

# **Block A: Membrane Biology & Biochemistry**

## **Lipid signalling and sphingolipid function**

25. - 29.11.2013

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## Programme of the week

- Monday

- general discussion: cellular signalling
- sphingosine-1-phosphate and neurodegeneration (Morbus Alzheimer)

- Tuesday

- bioactive fatty acid derivatives: endocannabinoids and eicosanoids
- sphingosine-1-phosphate and ceramide-1-phosphate in inflammation

- Thursday

- Samira Marx: Targeting sphingosine-1-phosphate axis in cancer

- Friday

- Saskia Neuert: Bioactive lipid mediators in skin inflammation and immunity

## Outline of objectives

### General aspects on cell signalling

Signalling via:

G-protein coupled receptors

Receptor tyrosine kinases

Nuclear receptors

Signalling lipids:

Fatty acids

Eicosanoids

Endocannabinoids

Sphingolipids (S1P, C1P)

Pathological implications:

Neurodegeneration (Alzheimer)

Inflammation

Cancer

### References:

Hagen et al. Subcellular origin of sphingosine-1-phosphate is essential for its toxic effect in lyase-deficient neurons. **J. Biol. Chem.** 284: 11346-53 (2009).

Hagen et al. Sphingosine-1-phosphate links sphingolipid metabolism to neurodegeneration via a calpain-mediated mechanism. **Cell Death Differ.** 18: 1356-1365 (2011)  
<http://www.nature.com/cdd/journal/vaop/ncurrent/full/cdd20117a.html>.

van Echten-Deckert & Walter "Sphingolipids: Critical players in Alzheimer's disease" **Prog Lipid Res** 51, 378-93 (2012)  
<http://dx.doi.org/10.1016/j.plipres.2012.07.001>

Kunkel et al. „Targeting the sphingosine-1-phosphate axis In cancer, inflammation and beyond“  
**Nature Rev, Drug Discovery**, 12:688-702 (2013).

Kendall & Nicolaou „Bioactive lipid mediators in skin Inflammation and immunity“  
**Prog. Lipid Res.**, 52:141-64 (2013).

Dragusin et al. „Effects of sphingosine-1-phosphate and ceramide-1-phosphate on rat intestinal smooth muscle cells: implications in postoperative ileus“ **FASEB J** 20, 1930-32 (2006).

Gurgui et al. „Dual action of sphingosine 1-phosphate in eliciting proinflammatory responses in primary cultured rat intestinal smooth muscle cells“ **Cellular Signalling** 22: 1727-33 (2010).

# Programme

## •Introduction

- Morbus Alzheimer: numbers and facts
- Sphingolipids: history, structure, metabolism

## •Sphingosine-1-phosphate (S1P) - bane and blessing

- biological activity and mechanism of action
- CIMES, a synthetic sphingosine analogue

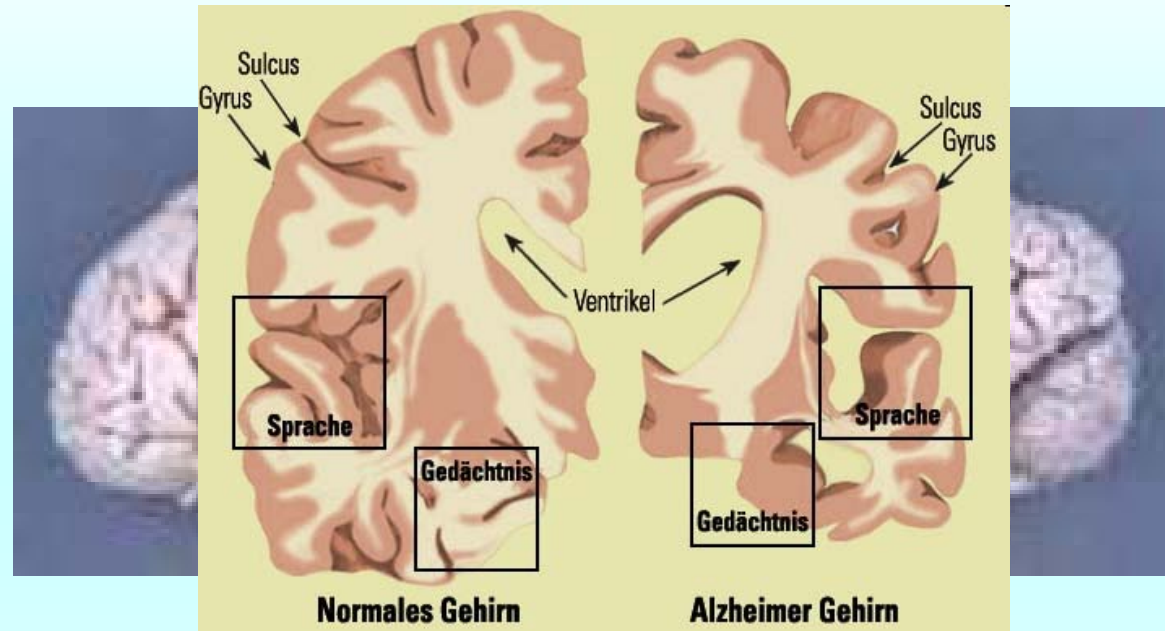
## •S1P-lyase KO and conditional KO

- molecular bases of S1P-induced neurotoxicity
- S1P-lyase-deficiency and neurodegeneration
- S1P-lyase-deficiency and synaptic plasticity

## •Conclusion and outlook

1906: 37. Meeting of doctors for the insane of southwest Germany  
in Tübingen

Alois Alzheimer reports about "a peculiar affection of the cerebral cortex"  
Auguste D.

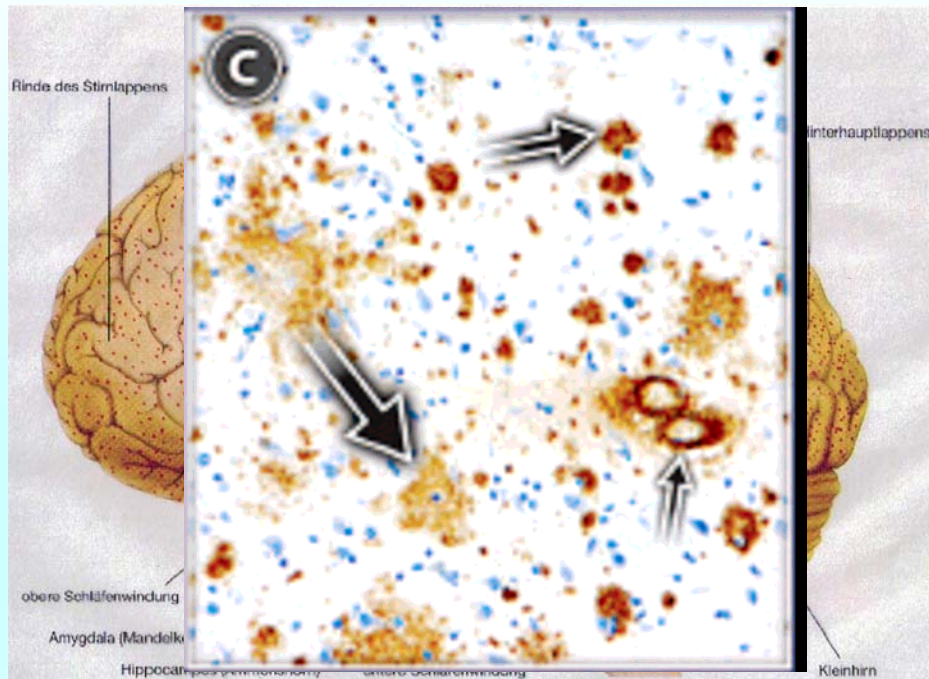


2011: World Alzheimer Report 2011

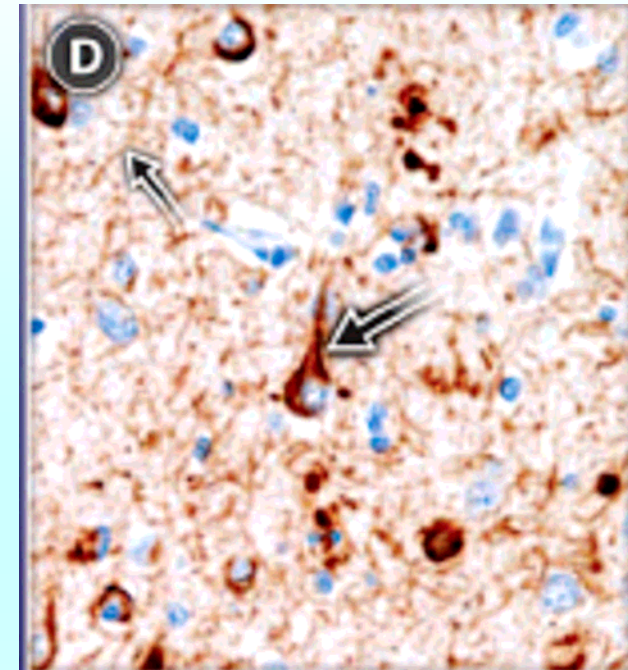
AD most common neurodegenerative disease  
worldwide 36 mill. cases (2030: 66 mill. 2050: 115 mill.)

Costs worldwide: 604 bill. USD in 2010 (1% of the global GDP)

## Histopathological findings reported by A. Alzheimer (1906)

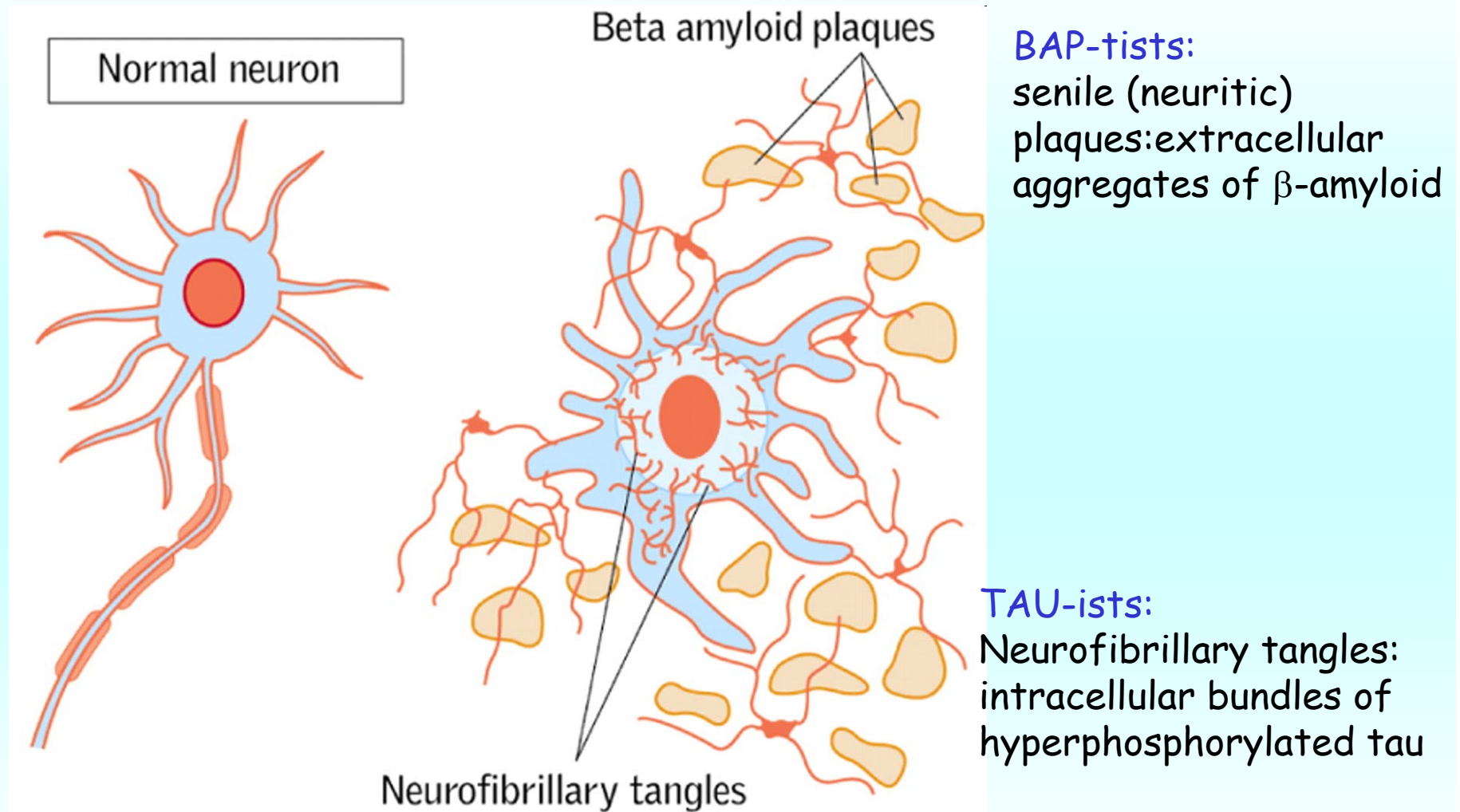


"Miliary foci distributed all over the cortex, caused by the infiltration of a peculiar substance into the cortex"

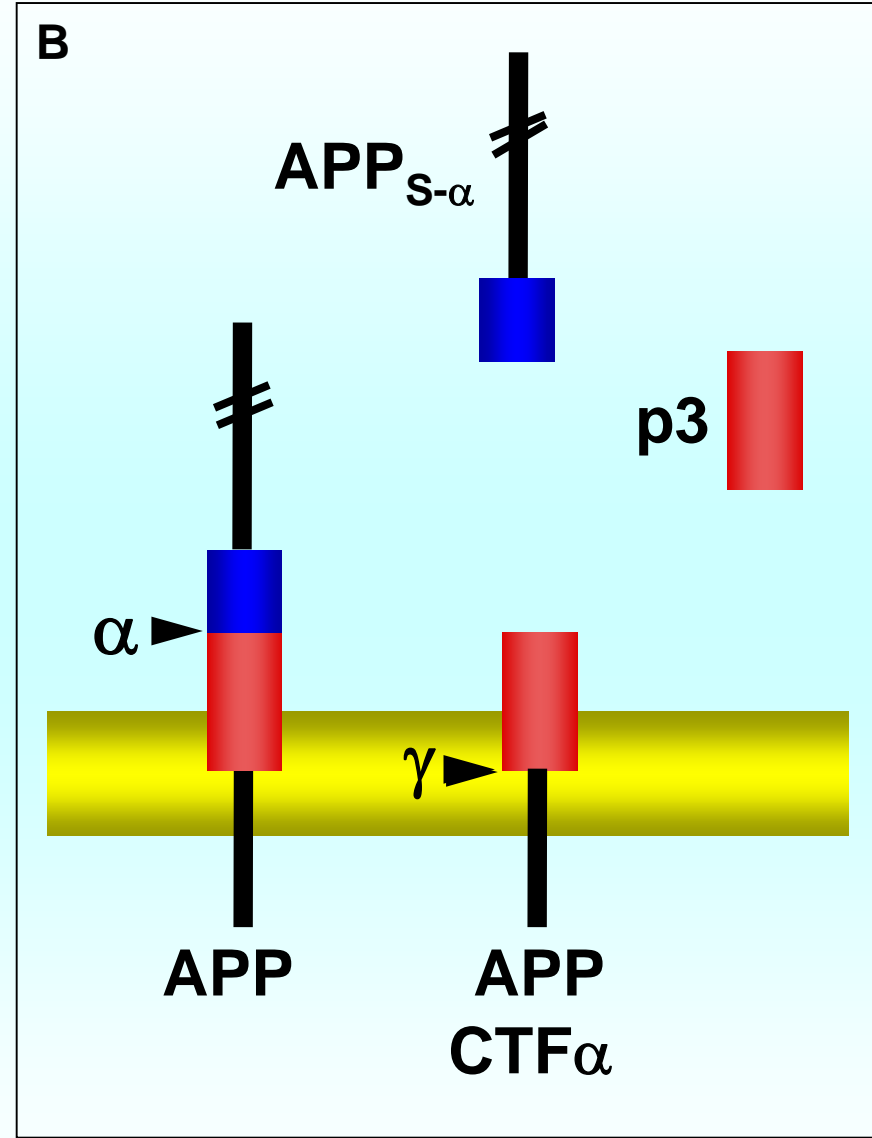
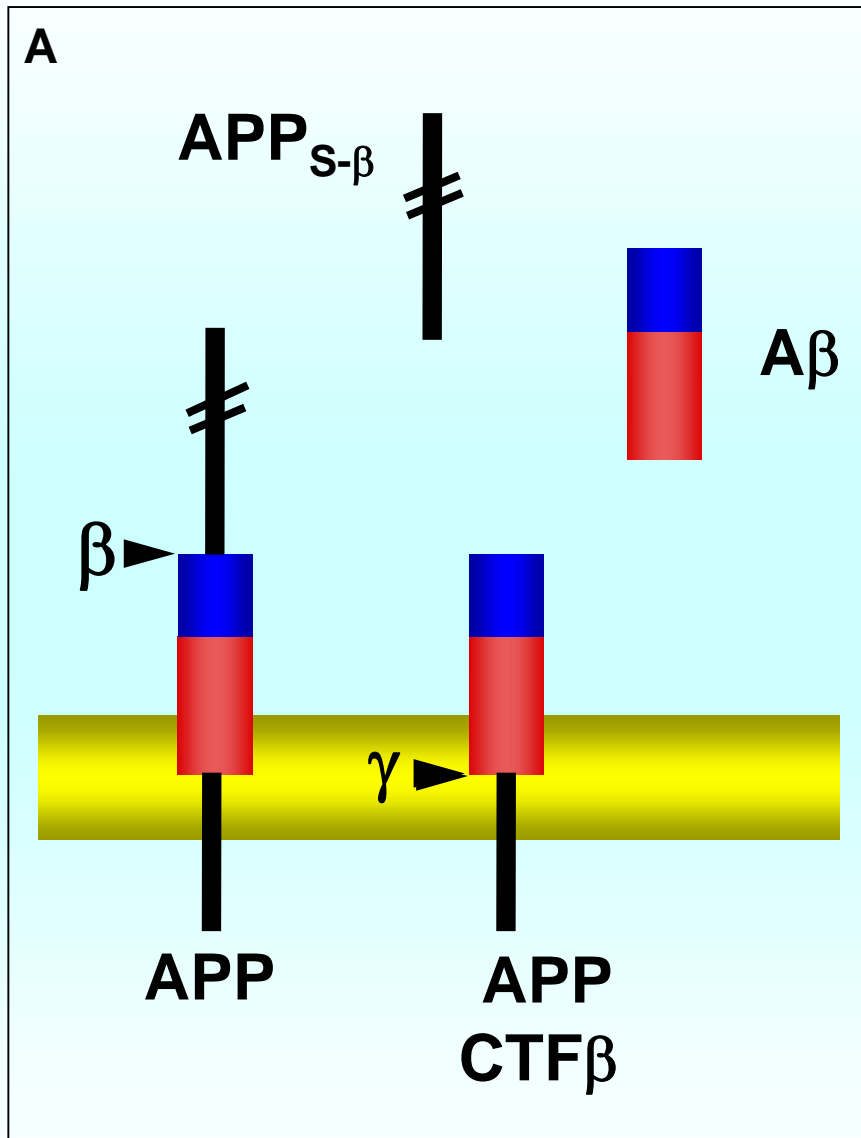


"Weird neurofibrillary changes, that appeared like very thick tangles filling not only the cell body but also neuronal processes"

## Key neuropathological elements of AD

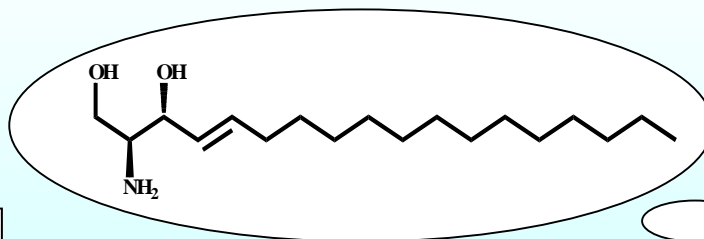


# Scheme of major proteolytic processing pathways of APP

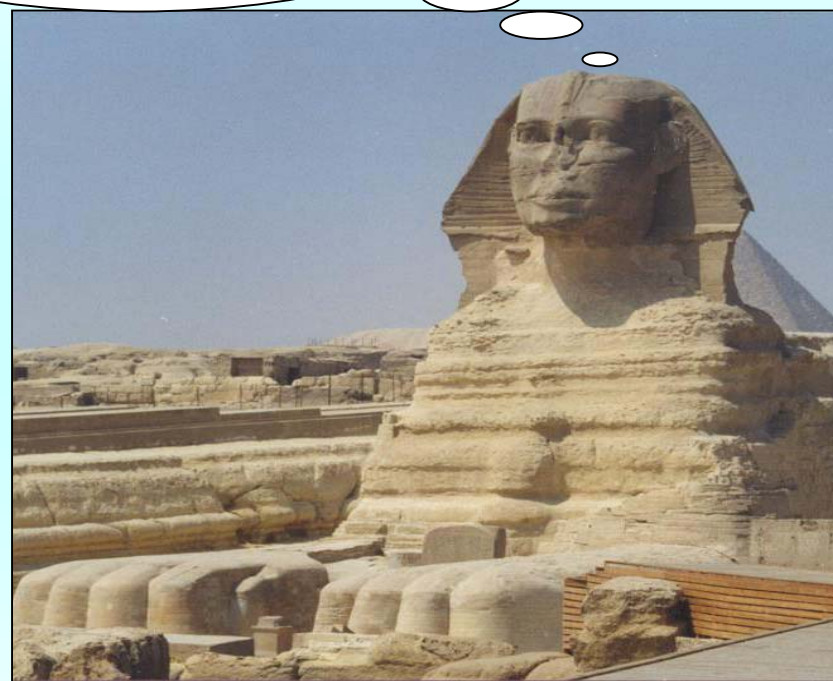




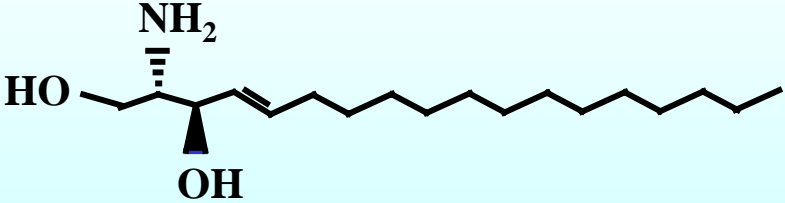
# Sphingolipids: History



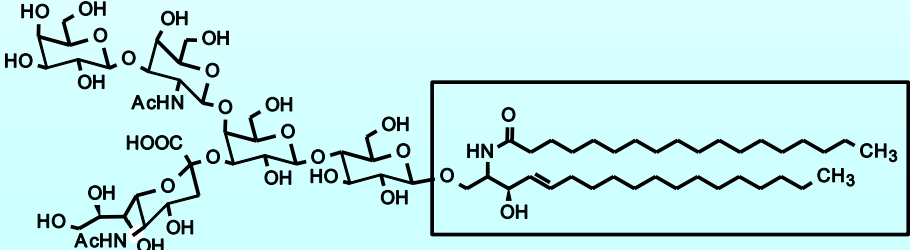
Johann Ludwig Wilhelm Thudichum  
1884



# Sphingolipids - Structure

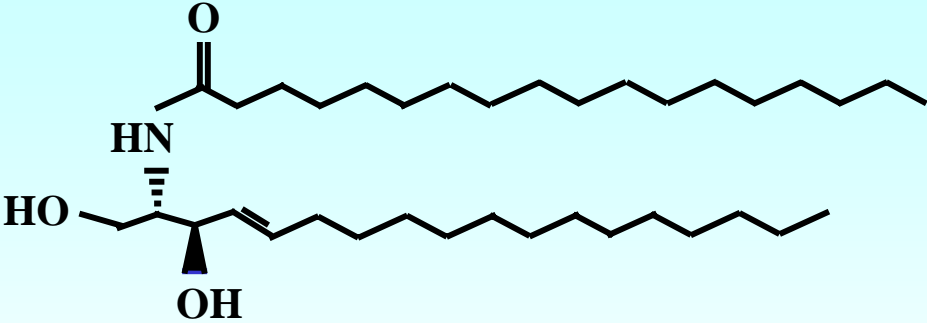


Sphingosine

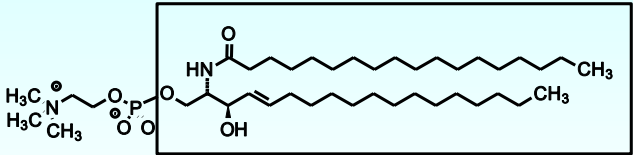


Ceramide

Ganglioside GM1



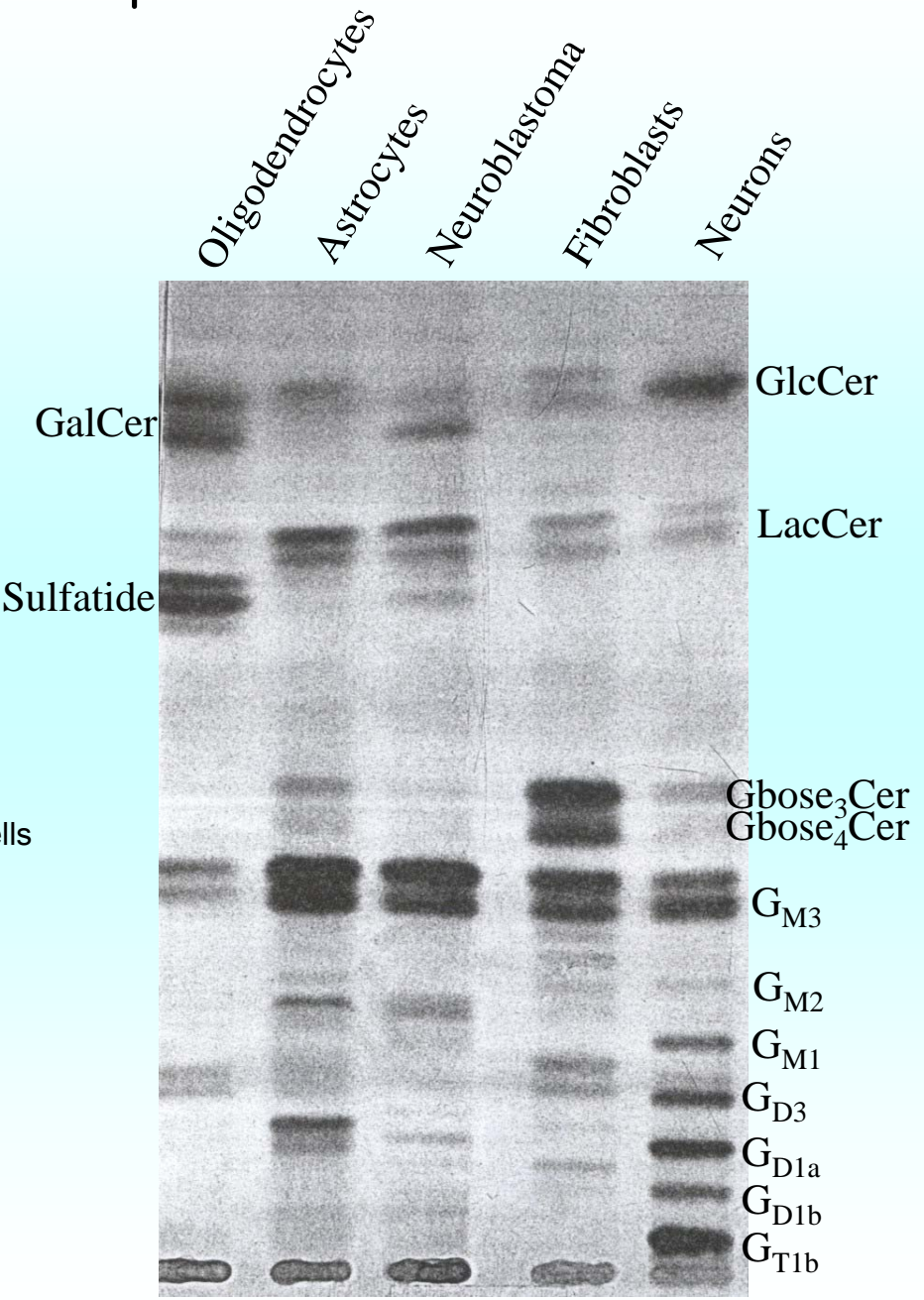
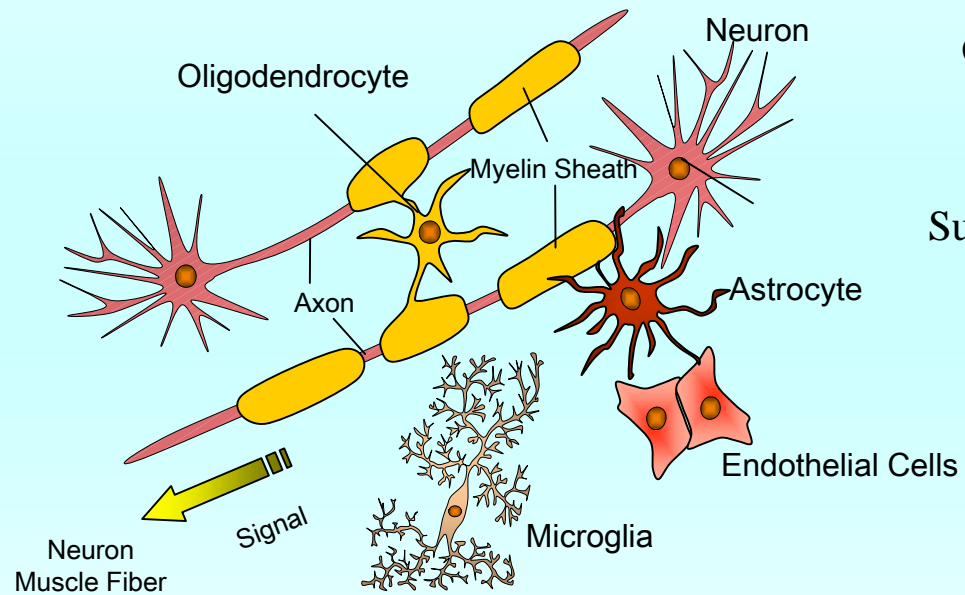
Ceramide



Ceramide

Spingomyelin

# Glycosphingolipids form cell type specific profiles

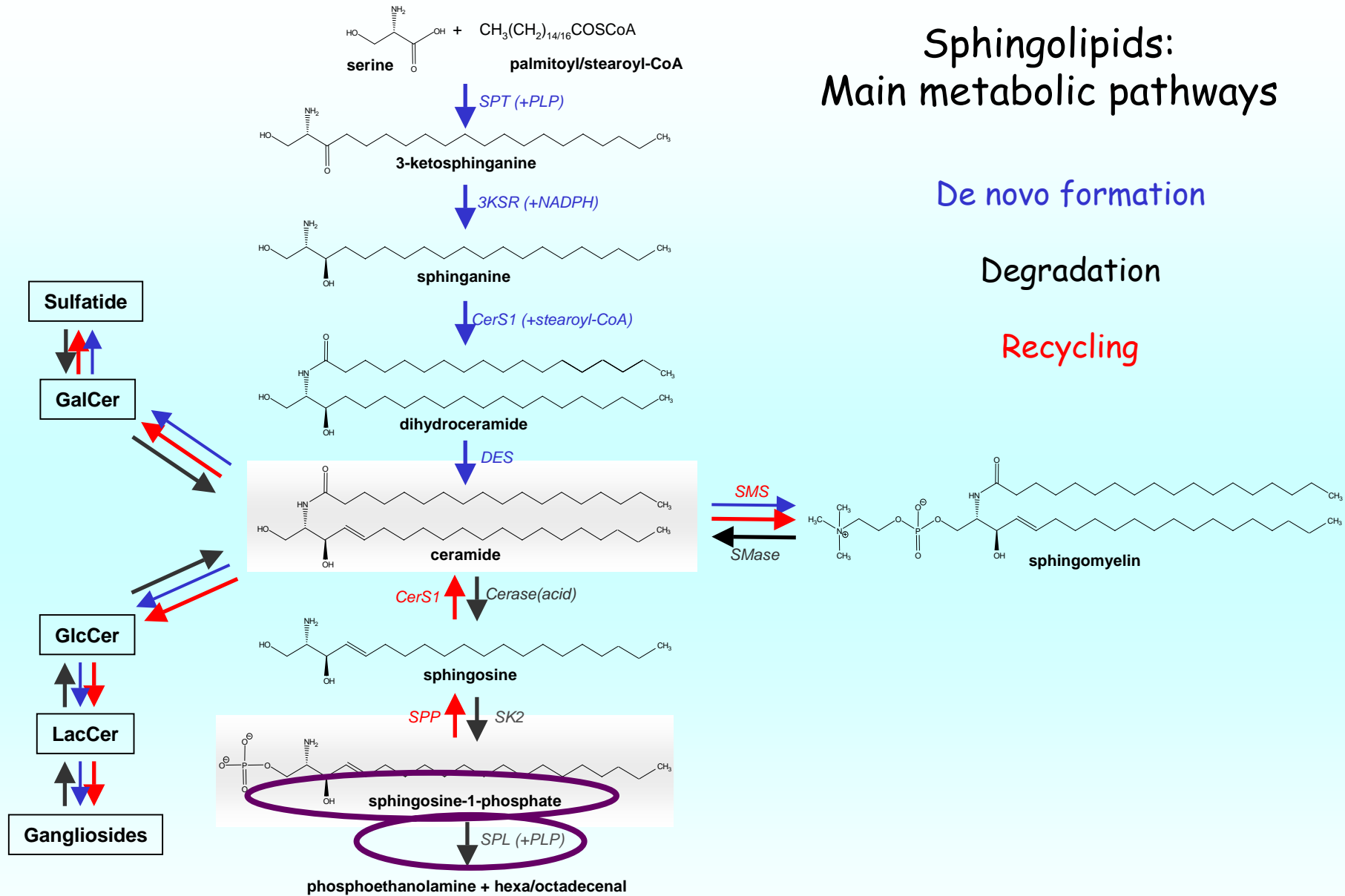


# Sphingolipids: Main metabolic pathways

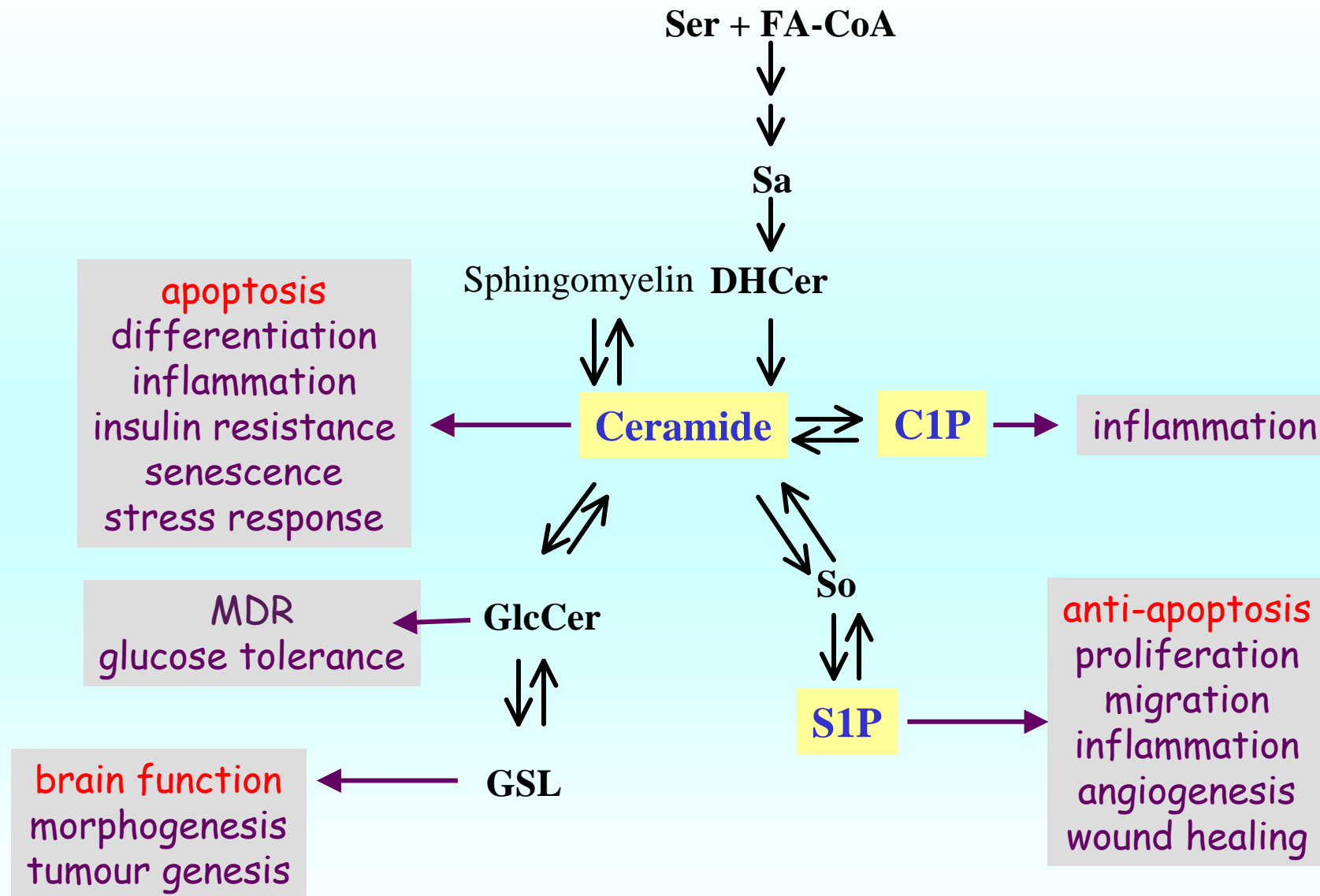
De novo formation

Degradation

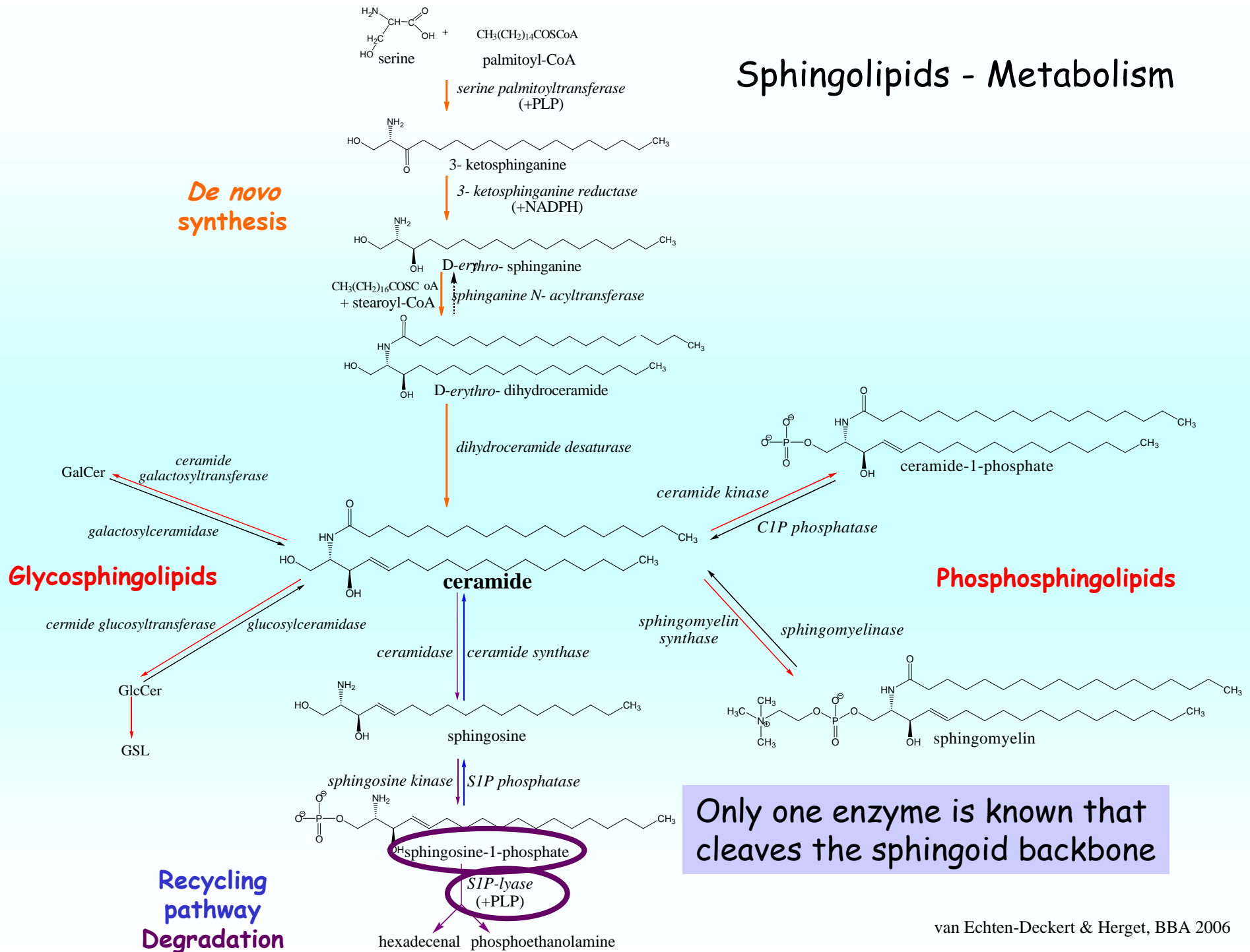
Recycling



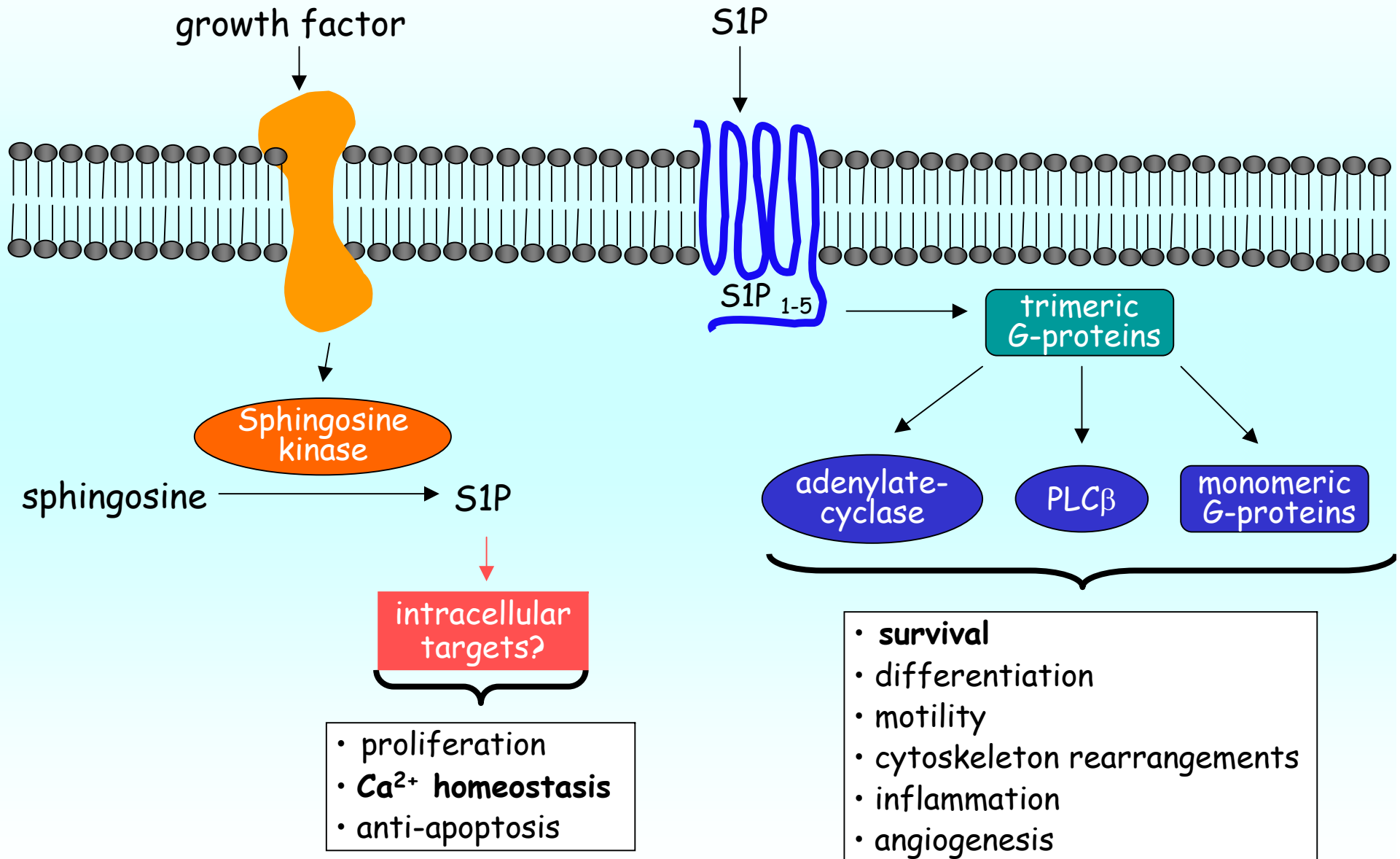
# Physiological/clinical relevance of bioactive sphingolipids



# Sphingolipids - Metabolism

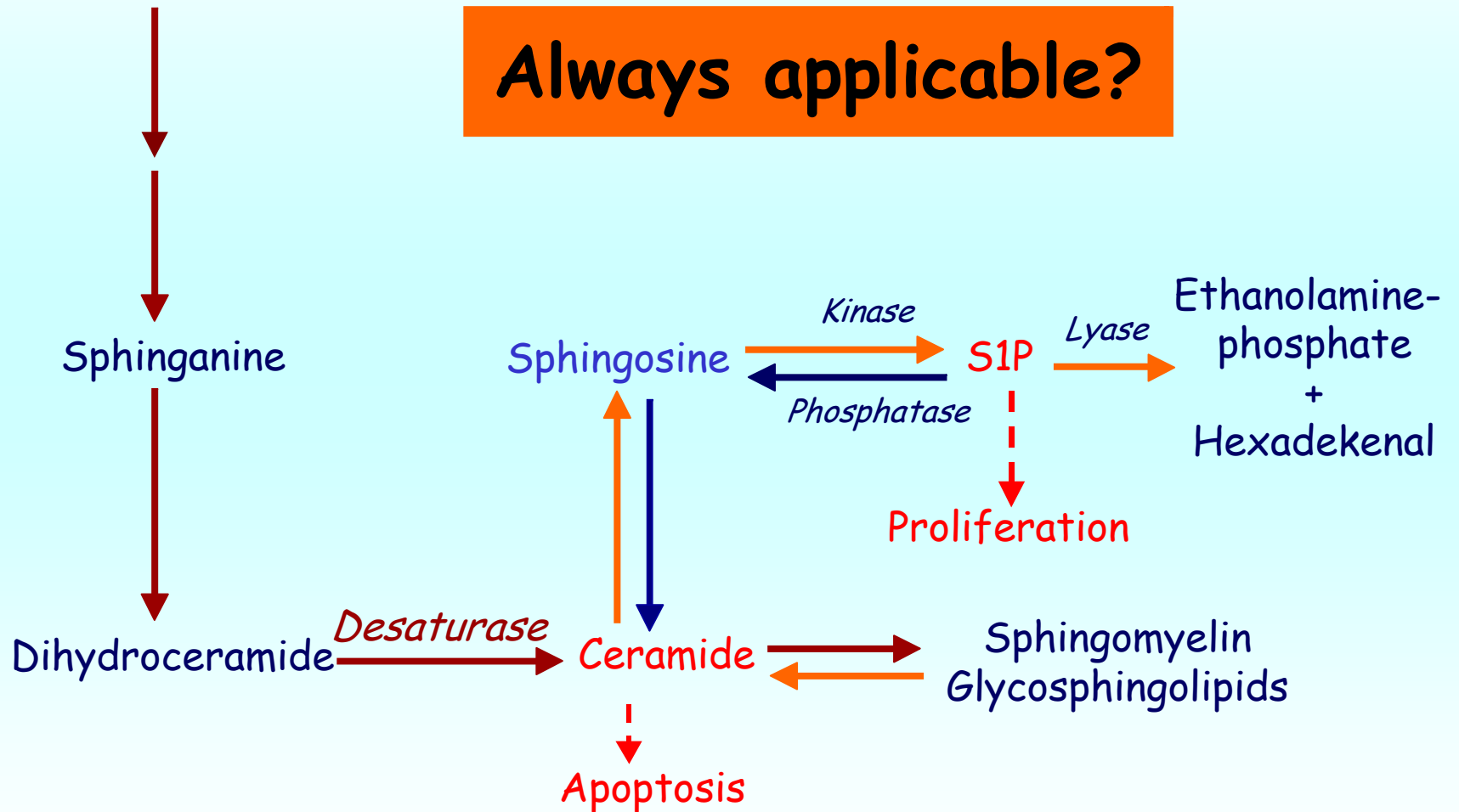


# Dual Action of S1P: Extracellular Ligand and Intracellular Second Messenger



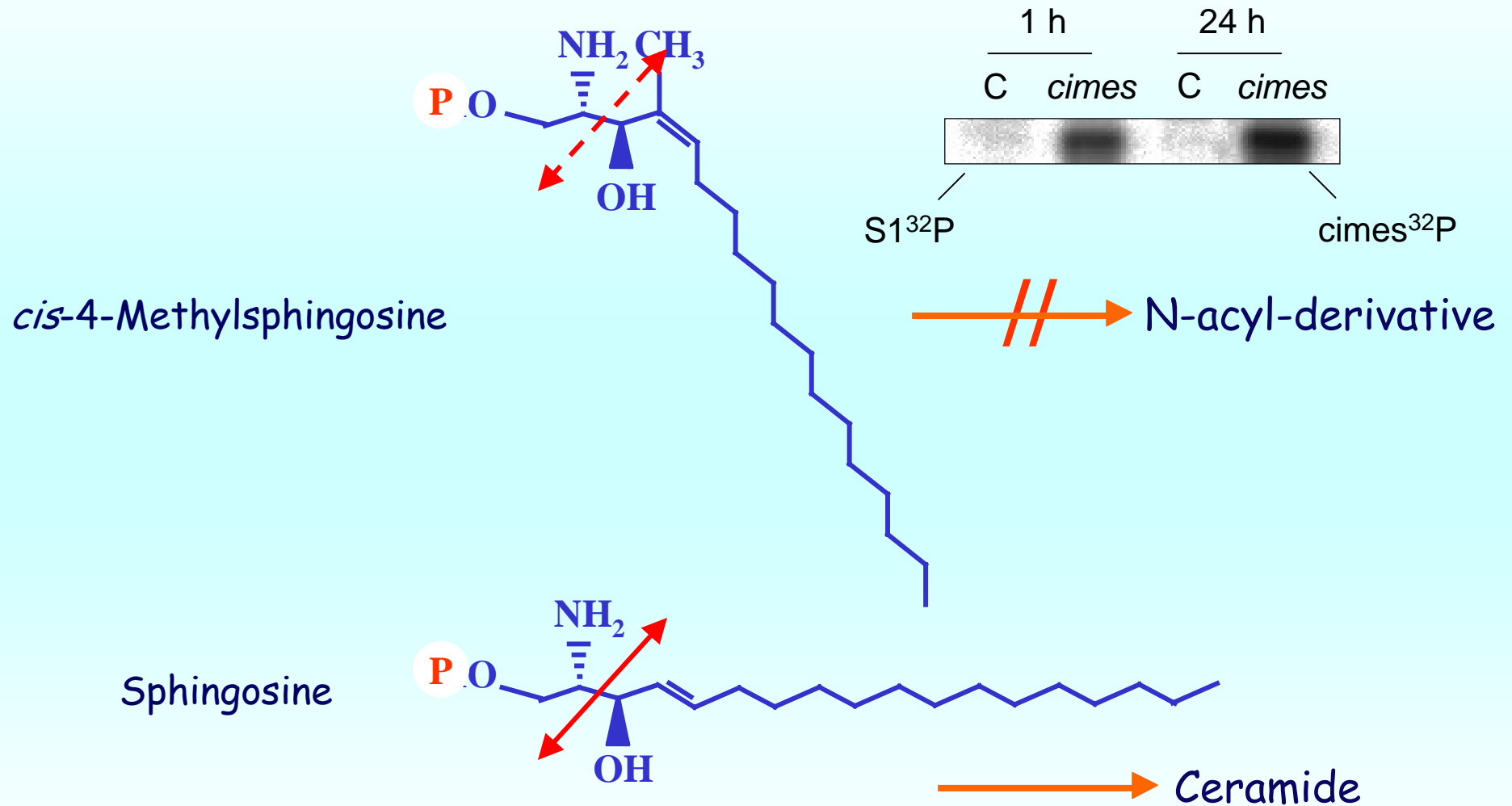
# The ceramide/S1P-rheostat in cell growth regulation

Serine + Palmitoyl-CoA

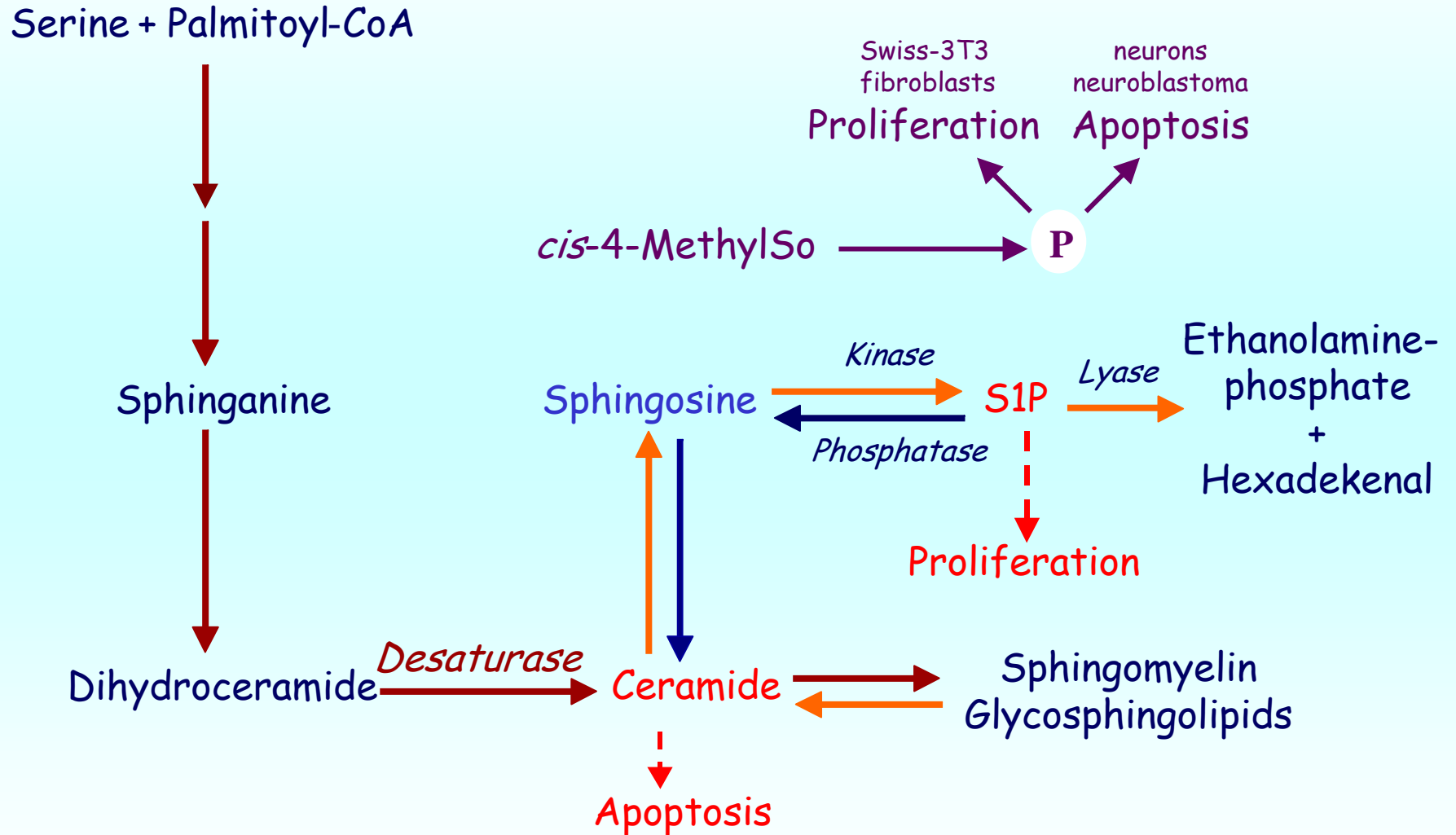




***cis*-4-Methylsphingosine (cimes) is a synthetic prodrug for a metabolically stable S1P-analogue**



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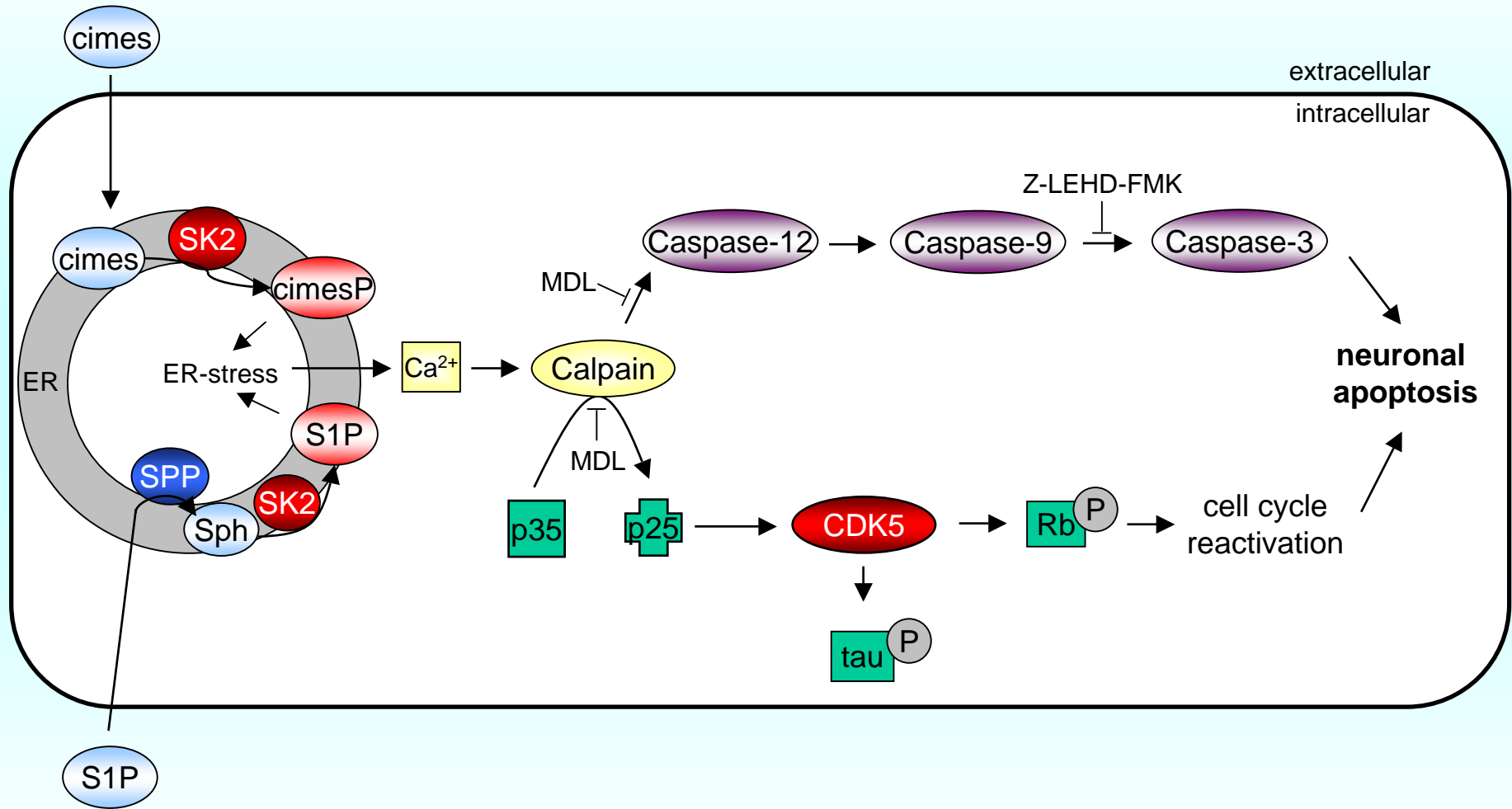


van Echten-Deckert et al. JBC 1997

van Echten-Deckert et al. JBC 1998

Nätzker et al. Biol Chem 2002

# Summary



## Conclusions and outlook

- Sphingosine-1-phosphate (S1P) is a neuronal death signal, when generated by SK2 and impaired degradation
- Calpain is an essential mediator of S1P-induced neurotoxicity
- On cellular and molecular level S1P neurotoxicity parallels that of  $A\beta$
- S1P-lyase expression is correlated with neuronal death
- S1P-lyase deficiency is correlated with Alzheimer characteristics:
  - Hyperphosphorylation of tau
  - Impaired APP-processing
  - Elevated levels of cholesteryl-ester

S1P stimulates BACE1, the rate-limiting enzyme for  $A\beta$  production  
(Takasugi et al., 2011, J. Neurosci.)

**Conditional knockout mouse: neuron-specific  
inactivation of S1P-lyase**