实用生物信息技术期末总结交流报告会

Semester Summary Seminar for Applied Bioinformatics Course

次级代谢产物及其生物合成基因簇

Secondary Metabolites and their Biosynthesis Gene Clusters

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中国农业科学院研究生院

2020级博士班

2020年12月12日

1. Secondary Metabolites

2. Biosynthesis Gene Clusters

3. Prediction

4. Outlook

1. 次级代谢产物 (Secondary Metabolites, SMs)

某种细胞或者某种生物体的特有代谢途径中产生的小分子化合物。

红豆杉

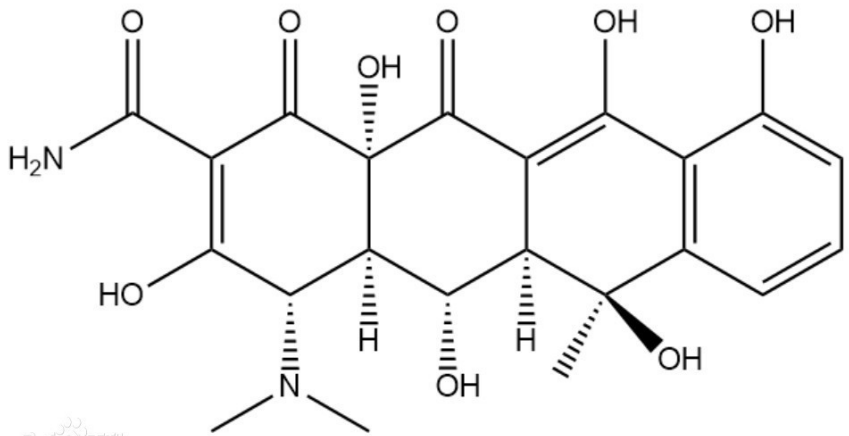
黄花蒿

人参

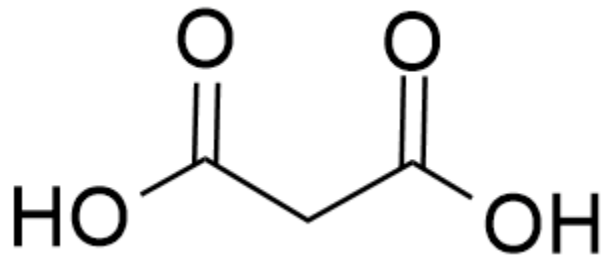
图片来源：百度百科

1.1 聚酮类化合物 (Polyketones,PKs)

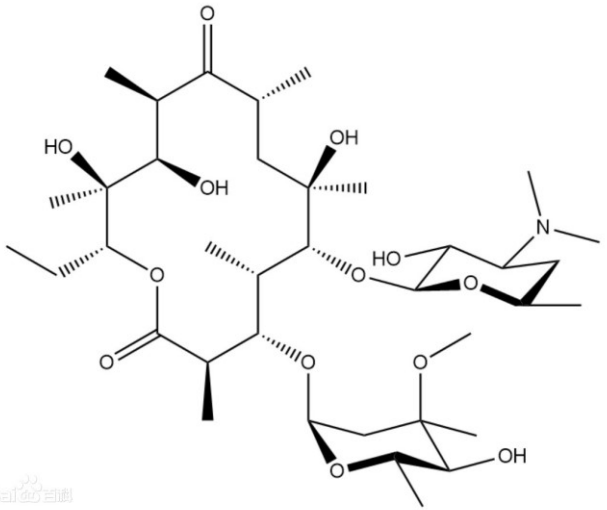
- 土霉素



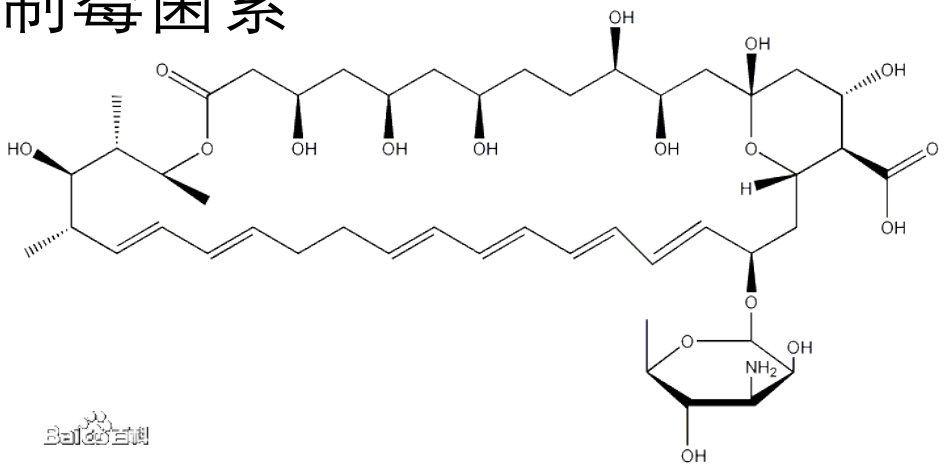
- 基本合成单元



- 红霉素



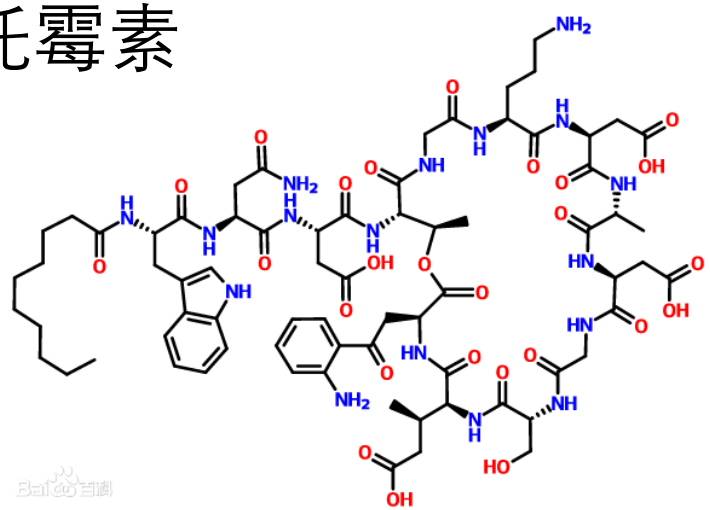
- 制霉菌素



图片来源：百度百科

1.2 肽类化合物 (Petides)

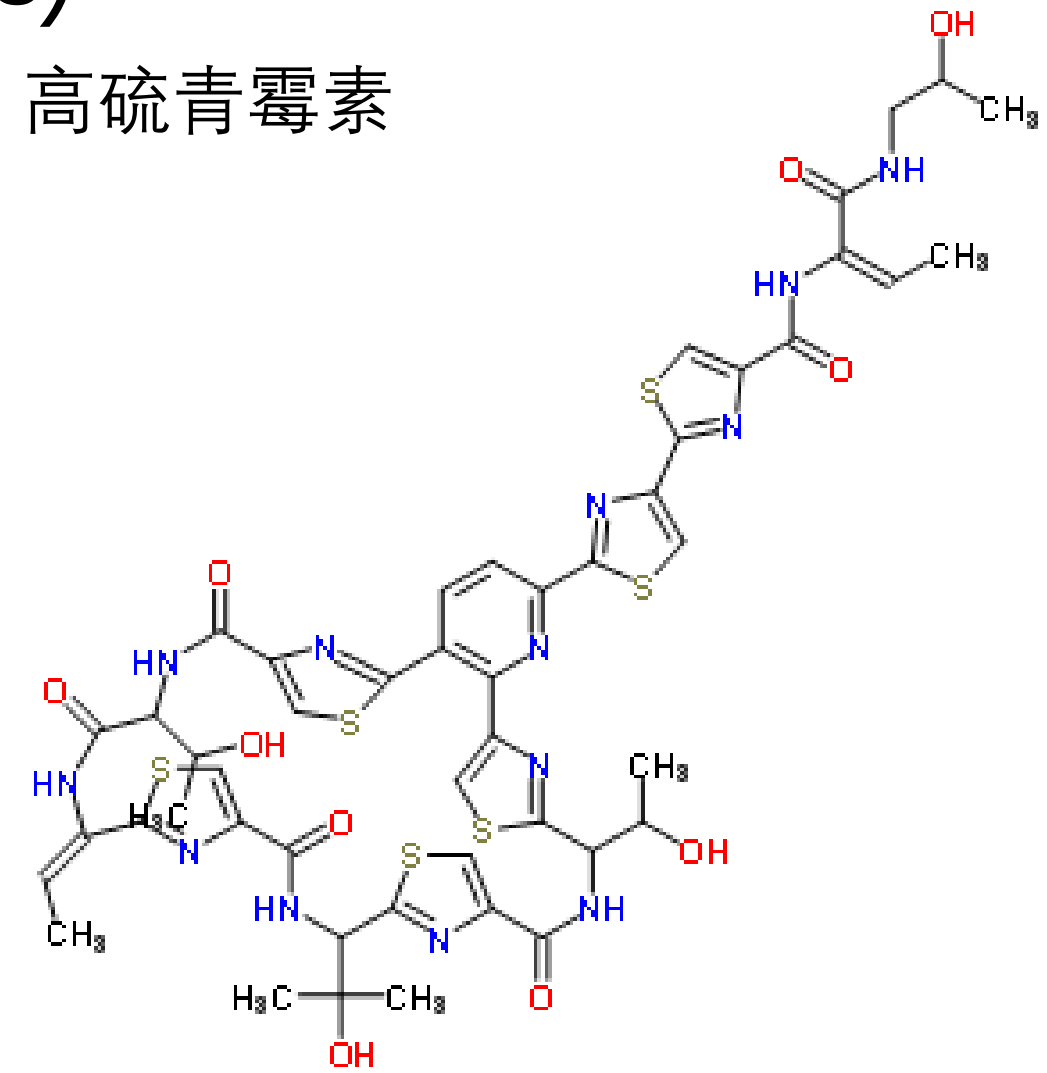
- 达托霉素



- 基本合成单元

天然氨基酸与非天然氨基酸

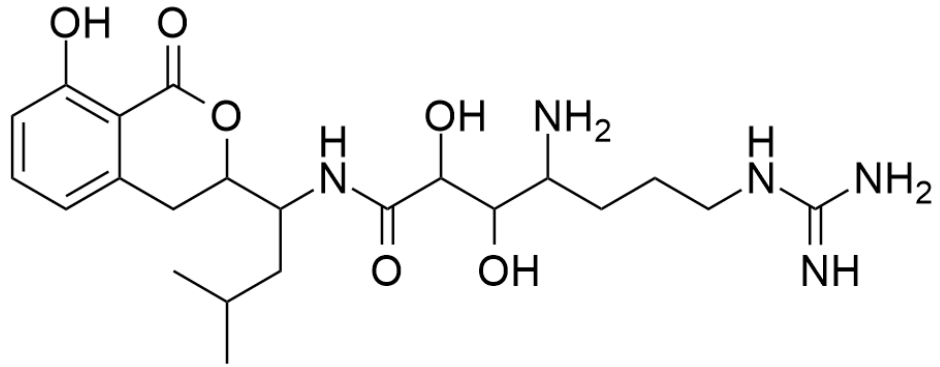
- 高硫青霉素



图片来源：百度百科

1.3 NRP-PK杂合化合物

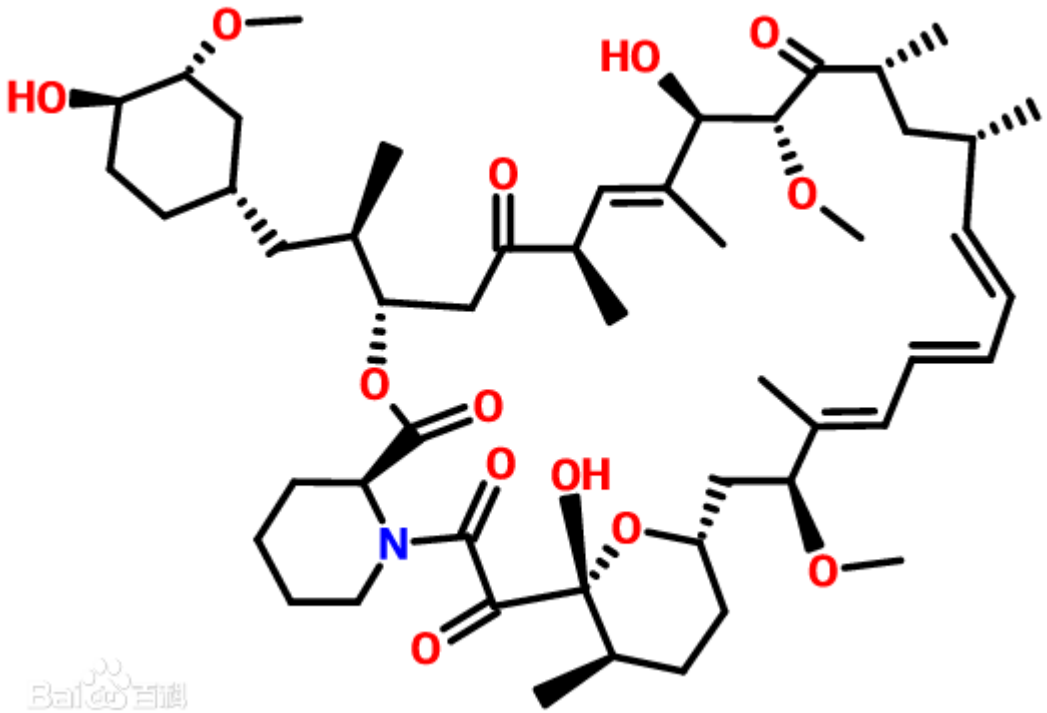
- Xenocoumacin, Xcn1



- 基本合成单元

丙二酸、氨基酸等

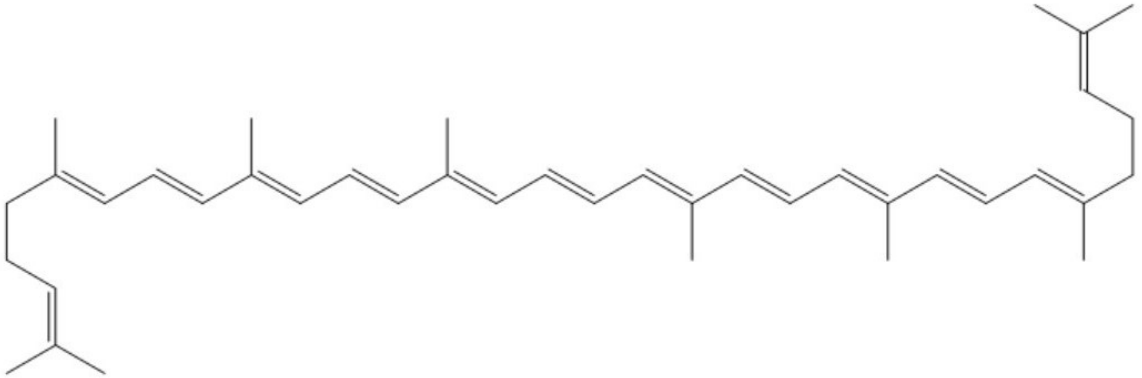
- 雷帕霉素



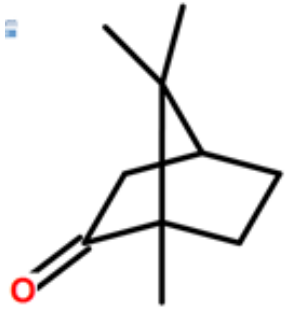
图片来源：百度百科

1.4 异戊二烯类/萜类化合物

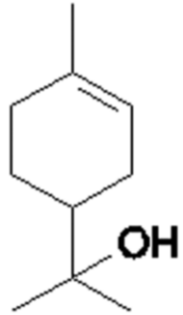
- 番茄红素



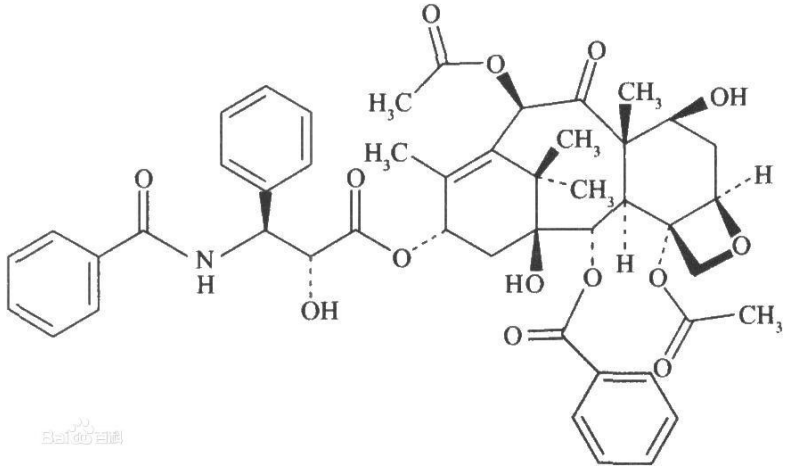
樟脑



松油醇



紫杉醇



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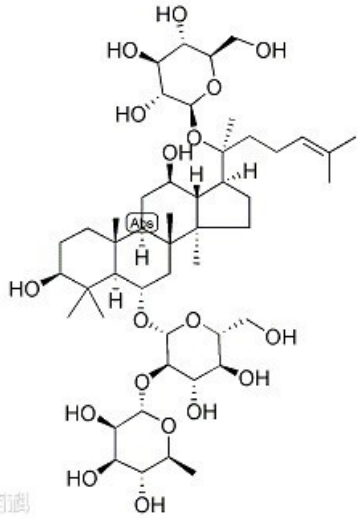
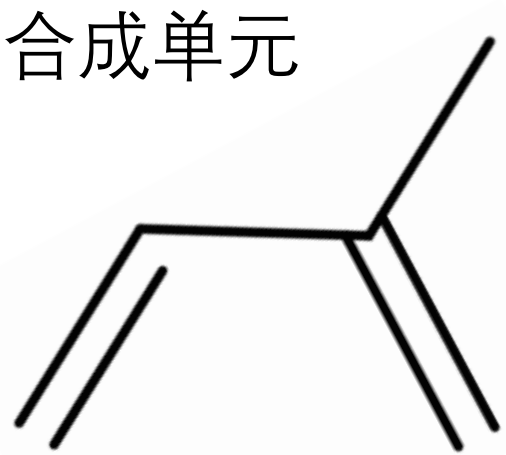


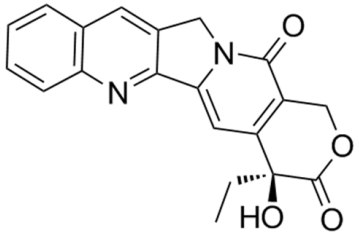
- 基本合成单元



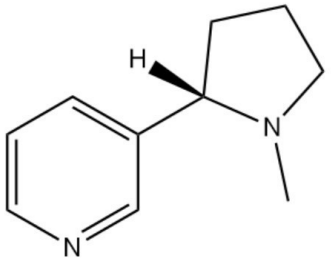
图片来源：百度百科

1.5 生物碱及其它化合物

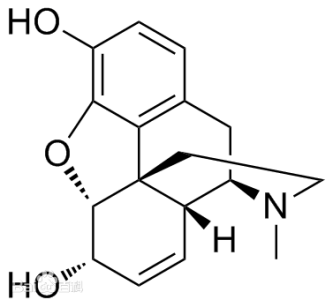
喜树碱



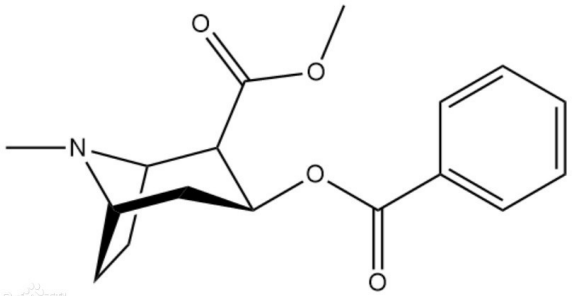
尼古丁



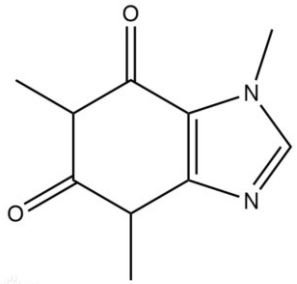
吗啡



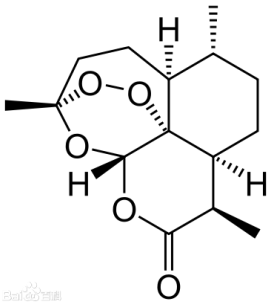
可卡因



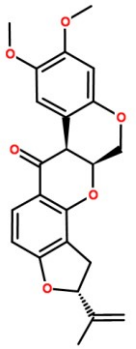
咖啡因



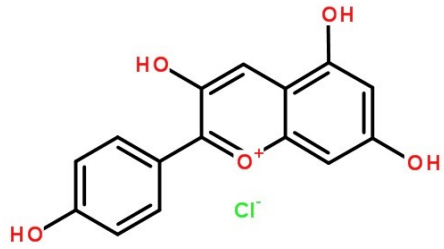
青蒿素



鱼藤酮



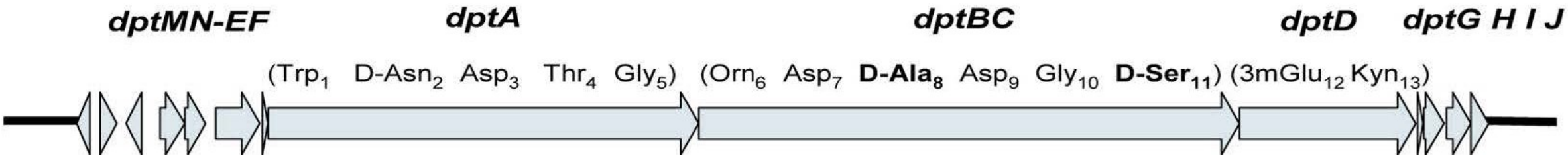
花青素



图片来源：百度百科

2. 生物合成基因簇 (Biosynthesis Gene Clusters，BGCs)

生物基因组中紧密相连，成簇存在，在功能上相互协同，形成合成次级代谢产物完整途径的一系列基因。



达托霉素生物合成基因簇 (Kien T. Nguyen, PNAS, 2006)

2.1 聚酮类化合物生物合成方式

聚酮类化合物的分子骨架主要由生物合成基因簇中的聚酮合酶(polyketide synthase，PKS)合成。PKS是一类具有多种功能域的大型合酶，该酶作用方式类似于脂肪酸合酶(fat acid synthase, FAS)。

AT: acyltransferase

ACP: acyl carder protein

TE: thioesterase

KS: keto-acyl synthase

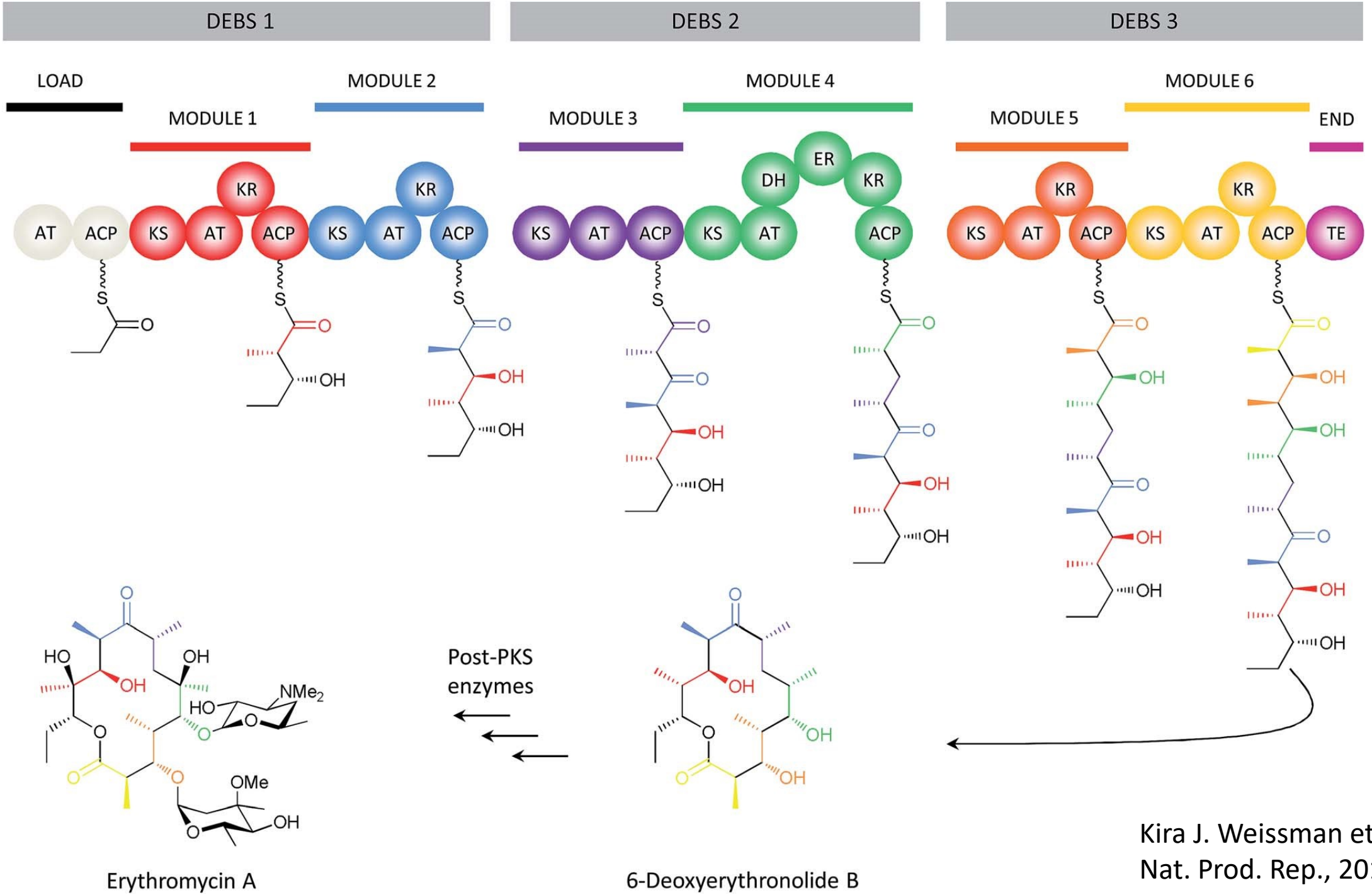
KR: ketoacyl reductase

DH: dehydratase

ER: enoylreductase

MT: meyl transferase

Cy: cyclase



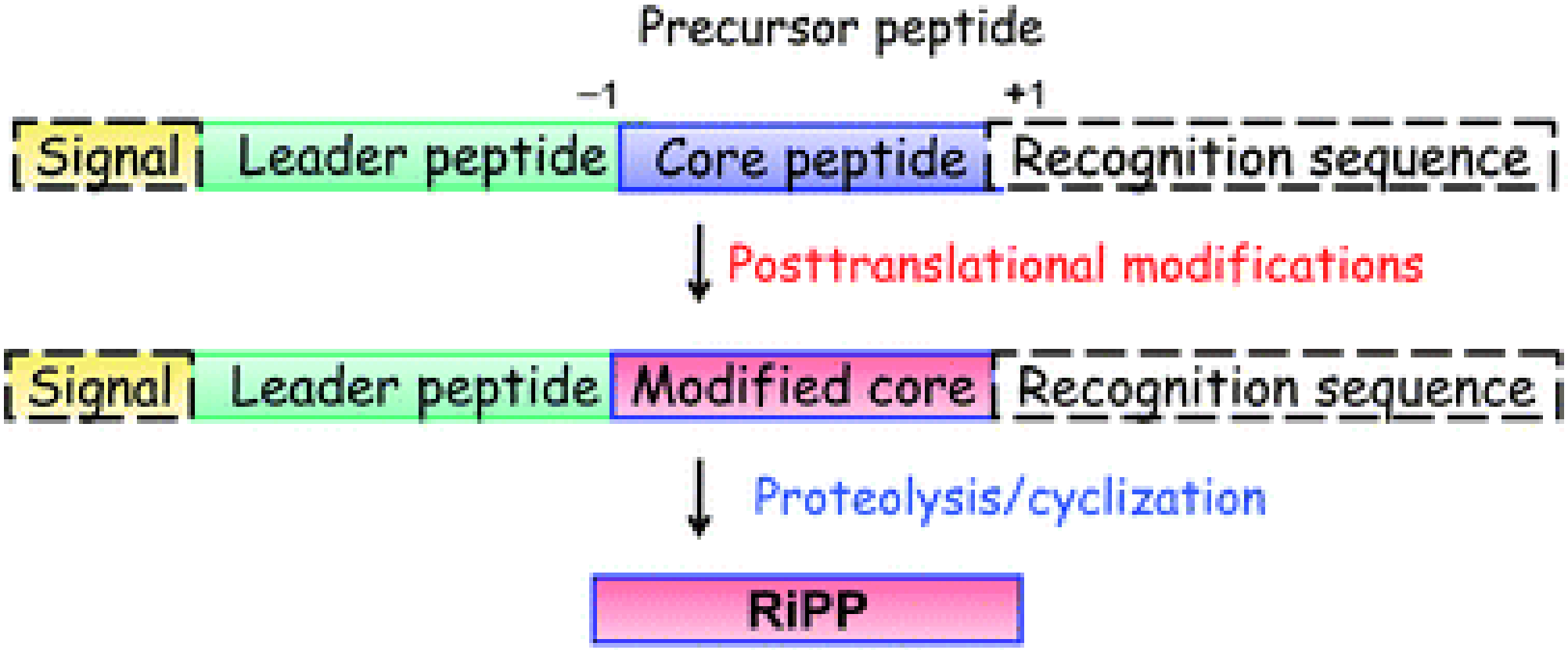
Kira J. Weissman et al.,
Nat. Prod. Rep., 2016

2.2 肽类化合物生物合成方式

1. 核糖体合成，经翻译后修饰形成，被称为核糖体合成翻译后修饰多肽(ribosomal posttranslational peptides, RiPPs)。

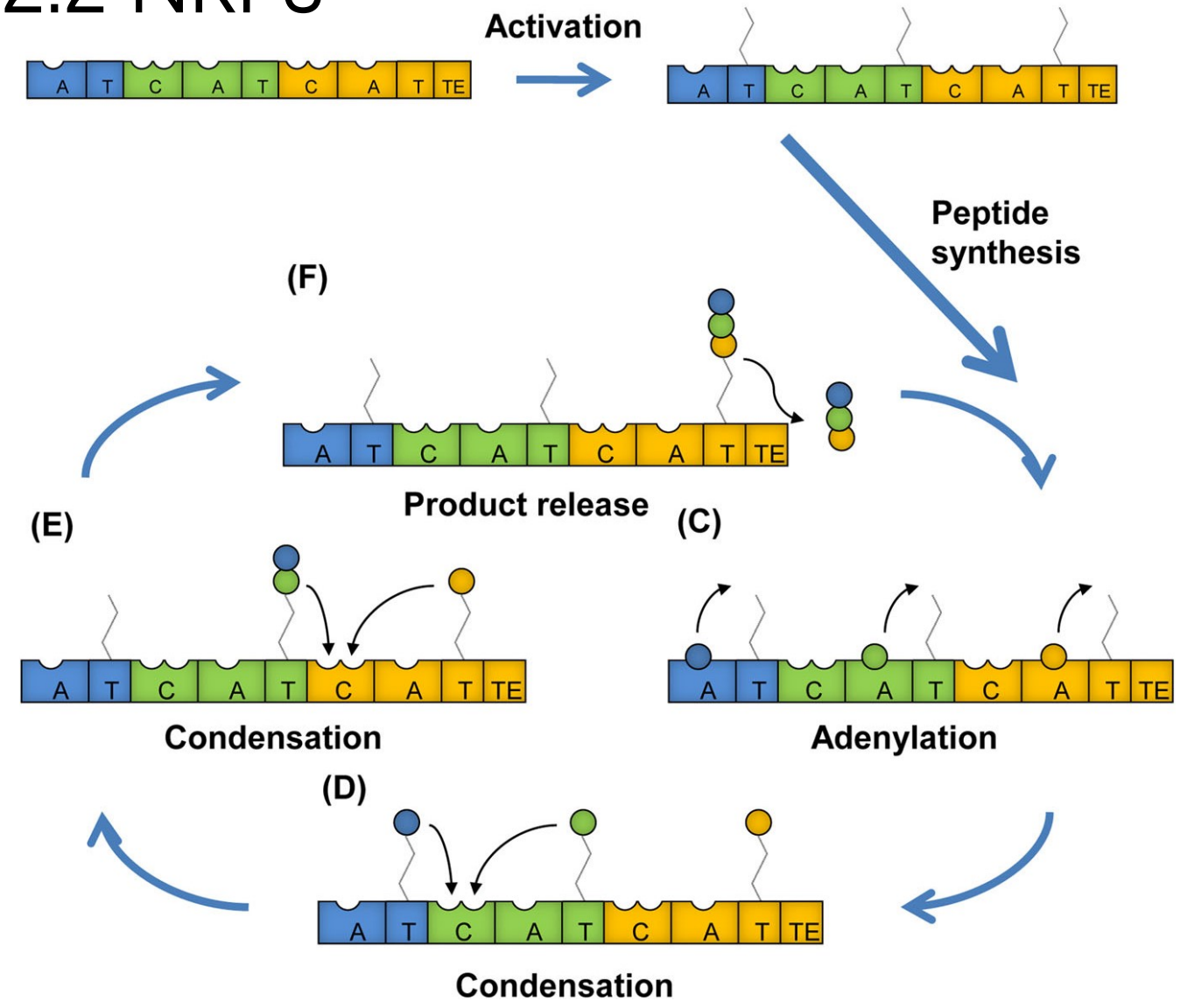
2. 利用非核糖体肽合成酶(non-ribosomal peptide synthetase，NRPS)合成分子骨架。NRPS也是一类具有多种功能域的大型合酶。

2.2.1 RiPPs



Paul G. Arnison et al, Nat. Prod. Rep., 2013

2.2.2 NRPS



A: adenylation domain

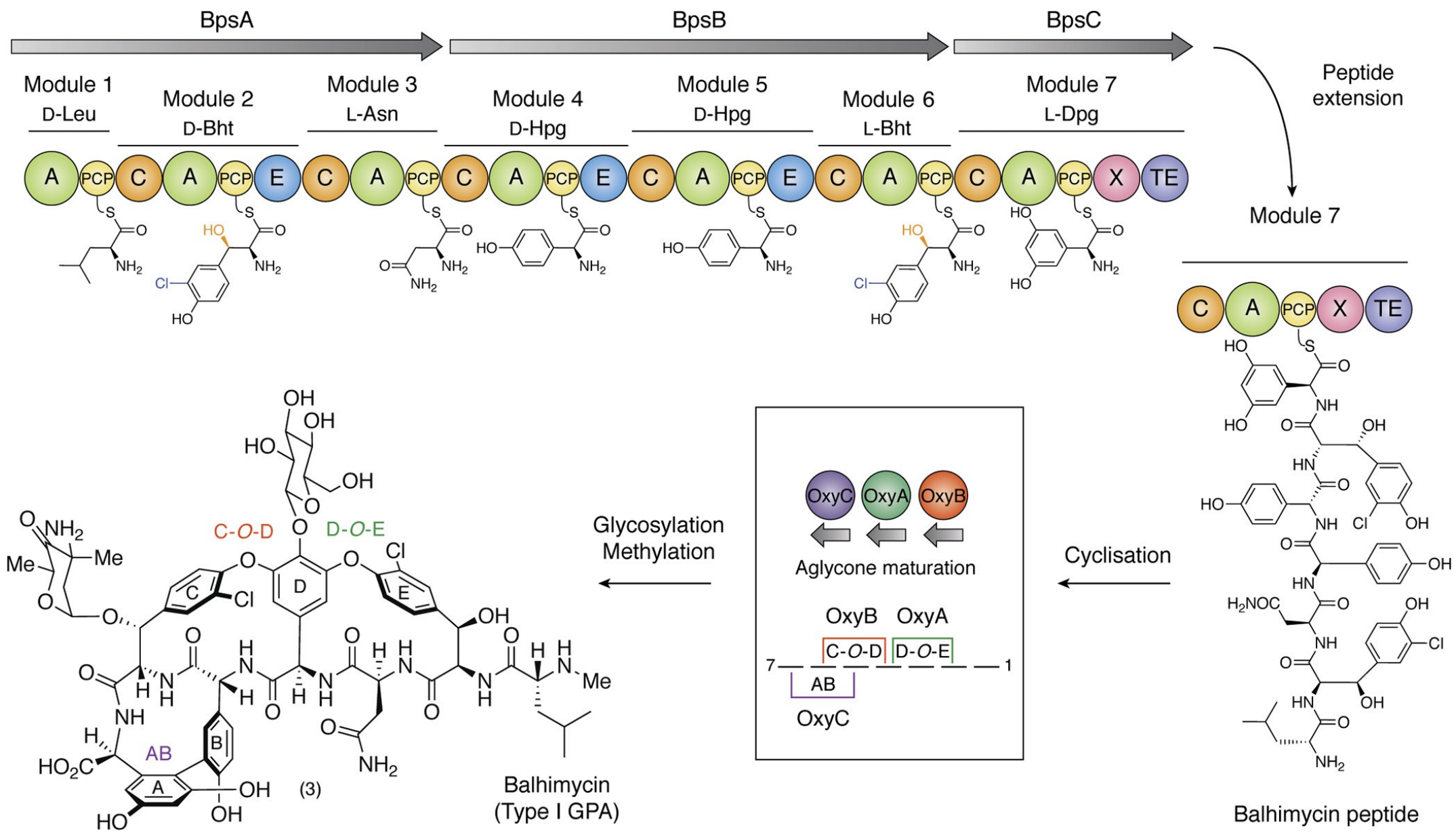
C: condensation domain

E: epimerization domain

PCP: peptidyl carrier protein

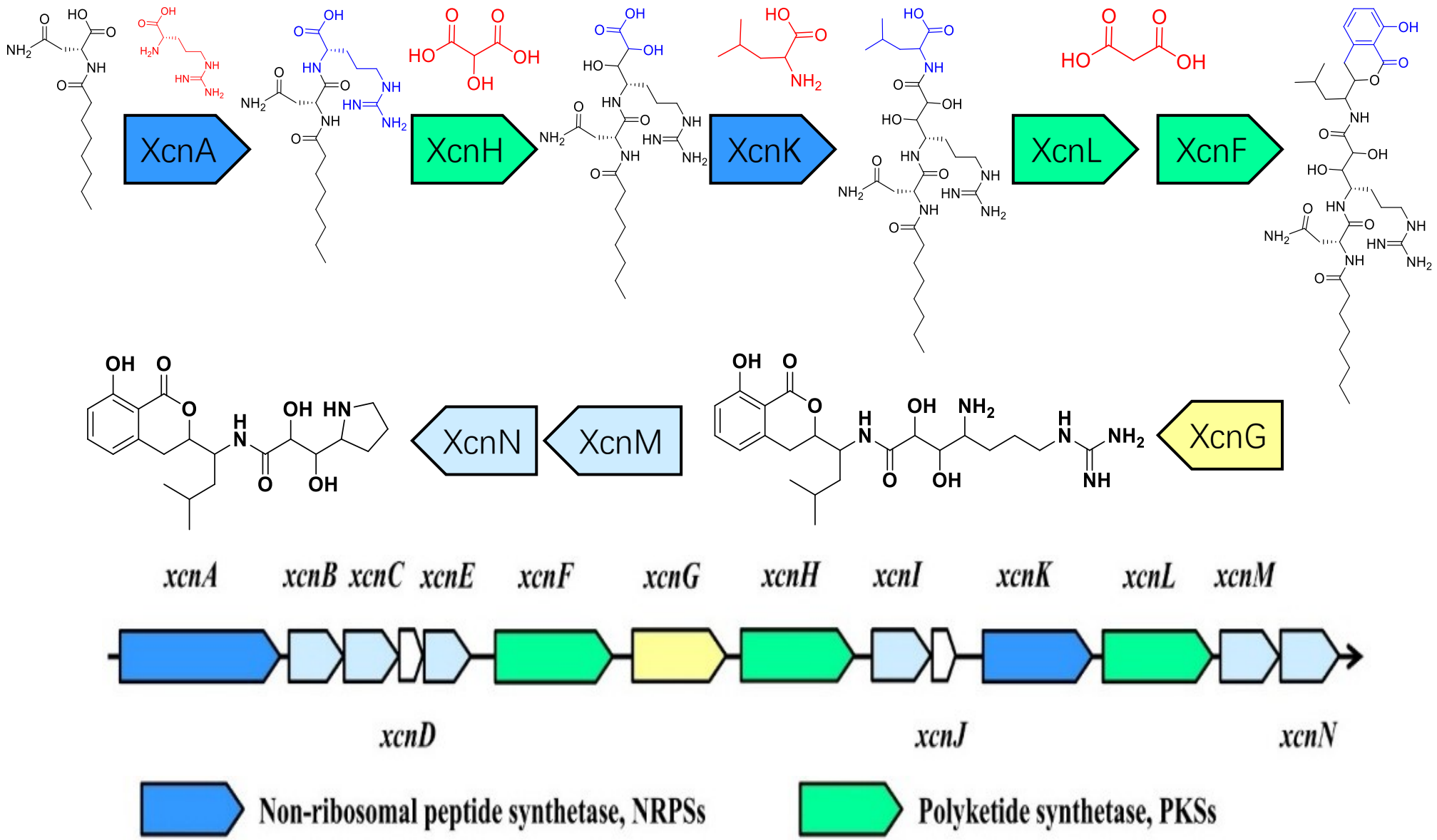
X: Oxy recruitment domain

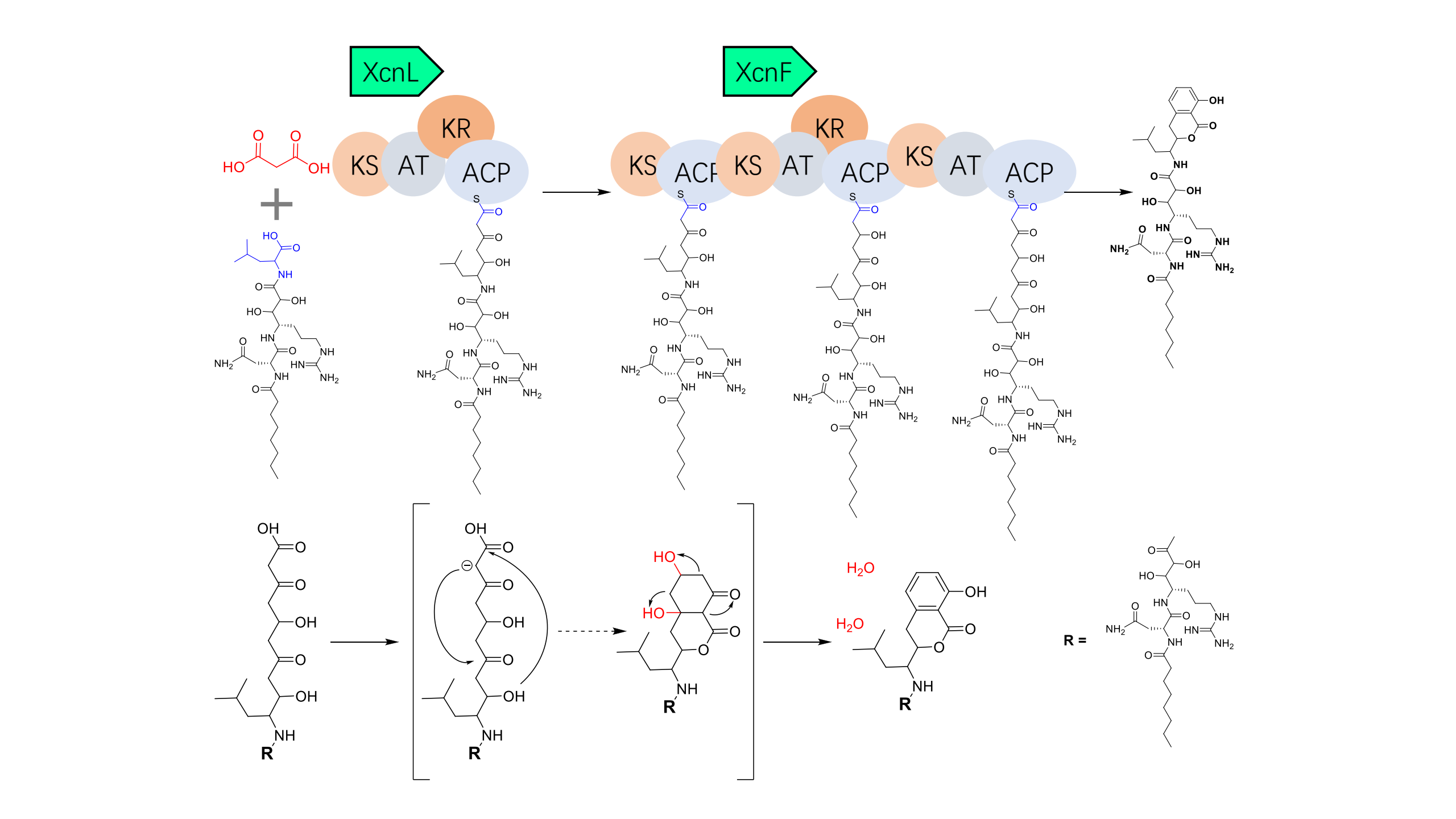
Mark J. Calcott & David F. Ackerley, Biotechnol Lett, 2014



Edward Marschall et al., J. Biol. Chem., 2019

2.2.3 NRPS-PKS


XcnA
XcnH
XcnK
XcnL
XcnF
XcnN
XcnM
XcnG
xcnA
xcnB
xcnC
xcnE
xcnF
xcnG
xcnH
xcnI
xcnK
xcnL
xcnM
xcnD
xcnJ
xcnN
Non-ribosomal peptide synthetase, NRPSs
Polyketide synthetase, PKSs


XcnL
KS
AT
ACP
KR
XcnF
KS
ACP
KS
AT
ACP
KR
KS
AT
ACP
R =

3. Prediction

3.1 结构域预测

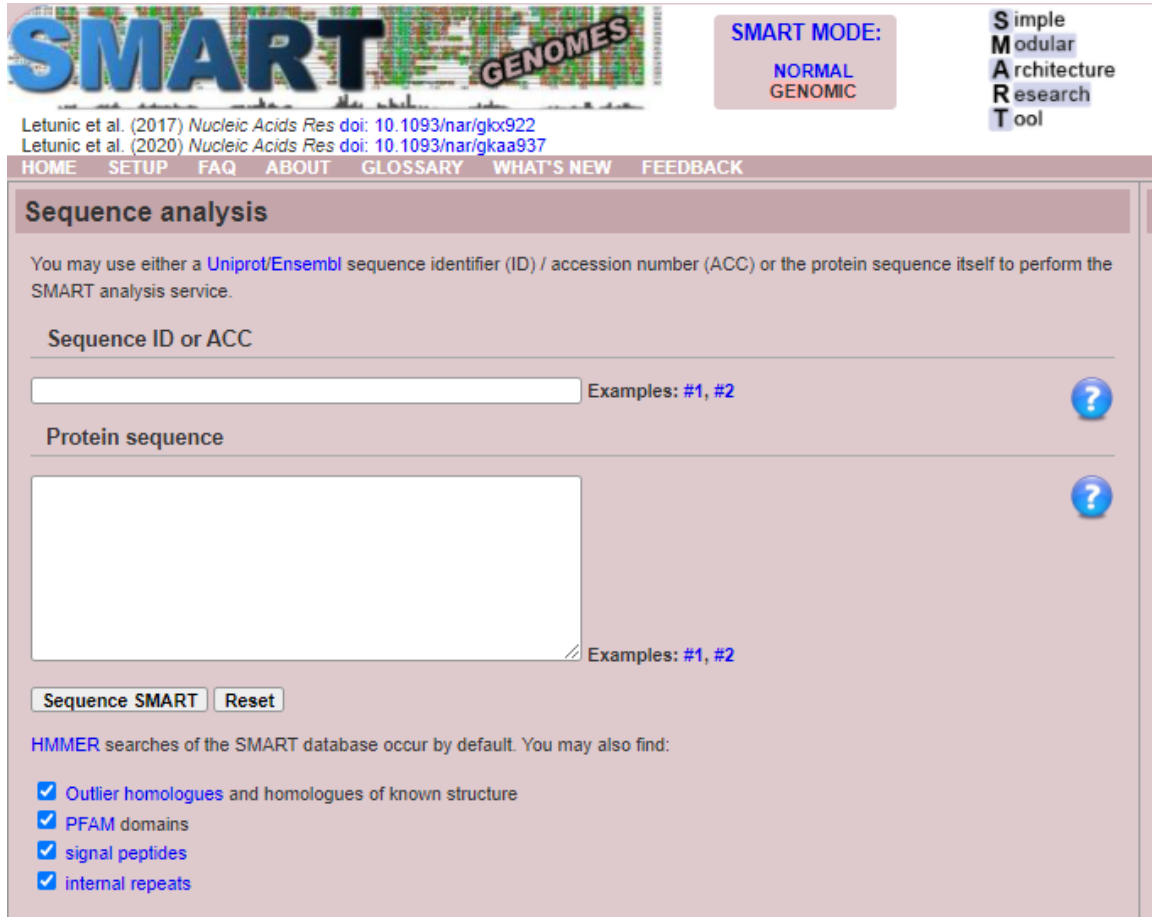
- http://smart.embl-heidelberg.de/
- https://www.ebi.ac.uk/interpro/
- https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi

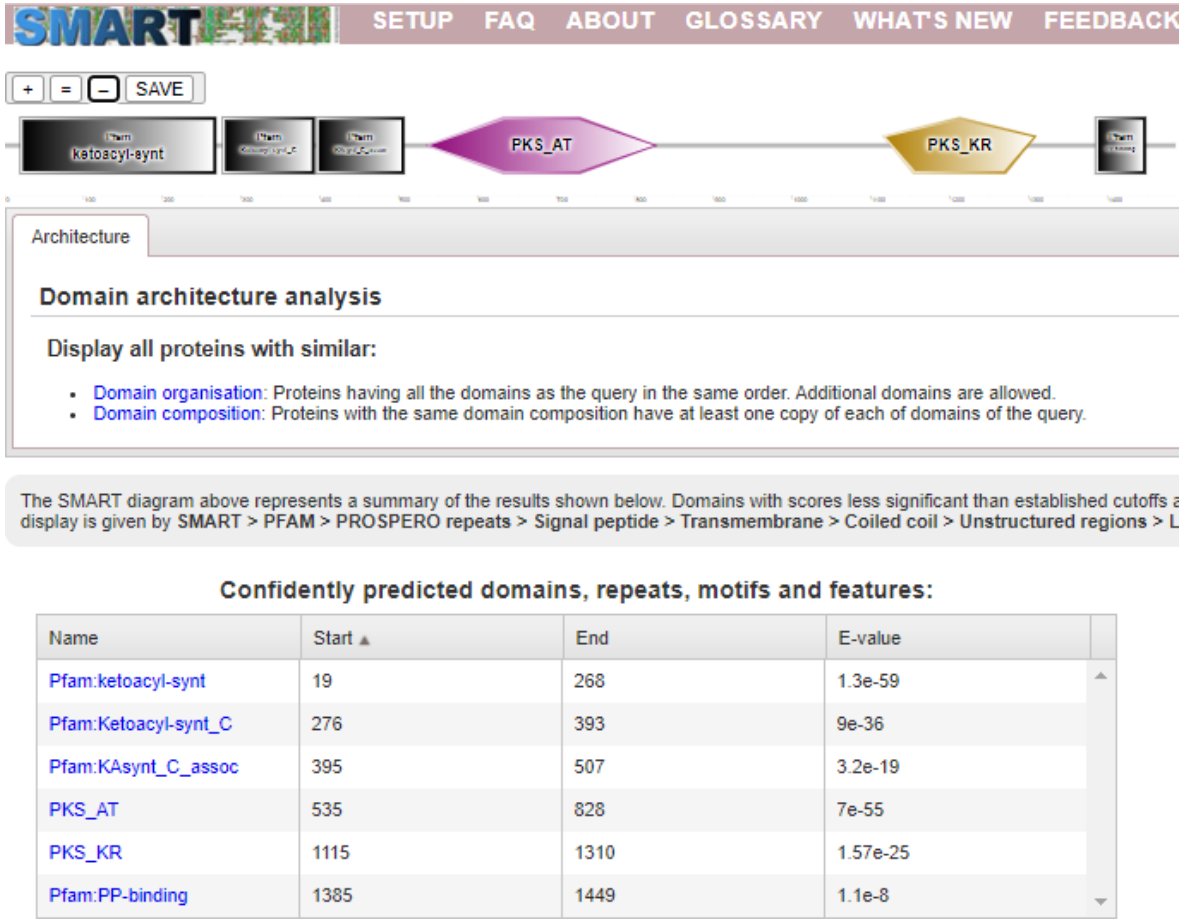
3.2 基因簇挖掘

- http://www.secondarymetabolites.org/
- https://antismash.secondarymetabolites.org/#!/start

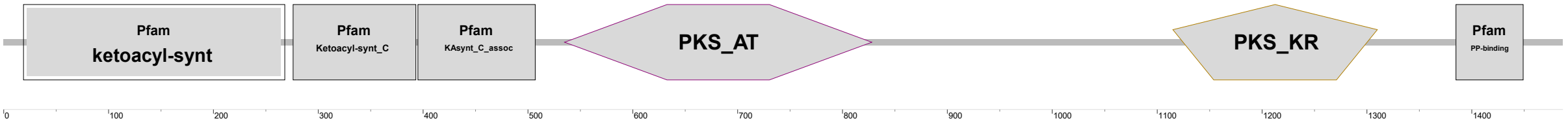
3.1 结构域预测

http://smart.embl-heidelberg.de/

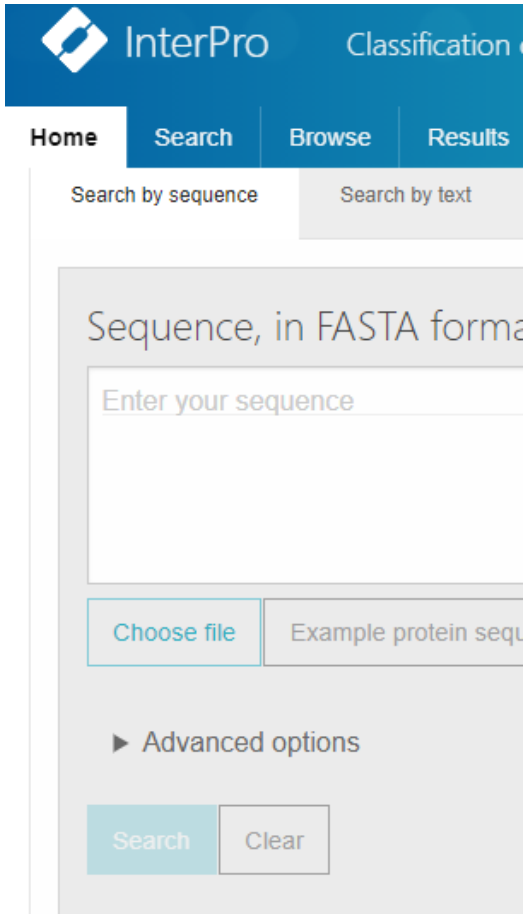


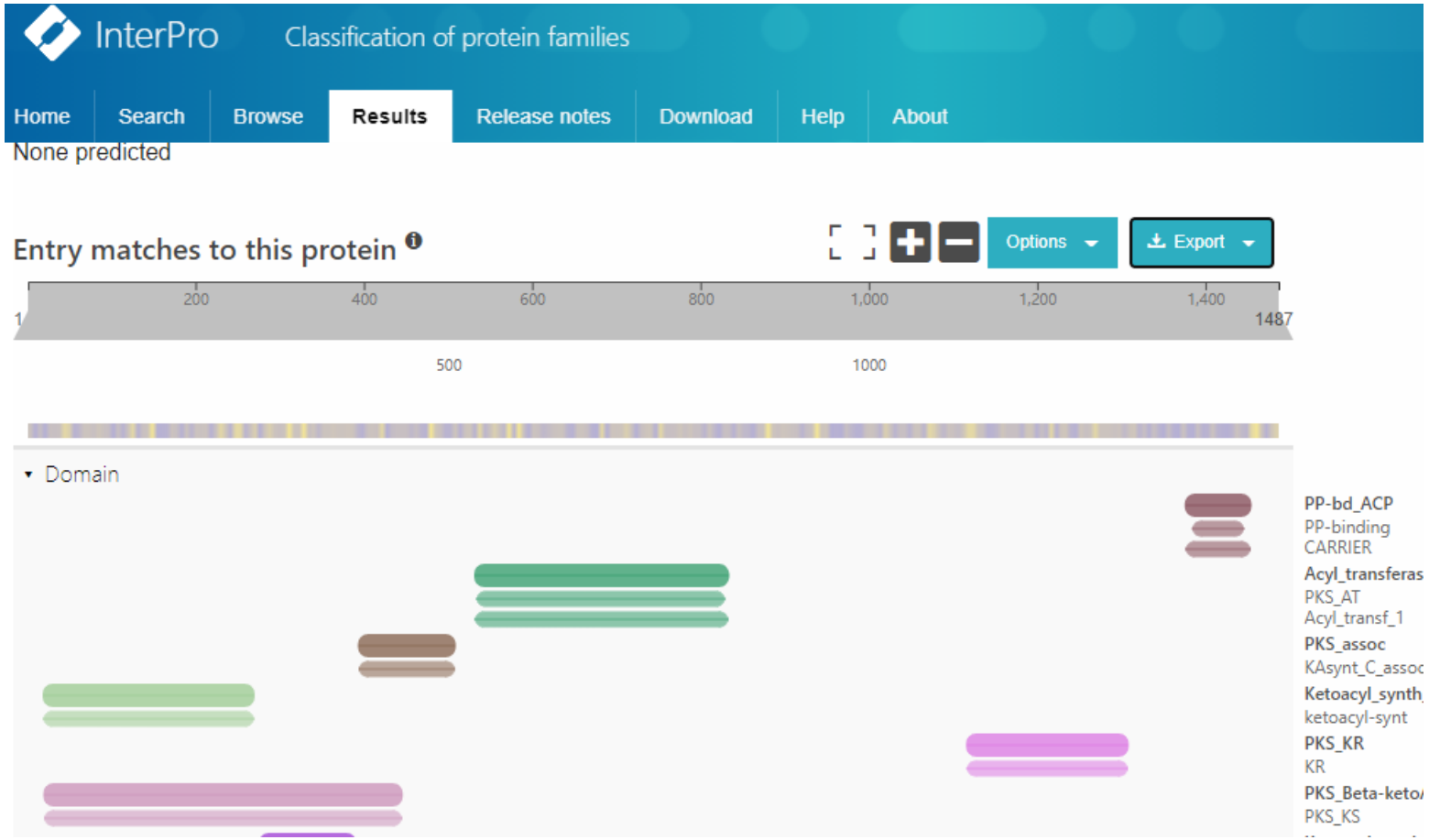


Name	Start ▲	End	E-value
Pfam:ketoacyl-synt	19	268	1.3e-59
Pfam:Ketoacyl-synt_C	276	393	9e-36
Pfam:KAsynt_C_assoc	395	507	3.2e-19
PKS_AT	535	828	7e-55
PKS_KR	1115	1310	1.57e-25
Pfam:PP-binding	1385	1449	1.1e-8

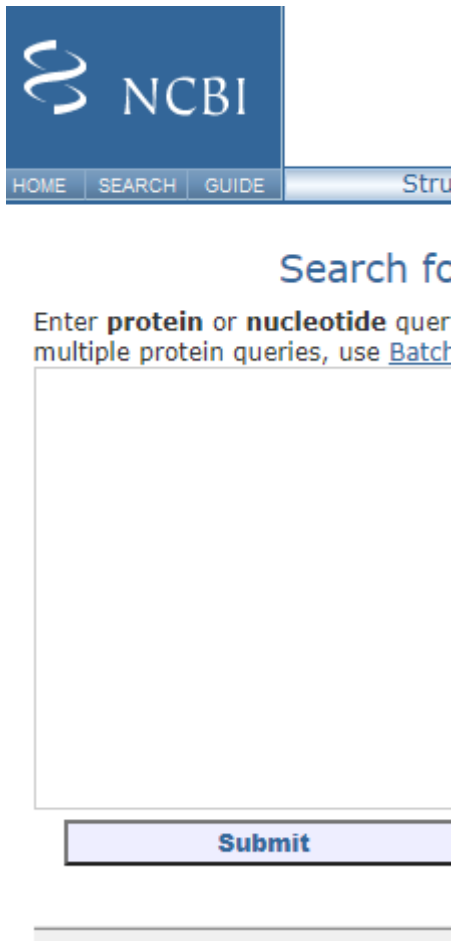


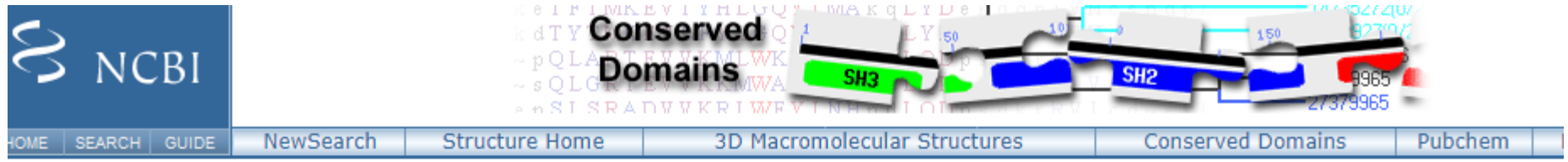
https://www.ebi.ac.uk/interpro/

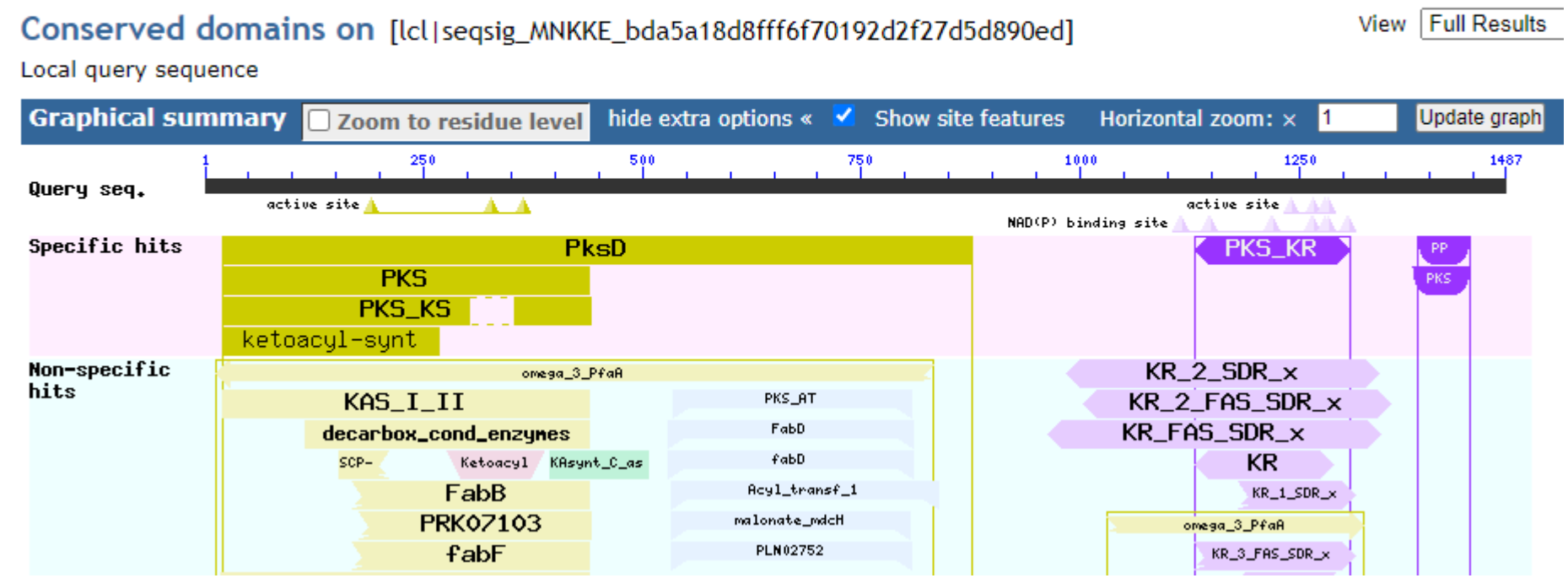




https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi



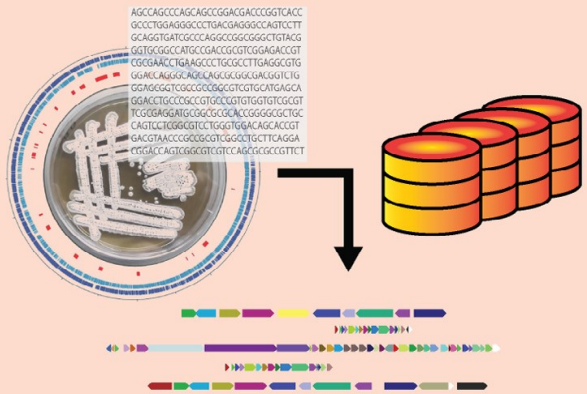




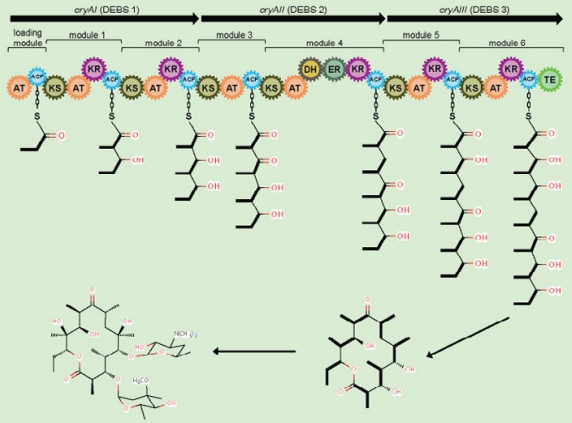
3.2 基因簇挖掘

Tools
2metDB
antiSMASH
BAGEL
CLUSEAN
ClusterFinder
ClustScan
eSNaPD
EvoMining
GNP/PRISM
NaPDoS
SMURF
Databases
Bactibase
ClusterMine360
CSDB
DoBISCUIT
IMG-ABC
MIBiG

Cluster mining tools & BGC databases



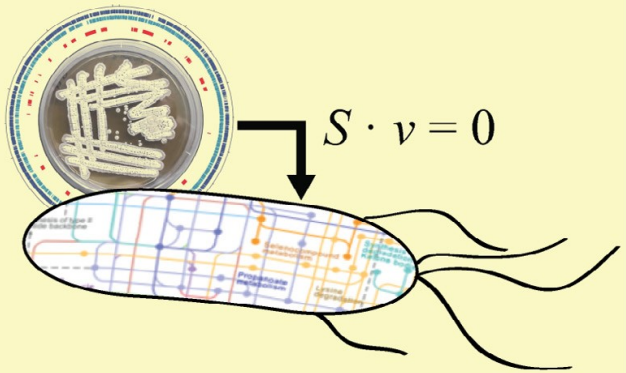
PKS/NRPS analysis tools



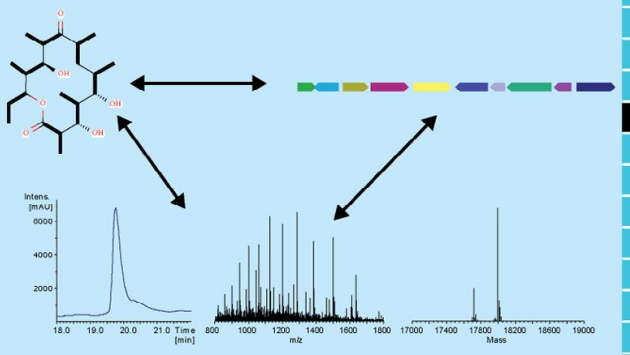
Tools
antiSMASH
ClustScan
GNP/PRISM
LSI-based pred.
MAPSI/ASMPKS
NaPDoS
NP.searcher
NRPS-PKS
NRPS/PKS SP
NRPSpredictor
NRPSsp
PKS/NRPS WS
PKSIIIexplorer
SBSPKS
SEARCHGTr
SEARCHPKS
SEQL-NRPS
SP Type I PKS

Tools
antiSMASH
CoReCo
FAME
GEMSiRV
MEMOSys
merlin
MetaFlux
MicrobesFlux
Model SEED
RAVEN
SuBliMinaL

Metabolic modeling tools



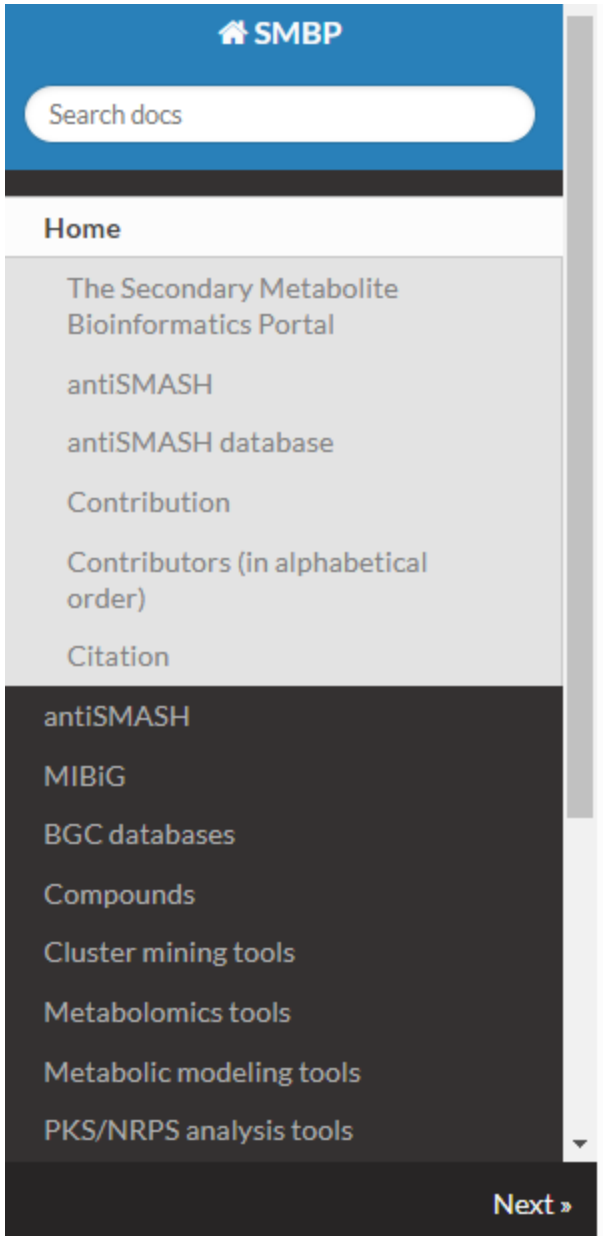
Compound databases & Metabolomics tools



Tools
Cycloquest
GNPS
GNP/iSNAP
NRPquest
RiPPquest
Pep2Path
Databases
Antibioticome
ChEBI
ChEMBL
ChemSpider
KNApSAcK
NORINE
Novel Antibiotics
PubChem
StreptomeDB

Weber T , Kim H U . Synthetic & Systems Biotechnology, 2016

http://www.secondarymetabolites.org/



Docs » Home

Welcome to www.secondarymetabolites.org

The Secondary Metabolite Bioinformatics Portal

Welcome to the new portal. Here you will find information on all aspects of Secondary Metabolite Bioinformatics, including hand-curated linkts to all major tools and databases commonly used in the field

antiSMASH

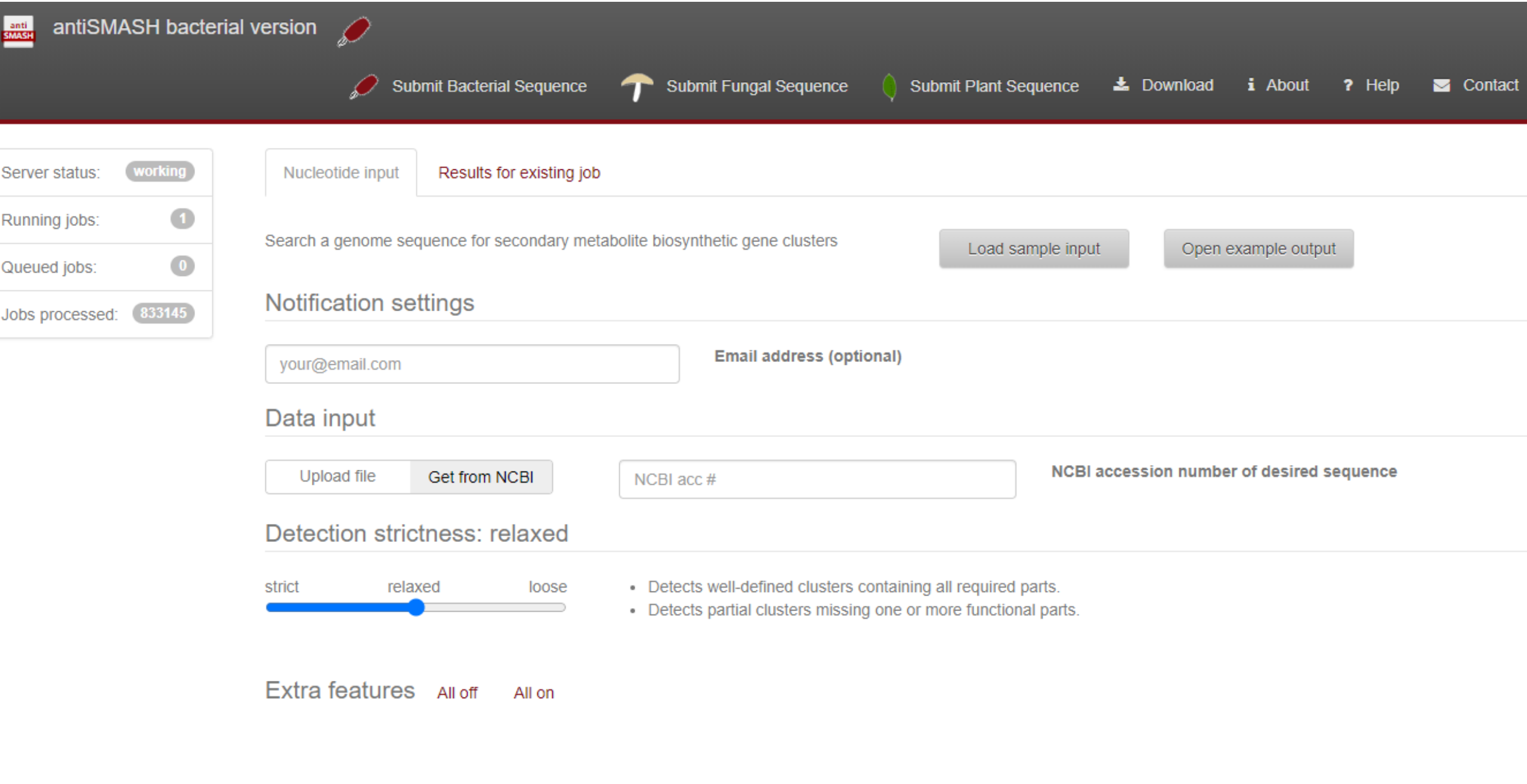
You are looking for our antiSMASH web-service? Please click here.

Click http://antismash.secondarymetabolites.org for a direct link to the service.

antiSMASH database

You are looking for our antiSMASH-database? Click http://antismash-db.secondarymetabolites.org for a direct link to the service.

https://antismash.secondarymetabolites.org/#!/start



antiSMASH version 5.2.0 | Download | About | Help | Contact

Select genomic region:

Overview | 1.1 | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 2.6 | 2.7 | 4.1 | 4.2 | 4.3 | 4.4 | 5.1 | 9.1 | 9.2 | 10.1 | 13.1 | 16.1 | 18.1 | 27.1

Identified secondary metabolite regions using strictness 'relaxed'

Compact view

Region	Type	From	To	Most similar known cluster		Similarity
Region 1.1	betalactone	569,415	595,271	lipopolysaccharide	Saccharide:Lipopolysaccharide	5%
Region 2.1	NRPS	1	47,014	xenoamicin A / xenoamicin B	NRP:Cyclic depsipeptide	45%
Region 2.2	T1PKS, NRPS	86,770	144,122			
Region 2.3	NRPS	178,506	234,015	nematophin	NRP	87%
Region 2.4	NRPS	254,851	310,555	nematophin	NRP	100%
Region 2.5	bacteriocin	312,386	322,589			
Region 2.6	NRPS	419,352	491,844	odilorhabdins	NRP	100%
Region 2.7	NRPS-like	531,623	572,153	xenematide	NRP	100%
Region 4.1	NRPS	10,787	61,947	xenematide	NRP	100%
Region 4.2	NRPS	83,686	168,629	xenoamicin A / xenoamicin B	NRP:Cyclic depsipeptide	25%
Region 4.3	NRPS-like	230,163	271,776			
Region 4.4	NRPS-like, thiopeptide	315,927	358,986	O-antigen	Saccharide	14%
Region 5.1	PpyS-KS	223,214	244,260	xenoamicin A / xenoamicin B	NRP:Cyclic depsipeptide	8%
Region 9.1	NRPS	79,853	126,075	tilivalline	NRP	47%
Region 9.2	NRPS-like	136,732	178,059	safracin A / safracin B	NRP	20%
Region 10.1	T1PKS, NRPS	11,078	89,813	xenocoumacin 1 / xenocoumacin II	NRP + Polyketide:Modular type I	100%
Region 13.1	nucleoside	62,440	84,566	TP-1161	RiPP:Thiopeptide	20%
Region 16.1	siderophore	2,311	26,843	putrebactin / avaroferrin	Other	100%
Region 18.1	NRPS	1	44,272	xenoamicin A / xenoamicin B	NRP:Cyclic depsipeptide	33%

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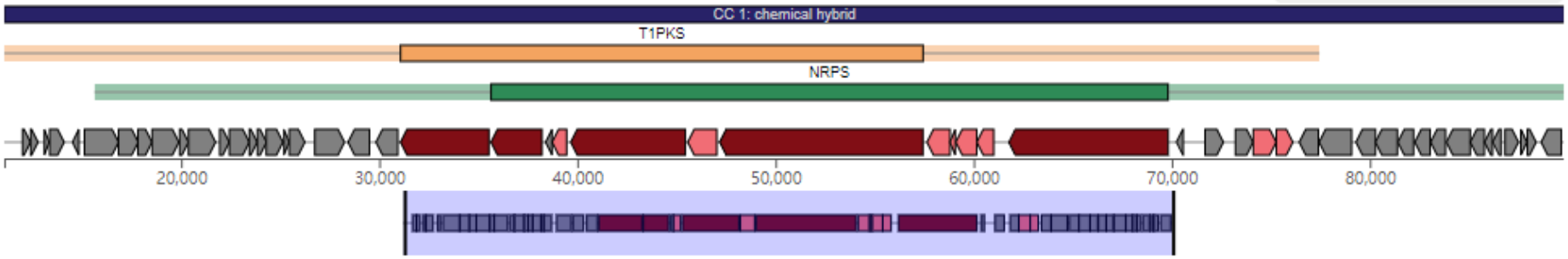
Select genomic region:

Overview | 1.1 | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 2.6 | 2.7 | 4.1 | 4.2 | 4.3 | 4.4 | 5.1 | 9.1 | 9.2 | 10.1 | 13.1 | 16.1 | 18.1 | 27.1

NZ_HF952051.1 - Region 1 - NRPS,T1PKS

Location: 11,078 - 89,813 nt. (total: 78,736 nt) Show pHMM detection rules used

Download region GenBank file



Legend:

core biosynthetic genes | additional biosynthetic genes | transport-related genes | regulatory genes | other genes | resistance

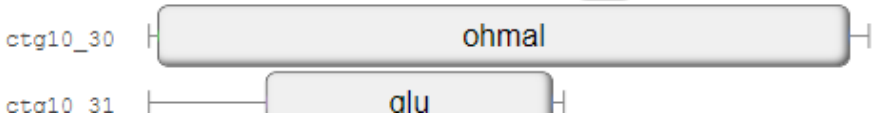
reset view | zoom to selection

NRPS/PKS domains | ClusterBlast | KnownClusterBlast | SubClusterBlast

Detailed domain annotation

Selected features only

Show module domains



Gene details

ctg10_30

Locus tag: ctg10_30
Protein ID: None
Gene: None
Location: 31,078 - 35,541, (total: 4464 nt)

biosynthetic (rule-based-clusters) T1PKS: PKS_AT
biosynthetic (rule-based-clusters) T1PKS: PKS_KS
biosynthetic-additional (rule-based-clusters) PP-binding
biosynthetic-additional (smcogs) SMCOG1093:Beta-ketoacyl synthase (Score: 68.1; E-value: 1e-20)

Active site details:

NCBI BlastP on this gene
View genomic context
MiBIG Hits

AA sequence: Copy to clipboard
Nucleotide sequence: Copy to clipboard

NRPS/PKS products | NRPS/PKS monomers

Predicted core structure(s)

For candidate cluster 1, location 11077 - 89813:

4. Outlook

通过将生物信息学与现代生物技术相结合，加快了SMs及其BGCs研究进程，加深科研人员对生物代谢行为的理解。当前对于SMs仍处于活性成分挖掘，分子基团的简单修饰改造阶段，相信随着研究的深入，我们能够从头设计全新的BGCs，生产新型化学结构的SMs。

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感谢批评指正