Lundbeck Foundation

Center for **B**iomembranes in **N**anomedicine

5th Conference - Spanish Platforms on Biomedical Knowledge, Barcelona, Feb 2012

Prof. Dimitrios Stamou

Head of the Bio-Nanotechnology and Nanomedicine Laboratory

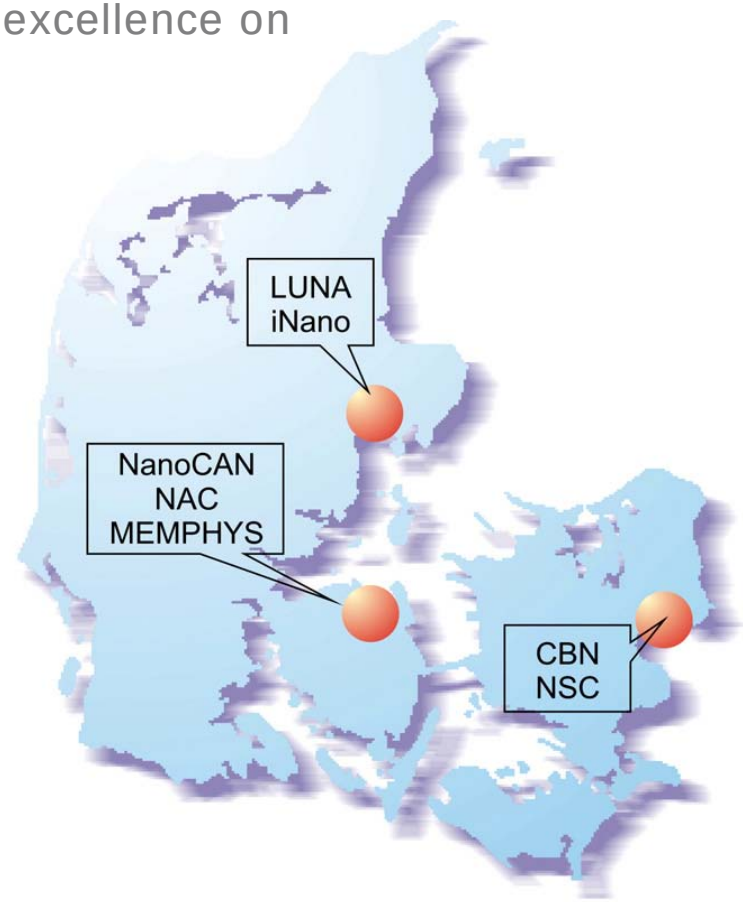
Director of Lundbeck Foundation Center Biomembranes in Nanomedicine

Department of Neuroscience and Pharmacology & Nano-Science Center

University of Copenhagen, Denmark

Outline of the talk

- The Lundbeck Foundation funded 3 centers of excellence on Nanomedicine in 2009 in Denmark
- for a five year period (non extendible)
- with a total of € ~14 million



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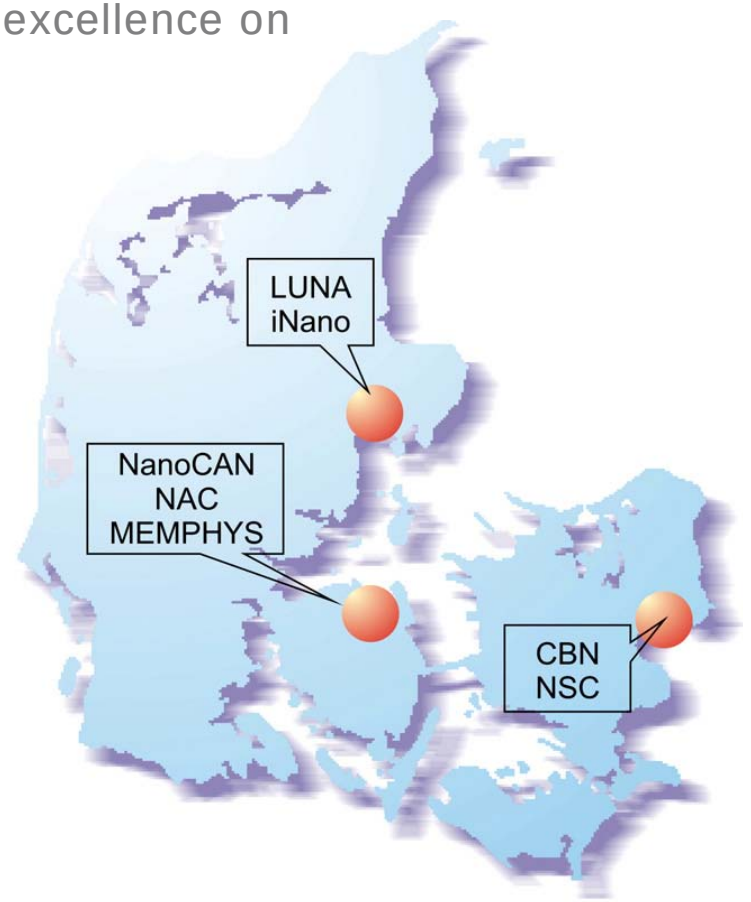
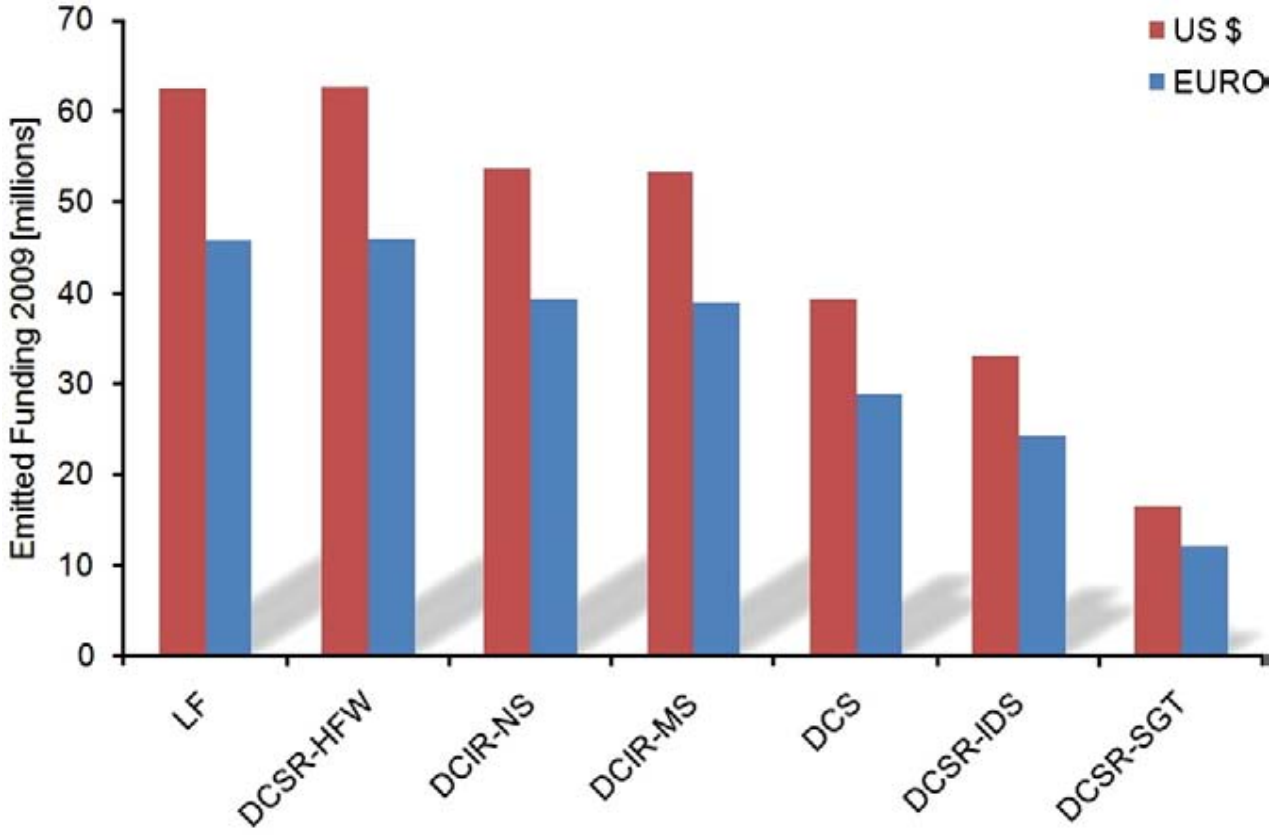
- The Lundbeck Foundation
- The call, Timeline
- Our view of Nanomedicine
- The three centers
- 3 short stories of science



LUNDBECKFONDEN

- The Lundbeck Foundation is a commercial foundation established in 1954. Its main objective is to
  - **maintain and expand the activities of the Lundbeck Group**
  - **provide funding for scientific research of the highest quality.**
- Revenue € ~2 billion
- The Foundation holds a substantial interest in the share capital of H. Lundbeck A/S, ALK-Abelló A/S and Falck A/S. In addition, a substantial portfolio of investments is managed and the entity Lundbeckfond Ventures has been established to investment in life science companies.
- In 2010, the Foundation granted € 51,5 million and expects to grant approx. € 53 million to research in biomedical and natural sciences in 2011.
- The Lundbeck Foundation has in recent years established 15 Centres of Excellence and several fellowships to outstanding researchers - Danish or foreign - who wants to establish their own research groups at Danish universities.

Private and public funding in Denmark



Timeline

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- Request for expressions of Interest, Jan 2008
- Expression of interest, April 2008
- 1st round January 2009, 15pg
- 2nd round June 2009, 25 pg
- Presentation August, 2009
- Decision, Sept 2009
- Signing of contracts, Oct 2009

Definitions

- ***Nanotechnology*** is broadly defined as the interdisciplinary science and technology whose unifying theme is the investigation and manipulation of matter at the atomic and molecular scale.

- ***Nanomedicine*** is defined as the application of nanotechnology to improving human health and is projected to impact specifically on prevention, diagnosis and treatment of diseases.

- Added value is found in novelty

Engineering vs Medicine, Timing

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- ***Nanotechnology*** originated from attempts to investigate and manipulate at the atomic and molecular scale hard–matter, however several pioneering innovations over the last decade have enabled the successful nanoscale study of complex biomolecular systems.

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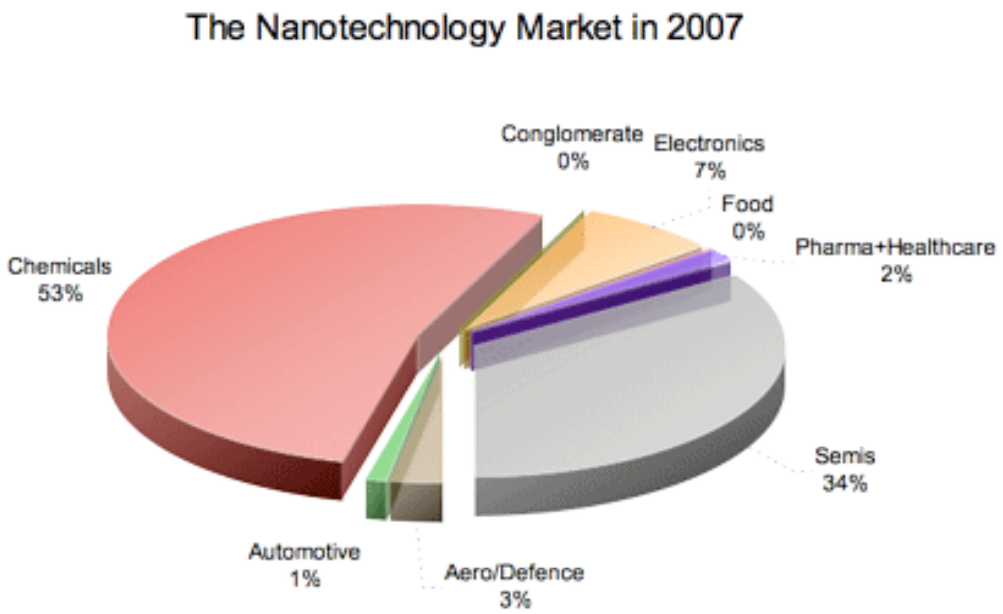
- ***Nanotechnology*** originated from attempts to investigate and manipulate at the atomic and molecular scale hard–matter, however several pioneering innovations over the last decade have enabled the successful nanoscale study of complex biomolecular systems.
- We therefore predict and anticipate that Nanotechnology, in the form of the newly conceived field of ***Nanomedicine,*** will make substantial contributions in the areas of prevention, diagnosis and treatment of diseases in the coming years.

Growth, Timing



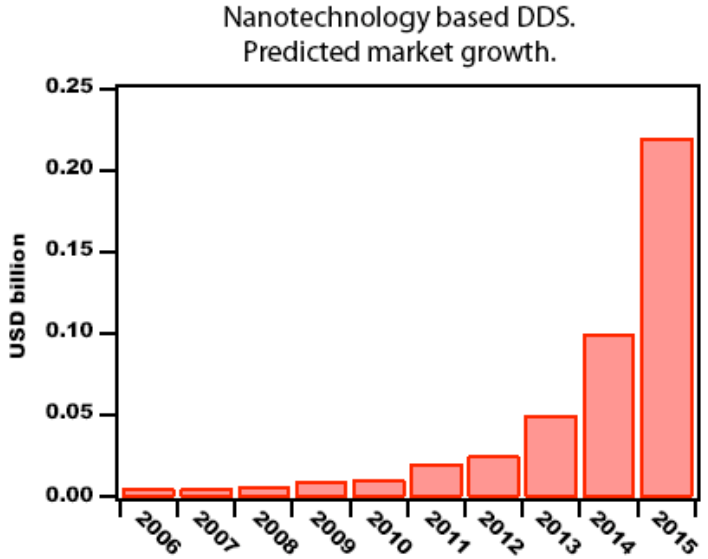


Figure 1. Pharma and healthcare currently represent only 2% of the nanotechnology market and are predicted to be one of its fastest rising segments.[1]

US-EU-DK, Timing

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- Denmark
  - — National program in Nanoscience
  - — Lundbeck could lead investment in Nanomed in EU

Bionanotechnology

Figure 2. Inauguration of the bionano laboratories at Nano-Science Center in 2004 by Danish Prime Minister Anders Fogh Rasmussen (right). That initiative was supported by ≈ 10 MDKK extraordinary KU funding in 2004- 05 and two new tenure track positions based at the Health Science Faculty KU. Left Rector Linda Nielsen, middle Center Director Thomas Bjørnholm

NIH roadmap: From BioNano to Health Care

Bionanotech → → **Health Care**

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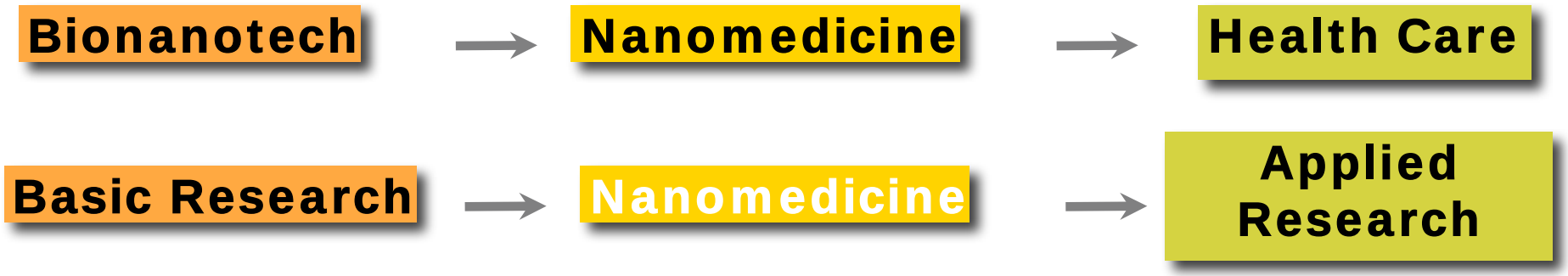
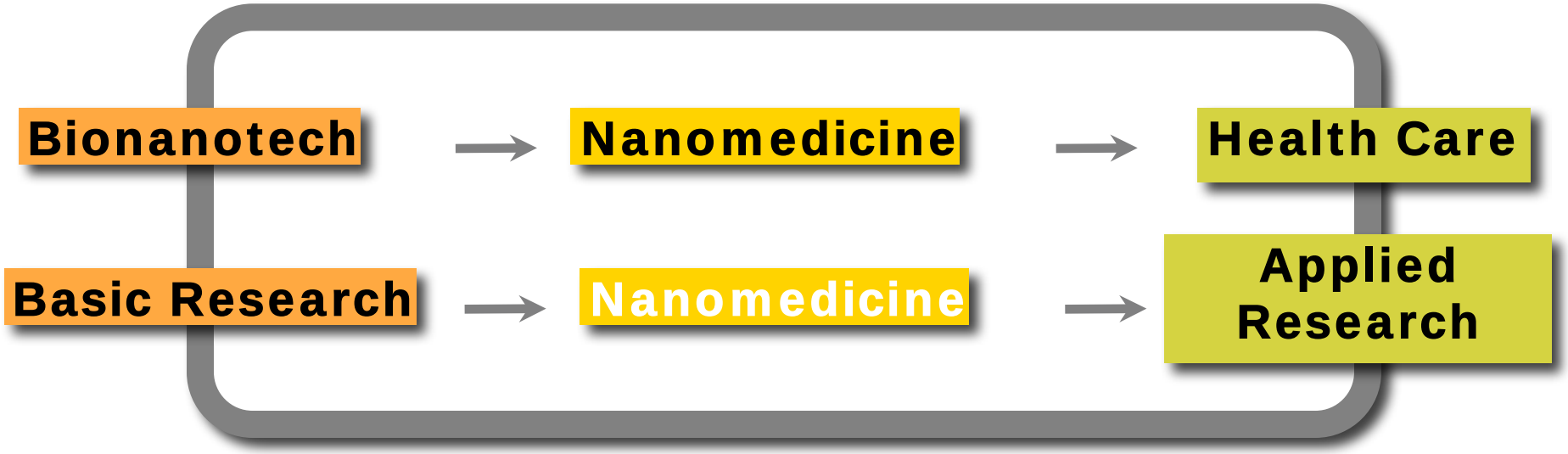


Lundbeck Foundation Center



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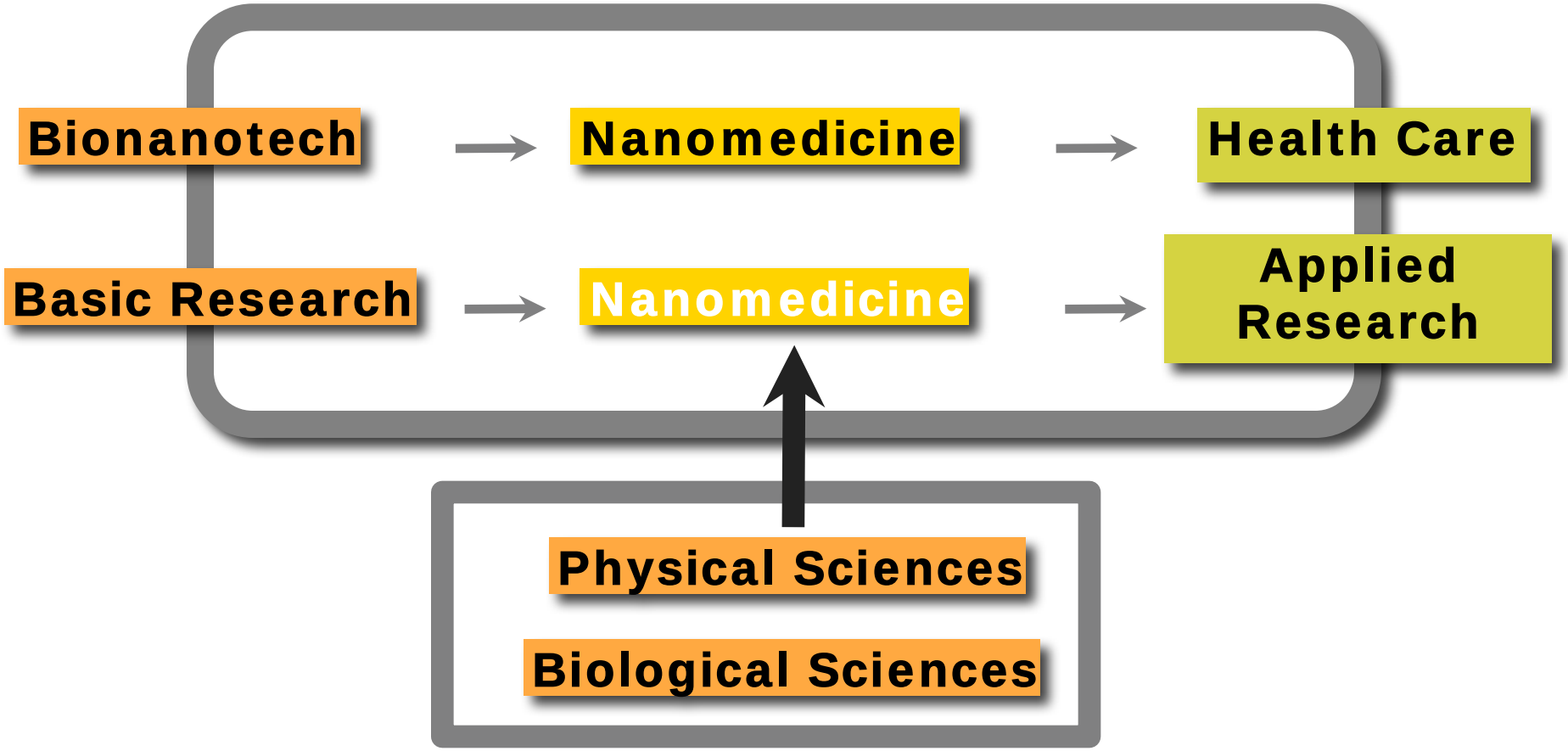
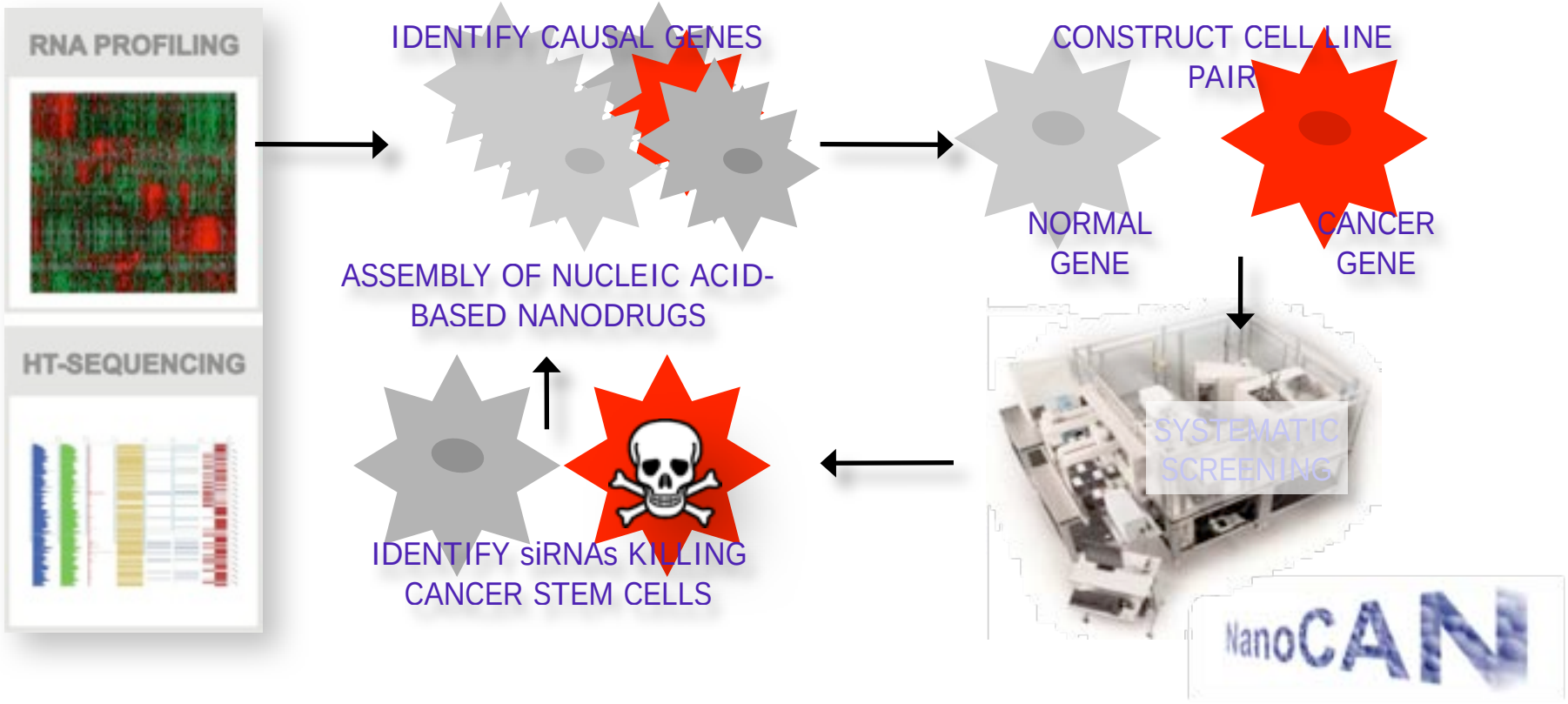


Three Nanomedicine Centers

- Center for Biomembranes in Nanomedicine (CBN)
  University of Copenhagen
- Nanomedicine center for individualized management of tissue damage and regeneration (LUNA)
  University of Aarhus
- Nanomedicine Center for Cancer Stem cell targeting therapeutics (NanoCAN)
  University of South Denmark

Lundbeckfonden Center NanoCAN

- Funding: 4.7 mio € for 2010-2014
- Goal: development of cancer stem cell targeting nucleic acid-based nanodrugs
- 8 research groups (chemistry, physics, biology, clinical); total staff: 31



THE LUNDBECK FOUNDATION NANOMEDICINE CENTER FOR INDIVIDUALIZED MANAGEMENT OF TISSUE DAMAGE AND REGENERATION

- Grant 4 mill EURO
- **PRMs** control the degenerative and generative imbalance in CVDs and MSDs and that characterization of the molecular processes will allow the identification of new therapeutic targets

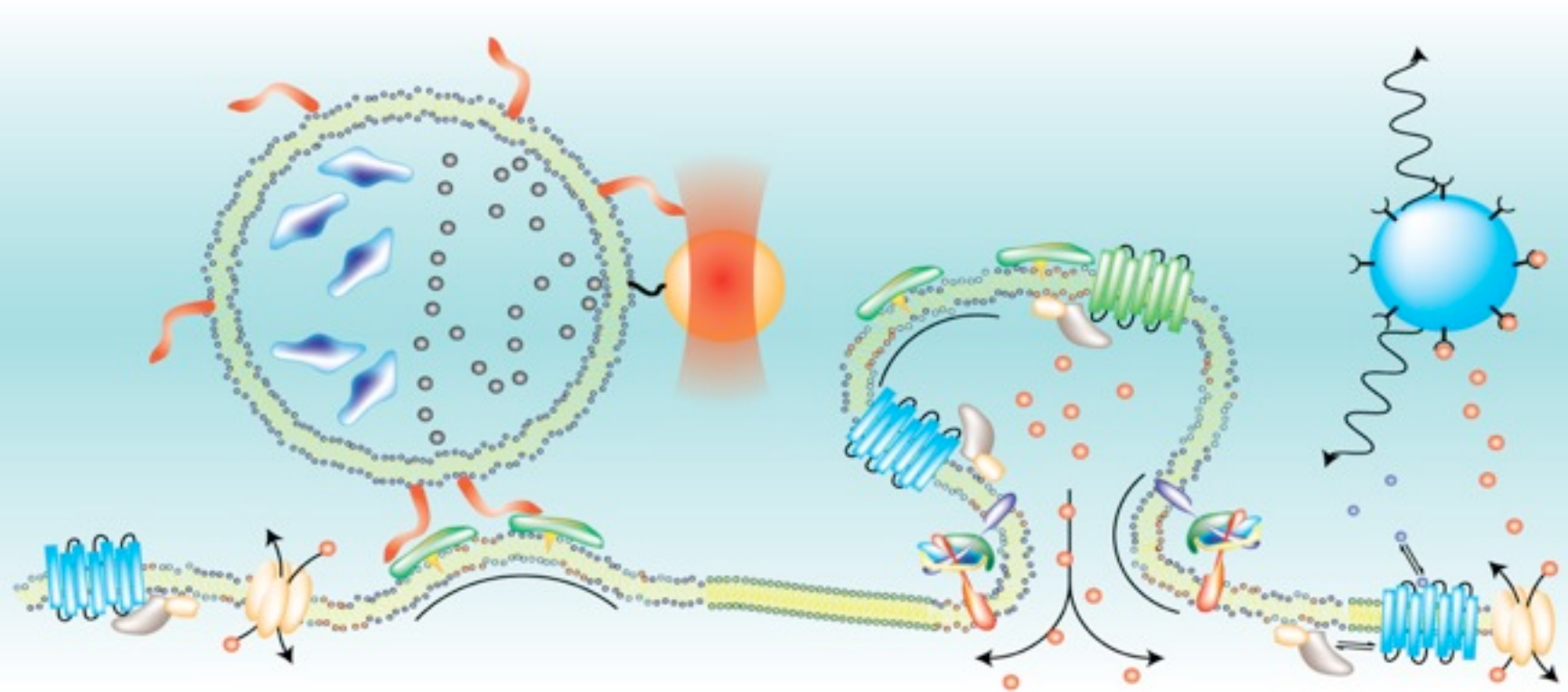
  This knowledge can be exploited by **nanomedicine** approaches for:

1. new drug design
2. drug delivery
3. bioimaging
4. tissue regeneration

to improve prevention, early diagnosis and treatment of **CVDs** and **MSDs**

Contact person: Jørgen Kjems, iNANO, Aarhus University (Head)
kjems@inano.dk – www.iNANO.dk

CBN is focused on: Signal transmission across biomembranes



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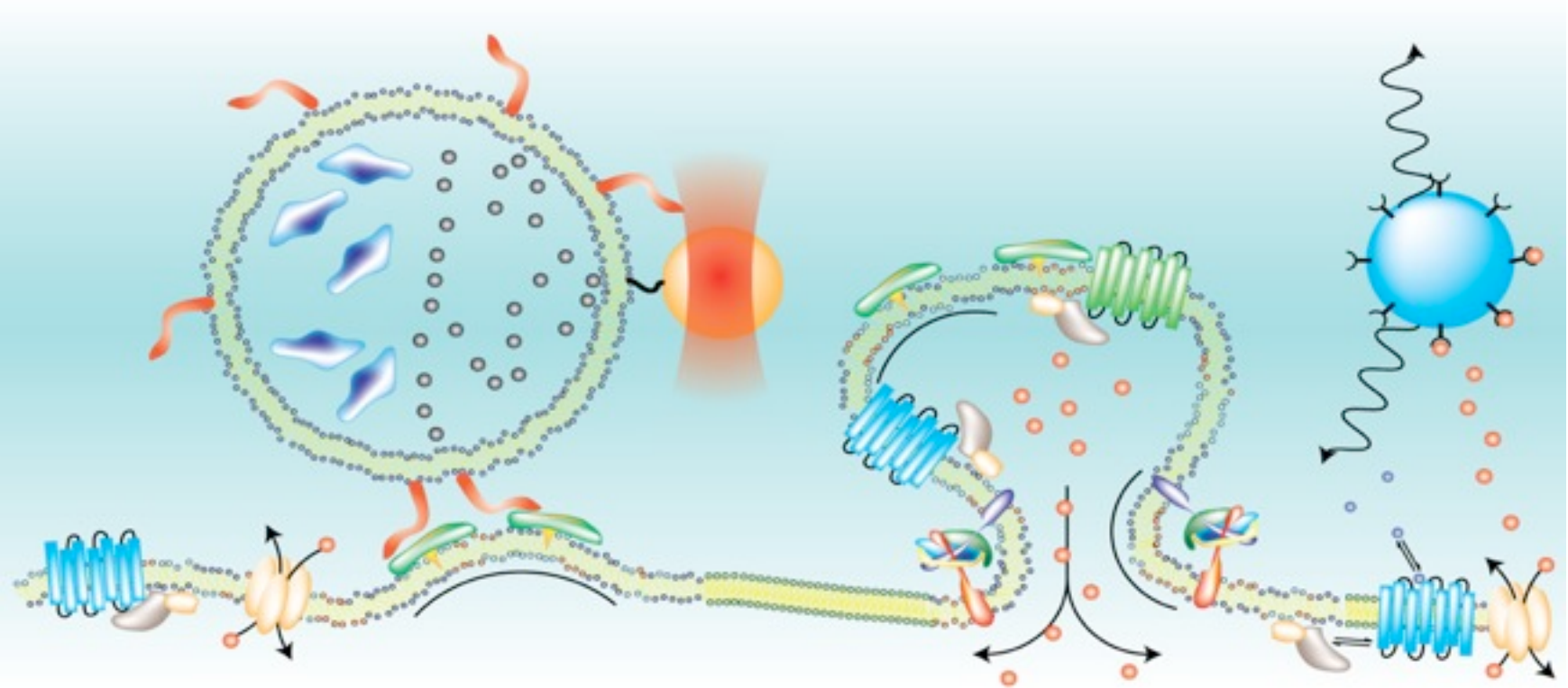
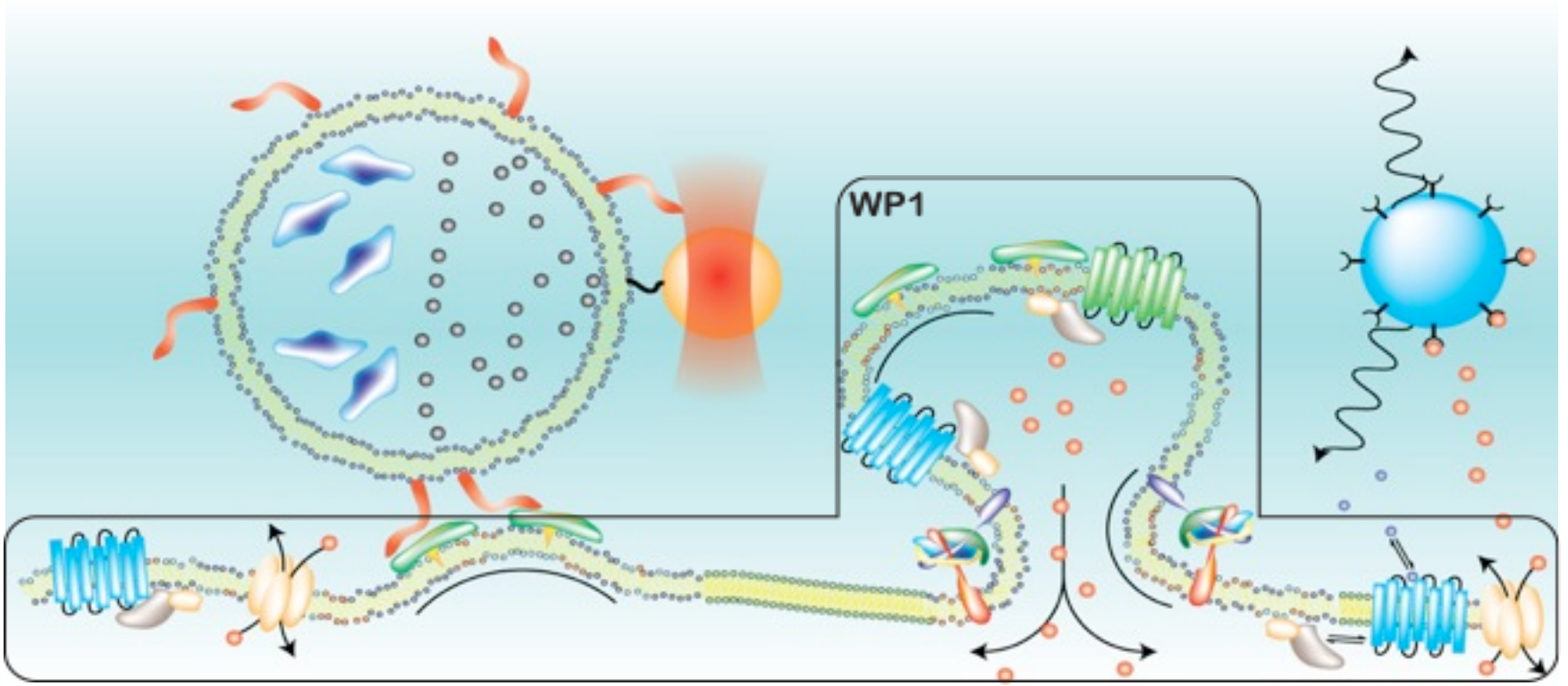


Aberant signal transmission is linked both to:

- **Diseases of the brain** (schizophrenia, depression, Parkinson's, Alzheimer's, neuropathic pain etc)
- **Microbial infections** (bacterial infections, viral infections)

Signal transmission across biomembranes



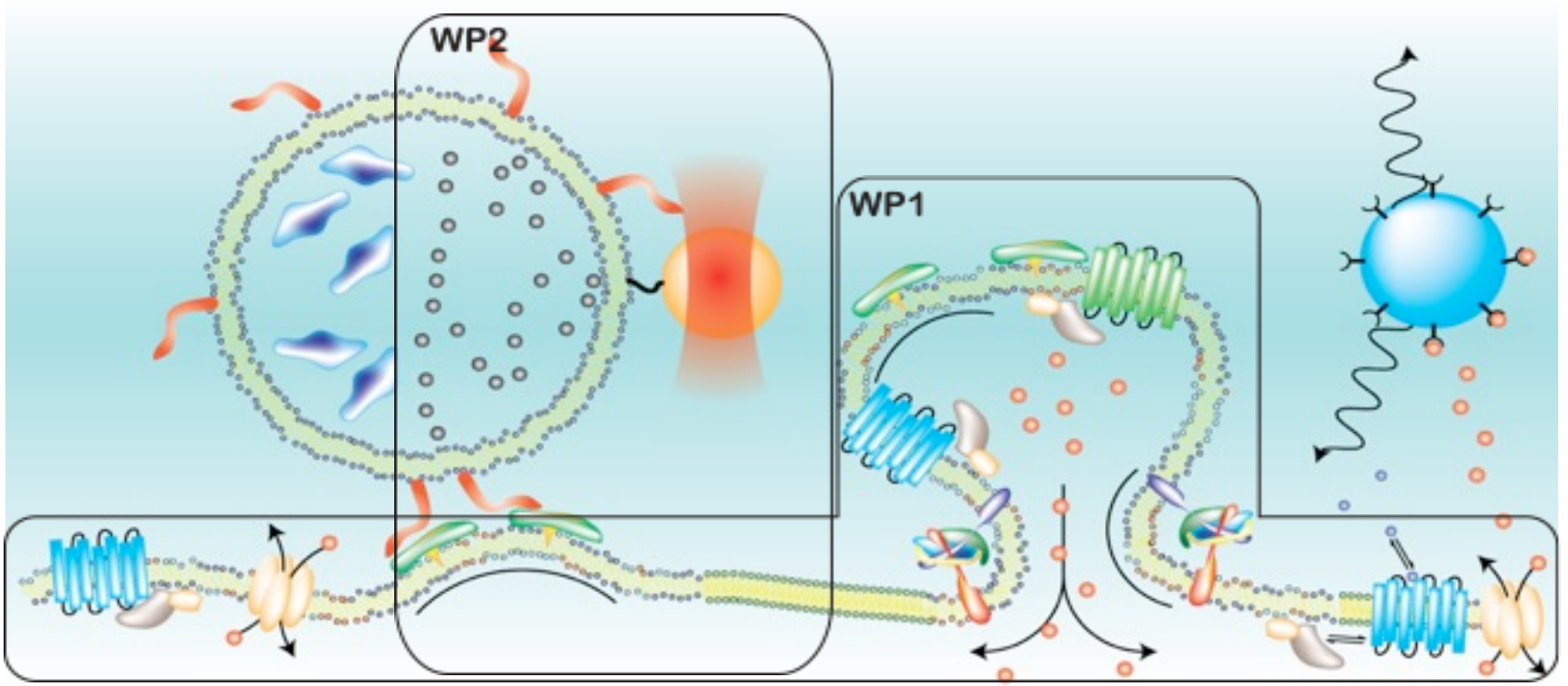
WP1 Nanoscale investigation of protein-membrane interactions

WP2 Intermembrane interactions studied on the nanoscale

WP3 Nanoscale biosensors for transmembrane signaling

WP4 Drug delivery with lipidic nanocontainers, mechanisms and toxicology on the nanoscale

Signal transmission across biomembranes



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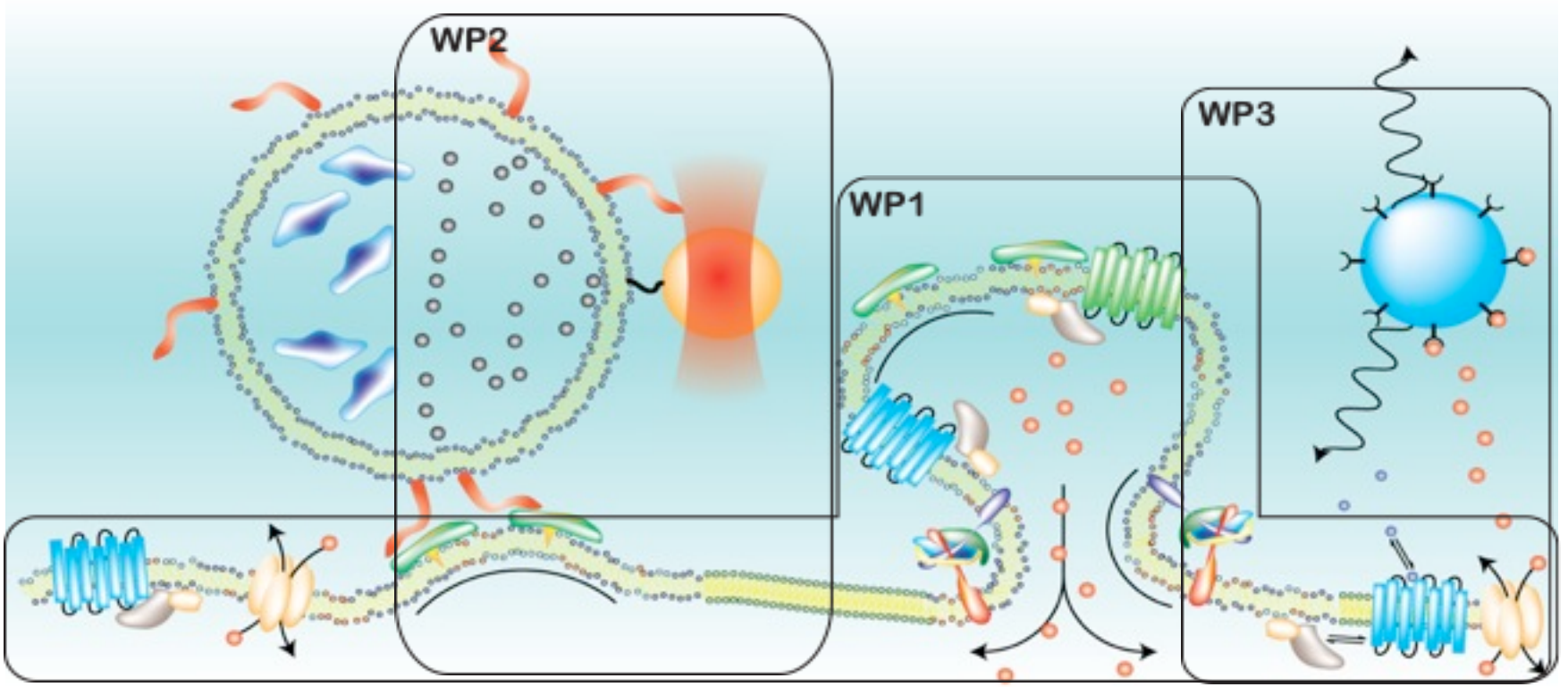

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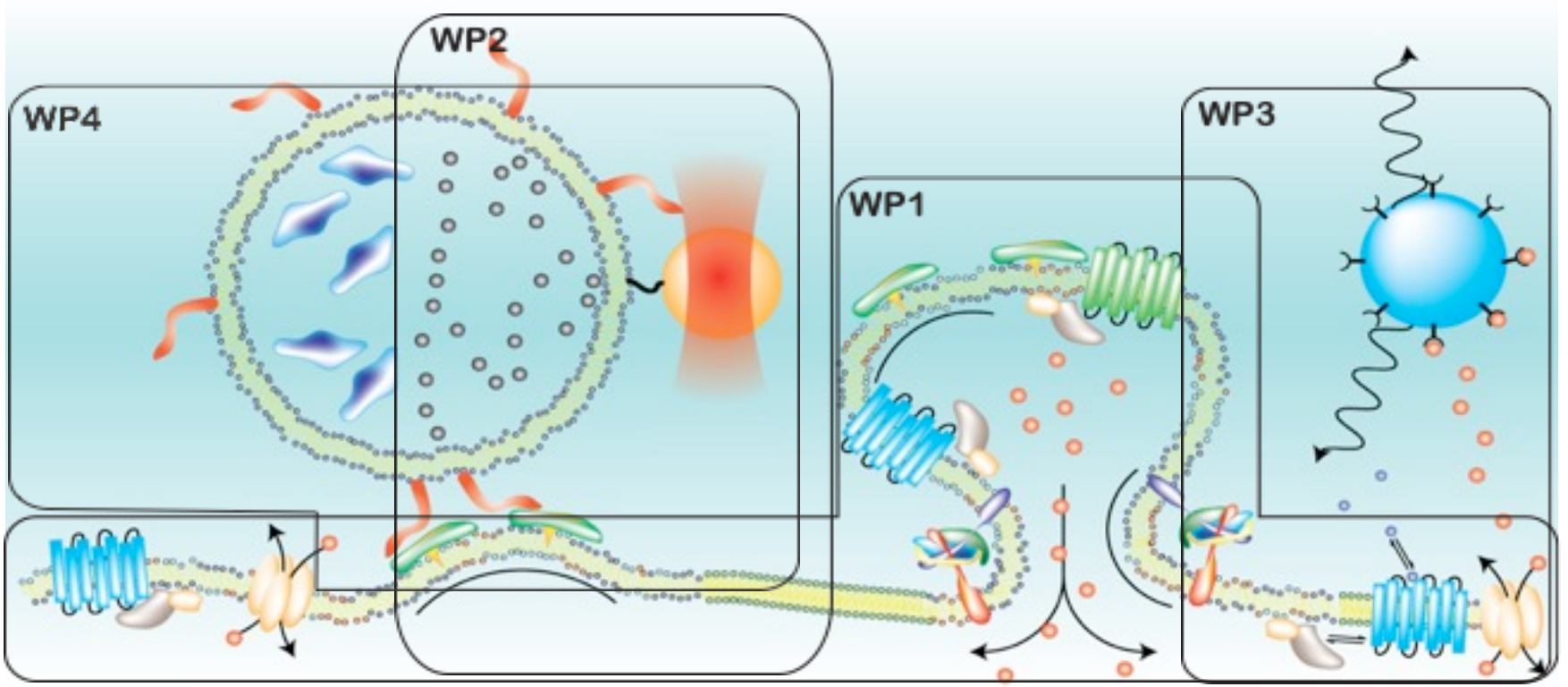

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Partners: expertise and contribution to WPs

Competences for Nanomedicine goals / Work Packages		WP1 Nanoscale protein-membrane interactions	WP2 Nanoscale inter-membrane interactions	WP3 Nano-biosensors	WP4 Drug delivery and nanotoxicology
CNS					
Neuropharmacology	• U Gether (UG)	■	■	■	■
Neurosecretion	• J Sørensen (JBS)	■	■	■	■
Infectious Diseases	• M Givskov (MG)	■	■	■	■
NanoTox.	• S Loft (SL)	■	■	■	■
BioNano					
Nanoscale membranes	• D Stamou (DS)	■	■	■	■
Nano-biosensors	• KL Martinez (KLM)	■	■	■	■
Biophysics					
Optical tweezers	• L Oddershede (LO)	■	■	■	■
Scattering techniques	• K Mortensen (KM)	■	■		■
NanoChemistry					
Nano-bioorganic chemistry	• KJ Jensen (KJJ)	■	■	■	■
Single molecule chemistry	• T Bjornholm (TB)	■	■	■	■

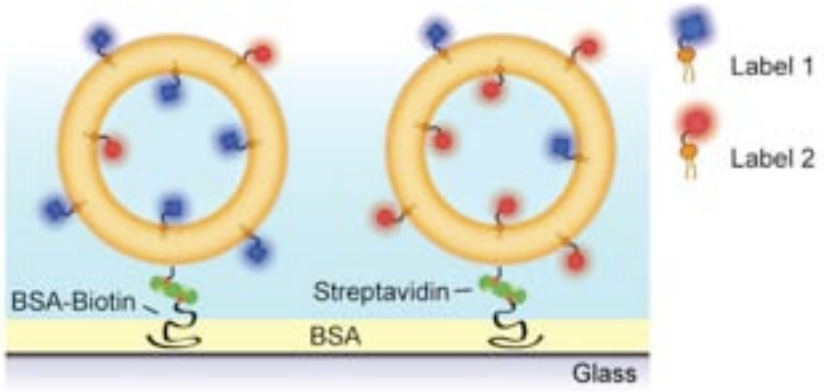
CBN our first year

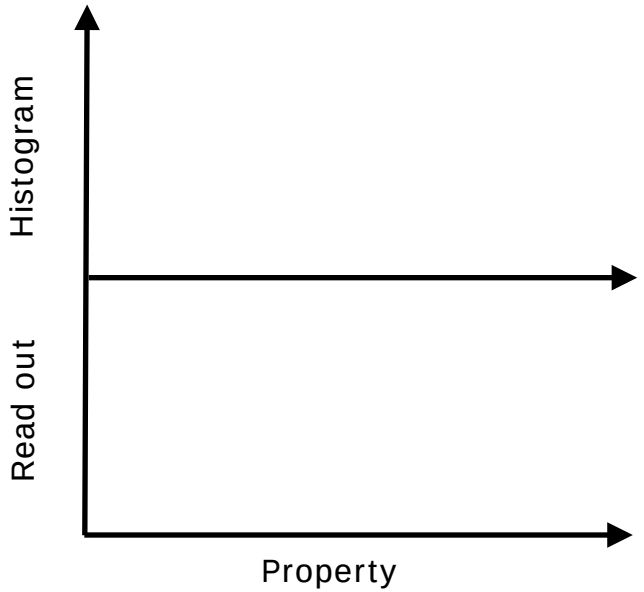
- The Center has hired 12 staff
- The Center has published 56 peer-reviewed scientific papers
- Including *Science (x1), Nature Clones (x3) and Proceedings of the National Academy of Sciences of the United States (x3).*
- Furthermore, CBN researchers and CBN affiliated staff have received approximately 15 million Danish kroner of cofinancing for their research.

Science Topics:

– Intrasample heterogeneity
– Counting SNAREs
– Zeptofluidics

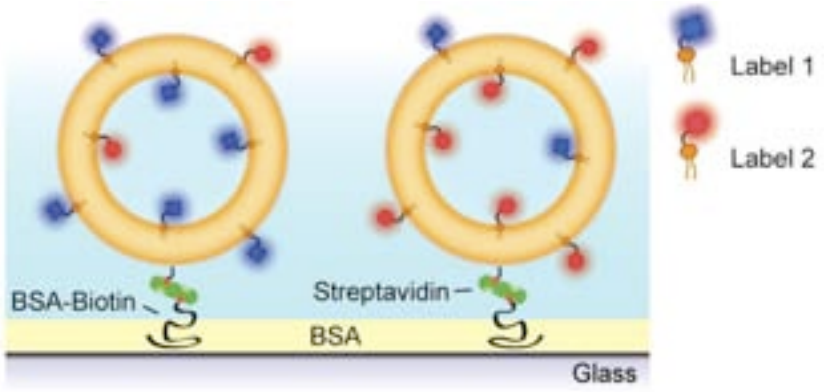
Intrasample nanoscale heterogeneity

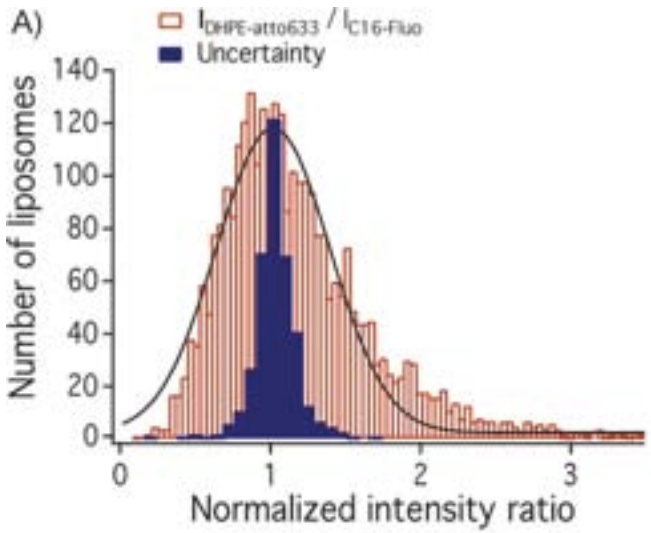


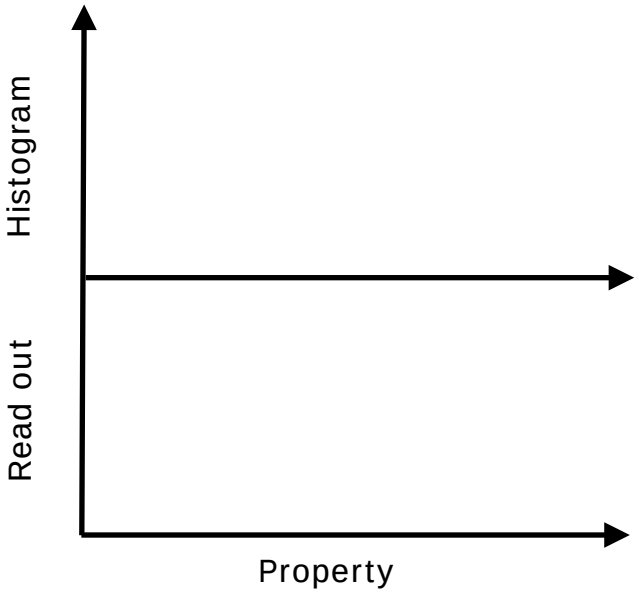


Lohse et al. JACS (2008)
Larsen et al. JACS(2011)
Elizondo et al. JACS (2012)

Intrasample nanoscale heterogeneity







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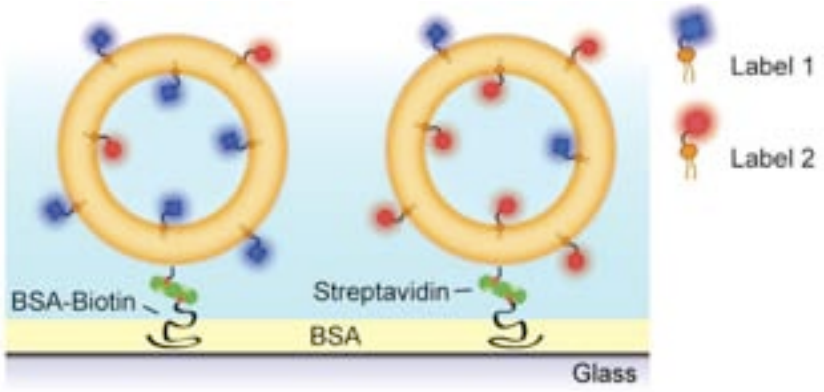

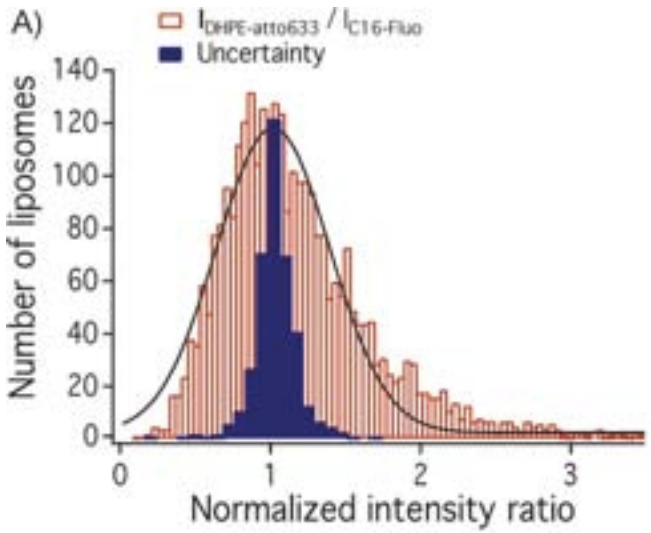

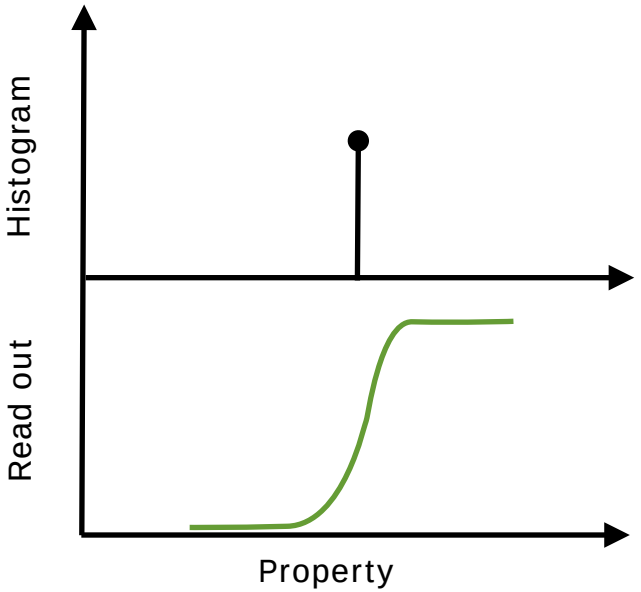

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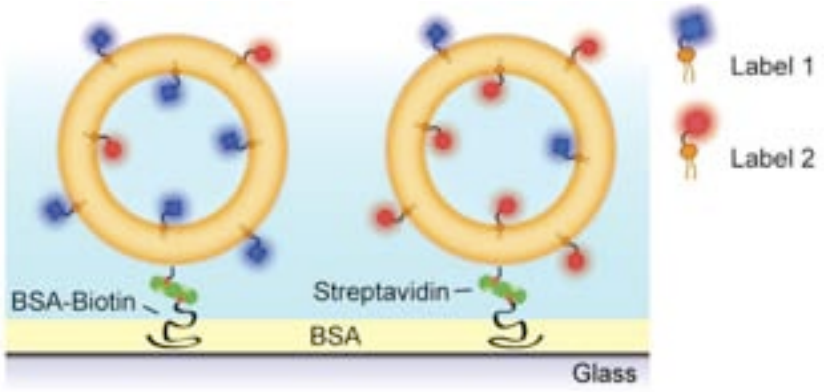

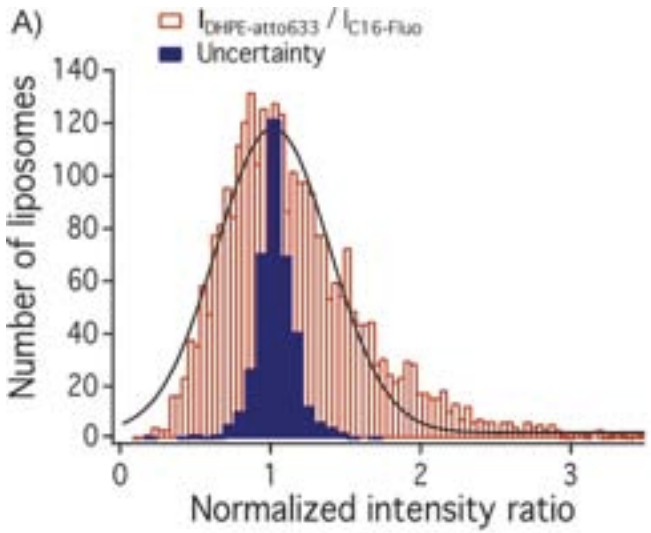

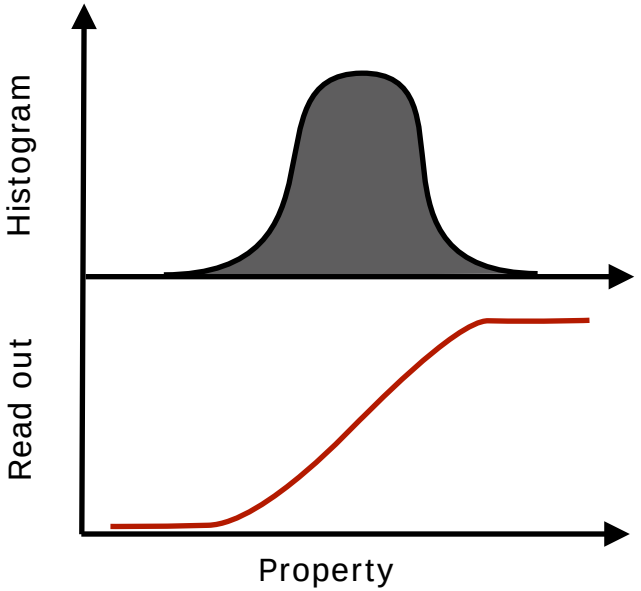

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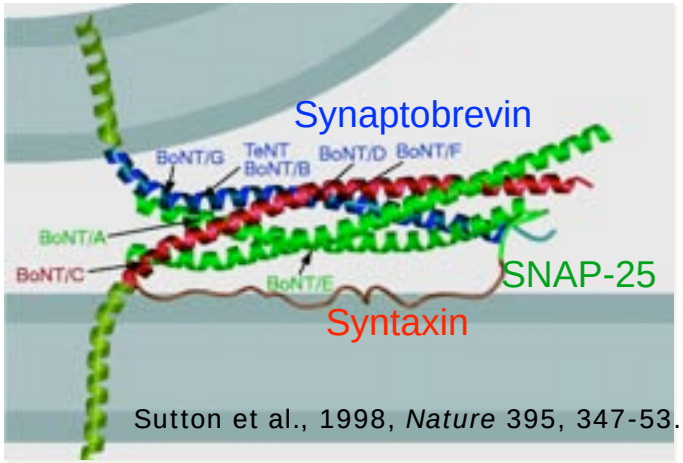
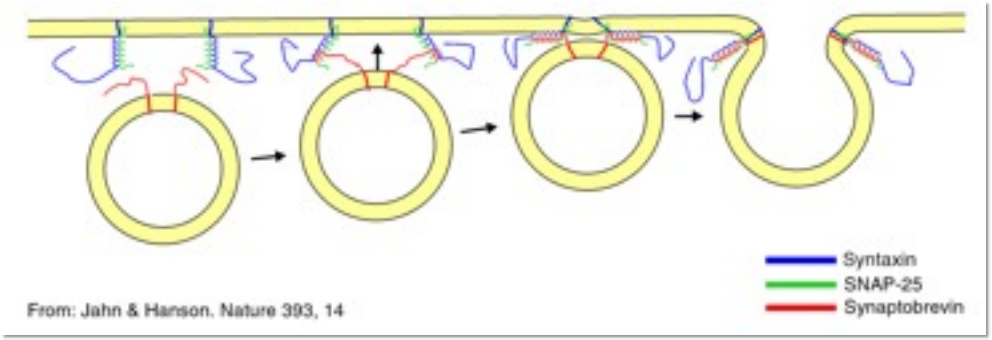
The SNARE-complex is essential for exocytosis

Jakob Sørensen, *Science*, 2011



Sutton et al., 1998, *Nature* 395, 347-53.

Zipper model for SNARE-action



From: Jahn & Hanson. Nature 393, 14

Secretion assay:
L5** mutant is dead for secretion

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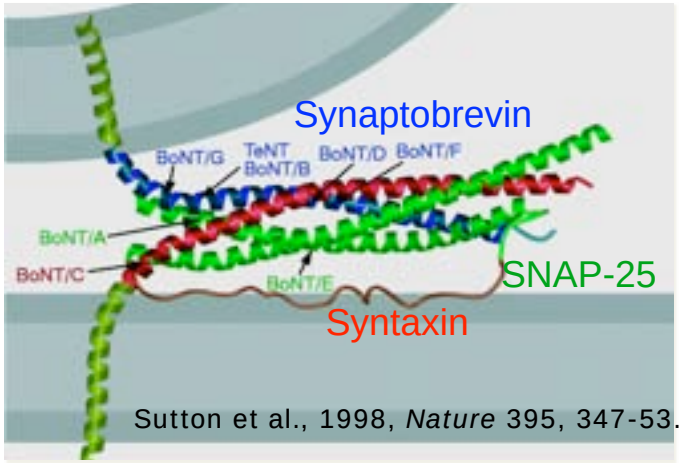

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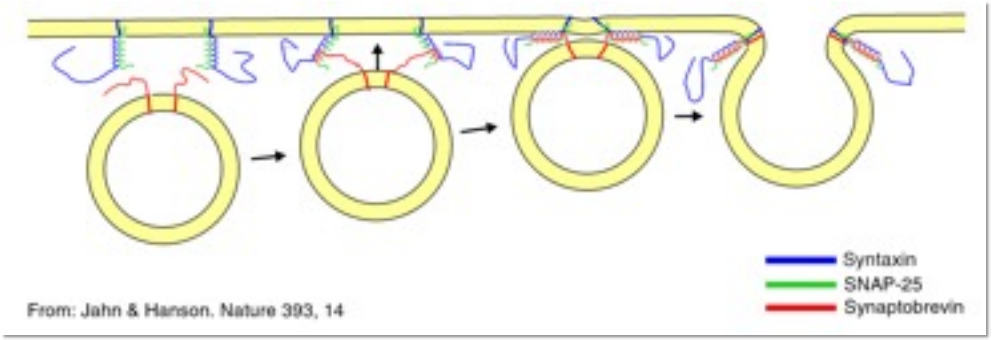

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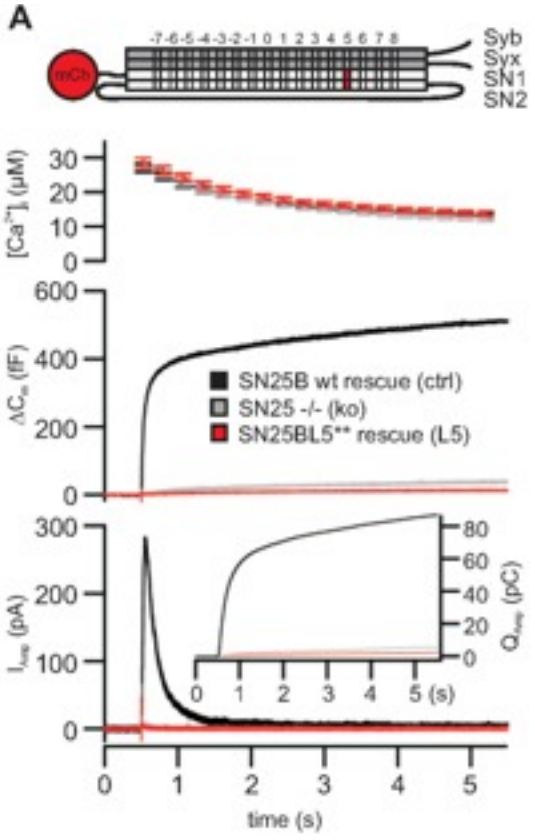
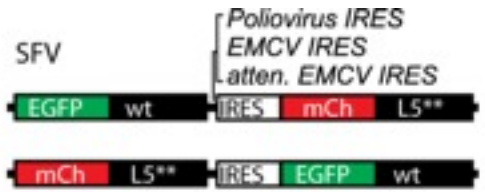
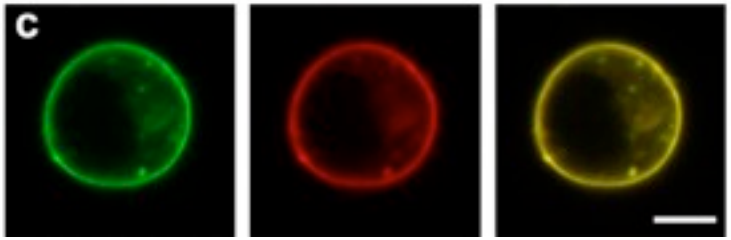


Titration with 'dead' L5** mutant reveals cooperativity of exocytosis

Cell-by-cell quantification of expression ratios using fluorescence tagging



Co-expression of two variants in same cell



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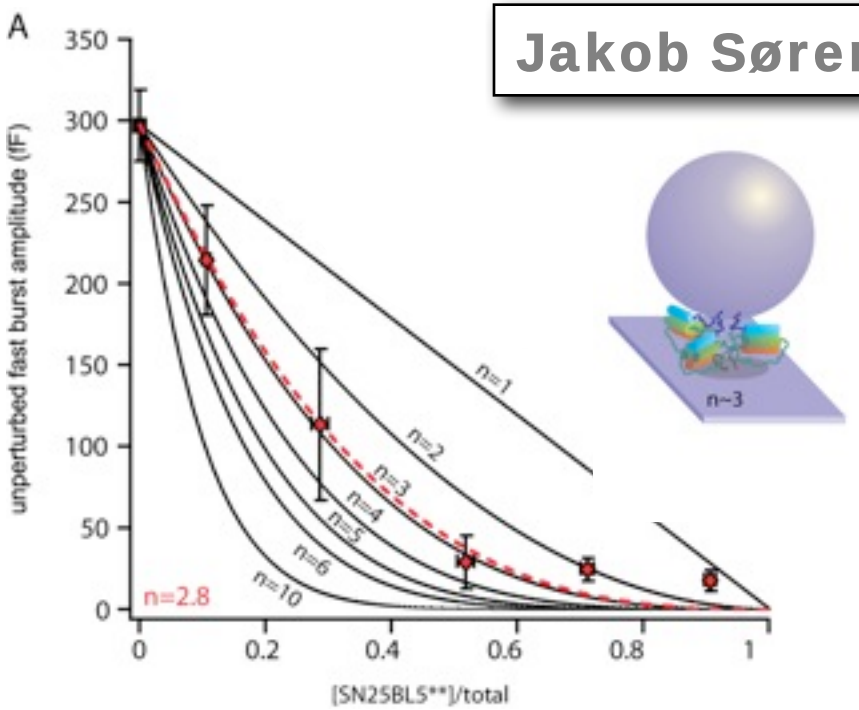
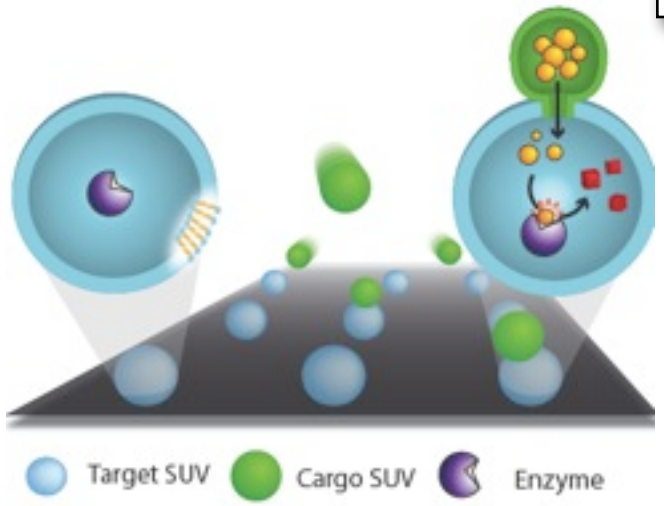


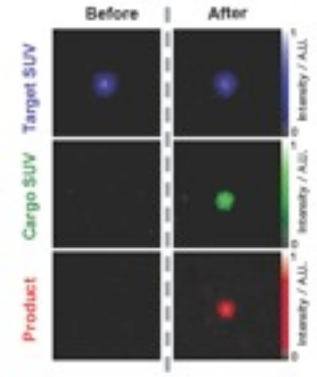
- Fast part of secretion has a higher cooperativity (~3) than slow parts (~1).
- Interpretation: fast part of secretion depends on a higher number of SNARE-complexes.
- Open question: does different secretion speeds in the nervous system depend on SNARE-complexes with different stoichiometries?

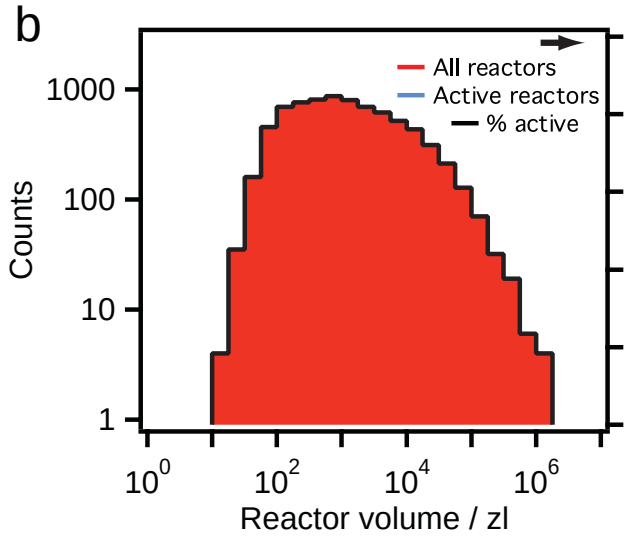
***Science*, 2011**

HT ultra miniaturized enzymatic reactions

Stamou, *Nature Nanotech.*, 2011







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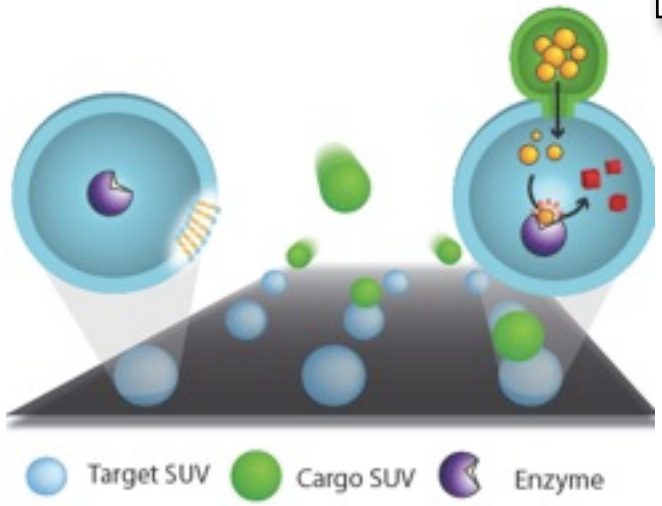
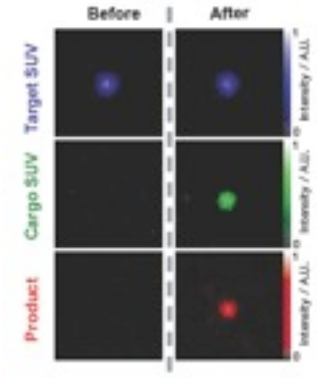
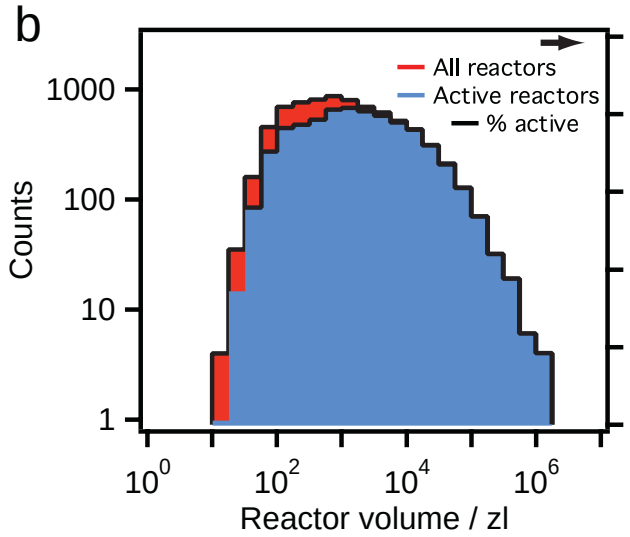
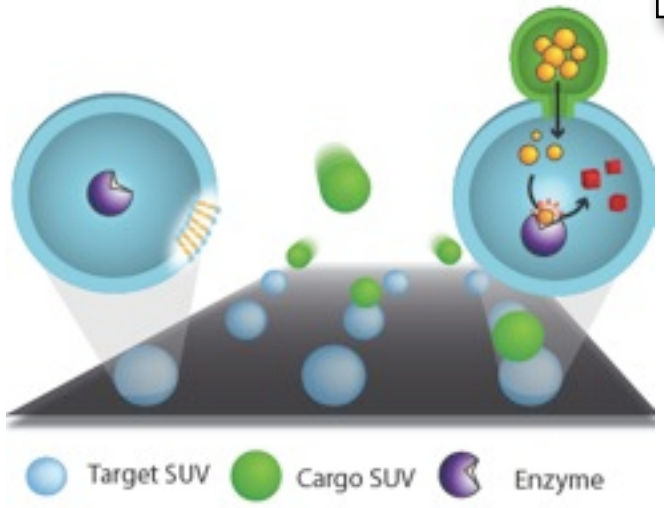


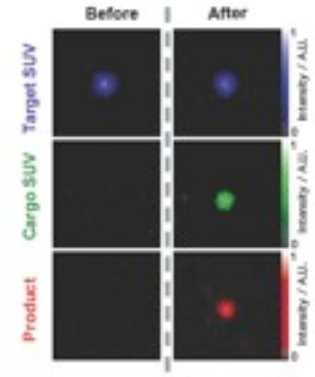


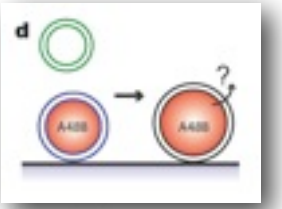


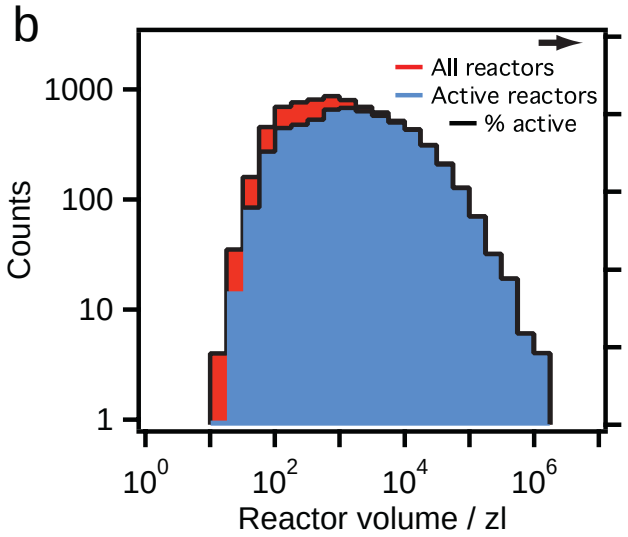
HT ultra miniaturized enzymatic reactions

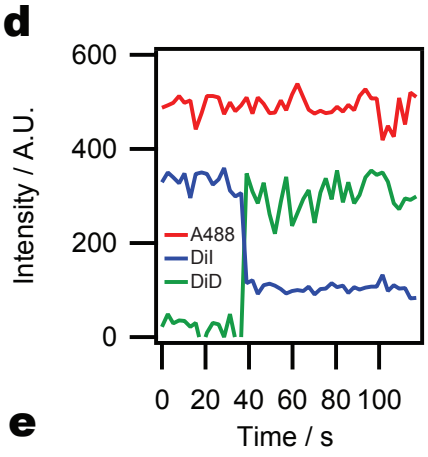
Stamou, *Nature Nanotech.*, 2011

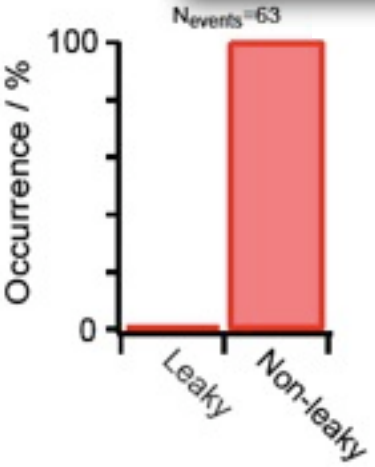












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- U Gether (UG)
- J Sørensen (JBS)

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- S Loft (SL)

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Thank you
&
The Lundbeck Foundation

Lundbeck Foundation Center for Biomembranes in Nanomedicine

Directors:	**Dimitris Stamou and Ulrik Gether**
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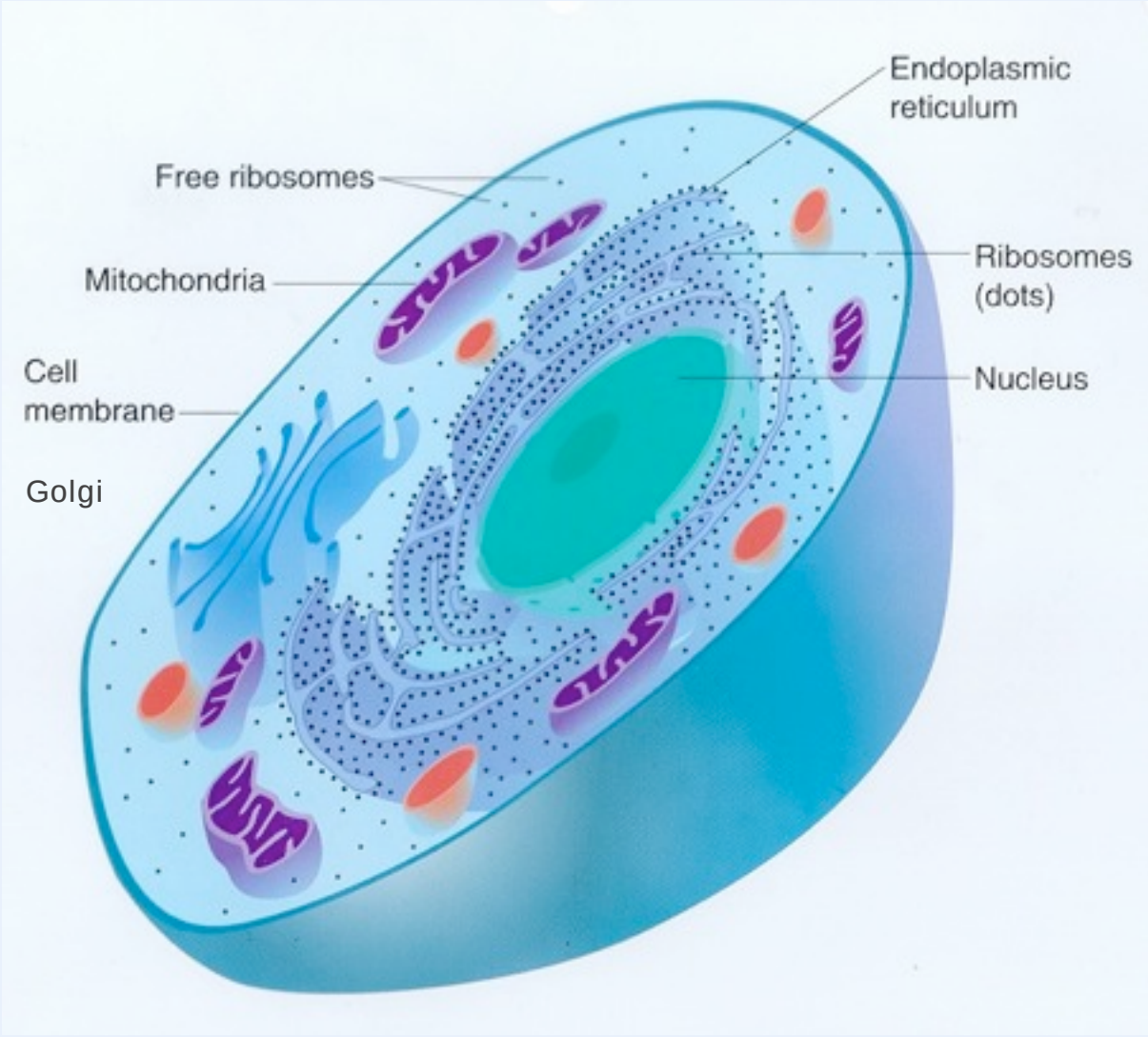
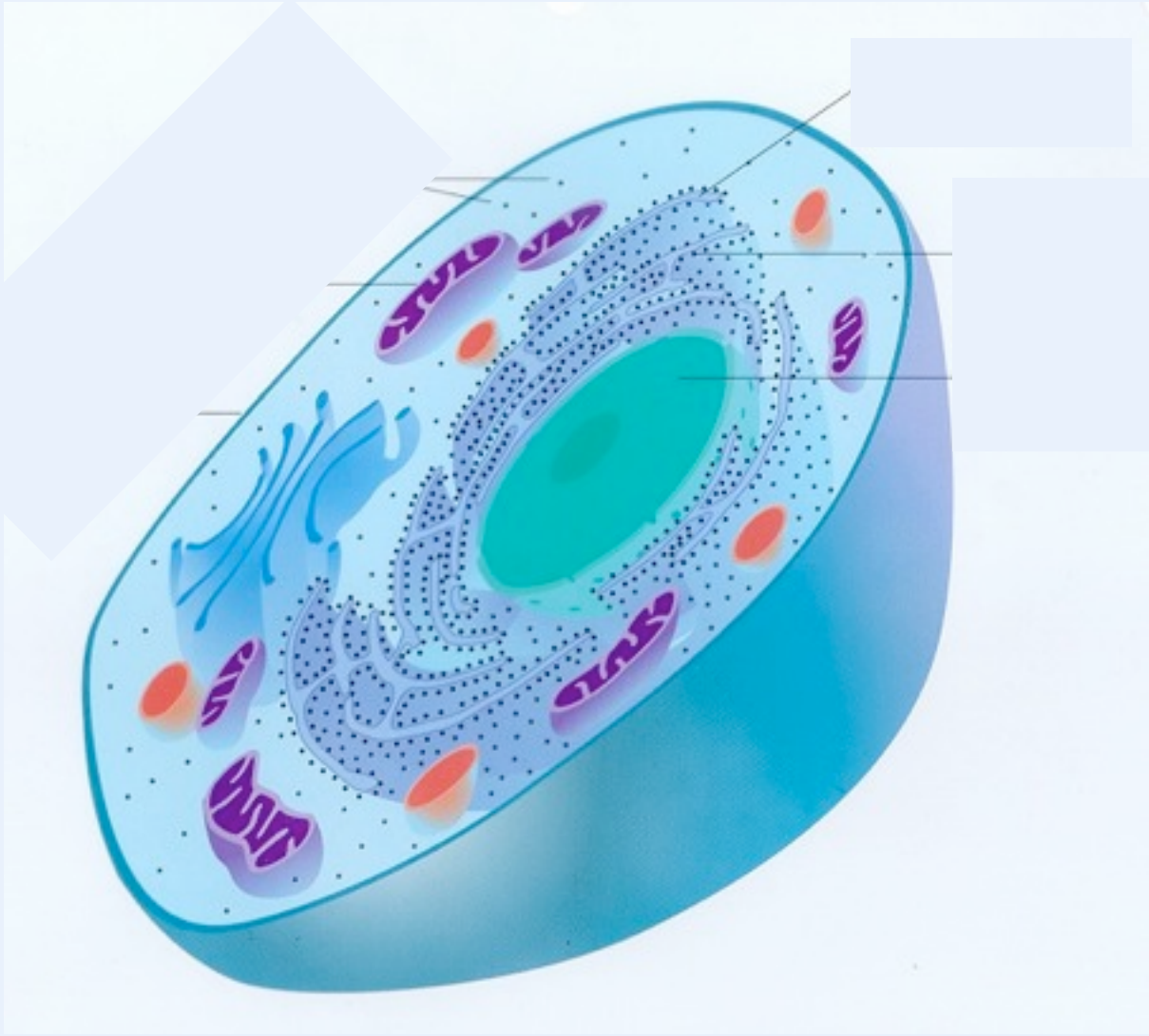
Nanoscale Membrane Anatomy: a conserved & regulated phenotype

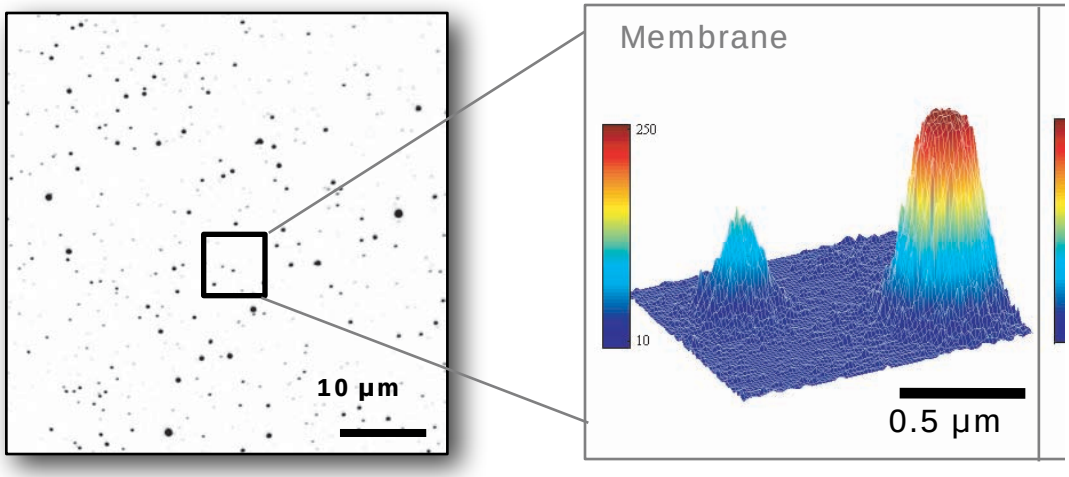


Nanoscale Membrane Anatomy: a conserved & regulated phenotype



Sensing of Membrane Curvature

Collaboration with U. Gether



FEBS Lett., 2010
JBC, 2010
EMBO J., 2009

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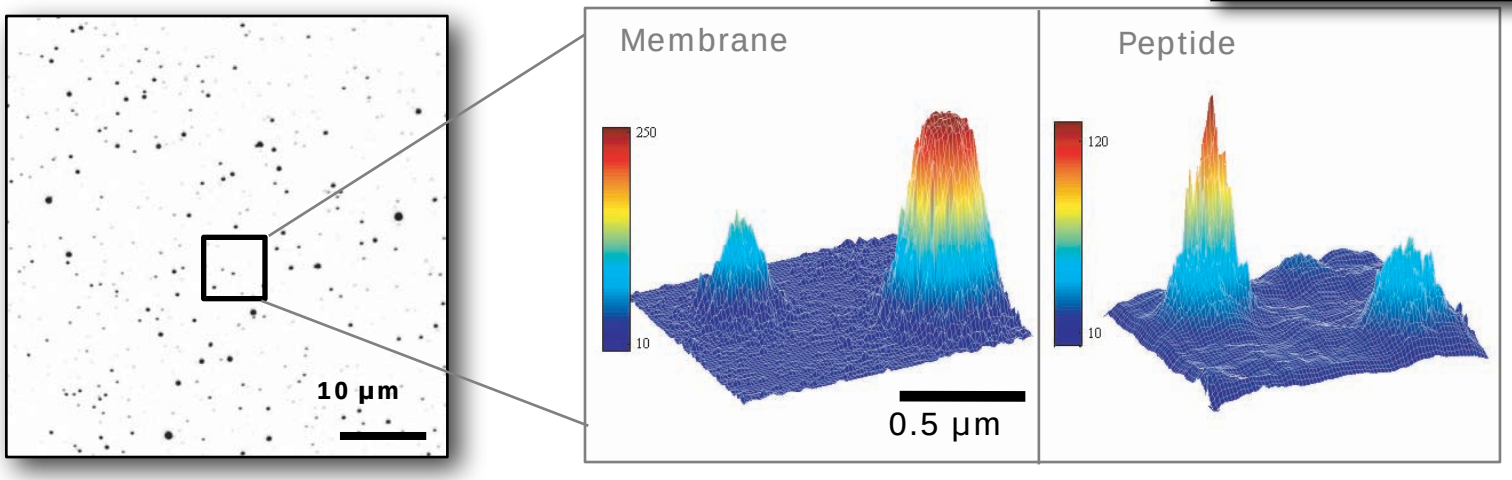

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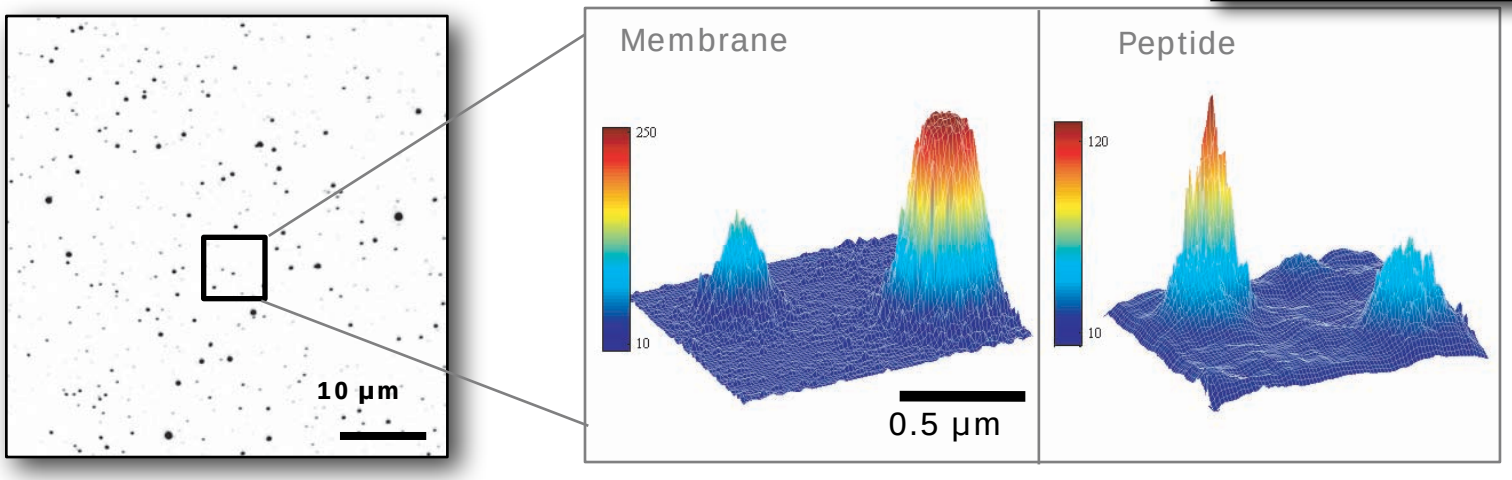

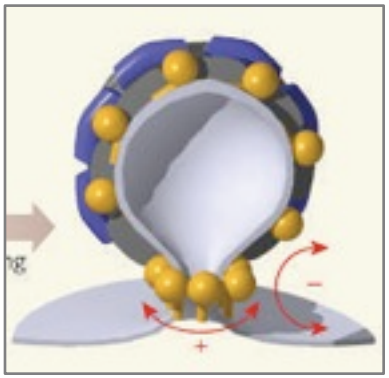

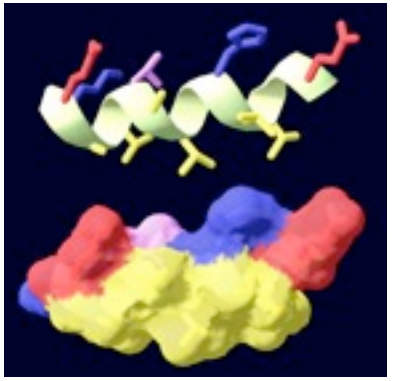

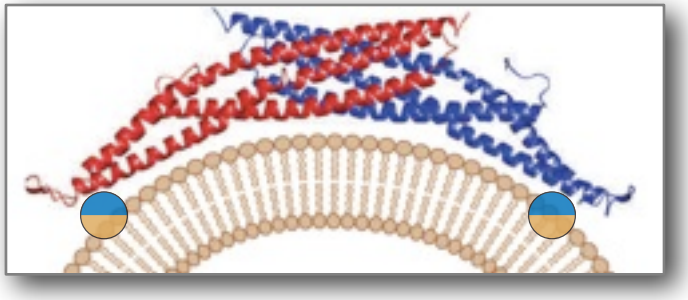

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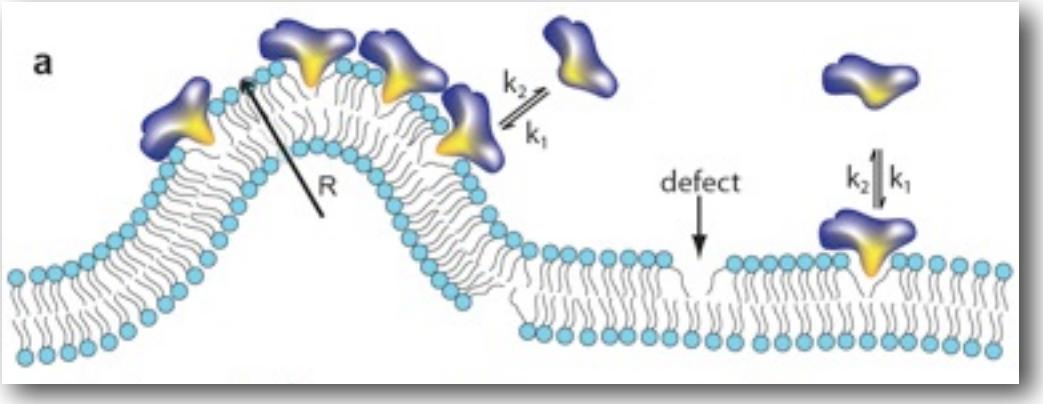
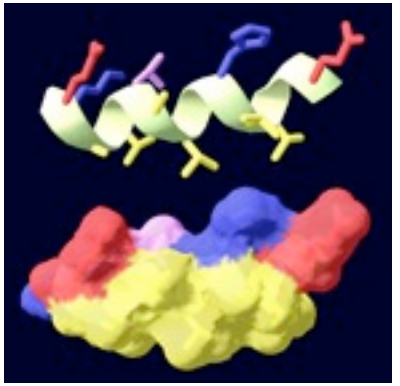
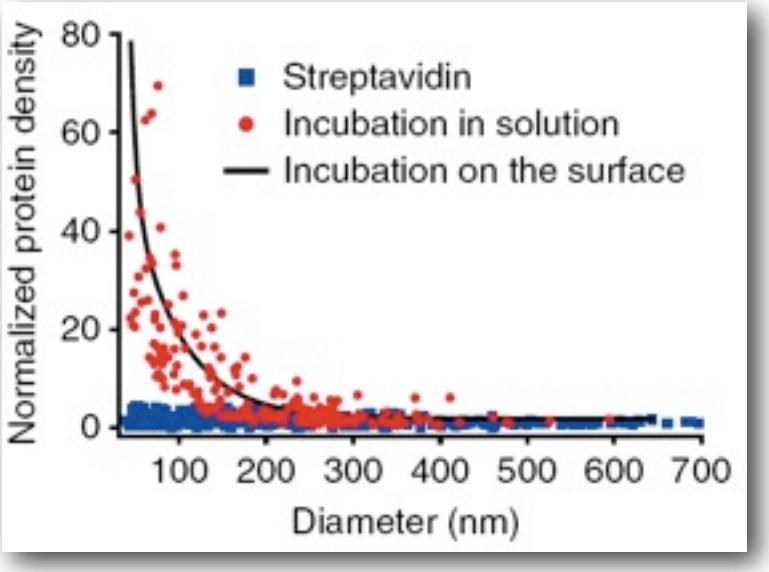
Model: same type of defects but at different densities







Nat Chem Biol, ***5*** *(11), 2009*

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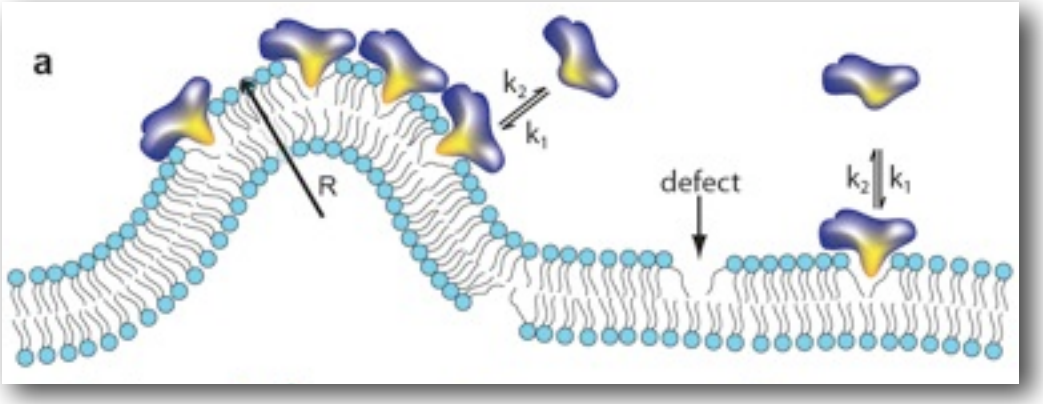

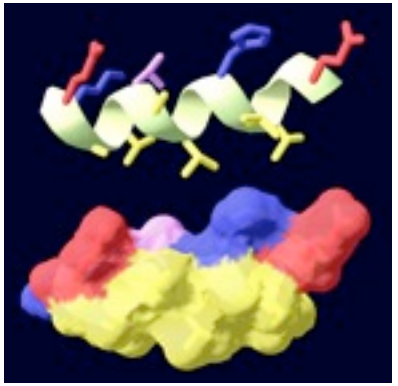

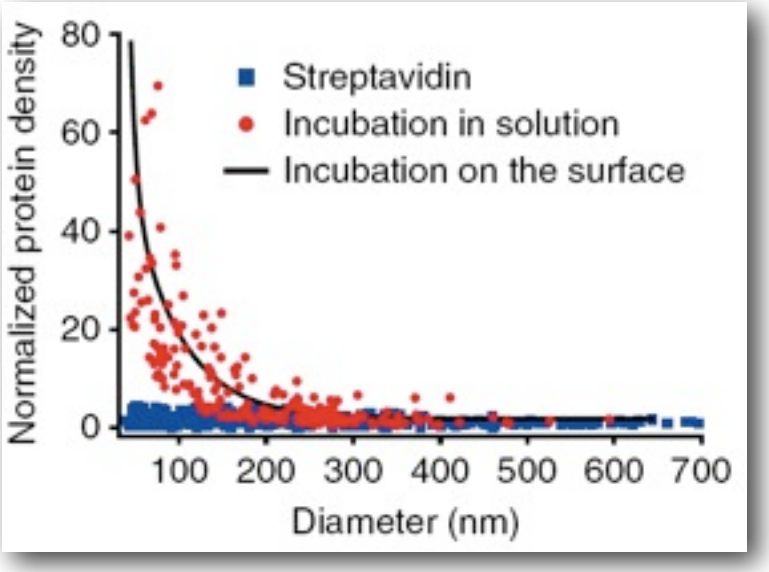

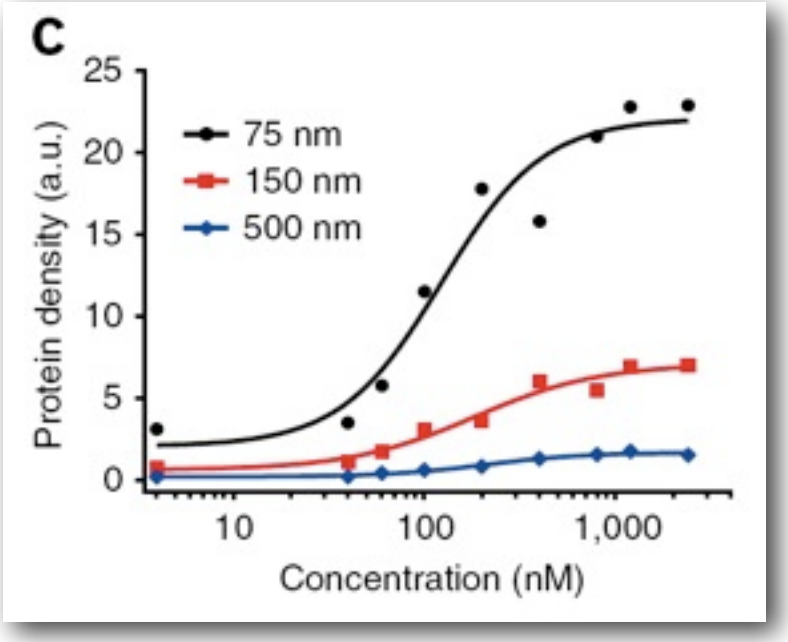

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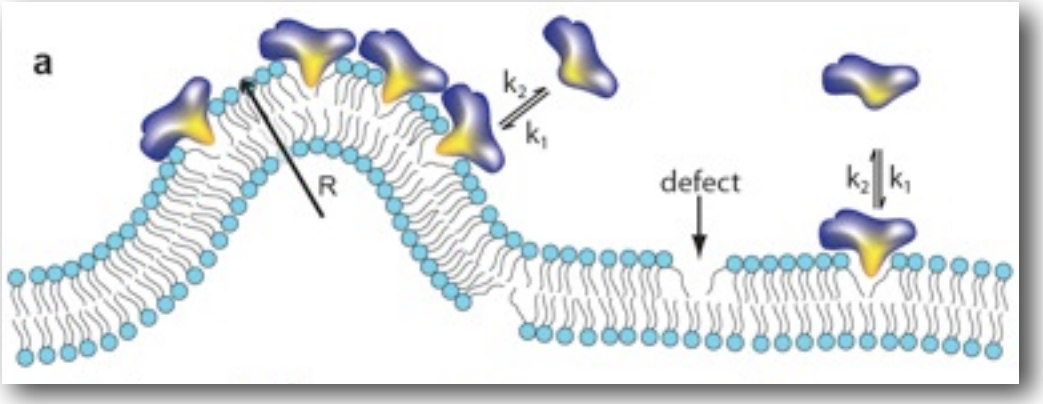

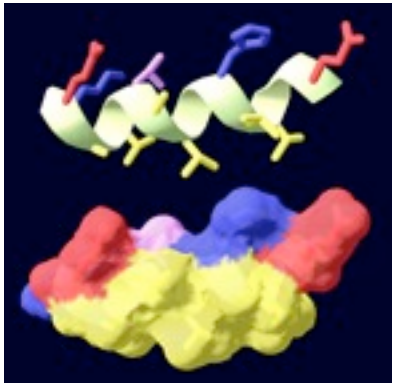

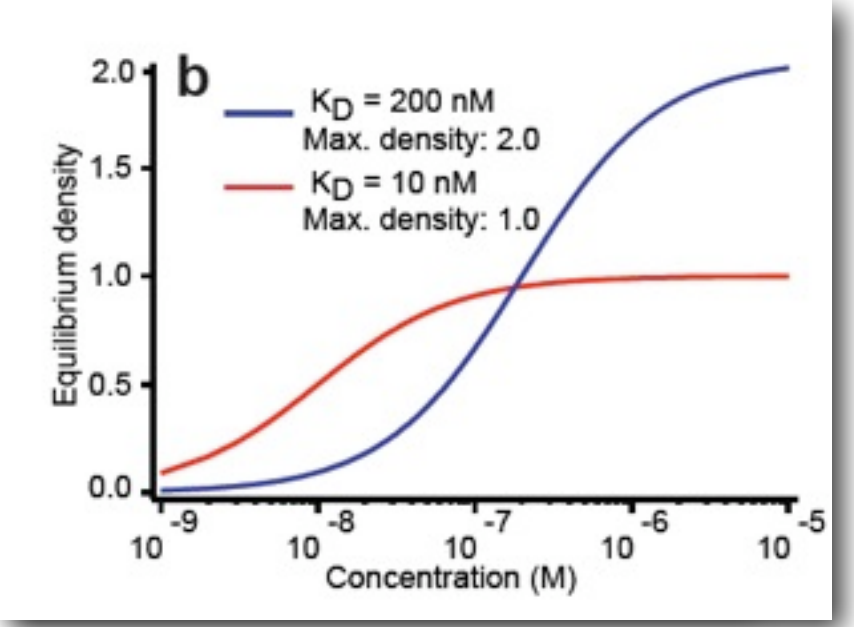

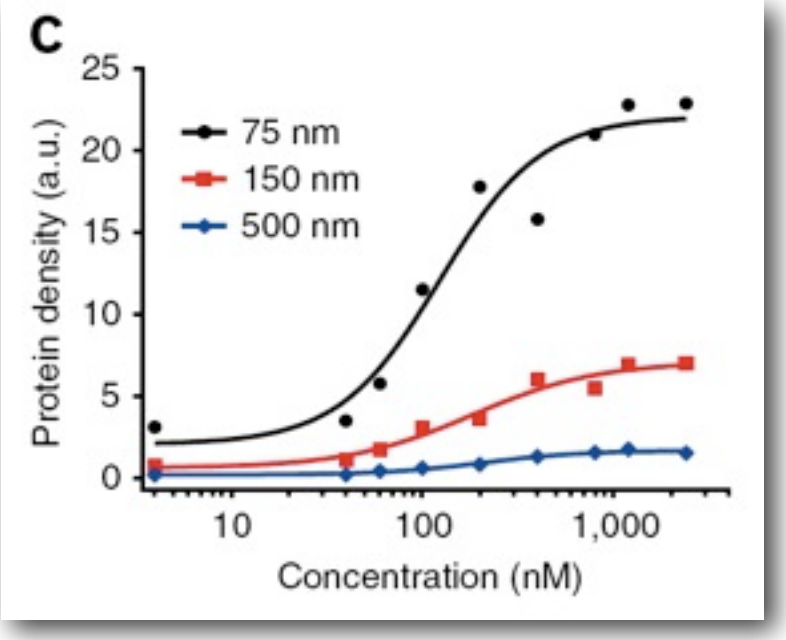

Nat Chem Biol, ***5*** *(11), 2009*

Prediction: Alkylated Proteins are sensors of membrane curvature

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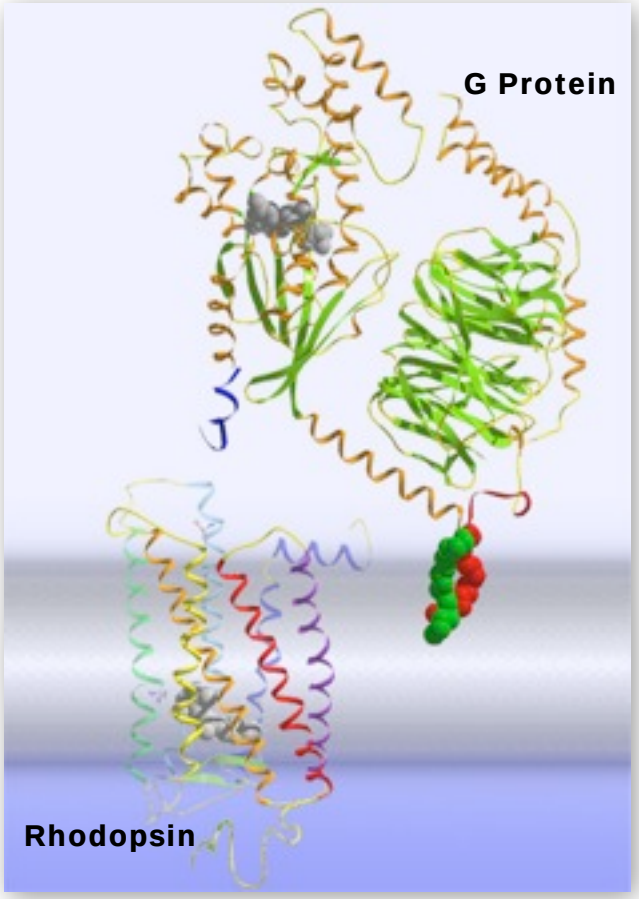
G protein provided by J.L. Baneres



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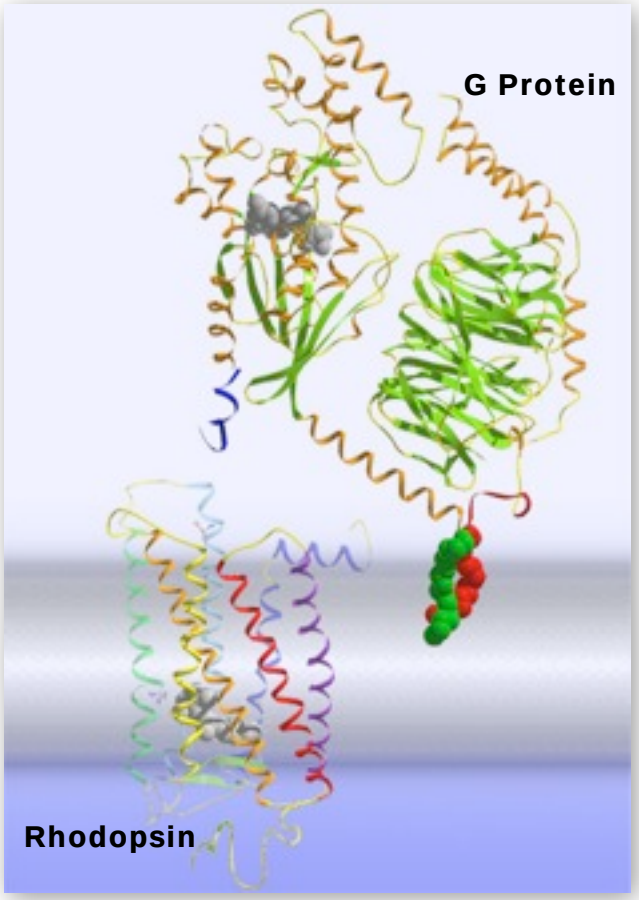
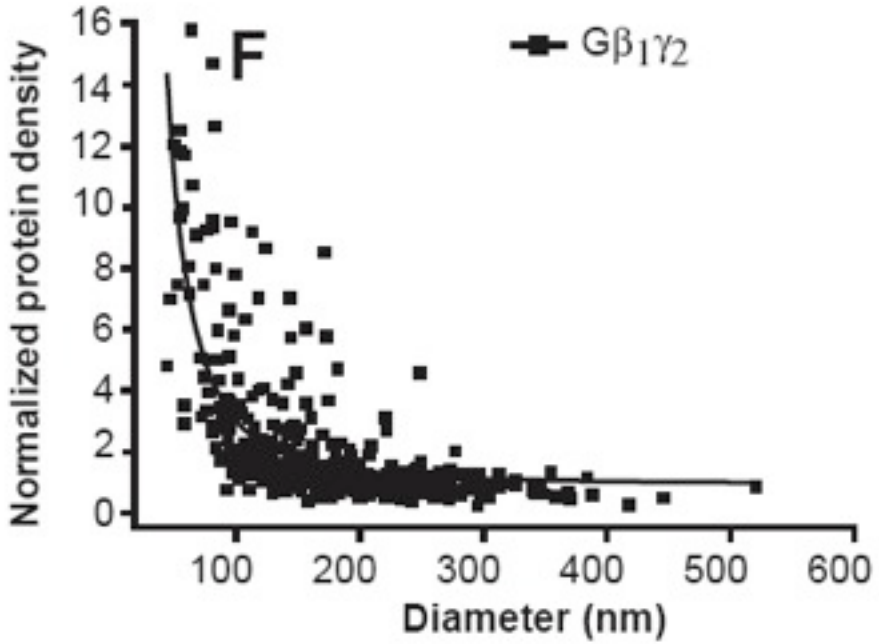
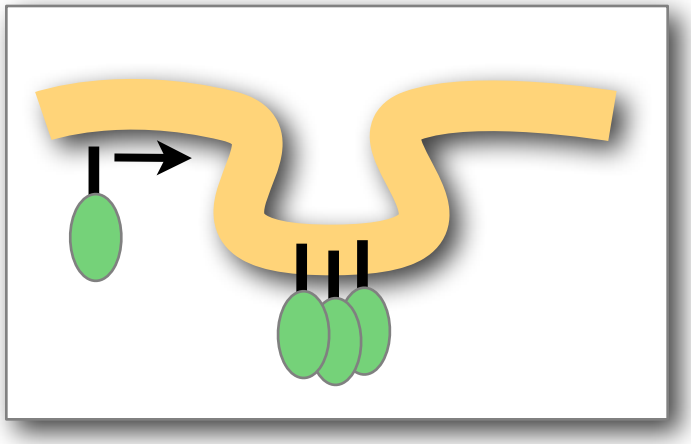




Rafts & Membrane Curvature



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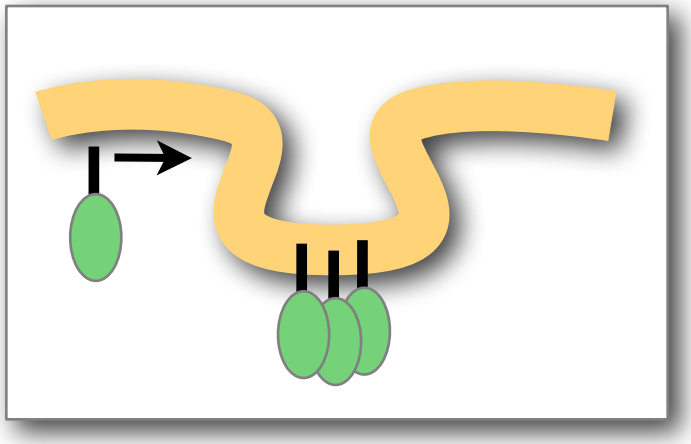

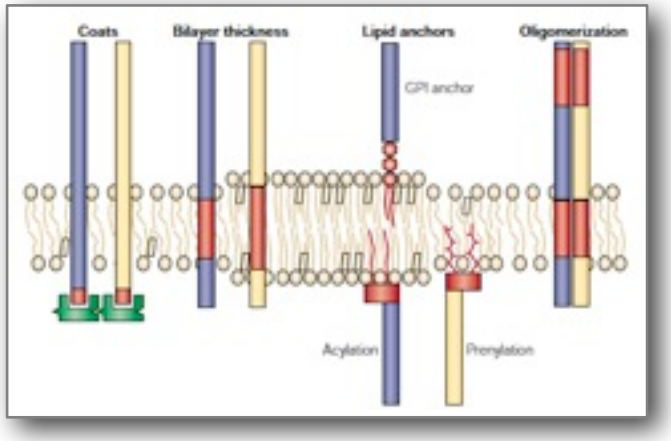

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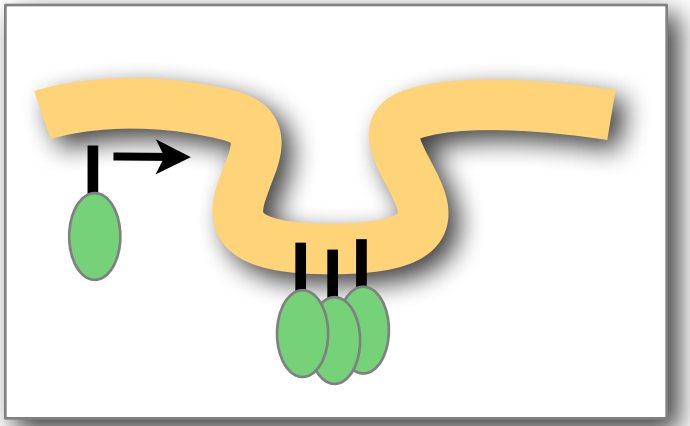
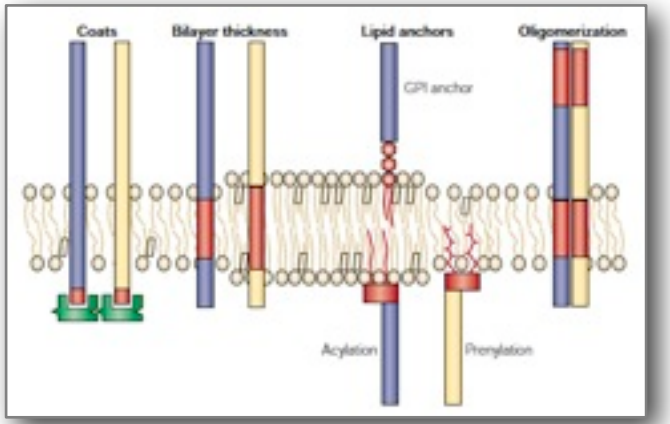
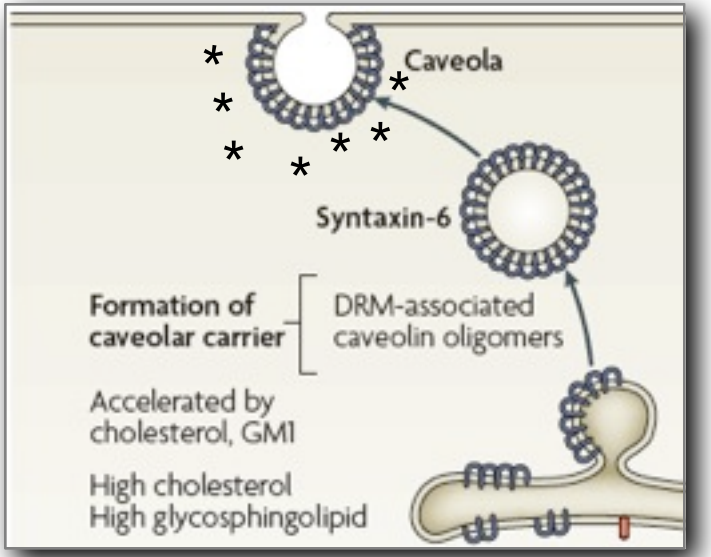
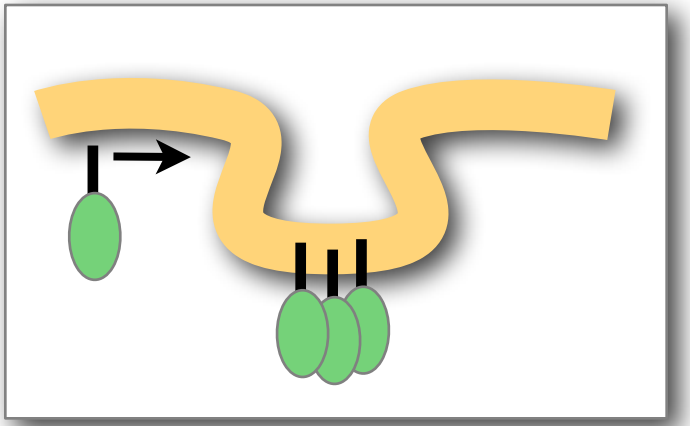


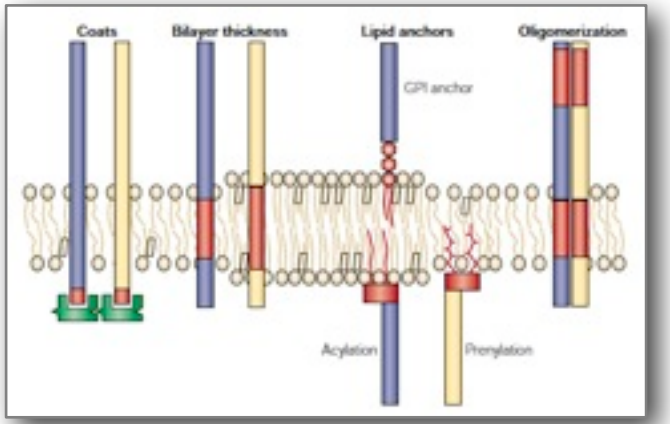


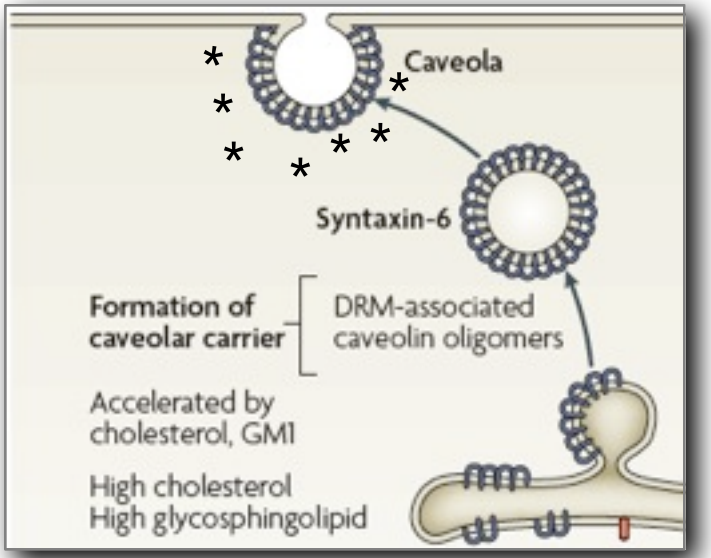


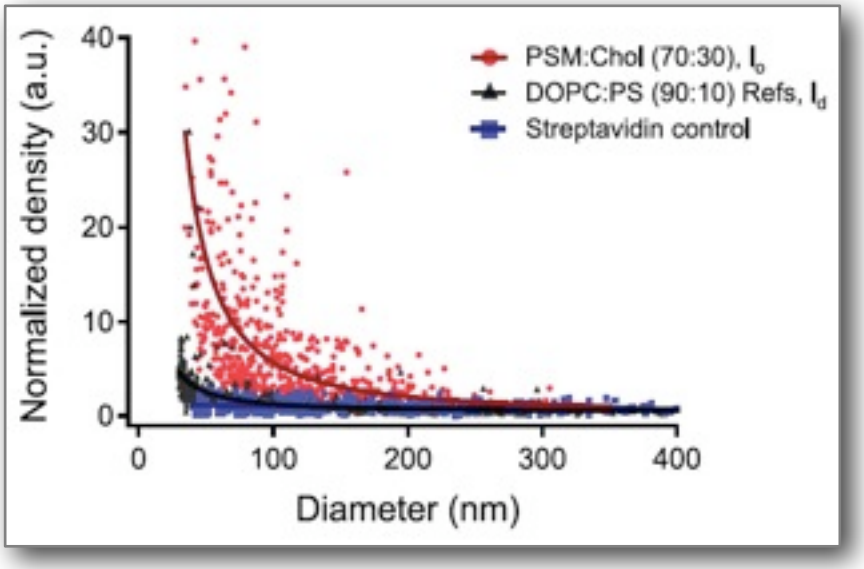
Simons et al, Nat Rev, 2007

Rafts & Membrane Curvature









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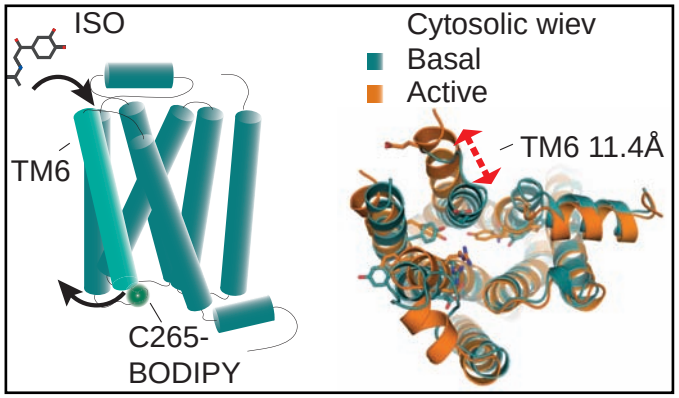
Optical measurements of agonist induced activation of b_2 Adrenergic Receptor

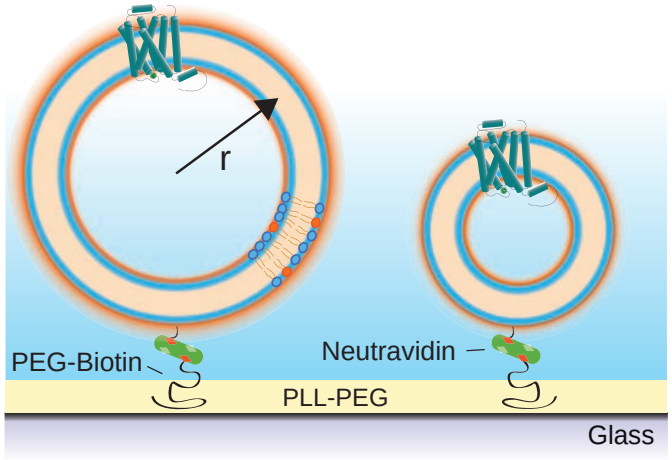
Influence of Membrane Curvature

Collab. B Kobilka

unpublished data



Rasmussen, *Nature*, 2011



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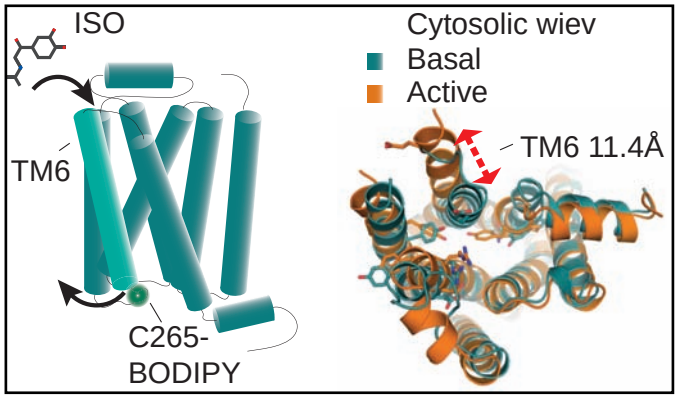

Rasmussen, *Nature*, 2011

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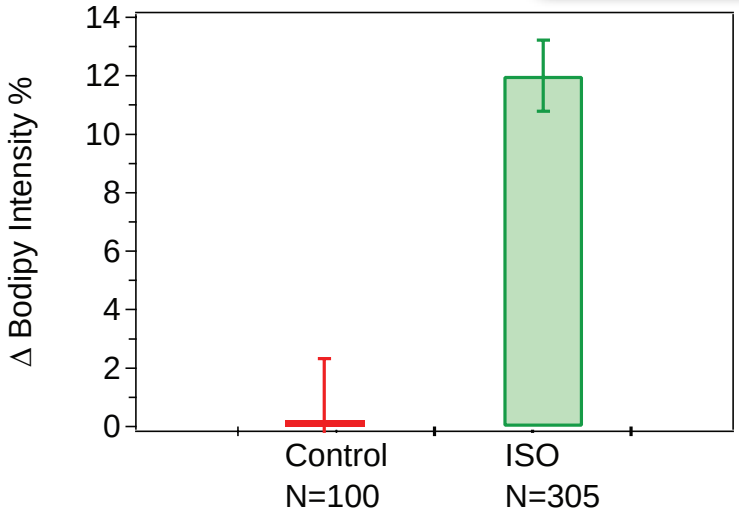

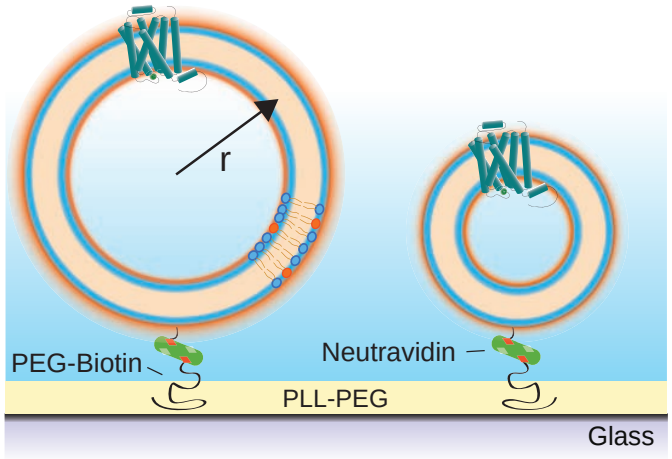

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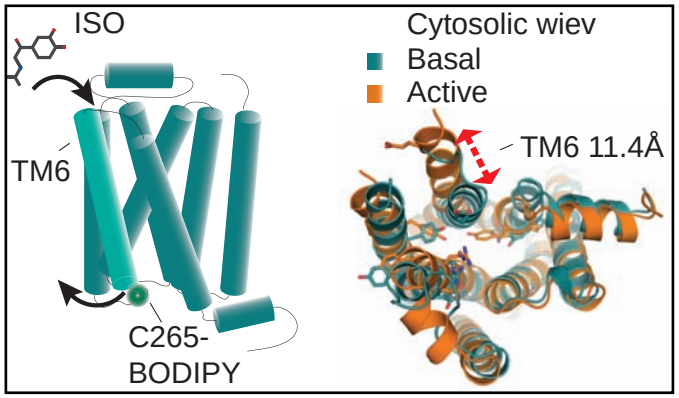
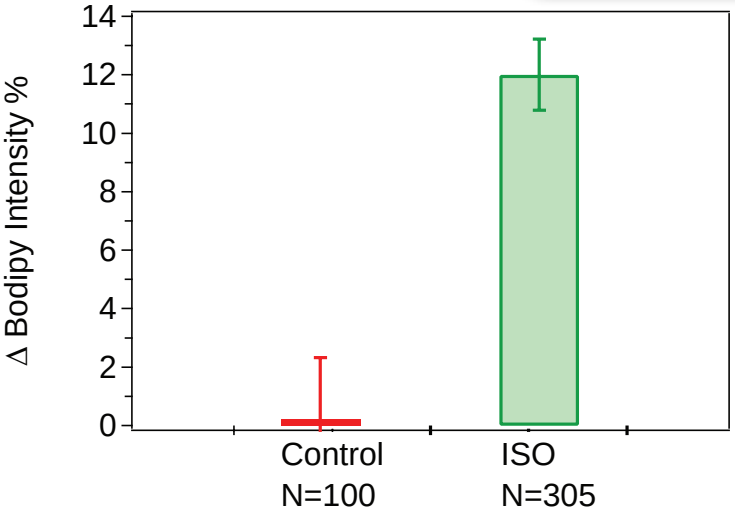
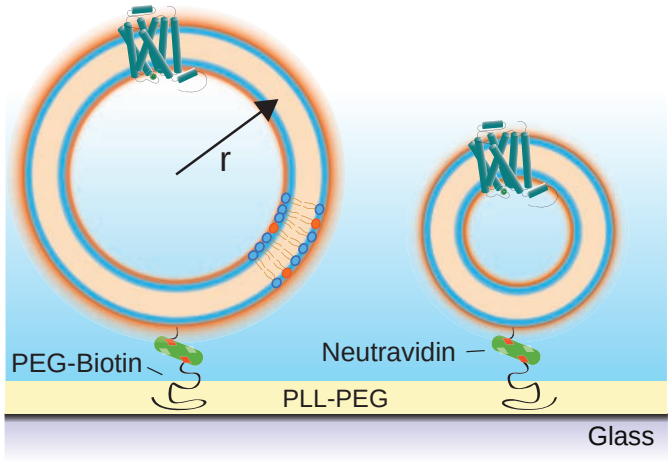
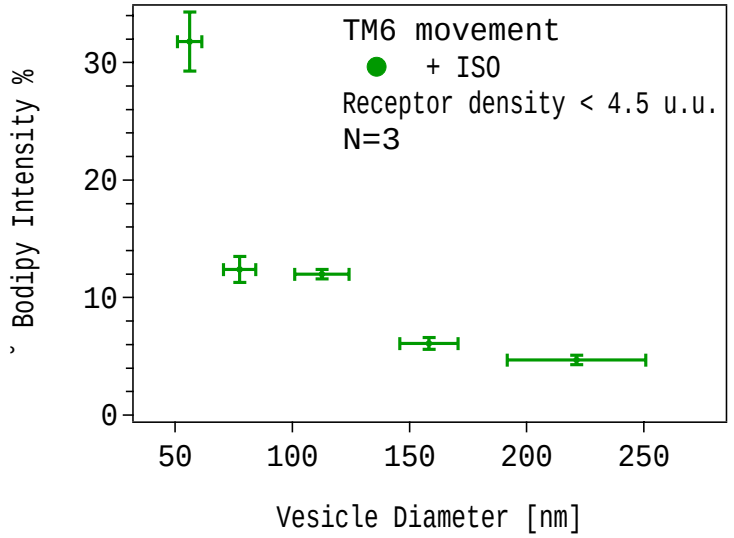


Rasmussen, *Nature*, 2011







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Influence of Membrane Curvature

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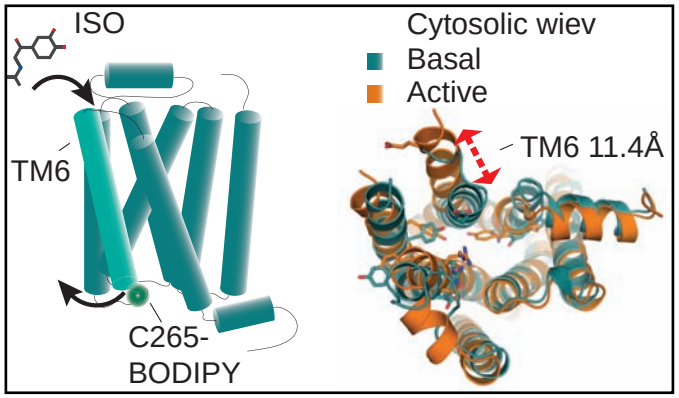

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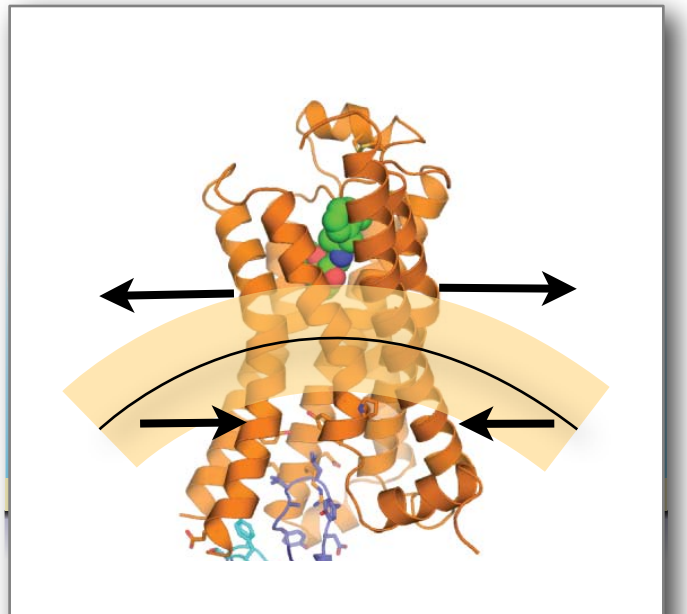

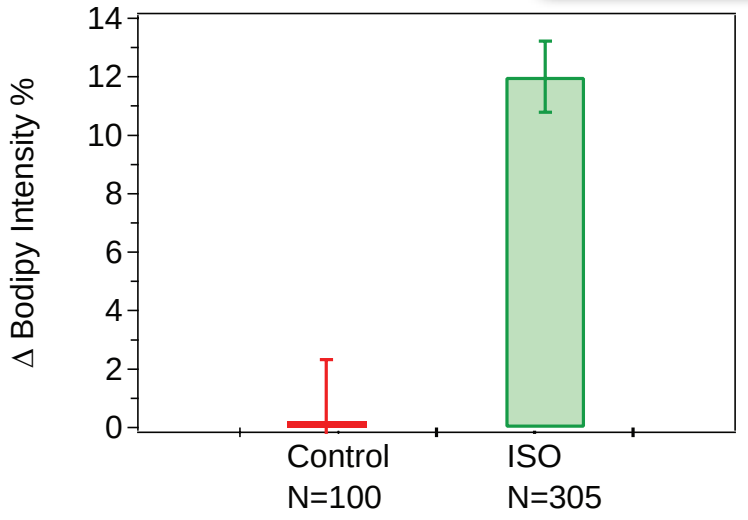

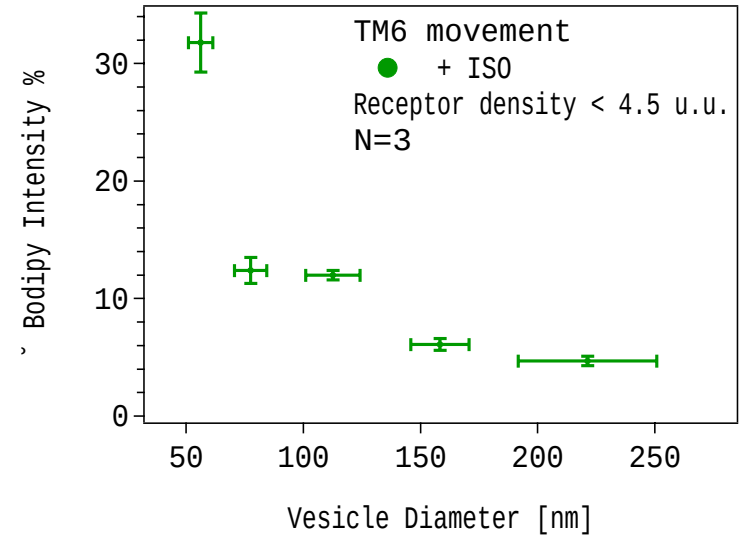

Collaborations and Alliances