

	(19) 대한민국특허청(KR) (12) 공개특허공보(A)	(11) 공개번호 10-2008-0095691 (43) 공개일자 2008년10월29일
(51) Int. Cl. <i>C12Q 1/68</i> (2006.01) (21) 출원번호 10-2007-0040518 (22) 출원일자 2007년04월25일 심사청구일자 없음	(71) 출원인 인하대학교 산학협력단 인천 남구 용현동 253 인하대학교 (72) 발명자 김응수 서울 송파구 오륜동 올림픽선수촌APT 120동 501호 임중혁 서울 구로구 가리봉1동 123-35 김명근 인천 연수구 연수1동 성일(아) 503/1006 (74) 대리인 이원희	

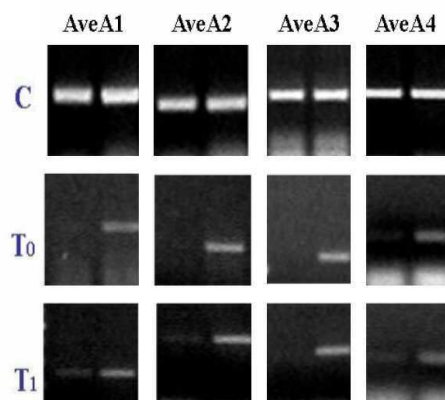
전체 청구항 수 : 총 28 항

(54) 에버멕틴의 고 생산 균주의 스크리닝 방법

(57) 요약

본 발명은 에버멕틴의 고 생산 균주의 스크리닝 방법에 관한 것으로, 에버멕틴 고생산균주에서 특이적으로 발현하는 유전자를 바이오마커로 하여 에버멕틴 고생산균주를 스크리닝하는 방법을 제공하며, 보다 구체적으로 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 통하여 에버멕틴 고 생산균주에서만 특이적으로 발현이 증가하는 49개의 유전자 및 발현이 감소하는 272개의 유전자를 선별하여 미지의 에버멕틴 고 생산균주를 스크리닝하는 방법을 제공하며, 상기 선별된 321개의 유전자가 돌연변이 또는 결실된 에버멕틴 생산균주를 제조하여, 상기 균주를 이용하여 에버멕틴을 저비용, 고효율로 생산하는 방법 및 상기 돌연변이 또는 결실된 균주를 이용하여 에버멕틴의 생산을 증강시키는 화합물을 스크리닝하는 방법을 제공한다.

대표도 - 도2



특허청구의 범위

청구항 1

하기의 유전자들로 이루어진 군으로부터 선택되는 어느 하나 이상인 것을 특징으로 하는 에버랙틴 고 생산균주 스크리닝용 바이오마커:

SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618), SAV7494(Accession No. NP_828670), SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293),

SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession

No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

청구항 2

제 1항에 있어서, 하기 유전자들로 이루어진 군으로부터 선택되는 어느 하나의 유전자는 에버랙틴 저 생산균주의 유전자 발현양보다 2배 이상 발현양이 증가하는 것을 특징으로 하는 에버랙틴 고 생산균주 스크리닝 바이오 마커:

SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).

청구항 3

제 1항에 있어서, 하기 유전자들로 이루어진 군으로부터 선택되는 어느 하나의 유전자는 에버랙틴 저 생산균주의 유전자 발현양보다 2배 이상 발현양이 감소하는 것을 특징으로 하는 에버랙틴 고 생산균주 스크리닝 바이오 마커:

SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No.

NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No.

NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

청구항 4

- 1) 균주의 전체 RNA를 추출하는 단계;
- 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버택틴 생산균주의 유전자 발현을 측정하는 단계; 및
- 3) 단계 2)의 측정된 데이터에서 제 1항의 스크리닝용 바이오마커의 발현 정도를 확인하여 에버택틴 고 생산균주를 선별하는 단계를 포함하는 에버택틴 고 생산균주 스크리닝 방법.

청구항 5

제 4항에 있어서, 단계 2)는 마이크로어레이 칩을 이용하여 유전자 발현을 측정하는 것을 특징으로 하는 스크리닝 방법.

청구항 6

에버택틴 고 생산균주 스크리닝용 키트.

청구항 7

제 6항에 있어서,

- 1) 제 1항의 스크리닝용 바이오마커의 유전자로 구성된 마이크로어레이 칩; 및
- 2) 표지물질

을 포함하는 것을 특징으로 하는 스크리닝용 키트.

청구항 8

제 7항에 있어서, 표지물질은 Cy3, Cy5인 것을 특징으로 하는 스크리닝 키트.

청구항 9

제 6항에 있어서, 제 1항의 바이오마커에 상보적이고 마커 유전자를 증폭할 수 있는 프라이머를 포함하는 스크리닝용 키트.

청구항 10

제 6항에 있어서, 제 1항의 바이오마커에 상보적이고 마커 유전자와 혼성화할 수 있으며 검출 가능한 프로브를 포함하는 것을 특징으로 하는 스크리닝용 키트.

청구항 11

제 10항에 있어서, 프로브는 방사성 동위원소, 형광물질 또는 염료인 것을 특징으로 하는 스크리닝용 키트.

청구항 12

- 1) 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 전체 RNA를 추출하는 단계;
 - 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 측정하는 단계;
 - 3) 단계 2)의 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하는 단계;
 - 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의 차이를 보이는 유전자를 선별하는 단계;
 - 5) 단계 4)의 선별된 유전자를 에버멕틴 저 생산균주에 도입하여 형질전환하는 단계; 및
 - 6) 단계 5)의 형질전환된 균주에서 에버멕틴을 생산하는 단계
- 를 포함하는 에버멕틴 고생산 방법.

청구항 13

제 12항에 있어서, 단계 1)의 에버멕틴 고 생산균주는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* ATCC31780) 또는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* L-9)인 것을 특징으로 하는 고생산 방법.

청구항 14

제 12항에 있어서, 단계 1)의 에버멕틴 저 생산균주는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* ATCC31267) 또는 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31272)인 것을 특징으로 하는 고생산 방법.

청구항 15

제 12항에 있어서, 단계 2)는 마이크로어레이 칩을 이용하여 유전자 발현을 측정하는 것을 특징으로 하는 고생산 방법.

청구항 16

제 12항에 있어서, 단계 4)는 유전자 발현이 2배 이상 증가 또는 감소하는 것을 선별하는 것을 특징으로 하는 고생산 방법.

청구항 17

제 12항에 있어서, 단계 5)의 선별된 유전자 중 에버멕틴 저 생산균주의 유전자 발현양보다 유전자 발현양이 2배 이상 증가하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것을 특징으로

하는 고생산 방법:

SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).

청구항 18

제 12항에 있어서, 단계 5)의 선별된 유전자 중 에버랙틴 저 생산균주의 유전자 발현양보다 유전자 발현양이 2배 이상 감소하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것을 특징으로 하는 고생산 방법:

SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No.

NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883),

SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

청구항 19

- 1) 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 전체 RNA를 추출하는 단계;
 - 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 측정하는 단계;
 - 3) 단계 2)의 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하는 단계;
 - 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의 차이를 보이는 유전자를 선별하는 단계;
 - 5) 단계 4)의 선별된 유전자를 에버멕틴 생산균주를 대상으로 돌연변이 또는 결실시키는 단계;
 - 6) 단계 5)의 돌연변이 또는 결실 균주에 피검 화합물을 처리하는 단계; 및
 - 7) 단계 6)의 균주의 에버멕틴의 생산을 증가시키는 피검 화합물을 동정하는 단계
- 를 포함하는 에버멕틴 생산 증강 화합물 스크리닝 방법.

청구항 20

제 19항에 있어서, 단계 1)의 에버멕틴 고 생산균주는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* ATCC31780) 또는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* L-9)인 것을 특징으로 하는 스크리닝 방법.

청구항 21

제 19항에 있어서, 단계 1)의 에버멕틴 저 생산균주는 스트렙토마이세스 에버미틸리스(*Streptomyces avermitilis* ATCC31267) 또는 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31272)인 것을 특징으로 하는 스크리닝 방법.

청구항 22

제 19항에 있어서, 단계 2)는 마이크로어레이 칩을 이용하여 유전자 발현을 측정하는 것을 특징으로 하는 스크리닝 방법.

청구항 23

제 19항에 있어서, 단계 4)의 유전자 발현이 2배 이상 증가 또는 감소하는 것을 특징으로 하는 스크리닝 방법.

청구항 24

제 19항에 있어서, 단계 5)의 선별된 유전자 중 에버멕틴 저 생산균주의 유전자 발현양보다 유전자 발현양이 2

배 이상 증가하는 유전자는 하기의 유전자는 하기로 이루어진 군으로부터 선택된 어느 하나인 것을 특징으로 하는 스크리닝 방법:

SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).

청구항 25

제 19항에 있어서, 단계 5)의 선별된 유전자 중 에버랙틴 저 생산균주의 유전자 발현양보다 유전자 발현양이 2배 이상 감소하는 유전자는 하기로 이루어진 군으로부터 선택된 어느 하나인 것을 특징으로 하는 스크리닝 방법:

SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No.

NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No.

NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

청구항 26

제 19항에 있어서, 단계 6)의 피검 화합물은 인공화합물 또는 천연 화합물 또는 이들의 유도체인 것을 특징으로 하는 스크리닝 방법.

청구항 27

제 12항 또는 제 19항의 방법에 의해 선별된 유전자를 돌연변이 또는 결실시키는 것을 특징으로 하는 신규한 에버맥틴 생산 균주.

청구항 28

제 27항에 있어서, 상기 유전자는 하기의 유전자로 구성된 군으로부터 선택된 어느 하나인 것을 특징으로 하는 신규한 에버맥틴 생산 균주:

SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618), SAV7494(Accession No. NP_828670), SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541),

SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450),

SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

명세서

발명의 상세한 설명

발명의 목적

발명이 속하는 기술 및 그 분야의 종래기술

- <8> 본 발명은 에버멕틴 고 생산균주의 스크리닝용 바이오마커, 에버멕틴 고 생산균주의 스크리닝 방법, 에버멕틴 고 생산균주 스크리닝용 키트, 에버멕틴 고 생산방법 및 에버멕틴의 생산을 증강시키는 화합물의 스크리닝 방법에 관한 것이다.
- <9> 스테렙토마이시스(*Streptomyces*)는 상업적으로 가치있는 다양한 효소 및 이차대사 산물을 생산하는 능력을 가진 것으로 널리 알려져 있다(Hwang, E. I., et al., *J. Microbiol. Biotechnol.* 15:909-912, 2005; Hwang, Y. S., et al., *Appl. Environ. Microbiol.* 69:1263-1269, 2003; Prasad, J. B. et al., *J. Microbiol. Biotechnol.* 16:764-770, 2006). 스트렙토마이시스 에버미틸리스(*Streptomyces avermitilis*)에 의해 생산된 에버멕틴(ivermectin)은 메틸화된 디옥시당 L-올레안드로스(oleandrose) 폴리케타이드의 이당류에 붙어있는 일련의 펜타사이클릭 마이크로락톤 타입 I 폴리케타이드(pentacyclic macrolactone type I polyketide)의 16중

중의 하나로서, 해당 숙주생물에 대한 낮은 수준의 부작용과 함께 다양한 선충 및 절지기생충(arthropod parasites)에 대해서 뛰어난 구충작용을 가지고 있다(Yoon, Y. J. *et al.*, *Appl. Microbiol. Biotechnol.* 63:626-634, 2004). *S. 에버미틸리스*에 의해 생성되는 8개의 주요 에버멕틴 화합물들은 C5, C22-C23 및 C26에서 구조적인 차이를 가지고 있다(Albers-SchG., *et al.*, *J. Am. Chem. Soc.* 103:4216-4221, 1981; Burg, R. W., *et al.*, *Agents Chemoter.* 15:361-367, 1979; Miller T. W., *et al.*, *Antimicrob. Agents Chemoter.* 15:368-371, 1979; 도 1 참조). 에버멕틴의 전체 생합성 메커니즘은 전구체 표지(precursor labeling), 차단 돌연변이 분석(blocked mutants analyses), 중간산물 특성화(intermediates characterization) 및 에버멕틴 생합성 효소의 실험관내 연구(in vitro studies of avermetin biosynthetic enzymes) 등의 실험을 통해서 밝혀졌다(Ikeda, H., *et al.*, *J. Bacteriol.* 169:5615-5621, 1987; Ikeda, H., *et al.*, *Chem. Rev.* 97:2591-2609, 1998; Omura S., *et al.*, *Proc. Natl. Acad. Sci. USA* 98:12215-12220: 2001). 현재 에버멕틴 생합성 유전자 클러스터의 뉴클레오티드 염기서열 및 *S. 에버미틸리스*의 전체 게놈은 분석되어 있다(Ikeda, H., *et al.*, *Nat. Biotechnol.* 21:505-506, 2003; Ikeda, H., *et al.*, *Proc. Natl. Acad. Sci. USA* 96:9509-9514, 1999). 그러나 정확한 생합성 염기서열 및 생합성에 대한 세부설명은 아직 설명되지 않았다. 특히, 에버멕틴 생합성을 조절하는 유전학적 요소들은 특정 경로 조절 유전자인 *aveR*(Ikeda, H., *et al.*, *Proc. Natl. Acad. Sci. USA* 96:9509-9514, 1999)에 대한 추정을 제외하고는 대부분 알려져 있지 않다. 스트렙토마이시스 종에 들어있는 다른 이차 대사물들의 생합성과 마찬가지로, 에버멕틴의 생합성은 복잡한 유전학적인 수준에 철저히 조절되는 것으로 믿어지므로, 야생형 *S. 에버미틸리스*(ATCC31267) 배양 내에서 매우 낮은 에버멕틴의 생산성을 야기한다(Yoon, Y. J. *et al.*, *Appl. Microbiol. Biotechnol.* 63:626-634, 2004).

<10> DNA 마이크로어레이 시스템을 포함하여 최근 오믹스 기술 (Omics-guided technology)들은 분자 유전학적 레벨에 있는 산업균주들에서 보이는 다양한 돌연변이의 식별에 적용되어 왔다. 에리스로마이신을 생성하는 *Sccharopolyspora erythraea* 및 타일로신을 생성하는 *S. fradiae*는 산업적인 방선균류를 사용한 첫 번째 작업인 연쇄 *S. coelicolor* DNA 마이크로어레이 시스템을 사용하여 성공적으로 분석되었다(Lum. A. M., *et al.*, *Metabol. Eng.* 6:186-196, 2003).

<11> 본 발명자들은 스트렙토마이시스 에버미틸리스(*Streptomyces avermitilis*)의 전체 게놈 칩을 이용하여 에버멕틴 고생산과 연관된 유전자를 밝혀냄으로써 본 발명을 완성하였다.

발명이 이루고자 하는 기술적 과제

<12> 본 발명의 목적은 에버멕틴 고 생산균주의 스크리닝용 바이오마커, 에버멕틴 고 생산균주의 스크리닝 방법, 에버멕틴 고 생산균주 스크리닝용 키트, 에버멕틴 고 생산방법 및 에버멕틴의 생산을 증강시키는 화합물의 스크리닝 방법을 제공하는 것이다.

발명의 구성 및 작용

<13> 상기 목적을 달성하기 위하여, 본 발명은 에버멕틴 고 생산균주 스크리닝용 바이오마커를 제공한다.

<14> 또한, 본 발명은 하기의 단계로 구성된 에버멕틴 고 생산균주 스크리닝 방법을 제공한다: 1) 균주의 전체 RNA를 추출하는 단계; 2) 단계 2)의 추출된 전체 RNA를 이용하여 에버멕틴 생산균주의 유전자 발현을 측정하는 단계; 및 3) 단계 2)의 측정된 데이터에서 상기 스크리닝용 바이오마커의 발현 정도를 확인하여 에버멕틴 고 생산균주를 선별하는 단계.

<15> 또한, 본 발명은 에버멕틴 고 생산균주 스크리닝용 키트를 제공한다.

<16> 또한, 본 발명은 하기의 단계로 구성된 에버멕틴 고생산 방법을 제공한다: 1) 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 전체 RNA를 추출하는 단계; 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 측정하는 단계; 3) 단계 2)의 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하는 단계; 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의 차이를 보이는 유전자를 선별하는 단계; 5) 단계 4)의 선별된 유전자를 에버멕틴 저 생산균주에 도입하여 형질전환하는 단계; 및 6) 단계 5)의 형질전환된 균주에서 에버멕틴을 생산하는 단계.

<17> 또한, 본 발명은 하기의 단계로 구성된 에버멕틴 생산 증강 화합물 스크리닝 방법을 제공한다: 1) 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 전체 RNA를 추출하는 단계; 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 측정하는 단계; 3) 단계 2)의 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하는 단계; 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의

차이를 보이는 유전자를 선별하는 단계; 5) 단계 4)의 선별된 유전자를 에버멕틴 생산균주를 대상으로 돌연변이 또는 결실시키는 단계; 6) 단계 5)의 돌연변이 또는 결실 균주에 피검 화합물을 처리하는 단계; 및 7) 단계 6)의 균주의 에버멕틴의 생산을 증가시키는 피검 화합물을 동정하는 단계.

<18> 아울러, 본 발명은 상기 방법으로 선별된 유전자를 돌연변이 또는 결실시킨 신규한 에버멕틴 생산 균주를 제공한다.

<19> 이하, 본 발명을 상세히 설명한다.

<20> 본 발명자들은 에버멕틴 고 생산균주인 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31780) 및 저 생산균주 *S. 에버미틸리스*(ATCC31267)를 배양하여 *S. 에버미틸리스* 전체 게놈 마이크로어레이 칩(CombiMatrix Co., Seattle, USA)를 이용하여 유전자 발현을 측정하였다. 아울러 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하여 유전자 발현이 2배 이상 차이가 나는 유전자를 선별하였다. 그 결과, 49개의 유전자가 에버멕틴 저 생산균주보다 에버멕틴 고 생산균주에서 2배 이상 발현이 증가하며, 272개의 유전자가 2배 이상 발현이 감소함을 확인하였다(표 1 및 2 참조). 또한 PKS 유전자를 포함한 에버멕틴 생합성 유전자들이 에버멕틴 고 생산균주에서보다 에버멕틴 저 생산균주에서 덜 발현됨을 확인하였다(표 3 참조). 특히 에버멕틴 특정경고 조절 유전자인 *aveR*이 에버멕틴 저 생산균주에서 약 80% 감소하여 발현되었다. 본 발명자들은 RT-PCR로 4개의 PKS 유전자 발현을 재확인하였다. 그 결과, 4개의 에버멕틴 PKS 유전자가 에버멕틴 고 생산균주보다 에버멕틴 저 생산균주에서 발현이 감소함을 확인하였다. 이를 통해 *aveR*의 고발현이 에버멕틴 PKS 유전자를 자극하기 위해 필요함을 알 수 있다.

<21> 본 발명은 에버멕틴 고 생산균주 스크리닝용 바이오마커를 제공한다.

<22> 상기 스크리닝용 바이오마커는 하기 유전자들로 이루어진 군으로부터 선택된 어느 하나 이상으로 구성되는 것을 특징으로 한다: SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618), SAV7494(Accession No. NP_828670), SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No.

NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No.

NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAP1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

<23> 상기 바이오마커에 있어서, 하기 유전자들로 이루어진 군으로부터 선택되는 어느 하나의 유전자는 에버랙틴 저 생산균주의 유전자 발현양보다 2배 이상 발현양이 증가하는 것이 바람직하다: SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).

<24> 상기 바이오마커에 있어서, 하기 유전자들로 이루어진 군으로부터 선택되는 어느 하나의 유전자는 에버랙틴 저 생산균주의 유전자 발현양보다 2배 이상 발현양이 감소하는 것이 바람직하다: SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No.

NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), 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NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433; SAV4096; SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

<25> 또한, 본 발명은 하기의 단계로 구성된 에버맥틴 고 생산균주 스크리닝 방법을 제공한다: 1) 균주의 전체 RNA를 추출하는 단계; 2) 단계 2)의 추출된 전체 RNA를 이용하여 에버맥틴 생산균주의 유전자 발현을 측정하는 단계; 및 3) 단계 2)의 측정된 데이터에서 상기 스크리닝용 바이오마커의 발현 정도를 확인하여 에버맥틴 고 생산균주를 선별하는 단계.

<26> 상기 스크리닝 방법에 있어서, 유전자 발현 측정 방법은 마이크로어레이 칩을 이용하는 것이 바람직하나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 대량 유전자 발현 측정 방법이라면 본 발명에 모두 이용 가능하다. 본 발명에서는 *S. 에버미틸리스* 전체 게놈 마이크로어레이 칩(CombiMatrix Co., Seattle, USA)을 이용하였으나 이에 한정되는 것은 아니다. 또한 유전자 발현을 측정하기 위하여 본 발명자들은 GenePix 6.0 소프트웨어(Axon Instruments, USA) 프로그램을 이용하여 분석하였으나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 마이크로어레이 칩 이미지 분석 프로그램이라면 본 발명에서 모두 사용 가능하다. 구체적으로 본 발명은 균주에서 전체 RNA를 분리한 후, 전체 RNA를 cDNA로 합성한 후, 다시 cDNA를 cRNA로 합성하면서 표지 물질을 표지할 수 있다. 이 때 표지물질로는 Cy3 또는 Cy5를 이용할 수 있다. 이후 표지된 cRNA를 마이크로어

레이 칩과 혼성화시키고, 반응시킨 마이크로어레이 칩의 이미지를 분석하여 유전자 발현을 측정할 수 있다.

<27>

<28> 또한, 본 발명은 에버택틴 고 생산균주 스크리닝용 키트를 제공한다.

<29> 상기 스크리닝용 키트는 상기 에버택틴 고 생산균주 스크리닝용 바이오마커의 유전자로 구성된 마이크로어레이 칩 및 표지물질로 구성되는 것이 바람직하다. 상기 표지물질로는 Cy3 및 Cy5인 것이 바람직하나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 유전자 표지 방법으로 마이크로어레이 칩 분석 방법에 이용할 수 있는 것이라면 모두 이용 가능하다.

<30> 또한, 상기 스크리닝용 키트는 상기 바이오마커에 상보적이고 마커 유전자를 증폭할 수 있는 프라이머로 구성되는 것이 바람직하다. 상기 프라이머의 디자인은 당해업계의 당업자에게 알려진 프라이머 디자인 방법을 통하여 상기 바이오마커의 유전자에 대응하는 프라이머를 제작할 수 있다.

<31> 아울러, 상기 스크리닝용 키트는 상기 바이오마커에 상보적이고 마커 유전자와 혼성화할 수 있으며 검출 가능한 프로브로 구성되는 것이 바람직하다. 상기 프로브로는 방사성 동위원소, 형광물질 또는 염료인 것이 바람직하다.

<32> 또한, 본 발명은 에버택틴 고생산 방법을 제공한다.

<33> 생산 방법은 하기와 같다: 1) 에버택틴 고 생산균주와 에버택틴 저 생산균주의 전체 RNA를 추출하는 단계; 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버택틴 고 생산균주와 에버택틴 저 생산균주의 유전자 발현을 특정하는 단계; 3) 단계 2)의 에버택틴 고 생산균주와 에버택틴 저 생산균주의 유전자 발현을 비교하는 단계; 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의 차이를 보이는 유전자를 선별하는 단계; 5) 단계 4)의 선별된 유전자를 에버택틴 저 생산균주에 형질전환하는 단계; 및 6) 단계 5)의 형질전환된 균주에서 에버택틴을 생산하는 단계.

<34> 상기 방법에 있어서, 단계 1)의 에버택틴 고 생산균주는 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31780)인 것이 바람직하나 이에 한정되는 것은 아니며, *S. 에버미틸리스*(*Streptomyces avermitilis* L-9)와 같은 당해업계의 당업자에게 공지된 에버택틴 고 생산균주라면 모두 사용 가능하다. 또한, 에버택틴 저 생산균주는 저 생산균주 *S. 에버미틸리스*(ATCC31267)인 것이 바람직하나 이에 한정되는 것은 아니며, *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31272)와 같은 당해업계의 당업자에게 공지된 에버택틴 저 생산균주라면 모두 사용 가능하다.

<35> 상기 방법에 있어서, 단계 2)의 유전자 발현 측정 방법은 마이크로어레이 칩을 이용하는 것이 바람직하나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 대량 유전자 발현 측정 방법이라면 본 발명에 모두 이용 가능하다. 본 발명에서는 *S. 에버미틸리스* 전체 게놈 마이크로어레이 칩(CombiMatrix Co., Seattle, USA)을 이용하였으나 이에 한정되는 것은 아니다. 또한 유전자 발현을 측정하기 위하여 본 발명자들은 GenePix 6.0 소프트웨어(Axon Instruments, USA) 프로그램을 이용하여 분석하였으나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 마이크로어레이 칩 이미지 분석 프로그램이라면 본 발명에서 모두 사용가능하다.

<36> 상기 방법에 있어서, 단계 4)의 유전자 발현이 2배 이상 증가 또는 감소하는 유전자를 선별하는 것이 바람직하다.

<37> 상기 방법에 있어서, 단계 5)의 선별된 유전자 중 유전자 발현이 2배 이상 증가하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것이 바람직하다: SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675),

SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).

<38>

상기 방법에 있어서, 단계 5)의 선별된 유전자 중 유전자 발현이 2배 이상 감소하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것이 바람직하다: SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No. NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754),

SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), SAV3209(Accession No. NP_824385), SAV6482(Accession No. NP_827658), SAV4999(Accession No. NP_826176), SAV4725(Accession No. NP_825902), SAV7479(Accession No. NP_828655), SAV4908(Accession No. NP_826085), SAV1861(Accession No. NP_823037), SAV3970(Accession No. NP_825147), SAV4950(Accession No. NP_826127), SAV7486(Accession No. NP_828662), SAV3129(Accession No. NP_824305), SAV6983(Accession No. NP_828159), SAV2208(Accession No. NP_823383), SAV1687(Accession No. NP_822863), SAV6275(Accession No. NP_827451), SAV3073(Accession No. NP_824249), SAV3691(Accession No. NP_824868), SAV2637(Accession No. NP_823813), SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433; SAV4096; SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060).

- <39> 또한, 본 발명은 에버멕틴 생산 증강 화합물의 스크리닝 방법을 제공한다.
- <40> 스크리닝 방법은 하기와 같다: 1) 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 전체 RNA를 추출하는 단계; 2) 단계 1)의 추출된 전체 RNA를 이용하여 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 측정하는 단계; 3) 단계 2)의 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 비교하는 단계; 4) 단계 3)의 비교된 유전자 발현 결과에서 발현의 차이를 보이는 유전자를 선별하는 단계; 5) 단계 4)의 선별된 유전자를 에버멕틴 생산균주를 대상으로 돌연변이 또는 결실시키는 단계; 6) 단계 5)의 돌연변이 또는 결실 균주에 피검 화합물을 처리하는 단계; 및 7) 단계 6)의 균주의 에버멕틴의 생산을 증가시키는 피검 화합물을 동정하는 단계.
- <41> 상기 방법에 있어서, 단계 1)의 에버멕틴 고 생산균주는 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31780)인 것이 바람직하나 이에 한정되는 것은 아니며, *S. 에버미틸리스*(*Streptomyces avermitilis* L-9)와 같이 당해업계의 당업자에게 공지된 에버멕틴 고 생산균주라면 모두 사용 가능하다. 또한, 에버멕틴 저 생산균주는 저 생산균주 *S. 에버미틸리스*(ATCC31267)인 것이 바람직하나 이에 한정되는 것은 아니며, *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31272)와 같이 당해업계의 당업자에게 공지된 에버멕틴 저 생산균주라면 모두 사용 가능하다.
- <42> 상기 방법에 있어서, 단계 2)의 유전자 발현 측정 방법은 마이크로어레이 칩을 이용하는 것이 바람직하나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 대량 유전자 발현 측정 방법이라면 본 발명에 모두 이용 가능하다. 본 발명에서는 *S. 에버미틸리스* 전체 게놈 마이크로어레이 칩(CombiMatrix Co., Seattle, USA)을 이용하였으나 이에 한정되는 것은 아니다. 또한 유전자 발현을 측정하기 위하여 본 발명자들은 GenePix 6.0 소프트웨어(Axon Instruments, USA) 프로그램을 이용하여 분석하였으나 이에 한정되는 것은 아니며, 당해업계의 당업자에게 알려진 마이크로어레이 칩 이미지 분석 프로그램이라면 본 발명에서 모두 사용가능하다.
- <43> 상기 방법에 있어서, 단계 4)의 유전자 발현이 2배 이상 증가 또는 감소하는 유전자를 선별하는 것이 바람직하다.
- <44> 상기 방법에 있어서, 단계 5)의 선별된 유전자 중 유전자 발현이 2배 이상 증가하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것이 바람직하다: SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No. NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618) 및 SAV7494(Accession No. NP_828670).
- <45> 상기 방법에 있어서, 단계 5)의 선별된 유전자 중 유전자 발현이 2배 이상 감소하는 유전자는 하기의 유전자들로 이루어진 군으로부터 선택된 어느 하나인 것이 바람직하다: SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174),

SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), 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SAV2646(Accession No. NP_823822), SAV6005(Accession No. NP_827182), SAV6679(Accession No. NP_827855), SAV2274(Accession No. NP_823450), SAV6546(Accession No. NP_827722), SAV56(Accession No. NP_821230), SAV5370(Accession No. NP_826547), SAV4920(Accession No. NP_826097), SAV6742(Accession No. NP_827918), SAV5271(Accession No. NP_826448), SAV5468(Accession No. NP_826645), SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433; SAV4096; SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), SAV4524(Accession No. NP_825701), SAV7256(Accession No. NP_828432), SAV4020(Accession No. NP_825197), SAV3932(Accession No. NP_825109), SAV3351(Accession No. NP_824527), SAV5053(Accession No. NP_826230), SAV554(Accession No. NP_821729), SAV5219(Accession No. NP_826396), SAV3970(Accession No. NP_825147), SAV2377(Accession No. NP_823553), SAV6149(Accession No. NP_827325), SAV6325(Accession No. NP_827501), SAV4484(Accession No. NP_825661), SAV2520(Accession No. NP_823696), SAV7069(Accession No. NP_828245), SAV6233(Accession No. NP_827409), SAV6649(Accession No. NP_827825), SAV1733(Accession No. NP_822909), SAV1107(Accession No. NP_822282), SAV6902(Accession No. NP_828078), SAV3142(Accession No. NP_824318), SAV5324(Accession No. NP_826501), SAV416(Accession No. NP_821591), SAV3944(Accession No. NP_825121), SAV459(Accession No. NP_821634), SAV6884(Accession No. NP_828060), SAV6274(Accession No. NP_827450), SAV7145(Accession No. NP_828321), SAV3529(Accession No. NP_824706), SAV1986(Accession No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060). 또한, 에버멕틴 생산균주는 에버멕틴을 생산하며, 스트렙토마이시스에 속하는 미생물이려면 모두 이용가능하며 에버멕틴 고 생산균주인 *S. 에버미틸리스* (*Streptomyces avermitilis* ATCC31780) 및 저 생산균주 *S. 에버미틸리스* (ATCC31267)을 이용하는 것이 바람직하나 이에 한정되는 것은 아니다. 돌연변이 또는 결실 방법은 당해업계의 당업자에게 알려진 방법이라면 모두 이용가능하다.

<46> 또한, 상기 방법에 있어서, 단계 6)의 피검 화합물은 인공화합물 또는 천연 화합물 또는 이들의 유도체를 이용하는 것이 가능하다.

<47> 아울러, 본 발명은 상기 방법으로 선별된 유전자를 돌연변이 또는 결실시킨 신규한 에버멕틴 생산 균주를 제공한다.

<48> 상기 선별된 유전자는 하기의 유전자로 구성된 군으로부터 선택된 어느 하나인 것이 바람직하나 이에 한정되는 것은 아니다: SAV128(Accession No. NP_821302), SAV213(Accession No. NP_821387), SAV424(Accession No. NP_821599), SAV573(Accession No. NP_821748), SAV594(Accession No. NP_821769), SAV696(Accession No. NP_821871), SAV724(Accession No. NP_821899), SAV856(Accession No. NP_822031), SAV1235(Accession No. NP_822410), SAV1405(Accession No. NP_822580), SAV1610(Accession No. NP_822786), SAV1686(Accession No. NP_822862), SAV1094(Accession No. NP_823080), SAV2090(Accession No. NP_823266), SAV2377(Accession No. NP_823553), SAV2441(Accession No. NP_823617), SAV2472(Accession No. NP_823648), SAV2486(Accession No.

NP_823662), SAV2895(Accession No. NP_923071), SAV2899(Accession No. NP_824075), SAV2929(Accession No. NP_824105), SAV2985(Accession No. NP_824161), SAV3445(Accession No. NP_824622), SAV3536(Accession No. NP_824713), SAV3746(Accession No. NP_824923), SAV3793(Accession No. NP_824970), SAV3818(Accession No. NP_824995), SAV3829(Accession No. NP_825006), SAV4023(Accession No. NP_825200), SAV4053(Accession No. NP_825230), SAV4498(Accession No. NP_825675), SAV4507(Accession No. NP_825684), SAV4536(Accession No. NP_825713), SAV4618(Accession No. NP_825795), SAV4688(Accession No. NP_825865), SAV5017(Accession No. NP_826194), SAV5146(Accession No. NP_826323), SAV5215(Accession No. NP_826392), SAV5316(Accession No. NP_826493), SAV5346(Accession No. NP_826523), SAV5590(Accession No. NP_826767), SAV5782(Accession No. NP_826959), SAV5833(Accession No. NP_827010), SAV6183(Accession No. NP_827359), SAV6469(Accession No. NP_827645), SAV6785(Accession No. NP_827961), SAV6892(Accession No. NP_828068), SAV7442(Accession No. NP_828618), SAV7494(Accession No. NP_828670), SAV3202(Accession No. NP_824378), SAV5202(Accession No. NP_826379), SAV4341(Accession No. NP_825518), SAV2033(Accession No. NP_823209), SAV7130(Accession No. NP_828306), SAV1211(Accession No. NP_822386), SAV5881(Accession No. NP_827058), SAV6549(Accession No. NP_827725), SAV3863(Accession No. NP_825040), SAV6678(Accession No. NP_827854), SAV7159(Accession No. NP_828335), SAV3343(Accession No. NP_824519), SAV6988(Accession No. NP_828164), SAV1845(Accession No. NP_823021), SAV5808(Accession No. NP_826985), SAV2998(Accession No. NP_824174), SAV2994(Accession No. NP_824170), SAV6938(Accession No. NP_828114), SAV5878(Accession No. NP_827055), SAV4364(Accession No. NP_825541), SAV4225(Accession No. NP_825402), SAV6380(Accession No. NP_827556), SAV4288(Accession No. NP_825465), SAV6616(Accession No. NP_827792), SAV4898(Accession No. NP_826075), SAV893(Accession No. NP_822068), SAV1077(Accession No. NP_822252), SAV6163(Accession No. NP_827339), SAV2803(Accession No. NP_823979), SAV3420(Accession No. NP_824597), SAV3192(Accession No. NP_824368), SAV1902(Accession No. NP_823078), SAV1221(Accession No. NP_822396), SAV2046(Accession No. NP_823222), SAV4614(Accession No. NP_825791), SAV2505(Accession No. NP_823681), SAV6770(Accession No. NP_827946), SAV4943(Accession No. NP_826120), SAV2690(Accession No. NP_823866), SAV4617(Accession No. NP_825794), SAV5033(Accession No. NP_826210), SAV1718(Accession No. NP_822894), SAV6124(Accession No. NP_827300), SAV4942(Accession No. NP_826119), SAV4697(Accession No. NP_825874), SAV4079(Accession No. NP_825256), SAV5935(Accession No. NP_827112), SAV3429(Accession No. NP_824606), SAV2456(Accession No. NP_823632), SAV6476(Accession No. NP_827652), SAV5829(Accession No. NP_827006), SAV4524(Accession No. NP_825701), SAV4484(Accession No. NP_825661), SAV4012(Accession No. NP_825189), SAV4074(Accession No. NP_825251), SAV2644(Accession No. NP_823820), SAV324(Accession No. NP_821498), SAV6492(Accession No. NP_827668), SAV6229(Accession No. NP_827405), SAV2164(Accession No. NP_823340), SAV2725(Accession No. NP_823901), SAV6007(Accession No. NP_827184), SAV5263(Accession No. NP_826440), SAV2866(Accession No. NP_824042), SAV5714(Accession No. NP_826891), SAV2701(Accession No. NP_823877), SAV4930(Accession No. NP_826107), SAV4430(Accession No. NP_825607), SAV7376(Accession No. NP_828552), SAV2888(Accession No. NP_824064), SAV5510(Accession No. NP_826687), SAV7141(Accession No. NP_828317), SAV5321(Accession No. NP_826498), SAV4095(Accession No. NP_825272), SAV3903(Accession No. NP_825080), SAV6897(Accession No. NP_828073), SAV6324(Accession No. NP_827500), SAV4917(Accession No. NP_826094), SAV5325(Accession No. NP_826502), SAV5028(Accession No. NP_826205), SAV6727(Accession No. NP_827903), SAV6649(Accession No. NP_827825), SAV5270(Accession No. NP_826447), SAV6685(Accession No. NP_827861), SAV231(Accession No. NP_821405), SAV3117(Accession No. NP_824293), SAV2611(Accession No. NP_823787), SAV1011(Accession No. NP_822186), SAV1460(Accession No. NP_822635), SAV2870(Accession No. NP_824046), SAV7177(Accession No. NP_828353), SAV3932(Accession No. NP_825109), SAV6635(Accession No. NP_827811), SAV6822(Accession No. NP_827998), SAV3483(Accession No. NP_824660), SAV6913(Accession No. NP_828089), SAV5048(Accession No. NP_826225), SAV6041(Accession No. NP_827217), SAV4882(Accession No. NP_826059), SAV5323(Accession No. NP_826500), SAV3805(Accession No. NP_824982), SAV4951(Accession No. NP_826128), SAV6176(Accession No. NP_827352), SAV4939(Accession No. NP_826116), SAV2503(Accession No. NP_823679), SAV3249(Accession No. NP_824425), SAV4939(Accession No. NP_826116), SAV98(Accession No. NP_821272), SAV2994(Accession No. NP_824170), SAV6870(Accession No. NP_828046), SAV3788(Accession No. NP_824965), SAV4748(Accession No. NP_825925), SAV6007(Accession No. NP_827184), SAV4954(Accession No. NP_826131), SAV5269(Accession No. NP_826446), SAV1430(Accession No. NP_822605), SAV4485(Accession No. NP_825662), SAV4042(Accession No. NP_825219), SAV3624(Accession No. NP_824801), SAV241(Accession No. NP_821415), SAV3016(Accession No. NP_824192), SAV4223(Accession No.

NP_825400), SAV373(Accession No. NP_821547), SAV4577(Accession No. NP_825754), SAV5159(Accession No. NP_826336), SAV6315(Accession No. NP_827491), SAV2992(Accession No. NP_824168), SAV1840(Accession No. NP_823016), SAV6677(Accession No. NP_827853), SAV4945(Accession No. NP_826122), SAV2627(Accession No. NP_823803), SAV1525(Accession No. NP_822700), SAV6127(Accession No. NP_827303), SAV3245(Accession No. NP_824421), SAV836(Accession No. NP_822011), SAV3346(Accession No. NP_824522), SAV4992(Accession No. NP_826169), SAV4944(Accession No. NP_826121), SAV4832(Accession No. NP_826009), SAV4485(Accession No. NP_825662), SAV5267(Accession No. NP_826444), SAV3516(Accession No. NP_824693), SAV3562(Accession No. NP_824739), SAV2652(Accession No. NP_823828), SAV1282(Accession No. NP_822457), SAV286(Accession No. NP_821460), SAV4991(Accession No. NP_826168), SAV5561(Accession No. NP_826738), SAV2284(Accession No. NP_823460), SAV2272(Accession No. NP_823447), SAV2858(Accession No. NP_824034), 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SAV7001(Accession No. NP_828177), SAV5204(Accession No. NP_826381), SAV2533(Accession No. NP_823709), SAV6329(Accession No. NP_827505), SAV2505(Accession No. NP_823681), SAV5193(Accession No. NP_826370), SAV392(Accession No. NP_821566), SAV2921(Accession No. NP_824097), SAV4731(Accession No. NP_825908), SAV3502(Accession No. NP_824679), SAV7486(Accession No. NP_828662), SAV5148(Accession No. NP_826325), SAV1203(Accession No. NP_822378), SAV5730(Accession No. NP_826907), SAV4585(Accession No. NP_825762), SAV4718(Accession No. NP_825895), SAV5674(Accession No. NP_826851), SAV7392(Accession No. NP_828568), SAV2665(Accession No. NP_823841), SAV1153(Accession No. NP_822328), SAV2050(Accession No. NP_823226), SAV957(Accession No. NP_822132), SAV4706(Accession No. NP_825883), SAV1p29(Accession No. NP_828778), SAV5445(Accession No. NP_826622), SAV7126(Accession No. NP_828302), SAV4958(Accession No. NP_826135), SAV2733(Accession No. NP_823909), SAV4932(Accession No. NP_826109), SAV4919(Accession No. NP_826096), SAV6677(Accession No. NP_827853), SAV5154(Accession No. NP_826331), SAV2724(Accession No. NP_823900), SAV1108(Accession No. NP_822283), SAV6233(Accession No. NP_827409), SAV2254(Accession No. NP_823430), SAV4578(Accession No. NP_825755), SAV6128(Accession No. NP_827304), SAV1958(Accession No. NP_823134), SAV5694(Accession No. NP_826871), SAV2989(Accession No. NP_824165), SAV4321(Accession No. NP_825498), SAV3116(Accession No. NP_824292), SAV4253(Accession No. NP_825430), SAV6508(Accession No. NP_827684), SAV2618(Accession No. NP_823794), SAV4820(Accession No. NP_825997), SAV3117(Accession No. NP_824293), SAV4486(Accession No. NP_825663), SAV98(Accession No. NP_821272), SAV4225(Accession No. NP_825402), SAV5433;SAV4096;SAV5322(Accession No. NP_826610), SAV4706(Accession No. NP_825883), SAV1424(Accession No. NP_822599), SAV1540(Accession No. NP_822716), SAV2695(Accession No. NP_823871), SAV7350(Accession No. NP_828526), SAV2813(Accession No. NP_823989), 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No. NP_823162), SAV4936(Accession No. NP_826113), SAV2237(Accession No. NP_823413), SAV1473(Accession No. NP_822648) 및 SAV6884(Accession No. NP_828060). 또한, 유전된 돌연변이 또는 결실시킨 신규 균주는 당해업계의 당업자

에게 공지된 방법을 이용하여 제조하는 것이 바람직하다.

<49> 이하, 본 발명을 실시예 및 제제예에 의하여 상세히 설명한다.

<50> 단, 하기 실시예 및 제제예는 본 발명을 구체적으로 예시하는 것이며, 본 발명의 내용이 실시예 및 제제예에 의해 한정되는 것은 아니다.

<51> <실시예 1> 마이크로어레이 분석을 통한 *S. 에버미틸리스*(ATCC31780) 및 *S. 에버미틸리스*(ATCC31267)의 유전자 발현 변화 조사

<52> ATCC(American Type Cell Collection)에서 구입한 에버멕틴 고 생산균주 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31780) 및 저 생산균주 *S. 에버미틸리스*(ATCC31267)는 NDYE 배지에 있는 셰이크 플라스크(shake flask) 배양 환경에서 배양하였다(Park, H.-S. *et al.*, *J. Microbiol. Biotechnol.* 15:66-71, 2005). 에버멕틴을 생산하기 위해서, 10% (v/v) *S. 에버미틸리스* 저장 용액을 규격 2 mm 짜리 글래스 비드(glass bead)를 포함하는 250 ml 짜리 배플 플라스크에 있는 25 ml의 배양배지에 접종되었으며, 이어서 30℃ 조건에서 200 rpm에서 일정하게 교반하여 배양하였다. 7일 간의 배양기간 동안 상층액 및 세포 샘플들이 채취되었으며, 에버멕틴 타이터(titer) 및 세포 성장의 광학적 농도 측정을 위해서 HPLC 분석이 수행되었다(Hwang, Y.S. *et al.*, *Appl. Environ. Microbiol.* 69:1263-1269, 2003; Lee, J. Y., *et al.*, *J. Biosci. Bioeng.* 89:606-608, 2000). 추출은 배양액의 일정량을 취하여 1 volume의 추출액(ethyl acetate)을 혼합하고, 14시간 동안 200 rpm, 30℃의 진탕 배양기에서 추출한 후 7000 rpm에서 10분간 원심분리 후 상등액을 취하고, 이를 다시 evaporation 후 메탄올(methanol)에 녹여 분석하였다. HPLC분석을 위한 이동상(mobile phase)는 메탄올:물(methanol:water)(85:15, v/v)을 사용하였고, 유속은 1.2 ml/min, column 온도는 40℃로 고정하였고, UV absorbance detector(Younlin Co., Korea)를 이용하여 246 nm에서 avermectin-type 대사산물의 생산량을 분석하였다. 전사체 단계에서 저 생산균주 및 고 생산균주 사이에 차이가 존재하는지를 판단하기 위해서, 모든 RNA가 정지단계(접종 후 132시간)에서 분리되었다. 생산자의 지시에 따라서 TriZol-reagent(Invitrogen, USA)를 이용하여 전체 RNA를 각각의 *S. 에버미틸리스* 균주로부터 분리하였으며, RNeasy 미니 키트를 이용하여 추출되었다(Ambion Inc., USA). 이후 상기 수득된 RNA를 이용하여 12,000개의 올리고뉴클레오티드를 포함하고 있는 *S. 에버미틸리스* 전체 게놈 마이크로어레이 칩(CombiMatrix Co., Seattle, USA)을 이용하여 분석하였다. 올리고 마이크로어레이 분석을 위한 형광 표지 프루브(probe)는 Amino allyl MessageAmp aRNA kit(Ambion Inc., USA)를 이용하여 준비하였다. 마이크로어레이 칩은 혼성화 캡(hybridization cap)과 결합한 후, 65℃ 조건에서 10분간 RNase가 제거된 증류수로 재수화시켰다. 이후 차단 용액[blocking solution: 6 SSPE, 20 mM EDTA, 0.05% Tween-20, 5 Denhardt's Solution, 0.05% SDS 및 100 ng/μl 분쇄된 연어정자(Sonicated Salmon Sperm) DNA]를 첨가하였고, 어레이는 45℃ 조건에서 30분간 방치하였다. cRNA 혼합물은 1X 파쇄 용액[fragmentation solution: 40 mM Tris-Acetate, pH 8.1, 100 mM KOAc, 30 mM MgOAc]을 이용하여 95℃에서 20분간 처리하여 파쇄하였다. 파쇄된 cRNA 샘플은 혼성화 용액[hybridization solution: 6 SSPE, 0.05% Tween-20, 20 mM EDTA, 25% DI Formamide, 0.05% SDS, 100 ng/ml 분쇄된 연어정자(Sonicated Salmon Sperm) DNA]를 이용하여 95℃에서 3분간 변성화하였다. 차단 용액을 혼성화 챔버에서 제거하고 난 후 혼성화 용액을 어레이에 적용하였다. 혼성화는 Fisher Scientific Isotemp hybridization incubator에서 45℃ 조건에 부드러운 교반을 통해 18시간 동안 방치하면서 수행하였다. 혼성화 이후에 어레이는 45℃ 조건에서 45℃로 데워진 6 SSPE, 0.05% Tween-20 용액을 이용하여 5분간 세척하였다. 이 후 실온에서 3X SSPE, 0.05% Tween-20 용액을 이용하여 5분간 2차 세척하였으며, 실온에서 0.5X SSPE, 0.05% Tween-20 용액을 이용하여 5분간 3차 세척하였고, 실온에서 2X PBS, 0.1% Tween-20 용액을 이용하여 5분간 4차 세척하였고, 마지막으로 2X PBS, 0.1% Tween-20 용액 및 2X PBS로 2회에 걸쳐 실온에서 5분간 세척하였다. 마이크로어레이는 GenePix 4000B Array Scanner(Axon Instruments, USA)를 이용하여 이미지화하였다. 이미지는 어레이가 2X PBS로 세척 후 건조되기 전에 LiferSlip glass coverslip(Erie Scientific, USA)으로 덮었다. 스캔된 어레이 이미지는 GenePix 6.0 소프트웨어(Axon Instruments, USA)에 의해 유전자의 발현비를 분석하였다.

<53> 에버멕틴 고 생산균주 *S. 에버미틸리스*(*Streptomyces avermitilis* ATCC31780) 및 저 생산균주 *S. 에버미틸리스*(ATCC31267)의 유전자 발현 변화를 마이크로어레이 칩으로 분석한 데이터를 분석한 결과, *S. 에버미틸리스*(ATCC31780)에서 최소 2배의 전사 레벨 증가를 보이는 49개의 유전자가 동정되었으며, 최소 2배의 전사 레벨 감소를 보이는 272개의 유전자가 동정되었다(표 1 및 2 참조). 이 중 *S. 에버미틸리스*(ATCC31780)에서의 전사보다 약 6.3배의 증가했으며 GntR-family 전사 조절자를 암호화하는 SAV4023(GenBank No. NP825200) 유전자가 동정되었다. 최근 *S. coelicolor*에서 동정된 유사 GntR-family 전사 조절자인 SCO7168은 탄소원에 반응하는 ABC 운송(transporter) 전사체를 조절하기 때문에 형태 형성 및 항생물질 생산에 필요한 것으로 보고되었다

(Hillerich, B. *et al.*, *J. Bacteriol.* 188:7477-7484, 2006). 이를 통해 에버맥틴 고생산이 SAV4023의 복잡한 상호작용들 때문일 수 있음을 알 수 있다.

<54> 또한 PKS 유전자를 포함하는 모든 에버맥틴 생합성 유전자들이 에버맥틴 고 생산균주 *S. 에버틸리스*(ATCC31780)에서보다 에버맥틴 저 생산균주인 *S. 에버틸리스*(ATCC31267)에서 상대적으로 적게 발현됨을 확인하였다(표 3). 특히 에버맥틴 특정경로 조절 유전자인 *aveR*이 저 생산균주 *S. 에버틸리스*(ATCC31267)에서 약 80% 적게 발현됨을 확인하였다.

표 1

<55>

Gene No.	GenBank No.	Proposed function	Ratio (31780/31267)
SAV128	NP_821302	two-component system response regulator	2.16
SAV213	NP_821387	RNA polymerase ECF-subfamily sigma factor	2.40
SAV424	NP_821599	RNA polymerase ECF-subfamily sigma factor	2.27
SAV573	NP_821748	hypothetical protein	2.04
SAV594	NP_821769	gas vesicle synthesis protein	2.09
SAV696	NP_821871	hypothetical protein	2.26
SAV724	NP_821899	dehydrogenase	2.17
SAV856	NP_822031	thioesterase	2.17
SAV1235	NP_822410	magnesium or manganese-dependent protein phosphatase	2.16
SAV1405	NP_822580	amidohydrolase	2.03
SAV1610	NP_822786	ferredoxin	2.55
SAV1686	NP_822862	oxidoreductase	2.04
SAV1904	NP_823080	hypothetical protein	2.02
SAV2090	NP_823266	xylitol oxidase	2.05
SAV2377	NP_823553	cytochrome P450	3.63
SAV2441	NP_823617	hypothetical protein	2.10
SAV2472	NP_823648	ppGpp synthetase/hydrolase	2.14
SAV2486	NP_823662	glutamate transporter permease	2.00
SAV2895	NP_824071	modular polyketide synthase	2.11
SAV2899	NP_824075	modular polyketide synthase	2.17
SAV2929	NP_824105	hypothetical protein	2.04
SAV2985	NP_824161	methyltransferase	2.61
SAV3445	NP_824622	phosphoribosylglycinamide formyltransferase	2.15
SAV3536	NP_824713	cytochrome P450	2.57
SAV3746	NP_824923	hypothetical protein	2.34
SAV3793	NP_824970	hypothetical protein	2.83
SAV3818	NP_824995	TetR-family transcriptional regulator	2.00
SAV3829	NP_825006	enoyl-CoA hydratase	2.02
SAV4023	NP_825200	GntR-family transcriptional regulator	6.37
SAV4053	NP_825230	ABC transporter ATP-binding protein	2.05
SAV4498	NP_825675	hypothetical protein	2.30
SAV4507	NP_825684	peptidase	2.25
SAV4536	NP_825713	two-component system sensor kinase	2.03
SAV4618	NP_825795	rRNA or tRNA methyltransferase	2.39
SAV4688	NP_825865	L-aspartate oxidase	2.07
SAV5017	NP_826194	cholesterol oxidase	2.04
SAV5146	NP_826323	ABC transporter ATP-binding protein	2.37
SAV5215	NP_826392	hypothetical protein	2.01
SAV5316	NP_826493	D-ribose ABC transporter permease protein	2.56
SAV5346	NP_826523	hypothetical protein	3.92
SAV5590	NP_826767	hypothetical protein	3.29

SAV5782	NP_826959	aldose 1-epimerase	2.68
SAV5833	NP_827010	secreted protein	2.46
SAV6183	NP_827359	hypothetical protein	2.03
SAV6469	NP_827645	hypothetical protein	2.35
SAV6785	NP_827961	RNA polymerase ECF-subfamily sigma factor	2.25
SAV6892	NP_828068	hydrolase	2.08
SAV7442	NP_828618	endo-1;3-beta-glucanase	2.15
SAV7494	NP_828670	hypothetical protein	2.08

표 2

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Gene No.	GenBank No.	Proposed function	Ratio (31780/31267)
SAV3202	NP_824378	thioesterase	0.318
SAV5202	NP_826379	ATP-dependent helicase	0.434
SAV4341	NP_825518	magnesium or manganese-dependent protein phosphatase	0.274
SAV2033	NP_823209	LuxR-family transcriptional regulator	0.344
SAV7130	NP_828306	cytochrome P450	0.467
SAV1211	NP_822386	oxidoreductase	0.442
SAV5881	NP_827058	AraC-family transcriptional regulator	0.466
SAV6549	NP_827725	FMNH ₂ -utilizing oxygenase	0.272
SAV3863	NP_825040	enoyl-CoA hydratase	0.404
SAV6678	NP_827854	proteasome component	0.411
SAV7159	NP_828335	succinate-semialdehyde dehydrogenase; NADP-dependent	0.439
SAV3343 Gene	NP_824519	phosphomannomutase	0.49
SAV6988	NP_828164	hypothetical protein	0.35
SAV1845	NP_823021	LysR-family transcriptional regulator	0.423
SAV5808	NP_826985	ATP/GTP-binding protein	0.483
SAV2998	NP_824174	pentalenene synthase	0.327
SAV2994	NP_824170	monooxygenase	0.438
SAV6938	NP_828114	inhibitor of KinA	0.467
SAV5878	NP_827055	2-keto-3-deoxygluconate 6-phosphate aldolase and 2-keto-4-hydroxyglutarate aldolase	0.408
SAV4364	NP_825541	dihydrolipoamide acyltransferase	0.453
SAV4225	NP_825402	regulatory protein	0.331
SAV6380	NP_827556	secreted acid phosphatase	0.46
SAV6616	NP_827792	polyketide cyclase	0.312
SAV4288	NP_825465	single-strand DNA-binding protein	0.253
SAV4898	NP_826075	hypothetical protein	0.345
SAV893	NP_822068	cold shock protein	0.376
SAV1077	NP_822252	melibiase	0.362
SAV6163	NP_827339	regulatory protein	0.475
SAV2803	NP_823979	trehalose synthase	0.296
SAV3420	NP_824597	ornithine aminotransferase	0.331
SAV3192	NP_824368	bifunctional protein	0.496
SAV1902	NP_823078	hypothetical protein	0.342
SAV1221	NP_822396	amino acid permease	0.495
SAV2046	NP_823222	5-methyltetrahydropteroyltriglutamate--homocysteine methyltransferase	0.297
SAV4614	NP_825791	anti-sigma factor antagonist	0.471
SAV2505	NP_823681	DNA-binding protein	0.318

SAV6770	NP_827946	oxidoreductase	0.486
SAV4943	NP_826120	30S ribosomal protein S5	0.356
SAV2690	NP_823866	hydrolase	0.488
SAV4617	NP_825794	hypothetical protein	0.498
SAV5033	NP_826210	transcriptional regulator	0.483
SAV1718	NP_822894	substrate-binding protein	0.429
SAV6124	NP_827300	cell division protein FtsZ	0.163
SAV4942	NP_826119	ribosomal protein L18	0.349
SAV4697	NP_825874	ATP-dependent Clp protease	0.392
SAV4079	NP_825256	hypothetical protein	0.431
SAV5935	NP_827112	NADPH-dependent F420 reductase	0.378
SAV3429	NP_824606	transferase	0.494
SAV2456	NP_823632	hypothetical protein	0.341
SAV6476	NP_827652	two-component system sensor kinase	0.291
SAV5829	NP_827006	hydrolase	0.353
SAV4524	NP_825701	transmembrane efflux protein	0.118
SAV4484	NP_825661	molecular chaperone DnaK	0.315
SAV4012	NP_825189	DNA-binding protein	0.367
SAV4074	NP_825251	phosphate ABC transporter permease protein	0.478
SAV2644	NP_823820	ribosomal protein S16	0.409
SAV324	NP_821498	ArsR-family transcriptional regulator	0.33
SAV6492	NP_827668	ferrichrome ABC transport system permease protein	0.376
SAV6229	NP_827405	secreted protein	0.478
SAV2164	NP_823340	hydrolase	0.495
SAV2725	NP_823901	transcriptional regulator	0.377
SAV6007	NP_827184	integral membrane protein	0.297
SAV5263	NP_826440	hypothetical protein	0.472
SAV2866	NP_824042	hypothetical protein	0.242
SAV5714	NP_826891	aminoglycoside N3-acetyltransferase	0.375
SAV2701	NP_823877	ATP/GTP-binding protein	0.432
SAV4930	NP_826107	ribosomal protein S19	0.323
SAV4430	NP_825607	hypothetical protein	0.309
SAV7376	NP_828552	[NiFe]hydrogenase expression/formation protein	0.427
SAV2888	NP_824064	ATP synthase protein I	0.475
SAV5510	NP_826687	hypothetical protein	0.463
SAV7141	NP_828317	acyl-CoA dehydrogenase	0.267
SAV5321	NP_826498	hypothetical protein	0.417
SAV4095	NP_825272	hypothetical protein	0.359
SAV3903	NP_825080	integral membrane protein	0.481
SAV6897	NP_828073	uracil permease	0.476
SAV6324	NP_827500	DNA-binding protein	0.496
SAV4917	NP_826094	30S ribosomal protein S12	0.416
SAV5325	NP_826502	hypothetical protein	0.261
SAV5028	NP_826205	transcriptional regulator	0.188
SAV6727	NP_827903	short chain dehydrogenase	0.493
SAV6649	NP_827825	serine protease	0.427
SAV5270	NP_826447	acetyltransferase	0.495
SAV6685	NP_827861	proteasome component	0.432
SAV231	NP_821405	MerR-family transcriptional regulator	0.346
SAV3117	NP_824293	RNA polymerase sigma-70 factor	0.318
SAV2611	NP_823787	AsnC-family transcriptional regulator	0.392
SAV1011	NP_822186	UDP-glucose 4-epimerase	0.397

SAV1460	NP_822635	ATP/GTP-binding protein	0.494
SAV2870	NP_824046	3-hydroxyacyl-CoA dehydrogenase	0.442
SAV7177	NP_828353	aldehyde dehydrogenase	0.217
SAV3932	NP_825109	cold shock protein	0.253
SAV6635	NP_827811	secreted protein	0.321
SAV6822	NP_827998	threonyl-tRNA synthetase	0.116
SAV3483	NP_824660	phosphoglycerate mutase	0.483
SAV6913	NP_828089	hypothetical protein	0.362
SAV5048	NP_826225	phosphomannomutase	0.489
SAV6041	NP_827217	quinolinate synthetase	0.488
SAV4882	NP_826059	NADH dehydrogenase I chain B	0.389
SAV5323	NP_826500	hypothetical protein	0.41
SAV3805	NP_824982	hypothetical protein	0.272
SAV4951	NP_826128	30S ribosomal protein S13	0.47
SAV6176	NP_827352	hypothetical protein	0.455
SAV4939	NP_826116	30S ribosomal protein S14	0.499
SAV2503	NP_823679	hypothetical protein	0.476
SAV4939	NP_826116	30S ribosomal protein S14	0.421
SAV3249	NP_824425	two-component system response regulator	0.47
SAV98	NP_821272	glycosyl hydrolase	0.488
SAV2994	NP_824170	monooxygenase	0.447
SAV6870	NP_828046	hypothetical protein	0.424
SAV3788	NP_824965	ADP-ribosylglycohydrolase	0.495
SAV4748	NP_825925	arginyl-tRNA synthetase	0.474
SAV6007	NP_827184	integral membrane protein	0.427
SAV4954	NP_826131	ribosomal protein L17	0.452
SAV5269	NP_826446	siderophore biosynthetic enzyme	0.354
SAV1430	NP_822605	hypothetical protein	0.468
SAV4485	NP_825662	heat shock protein GrpE	0.457
SAV4042	NP_825219	two-component system response regulator	0.426
SAV3624	NP_824801	hydrolase	0.428
SAV241	NP_821415	hypothetical protein	0.462
SAV3016	NP_824192	WhiB-family transcriptional regulator; role in cell cycle control	0.326
SAV4223	NP_825400	serine protease	0.433
SAV373	NP_821547	LysR-family transcriptional regulator	0.495
SAV4577	NP_825754	hypothetical protein	0.439
SAV5159	NP_826336	ATP-dependent Clp protease adaptor protein ClpS	0.288
SAV6315	NP_827491	transketolase	0.491
SAV2992	NP_824168	transport protein	0.469
SAV1840	NP_823016	dehydrogenase	0.465
SAV6677	NP_827853	AAA-family ATPase	0.405
SAV4945	NP_826122	50S ribosomal protein L15	0.406
SAV2627	NP_823803	30S ribosomal protein S2	0.396
SAV1525	NP_822700	muconolactone delta-isomerase	0.498
SAV6127	NP_827303	hypothetical protein	0.353
SAV3245	NP_824421	secreted protein	0.403
SAV836	NP_822011	efflux family protein	0.467
SAV3346	NP_824522	deoxyribose-phosphate aldolase	0.446
SAV4992	NP_826169	chaperonin GroEL	0.483
SAV4944	NP_826121	ribosomal protein L30	0.47
SAV4832	NP_826009	hypothetical protein	0.479

SAV448	NP_825662	heat shock protein GrpE	0.381
SAV5267	NP_826444	phosphoesterase	0.48
SAV3516	NP_824693	integral membrane protein	0.455
SAV3562	NP_824739	ribose-phosphate pyrophosphokinase	0.443
SAV2652	NP_823828	regulatory protein	0.471
SAV1282	NP_822457	two-component system response regulator	0.399
SAV286	NP_821460	large secreted protein	0.488
SAV4991	NP_826168	co-chaperonin GroES	0.2
SAV5561	NP_826738	GTP-binding protein LepA	0.14
SAV2284	NP_823460	isobutylamine N-hydroxylase	0.25
SAV2272	NP_823447	hypothetical protein	0.43
SAV2858	NP_824034	M protein	0.341
SAV3209	NP_824385	polyphosphate glucokinase	0.314
SAV6482	NP_827658	secreted protein	0.406
SAV4999	NP_826176	RNA polymerasesigma-70 factor	0.495
SAV4725	NP_825902	tryptophanyl-tRNA synthetase	0.396
SAV7479	NP_828655	beta-galactosidase precursor	0.314
SAV4908	NP_826085	preprotein translocase	0.465
SAV1861	NP_823037	DNA-binding protein	0.484
SAV3970	NP_825147	CarD-like transcriptional regulator	0.27
SAV4950	NP_826127	50S ribosomal protein L36	0.255
SAV7486	NP_828662	subtilisin inhibitor	0.194
SAV3129	NP_824305	ferredoxin	0.375
SAV6983	NP_828159	hypothetical protein	0.472
SAV2208	NP_823383	hypothetical protein	0.435
SAV1687	NP_822863	cell division protein; regulatory protein	0.47
SAV6275	NP_827451	export associated protein	0.499
SAV3073	NP_824249	glutaredoxin-like protein	0.46
SAV3691	NP_824868	transmembrane efflux protein	0.488
SAV2637	NP_823813	signal peptidase	0.434
SAV2646	NP_823822	prolyl-tRNA synthetase	0.444
SAV6005	NP_827182	glutamine synthetase	0.491
SAV6679	NP_827855	hypothetical protein	0.444
SAV2274	NP_823450	hypothetical protein	0.434
SAV6546	NP_827722	ABC transporter permease	0.478
SAV56	NP_821230	hypothetical protein	0.483
SAV5370	NP_826547	globin-like protein	0.483
SAV4920	NP_826097	elongation factor Tu	0.463
SAV6742	NP_827918	phenylalanyl-tRNA synthetase alpha subunit	0.494
SAV5271	NP_826448	monooxygenase	0.455
SAV5468	NP_826645	50S ribosomal protein L27	0.493
SAV7001	NP_828177	hypothetical protein	0.482
SAV5204	NP_826381	hypothetical protein	0.371
SAV2533	NP_823709	hypothetical protein	0.483
SAV6329	NP_827505	aminotransferase	0.48
SAV2505	NP_823681	DNA-binding protein	0.439
SAV5193	NP_826370	hypothetical protein	0.196
SAV392	NP_821566	hypothetical protein	0.396
SAV2921	NP_824097	two-component system response regulator	0.494
SAV4731	NP_825908	hypothetical protein	0.384
SAV3502	NP_824679	integral membrane protein	0.466
SAV7486	NP_828662	subtilisin inhibitor	0.199

SAV5148	NP_826325	AsnC-family transcriptional regulator	0.472
SAV1203	NP_822378	hypothetical protein	0.42
SAV5730	NP_826907	hypothetical protein	0.415
SAV4585	NP_825762	ion-transporting ATPase	0.208
SAV4718	NP_825895	hypothetical protein	0.366
SAV5674	NP_826851	deoxyguanosinetriphosphate triphosphohydrolase-like protein	0.424
SAV7392	NP_828568	two-component system response regulator	0.439
SAV2665	NP_823841	ribonuclease III	0.368
SAV1153	NP_822328	regulatory protein	0.249
SAV2050	NP_823226	hypothetical protein	0.472
SAV957	NP_822132	hypothetical protein	0.438
SAV4706	NP_825883	RNA polymerase ECF-subfamily sigma factor	0.456
SAP1p29	NP_828778	hypothetical protein	0.5
SAV5445	NP_826622	hypothetical protein	0.441
SAV7126	NP_828302	polypeptide deformylase	0.482
SAV4958	NP_826135	ribosomal protein S9	0.473
SAV2733	NP_823909	acetolactate synthase I large subunit	0.475
SAV4932	NP_826109	30S ribosomal protein S3	0.408
SAV4919	NP_826096	translation elongation factor G	0.451
SAV6677	NP_827853	AAA-family ATPase	0.427
SAV5154	NP_826331	hypothetical protein	0.429
SAV2724	NP_823900	proline dehydrogenase	0.422
SAV1108	NP_822283	hypothetical protein	0.279
SAV6233	NP_827409	30S ribosomal protein S1	0.433
SAV2254	NP_823430	cellulose binding protein	0.494
SAV4578	NP_825755	hypothetical protein	0.483
SAV6128	NP_827304	hypothetical protein	0.384
SAV1958	NP_823134	secreted protein	0.478
SAV5694	NP_826871	hypothetical protein	0.456
SAV2989	NP_824165	MarR-family transcriptional regulator	0.471
SAV4321	NP_825498	DNA topoisomerase IV subunit B	0.459
SAV3116	NP_824292	hypothetical protein	0.488
SAV4253	NP_825430	hypothetical protein	0.455
SAV6508	NP_827684	partitioning or sporulation protein	0.39
SAV2618	NP_823794	ABC transporter ATP-binding protein	0.48
SAV4820	NP_825997	cold shock protein	0.473
SAV3117	NP_824293	RNA polymerase sigma-70 factor	0.494
SAV4486	NP_825663	DnaJ protein	0.34
SAV98	NP_821272	glycosyl hydrolase	0.426
SAV4225	NP_825402	regulatory protein	0.162
SAV5433; SAV4096; SAV5322	NP_826610	hypothetical protein	0.255
SAV4706	NP_825883	RNA polymerase ECF-subfamily sigma factor	0.339
SAV1424	NP_822599	hypothetical protein	0.25
SAV1540	NP_822716	xanthine dehydrogenase	0.395
SAV2695	NP_823871	hypothetical protein	0.447
SAV7350	NP_828526	integral membrane protein	0.452
SAV2813	NP_823989	transmembrane efflux protein	0.471
SAV4524	NP_825701	transmembrane efflux protein	0.482
SAV7256	NP_828432	hypothetical protein	0.411

SAV4020	NP_825197	hydrolase	0.485
SAV3932	NP_825109	cold shock protein	0.469
SAV3351	NP_824527	RNA polymerase ECF-subfamily sigma factor	0.395
SAV5053	NP_826230	S-adenosyl-L-homocysteine hydrolase	0.42
SAV554	NP_821729	LacI-family transcriptional regulator	0.498
SAV5219	NP_826396	glycosyl transferase	0.498
SAV3970	NP_825147	CarD-like transcriptional regulator	0.353
SAV2377	NP_823553	cytochrome P450	0.31
SAV6149	NP_827325	transcriptional regulator	0.444
SAV6325	NP_827501	iron-regulated ABC-type transporter	0.439
SAV4484	NP_825661	molecular chaperone DnaK	0.258
SAV2520	NP_823696	hypothetical protein	0.497
SAV7069	NP_828245	GntR-family transcriptional regulator	0.498
SAV6233	NP_827409	30S ribosomal protein S1	0.457
SAV6649	NP_827825	serine protease	0.167
SAV1733	NP_822909	hypothetical protein	0.464
SAV1107	NP_822282	hypothetical protein	0.247
SAV6902	NP_828078	riboflavin synthase subunit alpha	0.391
SAV3142	NP_824318	hypothetical protein	0.458
SAV5324	NP_826501	hypothetical protein	0.498
SAV416	NP_821591	modular polyketide synthase	0.474
SAV3944	NP_825121	hypothetical protein	0.34
SAV459	NP_821634	heat shock protein	0.417
SAV6884	NP_828060	inositol-5-monophosphate dehydrogenase	0.277
SAV6274	NP_827450	export associated protein	0.454
SAV7145	NP_828321	hypothetical protein	0.278
SAV3529	NP_824706	NADH dehydrogenase	0.462
SAV1986	NP_823162	phenylacetic acid degradation protein	0.487
SAV4936	NP_826113	ribosomal protein L14	0.388
SAV2237	NP_823413	hypothetical protein	0.497
SAV1473	NP_822648	ATP/GTP-binding protein	0.316
SAV6884	NP_828060	inositol-5-monophosphate dehydrogenase	0.391

표 3

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Gene No.	GenBank No.	proposed function	Ratio (31780/31267)
SAV935	NP_822110	<i>aveR</i> (pathway specific positive regulator)	1.80
SAV936	NP_822111	<i>aveF</i> (C5-ketoreductase)	1.05
SAV937	NP_822112	<i>aveD</i> (C5-O-methyltransferase)	1.21
SAV938	NP_822113	<i>aveA1</i> (polyketide synthase)	1.30
SAV939	NP_822114	<i>aveA2</i> (polyketide synthase)	1.35
SAV940	NP_822115	<i>aveC</i> (CHC-B2:CHC-B1 ratio)	1.65
SAV941	NP_822116	<i>aveE</i> (cytochrome P450 hydroxylase)	1.12
SAV942	NP_822117	<i>aveA3</i> (polyketide synthase)	1.82
SAV943	NP_822118	<i>aveA4</i> (polyketide synthase)	1.06
SAV945	NP_822120	<i>aveB1</i> (glycosyl transferase)	1.12
SAV946	NP_822121	<i>aveB11</i> (dTDP-glucose 4,6-dehydratase)	1.30
SAV947	NP_822122	<i>aveB111</i> (glucose-1-phosphate thymidyltransferase)	1.28
SAV948	NP_822123	<i>aveB1V</i> (dTDP-4-keto-6-deoxy-L-hexose 4-reductase)	1.59
SAV949	NP_822124	<i>aveB1V</i> (dTDP-4-keto-6-deoxyhexose 3,5-epimerase)	1.21
SAV950	NP_822125	<i>aveB1V</i> (dTDP-4-keto-6-deoxy-L-hexose2,3-dehydratase)	1.68

SAV951	NP_822126	<i>aveBVII</i> (dTDP-6-deoxy-L-hexose 3-O-methyltransferase)	1.14
SAV952	NP_822127	<i>aveBVIII</i> (dTDP-4-keto-6-deoxy-L-hexose 2,3-reductase)	1.28

<58> <실시예 2> *S. 에버미틸리스*(ATCC31780) 및 *S. 에버미틸리스*(ATCC31267)상에서의 PKS 유전자 발현 조사

<59> 에버멕틴 PKS 유전자의 효율적인 발현이 에버멕틴 생합성에 있어서 중요한 첫 단계로 여겨지고, 이러한 유전자들이 AveR 조절자의 추정적인 목표로서 작용하기 때문에, 두 *S. 에버미틸리스* 균주 사이에 있는 네 개의 에버멕틴 PKS 유전자에 대한 비교 RT-PCR 분석을 수행하였다. 본 발명자들은 ExTaq 중합효소(TakaRa, Japan)를 사용해 전체 RNA의 5 ng을 주형(template)으로 하여 수행되었다. 첫 번째 가닥 cDNA 합성조건은 50℃에서 60분이었으며, 이어서 96℃에서 2분이었고, 증폭 조건은 96℃ 15초에서 30회, 62℃에서 30초 및 72℃에서 1분이었다. 이때 사용한 프라이머는 하기와 같다: aveA1: 5'- AAA CCG CCT GGG AAA CCA TC -3'(서열번호 1) 및 5' - CGC AGT TCG ACA CCC ATG AC -3'(서열번호 2); aveA2: 5'- GCG ACT GGT CAA GTC AGC GA -3'(서열번호 3) 및 5'- GTA CTG CGC GCC TCC TCA GT -3'(서열번호 4); aveA3: 5'- CAC CTC GTA CAC CCG CTG TG -3'(서열번호 5) 및 5'- GTC CAT AGG CCT GCG GAA TG -3'(서열번호 6); aveA4: 5'- CGA GGA CCC TGG TGT TCG AC -3'(서열번호 7) 및 5'- ACA ATG GCA ATC GGC TCG TC -3'(서열번호 8).

<60> 그 결과, 예상했던 바와 같이 네 개의 에버멕틴 PKS 밴드들은 저 생산균주 *S. 에버미틸리스*(ATCC31267)에서 현저히 비효율적으로 증폭되었는데(도 2), 이는 aveR의 고 발현이 에버멕틴 PKS 유전자를 자극하기 위해 필요함을 알 수 있다.

발명의 효과

<61> 본 발명은 에버멕틴 고 생산균주와 에버멕틴 저 생산균주의 유전자 발현을 통하여 에버멕틴 고 생산균주에서만 특이적으로 발현이 증가하는 49개의 유전자 및 발현이 감소하는 272개의 유전자를 선별하여 미지의 에버멕틴 고 생산균주를 스크리닝하는데 유용하며, 동정된 에버멕틴 고 생산균주의 321개의 바이오마커를 돌연변이 또는 결실된 에버멕틴 생산균주를 제조하여, 상기 균주를 이용하여 에버멕틴을 저비용, 고효율로 생산하는 방법 및 에버멕틴의 생산을 증강시키는 화합물을 스크리닝하데 유용하다.

도면의 간단한 설명

<1> 도 1은 에버멕틴 생합성 경로 및 화학적 구조이다.

<2> 도 2는 PKS 유전자인 AveA1, AveA2, AveA3 및 AveA4의 유전자 발현을 에버멕틴 고 생산균주와 에버멕틴 저 생산균주에서 확인한 젤 사진이다:

<3> 첫 번째 줄 : 에버멕틴 저생산 균주(*S. avermitilis* ATCC31267);

<4> 두 번째 줄 : 에버멕틴 고생산 균주(*S. avermitilis* ATCC31780);

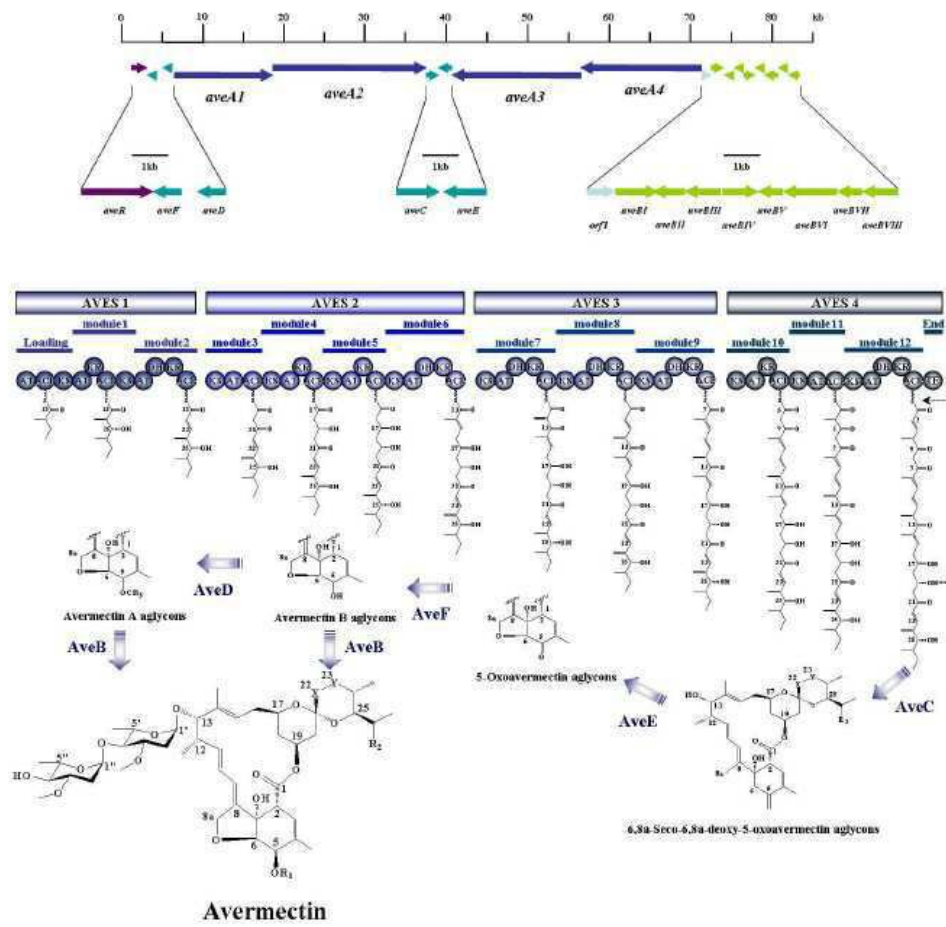
<5> C : 전체 RNA;

<6> T₀ : 36시간; 및

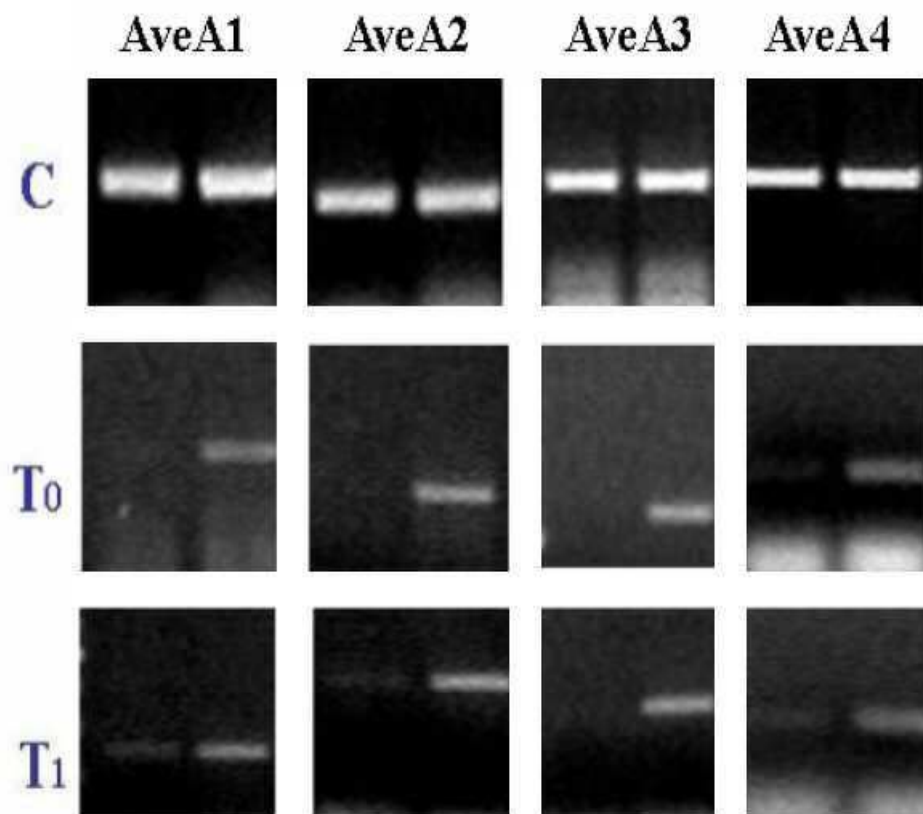
<7> T₁ : 132시간.

도면

도면1



도면2



서열 목록

- <110> INHA UNIVERSITY INDUSTRY PARTHNERSHIP INSTITUTE
- <120> The screening method of high production microorganism of avermectin
- <130> 7p-03-07
- <160> 8
- <170> Kopatent In 1.71
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