

## How does the Synapse Work?

Josep Rizo (Jose Rizo-Rey)

Department of Biophysics

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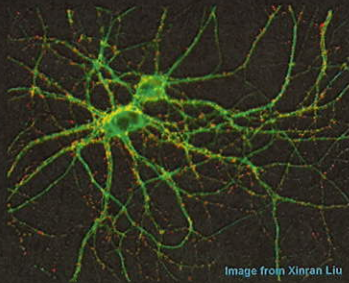
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The brain is an extremely complex communications network

- Interneuronal communication occurs at synapses
- The brain has about 100 billion neurons
- Each neuron forms an average of 10,000 synapses
- Some neurons can even form 150,000 synapses

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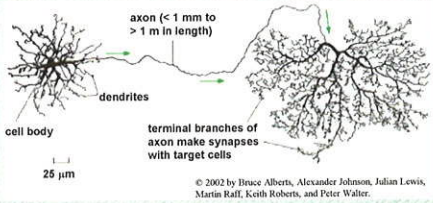
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**Typical neuron of a vertebrate animal**

- cell body
- dendrites: receive synaptic inputs
- axons: carry signals and transmit them to other cells
- axons and dendrites communicate at synapses



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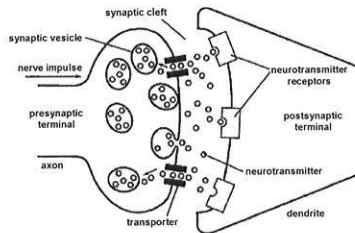
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**Synapses are sites where two cells come into close proximity, which allows fast transfer of signals between them**



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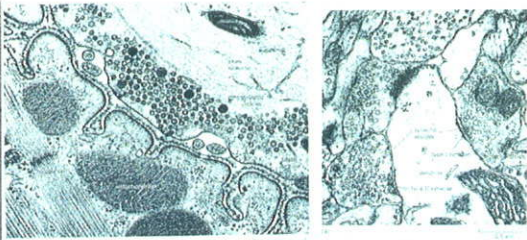
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**neuromuscular junction**

**brain synapses**



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### Complexity of the nervous system



© 2002 by Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter.

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- Synaptic transmission is not just a means to transfer signals between neurons
- Plastic changes in the efficiency of neurotransmitter release (presynaptic plasticity) or in the response of the postsynaptic terminal (postsynaptic plasticity) underlie many forms of information processing in the brain
- Learning and memory depend in part on these plastic changes

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### Many neurological disorders arise from defects in synaptic transmission

- Most of these disorders, including for instance Alzheimer's disease, are treated with drugs that enhance synaptic transmission
- Disorders with at least some presynaptic origin include among others schizophrenia, bipolar disorder and myasthenia gravis

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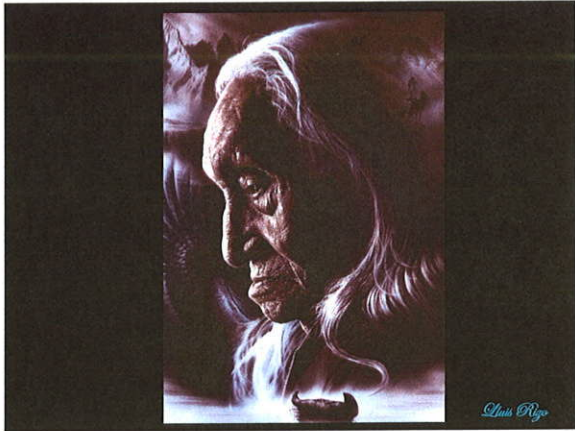
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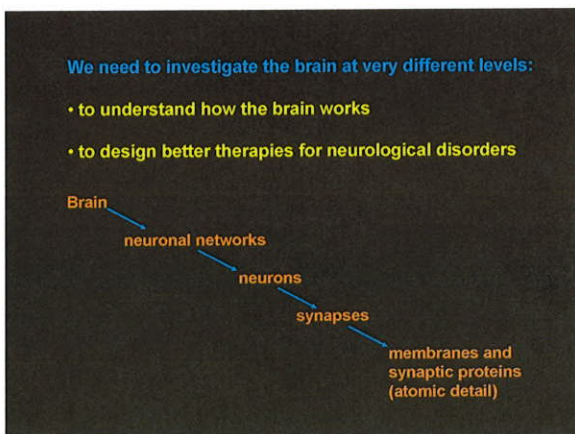
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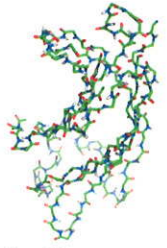
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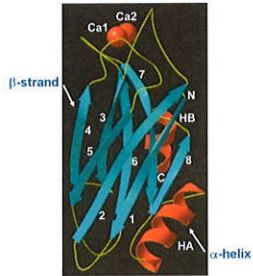
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The three-dimensional structures of proteins can be represented in different ways, depending on the features that need to be emphasized



stick model  
only backbone atoms shown



ribbon diagram

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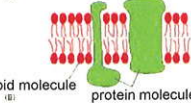
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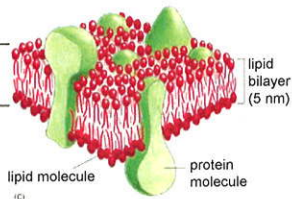
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Cellular membranes are composed of lipids and proteins

electron microscopy image  
of a cellular membrane



lipid molecule  
protein molecules



lipid bilayer  
(5 nm)  
protein molecule

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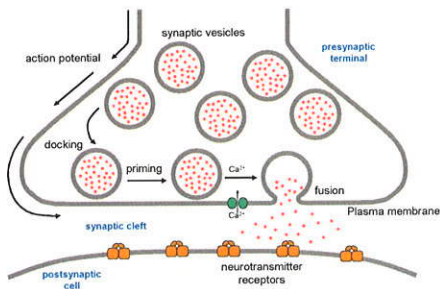
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Neurotransmitter release involves fusion between the synaptic vesicle and presynaptic plasma membranes




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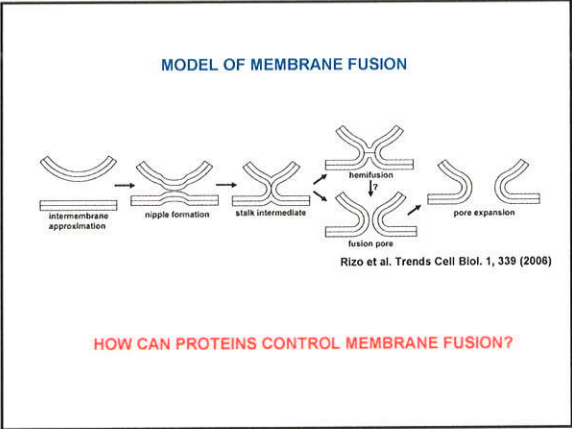
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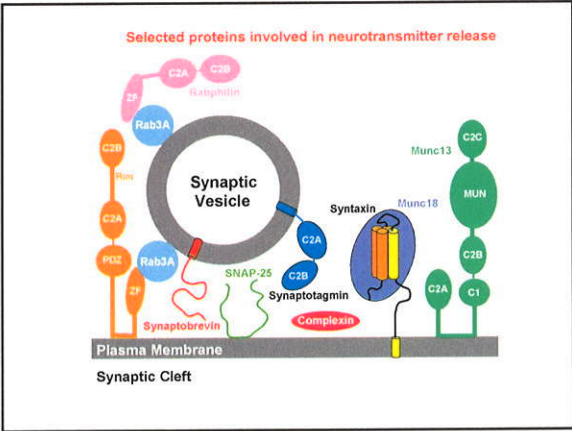
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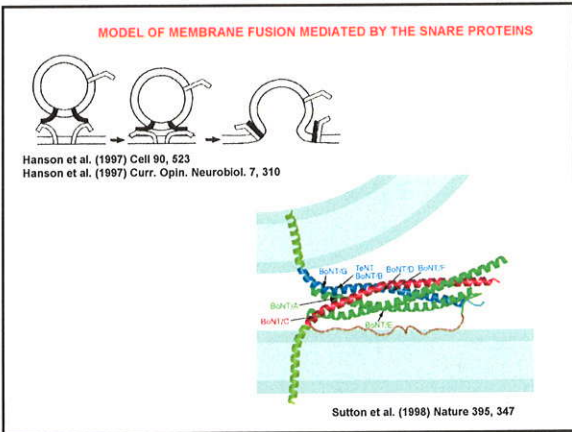
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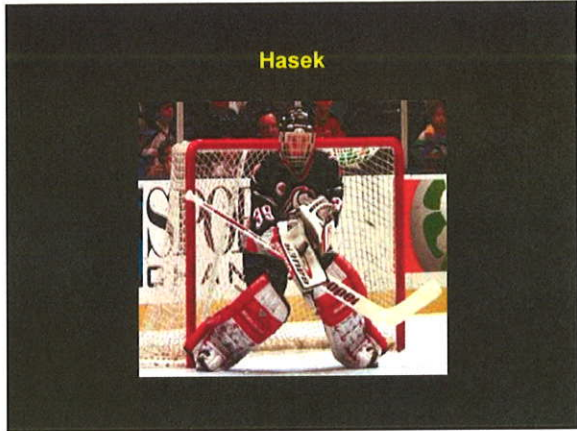
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Structural and biochemical analyses of the synaptotagmin-1 C<sub>2</sub> domains have shown that they bind multiple calcium ions and they interact with negatively charged phospholipids in a calcium-dependent manner

Sutton et al. Cell 80, 929 (1995)  
 Shao et al. Science 273, 248 (1996)  
 Shao et al. Biochemistry 37, 16106 (1998)  
 Fernandez et al. Neuron 32, 1057 (2001)

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Calcium dependent phospholipid binding to the synaptotagmin-1 C<sub>2</sub> domains involves a combination of different types of interactions

Zhang et al., Biochemistry 37, 12395 (1998)

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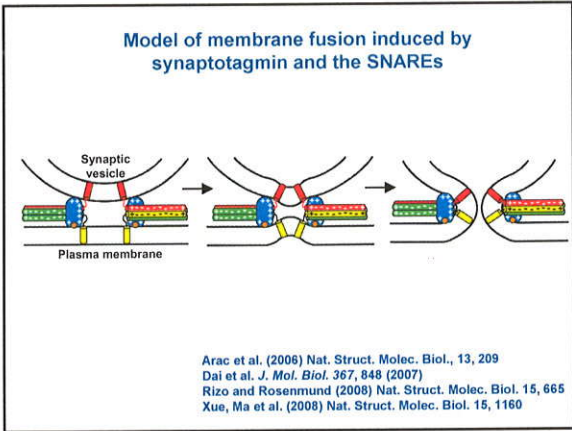
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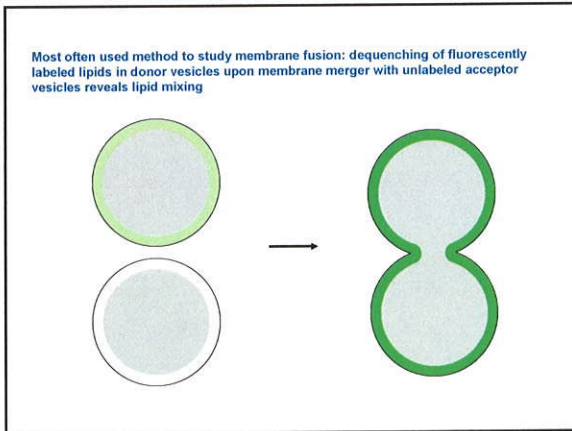
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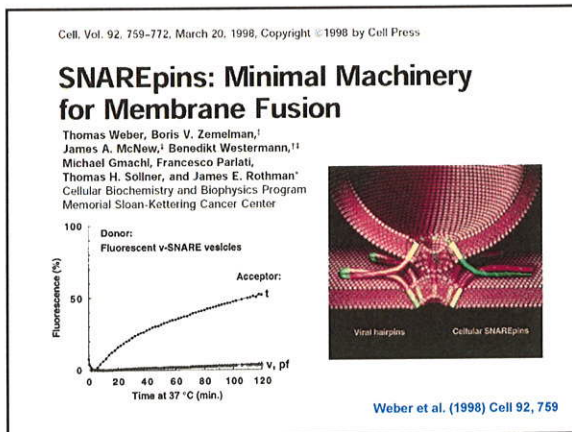
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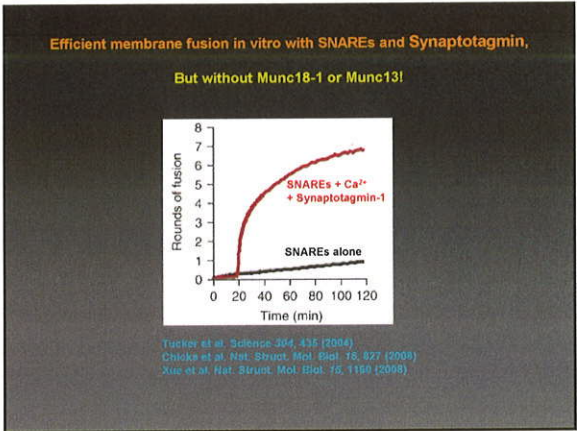
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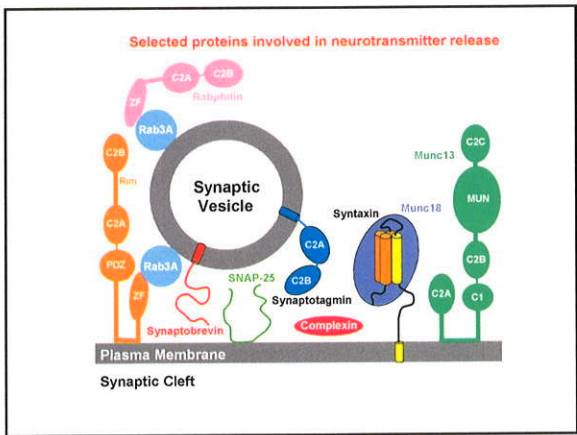
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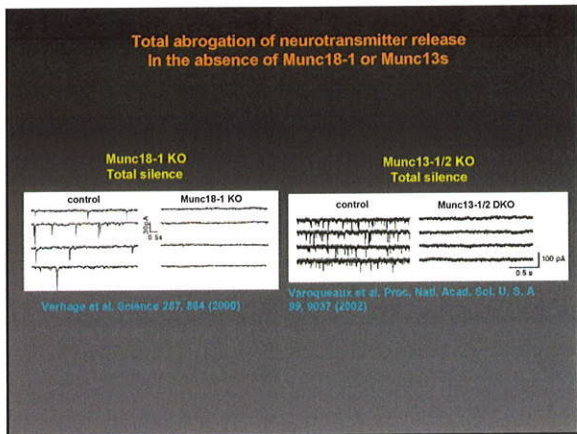
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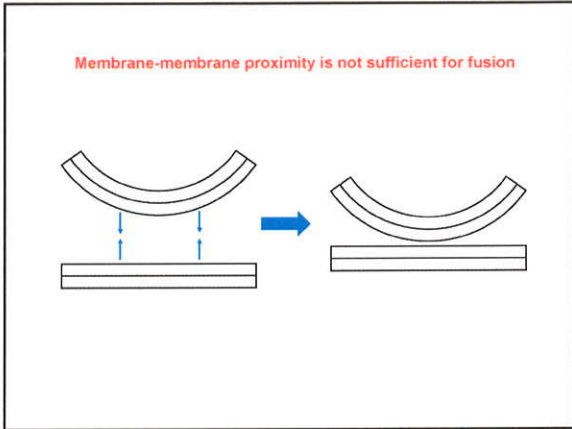
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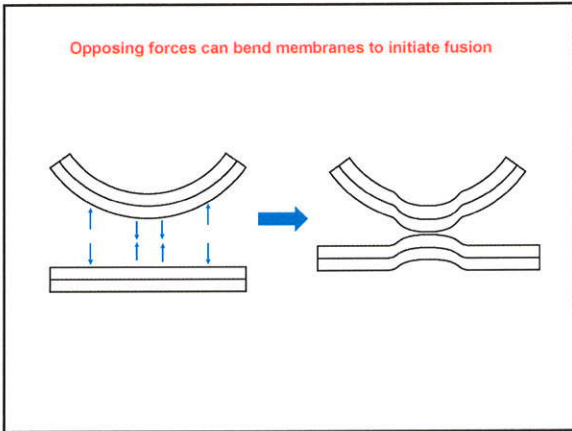
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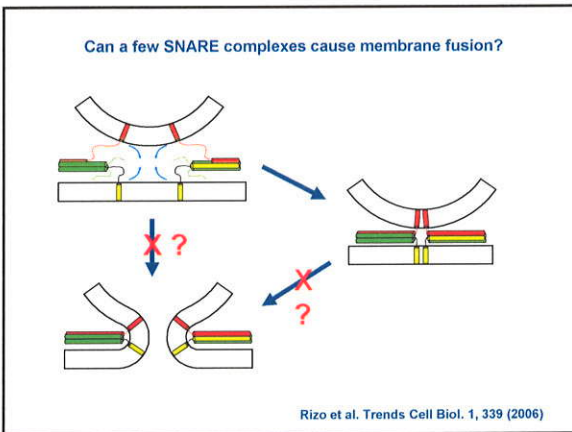
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*Give me a support point and I will lift the world*  
Arquimedes

Munc18-1?  
Munc13?

- It is essential to correlate in vitro with in vivo results
- We need to understand what are the functions of Munc18-1 and Munc13

Rizo et al. Trends Cell Biol. 1, 339 (2006)

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**Working model of Munc18-1 function**

Munc18-1  
synaptobrevin  
SNAP-25  
Munc13?  
syntaxin closed

Fernandez et al. *Cell* 18, 841 (1998); Dulubova et al. *EMBO J.* 18, 4372 (1999); Yamaguchi et al. *Developmental Cell* 2, 295 (2002); Dulubova et al. *EMBO J.* 21, 3620 (2002); Dulubova et al. *PNAS* 100, 32 (2003); Dulubova et al. *PNAS* 104, 2697 (2007); Deak, Xu et al., *J. Cell. Biol.* 184, 751 (2009); Xu et al., *Biochemistry* 49, 1568 (2010)

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**The Munc13 MUN domain catalyzes opening of syntaxin-1**

Munc18-1  
MUN  
Munc18-1  
SNARE complex  
Syntaxin-1 (closed)  
Syntaxin-1 (open)  
Syntaxin-1 (open)

Ma et al., *Nat. Struct. Molec. Biol.* 18, 542 (2011)

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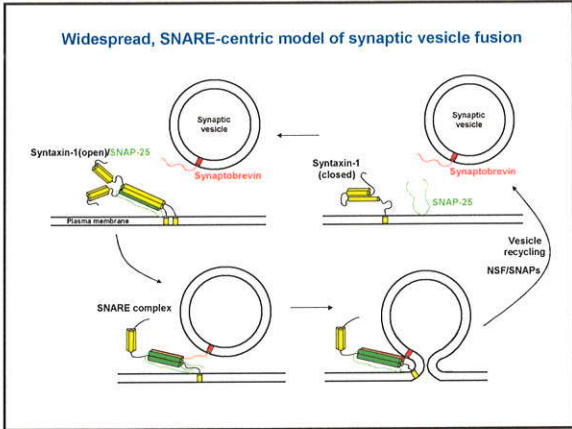
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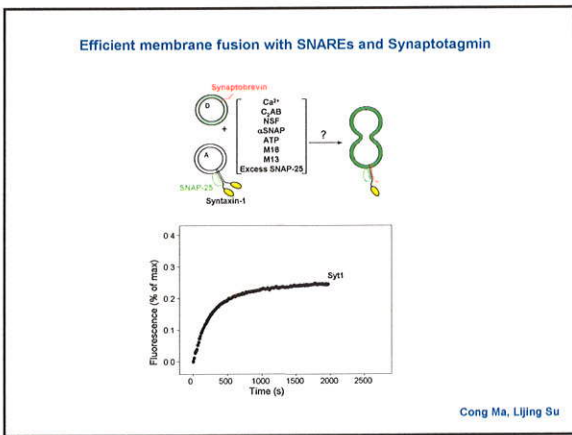
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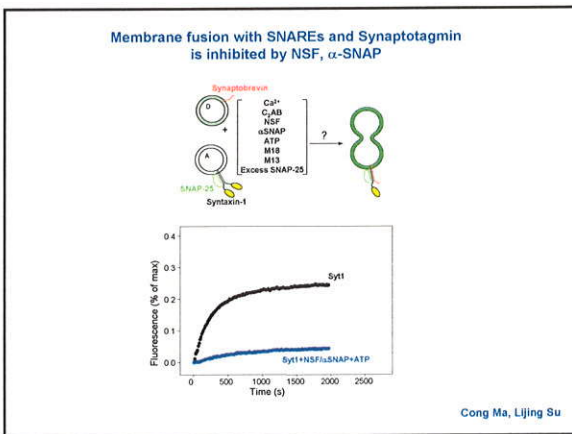
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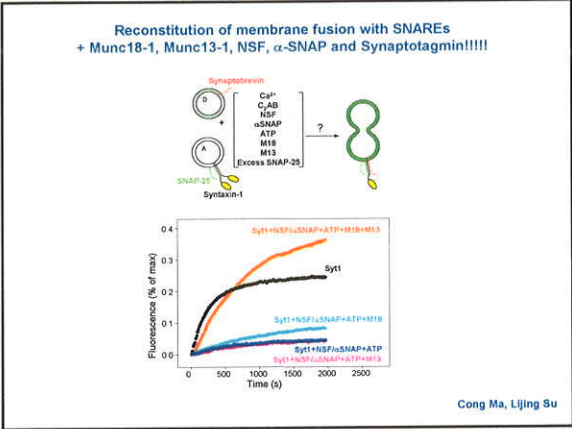
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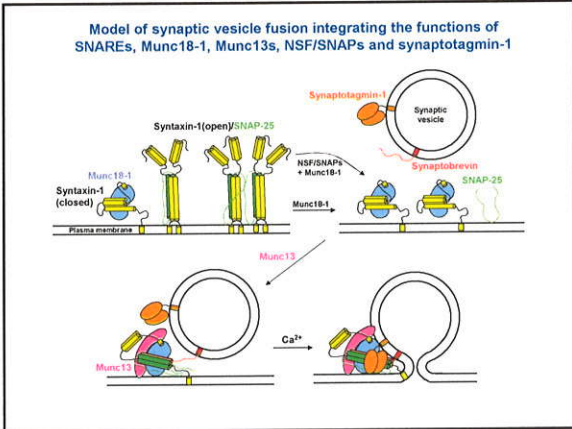
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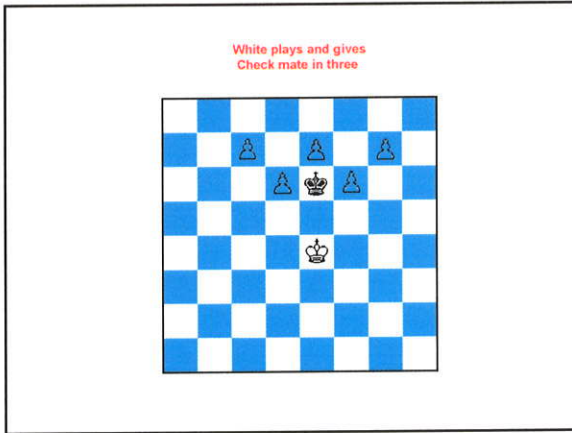
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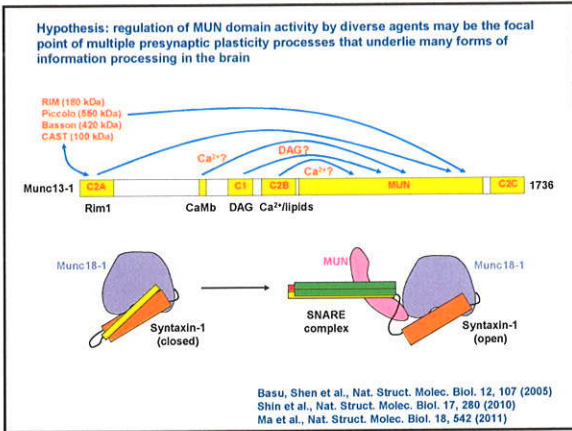
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