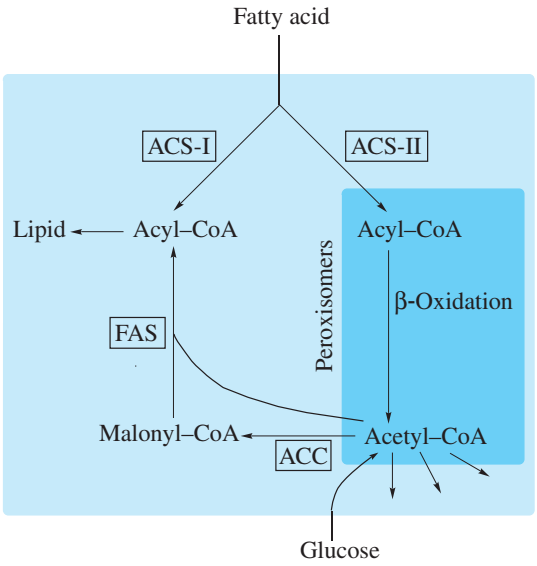
Triacsin ©

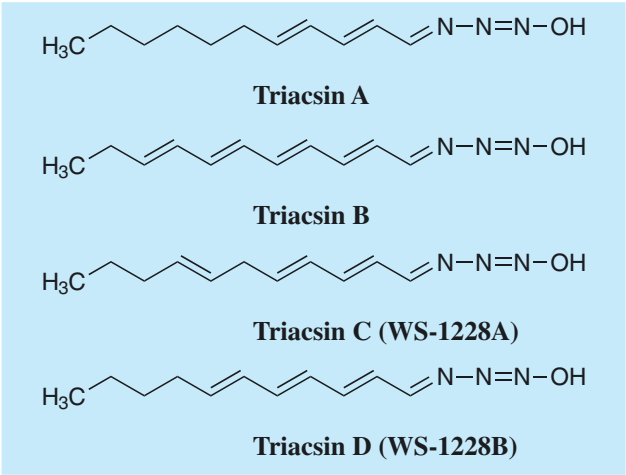
1. Discovery, producing organism and structures[1-4)]

Microbial inhibitors of fatty acid metabolism were screened by an assay system using acyl-CoA synthetase I (ACS-I)-deficient (L-7) and fatty acid synthase (FAS)-deficient(A-1) mutants of *Candida lipolytica*. Triacsins were isolated from the culture broth of the actinomycete strain SK-1894 and recognized as acyl-CoA synthetase inhibitors since they showed inhibitory activity against growth of mutant A-1, but not against mutant L-7[2,3)]. Triacsins C and D were identified as WS-1228 A and B, respectively, originally isolated as vasodilators[4)]. No correlation was observed between the two activities. The first total synthesis of triacsin C (WS-1228A) was reported by Tanaka *et al*.[5)]



Fatty acid metabolism of *C. lipolytica*

Streptomyces sp. SK-1894



2. Physical data (Triacsin C)[1)]

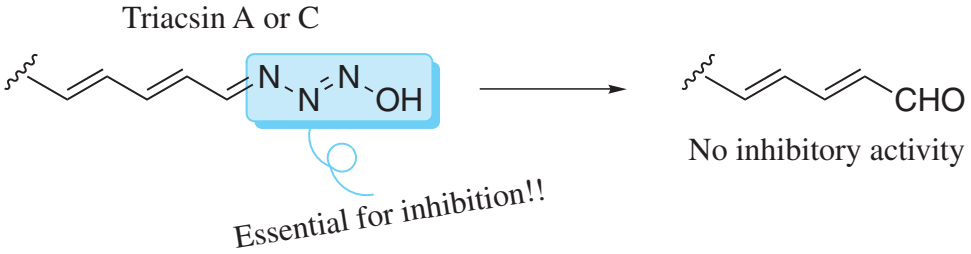
Yellow powder. $C_{11}H_{17}N_3O$; mol wt 207. Sol. in acetone, EtOAc, EtOH. Insol. in H_2O.

3. Biological activity[6)]

1) Inhibition of long chain acyl-CoA synthetase

Enzyme source	IC_{50} (μM)				Reference
	Triacsin A	Triacsin B	Triacsin C	Triacsin D	
Pseudomonas fraji	26	> 150	17	>150	1
Pseudomonas aeruginosa	17	> 200	3.6	>200	5
Rat liver	18	> 200	8.7	>200	5
Raji cells	12	> 100	6.3	>100	6
HSDMICI cells					
Long chain ACS	NT	NT	0.48	NT	7
Arachidonoyl-CoA synthetase	NT	NT	8.5	NT	7
Candida lipolytica					
ACS –I	5.5	> 50	4.0	>50	

2) *N*-Hydroxytriazene moiety is essential for acyl-CoA synthetase inhibition.



3) Triacsin A inhibits *P. aeruginosa* acyl-CoA synthetase competitively with respect to the substrate oleic acid (Km 101 μM, Ki 8.97 μM) and non-competitively with respect to CoA and ATP[6].

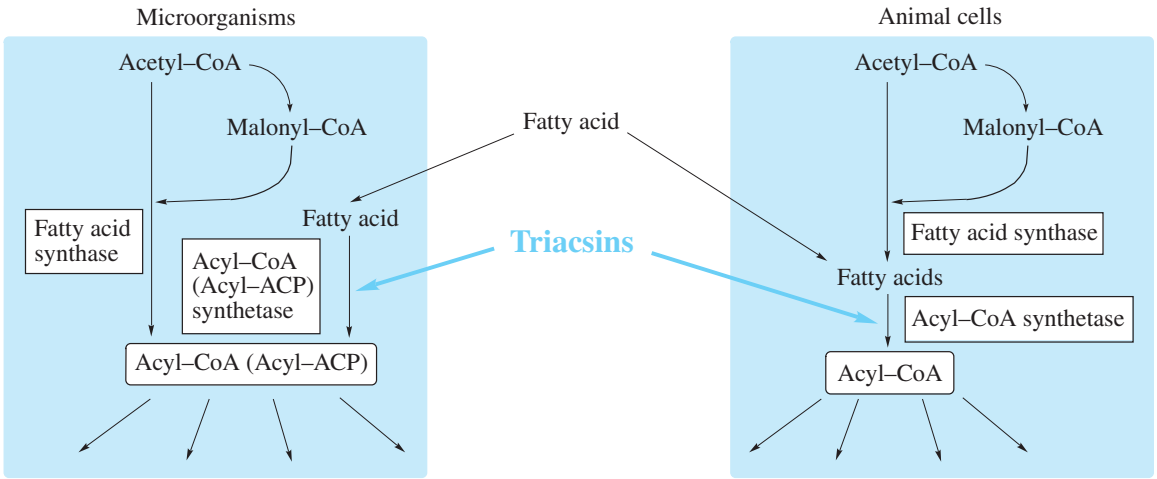
4) Inhibitory activity against the acyl-CoA synthase family[7-11]

Isoform	Main substrate	Characteristic	Inhibition by triacsin C
Saccharomyces cerevisiae[7]			
Faa1p	C14:0, C15:0	Activate imported FA, phospholipid synthesis	>500 μM
Faa2p	C9:0 - C13:0	Activate endogenous FA, similar to mammalian ACS	80 nM
Faa3p	C16:1, C18:1	Phospholipid synthesis, similar to Faa1p	>500 μM
Faa4p	C14:0, C16:0 C16:1, C18:1	Activate imported FA, *N*-myristoylation	4.5 μM
Rat[8,9]			
ACS1	C12-18 (sat.) C16-20 (unsat.)	All tissues, triacylglycerol synthesis	4-6 μM
ACS2[10]	C12:0-C18:0	Brain	NT
ACS3[11]	C12-14 (sat.) C16-20 (unsat.)	Brain, lipid synthesis	NT
ACS4	C20:4, C20:5	Steroidogenic tissues, triacylglycerol synthesis	4-6 μM
ACS5	C12-18 (sat.) C16-20 (unsat.)	Intestine, involved in ß-oxidation	>10 μM

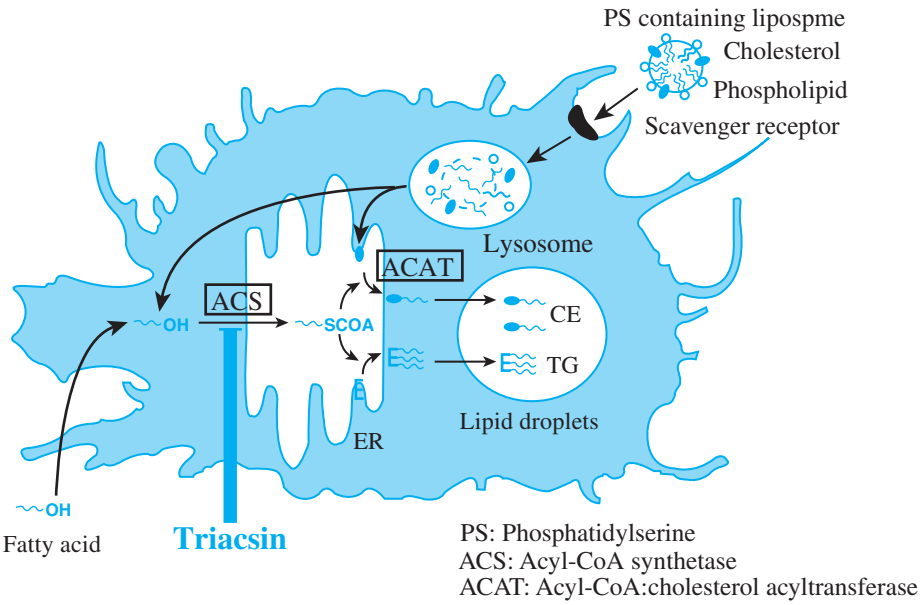
Faap; fatty acid activation protein, ACS; acyl-CoA synthetase, NT; not tested

4. Application[12-21]

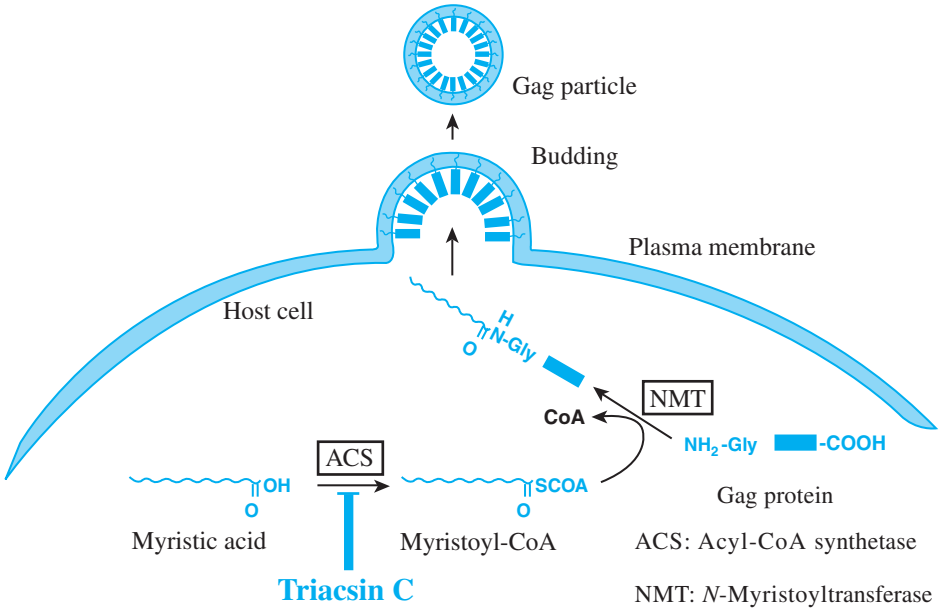
1) Triacsins were found to be lethal to animal cells but not to microorganisms[12]. This may be due to the different end products (free fatty acid or acyl-CoA) produced by fatty acid synthases.



2) Triacsin C inhibited the macrophage-derived foam cell formation completely by depleting acyl-CoA required for synthesizing cholesteryl esters (CE) and triacylglycerols (TG)[14].



3) Complete inhibition of HIV gag myristoylation by triacsin C caused inhibition of HIV particle budding[15].



4) Triacsins are used as useful tools in cell biology and biochemistry[14-21].

1. Function of fatty acyl-CoA[14,15,22,23]
2. Metabolism of lipid-related bioactive compounds[18,19] and lipoprotein[20]

5) Triacsin C exhibited antimalarial activity against both Kl and FCR strain of *P. falciparum*.[25]

5. Triacsin C is commercially available from Biomol Kyowa Medix.

6. References

1. [347] S. Ōmura *et al*., *J. Antibiot*. **39**, 1211-1218 (1986)
2. [449] H. Tomoda & S. Ōmura, *J. Antibiot*. **43**, 1207-1222 (1990)
3. H. Tomoda & S. Ōmura, In "The Search for Bioactive Compounds from Microorganisms" (Ed. by S. Ōmura) pp.161-170, Springer-Verlag (1992)
4. K. Yoshida *et al*., *J. Antibiot*. **35**, 151-156 (1982)
5. H. Tanaka *et al*., *Tetrahedron Lett*. **22**, 3421-3422 (1981)
6. [374] H. Tomoda *et al*., *Biochim.. Biophys. Acta*. **921**, 595-598 (1987)
7. L. J. Knoll *et al*., *J. Biol. Chem*. **270**, 20090-20097 (1995)
8. M. Lewin *et al*., *J. Biol. Chem*. **276**, 24674-24679 (2001)
9. J. H. Kim *et al*., *J. Biol. Chem*. **276**, 24667-24673 (2001)
10. C. Sevoz *et al*., *Drug. Metab. Dispos*. **28**, 398-402 (2000)
11. T. Fujino *et al*, *J. Biol. Chem*. **271**, 16748-16752 (1996)
12. [460] H. Tomoda *et al*., *J. Biol. Chem*. **266**, 4214-4219 (1991)
13. [417] E. J. Hartman *et al*., *Prostaglandins* **37**, 655-671 (1989)
14. [720] I. Namatame *et al*., *J. Biochem*. **125**, 319-327 (1999)
15. [603] Y. Morikawa *et al*., *J. Biol. Chem*. **271**, 2868-2873 (1996)
16. N. Pfanner *et al*., *Cell* **59**, 95-102 (1989)
17. H. M. Korchak *et al*., *J. Biol. Chem*. **269**, 30281-30287 (1996)
18. [487] S. Oh-ishi *et al*., *Jpn. J. Pharmacol*. **59**, 417-418 (1992)
19. [496] M. Hayashi *et al*., *Biochem. Biophys. Res. Commun*. **188**, 1280-1285 (1992)
20. X. Wu *et al*., *J. Biol. Chem*. **269**, 12375-12382 (1994)
21. [416] H. Tomoda & S. Ōmura, In "Novel Microbial Products for Medicine and Agriculture" (Eds. by L. Demain *et al*.) pp.171-177, Elsevier (1989)
22. E. Iorio *et al*., *Biophys. Acta* **1634**, 1-14 (2003)
23. M. Shimabukuro *et al*., *Proc. Natl. Acad. Sci, USA* **95**, 2498-2502 (1998)
24. A. M. Hall *et al*., *J. Biol. Chem*. **278**, 43008-43013 (2003)
25. [942] H. Ui *et al*., *J. Antibiot*. **60**, 220-222 (2007)