JSS / NANO2, 2014

Nano Machinery & Imaging
Towards Personalized Medicine

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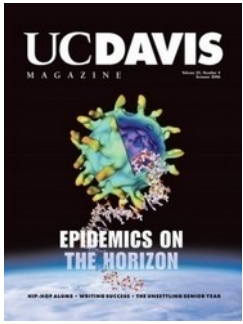
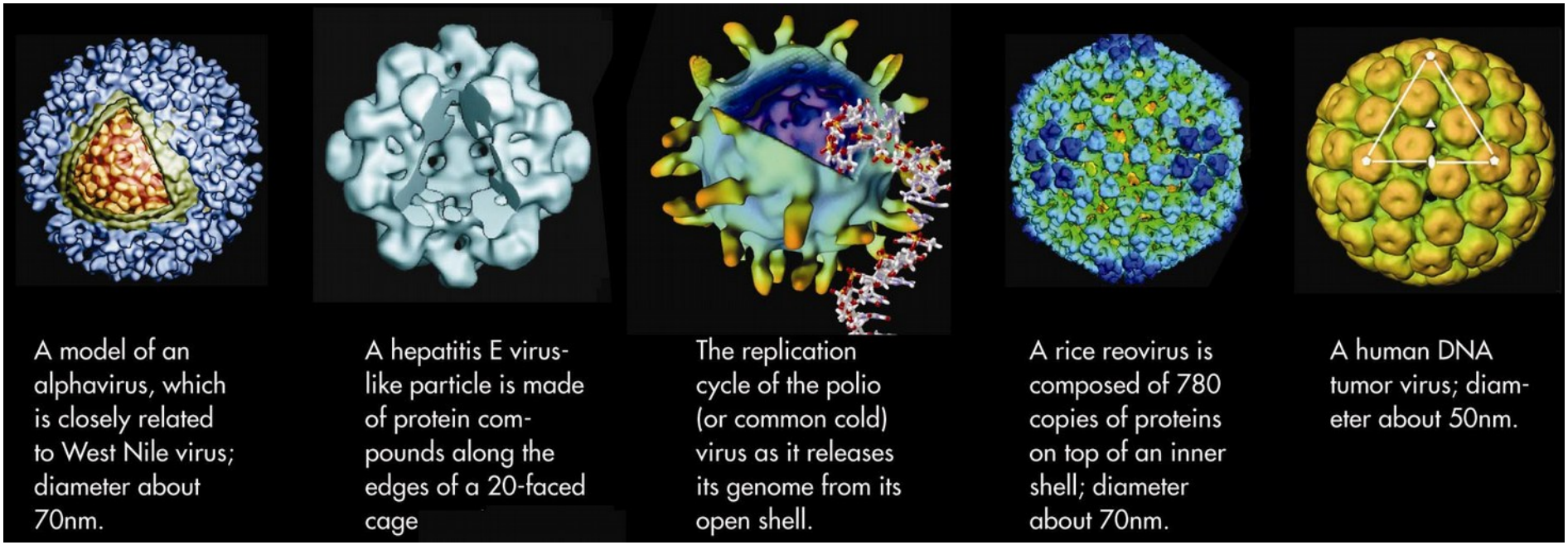
University of California
http://pioms.ucdavis.edu

NIH Roadmap MHRP U.S. MILITARY HIV RESEARCH PROGRAM NOVARTIS



Conformational proteomics for nanomedicine



Model approximation / deformation to prevent bias

- **knowledge base**
- **averaged mass**
- **majority call / population convergence**
- **familiar object assumption**
- **geometry common lines**
- **single molecule reconstruction**

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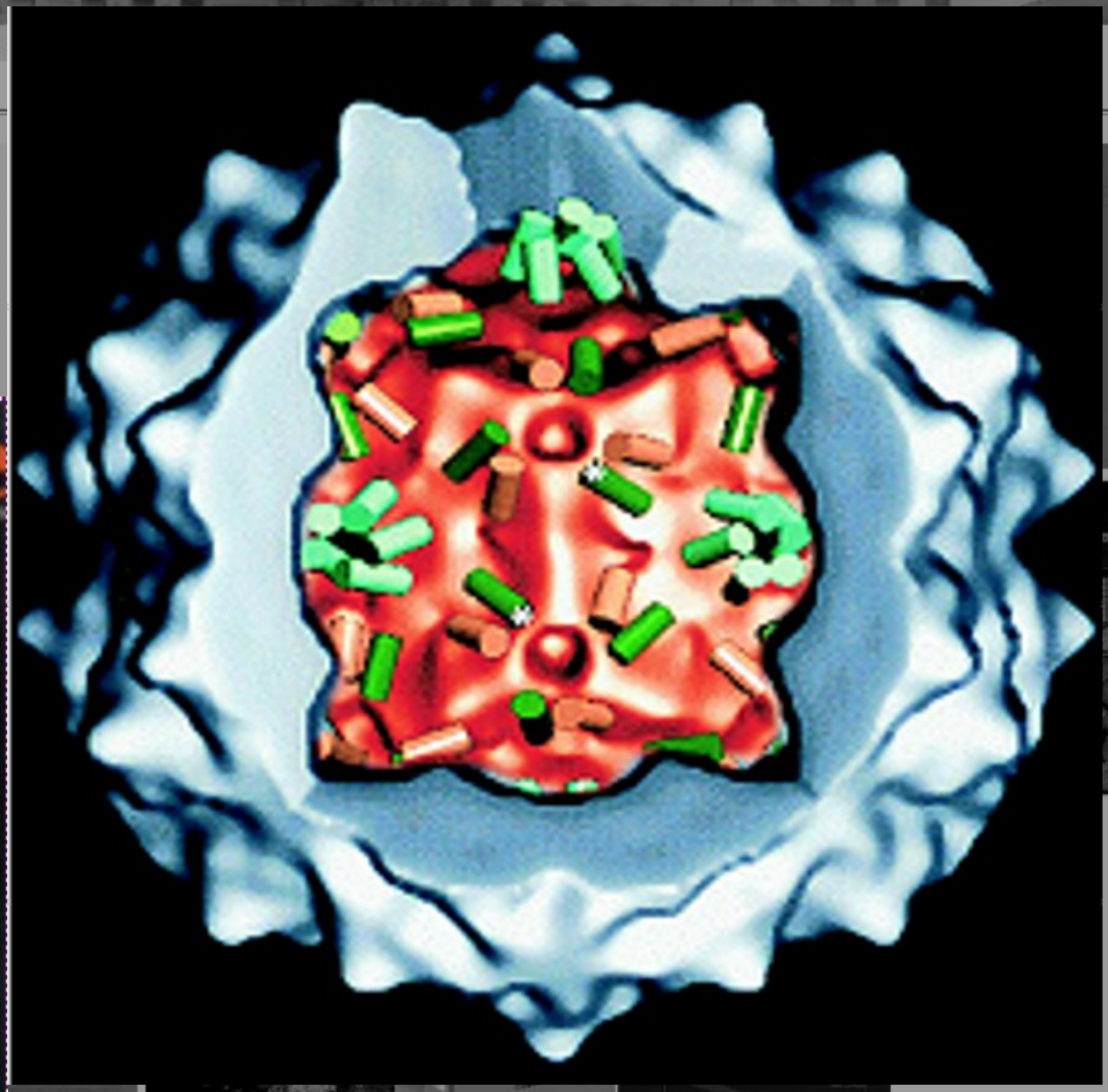
Cheng et al. Structure (1994)

Genome In/Out via a 30nm particle



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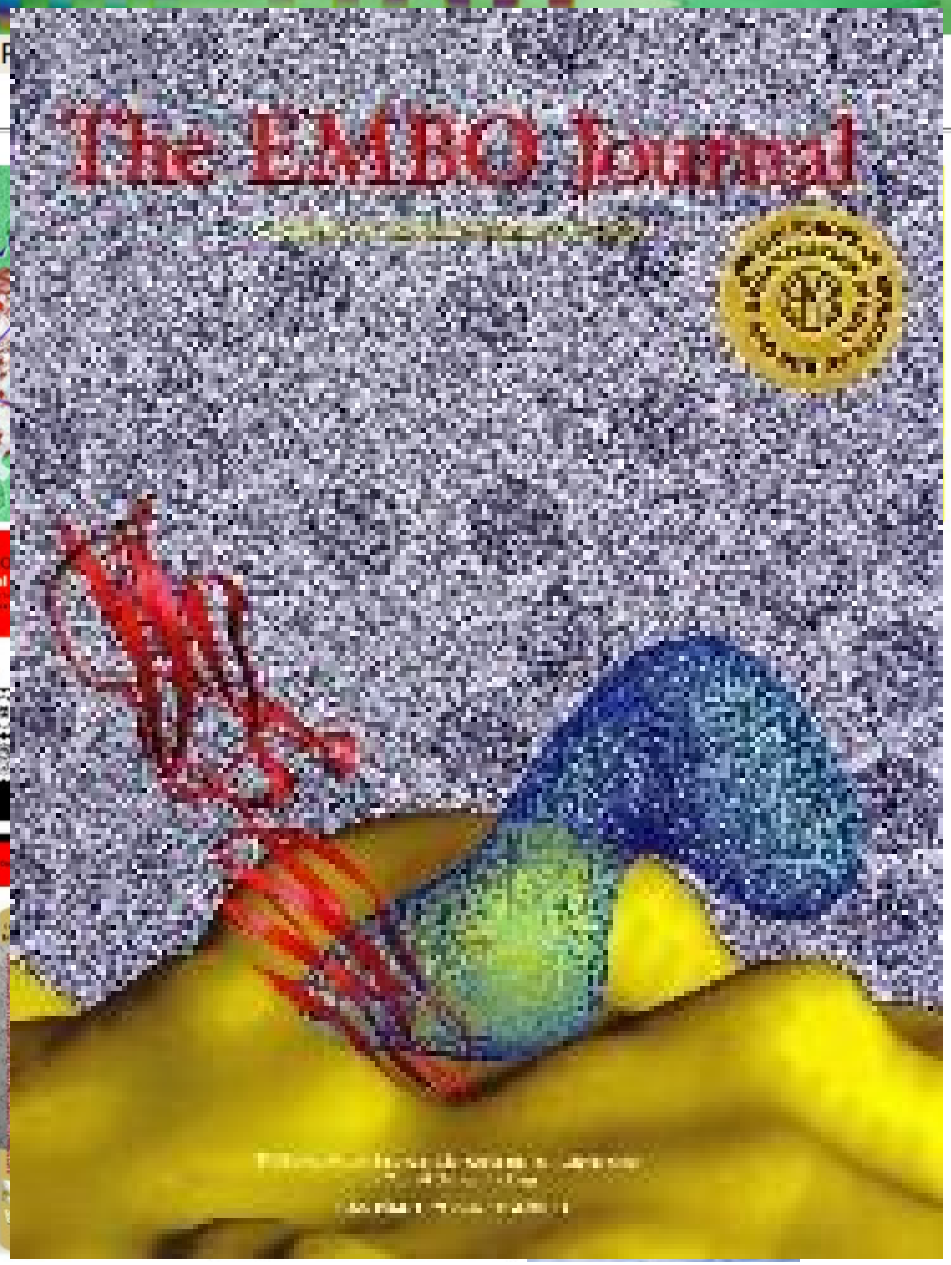
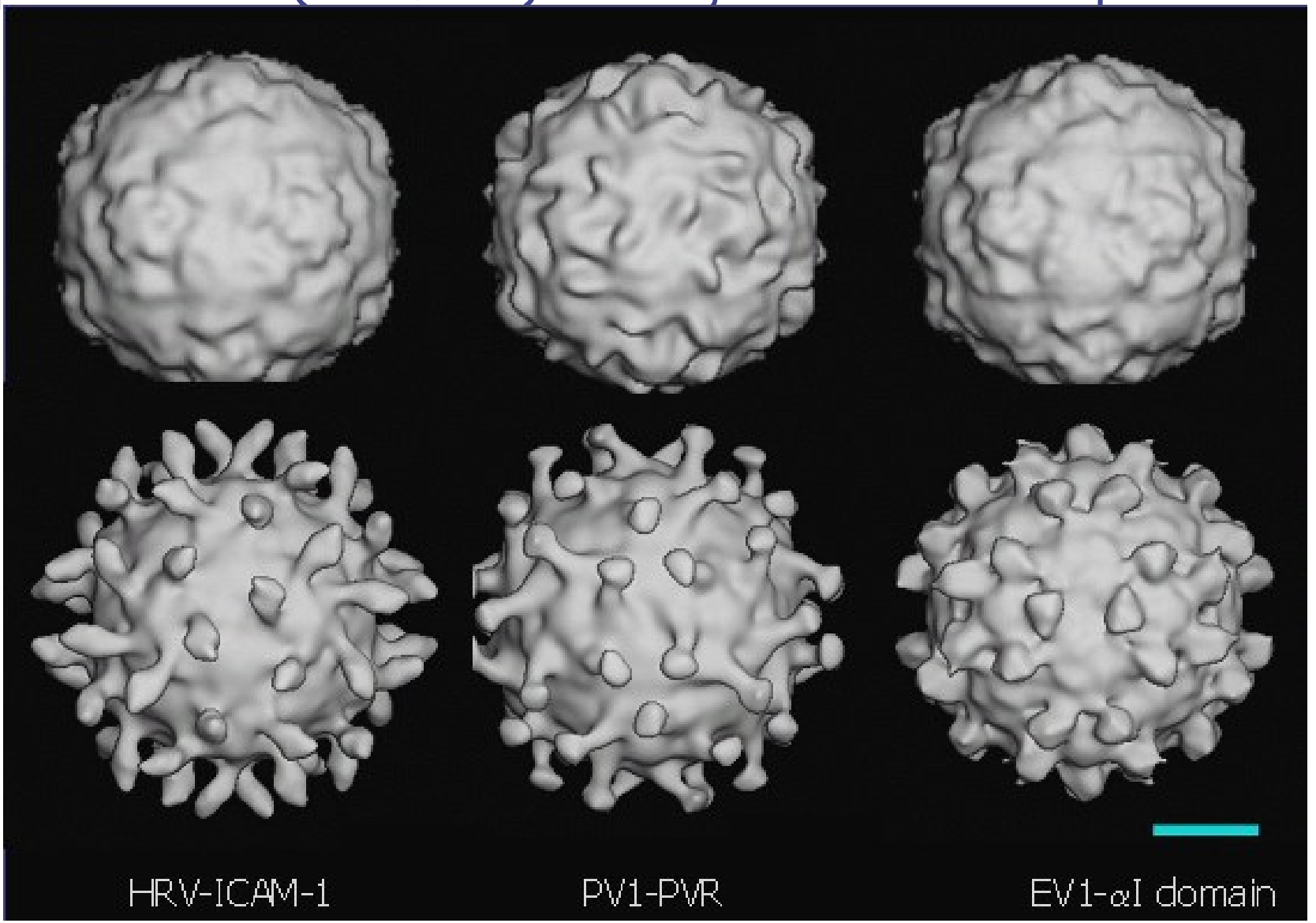


Case 3
Time domain

polyvalence in host recognition

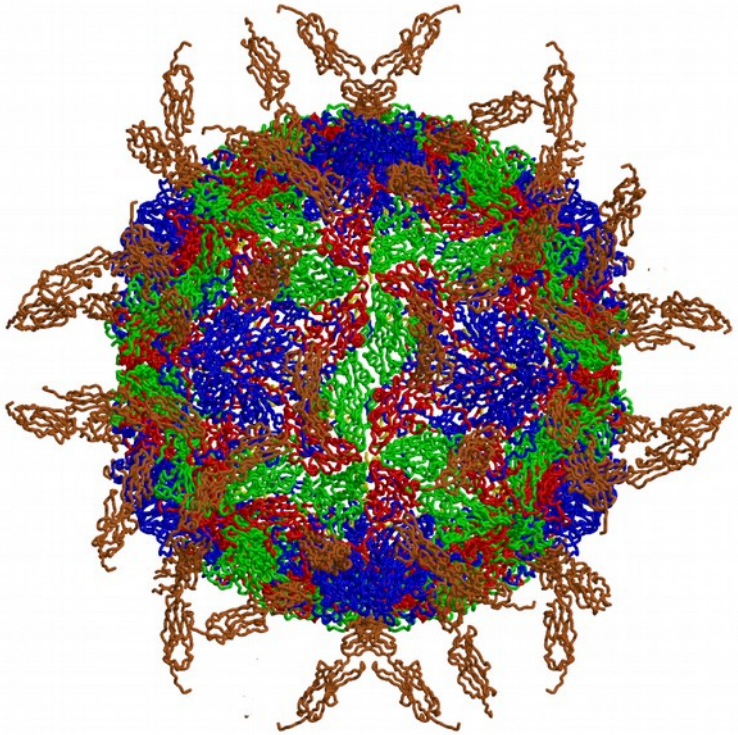
picornavirus (30nm dia) binding to cellular receptor



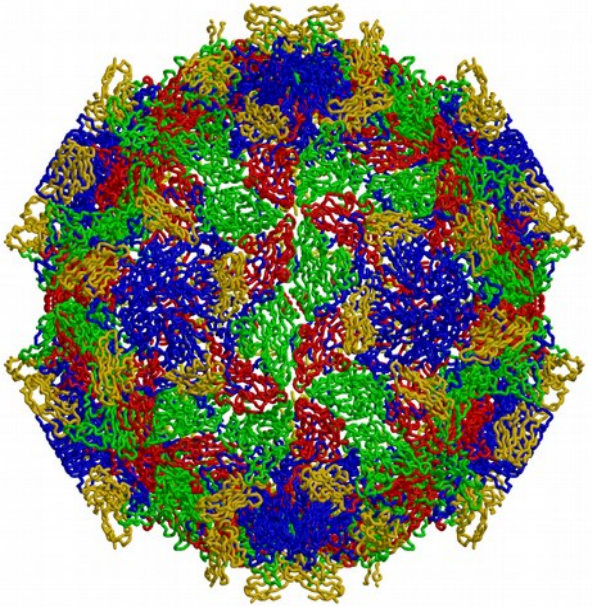
Human rhino Polio Echo 1

Multi-resolution approach

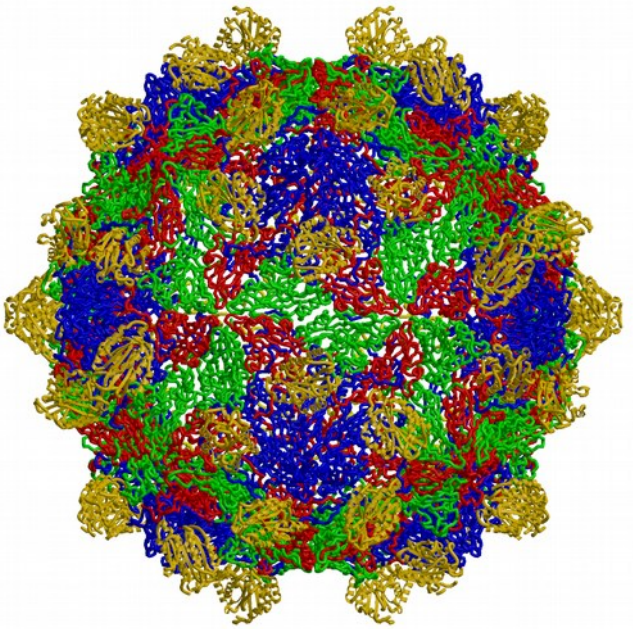
viruses have evolved to use different receptors for cell recognition and entry



Rhinovirus 3



Poliovirus 1



Echovirus 1

EMBO J. 2000; JV 2003; JBC 2004

US20120301494 A1 (2012)
US20120064169 A1 (2012)

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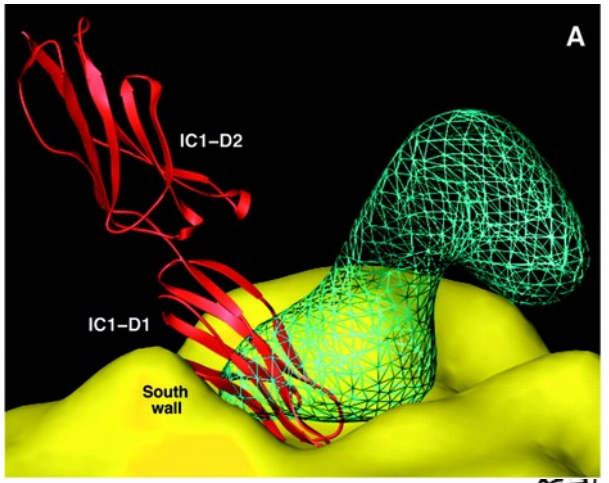
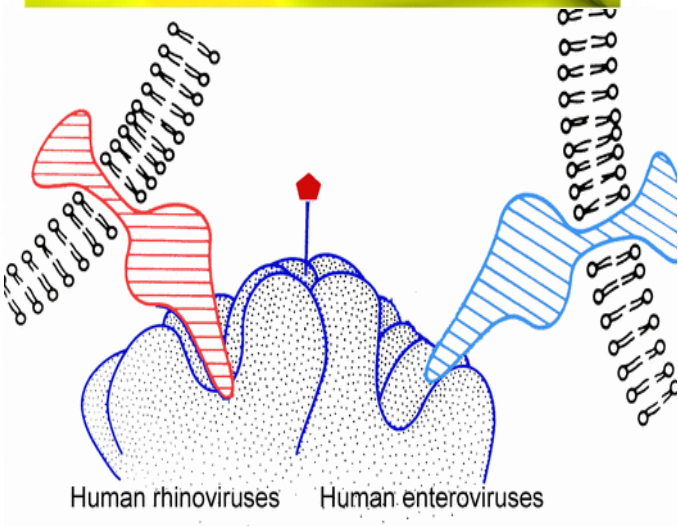
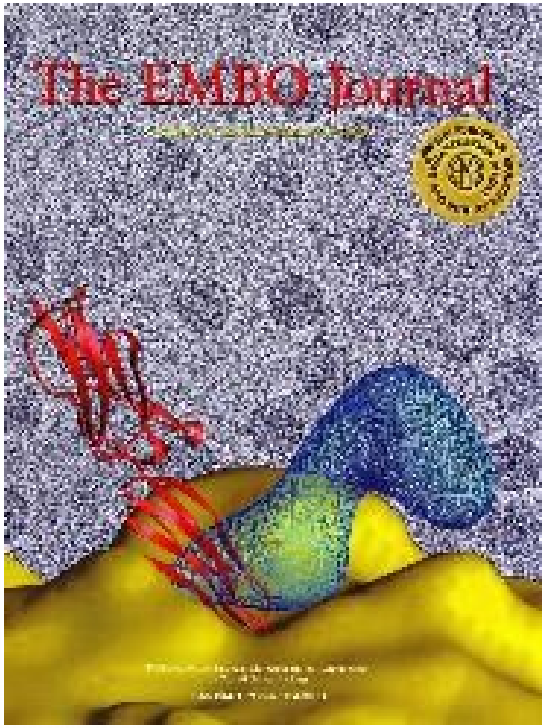
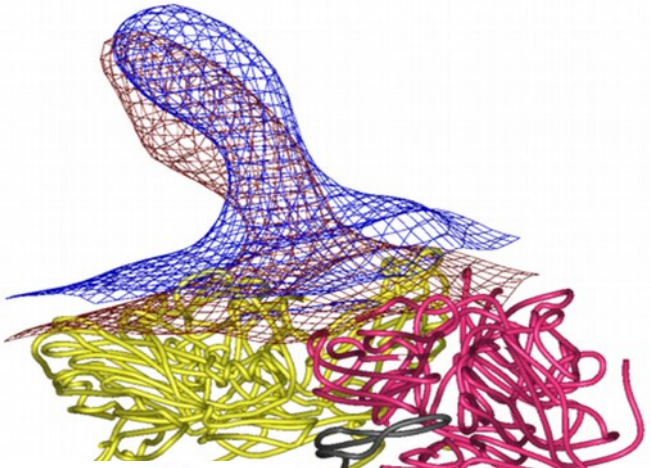
picornaviruses have evolved to use different receptors for cell recognition and entry

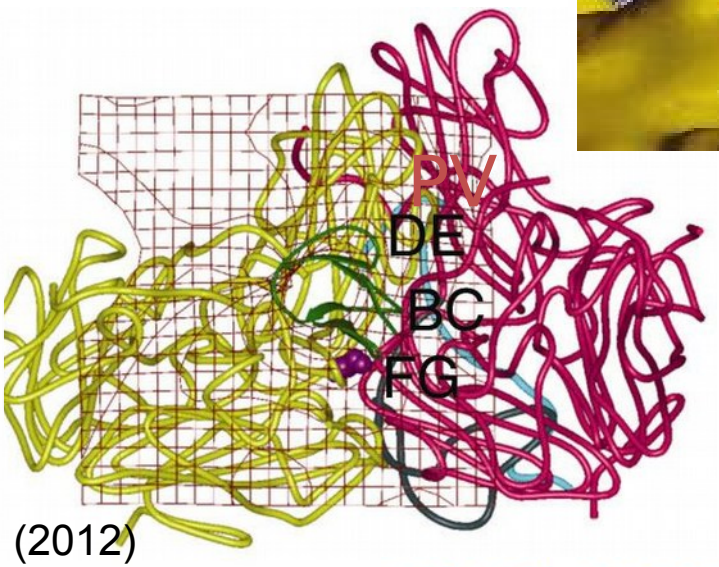




Canyon targeted for conserved receptor binding site







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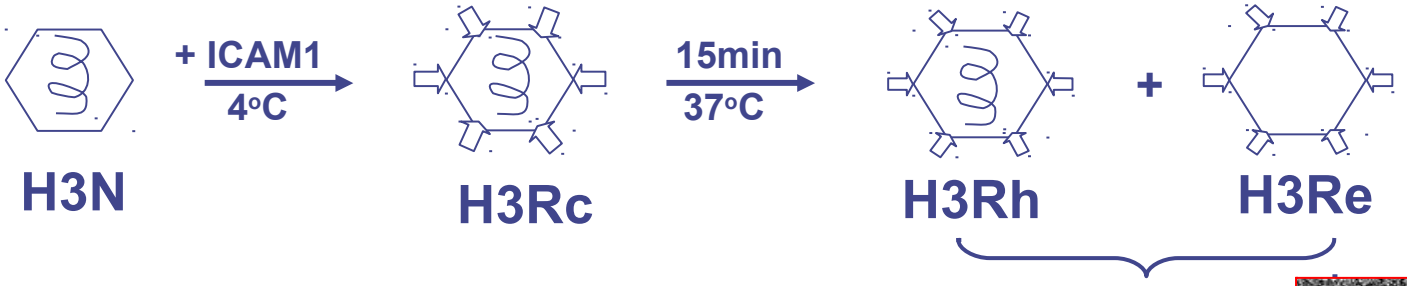
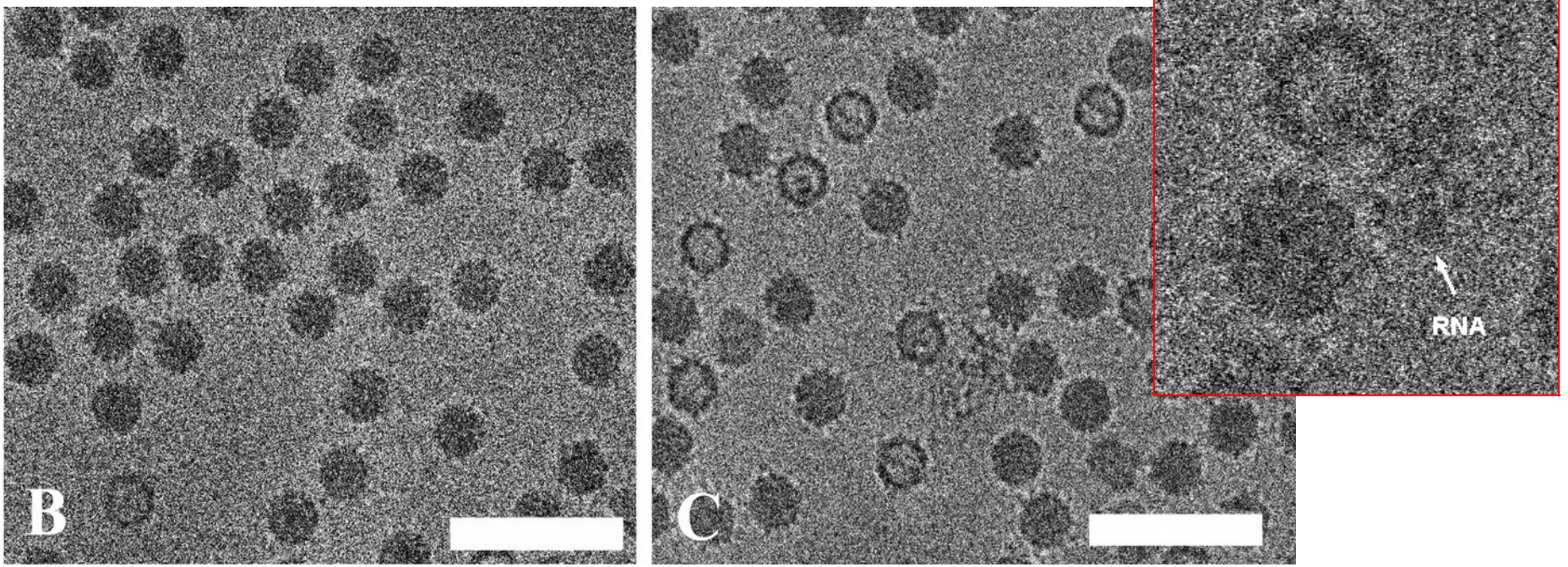
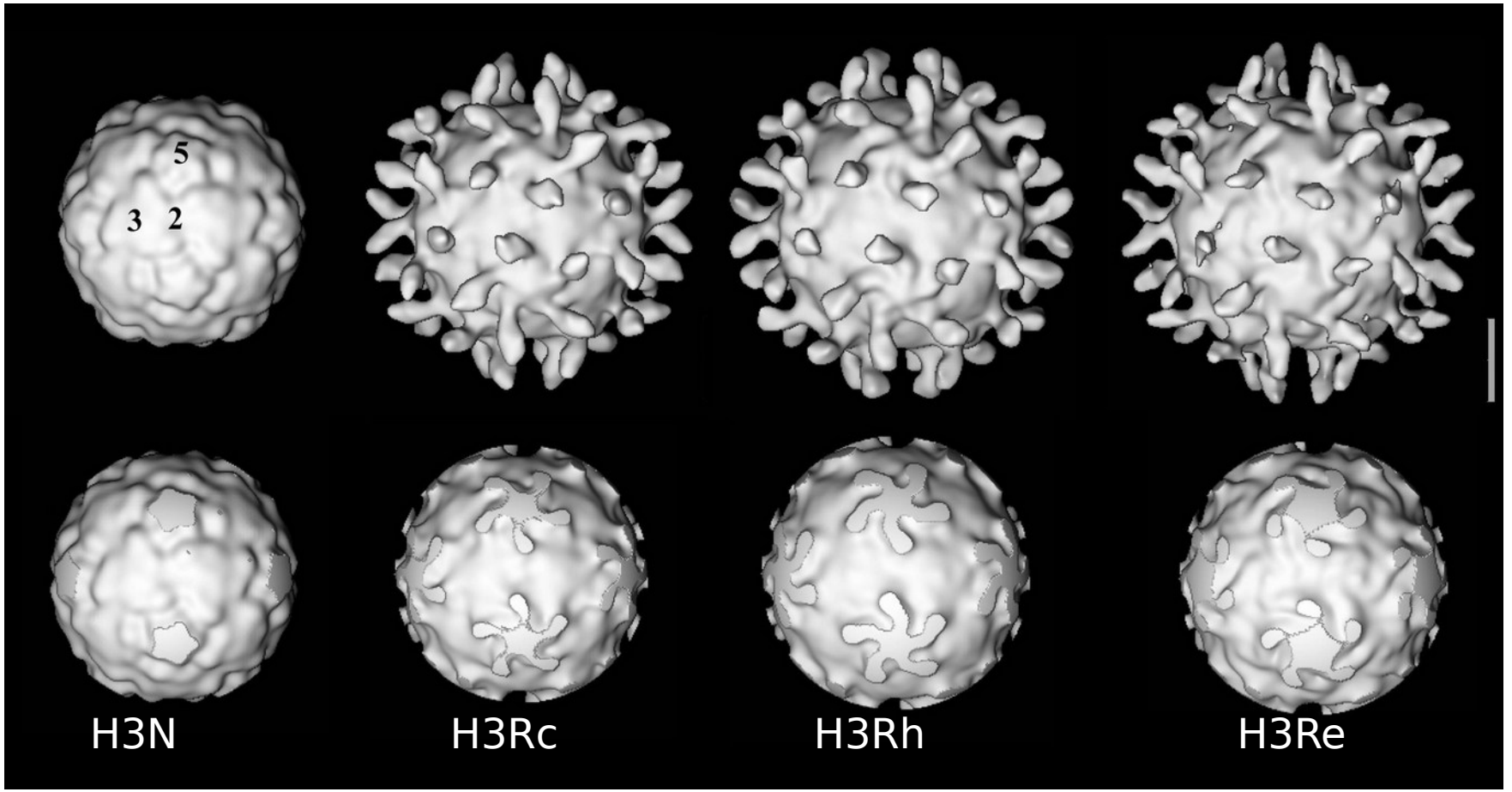
Receptor-mediated uncoating (HRV3)





3D reconstructions of HRV uncoating intermediates



US20120301494 A1 (2012)
US20120064169 A1 (2012)

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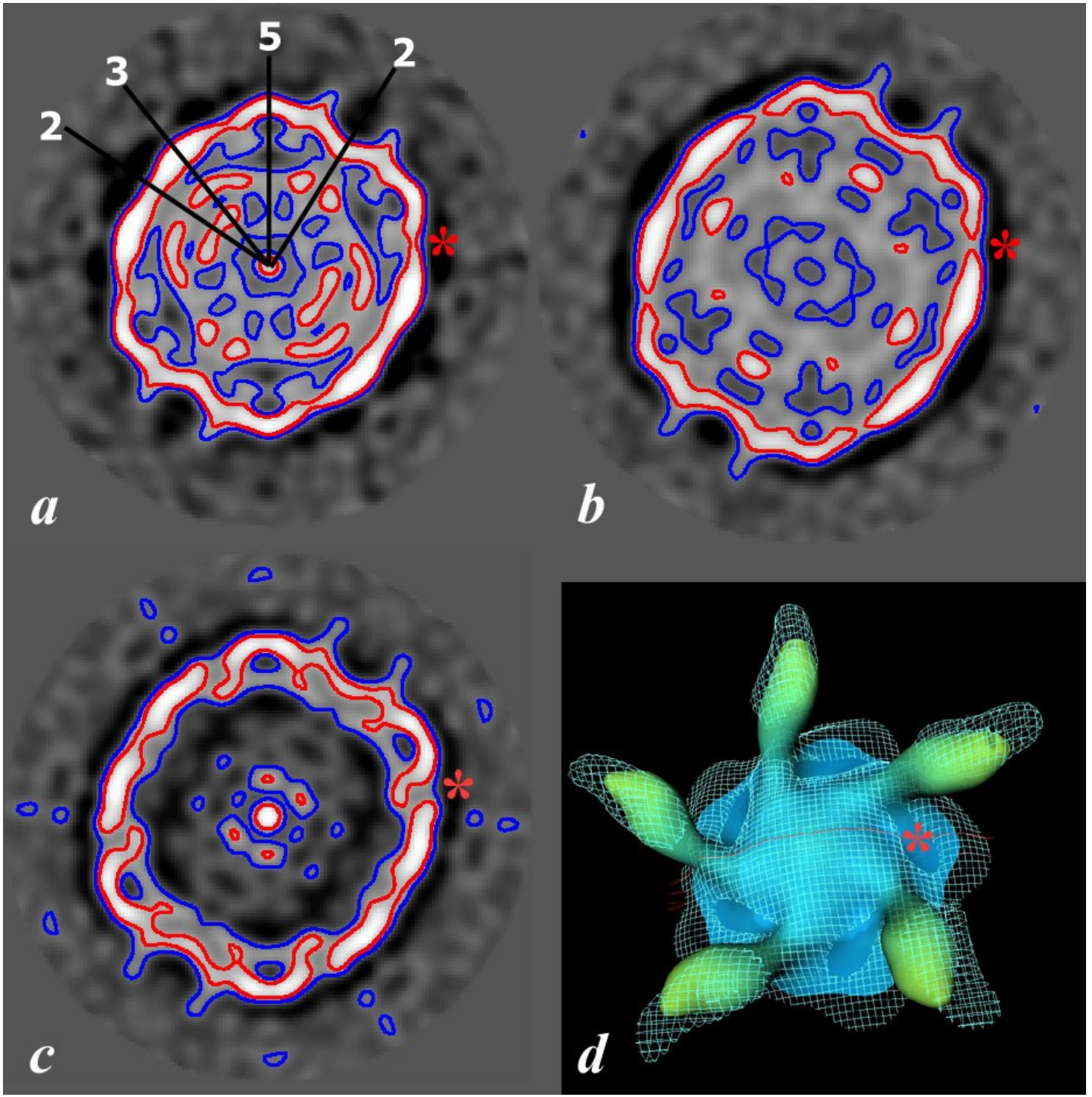
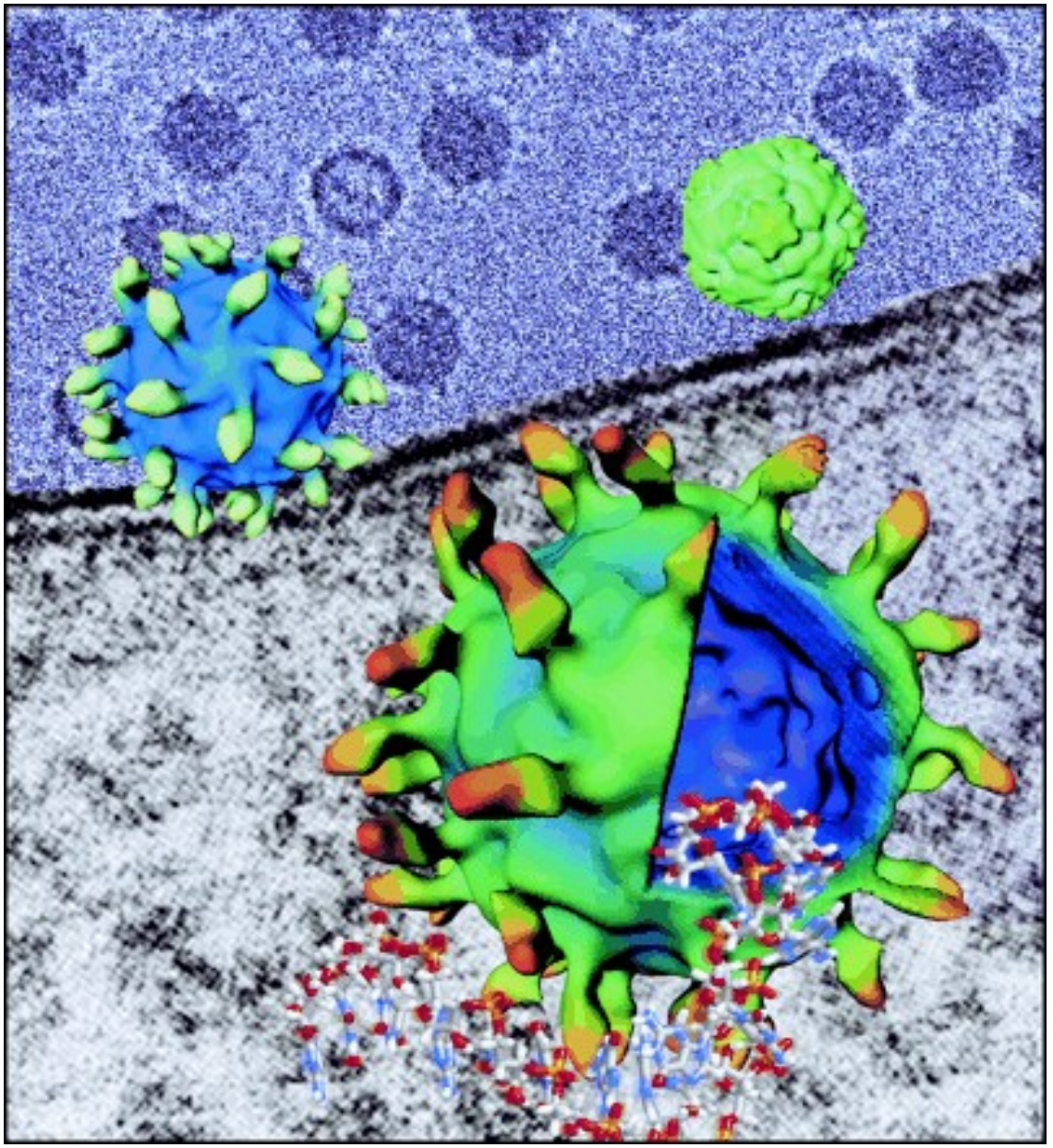
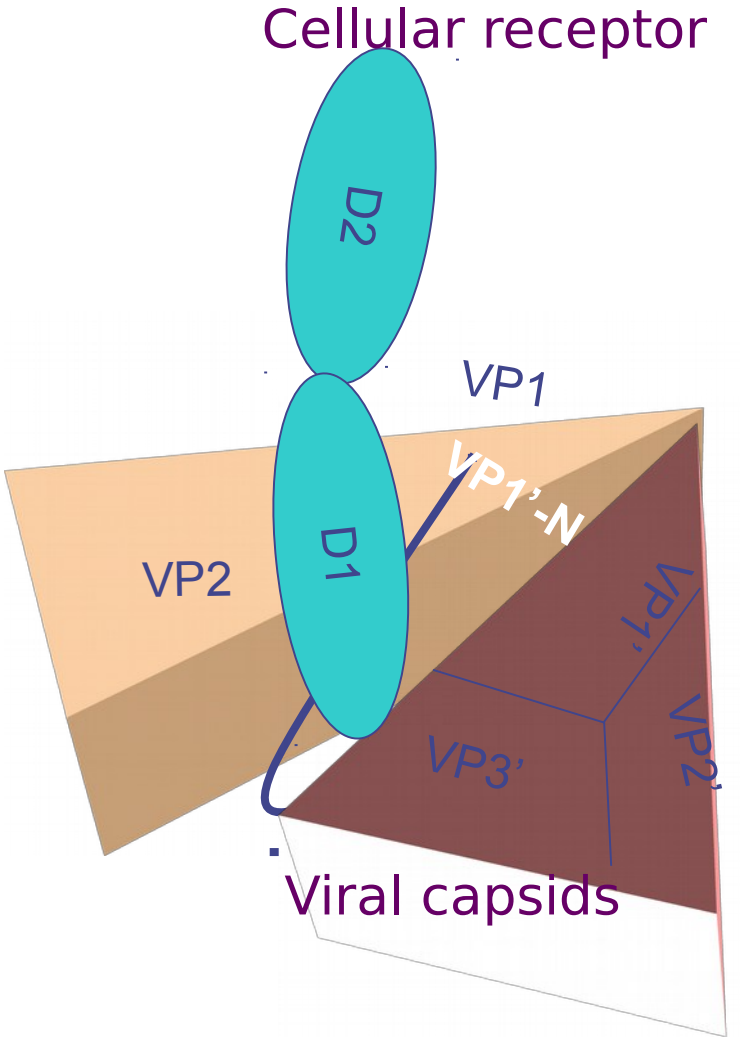

5
3
2
2
a
b
c
d

viral capsid '*breathing*' - multi-function antiviral peptide

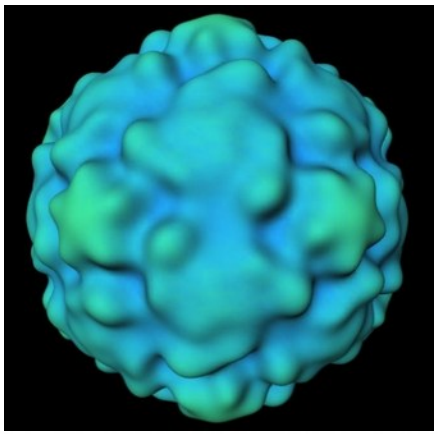


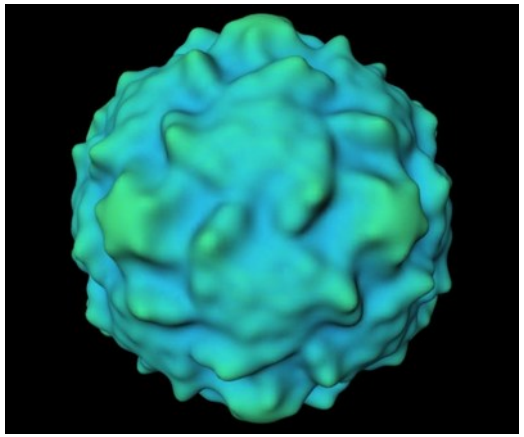


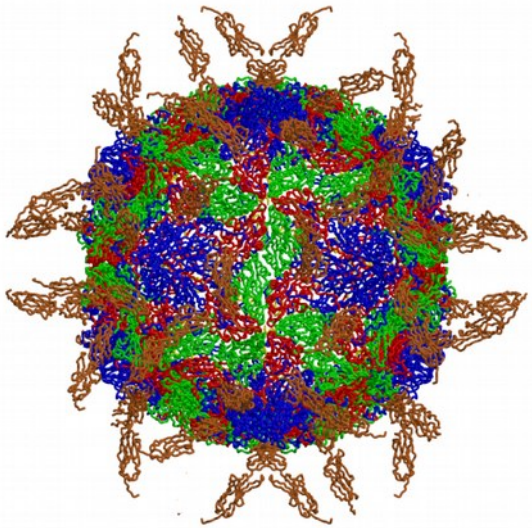
J Biol Chem, 279, 11632 '04
J Virol. 77, 6101 '03
EMBO J., 19, 1207 '00

Xing et al., *JBC,* 279:11632 & Xing et al., EMBO J, 19:1207

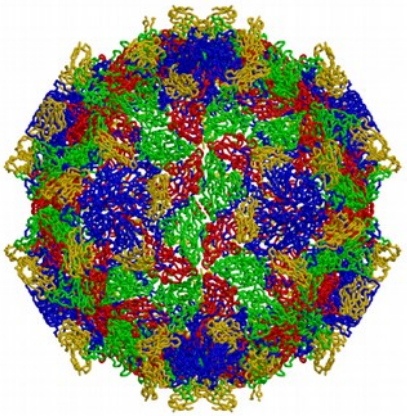
deep to the canyon – preserved interaction with cellular receptors



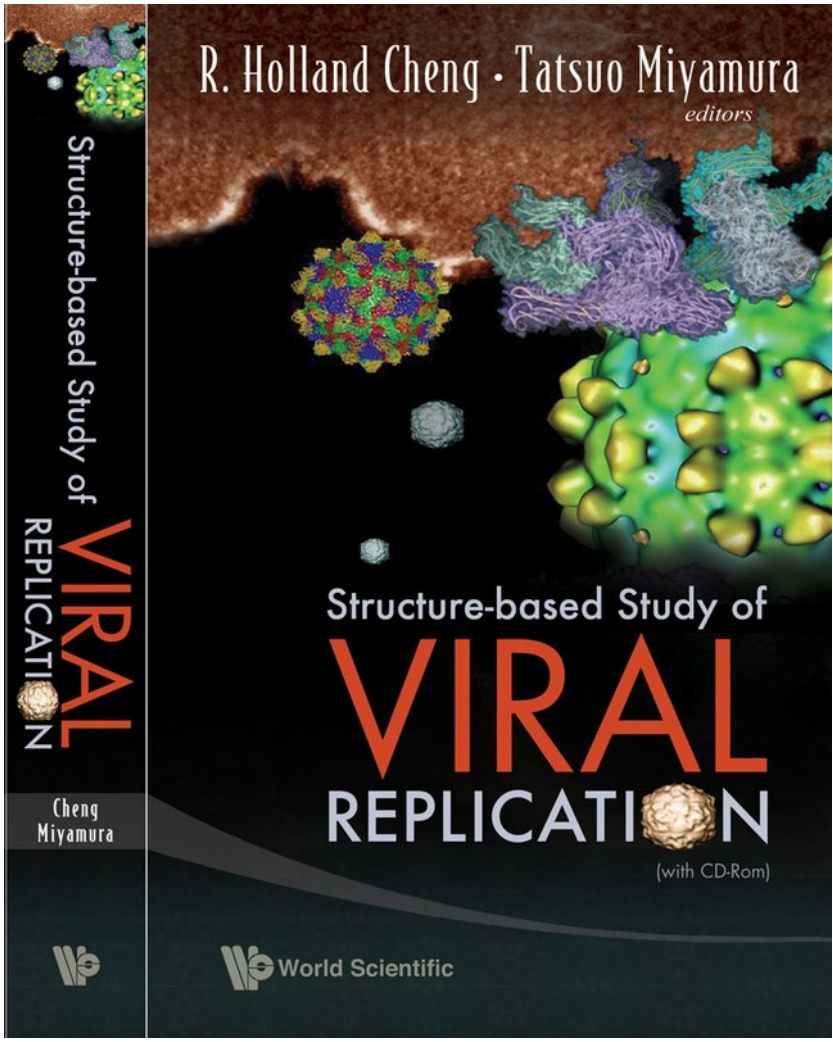




Rhinovirus 3



Poliovirus



Echovirus

formfunction

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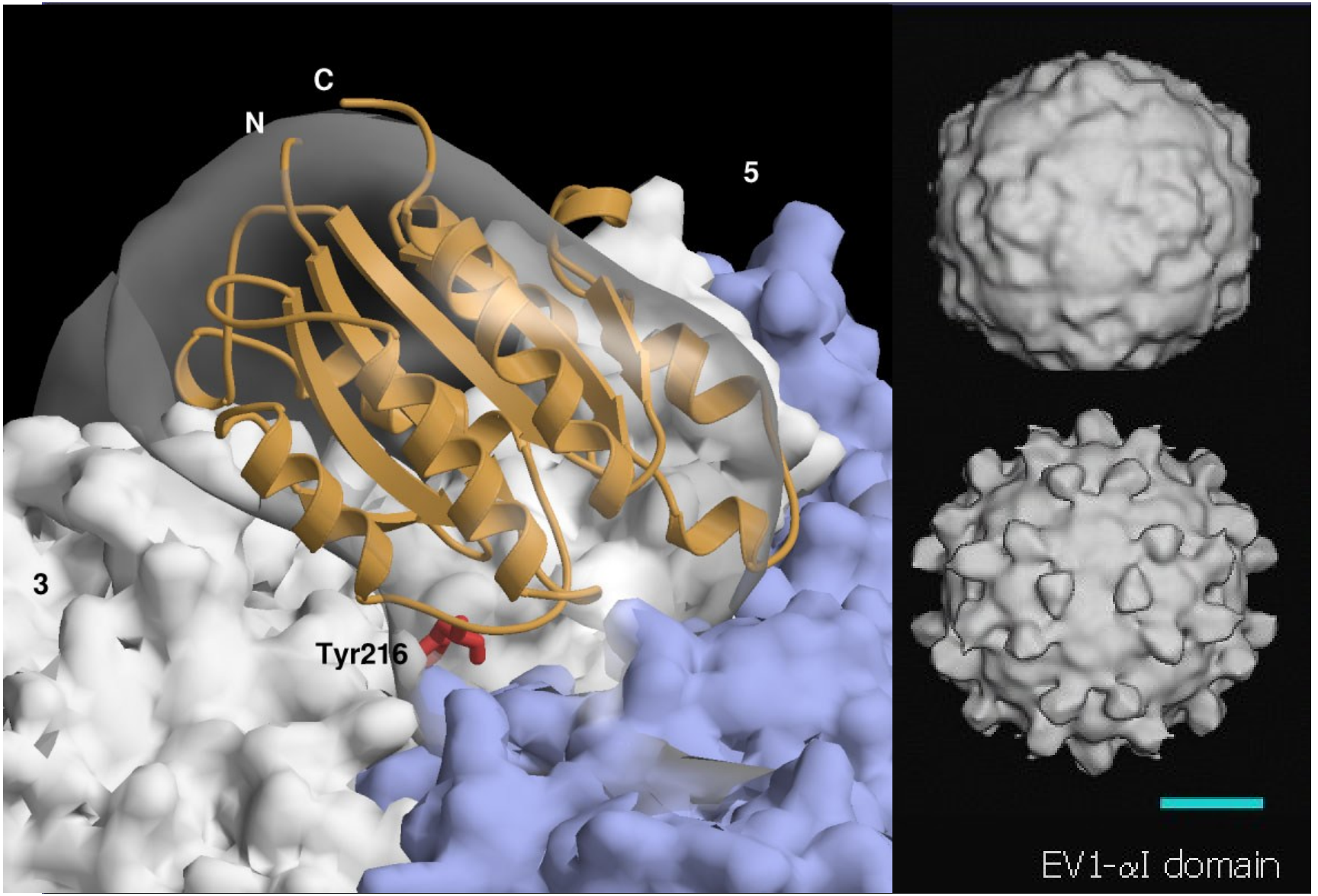
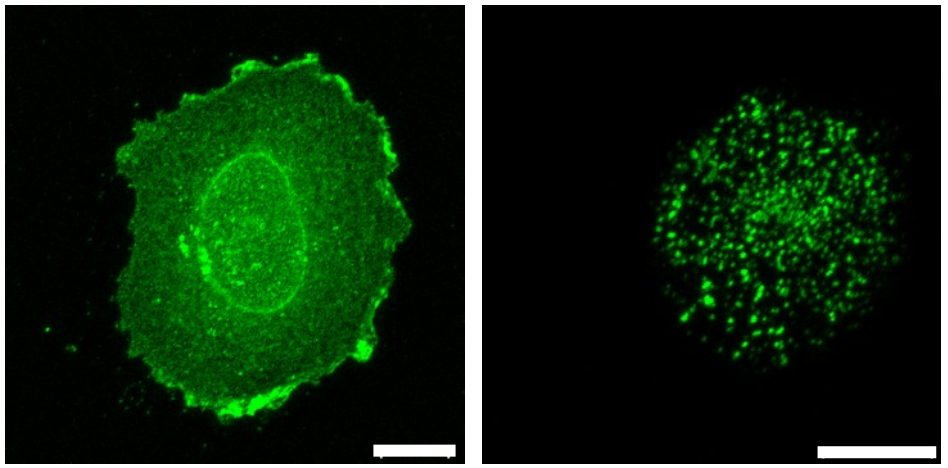
Echovirus 1 + integrin (α-I domain)



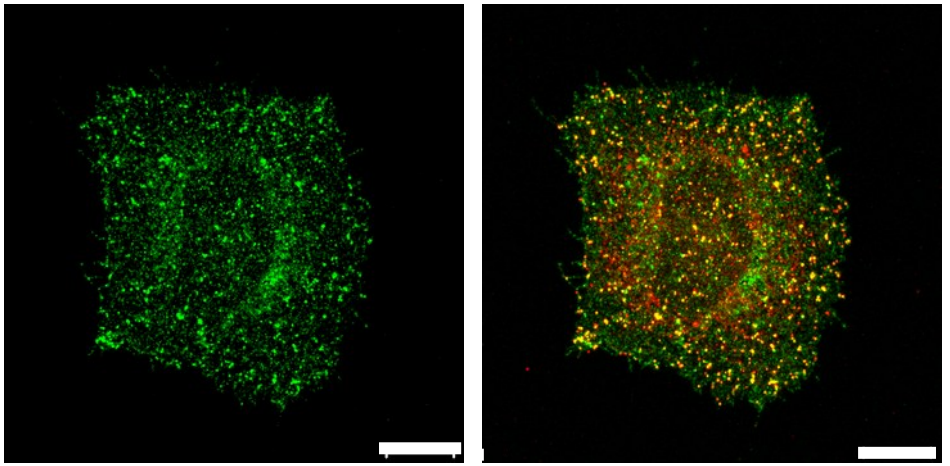
EV1 enters the cell *via* integrin clusters

Signaling by polyvalent interactions



control cell
green=α2β1 integrin

+ antibody
green=α2β1 integrin

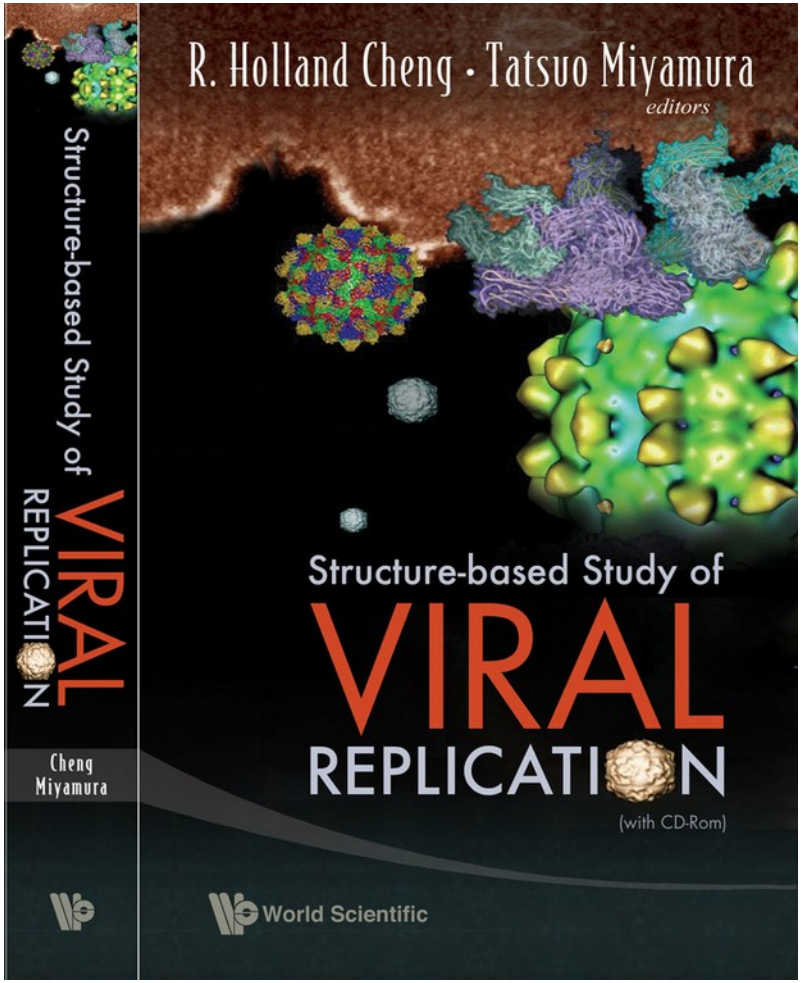


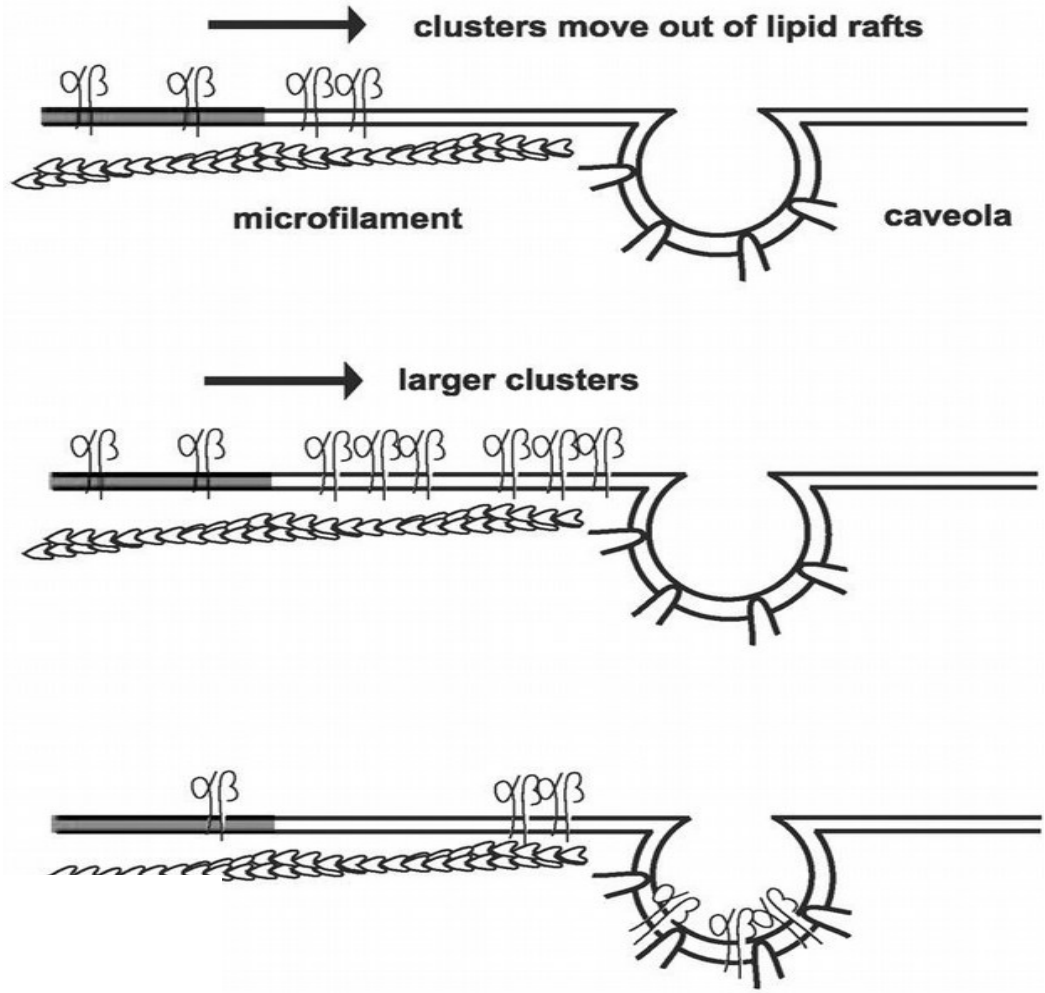
+ EV1
green=α2β1 integrin

+ EV1
red=EV1, yellow=merge

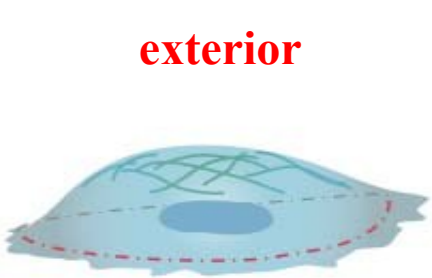
- the binding of viral capsid to the integrin transduces signaling inside the cells (outside-in signaling), although integrin functions are regulated in parallel by inside-out signaling
- virus entry and signaling using cells expressing recombinant integrins and other immobilized systems with soluble proteins

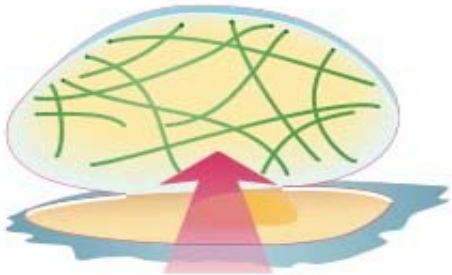
Bars = 10μm.



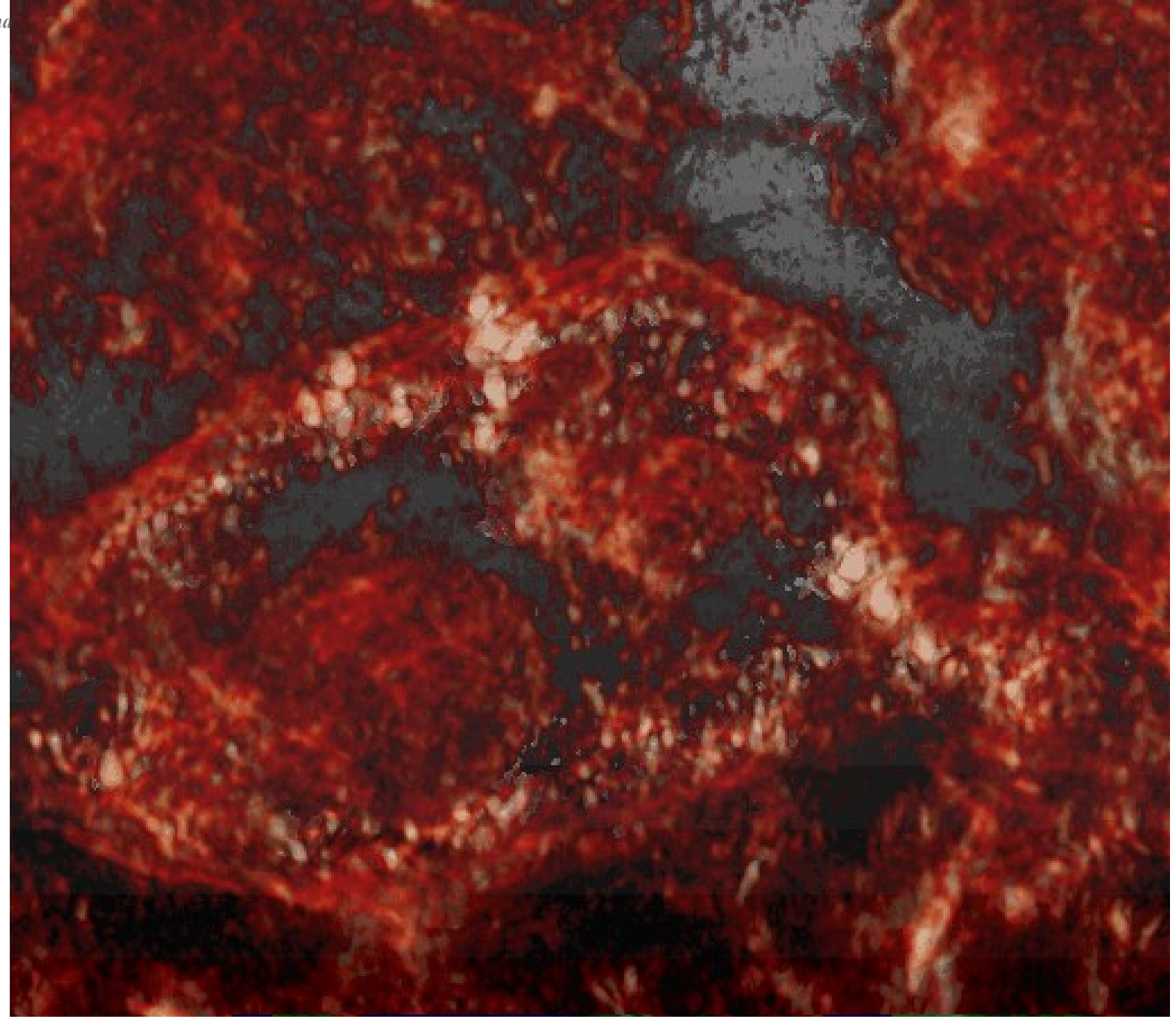


exterior





interior



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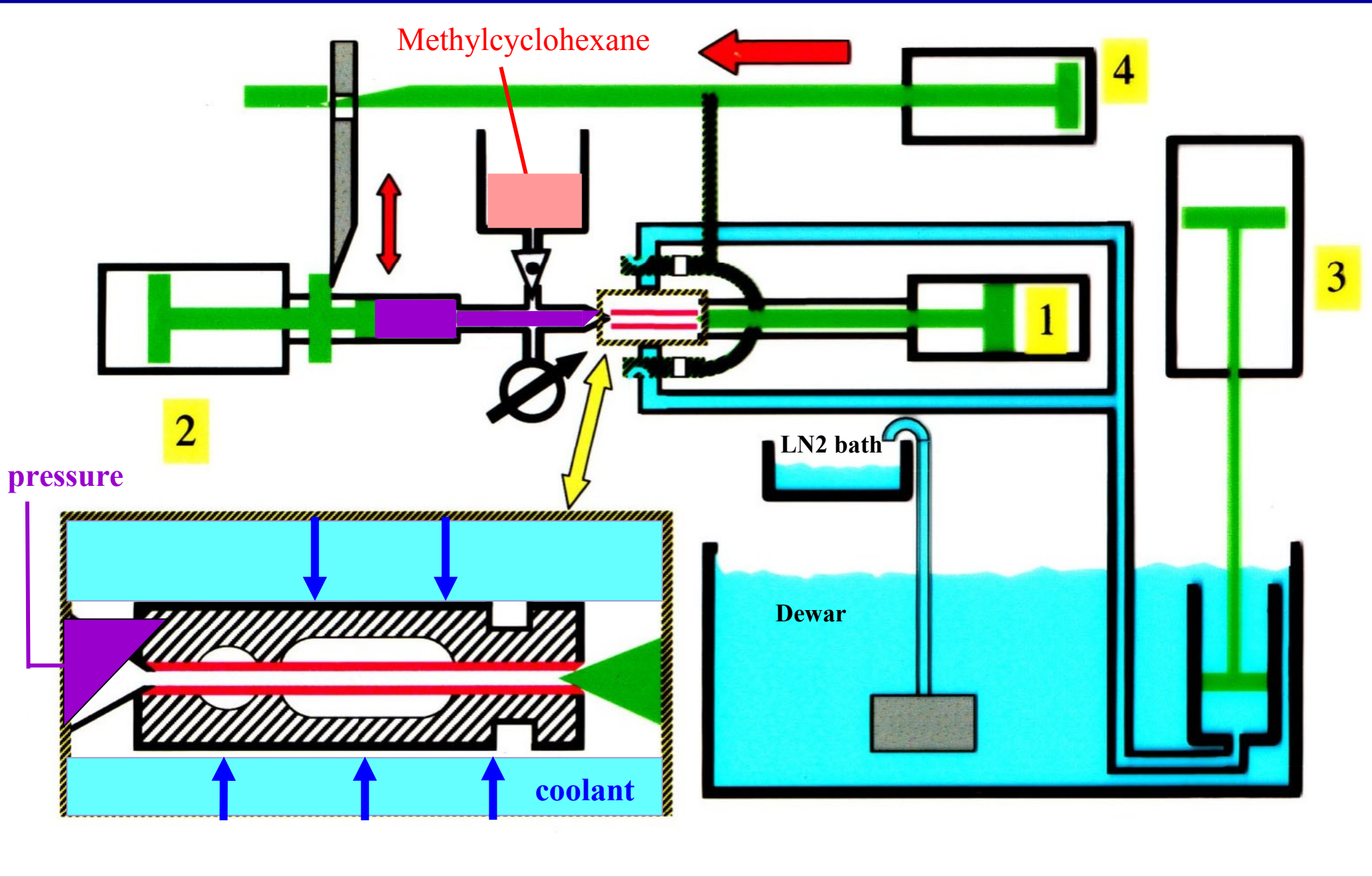
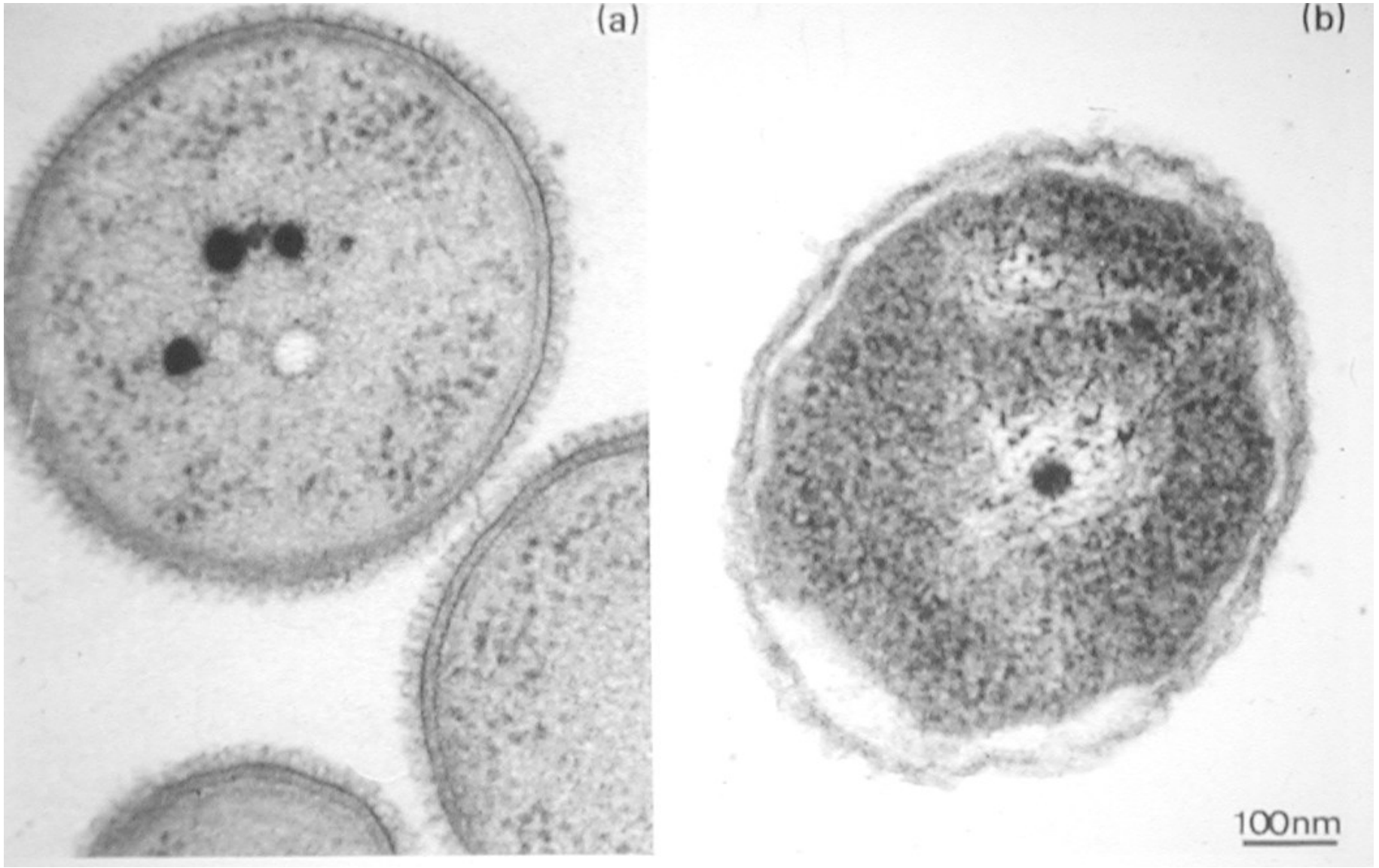
In EM PACT, the pressure and the cooling are separated.



HPF vs Chemical fixation: *Pseudomonas fluorescens*

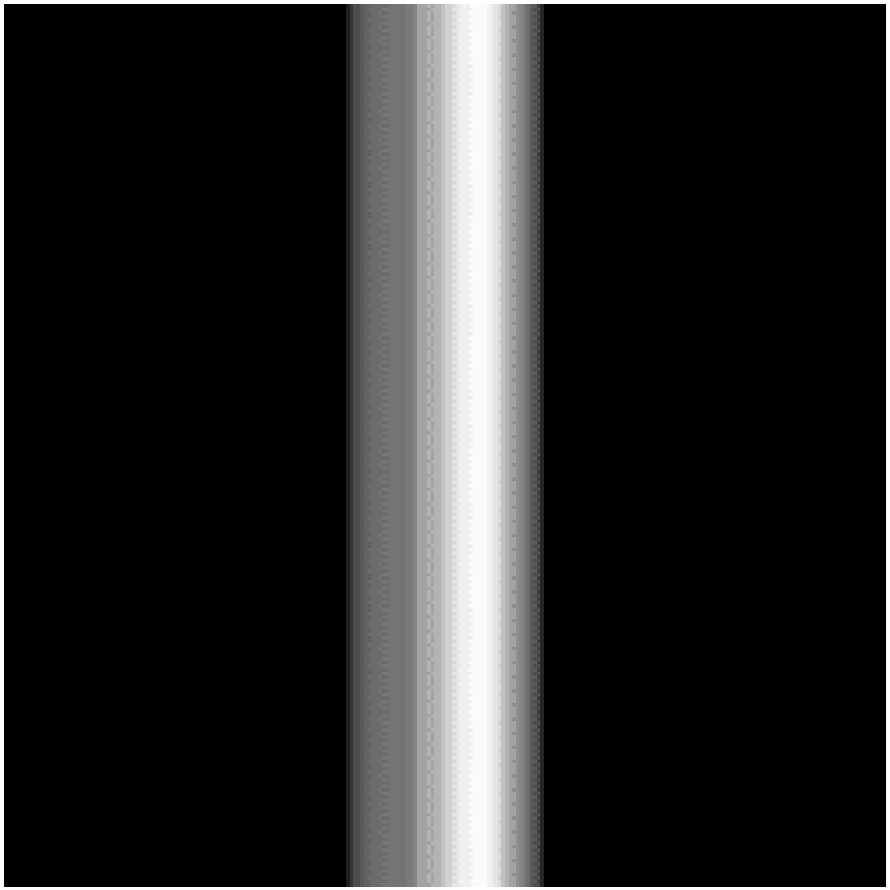


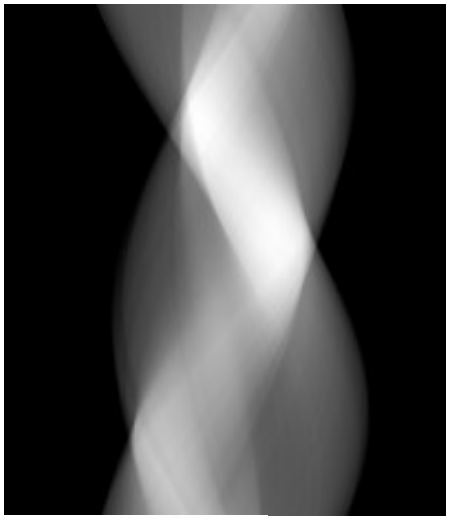
Cryofixation

Chemical fixation

Kellenberger, E. 1990. J. Microscopy 161(2):183-203.

Technical revisit / Back-projection





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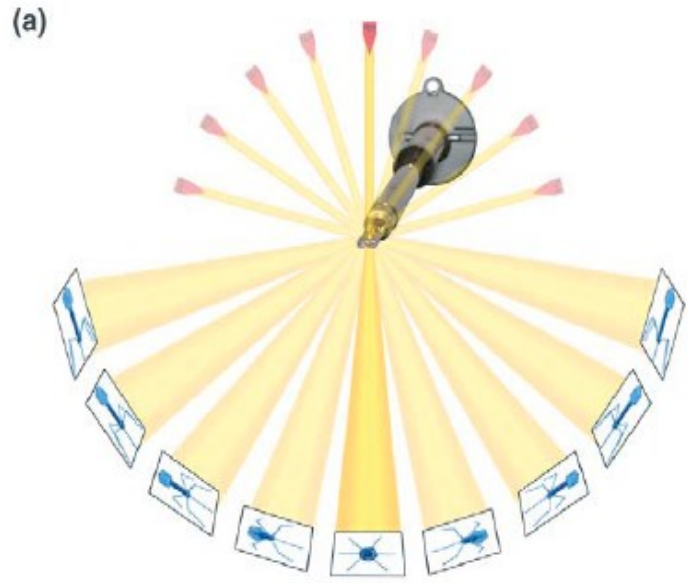
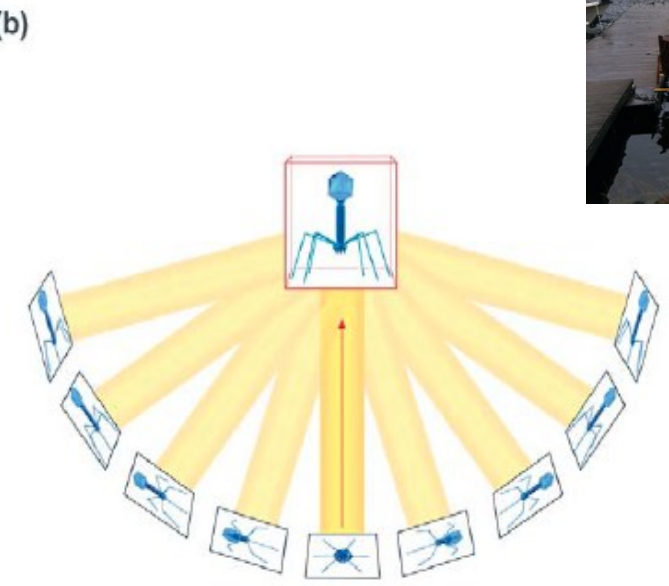
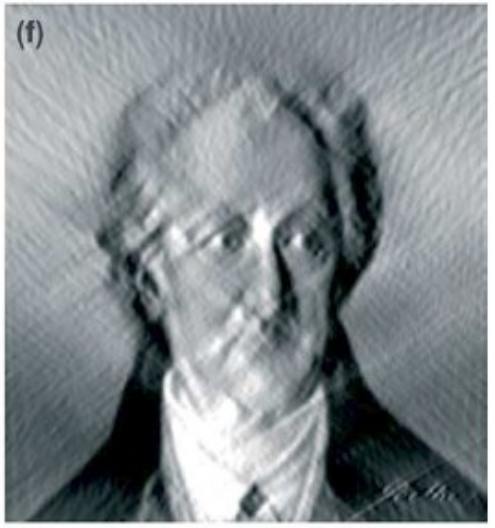


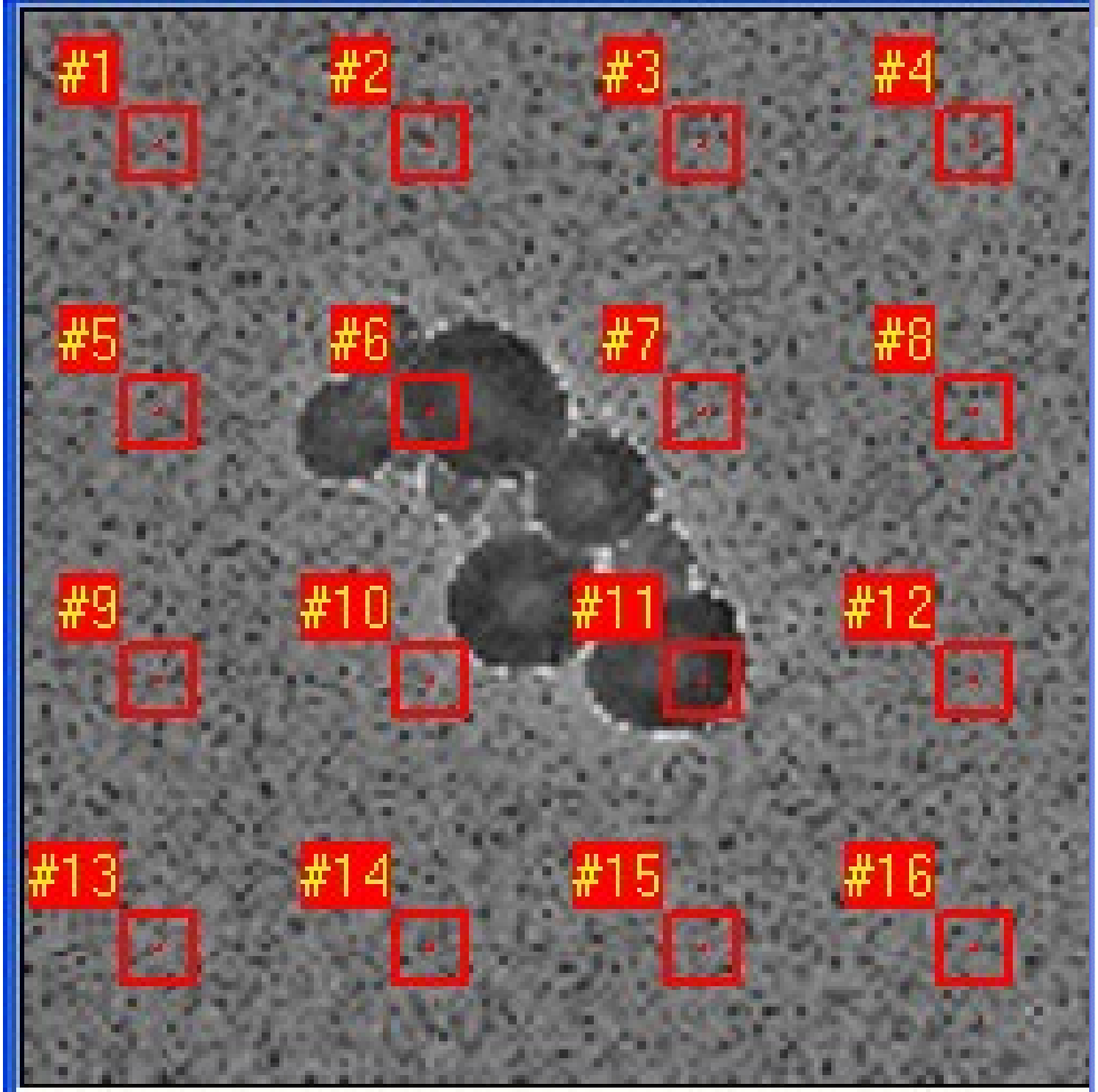


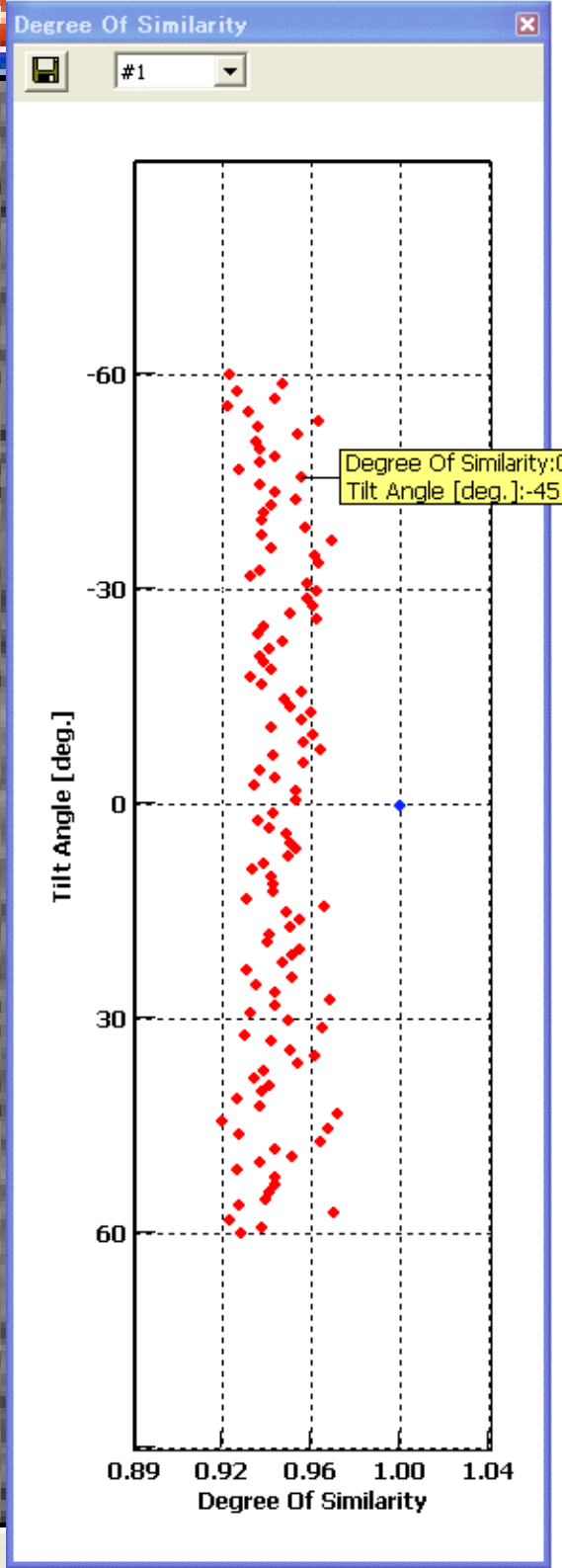


2º increment
-90º ~90º

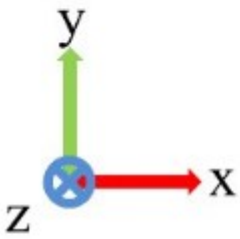
2º increment
-60º ~60º

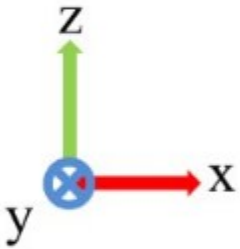
McIntosh et al., 2005


#1
#2
#3
#4
#5
#6
#7
#8
#9
#10
#11
#12
#13
#14
#15
#16


Degree Of Similarity
#1
-60
-30
0
30
60
Tilt Angle [deg.]
Degree Of Similarity:0.958
Tilt Angle [deg.]:-45.9700
0.89
0.92
0.96
1.00
1.04
Degree Of Similarity

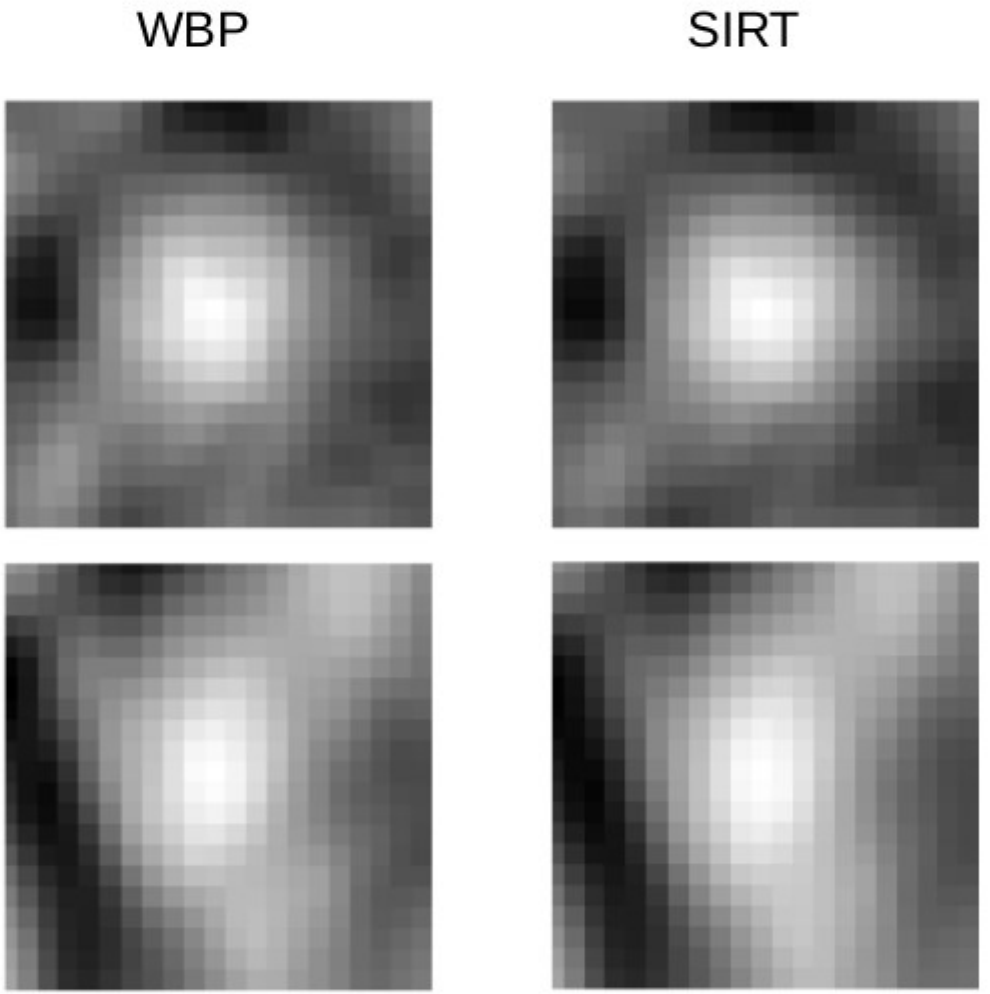
Gold particle reconstructions





Elongation

- WBP: 1.57 Â± 0.09
- SIRT: 1.67 Â± 0.14



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Posterior Expectation Maximization

- No morphological prior!
- Poisson distribution assumed
- Median filter used as regularization

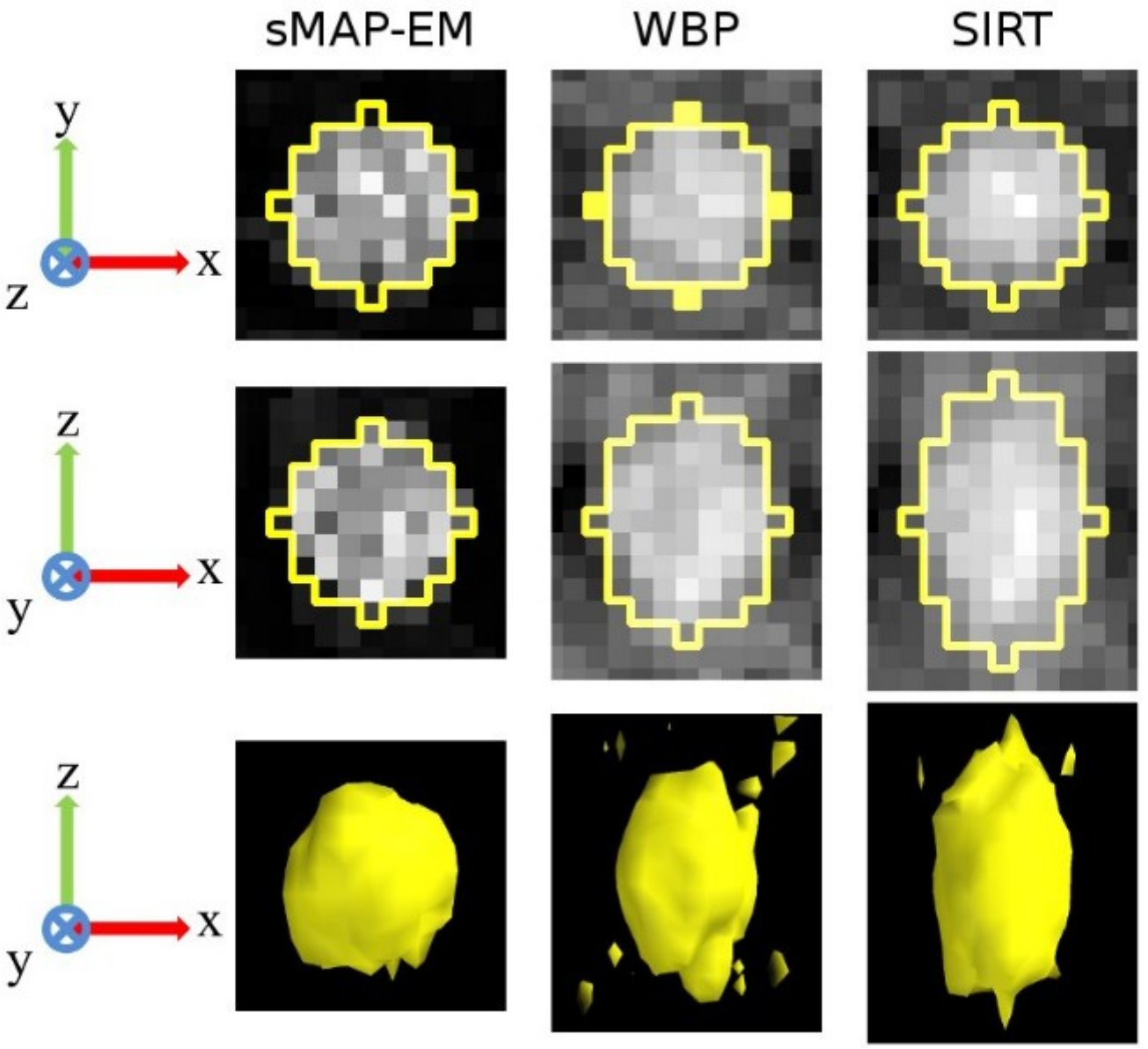
Based on Bayesian inference:

$$p(f|g) = p(g|f)p(f) / p(g)$$

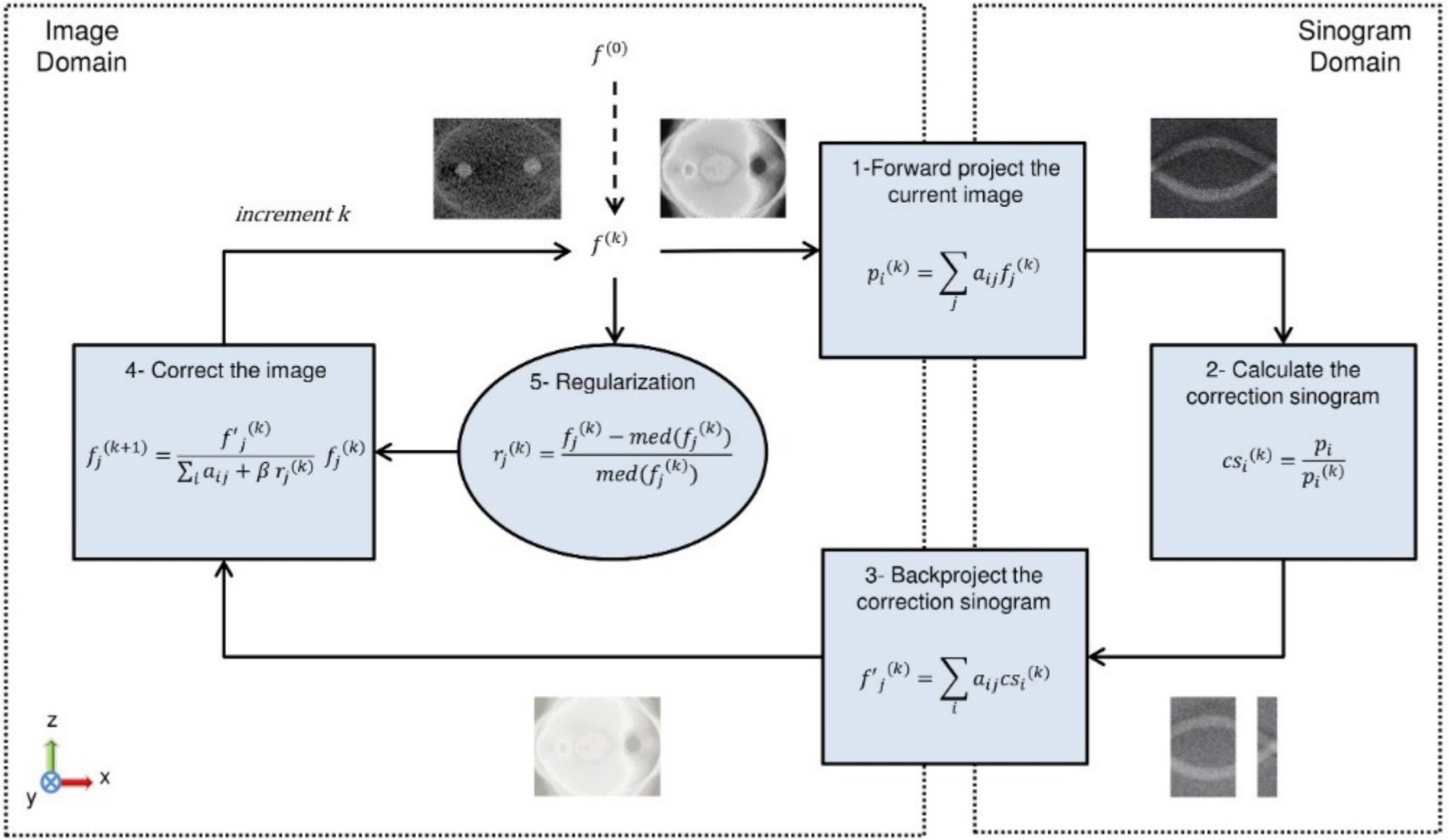
p(f|g) is posterior probability

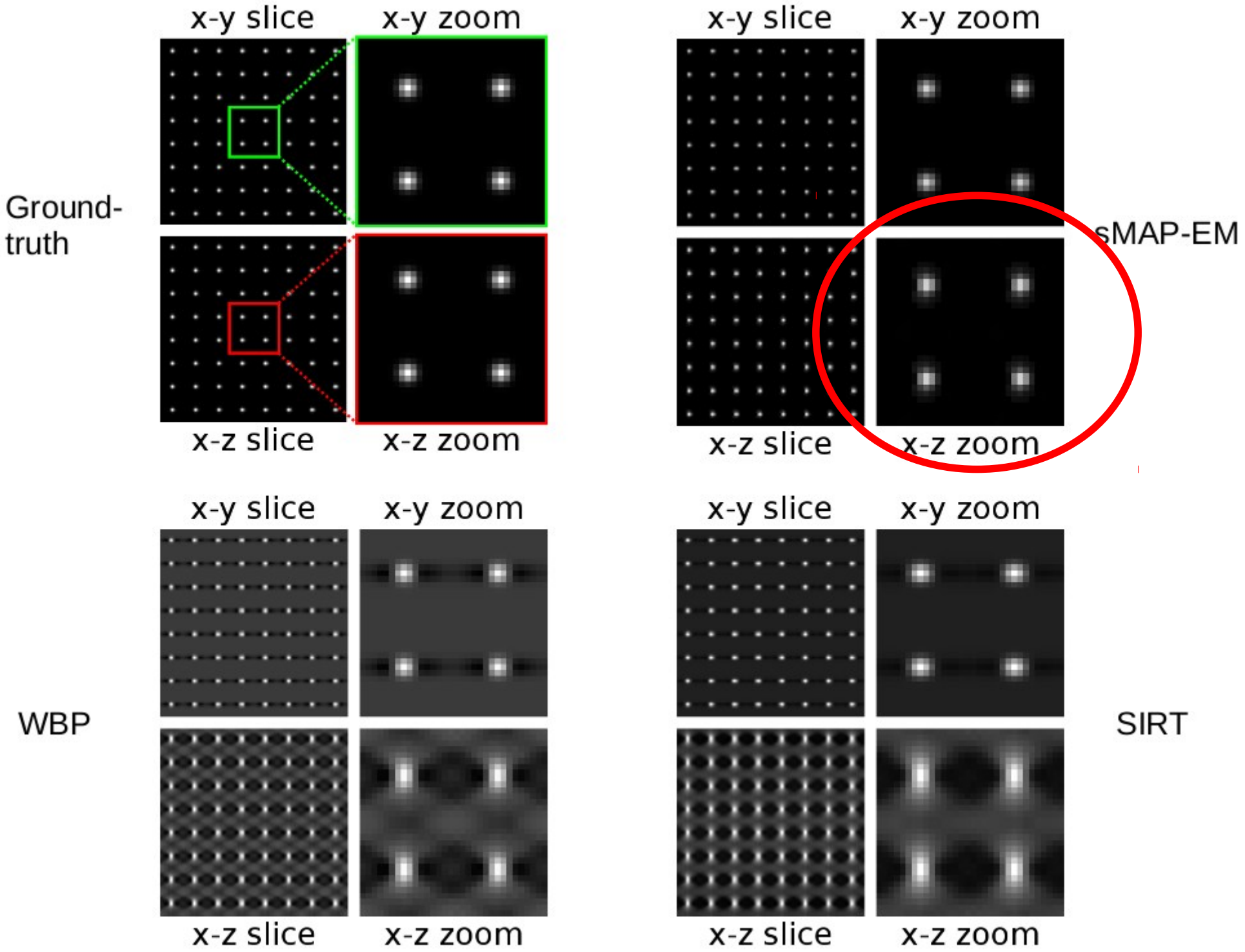
p(g|f) is likelihood (image acquisition)
p(f) is prior probability
p(g) is marginal probability

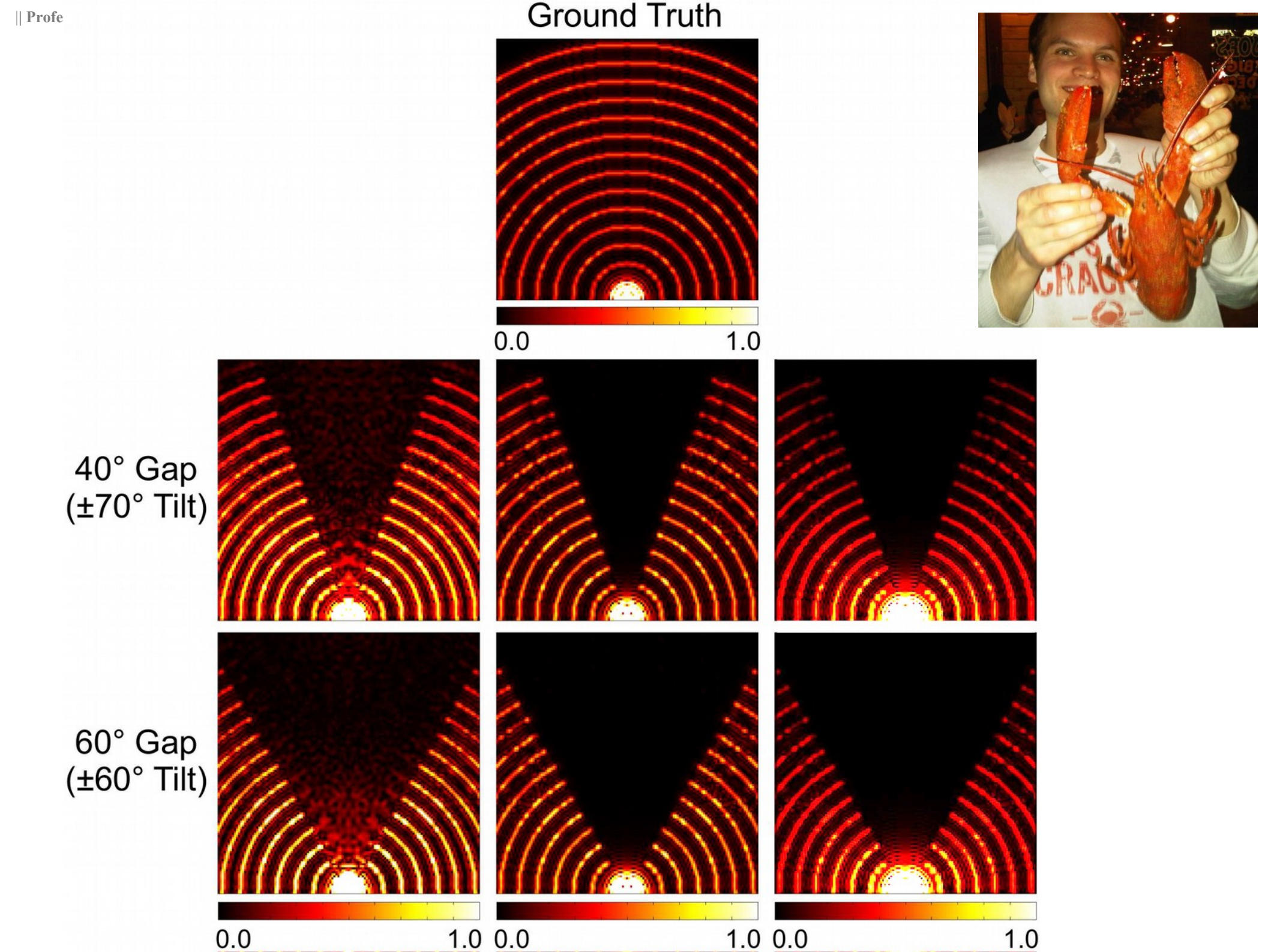
Ellipsoid fitting



sMAP-EM flowchart




Ground-truth
x-y slice
x-y zoom
x-z slice
x-z zoom
sMAP-EM
x-y slice
x-y zoom
x-z slice
x-z zoom
WBP
x-y slice
x-y zoom
x-z slice
x-z zoom
SIRT
x-y slice
x-y zoom
x-z slice
x-z zoom

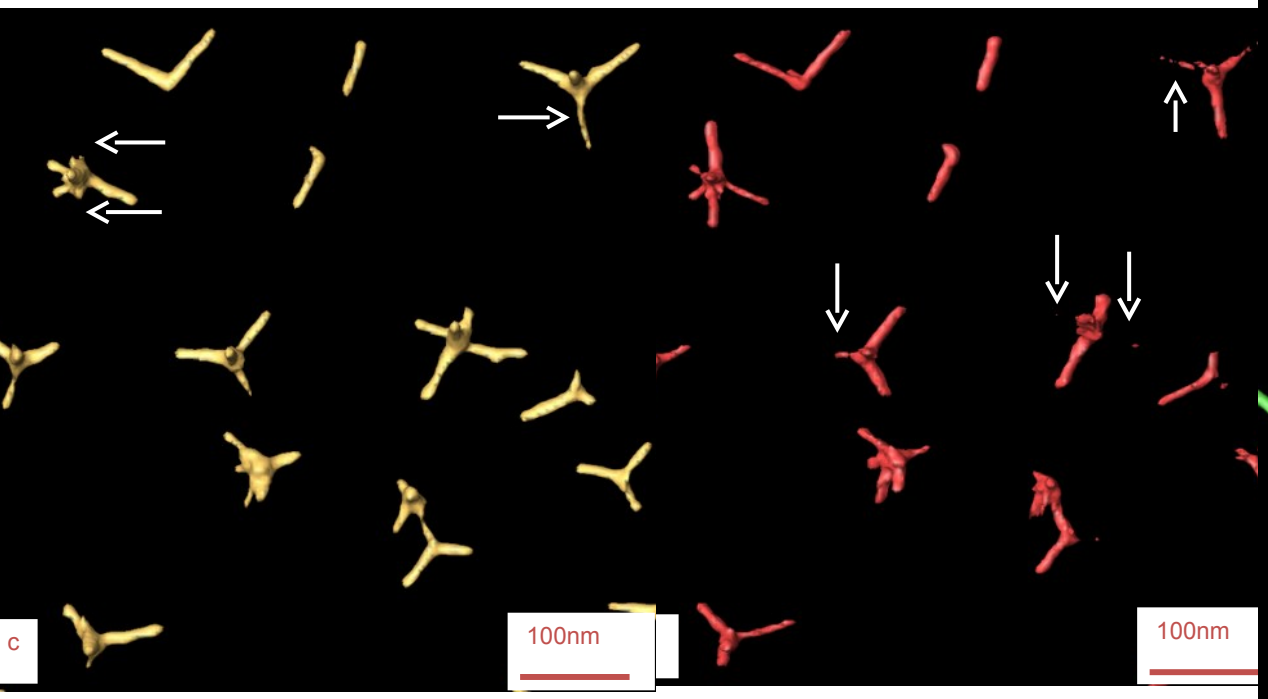

Ground Truth
0.0
1.0
40° Gap
(±70° Tilt)
60° Gap
(±60° Tilt)
0.0
1.0
0.0
1.0
0.0
1.0

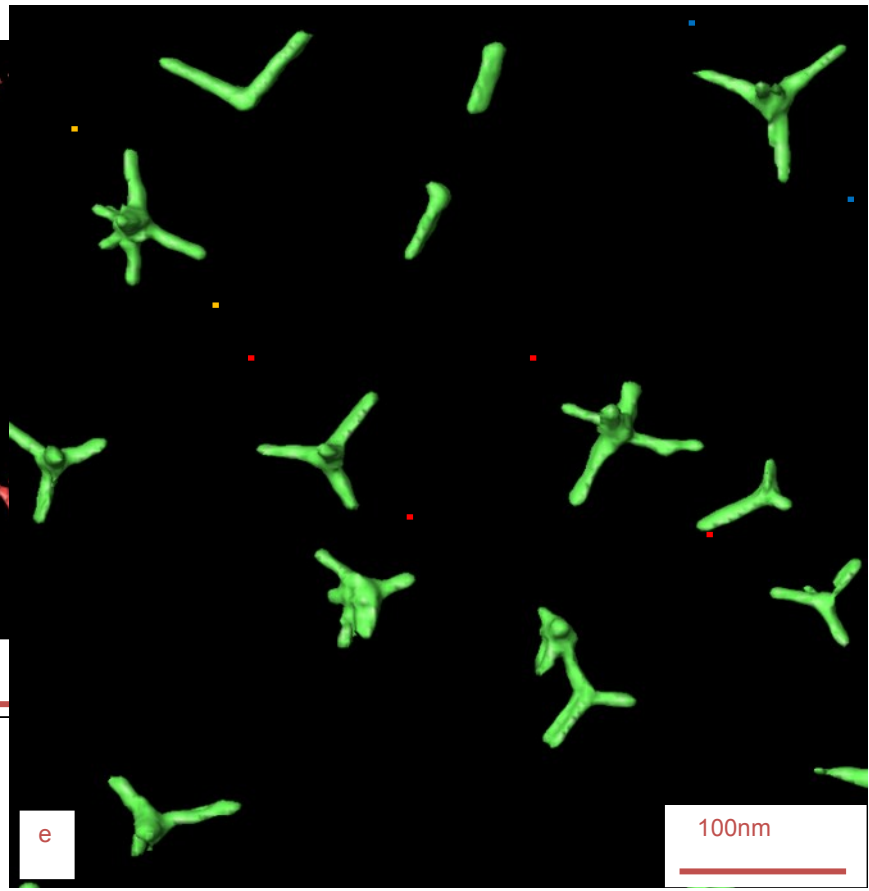
Dual Axis Reconstruction

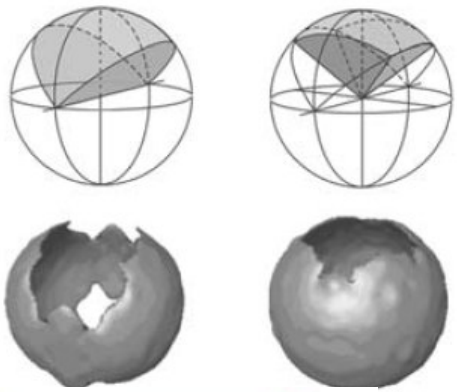
Single Tilt Series

90°- Single Tilt Series

Dual Axis Reconstruction







Tilt range	Single	Double
±70°	78%	93%
±60°	67%	84%
±45°	50%	67%

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Figure6
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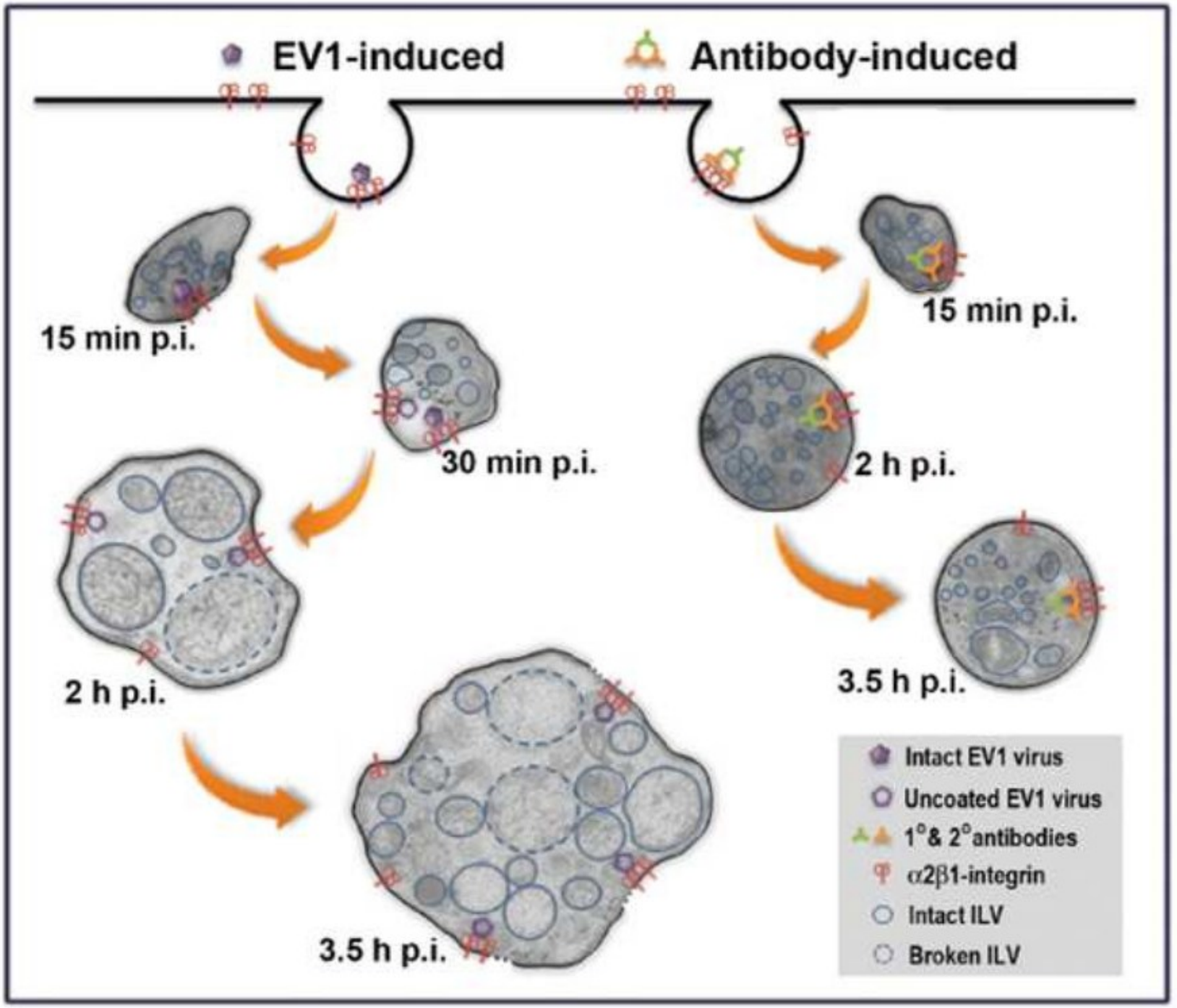
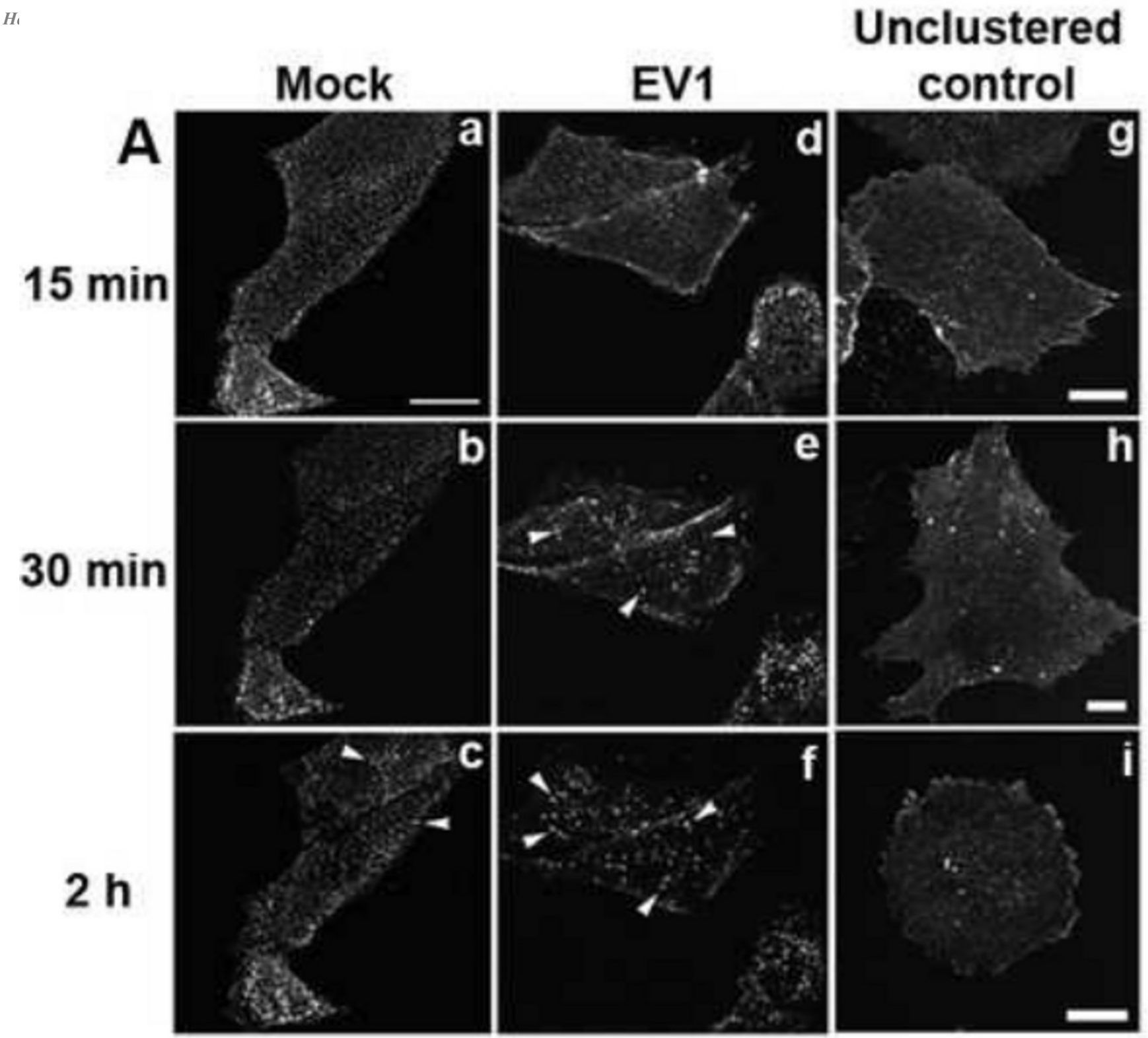
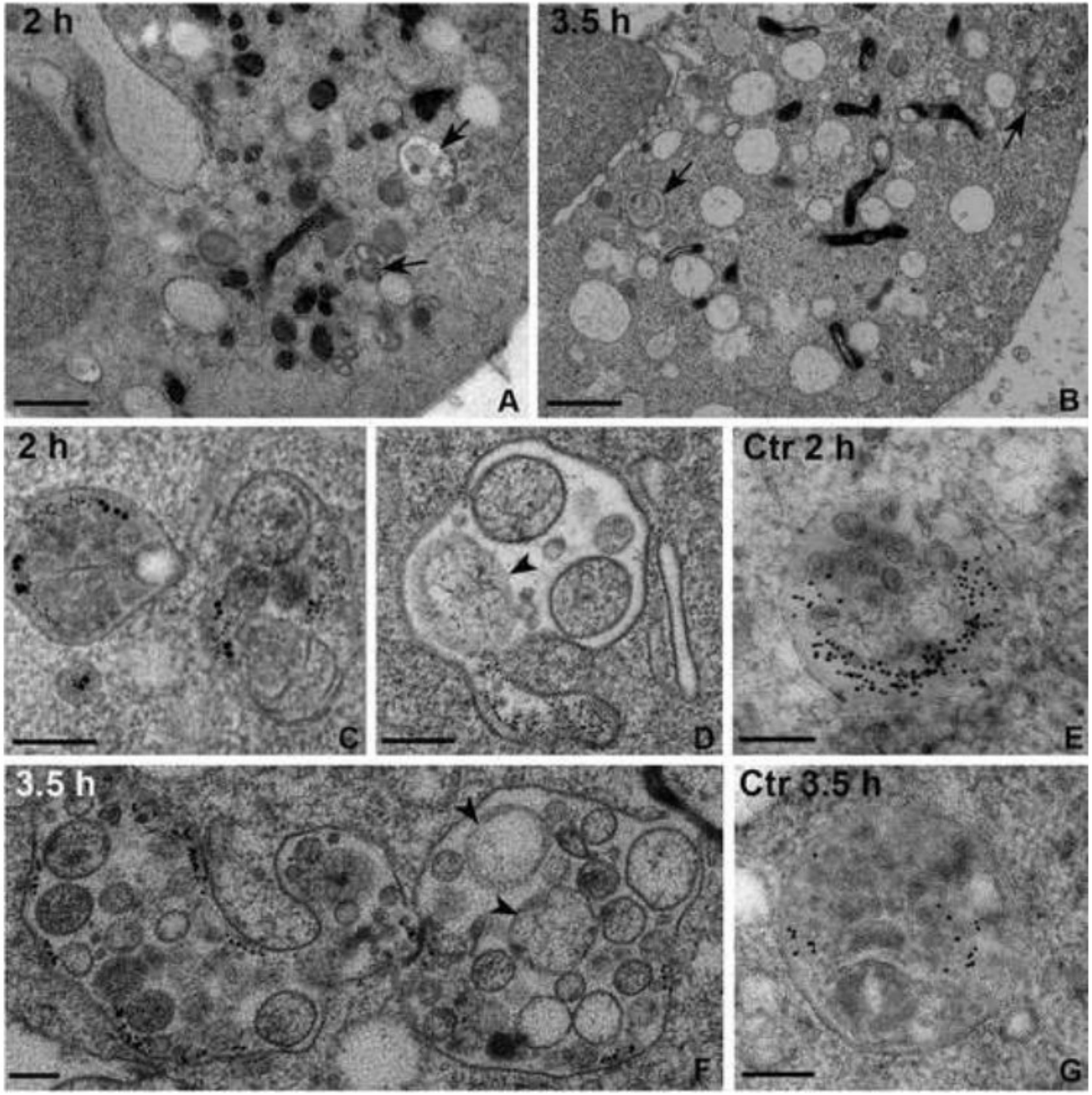
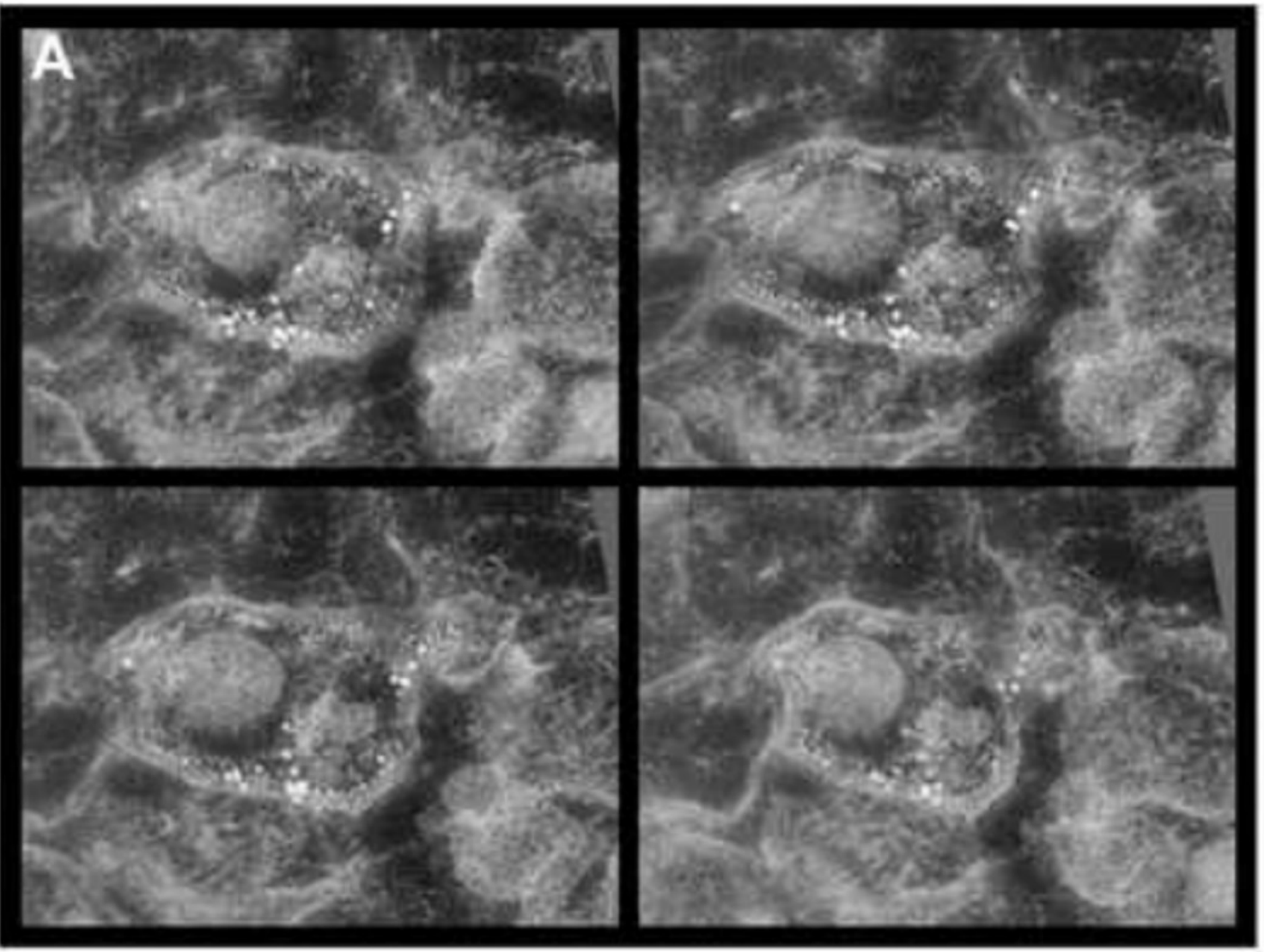
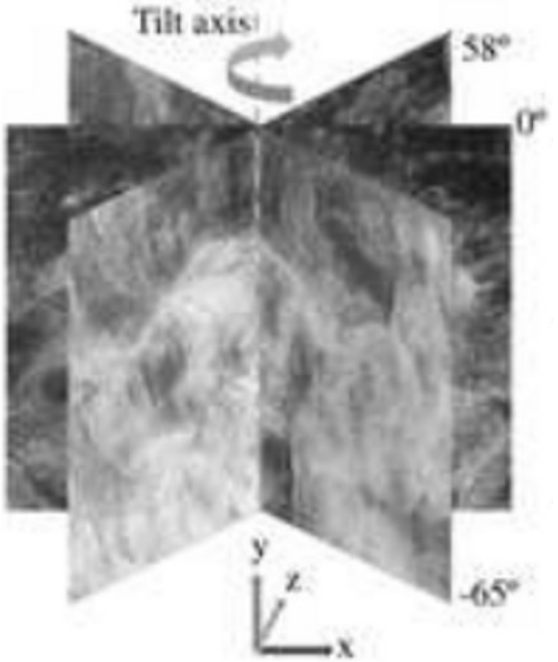



Mock
EV1
Unclustered control
A
15 min
30 min
2 h
a
b
c
d
e
f
g
h
i


2 h
A
3.5 h
B
2 h
C
D
Ctr 2 h
E
3.5 h
F
Ctr 3.5 h
G



B



US20120301494 A1 (2012)
US20120064169 A1 (2012)

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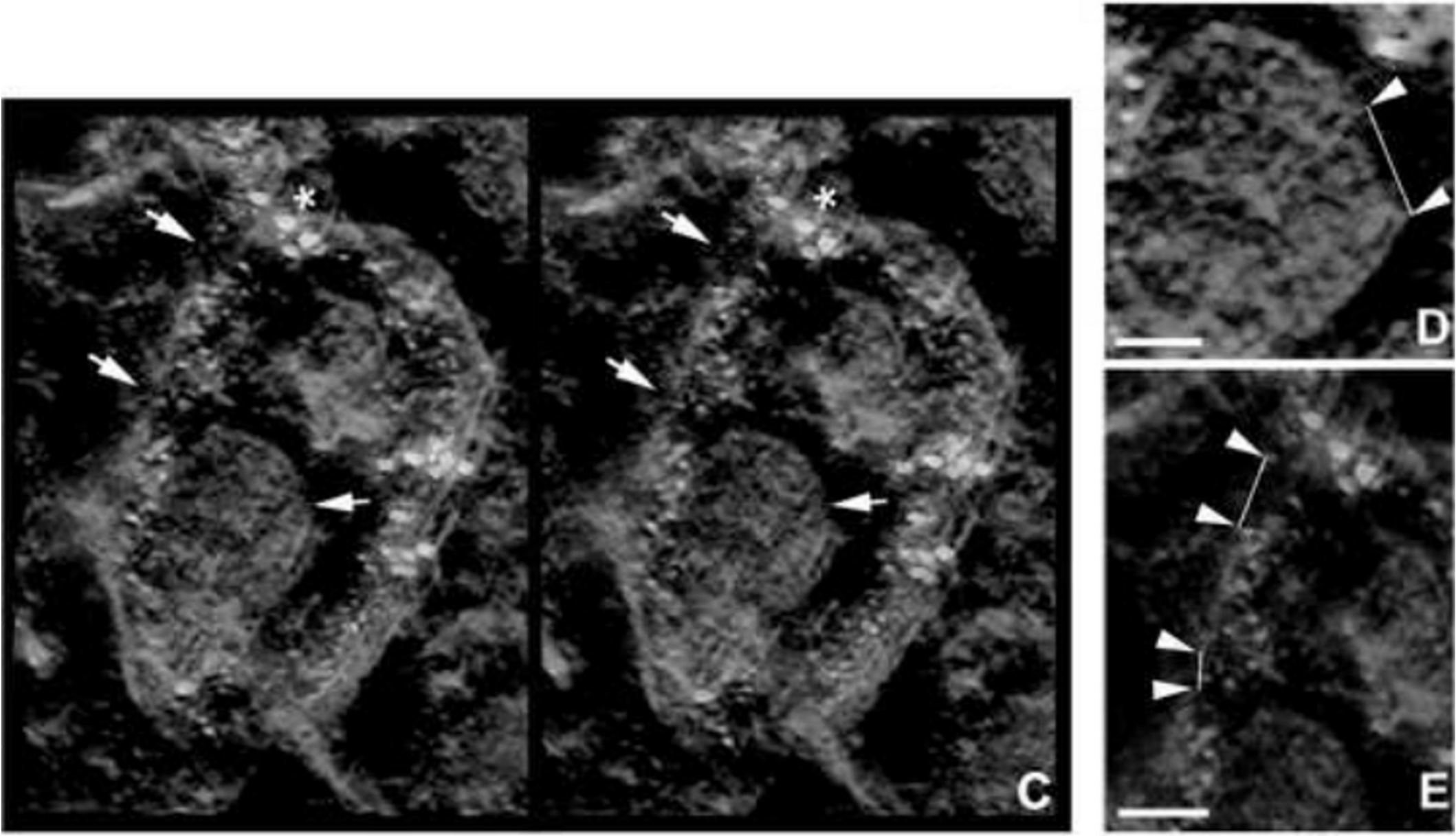

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US20120064169 A1 (2012)

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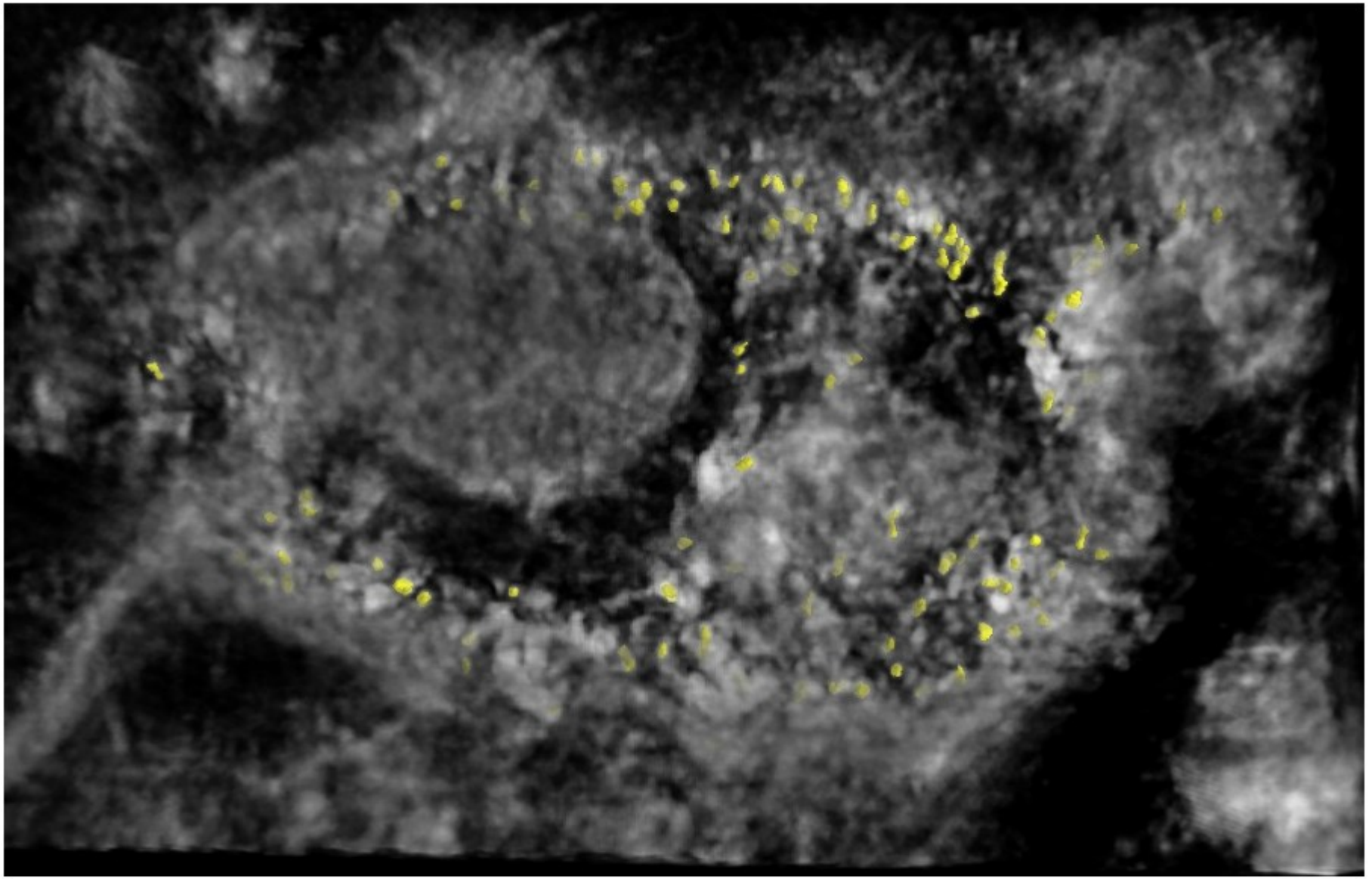
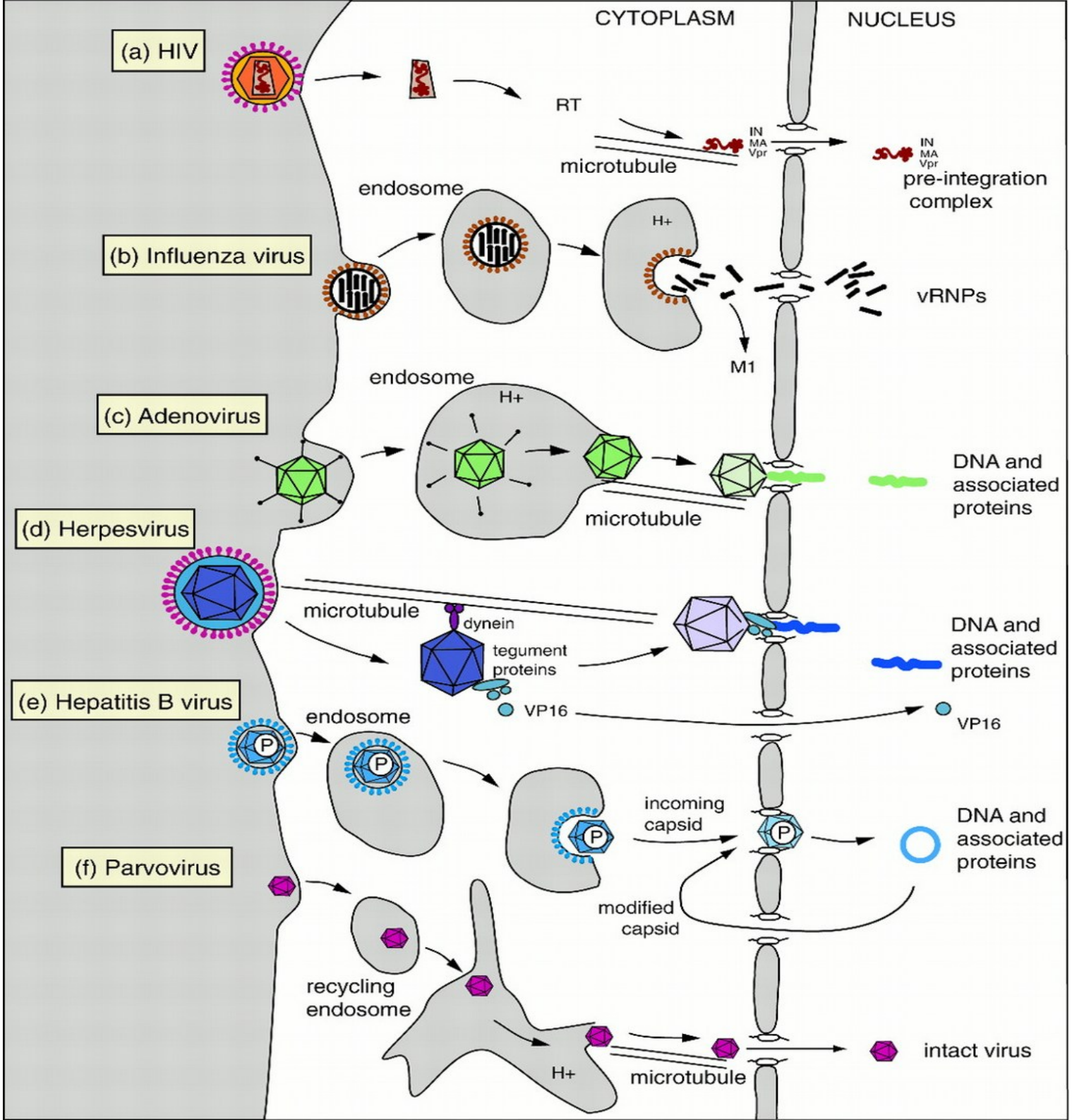
Isotropic resolution is essential to correlate integrin distribution with MVB ruptures

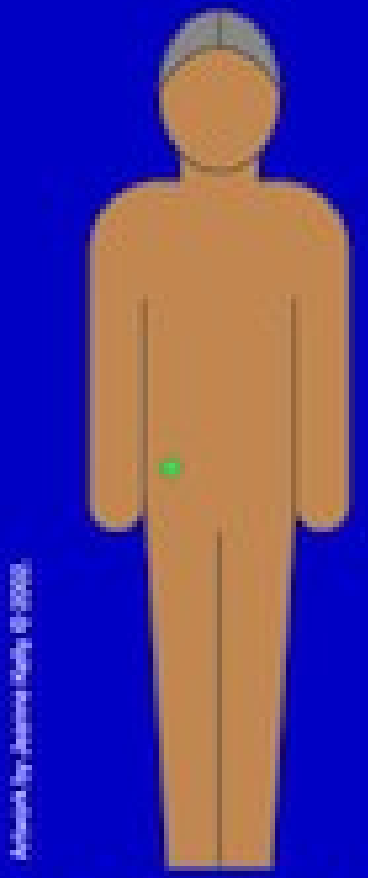


Nuclear entry

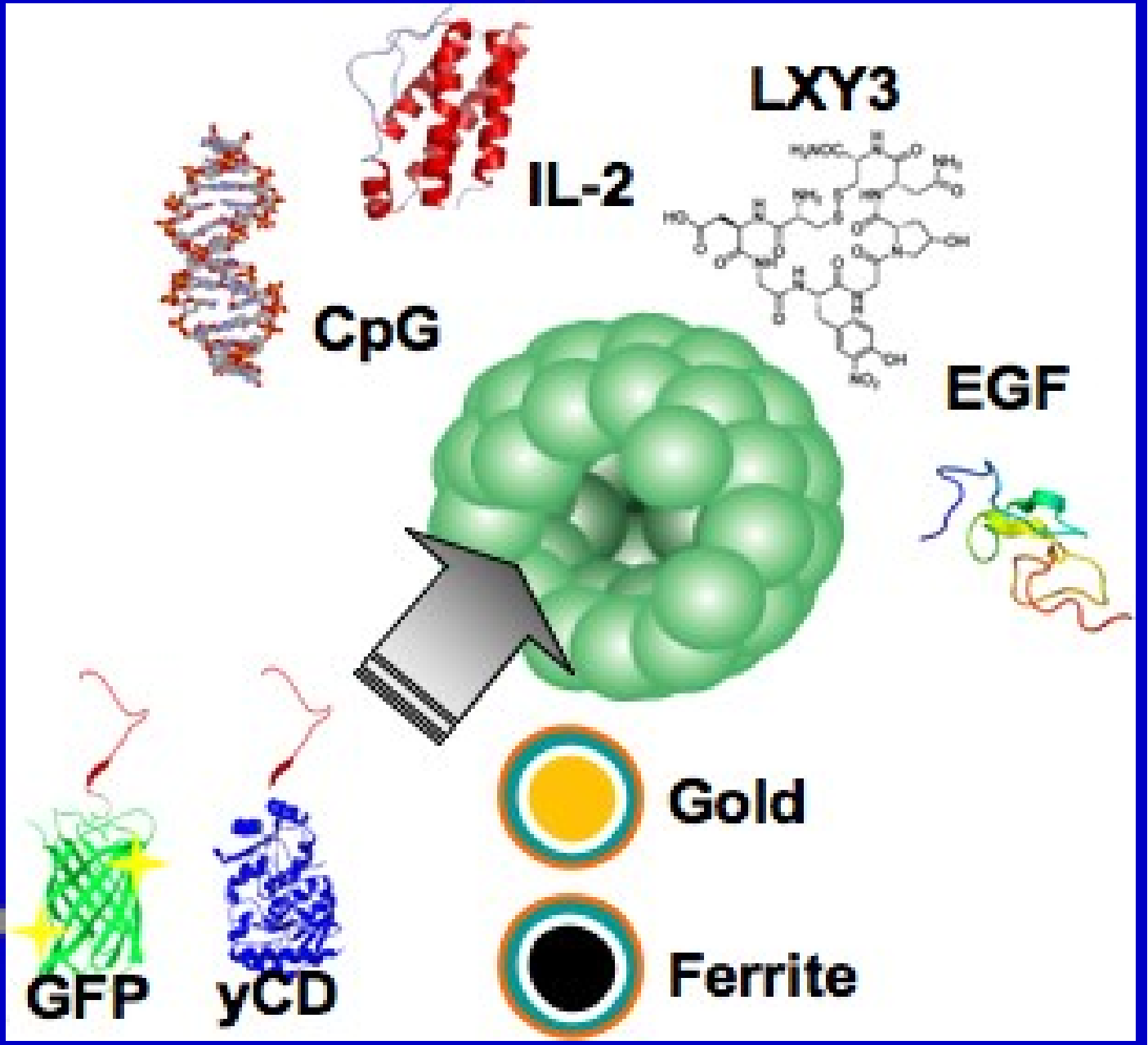
Protein capsid as image agents in signal enhancement



Nanodevices Can Improve Cancer Detection and Diagnosis



Nanotechnology



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Chemically Activatable Nanocapsid Functionalized For Cancer Targeting

Tech ID: 24218 / UC Case 2014-684-0

Abstract

Researchers from the University of California, Davis have engineered a HEV-based nanoparticle that selectively targets cancerous breast tissue. These multi-functional nanoparticles are conjugated to cancer ligands, which makes them highly specific for cancer cells while enabling the delivery of therapeutics to those cells. The HEV-based nanoparticles provide for a multifunctional platform capable of carrying simultaneously cell adhesion tags, biomarkers, imaging probes as well as DNA vaccine for image-guided drug delivery.

Full Description

Background

Nanocarriers have been constructed from biological and chemical substances such as albumin and solid metal-containing particles, respectively. Virus-like particles (VLPs) have been used as nanocarriers to display foreign epitopes and also deliver small molecules. Nanocarriers as drug delivery systems enable a sophisticated approach to combat many diseases, including cancer.

Novel therapy