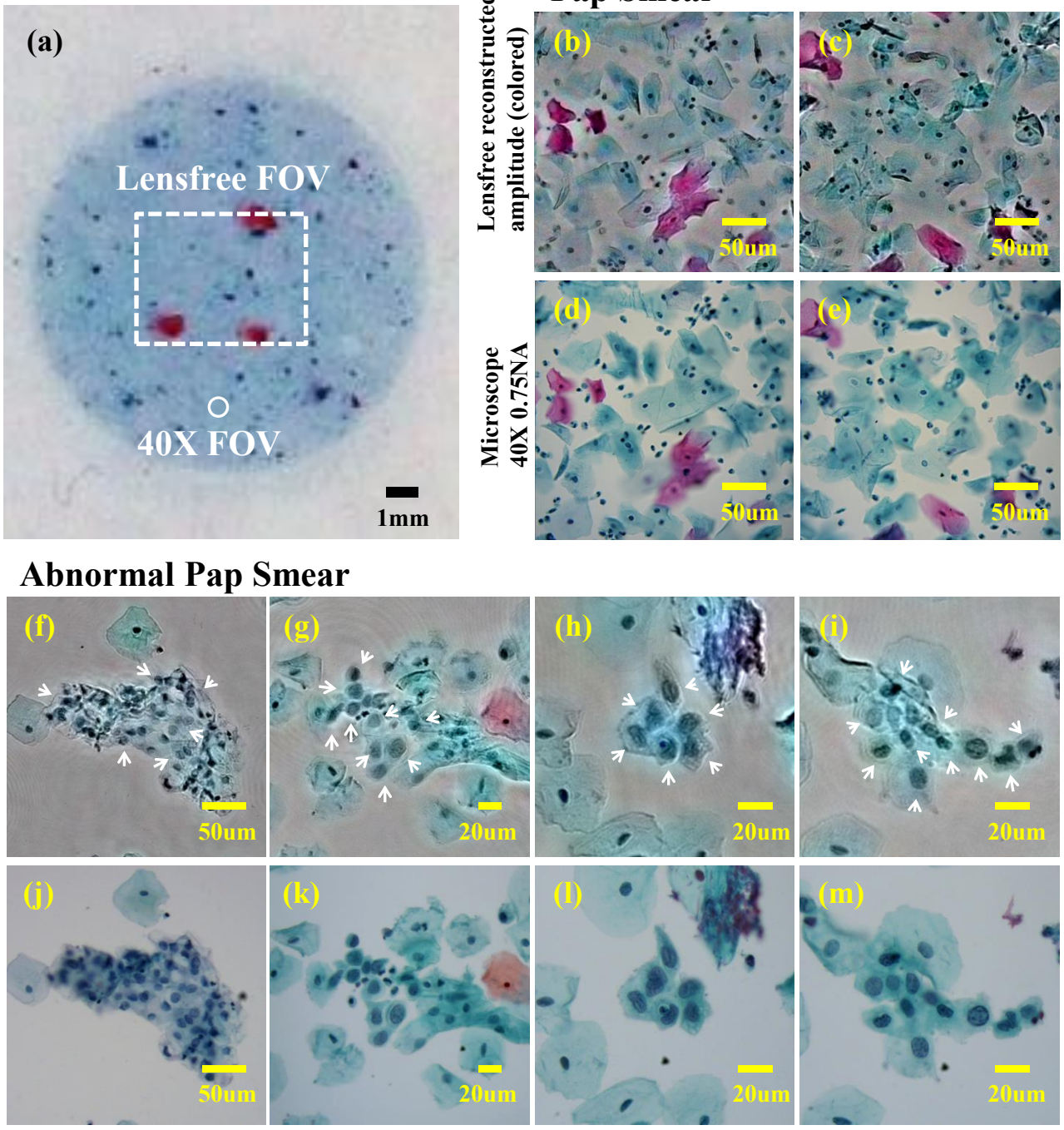


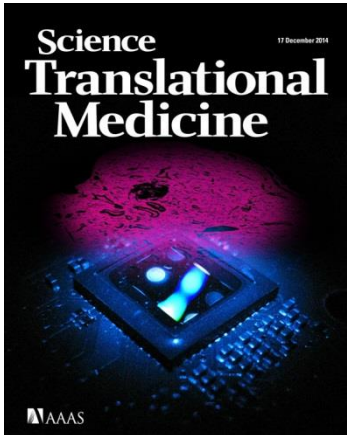
Science Translational Medicine - AAAS (2014)

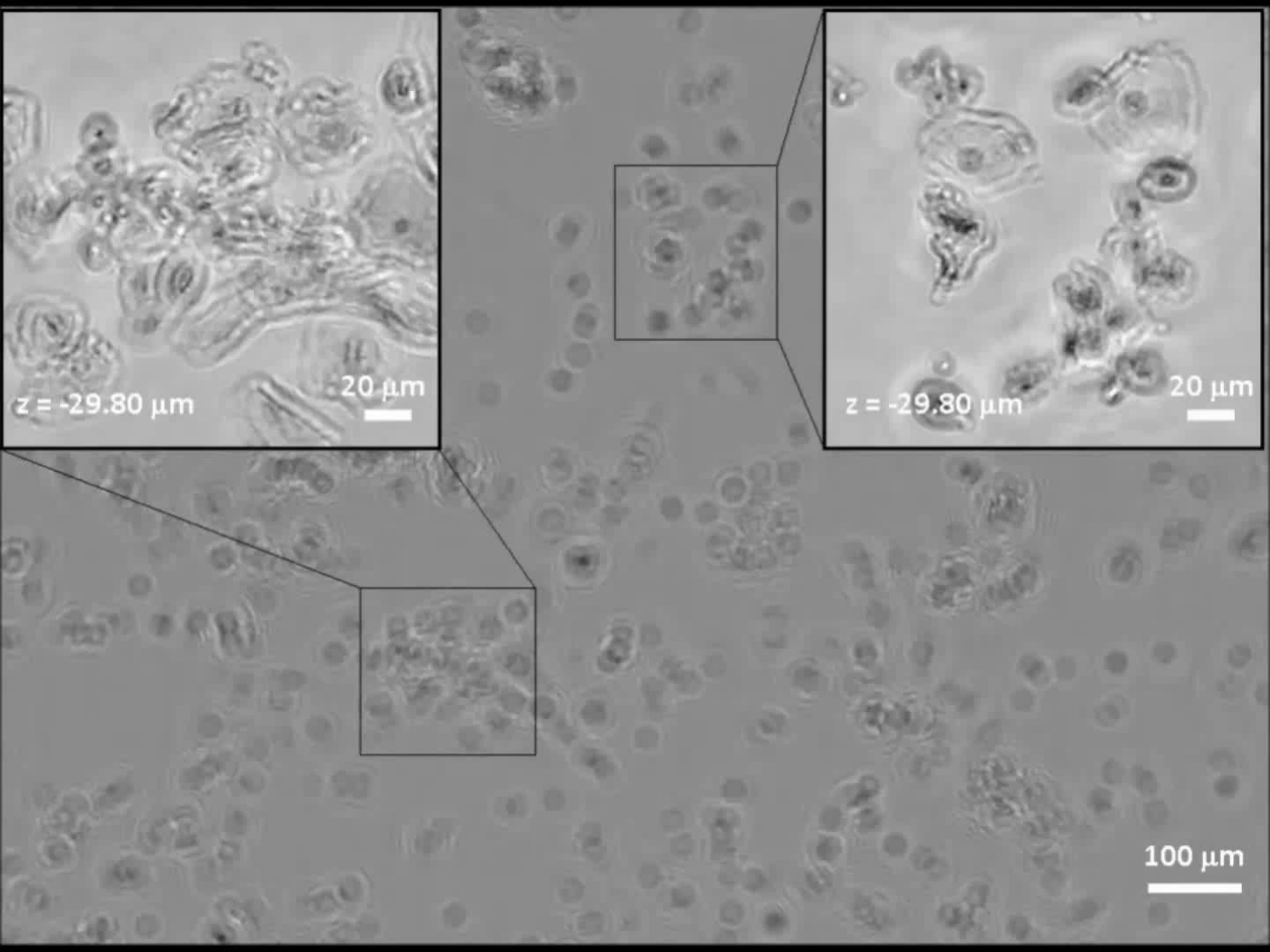


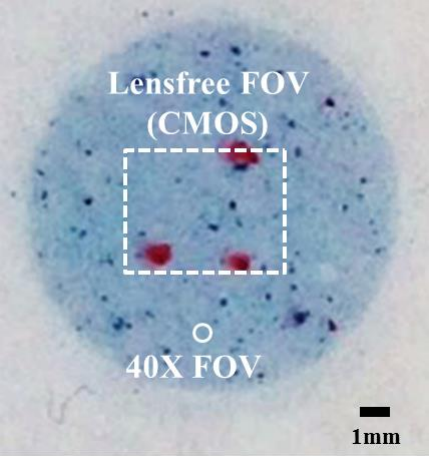
Science Translational Medicine - AAAS (2014)

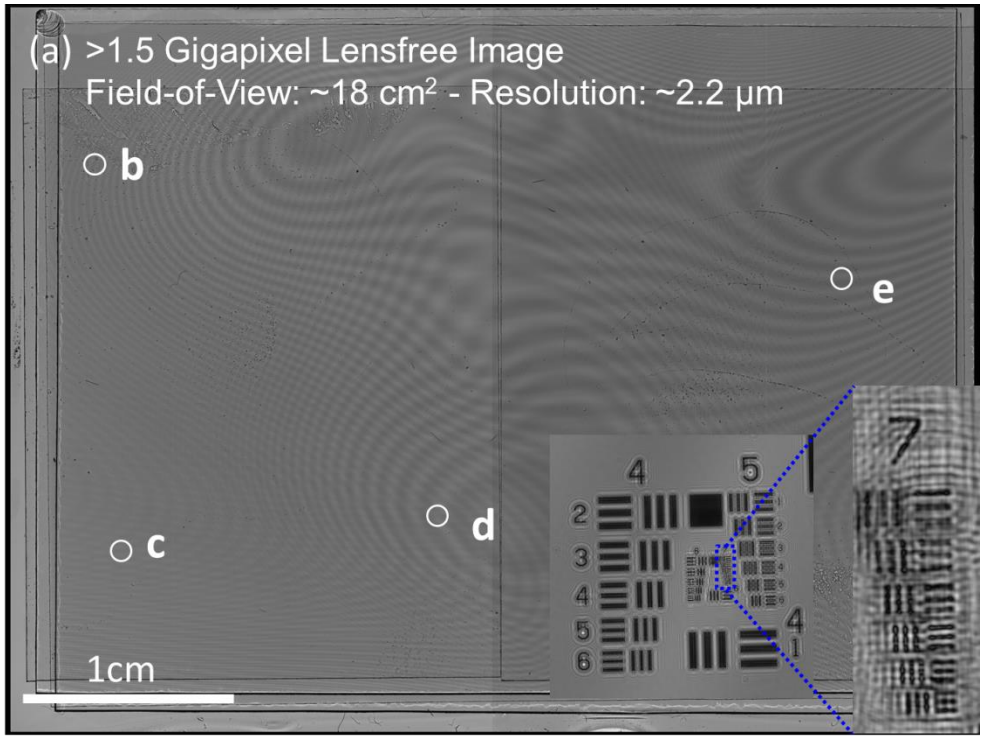


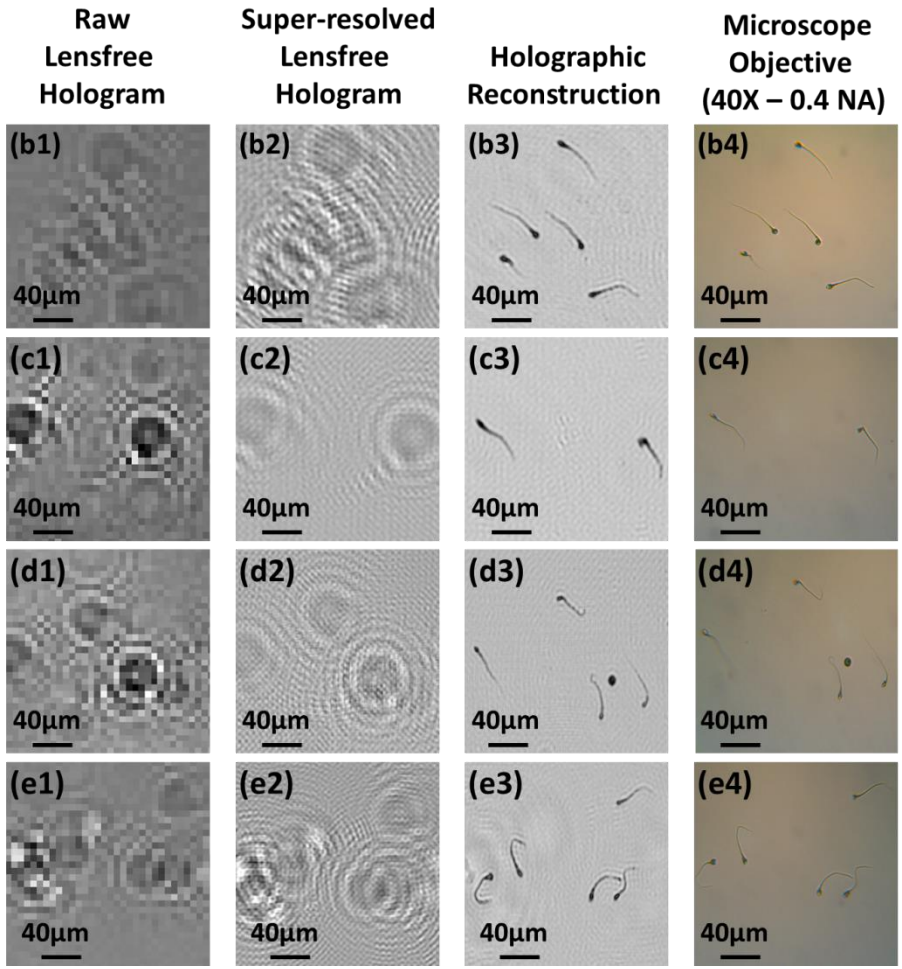

Pap Smear
(a)
Lensfree FOV
40X FOV
1mm
Lensfree reconstructed amplitude (colored)
Microscope 40X 0.75NA
(b)
(c)
(d)
(e)
50um
Abnormal Pap Smear
Lensfree reconstructed amplitude
Microscope 40X 0.75NA
(f)
(g)
(h)
(i)
(j)
(k)
(l)
(m)
50um
20um


Science
Translational
Medicine
17 December 2014
AAAS


z = -29.80 µm
20 µm
z = -29.80 µm
20 µm
100 µm



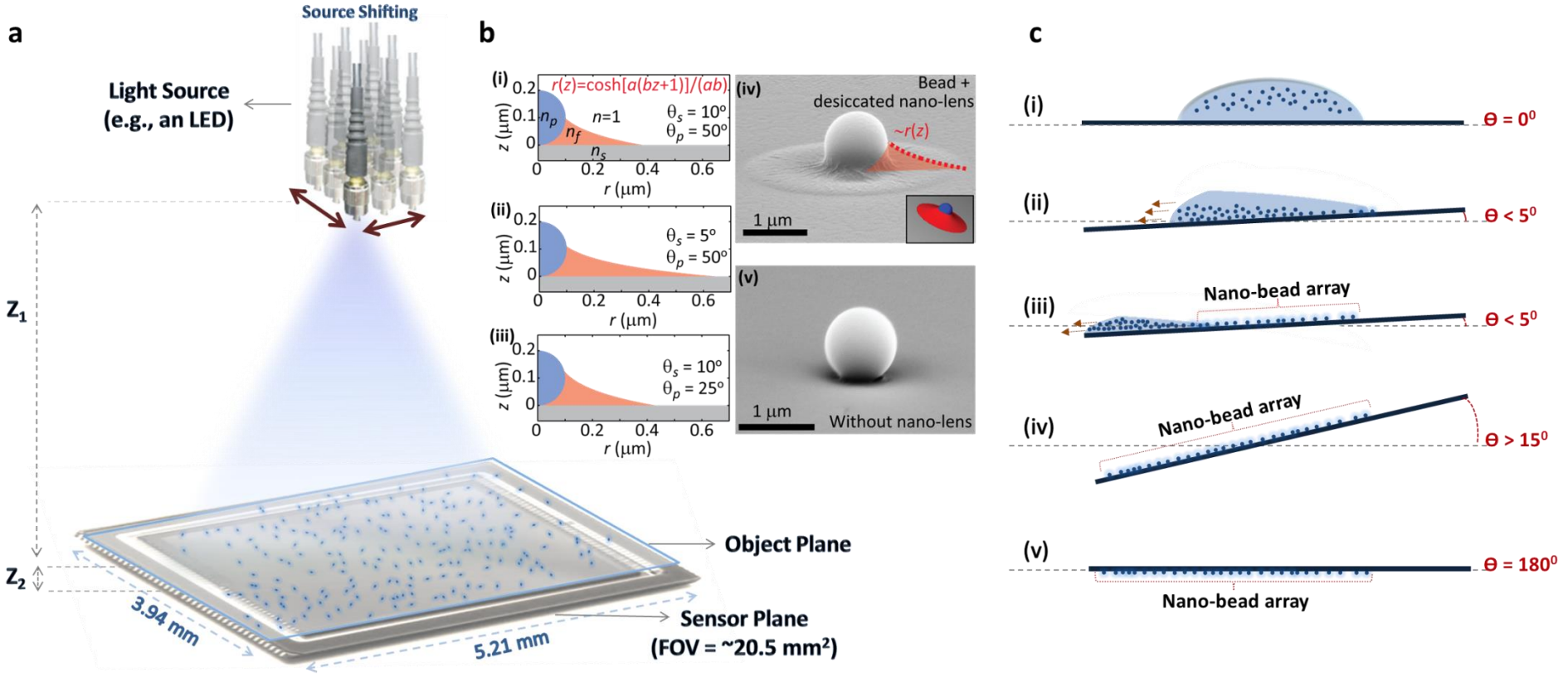




Field-of-view
Sample Volume

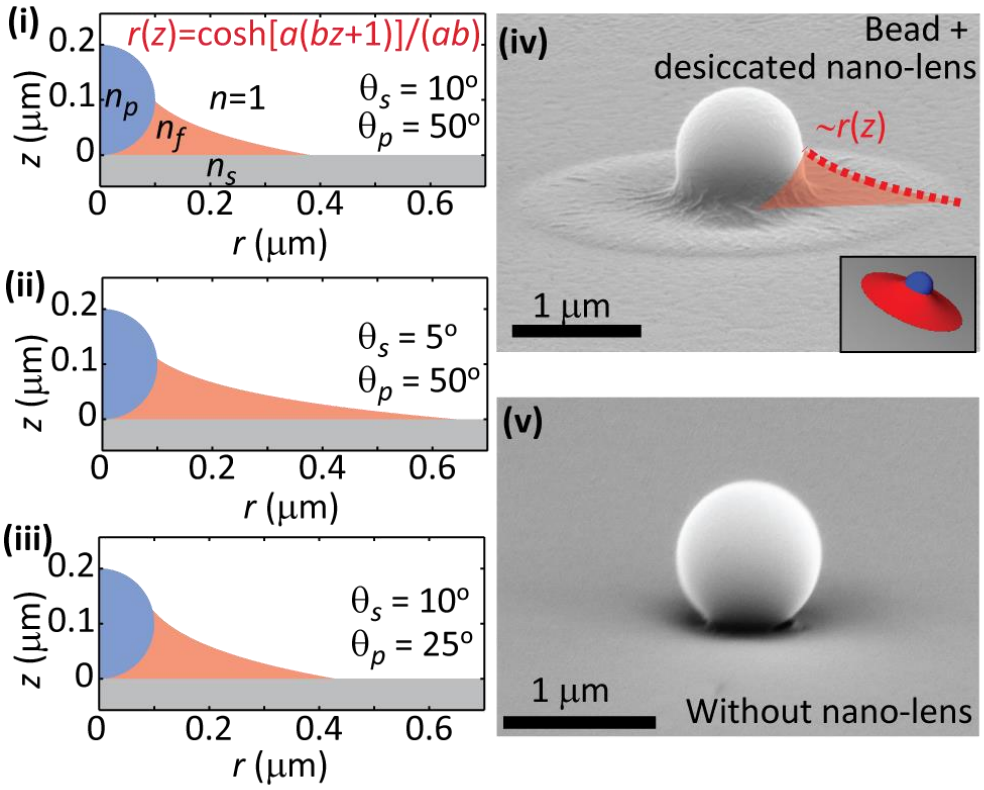
Resolution

Wide-field on-chip imaging of single viruses and nano-particles using self-assembled nano-lenses

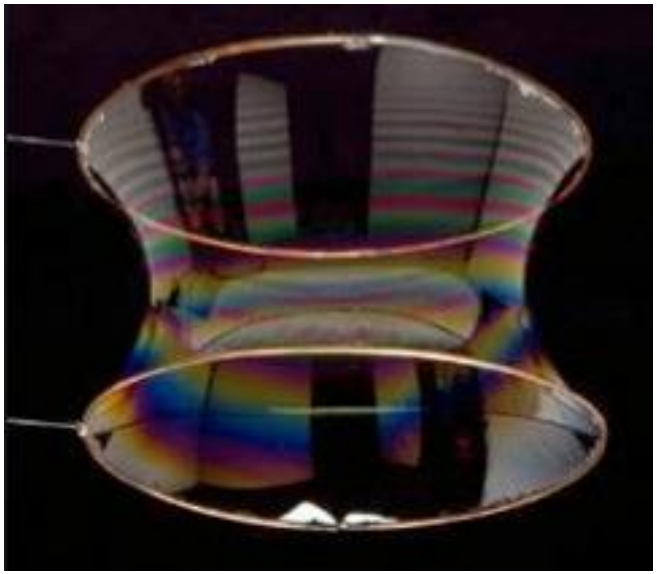


Nature Photonics (2013)

Nano-Catenoid Lenses for Imaging of Single Nano-particles



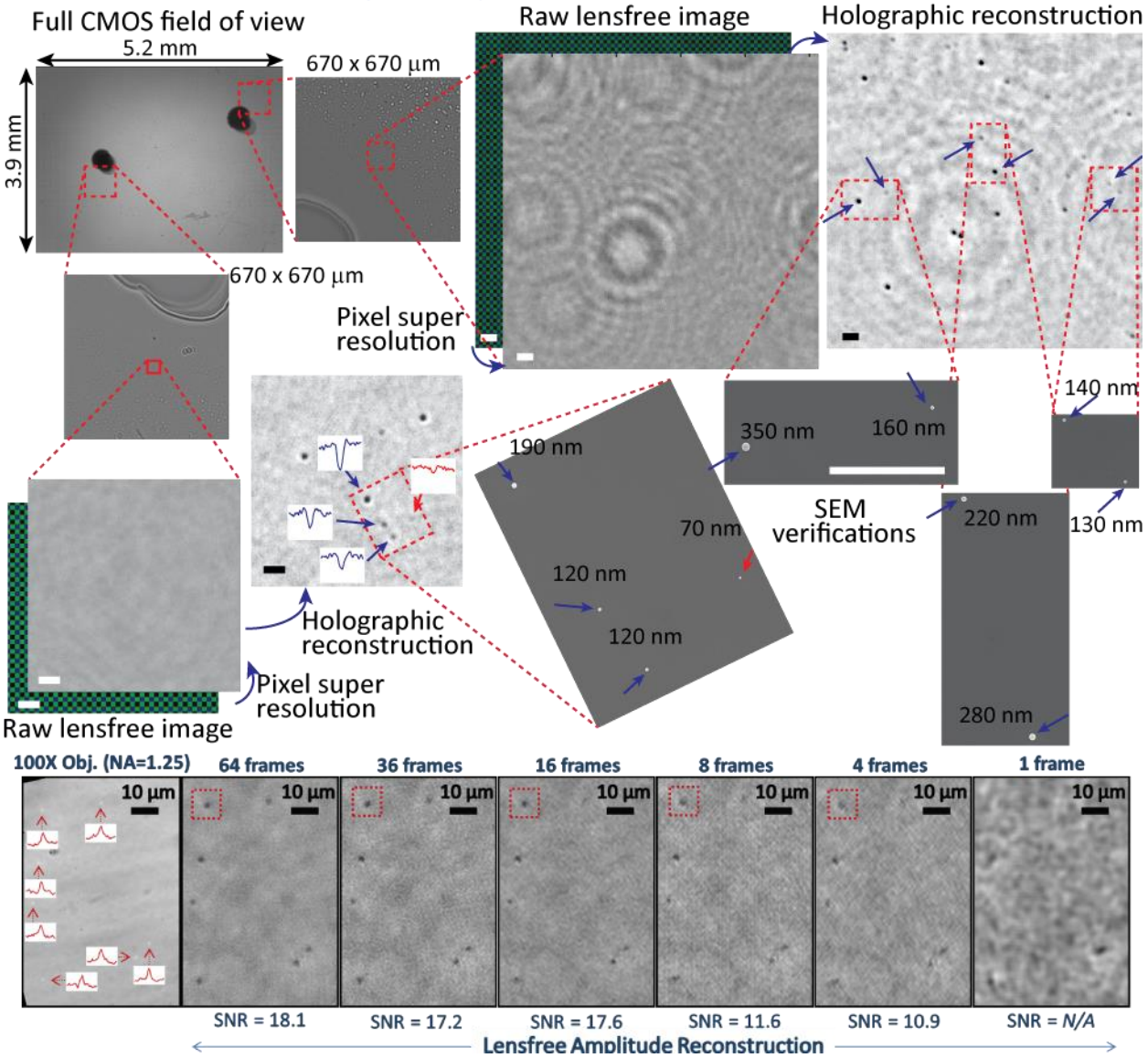
Nano-catenoid lenses



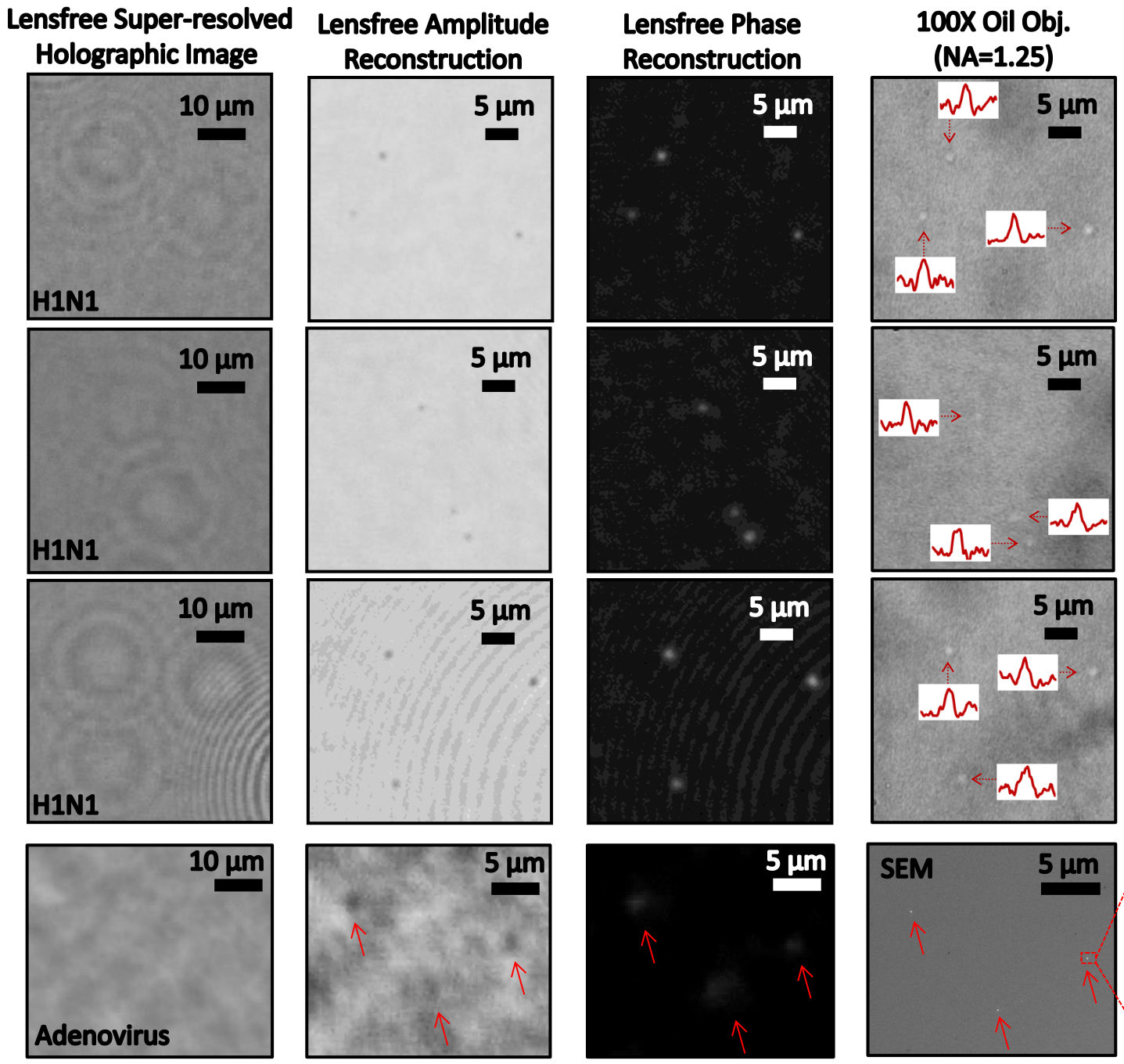
Two Rings in Soap Solution Form a ***Catenoid*** – i.e., a ***Minimal Surface*** that is self-assembled to have Zero Mean Curvature.
(L. Euler - 1744)

Nature Photonics (2013)

Wide-field on-chip imaging of single viruses and nano-particles using self-assembled nano-lenses

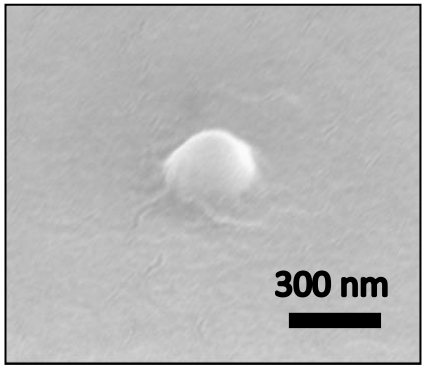


Nature Photonics (2013)

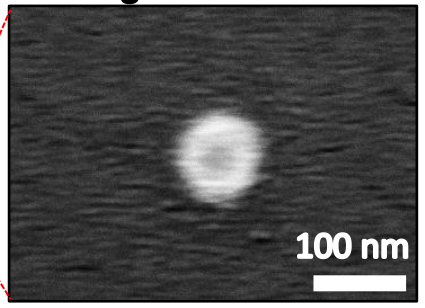


Nature Photonics (2013)

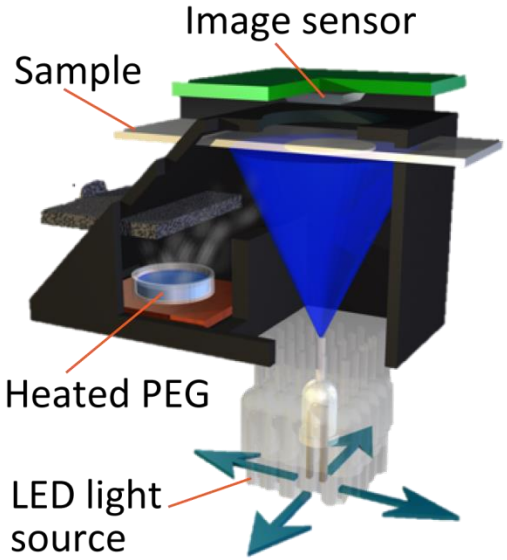
Scanning Electron Microscope (SEM) Image of a single H1N1 virus



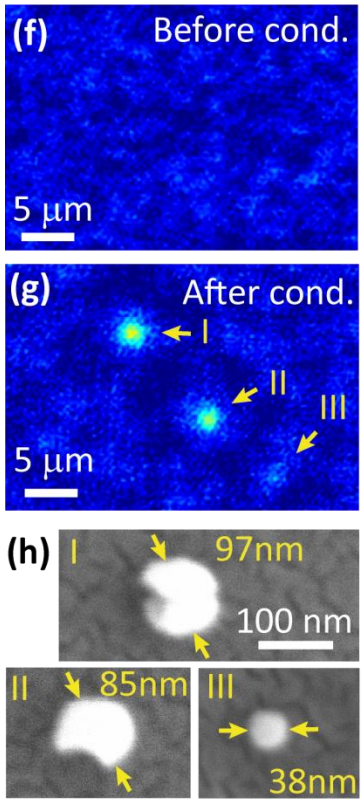
SEM Image of a single adenovirus



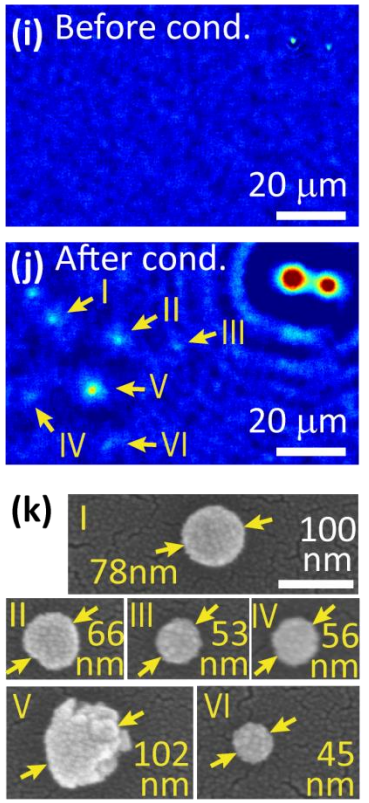
Vapor condensed Tunable Nano-lenses



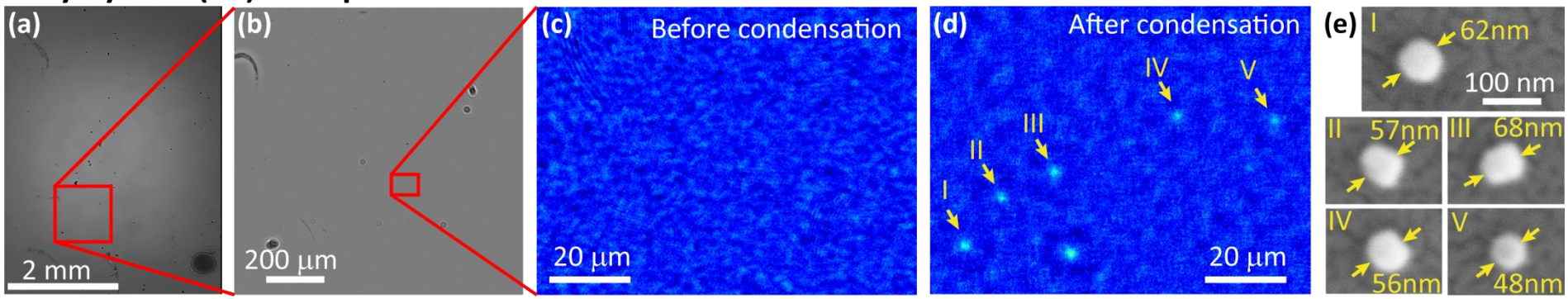
PS nanoparticles:



Au nanoparticles:

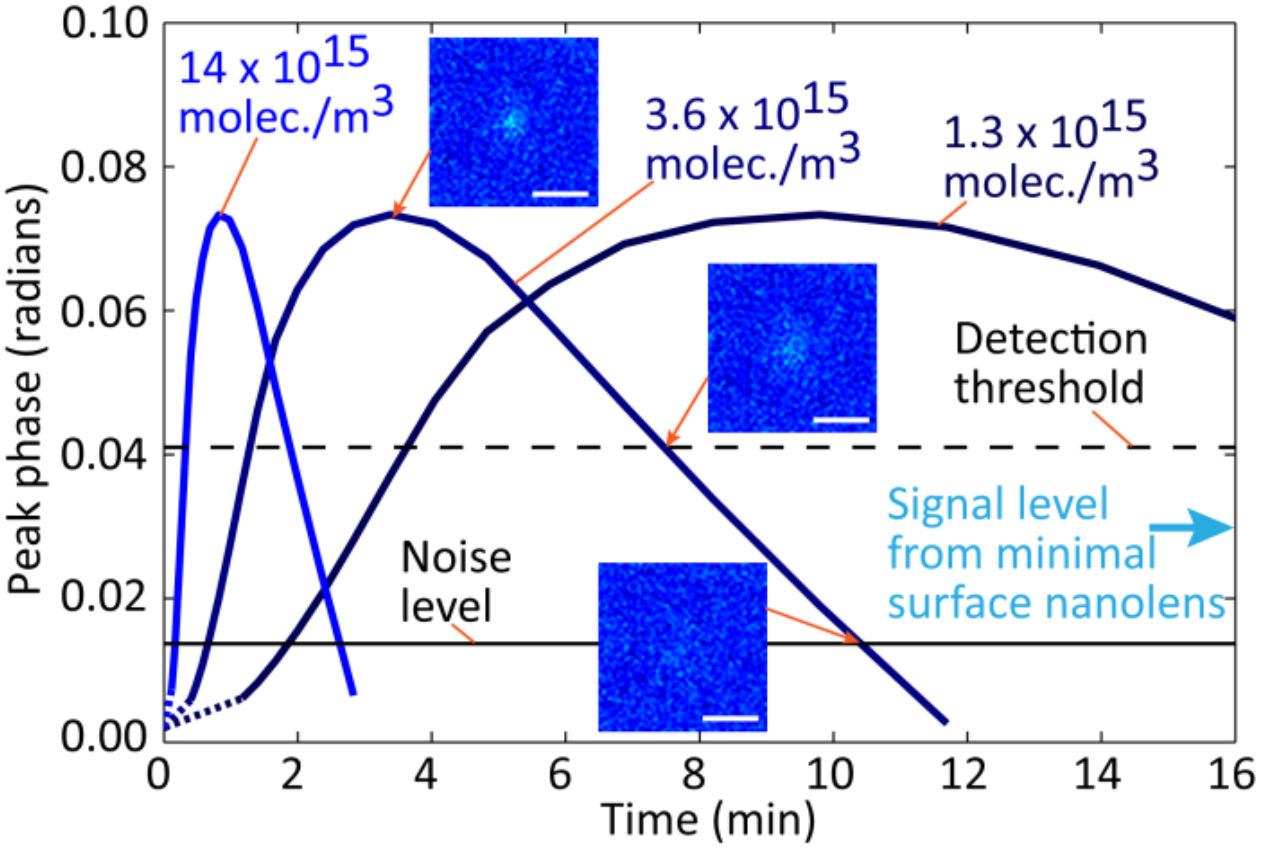


Polystyrene (PS) nanoparticles:

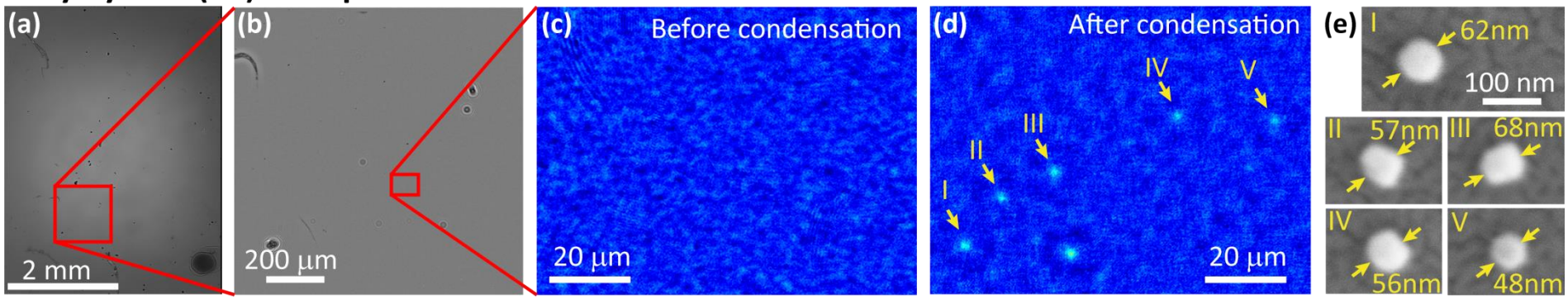


ACS Nano (2014)

Vapor condensed Tunable Nano-lenses

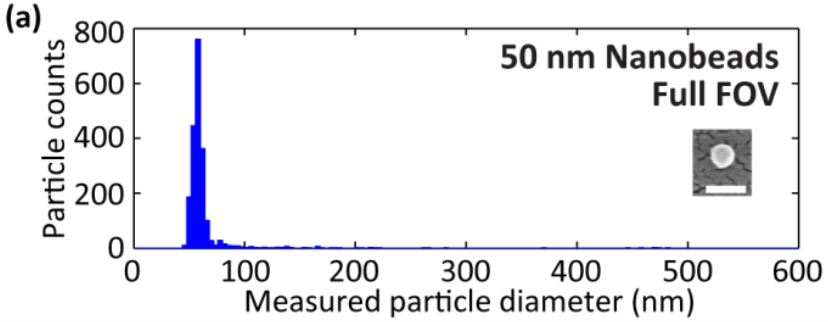


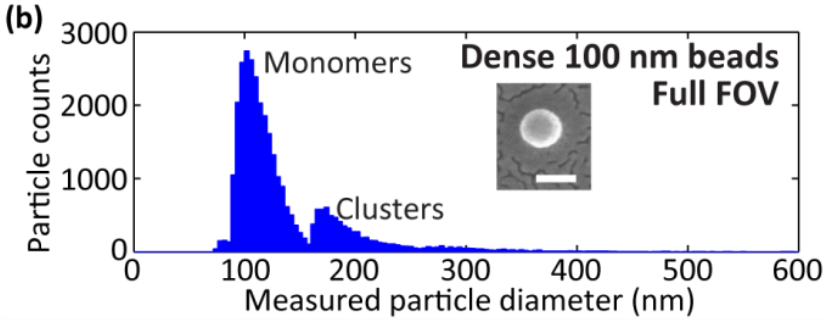
Polystyrene (PS) nanoparticles:

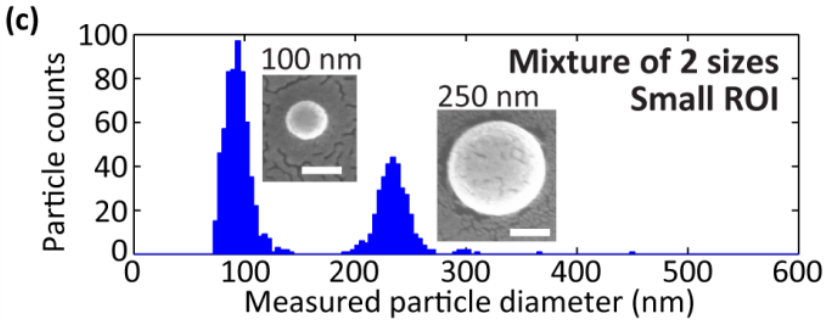


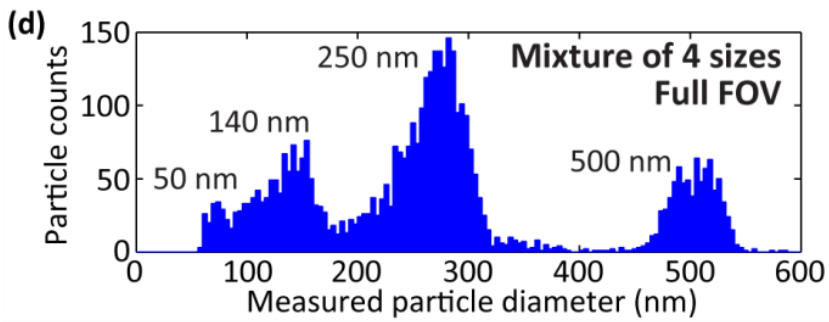
ACS Nano (2014)

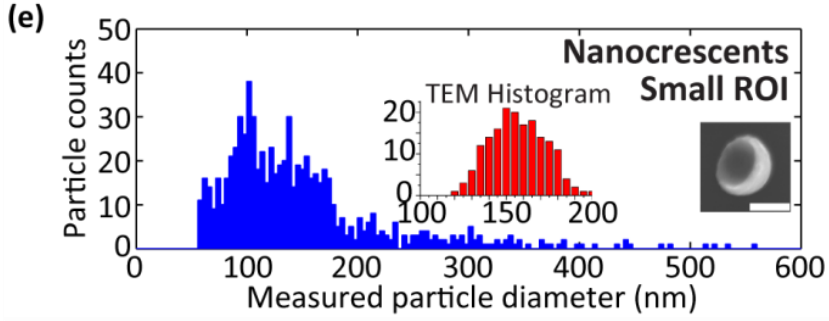
Vapor condensed Tunable Nano-lenses

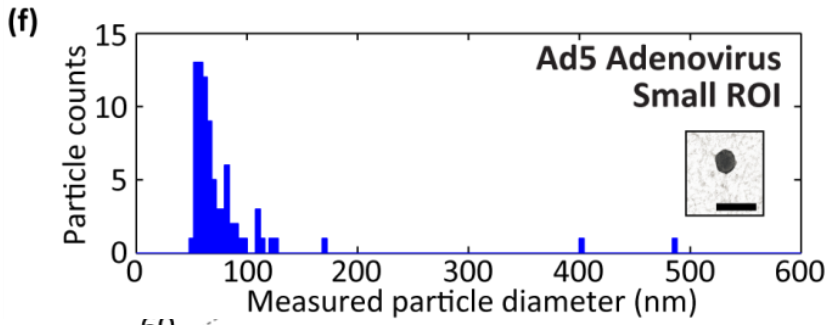




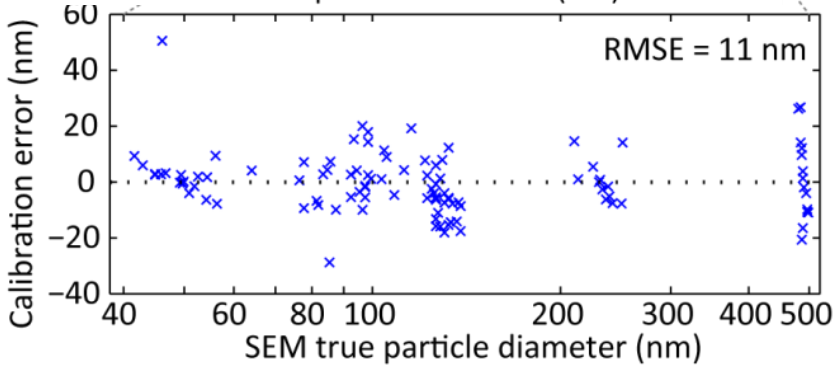


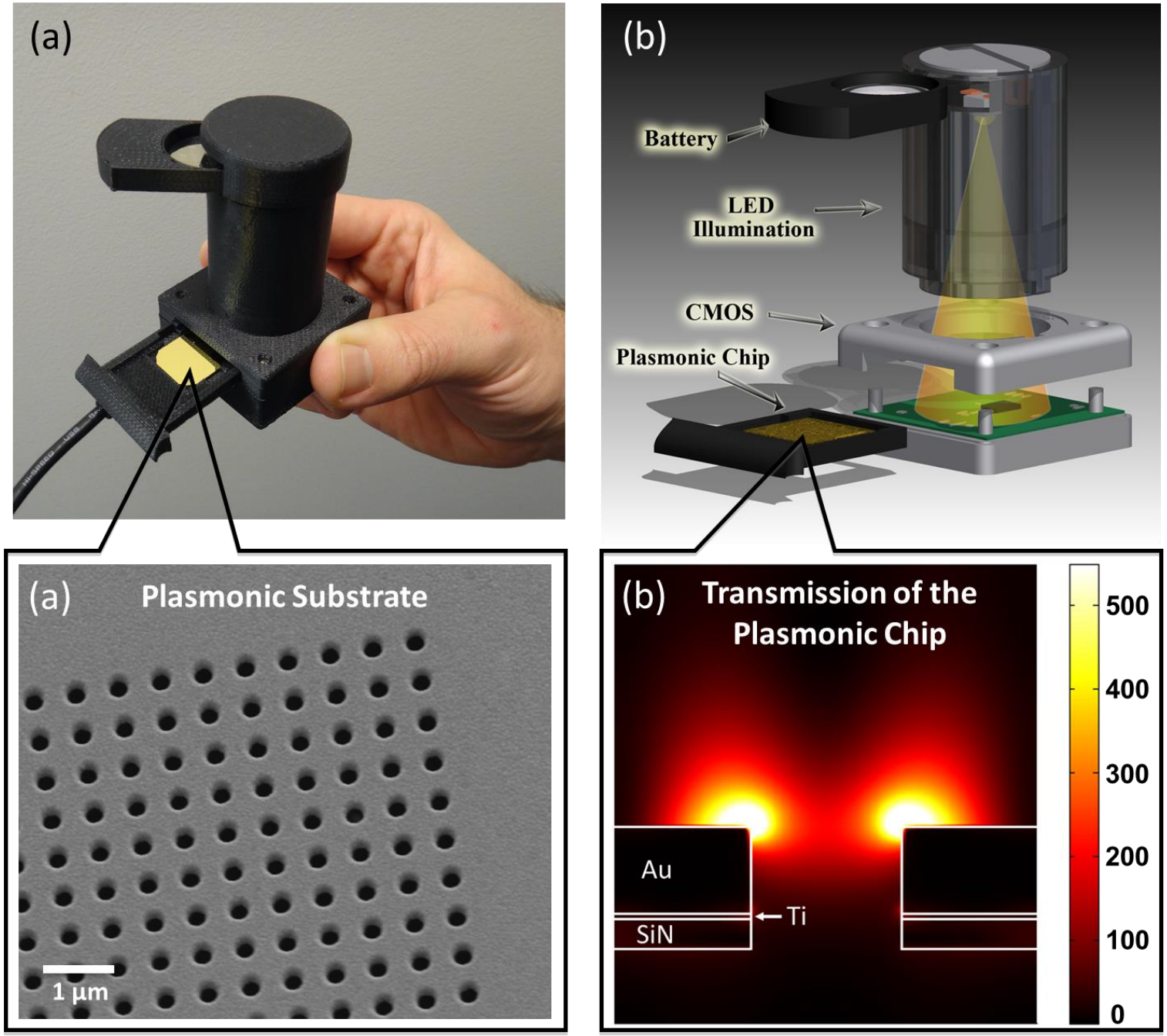




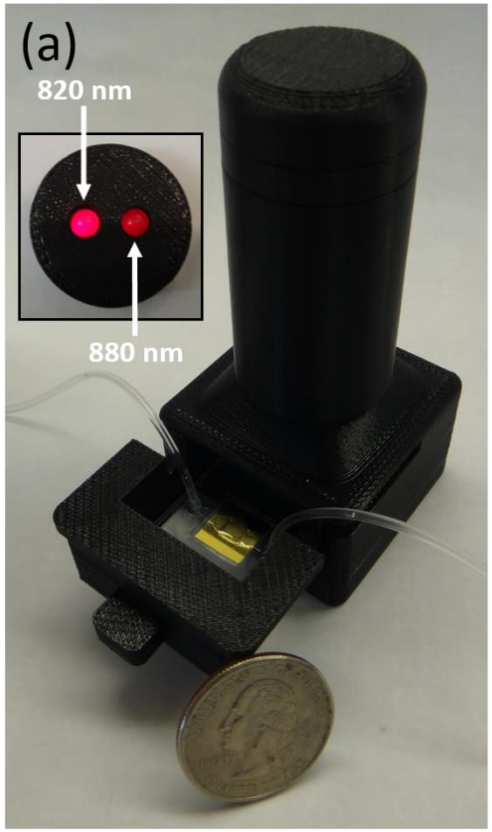


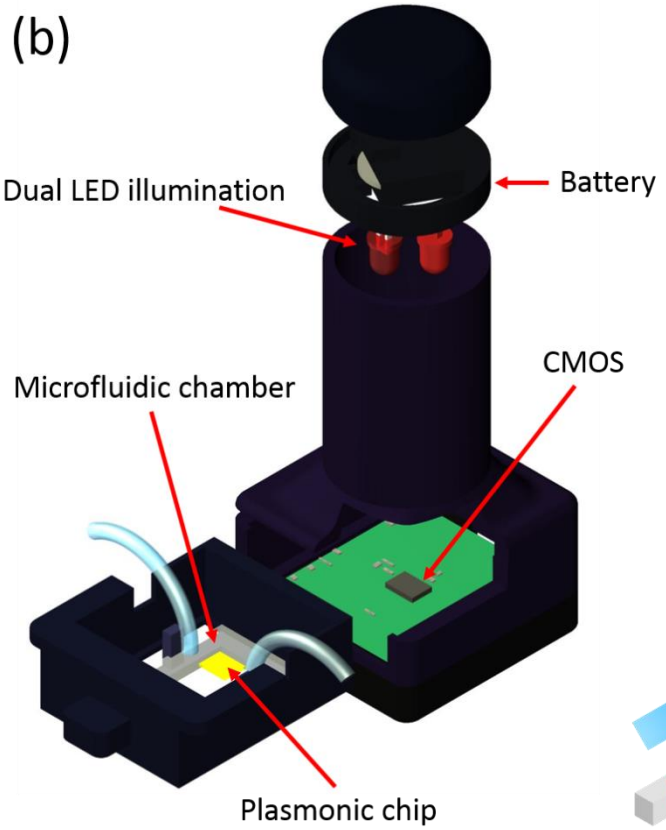
Sizing accuracy
~11 nm

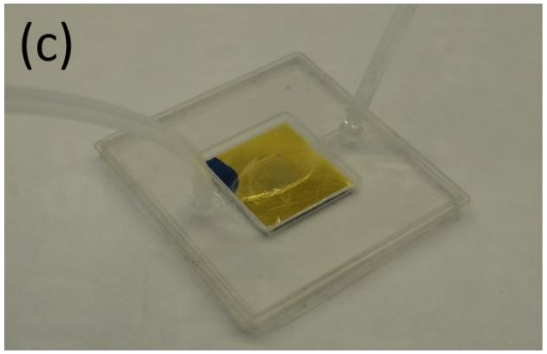


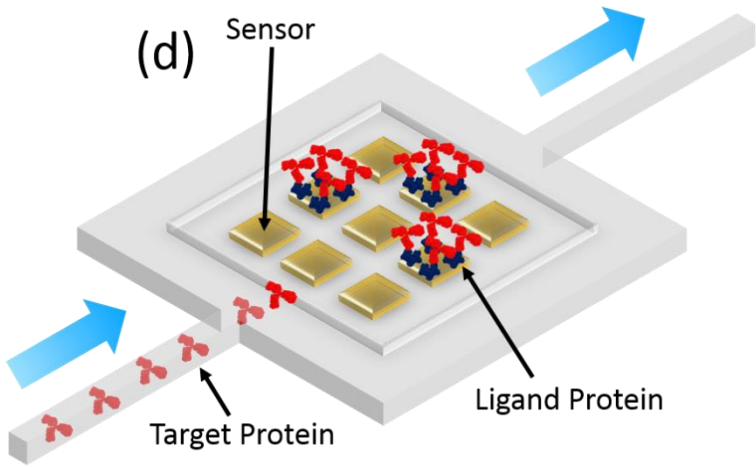


Light: Science and Applications – NPG (2014)

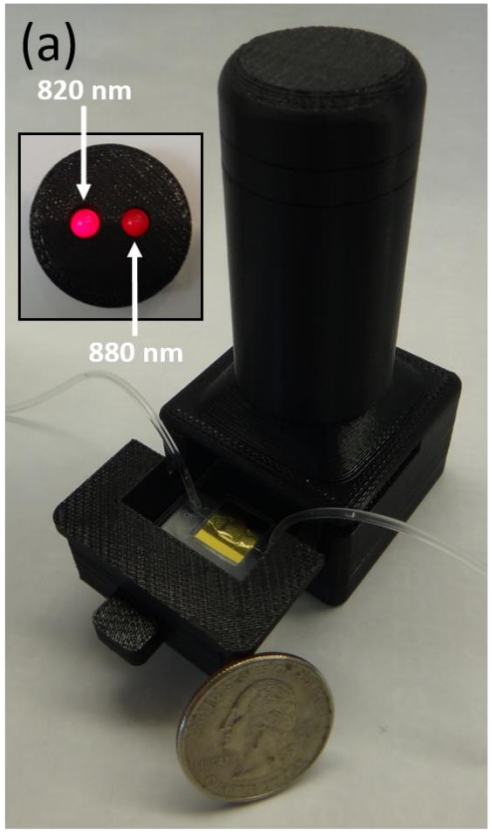


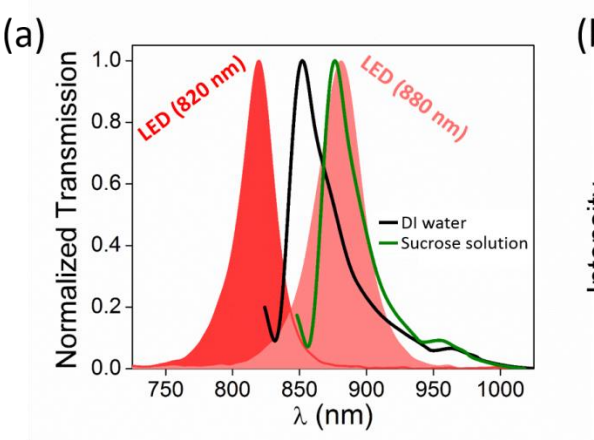


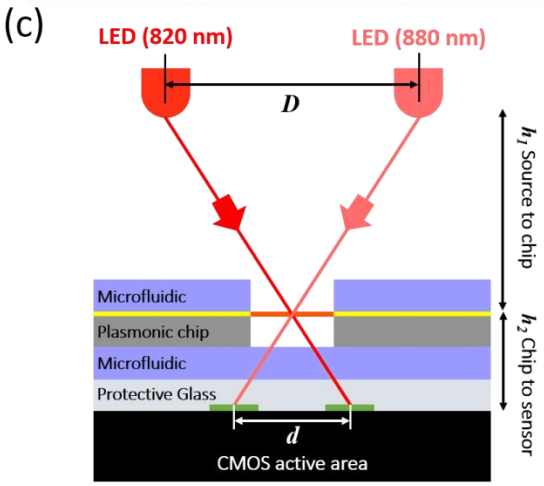


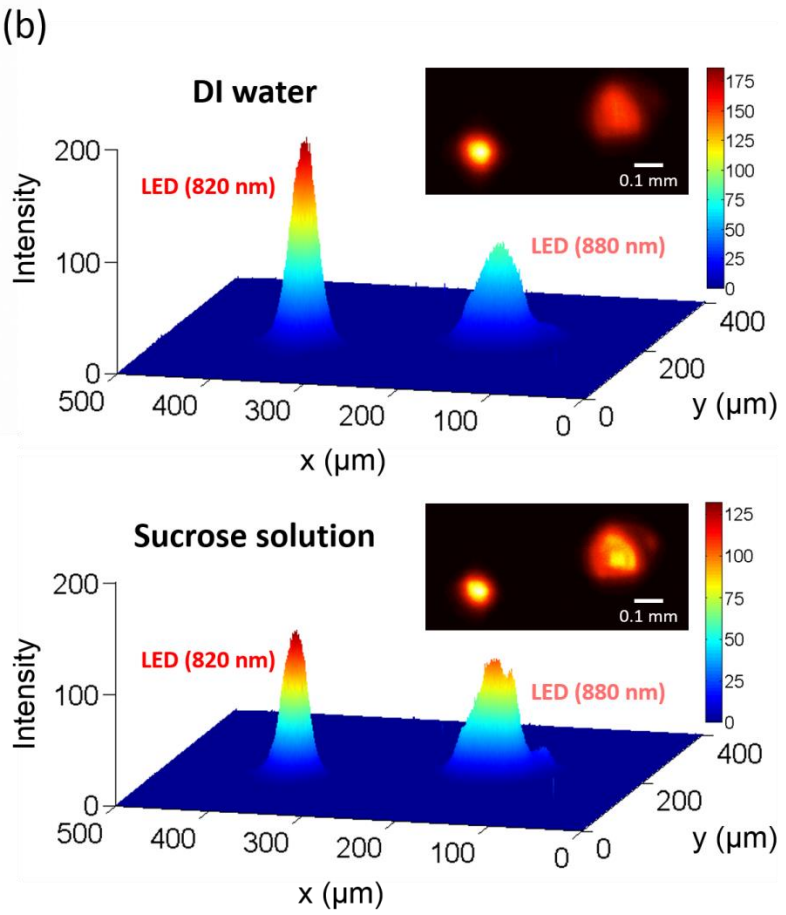


Sci. Reports – NPG (2014)

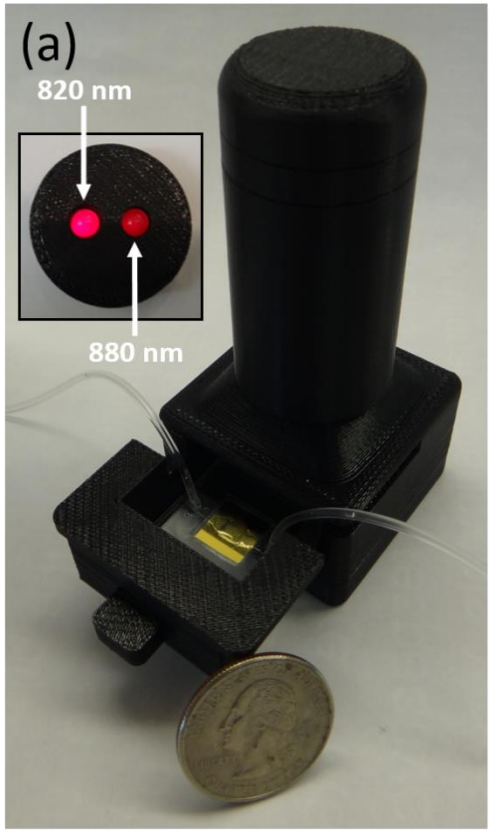


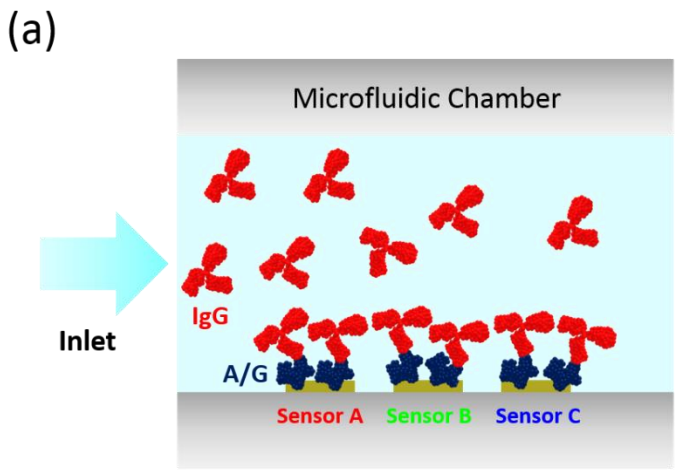


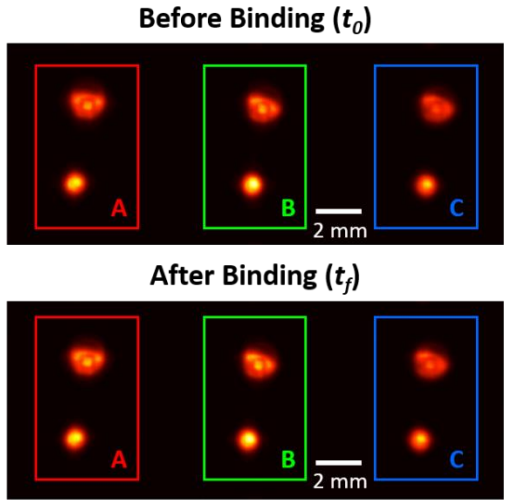


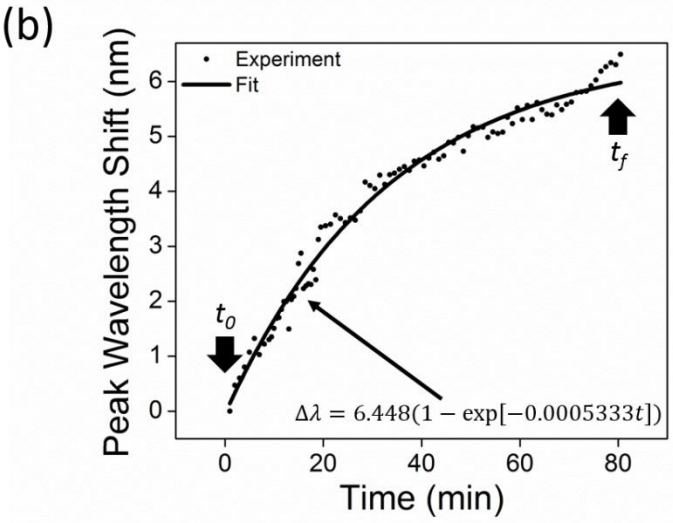


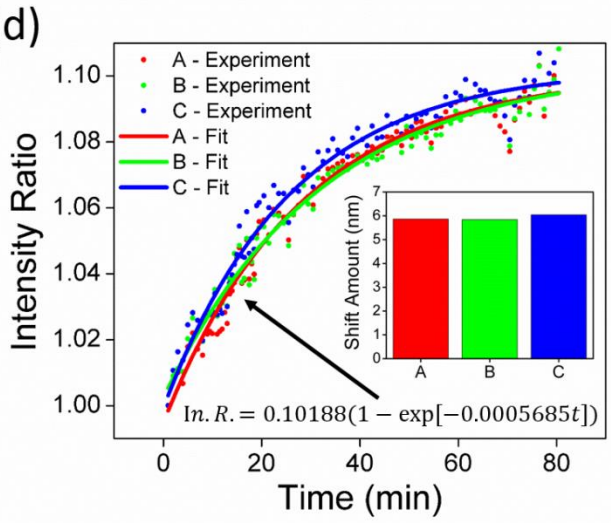
Sci. Reports – NPG (2014)



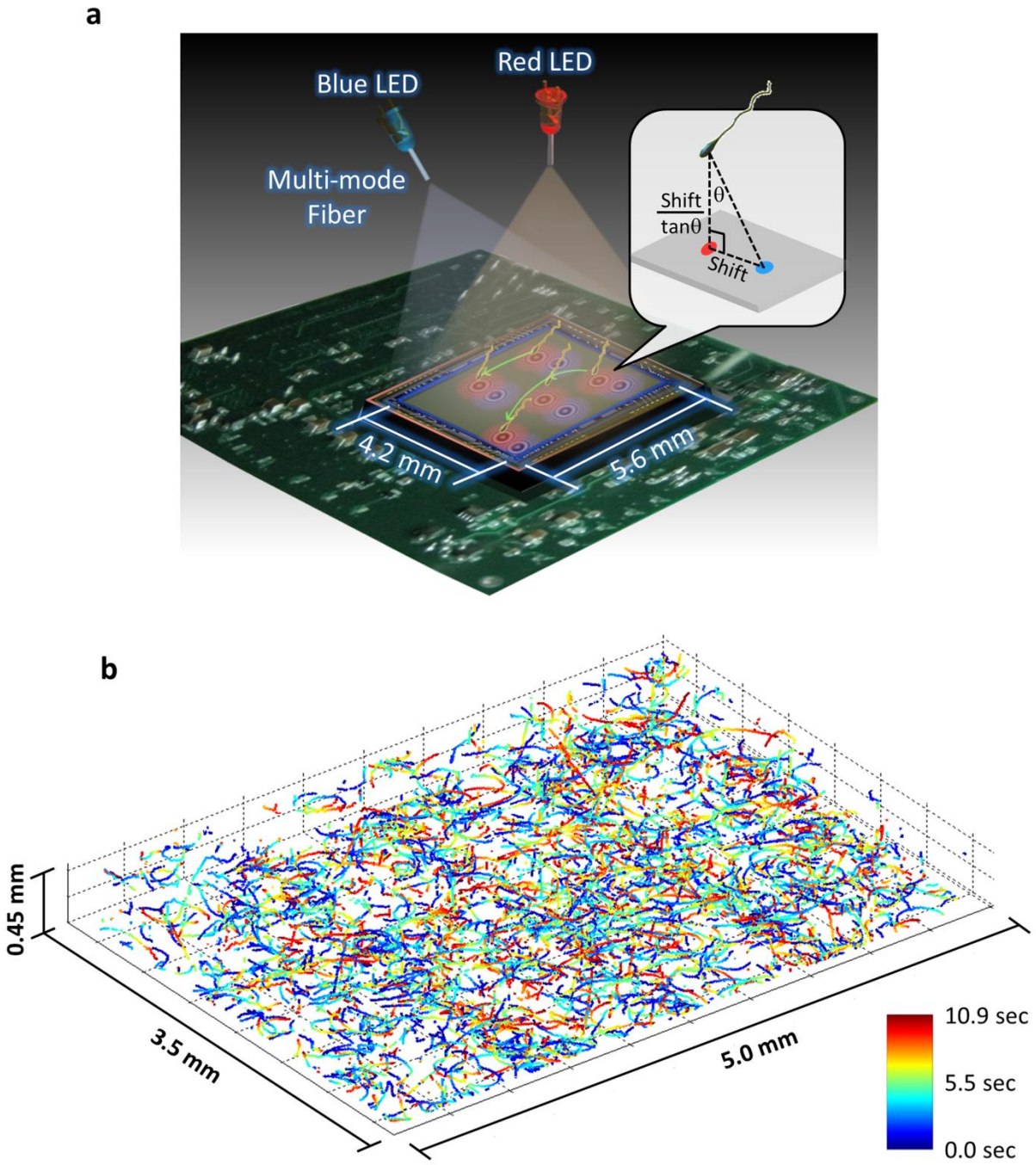








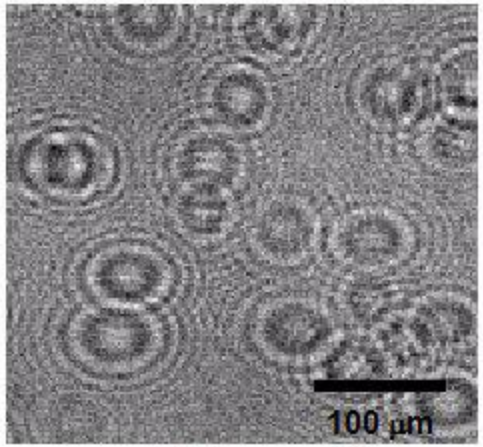
Sci. Reports – NPG (2014)


a
Blue LED
Red LED
Multi-mode
Fiber
Shift
tanθ
θ
Shift
4.2 mm
5.6 mm
b
0.45 mm
3.5 mm
5.0 mm
10.9 sec
5.5 sec
0.0 sec

PNAS, 2012

0.0 ms

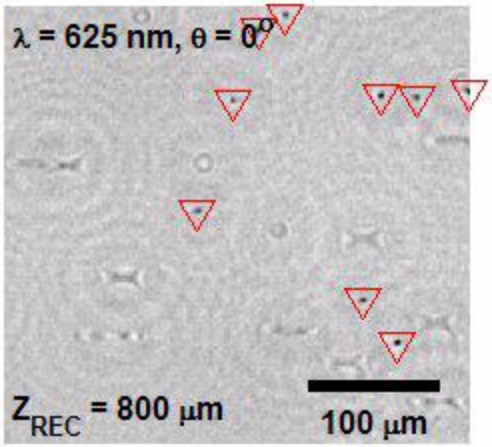
Lensfree Hologram



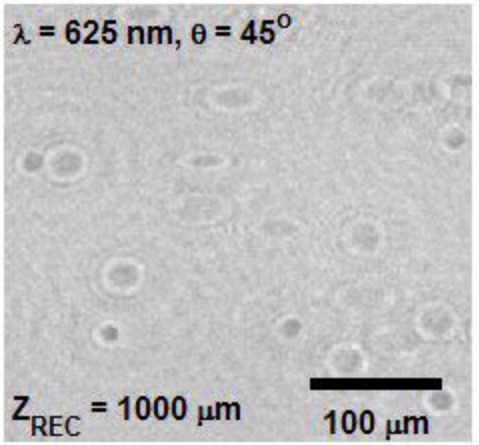
λ = 625 nm, θ = 0°

λ = 470 nm, θ = 45°

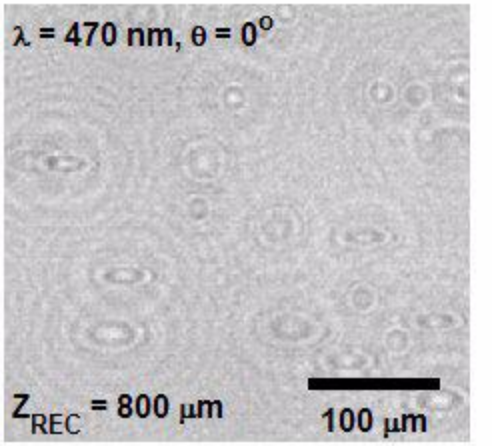
Reconstruction



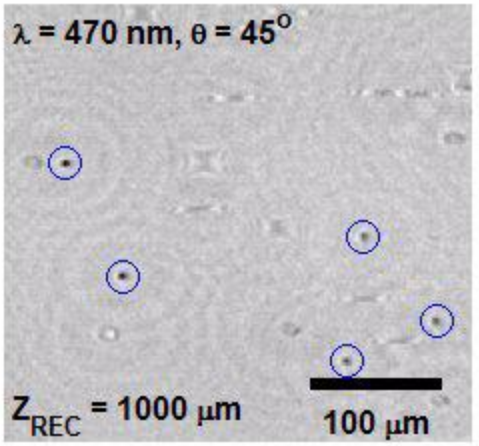
Reconstruction

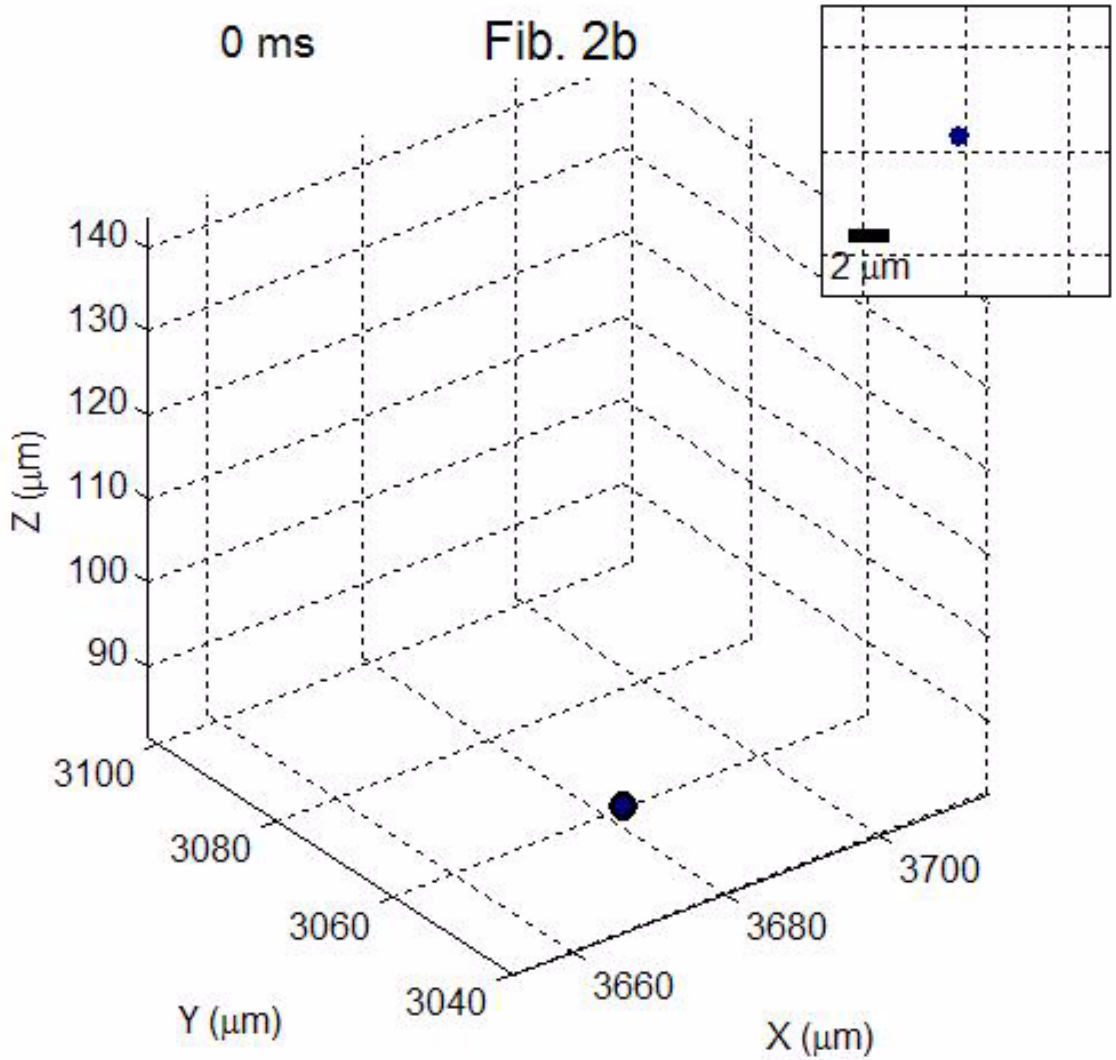


Reconstruction

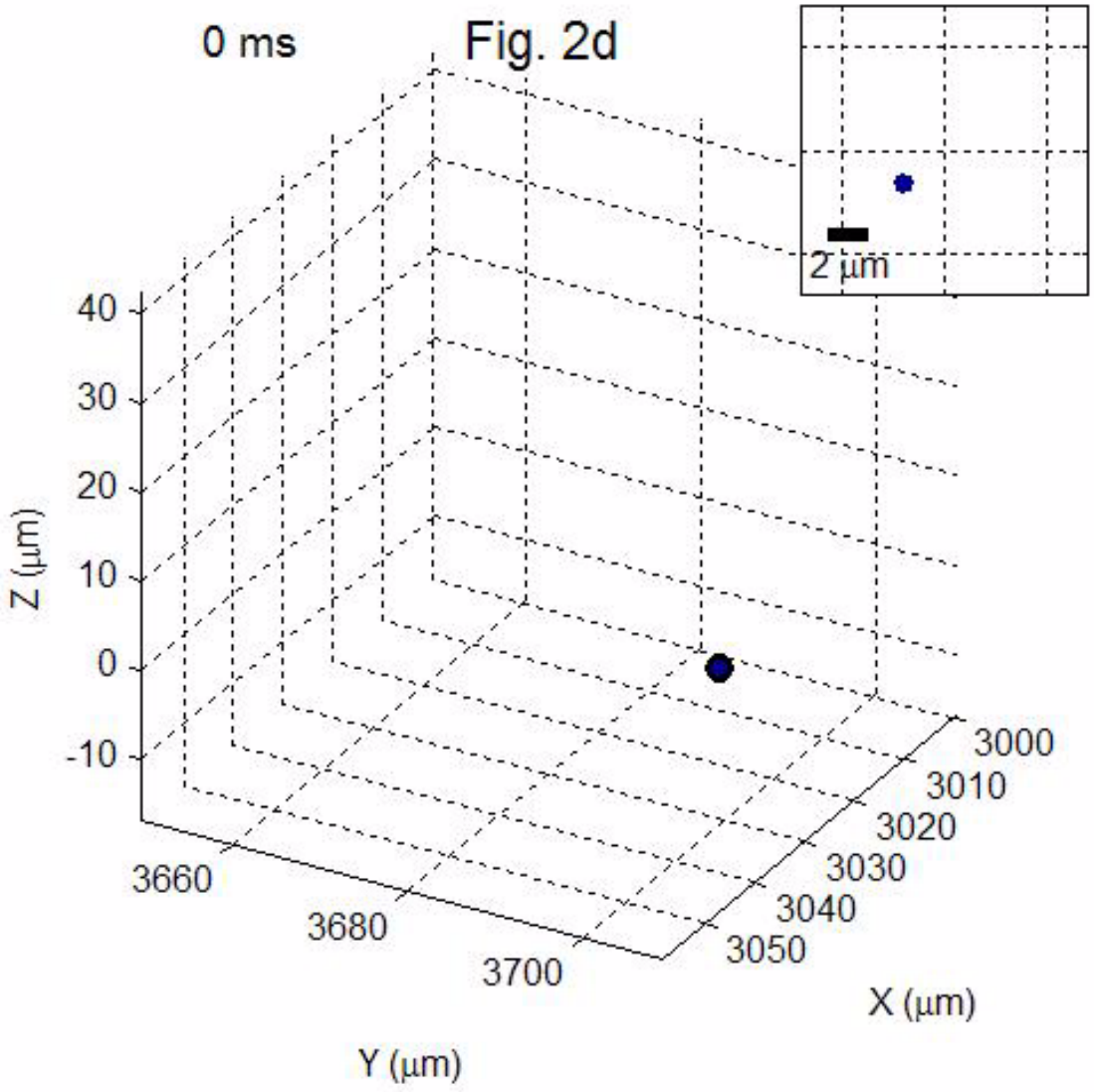


Reconstruction

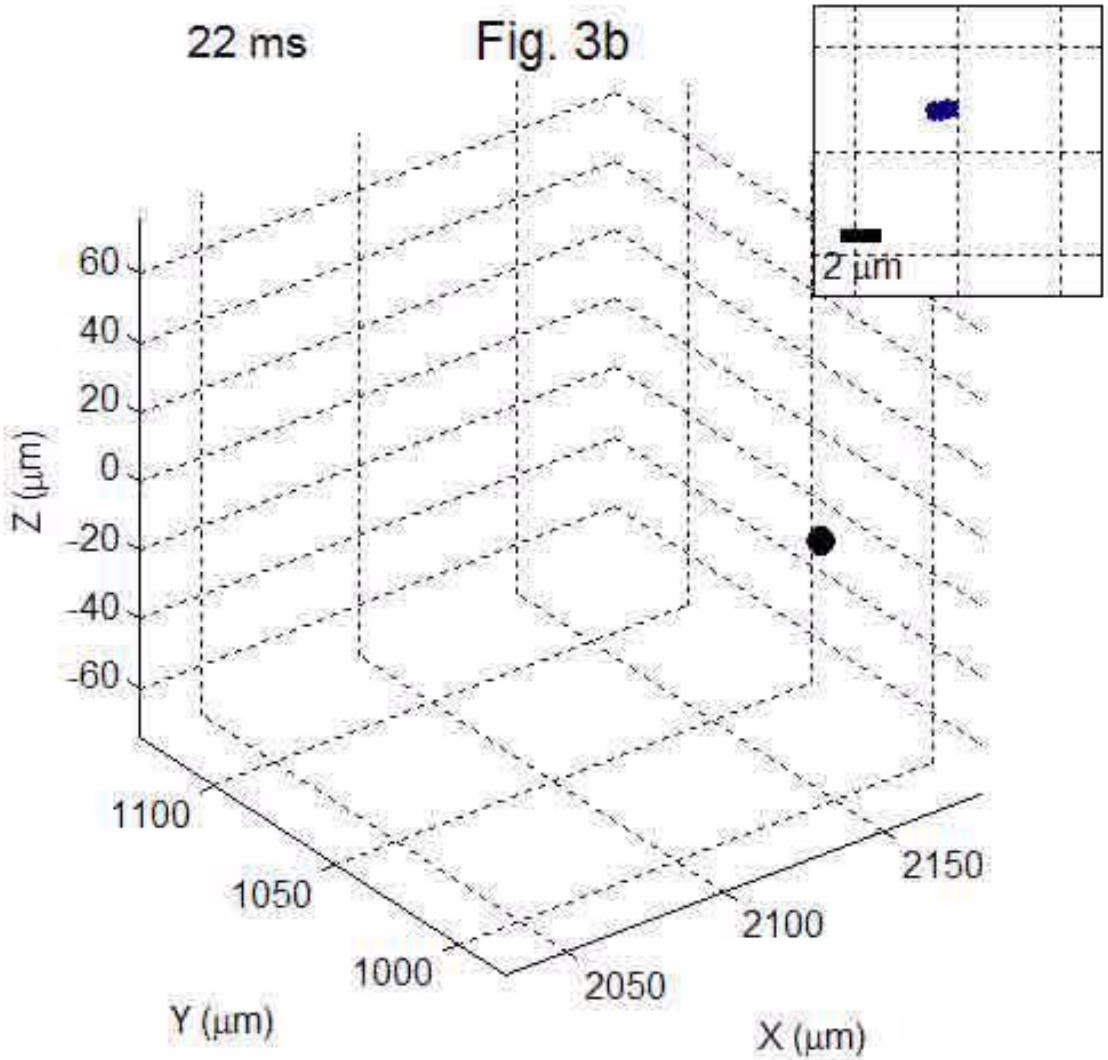



0 ms
Fib. 2b
2 µm
140
130
120
110
100
90
Z (µm)
3100
3080
3060
3040
Y (µm)
3660
3680
3700
X (µm)

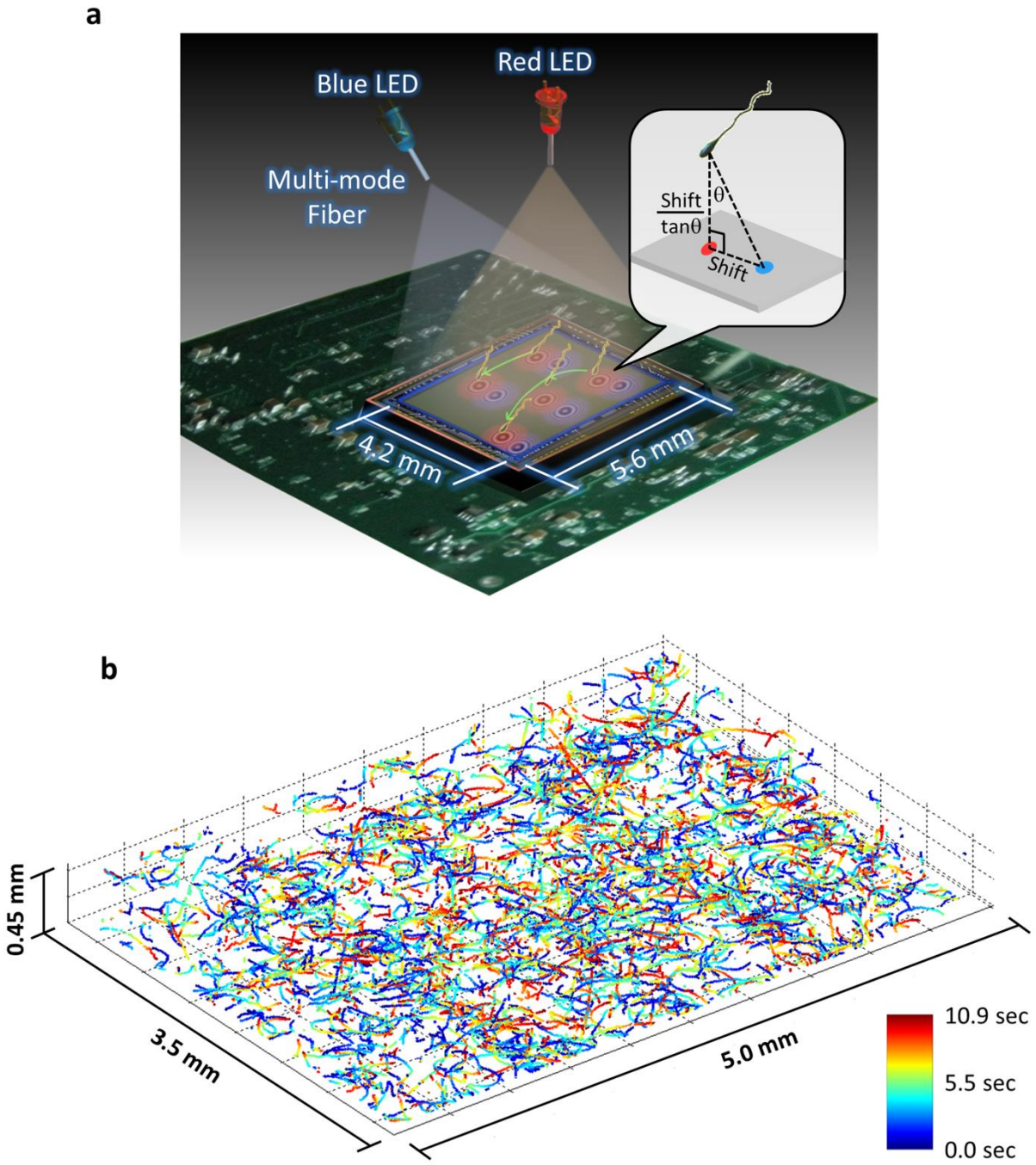
PNAS, 2012


0 ms
Fig. 2d
2 µm
40
30
20
10
0
-10
Z (µm)
3660
3680
3700
Y (µm)
3000
3010
3020
3030
3040
3050
X (µm)

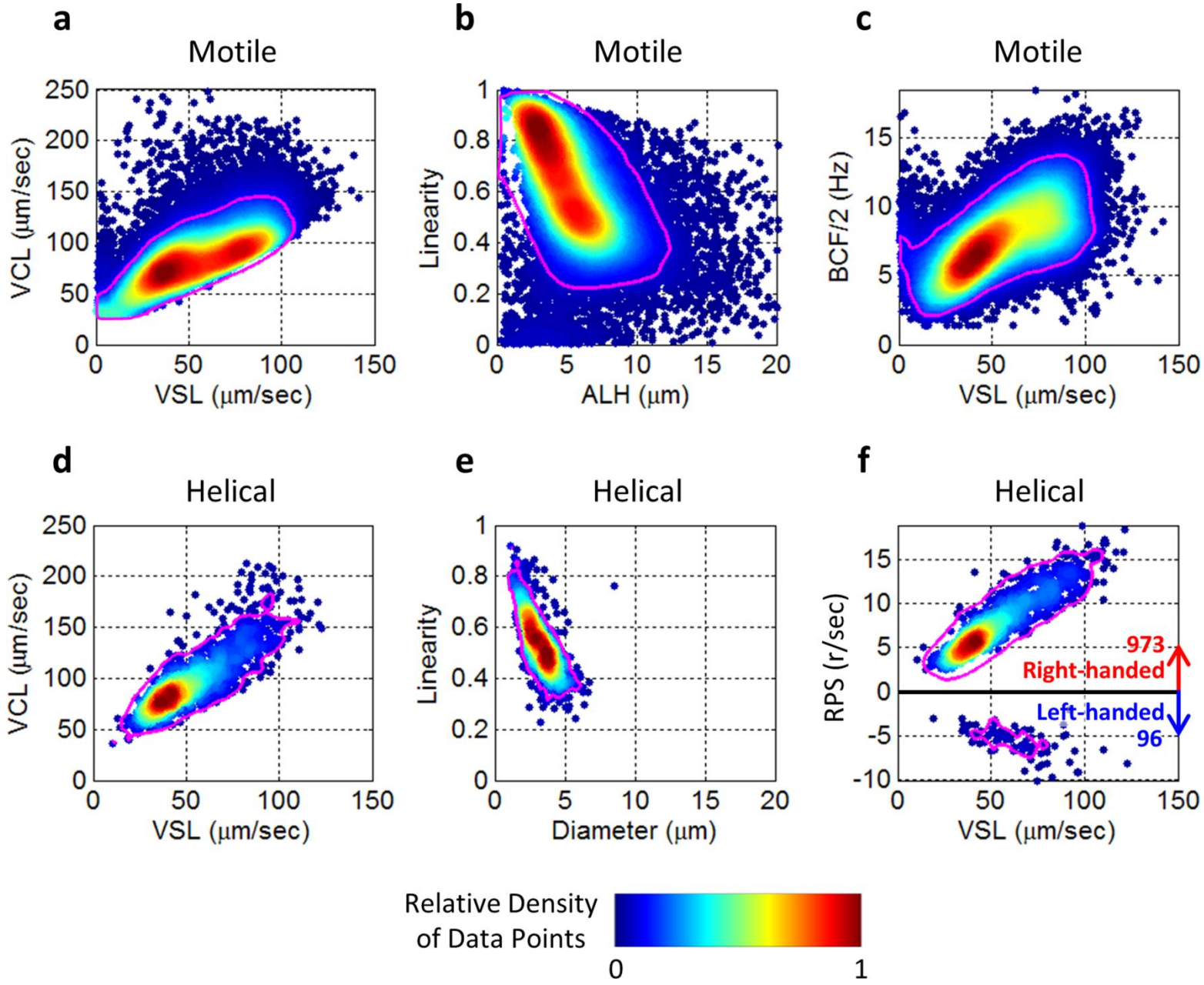
PNAS, 2012


22 ms
Fig. 3b
2 µm
60
40
20
0
-20
-40
-60
Z (µm)
1100
1050
1000
Y (µm)
2050
2100
2150
X (µm)

PNAS, 2012


a
Blue LED
Red LED
Multi-mode
Fiber
Shift
tanθ
θ
Shift
4.2 mm
5.6 mm
b
0.45 mm
3.5 mm
5.0 mm
10.9 sec
5.5 sec
0.0 sec

PNAS, 2012


a
Motile
VCL (μm/sec)
VSL (μm/sec)
b
Motile
Linearity
ALH (μm)
c
Motile
BCF/2 (Hz)
VSL (μm/sec)
d
Helical
VCL (μm/sec)
VSL (μm/sec)
e
Helical
Linearity
Diameter (μm)
f
Helical
RPS (r/sec)
973
Right-handed
Left-handed
96
VSL (μm/sec)
Relative Density
of Data Points
0
1

PNAS, 2012

Sperm Trajectories form Chiral Ribbons

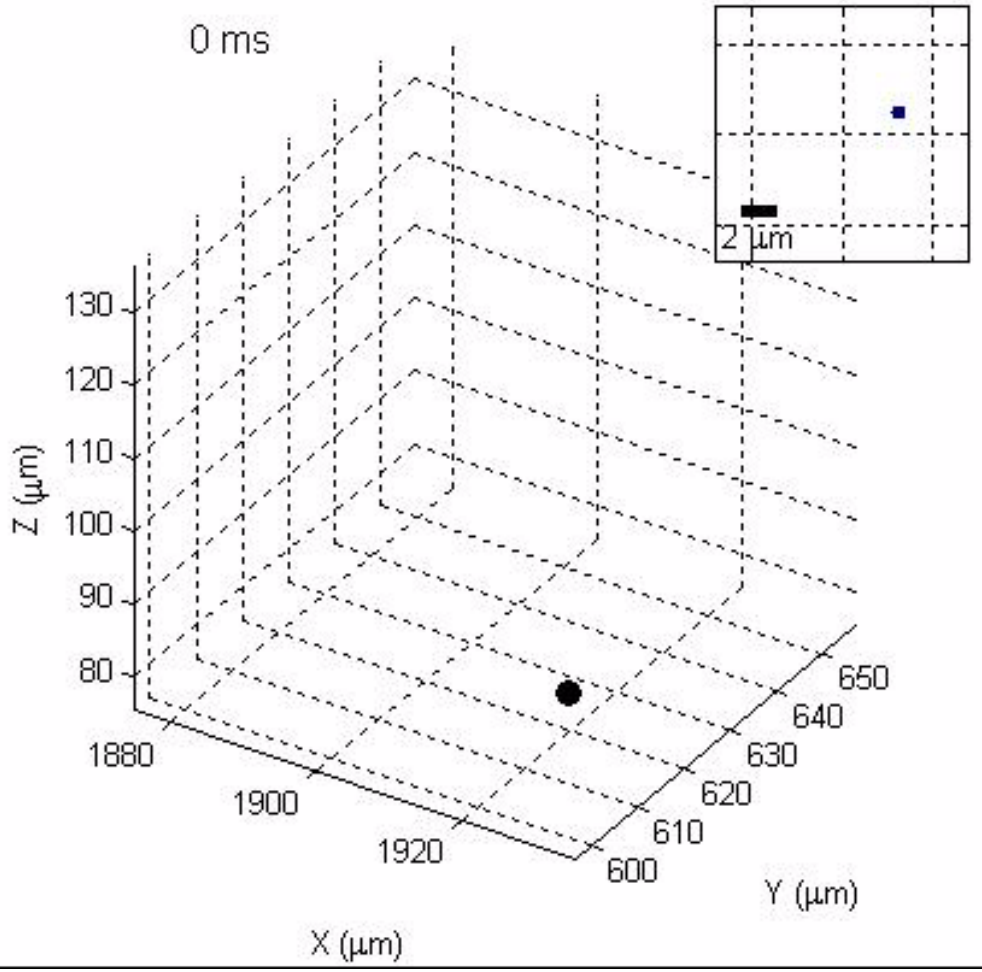
Helical Ribbon

Twisted Ribbon

Scientific Reports, 2013

Sperm Trajectories form Chiral Ribbons

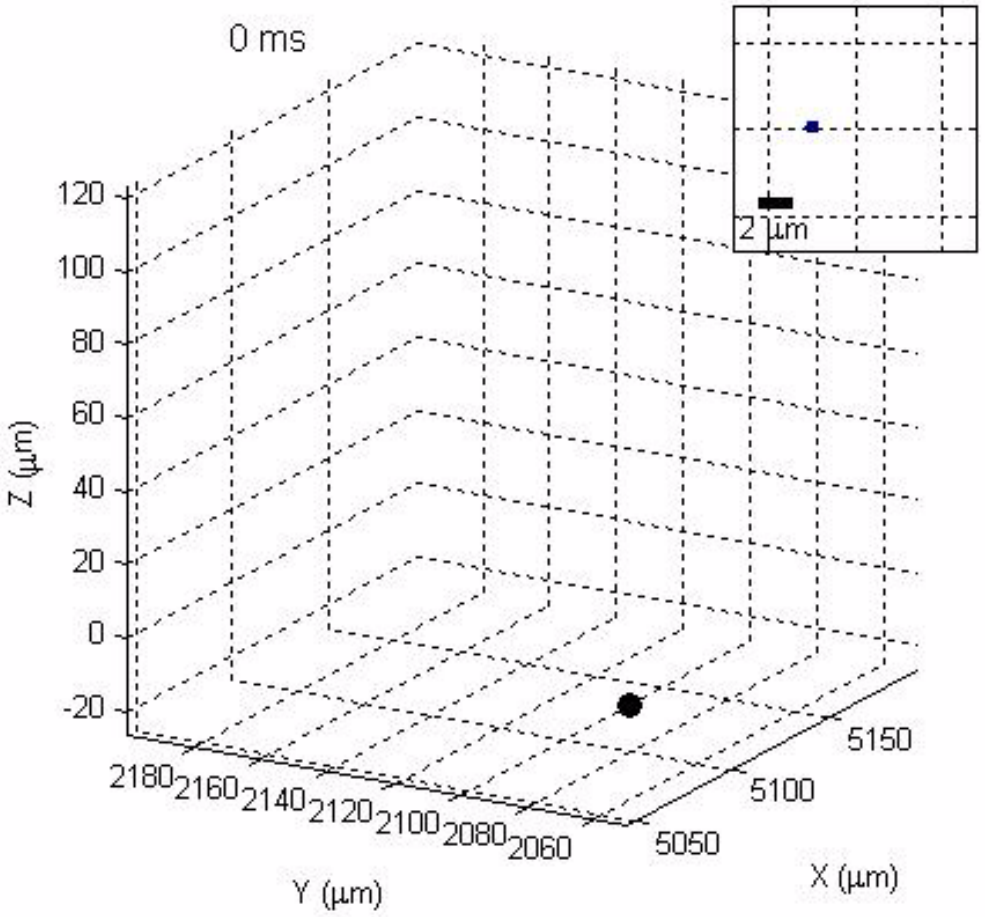
Helical Ribbon



Scientific Reports, 2013

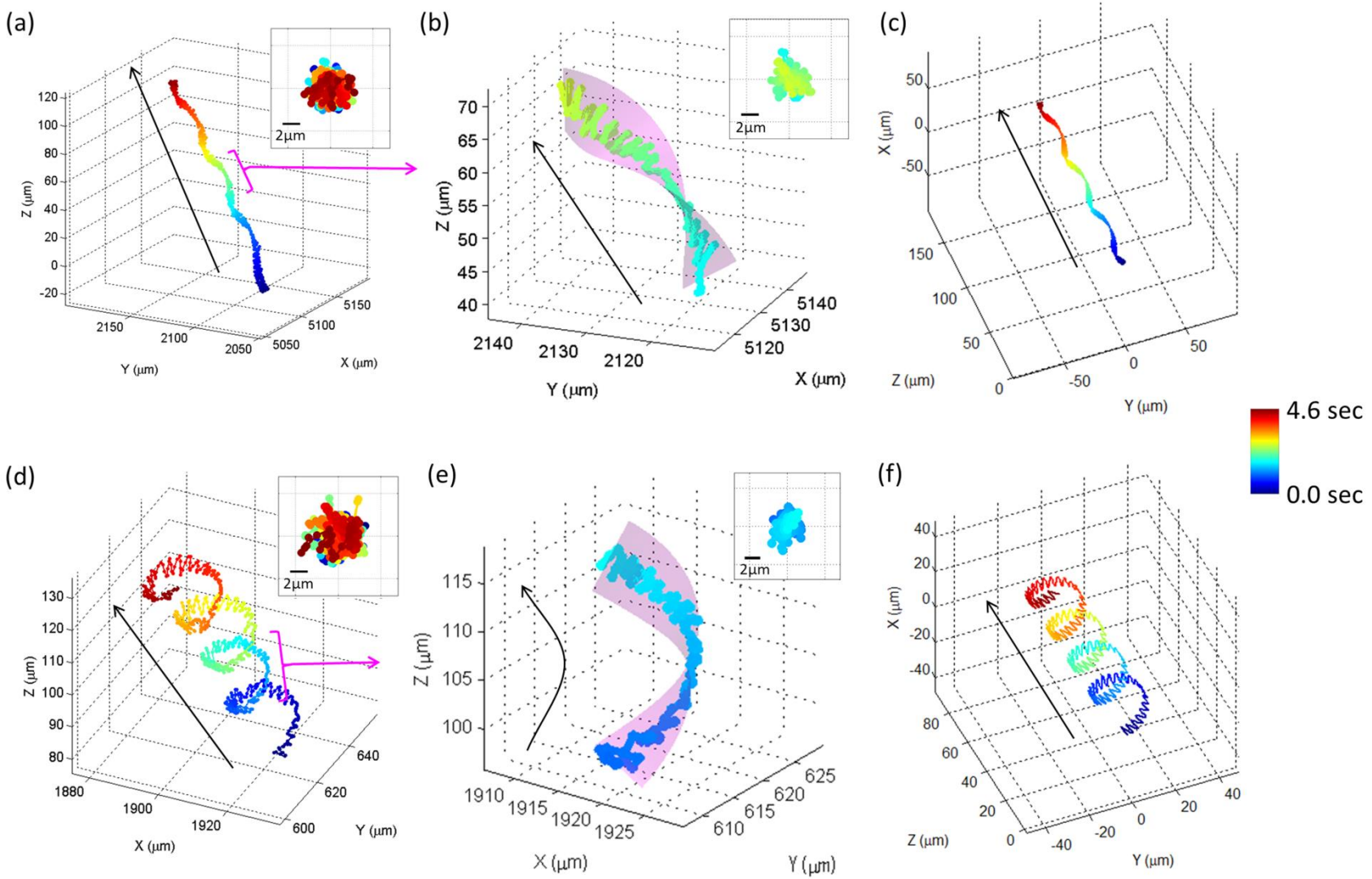
Sperm Trajectories form Chiral Ribbons

Twisted Ribbon



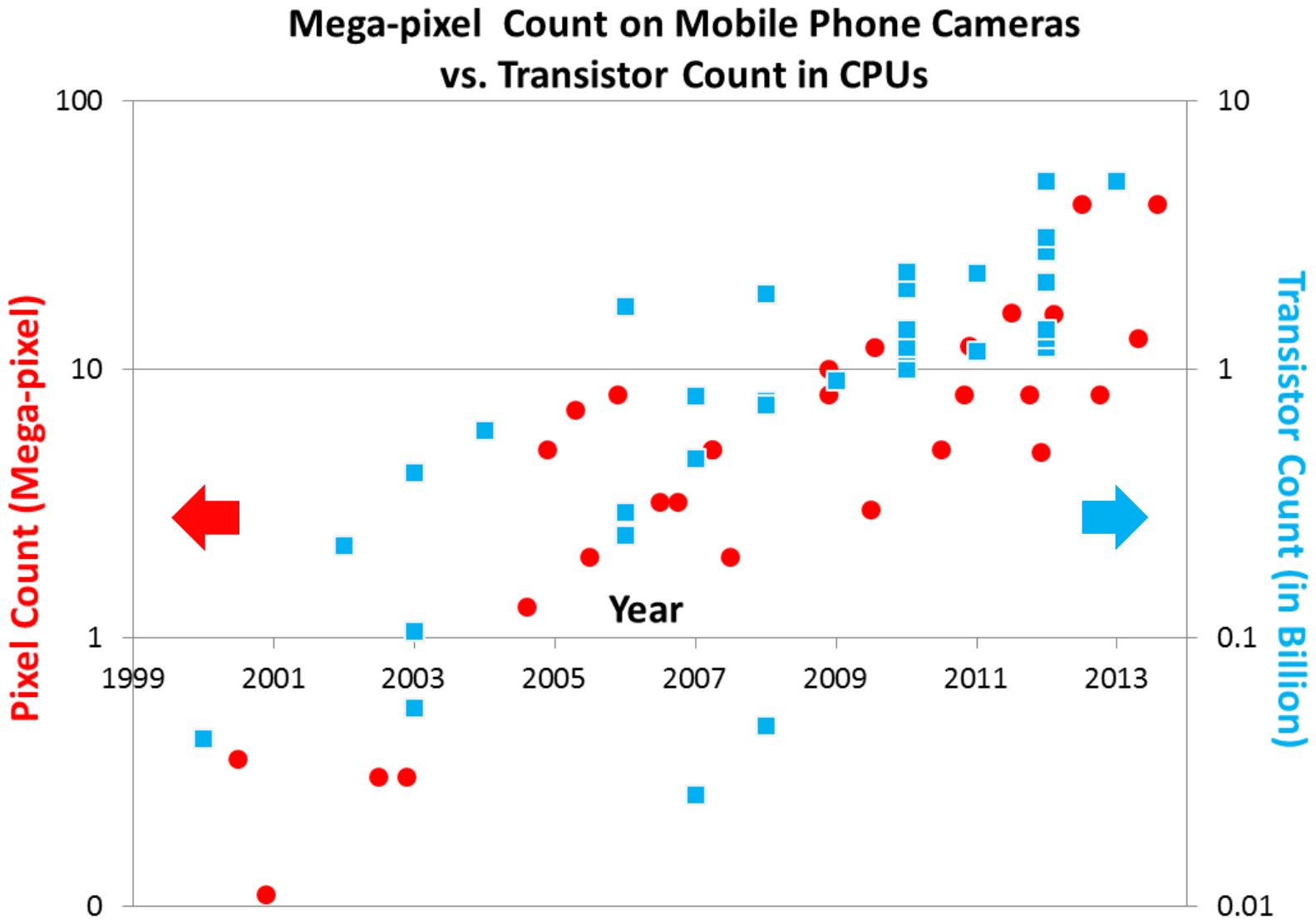
Scientific Reports, 2013

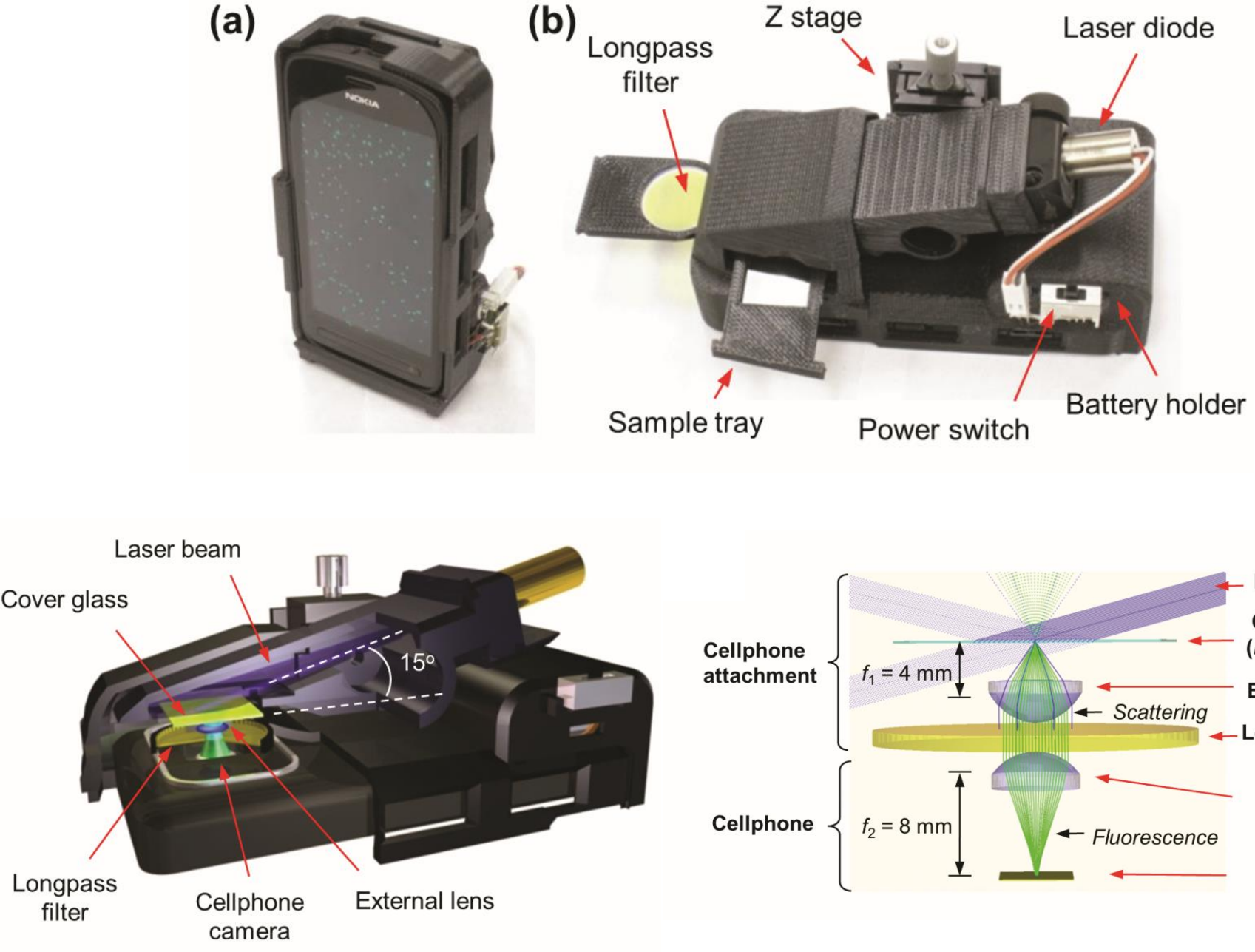
Sperm Trajectories form Helicoids (Also Minimal Surface)



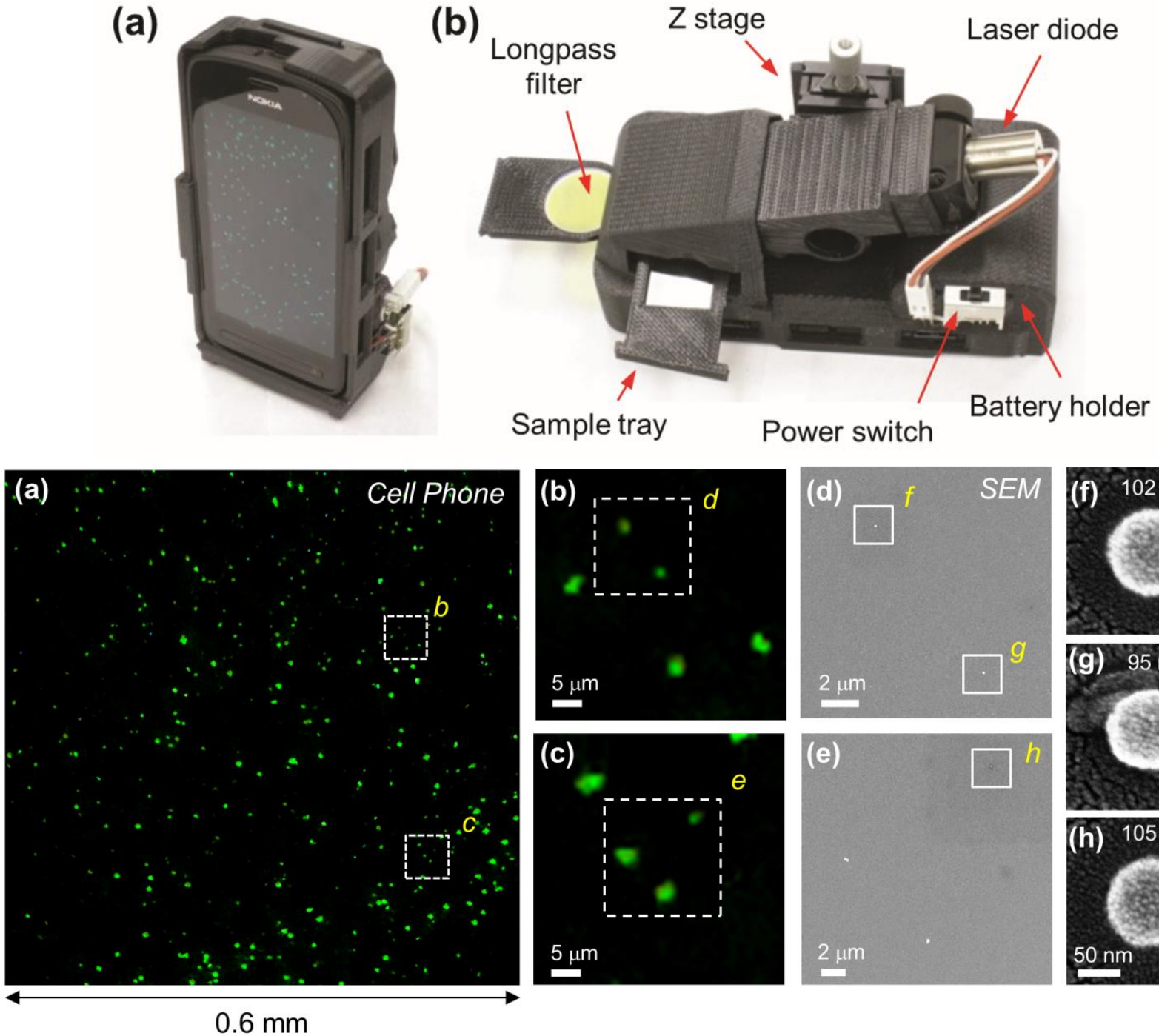
Scientific Reports, 2013

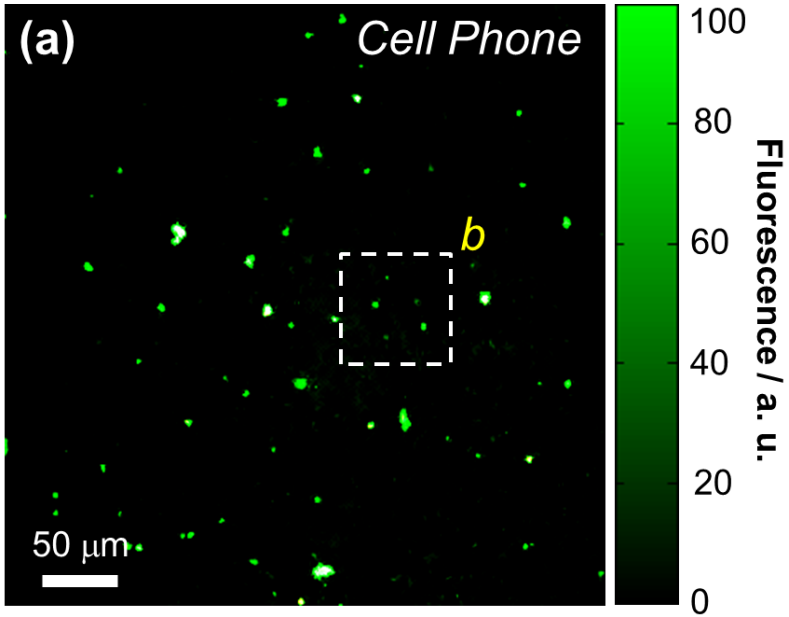
A different view of the Moore's Law

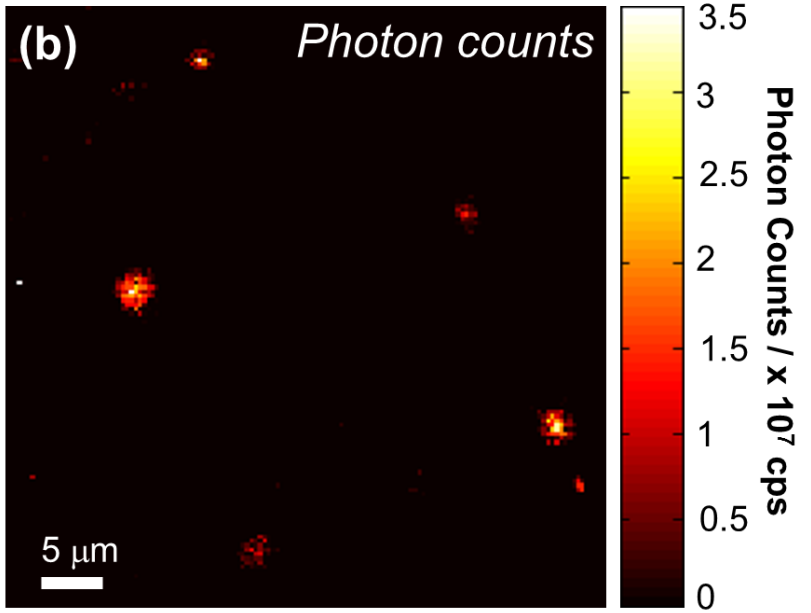


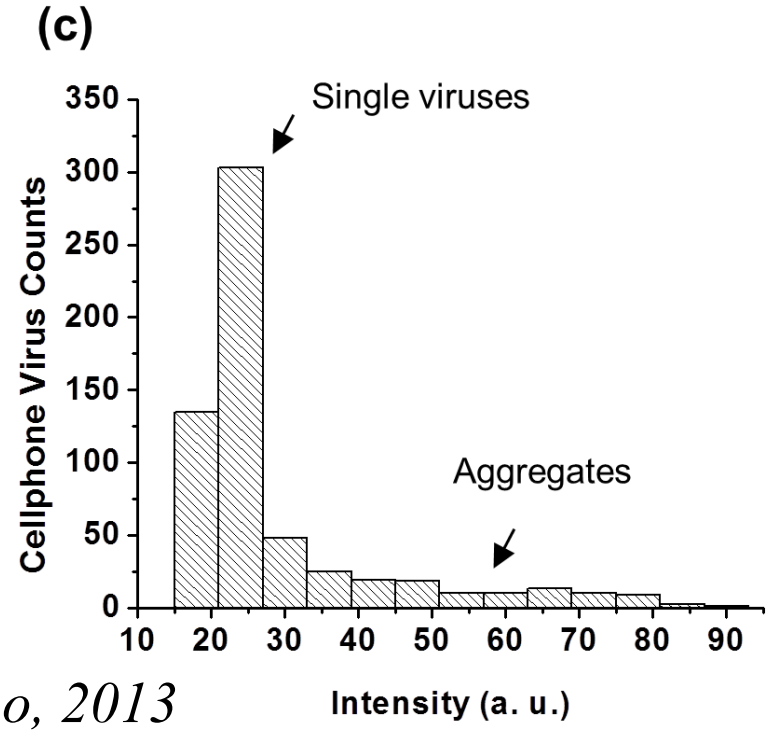


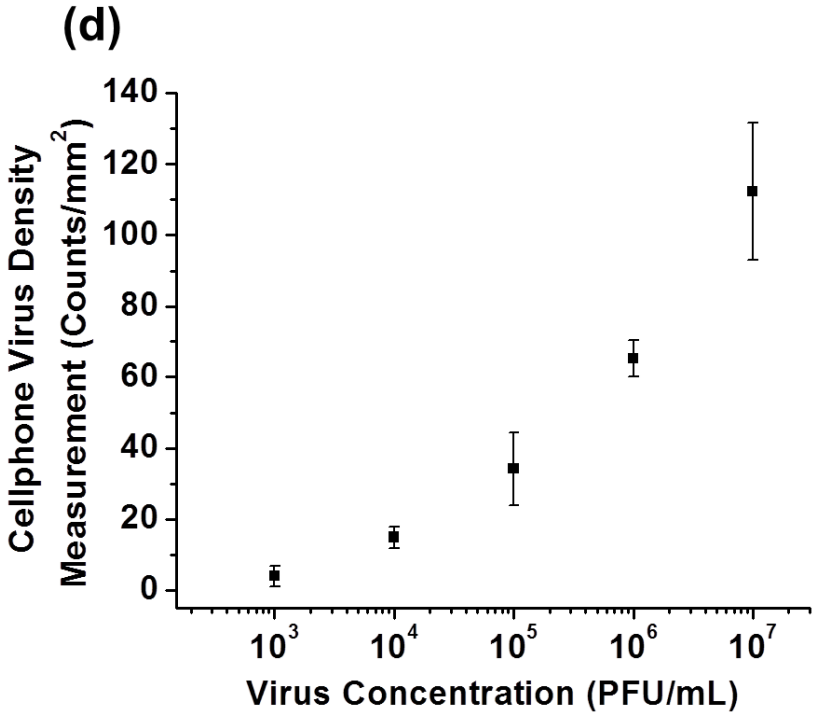
ACS Nano, 2013


(a)
(b)
Longpass filter
Z stage
Laser diode
Sample tray
Power switch
Battery holder
(a)
Cell Phone
b
c
0.6 mm
(b)
d
5 μm
(c)
e
5 μm
(d)
f
g
SEM
2 μm
(e)
h
2 μm
(f)
102 nm
(g)
95 nm
(h)
105 nm
50 nm







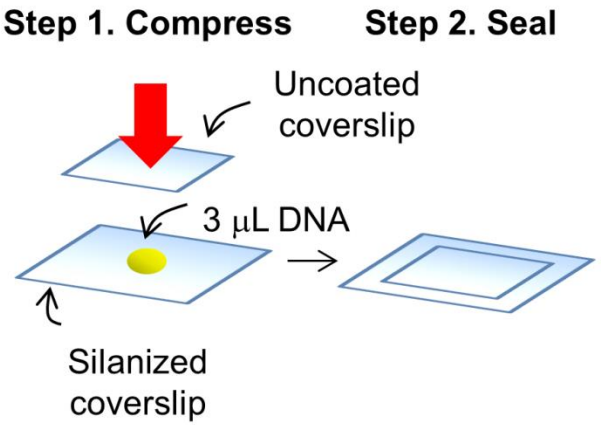


ACS Nano, 2013

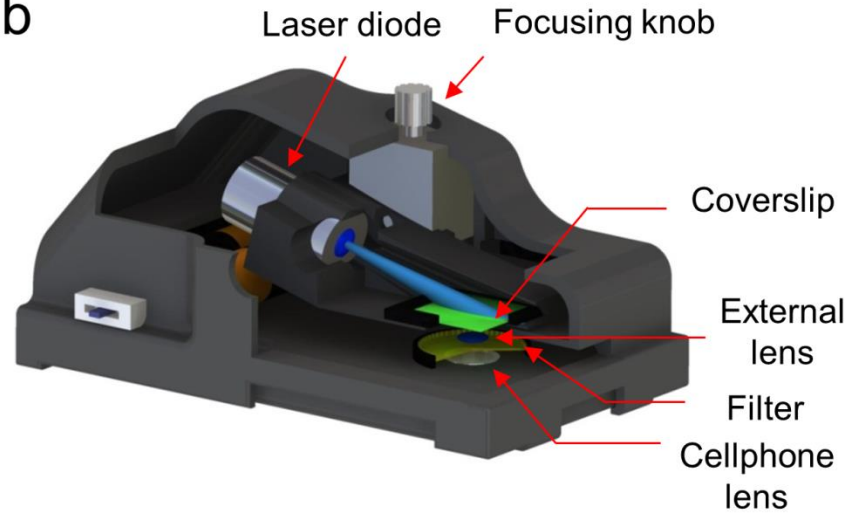
Imaging and Sizing of Single DNA Molecules on a Mobile-Phone

a

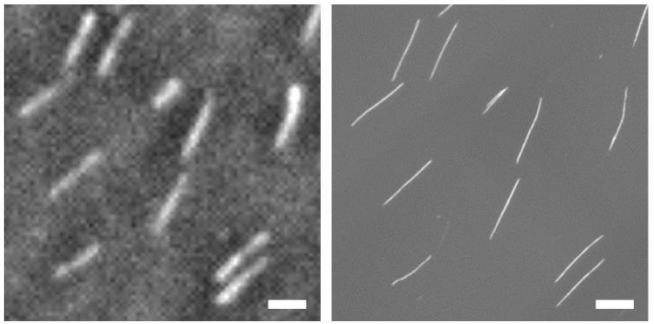
c



b

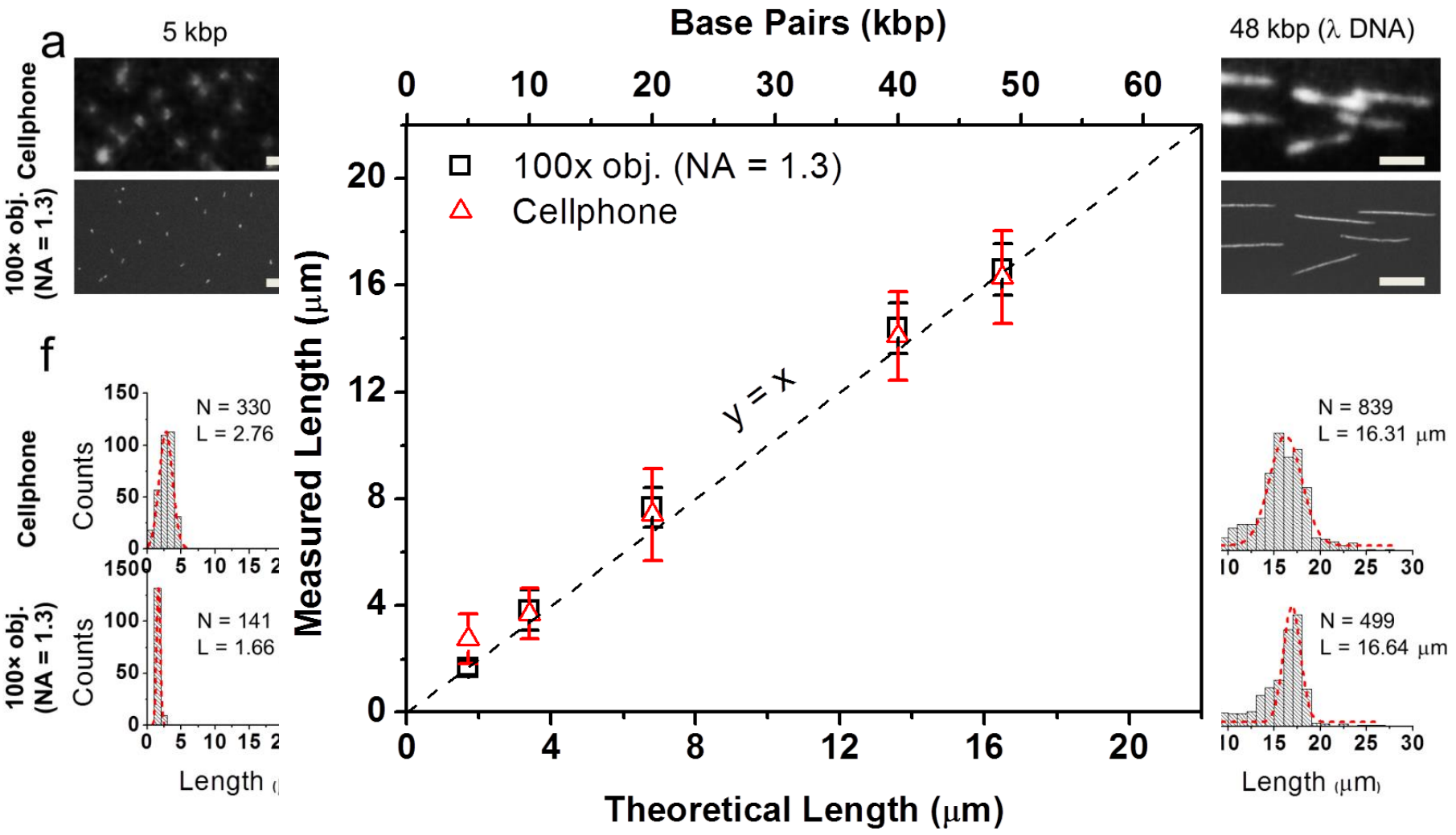


d



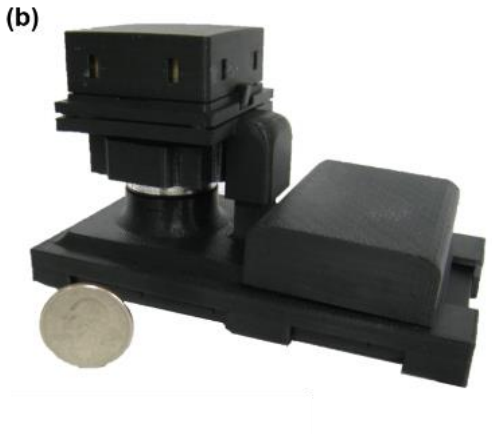
ACS Nano, 2014

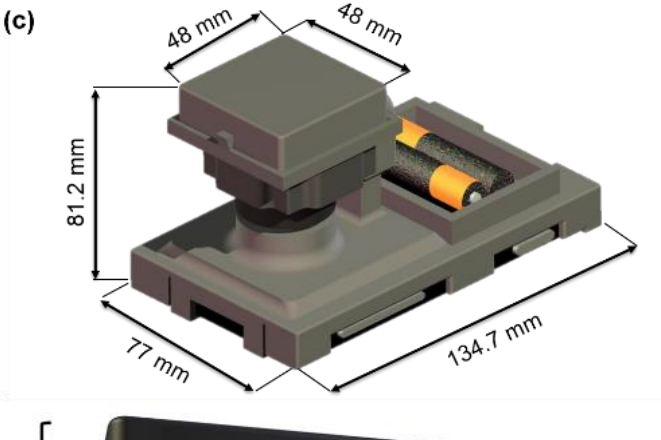
Imaging and Sizing of Single DNA Molecules on a Mobile-Phone

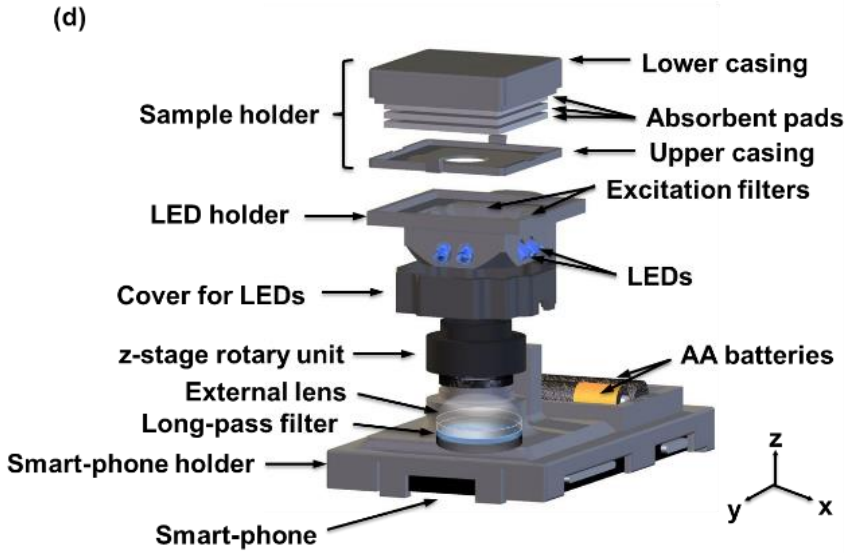


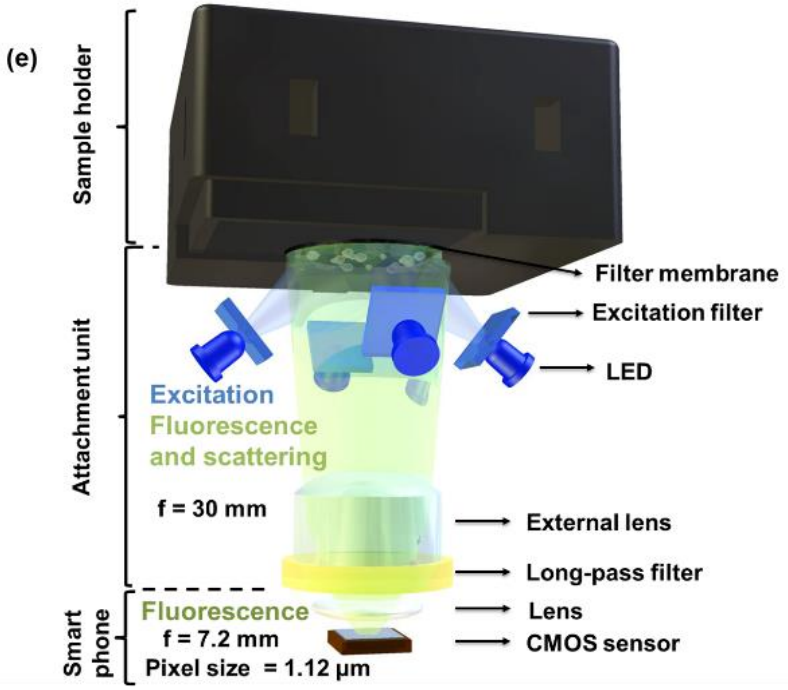
ACS Nano, 2014

Quantification of Giardia lamblia cysts using mobile-phone based fluorescent microscopy and machine learning

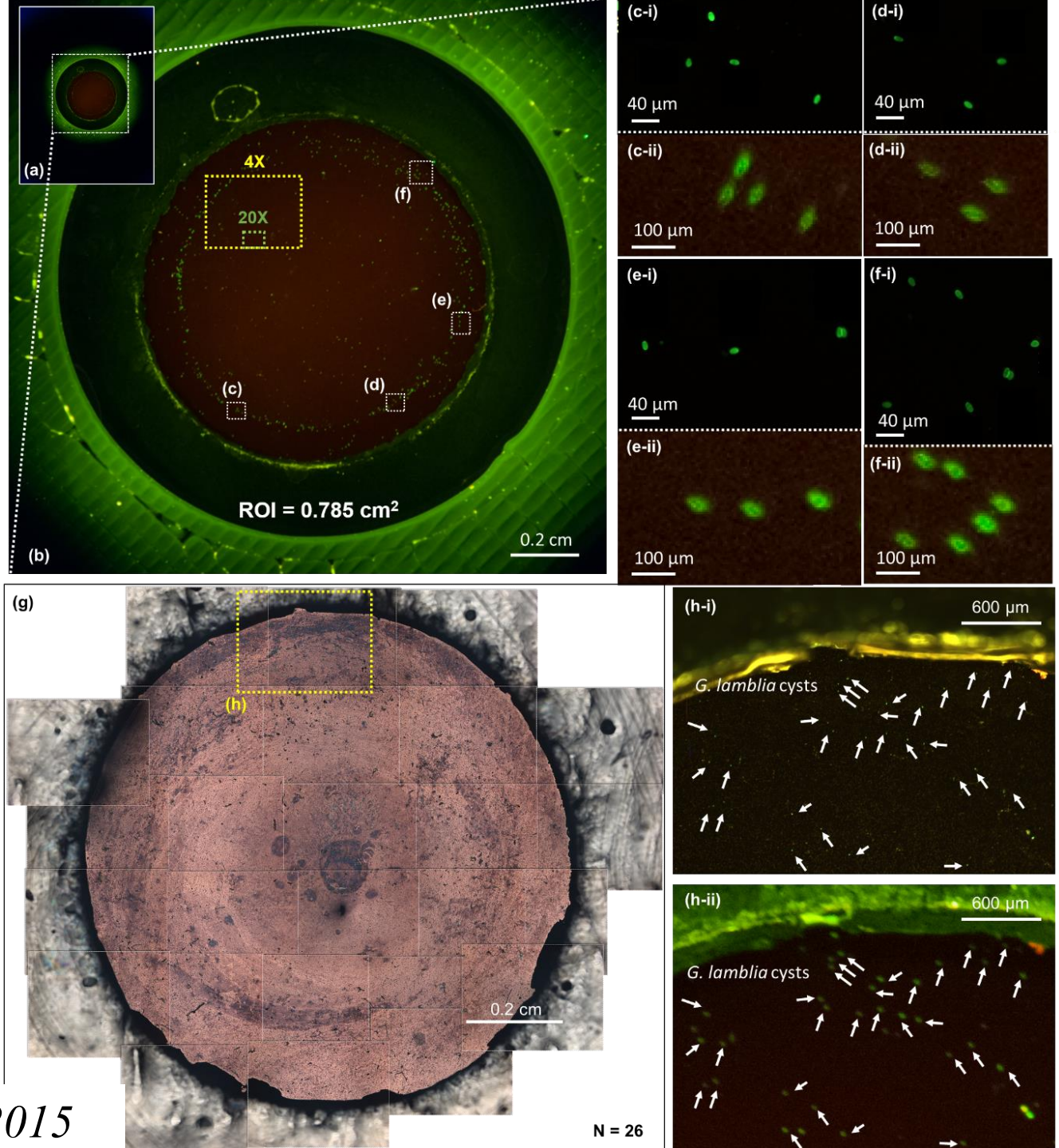






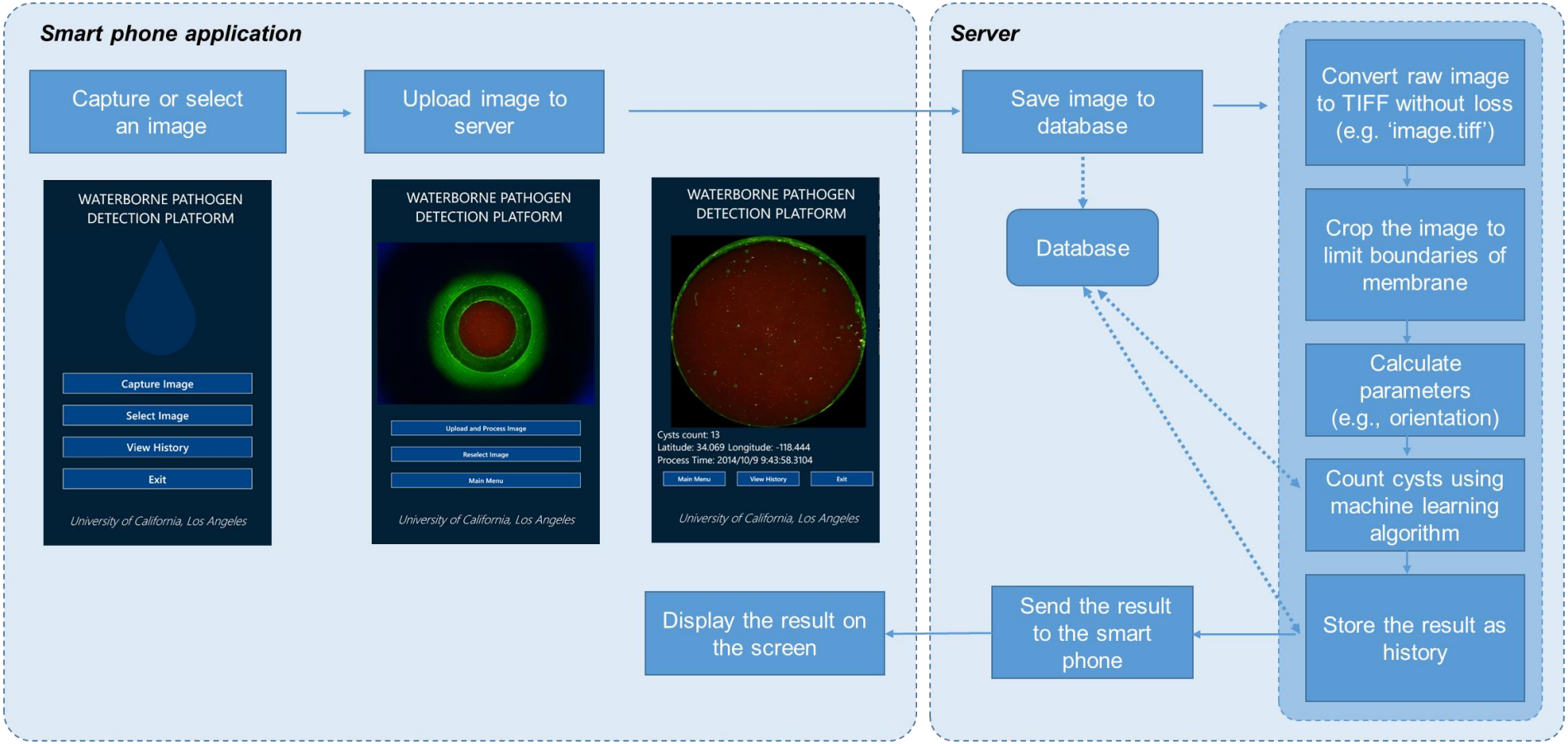


Lab Chip, 2015



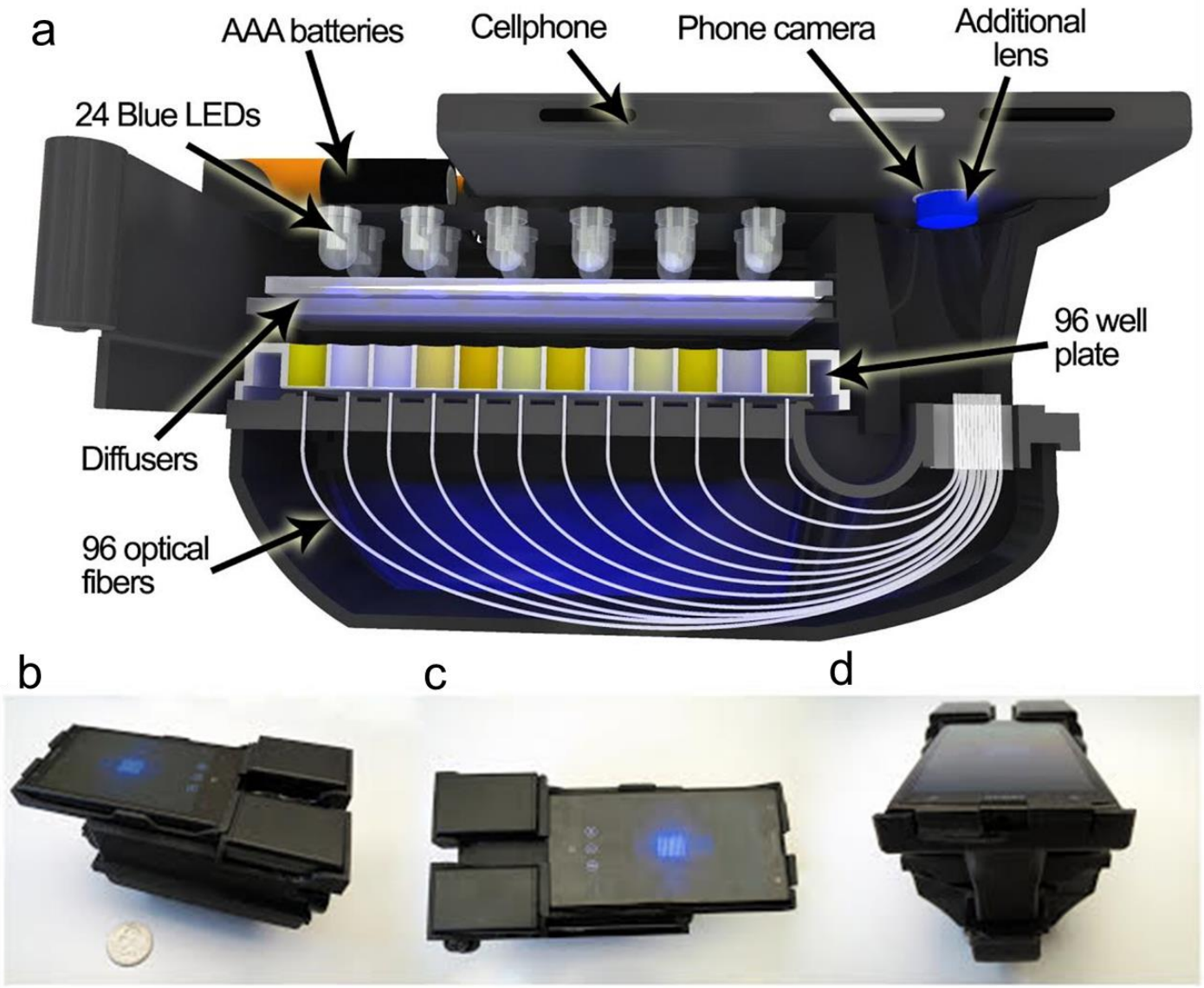
Lab Chip, 2015

Quantification of Giardia lamblia cysts using mobile-phone based fluorescent microscopy and machine learning

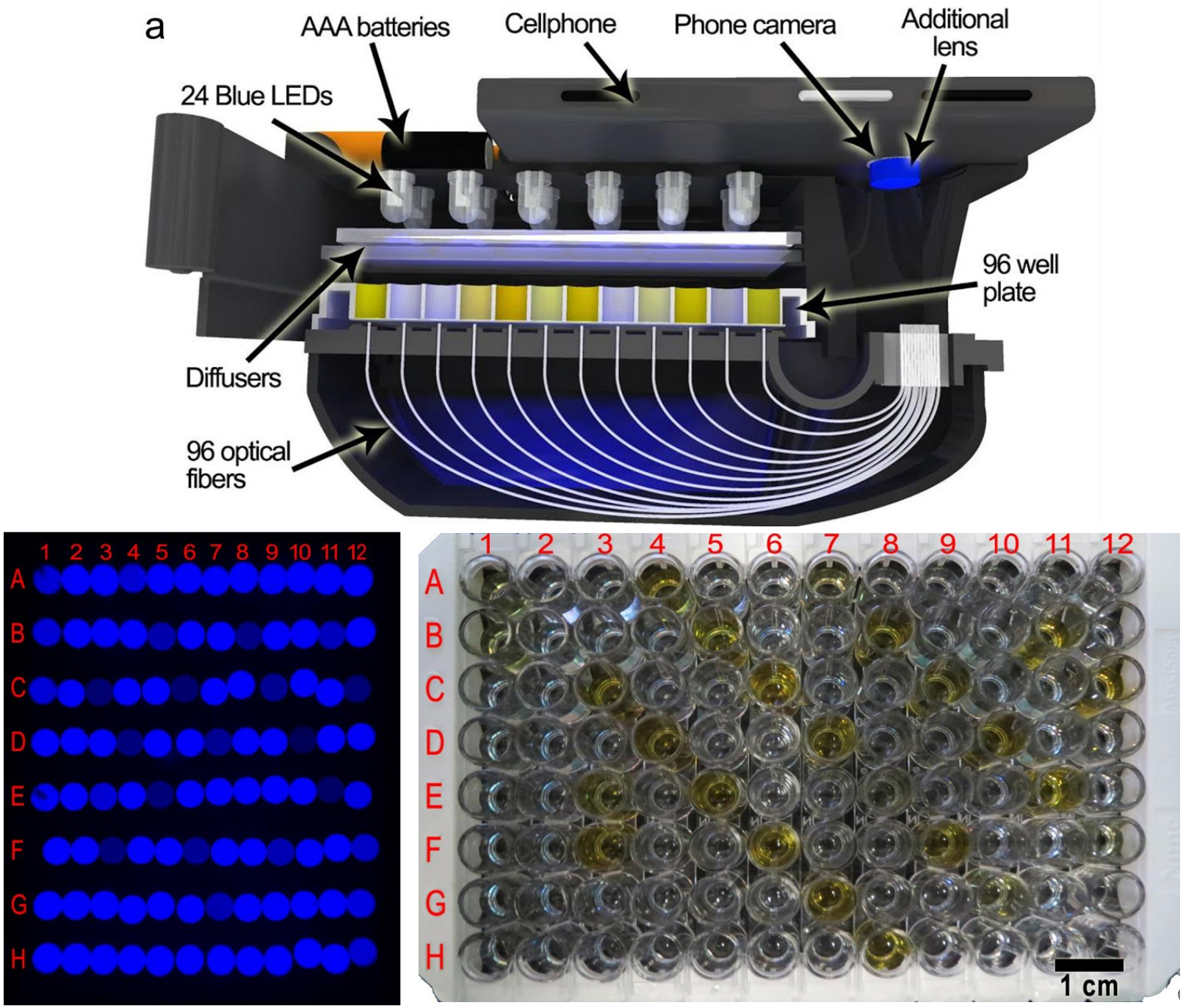


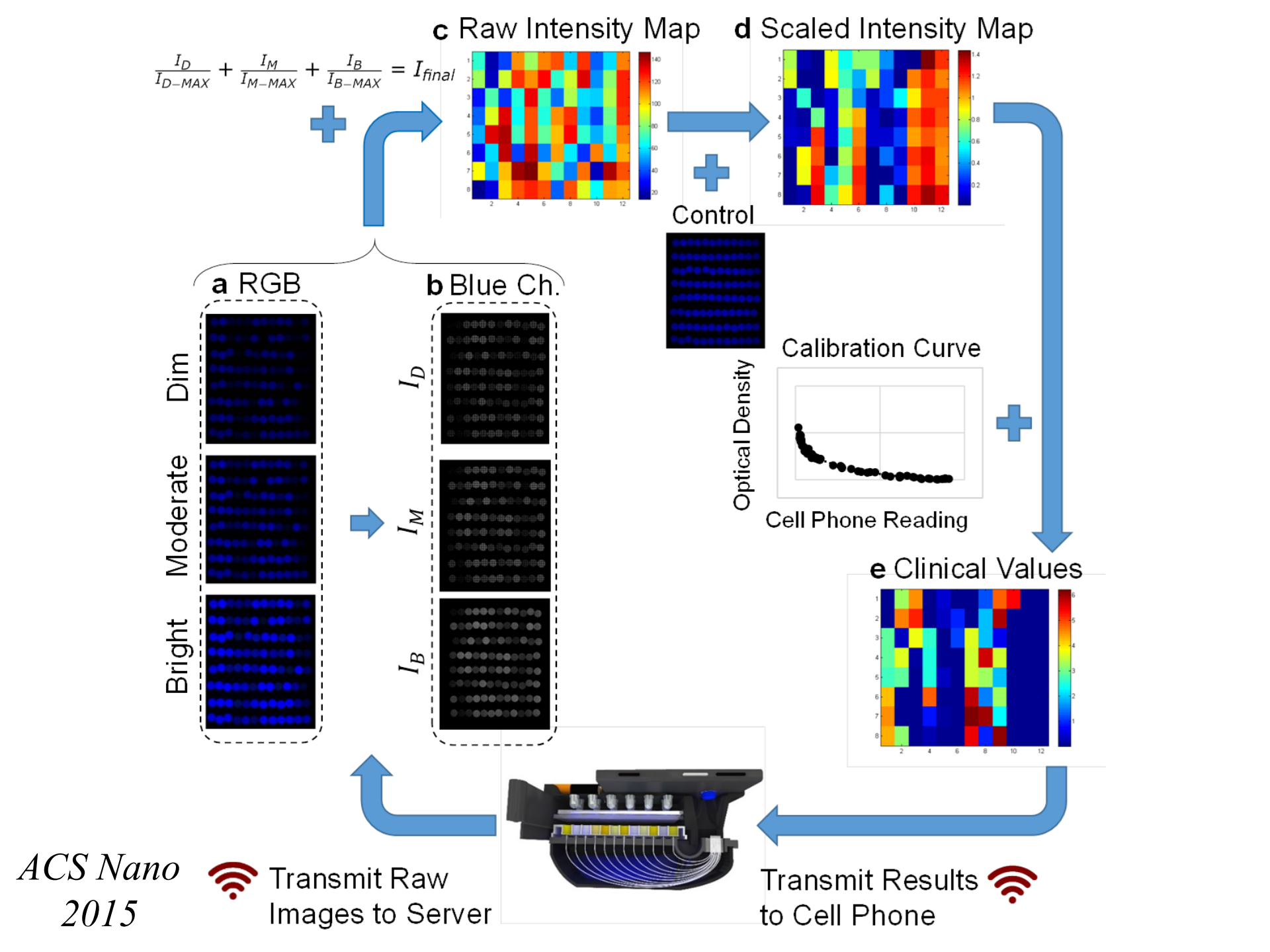
Lab Chip, 2015

Cellphone-Based Hand-Held Micro-Plate Reader for Point-of-Care ELISA Testing

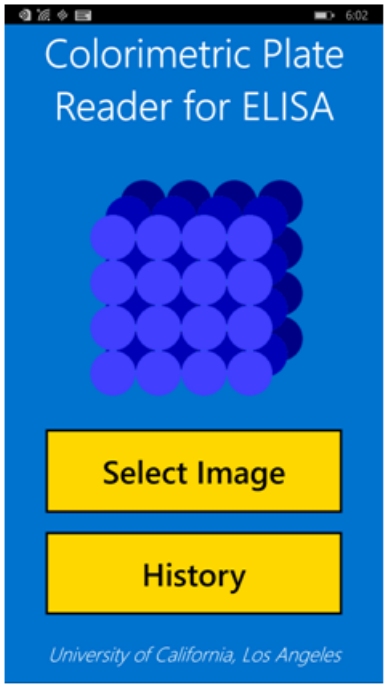


ACS Nano 2015

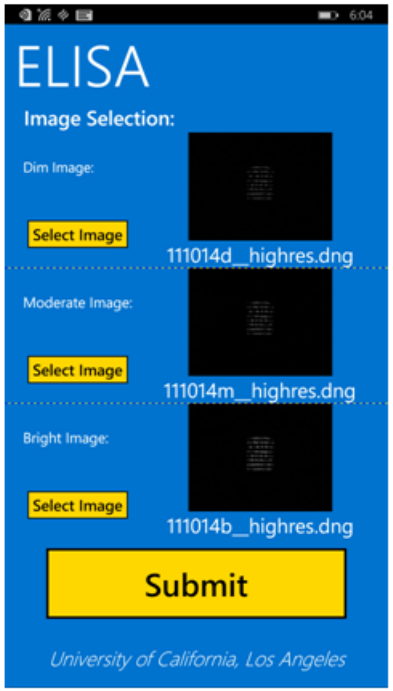

a
AAA batteries
Cellphone
Phone camera
Additional lens
24 Blue LEDs
96 well plate
Diffusers
96 optical fibers
1 2 3 4 5 6 7 8 9 10 11 12
A
B
C
D
E
F
G
H
1 cm


$\frac{I_D}{I_{D-MAX}} + \frac{I_M}{I_{M-MAX}} + \frac{I_B}{I_{B-MAX}} = I_{final}$
c Raw Intensity Map
d Scaled Intensity Map
Control
a RGB
Dim
Moderate
Bright
b Blue Ch.
I_D
I_M
I_B
Calibration Curve
Optical Density
Cell Phone Reading
e Clinical Values
Transmit Raw Images to Server
Transmit Results to Cell Phone
ACS Nano 2015

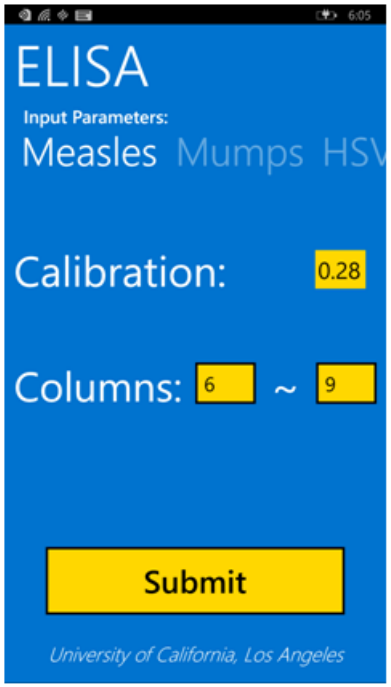
a



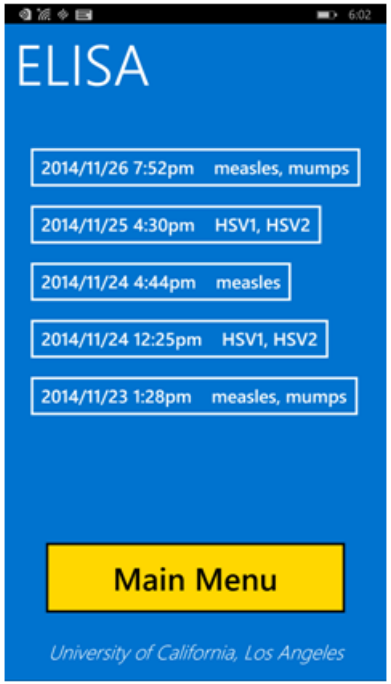
b



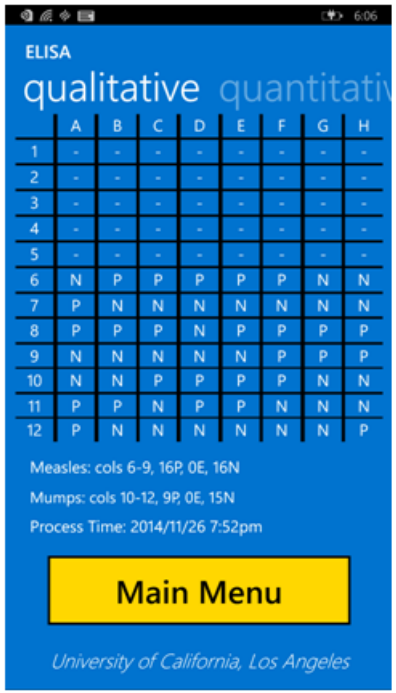
c



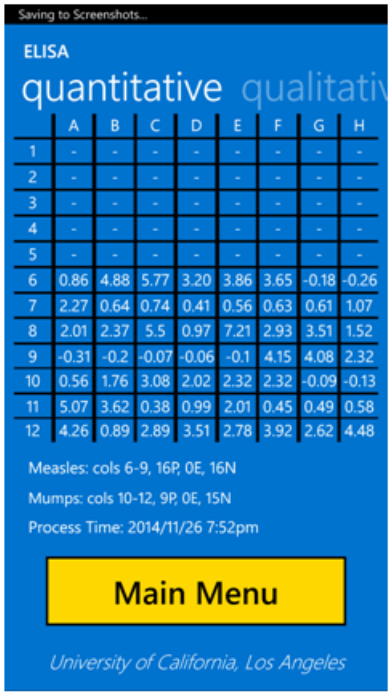
d



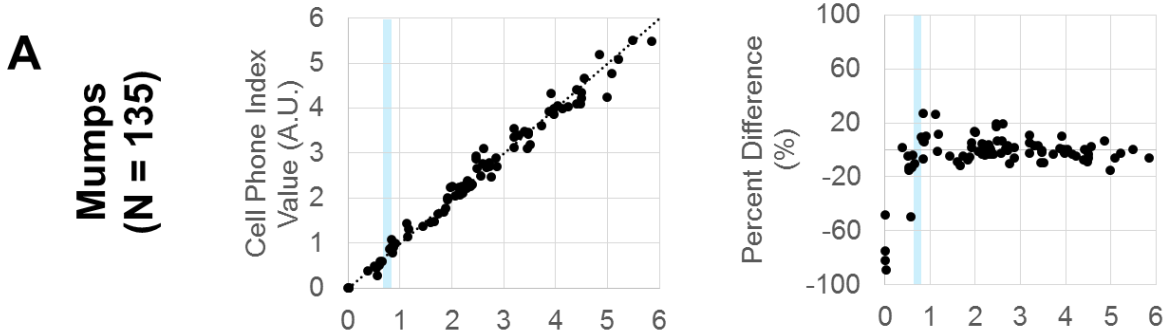
e

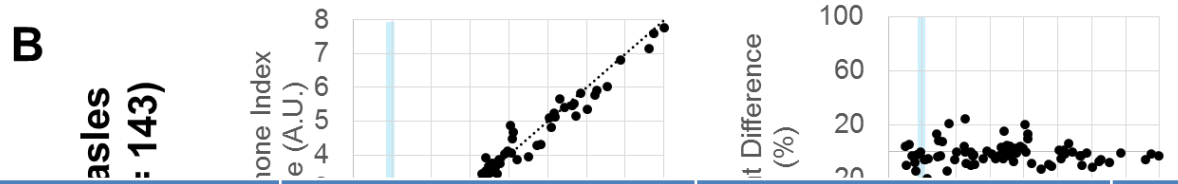


f

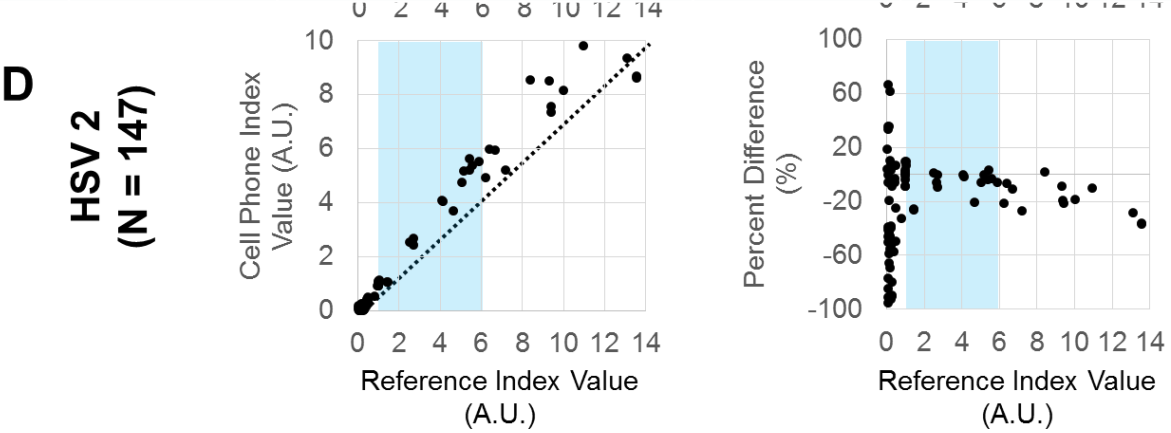


ACS Nano 2015





	Mumps		Measles		HSV 1		HSV 2	
N	133		138		151		149	
Analysis Type	Curve Fitting	M.L	Curve Fitting	M.L	Curve Fitting	M.L	Curve Fitting	M.L
Specificity	92.70% ± 0.49%	97.37% ± 2.63%	92.09% ± 0.77%	94.56% ± 3.43%	100.00% ± 0.00%	100.00% ± 0.00%	100.00% ± 0.00%	100.00% ± 0.00%
Sensitivity	100.00% ± 0.00%	100.00% ± 0.00%	98.39% ± 0.42%	99.47% ± 0.59%	97.32% ± 0.32%	100.00% ± 0.00%	100.00% ± 0.00%	100.00% ± 0.00%
Agreement	97.21% ± 0.41%	99.61% ± 0.39%	96.08% ± 0.32%	98.56% ± 0.53%	97.16% ± 0.55%	99.42% ± 0.43%	98.66% ± 0.22%	99.41% ± 0.44%



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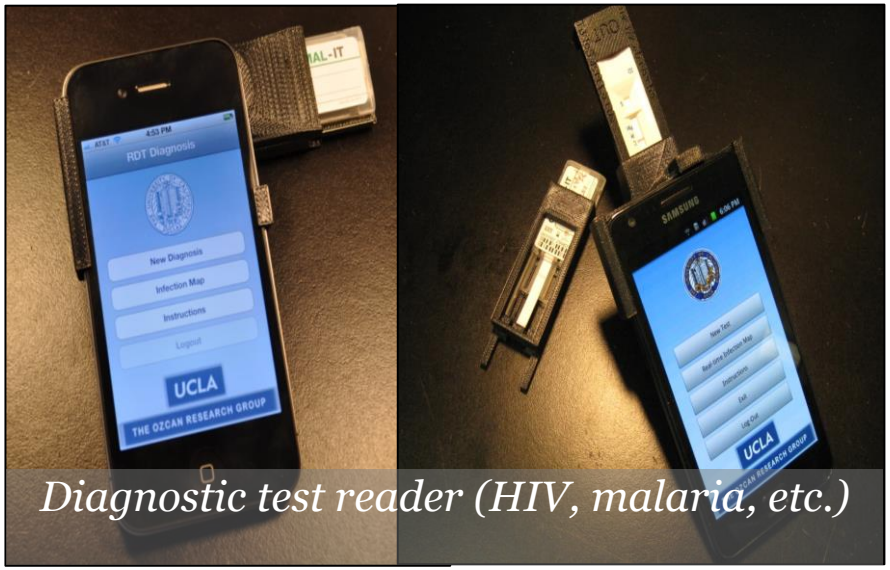
Providing a new platform for telemedicine

E. coli sensor

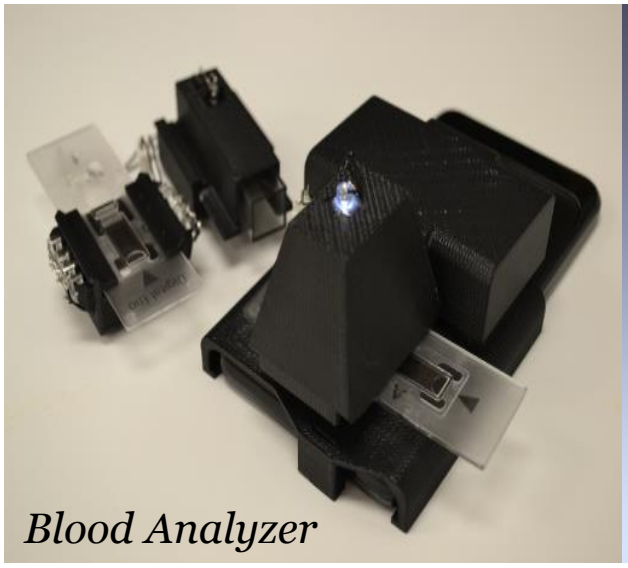
Allergen detector

Heavy metal detector

Google Glass based Diagnostics



Diagnostic test reader (HIV, malaria, etc.)



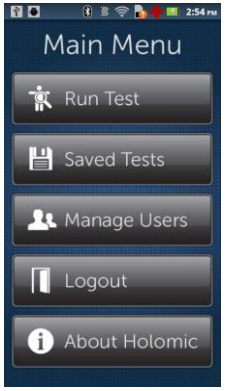
Blood Analyzer

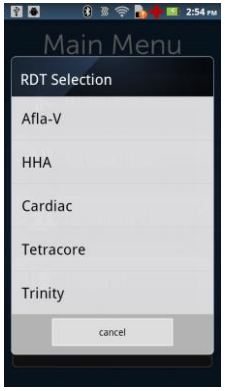
Blood Analyzer

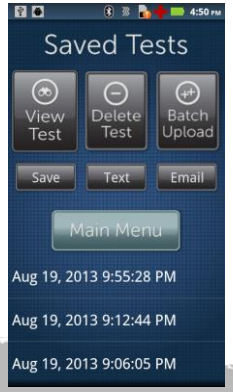
http://holomic.com/

HOLOMIC LLC

Mobile microscopy wherever you need it







Holomic has sales in >10 countries in four continents

HOLOMIC RAPID TEST READERS

- Proven Accuracy
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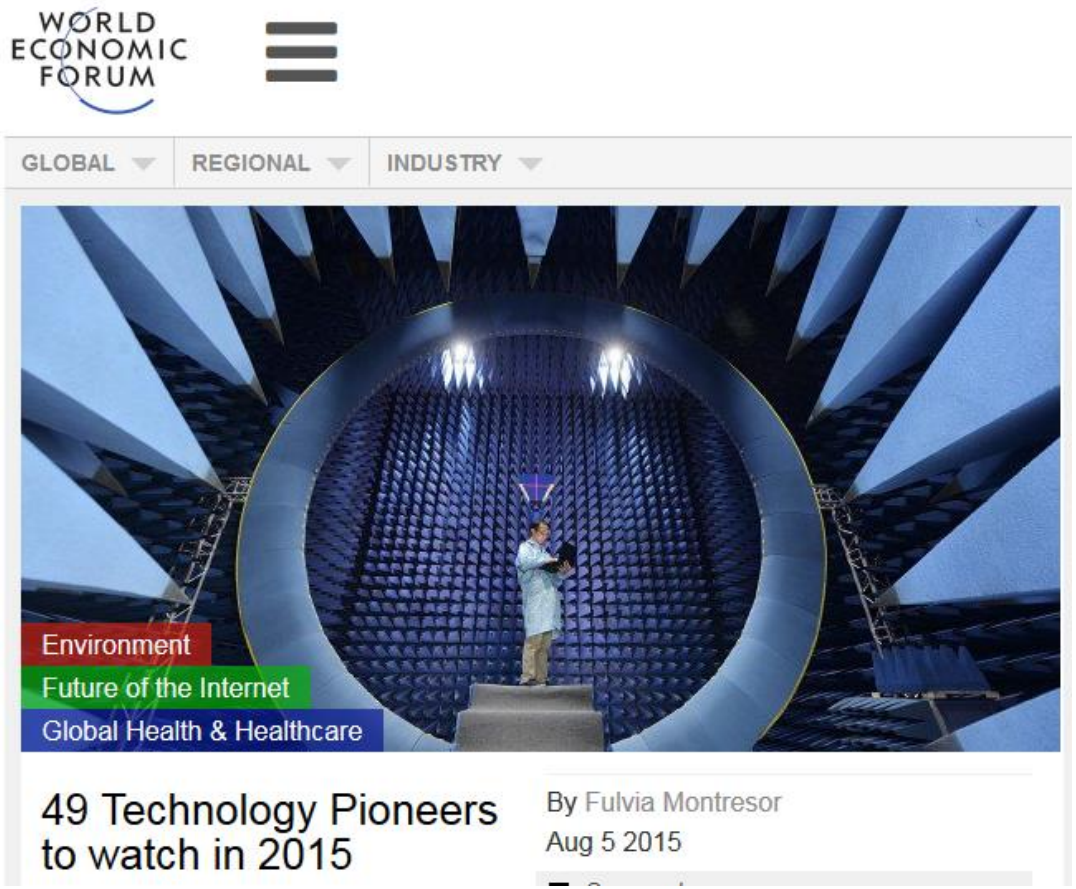
  - ❑ Chromatographic & Fluorescent
- Global Sales
  - ❑ RDT vendors- Infectious, Agriculture, Drugs, Bioterror, Lifestyle
  - ❑ Global health
  - ❑ Workforce, Forensic, Transport
- Complete Solution
  - ❑ Test Developer for Manufacturers
  - ❑ CLOUD Server & Distribution Services
- CE Mark

http://holomic.com/

Holomic @ the World Economic Forum Technology Pioneers List, 2015



The World Economic Forum selected Holomic among the Technology Pioneers 2015 - among the most promising 49 early-stage companies in the world.

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